PHENYLALKYLAMINES OF POTENTIAL BIOLOGICAL INTEREST

THESIS

presented by

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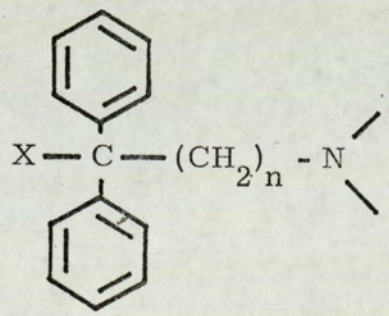
SUMMARY

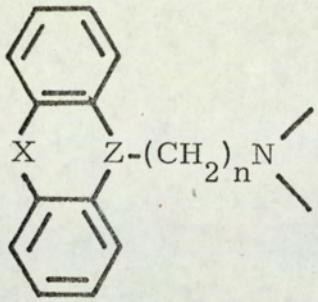
As a result of a preliminary biological screen certain basic compounds containing a tricyclic system in which one of the rings was heterocyclic were found to exhibit antiviral activity against both DNA and RNA type viruses.

Certain other basic compounds containing two phenyl groups connected to the same carbon atom and separated from the basic group by a methylene chain also appeared to have this activity. At the outset it was realised that compounds of this nature might also exhibit useful pharmacological activity

In the present investigation it was thought desirable to prepare compounds of the general type:

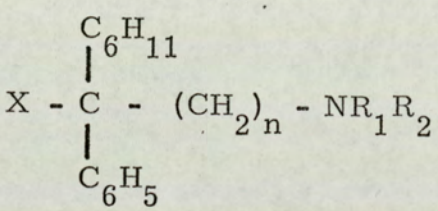


and possibly to further investigate the structure activity relationships by preparing analogues of the type:



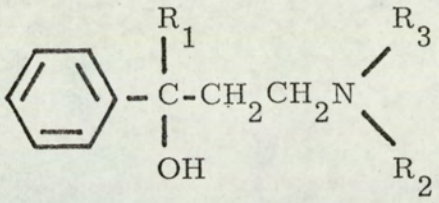
where Z = N or C, and X is a bridging group.

During the present investigation compounds of the following types were prepared, the first being of the general formula



where X = CN, H, or C_6H_5, and NR_1R_2 = dimethylamino, morpholino. These were synthesised by the condensation of diphenylacetonitrile with the appropriate chloro-amine, and removal of the cyano group with sodamide. One of the phenyl rings was selectively reduced by a catalytic hydrogenation, steric factors playing a role. Several of these compounds showed promising antiviral activity.

A closely related series,



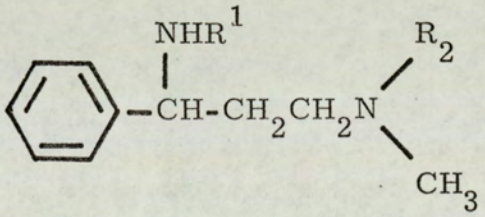
where R_1 = phenyl, cyclohexyl, methyl, n-butyl, p-tolyl.

R_3 = methyl, ethyl, n- butyl;

R_2 = methyl, 2-hydroxyethyl;

were synthesised by modified Grignard, aryl-lithium, or alkyl-lithium addition to the appropriate Mannich bases.

Methods of amination of Mannich bases were investigated, either by reductive amination or by isolation of their ketimines to provide a facile route for the synthesis of a further series of compounds:



where R^1 = an alkyl or acyl group

R^2 = methyl or 2-hydroxyethyl.

The synthetic route adopted was that of alkylation or acylation of the diamine resulting from reduction of the oxime of the Mannich base.

The lability of the terminal dialkylamino group was noted, and the ability of this series to undergo ring closure was demonstrated.

A substantial number of these compounds were assessed for antiviral and other pharmacological activity.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Professor N. J. Harper for his help and supervision of the research programme described in this thesis.

I also thank Dr. J. R. Raines for his advice during the course of this work and Miss G. Burrows for typing the manuscript.

I am indebted to Sterling-Winthrop Ltd. for the award of a scholarship during the period in which the work was carried out.

CONTENTS

SECTION I

INTRODUCTION

Progress in the treatment of viral infections has been much slower than that of bacterial infections, and whilst vaccines continue to be developed and improved, their inherent disadvantages make an anti-viral agent of synthetic origin an attractive proposition both in the medical and commercial sense. A great deal of effort has been put into the search for such antiviral compounds but unfortunately the rewards so far have been meagre, and the few compounds of any clinical significance have often arisen from other, more fruitful, fields of research.

One is tempted to draw analogies between the fields of bacterial and viral chemotherapy but when one considers the number of additional problems involved in viral chemotherapy one can realise why progress is much slower. Firstly, there is a much more intimate relationship between the virus and the host cell which makes any selective inhibition very difficult. Indeed, there are several viral inhibitors which inhibit viral protein synthesis but at virustatic concentrations are toxic to normal cells. This intimate relationship between virus and host would also explain the poor

correlation between in vivo and in vitro screening results which has, and still does, lead to many "false positives". Even when the ideal antiviral agent has been found there still remains the problem of treatment, for often by the time symptoms appear it is too late to start treatment because viral multiplication will already have taken place and will probably be coming to its end. For this reason the prospects for a prophylactic antiviral drug are likely to be better than one for therapeutic treatment. With a few exceptions the existing antiviral drugs are only of prophylactic use.

Possible mode of action of an antiviral agent.

The aim of viral chemotherapy has been the discovery of viral inhibitors capable of acting at one of the phases of virus multiplication. Briefly these can be listed as -

(i) Extracellular virus particles which have been released from infected cells.

(ii) Adsorption on to, followed by penetration into susceptible cells, generally believed to be an electrostatic or an enzymatic process.

(iii) An eclipse phase during which the virus has entered the cell and lost its infectivity.

(iv) Synthesis and maturation of new virus particles in which

the host cell metabolism is redirected into the manufacture of various precursor parts of the virus.

(v) Release of virus particles from the infected cells, about which little is yet understood.

In addition an antiviral agent could act indirectly by stimulating the release of interferon (a natural antiviral substance) from the host cells. A further attribute of the ideal therapeutic agent should be to beneficially modify cell or tissue damage resulting from viral multiplication.

Methods of screening.

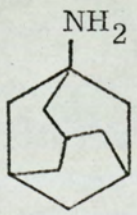
In common with other fields of virology, screening technology is being developed continually. Advances in tissue culture techniques and the adaptation of viruses to growth in tissue cultures has provided useful tools for studying virus - host cell interactions at cellular level, for the screening of potential antiviral agents and for the elucidation of their modes of action. Some viruses which do not produce plaques in tissue culture will grow in eggs; inoculation with virus followed by treatment with the compound to determine if the virus will multiply, can be used as a screen. Methods using de-embryonated eggs have been developed recently.

The ultimate and most meaningful test for any antiviral agent is to determine whether it will prevent infection in animals. Influenza virus will produce lung lesions in mice while vaccinia lesions can be produced in rabbits. The infections usually produce death. As an alternative use can be made of oncogenic viruses such as Rous sarcoma virus, in which case an infected animal will die from cancer.

Some synthetic antiviral agents.

Adamantanamine hydrochloride (Amantadine)

Laboratory tests have demonstrated the antiviral effects of some cationic substances, some of very simple structure. The most promising is the symmetrical amine, 1 - aminoadamantane (1).



(1)

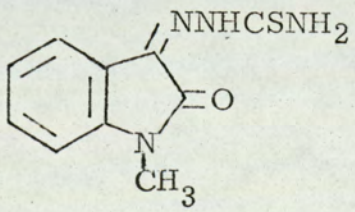
Reports on the antiviral range of this drug have varied slightly but it appears to have moderate prophylactic activity against Influenza

A2 virus. It has no therapeutic activity. A controlled prophylactic trial carried out by Wendel (1964) among 800 prison volunteers reduced clinical illness by 77% and the infection rate by 31%. Its usefulness is somewhat limited by its toxicity.

Electron micrographs suggest that influenza virus particles are taken into mammalian cells by phagocytosis. Salts of quite simple aliphatic amines and even ammonium chloride prevent this engulfment, thus suggesting that these cationic substances may interfere with penetration by accumulating at the cell surface and altering the charge.

Thiosemicarbazones

As early as 1950, thiosemicarbazones have been known to inhibit the growth of poxviruses at which time Hamre et al. showed that p-aminobenzaldehyde thiosemicarbazone could partially protect chick embryos or mice against infection by vaccinia virus. Subsequently many thiosemicarbazone derivatives were prepared, the most clinically successful being N-methylisatin-β-thiosemicarbazone (methisazone, Marboran), (2). During a smallpox outbreak in Madras,

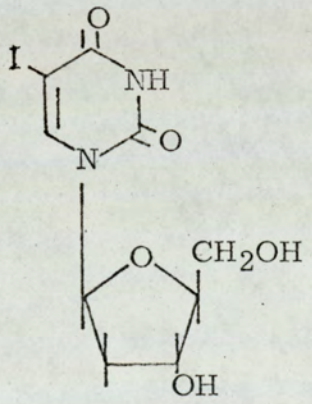


(2)

the drug was given to 1,100 known contacts. Only three cases, all mild, occurred but in a similar number of untreated people 78 contracted smallpox and 12 died of it (Bauer et al. 1963). It has been suggested that methisazone and its derivatives owe their action to a chelation mechanism in which an essential metal ion is held between the oxygen atom and the second nitrogen of the side chain (O'Sullivan and Sadler, 1961).

Pyrimidines

This group of compounds includes the only clinically successful drug to be developed from a purely logical approach, namely 5-iodo-2'-deoxyuridine (IUDR), (3). It is structurally similar to



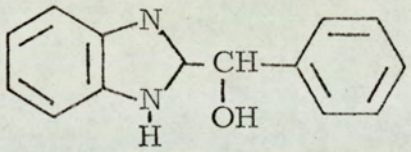
(3)

thymidine and competes with it in the synthesis of DNA in viruses such as herpes and vaccinia. Even so, its clinical success depends on the fact that it may be used locally in herpetic keratitis of the eye, terminating quickly a long-lasting and painful disease. It is too toxic

for systemic use.

Benzimidazoles

The most potent member of this group of compounds is 2-∝-hydroxybenzylbenzimidazole (HBB), (4). It is active mainly against polio viruses by interfering with the synthesis of RNA



(4)

polymerase, possibly by a hydrogen bonding or chelating mechanism. Guanidine has similar antiviral activity and is thought to act by a similar mechanism.

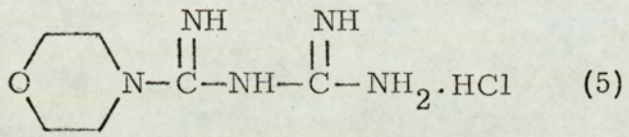
Pteridines

The folic acid antagonist amethopterin (Methotrexate) which is in regular use in leukemia therapy, has been demonstrated to have antiviral activity (Smith et al. 1960). Subsequently the structure - activity relationships of several pteridine derivatives was studied and more were found to possess significant antiviral activity (Hegarty, 1965).

Biguanides

Again from another field of research - antimalarial chemotherapy -

the screening of a large number of biguanides resulted in the discovery by Melander (1960) that N', N'-anhydro-bis (β-hydroxyethyl) biguanide hydrochloride (ABOB), (5), was effective in mice infected with influenza virus. The drug is marketed in a formulation as

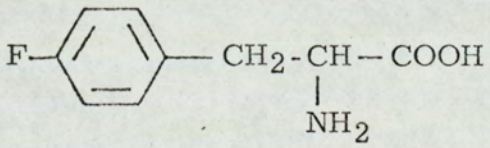


(5)

Virugon and Flumidin, but its clinical efficacy seems to be in dispute.

Amino acid antagonists

A number of amino acid analogues have been shown to possess antiviral activity, but most emphasis has been placed upon p-fluorophenylalanine (FPA), (6). It has been demonstrated to inhibit



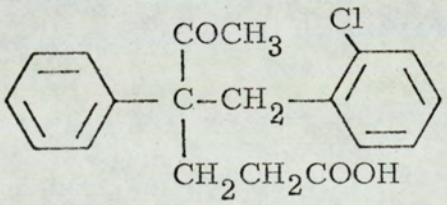
(6)

viral RNA formation thus preventing the growth of influenza and polio virus in tissue cultures.

virus in tissue cultures.

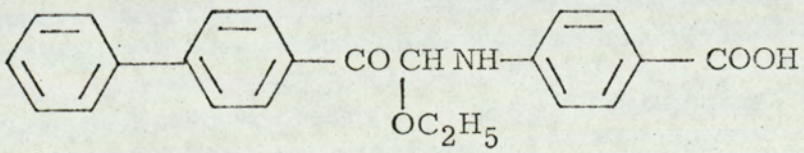
Miscellaneous compounds

The number and variety of chemical compounds reported in the literature to have antiviral activity are legion: acridines, anti-inflammatory agents and several antibiotics naming but a few. Such is the variety of chemical structures that it is difficult to visualise any structure-activity relationships or any single moiety which may be regarded as essential for antiviral activity. However, many independent reports have recently shown antiviral activity, mainly against influenza in compounds loosely related to diphenylmethane. For example it was shown (Liu et al. 1951), that the compound caprochlorone (7) was highly effective against influenza in embryonated eggs.



(7)

Also, Cavallini (1964) developing from a structure (8) which he had



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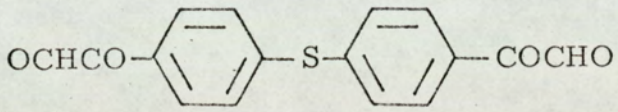
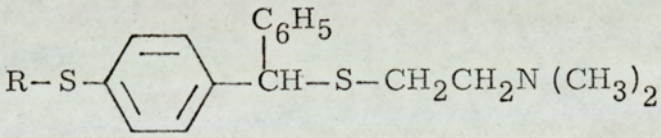
previously shown to be active, found the best antiviral activity to be exhibited by compound (9), a diphenylsulphide derivative. Similarly,



(9)

the following structures (10 - 13) and their many analogues have been shown by Japanese workers to possess antiviral activity against influenza and Japanese encephalitis, (Tsuji et al. 1960; Masako et al, 1960; Takada and Toyoshima, 1960).



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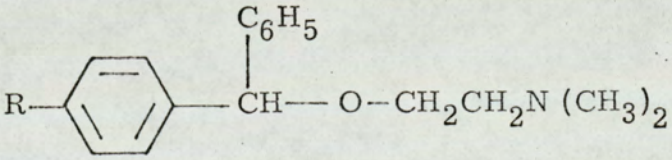

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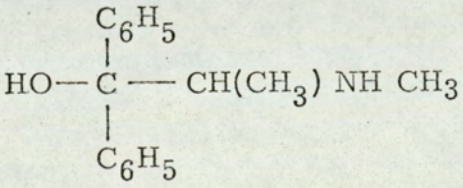

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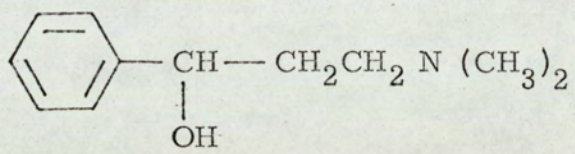
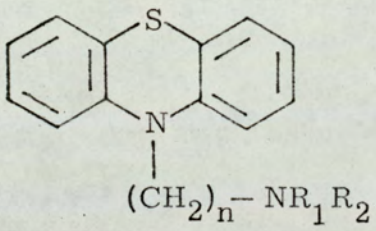


(13)

In conclusion, whilst there are few antiviral drugs available for clinical use, the fact that there are many active compounds without excessive toxicity is encouraging. Studies on the mode of action of these compounds will lay the basis for the development of a more rational approach to chemotherapy. Meanwhile, the evaluation and re-evaluation of both existing and future compounds by improved techniques will undoubtedly lead to the long awaited "break-through".

AIMS AND OBJECTS OF THE PRESENT INVESTIGATION

As a result of biological screening for antiviral activity it was found that some compounds consisting essentially of a tricyclic system possessed antiviral activity against Vaccinia (a DNA virus) and Influenza PR8 (an RNA virus). Examples of such compounds were phenothiazines of the type (1) and iminodibenzyl compounds of type (2),



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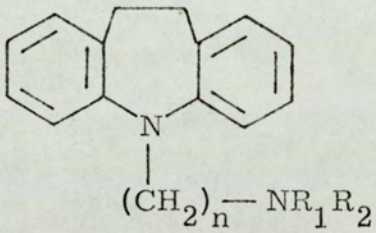


(2)

where n = 2 - 4 and NR_1R_2 is a basic group.

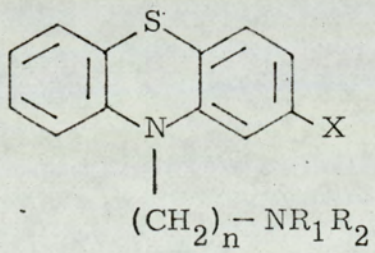
The CNS activity of phenothiazines and iminodibenzyl compounds is well known with such drugs as chlorpromazine and imipramine. This suggested that compounds which might have CNS activity could possibly have antiviral activity too.

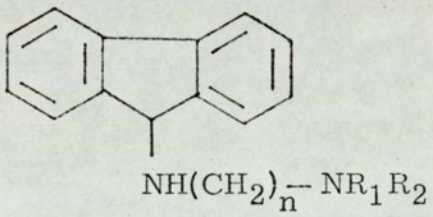
The activity against influenza was a particular attraction and it was considered of interest to explore the structure-activity relationships of some tricyclic and bicyclic systems preferably containing a basic

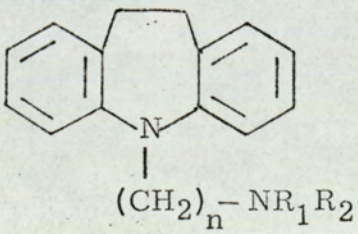
moiety.

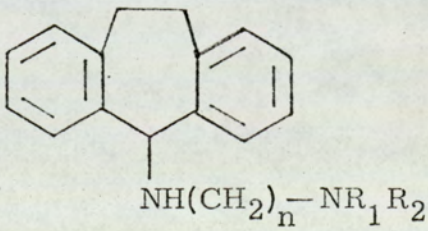
It was recognised at the outset that the meaningful screening of antiviral compounds has plagued workers in this field since there are marked difficulties in extrapolating in vitro and animal in vivo tests to man. However, the proposed synthetic programme had the additional advantage that if the antiviral screening proved difficult to interpret, the nature of the compounds was such that screening for CNS activity could be of value.

To follow the antiviral lead it was considered desirable to prepare compounds of the following type and to test some which were already available.





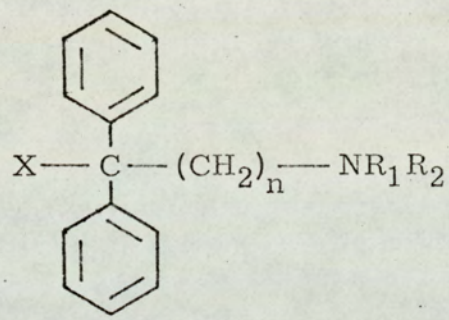




where n = 2 or 3; x = Cl or CF_3;

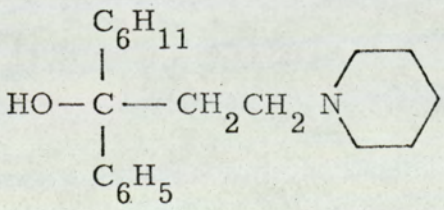
NR_1R_2 = phthalimido or an amino group.

Parallel studies soon indicated that a tricyclic system was not essential for antiviral activity and effort was directed into the preparation of some diphenylmethyl derivatives with the general structure (3) which turned out to have greater antiviral activity. Basic diphenylmethyl



(3)

derivatives have been the subject of a number of investigations to exploit their biological activity. Successes in this field have produced several drugs which have found wide use in clinical practice as antispasmodics such as Benzhexol ("Artane") (4); antihistamines, for example Aspasan (5); and analgesics, of which methadone (6) is a notable example.



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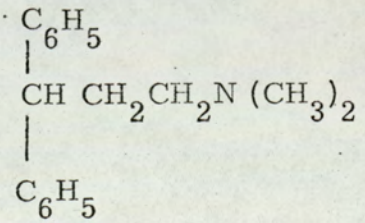

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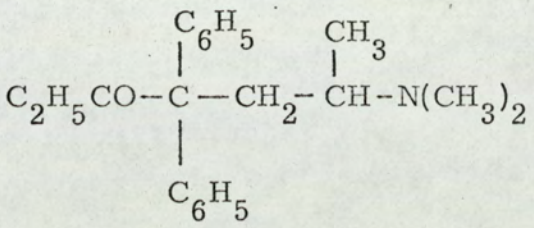


(6)

It has already been noted that similar structures have been reported to possess antiviral activity (Tsuji et al. 1960; Masako et al. 1960; Takada and Toyoshima, 1960).

In the present investigation the effects of making various modifications to the basic structure (3) were observed by synthesising a series of compounds where -

(i) one of the phenyl groups was reduced to cyclohexyl or replaced by an alkyl group;

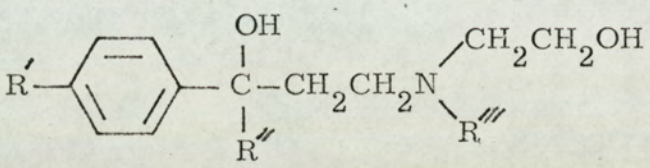
(ii) The hydrogen atom (substituent X) was replaced by cyano, hydroxyl or phenyl groups.

(iii) The length of the carbon chain was varied.

(iv) The substituents of the tertiary amino group were modified.

It was surprising to note that in the extensive field of phenylpropylamines no instances were found where an alcoholic moiety had been introduced into one of the tertiary amino substituents. The rationale

behind the introduction of such a grouping, with particular reference to the work of Archer (1967), will be discussed later. It was therefore of interest to prepare such a series of compounds (7) and compare their



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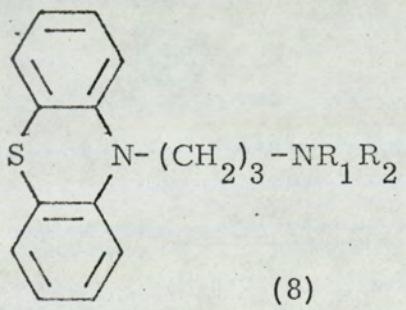
biological activity with the previously known dialkylamino analogues.

It has been seen that antiviral activity was exhibited by phenothiazine derivatives (8) in which the ring nitrogen was separated from a side chain nitrogen atom by three carbon atoms. It was therefore considered to be of interest to prepare a further series of compounds (9) where a propanediamine structure possessed cyclic or bulky alkyl



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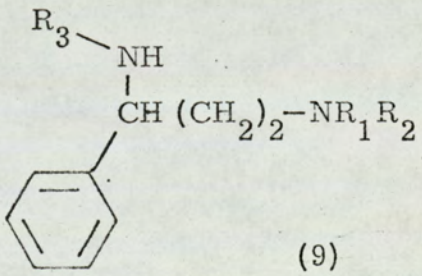

(9)

substituents on one of the nitrogen atoms. Surprisingly few derivatives of 3-dimethylamino-1-phenylpropylamine have been reported and the

preparation of such compounds for biological assessment appeared attractive. The preparation of such compounds both from the parent amine and by direct reductive amination was studied in detail.

In summary, it was considered desirable to explore the antiviral and the pharmacodynamic activities of a series of compounds starting with tricyclic systems containing two phenyl rings followed by bicyclic systems consisting of two phenyl rings, thence to compounds of the diphenyl type containing a nitrogen atom adjacent to the rings. The following types of compound were synthesised:

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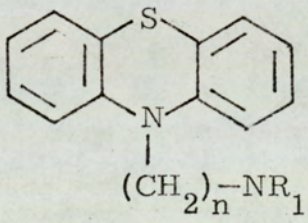

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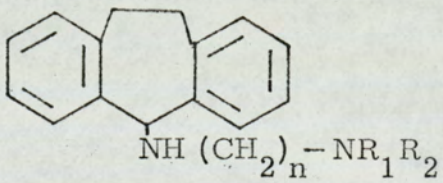
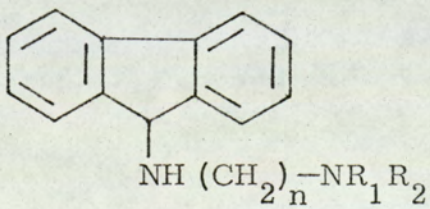
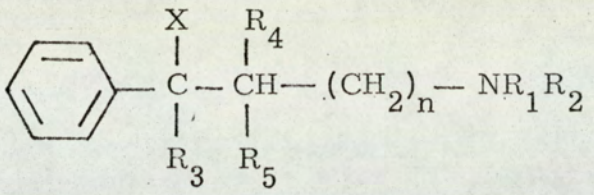
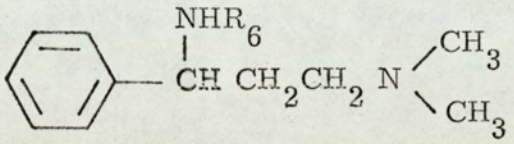


(c)





(d)



(e)

where NR_1R_2 = dimethylamino
morpholino
pyrrolidino
hydroxyethylmethylamino
hydroxyethyl-n-butylamino

R_3 = methyl, phenyl, cyclohexyl, n-butyl, p-tolyl

x = H; CN, OH, C_6H_5

R4 = R_5 = H or CH_3

n = 0 - 3

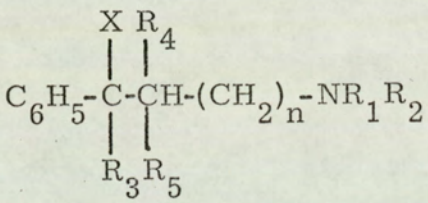
R6 = various acyl or alkyl groups.

SECTION II

DESCRIPTION AND DISCUSSION OF THE EXPERIMENTAL :

PREPARATION OF PHENYLALKYLAMINES

During the present investigation it was considered desirable to prepare and asses biologically compounds of the type (1)



(1)

where NR_1R_2 = dimethylamino, morpholino, pyrrolidino, hydroxyethylmethylamino, hydroxyethylethylamino and hydroxyethyl-n-butylamino;

R_3 = methyl, phenyl, cyclohexyl, n-butyl, p-tolyl;

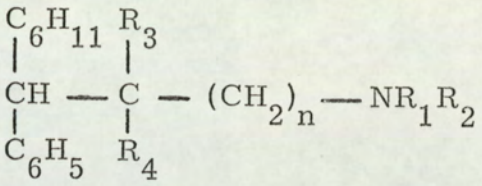
X = H, CN, OH, C_6H_5;

R_4 = R_5 = H, CH_3;

n = 0, 1, 2.

[A] Diphenyl- and cyclohexylphenylalkylamines

It was considered desirable to prepare compounds for comparison in which one phenyl ring was fully saturated to give cyclohexylphenyl derivatives (2).



(2)

where NR_1R_2 = dimethylamino morpholino, pyrrolidino;

$R_3 = R_4 = H, CH_3$;

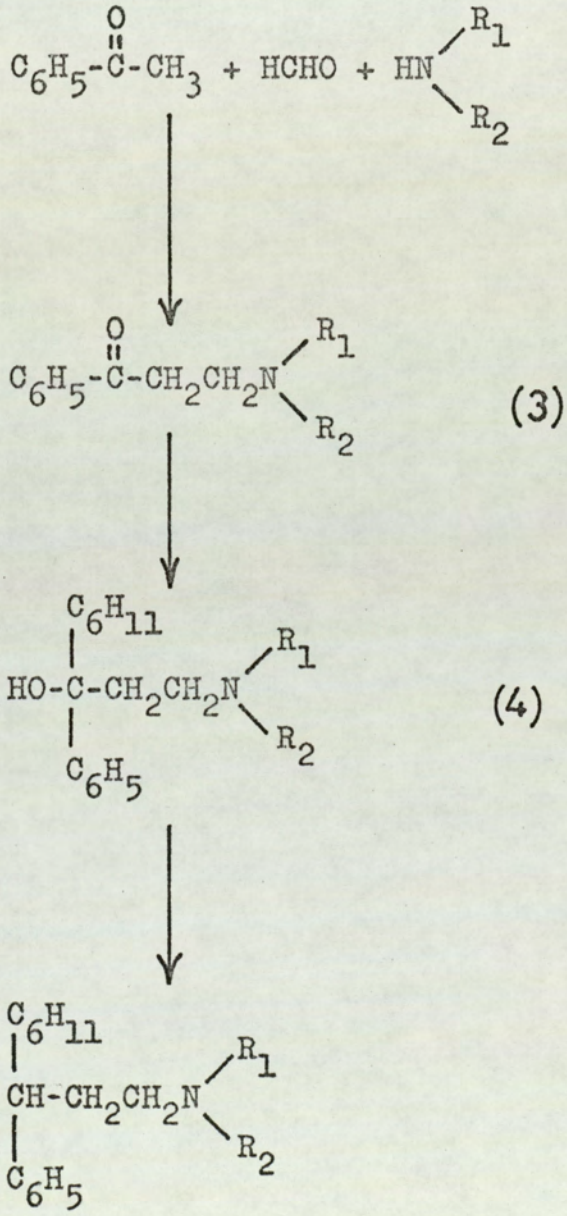
n = 0, 1, 2.

The possible routes for the synthesis of these compounds are summarised on Flow Sheets (I) and (II).

(i) From dialkylaminoalkanols (Flow sheet I)

In a search for anticonvulsant compounds Ruddy and Buckley (1950) prepared a series of 1-cyclohexyl-3-dialkylamino-1-phenyl-propan-1-ols (4) by treating the appropriate Mannich base (3) with cyclohexylmagnesium bromide. The hydroxyl group was then removed by heating with red phosphorus and hydrogen iodide in acetic acid. This route is limited by the Mannich reaction to the synthesis of 1-propanols and propanes and although low yields were reported in using cyclohexylmagnesium bromide, this method was modified for use in the present investigation to produce a novel series of aminopropanols which will be described later.

FLOW SHEET I


C6H5-C(=O)-CH3 + HCHO + HN(R1)(R2)
C6H5-C(=O)-CH2CH2N(R1)(R2)
(3)
HO-C(C6H11)(C6H5)-CH2CH2N(R1)(R2)
(4)
CH(C6H11)(C6H5)-CH2CH2N(R1)(R2)

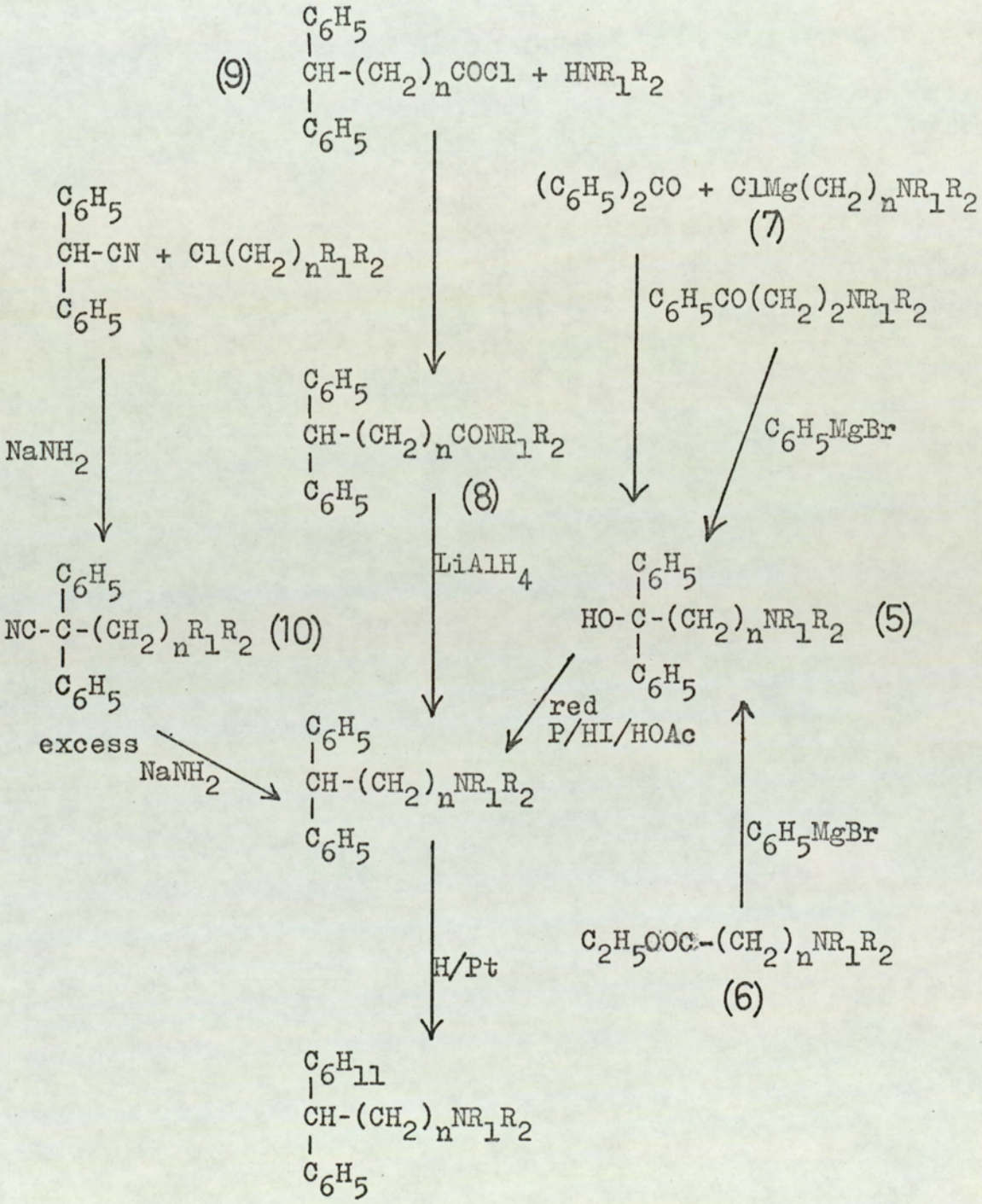
(ii) The synthesis of diphenylalkylamines

Diphenyl alkylamines may be synthesised by a variety of routes (Flow Sheet II). An obvious method is to dehydroxylate (by the method described above), the diphenylcarbinol (5) resulting from the treatment of a Mannich base with phenylmagnesium bromide. The limitation of the Mannich reaction can be overcome in this case either by adapting the method used by Adamson (1949) who prepared amino-carbinols by treating a substituted ethyl β-aminopropionate (6) with phenyl magnesium bromide, or by treating benzophenone with the Grignard reagent formed from an alkylaminoalkylchloride (7), (Seidlova, 1965).

An alternative route would be to reduce the amide (8) resulting from the treatment of a diphenylcarboxylic acid chloride (9) with an appropriate secondary amine. This route was in fact used by Ide et al.(1959) who prepared N-(2, 2-diphenylethyl)pyrrolidine from diphenylacetyl chloride. This method suffers from the disadvantage that it would involve the synthesis of individual diphenylcarboxylic acid chlorides.

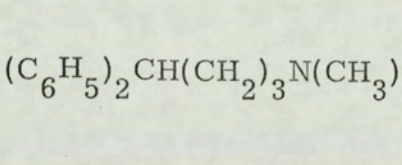
A further route utilised the reactive hydrogen atom of diphenylacetonitrile which is condensed with various alkylaminoalkyl halides. By this method Ruddy and Buckley, (1951) prepared various 3-phenylpropylamines as antispasmodics by reacting the

FLOW SHEET II

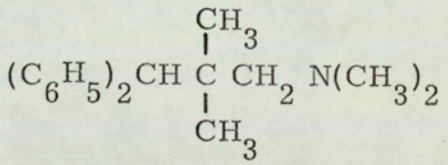


appropriate phenylacetonitrile with an aminoethyl chloride in the presence of sodamide. The basic nitriles (10) thus produced were treated with excess sodamide in order to replace the cyano group with hydrogen, (Office of the Publication Board, 1951).

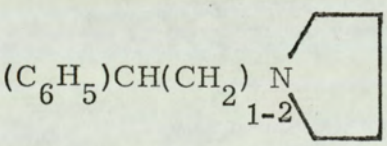
In the present investigation the diphenylaminoalkyl nitriles prepared by the latter route were made available, and treatment with an excess of freshly prepared sodamide in refluxing toluene gave the required diphenyl alkylamines (11) in good yield in all cases. Examples of compounds prepared in this way were:-



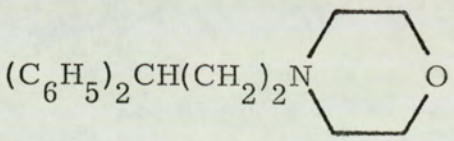
(11a)



(11d)



(11b)



(11c)

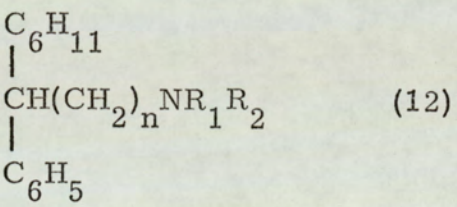
(iii) Partial hydrogenation of diphenyl compounds.

The reduction of aromatic systems by hydrogen in the presence of noble metal catalysts is well known and has been reviewed by Bond (1967) and Augustine (1965). In the task at hand care had to be taken to avoid the hydrogenolysis of the C - N bond, and for this reason the use of palladium was rejected, but ruthenium,

rhodium or platinum were considered suitable. Zenitz et al. (1947) used Adam's platinum catalyst in the hydrogenation of β-phenylalklamines to β-cyclohexylalkylamines,and in doing so, found that it was necessary to use the free base dissolved in acetic acid rather than the hydrochloride in aqueous solution. Their findings also verified that the alkylamine side chain was unaffected under these conditions. The method of Zenitz et al. was later modified for the synthesis of 3-amino-1-cyclohexyl-1-phenyl-propan-1-ols by Adamson (1951) who found it a more suitable route than that via the Grignard reaction. Adamson showed that diphenylcarbinols absorbed hydrogen continuously to give dicyclohexylcarbinols, there being no abrupt change in the rate of absorption at a point which would correspond to the saturation of only one of the phenyl groups. However, the reaction does proceed in a stepwise manner, for it was possible to stop the hydrogenation at a stage which allowed the isolation in good yield of the desired cyclohexylphenycarbinols. This was substantially in agreement with the findings of Smith et al. (1949), who made kinetic and analytical studies of the catalytic hydrogenation of compounds containing more than one phenyl nucleus. Adamson also found it

advisable to allow absorption of 10 - 15% in excess of the 3 moles of hydrogen theoretically required, otherwise unchanged diphenylcarbinol, difficult to remove by crystallisation was present in the product, whereas dicyclohexyl carbinols have a higher solubility in organic solvents.

In the present investigation the diphenylalkylamines were hydrogenated in acetic acid with Adam's catalyst and absorbed hydrogen at a steady rate at room temperature and atmospheric pressure. In this way the following [12] were prepared. An exception



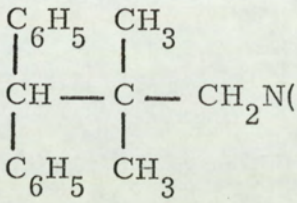
(12)

(a) n = 2, NR_1R_2 = morpholino

(b) n = 3, NR_1R_2 = dimethylamino

(c) n = 1, NR_1R_2 = pyrrolidino

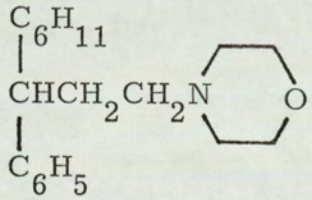
was compound (11d) which failed to absorb any hydrogen



(11d)

over several days at 90 lb./sq. ins. pressure when treated with Adam's catalyst. This result was predictable due to the fact that the presence of the methyl groups in the 2-position exert a steric effect in preventing the phenyl rings from approaching close enough to the surface of the catalyst.

The products were recrystallised to constant melting points and it was possible to confirm the cyclohexyl structure by n. m. r., noting especially the ratio of the number of phenyl protons to the number of cyclohexyl protons. For example the following compound (11c) gave

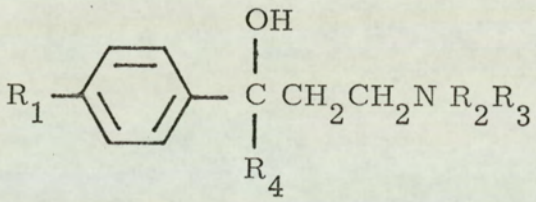


. HCl (11c)

the n. m. r. spectrum, τ (D_2O), 2.8 (s, 5H, C_6H_5); 6.1 (m, 4H, CH_2OCH_2); 6.8 - 7.5 (m, 6H, $CH_2N(CH_2)_2$); 7.6 - 7.9 (m, 3H, CH_2CH); 8.5 - 9.5 (m, 11H, C_6H_{11}).

[B] 1,1-Disubstituted alkylaminopropanols

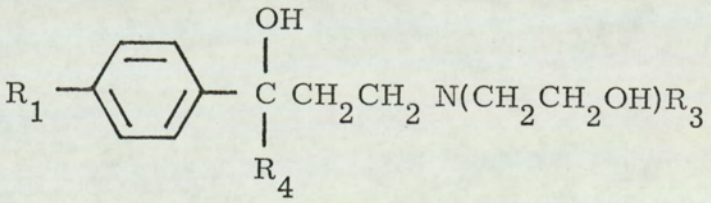
1,1-Disubstituted alkylaminopropanols (13) have for a number of years been of great interest to the medicinal chemist and



(13)

as a result have been investigated by various workers for use as antimalarials (Spaeth et al., 1946), antispasmodics (Denton 1950, Adamson, 1951) and their esters as anaesthetics (Nazarov and Cherkasova, 1955).

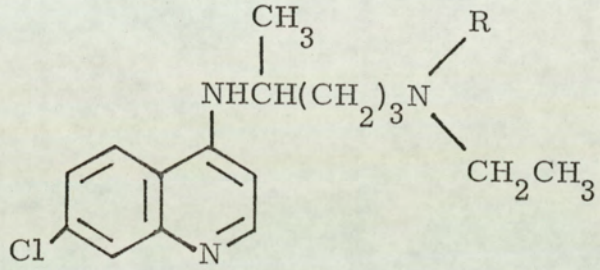
It was therefore surprising to find that, to date, no reports had been made of any hydroxyethylamino analogues (13a), for



(13a)

the substitution of this alcoholic group for an alkyl group might exert a profound effect on the biological activity. Such an example is to be found in the field of antimalarial drugs, for Surrey and Hamer (1950)

showed that the hydroxyethyl analogue of chloroquine not only exerted its action more quickly but was less toxic and still had

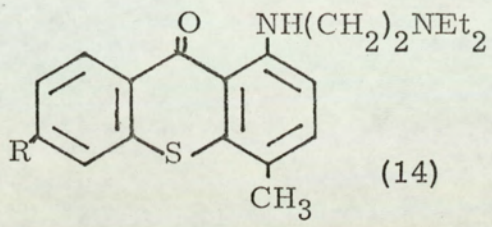


R = CH_2CH_3 (Chloroquine)

= CH_2CH_2OH ("Plaquenil")

seven times the activity of quinacrine against Plasmodium lophurae. After clinical evaluation the drug was marketed under the name "Plaquenil".

A further interesting example arises in the field of schistosomicidal agents. In 1961, in summarising the structure-activity relationships in several schistosomicidal compounds, Gönnert came to the conclusion that the biological activity of compounds such as Miracil D (14) depended on the species of the host:



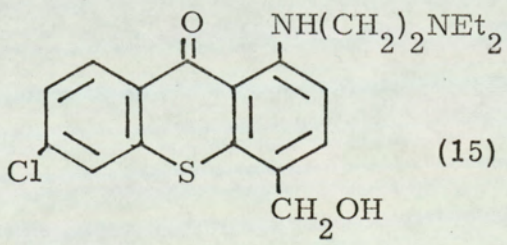
(14)

R = H, Miracil D ED_{50} (Mouse) = 46.0 mg./kg,

Mouse +, monkey +++, man +.

R = Cl , 6-Chloro-Miracil D ED_{50} (Mouse) = 13.3 mg./kg.

However, Archer (1967), examining the metabolism of Miracil D, found that hydroxylation of the methyl group to give Hycanthone (15)

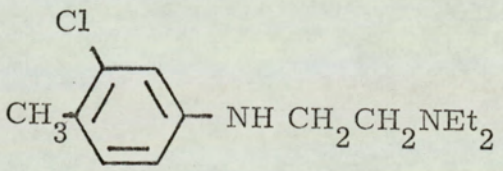


(15)

R = H Hycanthone ED_{50} (Hamster) = 0.93 mg./kg.

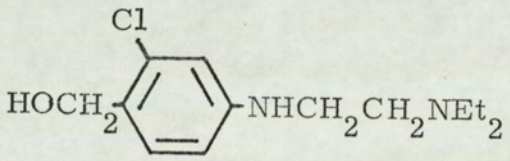
R = Cl:- 6-Chlorohycanthone ED_{50} (Hamster) = 6.0 mg/kg.

was the key metabolic step and that 6-Chloro-Miracil D which is inactive in monkeys was not hydroxylated in this species. He attributed the greater activity of the chloro compound in mice to a more efficient enzymatic hydroxylation rather than its intrinsic schistosomicidal activity. Archer went on to show that the enhanced activity of the hydroxy compounds applied not only to congeners of Miracil D and Hycanthone but to a series of compounds related to Mirasan (16) and its hydroxylated metabolite (17).



(16)

Mirasan ED_{50} 45 mg./kg. (Hamster)



(17)

ED_{50} 9.0 mg./kg. (Hamster)

These findings lead one to suggest that hydroxylation may be one of the metabolic pathways for some dialkylaminopropanols of structure (13), and it was therefore of interest to examine the biological activity of such compounds.

Most workers invariably prepared their alkylaminopropanols by treating β-aminoketones (18) with organometallic reagents, a fact which is not surprising since these intermediates were readily available by the Mannich reaction.

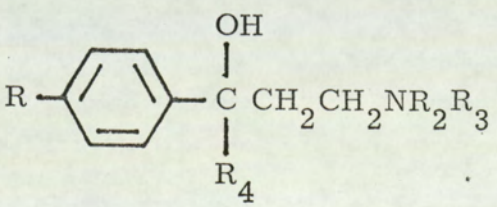
$$ArCOCH_3 + (CH_2O)_n + NHR_2R_3 \longrightarrow Ar\ COCH_2CH_2NR_2R_3$$

(18)

However, alternative routes were available for use where there are two identical aryl or alkyl groups in the 1-position, for example in the preparation of diphenyl compounds, which have been outlined already (Flow Sheet II).

(i) Preparation of the β-aminoketones

Where group R_4 is different to the aryl group (19), the route via the β-aminopropiophenone is the one of choice.



(19)

The Mannich reaction is ideal for this purpose, and is in fact often exemplified by the classical preparation of 3-dimethylaminopropiophenone (Mannich and Heilner, 1922). It is not of course the only route, for example Walker (1962) in a study of the vinylogous amides of 2-methylaminoethanol, prepared 3-[N-methyl-N-)2-hydroxyethyl)amino]-propiophenone (20) by reducing 1-[N-methyl-N-(2-hydroxyethyl)amino]-2-benzoylethylene with lithium aluminium hydride in 53% yield. However, of these,

$$C_6H_5COCH_2CHO + CH_3NHCH_2CH_2OH$$

$$\downarrow -H_2O$$

$$C_6H_5COCH{=}CHN(CH_3)CH_2CH_2OH$$

$$\downarrow [H]$$

$$C_6H_5COCH_2CH_2N(CH_3)CH_2CH_2OH \qquad (20)$$

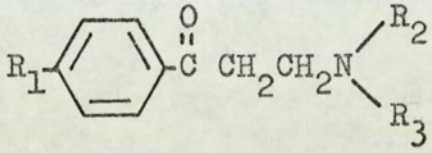
the Mannich reaction is obviously the more facile and economical to use.

(ii) Preparation of β-hydroxyethylaminoketones

No difficulties were encountered in the use of N-alkylethanolamines in the Mannich reaction except in the case of

TABLE I

Mannich Bases



No.	R_1	R_2	R_3	% yield	m.p. HCl salt
21	H	CH_3	CH_3	70	153-154°
22	H	CH_2CH_2OH	CH_3	35	150-152°
23	H	CH_2CH_2OH	CH_2CH_3	55	101-102°
24	H	CH_2CH_2OH	$(CH_2)_3CH_3$	30	92-93°
25	CH_3	CH_2CH_2OH	CH_3	30	90-91°
26	OH	CH_2CH_2OH	CH_3	80	125-126°
27	H	CH_2CH_2OH	CH_2CH_2OH	55	97-98°

compounds (24 and (25), Table 1, where the deliquescent nature of the Mannich base hydrochlorides made crystallisation difficult. This problem was overcome by the omission of aqueous hydrochloric acid from the reaction mixture and by careful recrystallisation from dry solvents. Following the modified procedures of Blicke and Johnson (1956) and Maxwell (1965), a solution of the appropriate ethanolamine in ethanol was acidified with a slight excess of hydrogen chloride (considerable cooling was necessary). An equimolar proportion of the appropriate acetophenone and paraformaldehyde (40 g. per mole) was added and refluxed, usually for 18 hours. In some cases the product was isolated simply by removing the ethanol under reduced pressure, triturating with ether (to remove unreacted acetophenone) and crystallising from acetone to give yields of 55 - 80%. Where this procedure proved unsuccessful, it was necessary to dissolve the residue in water, liberate the free base, and extract exhaustively with ether. The dried extracts were then evaporated and treated with hydrogen chloride to give the pure hydrochlorides which could then be recrystallised from acetone/ether or ethanol/ether mixtures. This process reduced the total yields to 30 - 50%. Vacuum distillation of the free bases was not attempted due to the possibility of cleavage or

dehydration, for example:

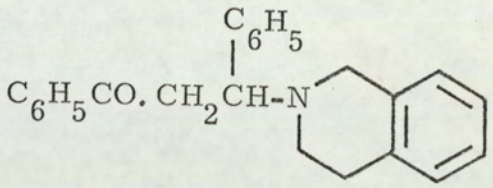
$$C_6H_5COCH_2CH_2NMe_2 \longrightarrow C_6H_5COCH{=}CH_2 + NHMe_2$$

(iii) Reaction of β-aminoketones with organometallic reagents

The reaction of β-aminoketones with Grignard reagents was first reported by Kohn (1907) and Mannich and Hof (1927). Further work by Spaeth et al.(1946) found that pure aminoalcohols could be isolated in only 15 - 33% yields from the reaction of 1-dialkylamino-3-butanones with aryl Grignard reagents. The products were difficult to purify and often formed oily salts even when pure. Spaeth attributed the poor yields to a side reaction which gave the dialkylamine and the product of simple hydrolysis of the Grignard reagent:

$$CH_3CO.CH_2CH_2NR_2 + \text{Aryl Mg X} \longrightarrow CH_3COCH{:}CH_2 + \text{Aryl.H} + R_2NM_g\,X$$

However, he found no unsaturated substances in the product and presumed that the methyl vinyl ketone produced had reacted with the Grignard reagent or had polymerised. Cromwell and Burch (1944) had also experienced slow and incomplete reaction of phenyl magnesium bromide with compound (28) and attributed this to the



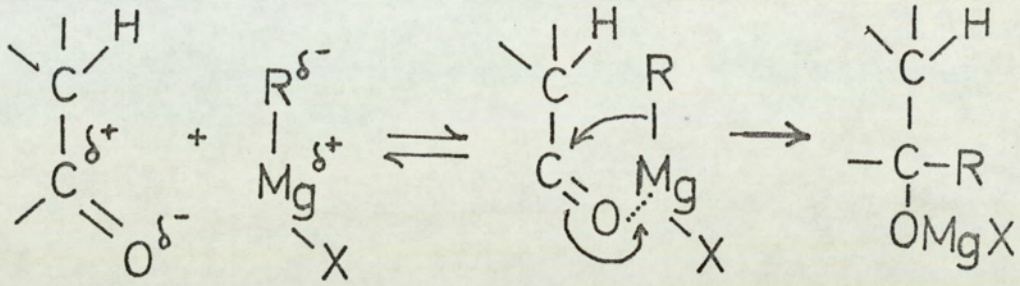
(28)

hindering and electron attracting effect of the phenyl group, along with a similar effect of the tetrahydroisoquinolo group in the β-position. Methylmagnesium iodide however, added readily to the same ketone. Similar reasoning may be applied to the aminopropiophenones in the present study.

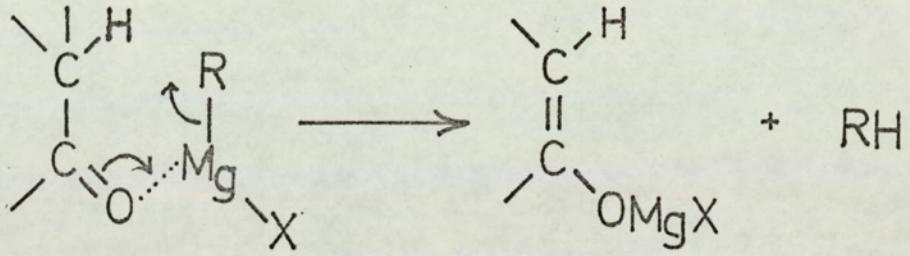
The poor yields obtained by Denton and Ruddy (1949) for 1-cyclohexyl-1-phenyl-propanols prompted Adamson (1951) to prepare these compounds by partial catalytic reduction of diphenylpropanols. However, in the present investigation satisfactory yields were obtained by following the method of Kharasch and Reinmuth (1954), the choice of halide, (cyclohexyl chloride as opposed to bromide), its concentration and rate of addition being important.

The mechanisms of the Grignard reaction are nowadays better understood (Hagira, 1968), and it is now known that where the ketone is sterically hindered or if the R group of RMg X is bulky, then enolisation or reduction are likely to occur as side reactions:

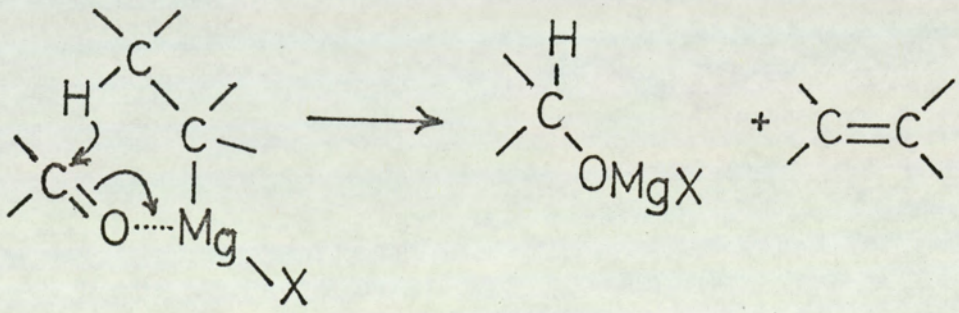
(normal addition:):



(enolisation):



If R in RMg X has at least one β-hydrogen, then reduction is a further possibility:



Some of these difficulties may be overcome in several ways. Nazarov and Cherkasova (1955) for example, found that

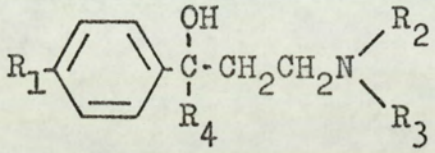
simply by adding the β-aminoketone as the hydrochloride salt rather than the free base improved yields to 80 - 90%. This may suggest that the protonated nitrogen prevents enolisation from occurring.

As the majority of the aminopropanols in the present investigation were unstable to vacuum distillation, it was essential that the products of the reaction were sufficiently pure to allow crystallisation. In one case (36) Table II, separation of the product from impurities on an alumina column was necessary. It was found that normal reaction times and temperatures often resulted in a large proportion of the starting ketone in the product, whereas the displacement of the ether by a higher boiling solvent such as toluene or xylene gave aminopropanols which were often sufficiently pure to crystallise as their free bases. In all cases a large excess (about 3 - 5 molar) of the organometallic reagent was used, particularly when the Mannich base possessed a hydroxyl group or when it was used as the hydrochloride salt.

The Grignard reaction mixtures were treated with dilute hydrochloric acid with cooling, washing the aqueous layer well with ether to remove non-basic impurities. The free bases were then liberated from the aqueous layer by the addition of aqueous ammonia and extracting exhaustively with ether.

TABLE II

Alkylaminopropanols



Cpd. No.	R_1	R_4	R_2	R_3	Method ‡
29	H	CH_3	CH_3	CH_3	L
30	H	$(CH_2)_3CH_3$	CH_3	CH_3	G
31	H	C_6H_5	CH_3	CH_3	L
32	H	CH_3	CH_2CH_2OH	CH_3	L
33	H	$(CH_2)_3CH_3$	CH_2CH_2OH	CH_3	G
34	H	C_6H_5	CH_2CH_2OH	CH_3	L
35	H	C_6H_{11}	CH_2CH_2OH	CH_3	G
36	CH_3	C_6H_5	CH_2CH_2OH	CH_3	L
37	H	C_6H_5	CH_2CH_2OH	CH_2CH_3	L
38	H	C_6H_5	CH_2CH_2OH	$(CH_2)_3CH_3$	L

‡ L = alkyl or aryl-lithium reaction; G = Grignard reaction.

It was found that in the majority of the reactions attempted, the use of aryl or alkyl-lithium reagents gave purer products with shorter reaction times and lower temperatures that the corresponding Grignard reagents. This was to be expected because of the smaller molecular size and greater reactivity, making them the reagents of choice. Lithium aryls and alkyls are also usually more stable in ethereal solutions, one notable exception being cyclohexyl-lithium. Gilman et al (1933) found that a reaction took place between cyclohexyl bromide and lithium in ether, but no appreciable quantity of organo-lithium was formed, and at best they only obtained a 24% yield when using cyclohexyl chloride. This may now be explained by the findings of Spietter and Harris (1966) who reported that cyclohexyllithium at room temperature for 24 hours cleaved ethyl ether to from cyclohexylethyllithium (39)

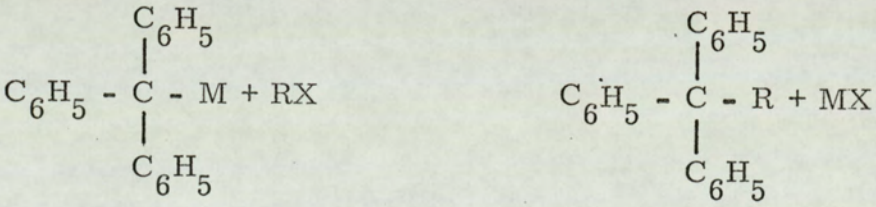
$$C_6H_{11}Li \xrightarrow[25°,\ 24hr.]{(Et)_2O} C_6H_{11}CH_2CH_2Li \qquad (39)$$

The only way to avoid this was to maintain the ethereal solution at or below - 10°. Obviously the rate of reaction with aminopropiophenones at this temperature would be far too slow, and in this case the use of the Grignard reagent was necessary.

The lithium reagents were hydrolysed and isolated in a similar manner to the Grignard reagents. The free bases of the aminopropanols, when obtainable, were low melting point solids easily recrystallised from petroleum ether. Their hydrochlorides on the other hand were often hygroscopic and required slow recrystallisation giving low yields from ethanol/ether or acetone/ether mixtures.

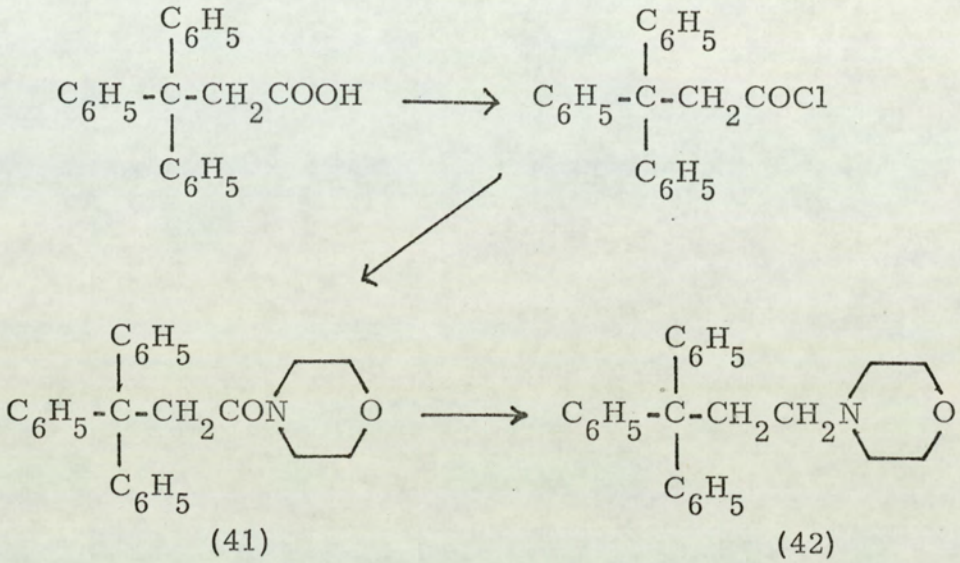
[C] PREPARATION OF A TRIPHENYLALKYLAMINE

Having prepared several diphenylalkylamines for use in anti-viral studies, it was desired to prepare at least one triphenylalkylamine to observe the effect of introducing a third aromatic substituent. Martensson and Nilsson (1965) used two routes to prepare several 3, 3, 3-triphenylalkylamines (40) and their quaternary salts for use as potential cholinergics and spasmolytics. Most of these compounds with an unbranched alkyl chain were synthesised by a fairly simple direct alkylation of tertiary aminoalkyl halogenides with the alkali metal compound of triphenylmethane. Another suitable route is via the



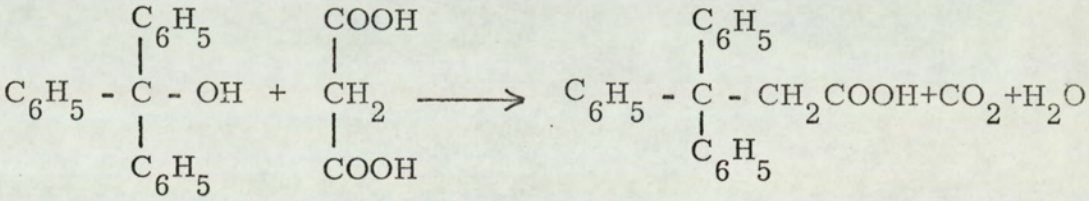
(40)

corresponding N, N-disubstituted carbonamide (41), followed by reduction with lithium aluminium hydride. The latter method



(41) (42)

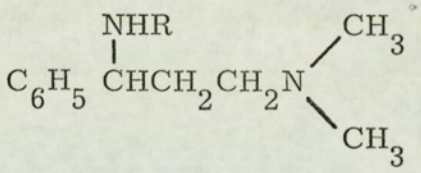
was chosen in order to study the biological activity of the intermediate amide. It is well known that 3, 3, 3-triphenyl-propionic acid can be easily made by merely heating a mixture of malonic acid and triphenylcarbinol, Fosse (1907, 1931), Hellerman (1927). Treatment of the acid made in this manner with thionyl



chloride gave the acid chloride in good yield, and was converted to the amide by treatment with morpholine. Reduction with lithium aluminium hydride using tetrahydrofuran as the solvent gave the amine (42) in good yield.

[D] PREPARATION OF 3-DIMETHYLAMINO-1-PHENYL-PROPANEDIAMINES

One of the aims of the present investigation was to prepare compounds of type (43)

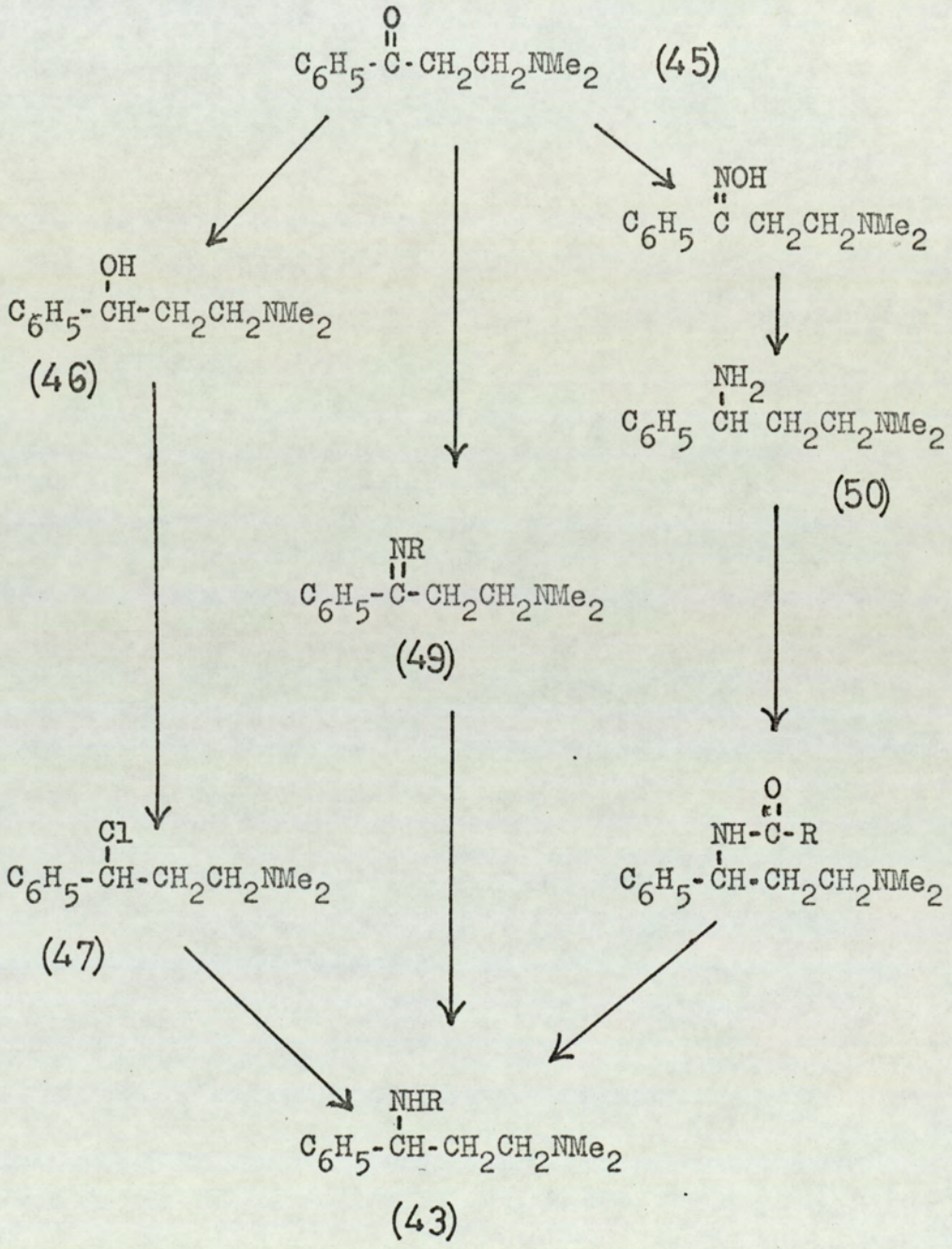


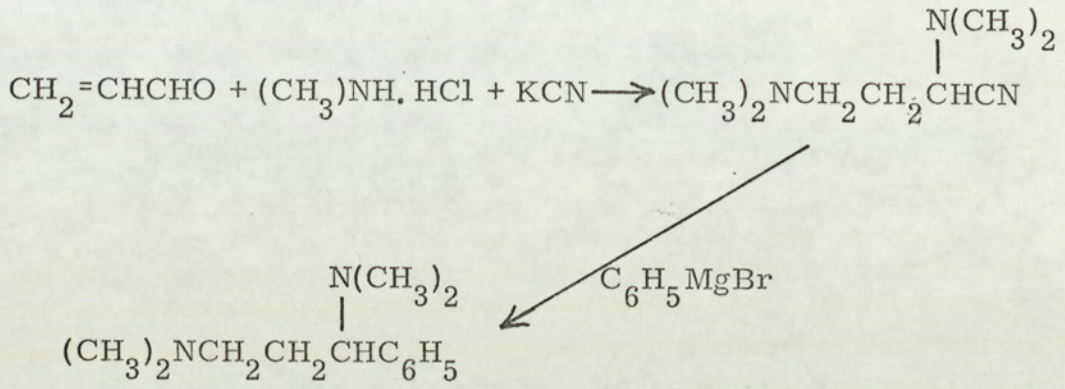
(43)

where R may be a variety of alkyl, aryl or acyl groups.

The most straightforward methods available for the synthesis of these compounds is shown on Flow Sheet III, and can be seen to involve the amination of 3-dimethylaminopropiophenone, which is a readily synthesised Mannich base. However, a different approach can be used in one or two specific cases, for example where all the amino substituents are identical, as in the synthesis of 1,3-di-(dimethylamino)-1-phenylpropane (44) by Bruylants (1925) which relied on the influence of the α-dimethylamino group in bringing about the exchange of CN for RMgX.

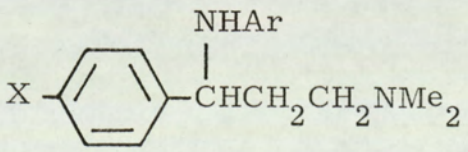
FLOW SHEET III





(44)

Introduction of the second amino group could be approached in several ways, (Flow Sheet III). One rather tedious method involves a Meerwein-Pondoorf-Verley reduction of the amino-ketone (45) (Nobles and Burckhalter, 1958), and conversion of the resulting secondary alcohol (46) to the alkyl chloride (47) with thionyl chloride. The chloro-amine thus produced can then be condensed with the appropriate amine. This method was in fact used by Nazar Singh and Sukhdev Singh (1967) to prepare simple aryl derivatives of the type (48) which would



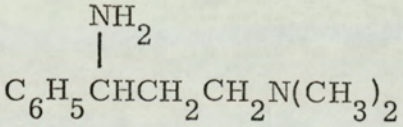
(48)

of course have been difficult to prepare from the less reactive aryl halides.

The possibility of direct amination of the carbonyl group either in one stage - reductive amination - or by isolating the Schiff's base (49) followed by its reduction presented an attractive route in theory but, as will be discussed later, proved somewhat difficult in practice unless the amino addendum was small, for example, ammonia or ethylamine.

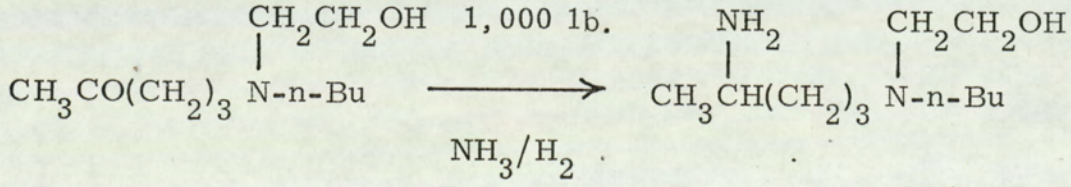
(a) Preparation of 3-dimethylamino-1-phenyl-propylamine.

The most suitable route, and the one used in the present investigation, involved the isolation of the diamine (50), and the



(50)

chemical modification of its primary amino group. The synthesis of this compound could conceivably have been achieved by reductive amination of the Mannich base, and such a method has been reported for N'-n-butyl-N'-(2-hydroxyethyl)-1,4-pentanediamine (51) by Surrey (1950), but in the present situation, the high pressure



(51)

required negated its use.

However, as the oxime of 3-dimethylaminopropiophenone can be readily synthesised (Mannich and Heilner, 1922), its reduction to give the diamine provided the most convenient route. By this method, an aqueous solution of 3-dimethylaminopropiophenone hydrochloride and an excess of hydroxylamine hydrochloride was made alkaline with aqueous sodium carbonate solution. Warming on a steam-bath gave the oxime-base in almost quantitative yield.

The reduction of 3-dimethylaminopropiophenone oxime has been reported by Terent 'ev and Gusar (1965) in a study of the reduction of various oximes with sodium in liquid ammonia, which they claim is a superior method to reduction with sodium in alcohol. They submit that the lower reaction temperature prevented the formation of resinification products, and enabled the use of a precise quantity of the reducing agent. The oxime has also been reduced by catalytic hydrogenation at high pressure in liquid ammonia using Raney nickel as catalyst (Lilly, 1955).

In the present investigation good yields of diamine were obtained by reduction with lithium aluminium hydride and with sodium in alcohol. The latter method (Lycan et al., (1943) was

found suitable provided certain precautions were taken. A solution of carefully dried oxime base in anhydrous ethanol (Vogel p. 167) was brought to its boiling point, and sodium metal was added as rapidly as possible without loss of ethanol. As soon as the metal had dissolved, water was added and the alcohol removed, thus minimising resinification.

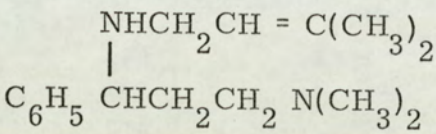
(b) Reactionsof 3-dimethylamino-1-phenylpropylamine.

(i) Alkylation.

Alkylation of the primary amino group proved difficult, a fact which was undoubtedly due to the presence of the phenyl group in the 1-position, which might be expected to cause steric hindrance, and also reduce the nucleophilicity of the amino group. Formation of complex mixtures of secondary, tertiary and quaternary amines is also a possibility.

Consequently the most successful reactions occured with small, reactive alkylating reagents. However, in the present investigation it was required to introduce several bulky alkyl groups, whose corresponding alkyl chlorides were not very reactive. This necessitated more vigorous reaction conditions, which in turn meant more side reactions, and the associated difficulties of purifying and isolating the product, the amines usually decomposing on distillation.

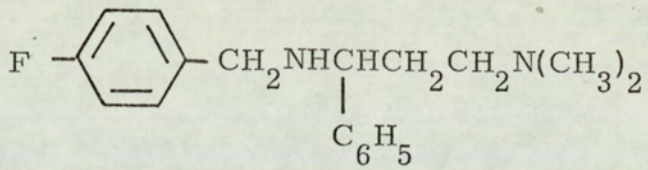
Such an example was the attempted preparation of 1-dimethylalkylamino-3-dimethylamino-1-phenylpropane (52).



(52)

A preliminary attempt was made by heating a mixture of the diamine, 1-chloro-3-methyl-2-butene and sodium carbonate in benzene for 24 hours. Isolation of the basic products of the reaction mixture gave an oil whose infra-red spectrum showed no C = C absorption. Preparation of the hydrochloride salt confirmed that the product was starting material. The reaction was repeated using dimethylformamide as solvent (Archer 1964) and again heating under reflux for 24 hours. Infra-red spectroscopy of the basic constituents of the reaction mixture showed the presence of secondary amine NH at 3200 and trisubstituted C = C at 1665 $cm.^{-1}$ In addition the n. m. r. spectrum indicated the presence of the ethylenic proton (4. 9 τ, 1H) and integrated correctly for structure (52). However, attempts at isolating a crystalline derivative such as the hydrochloride, methiodide or picrate failed, despite further purification by column chromatography.

Similar results were obtained when 3-dimethylamino-1-phenyl-propylamine, p-fluorobenzyl chloride and sodium carbonate were heated under reflux in dimethylformamide for 24 hours in an attempt to prepare compound (53).

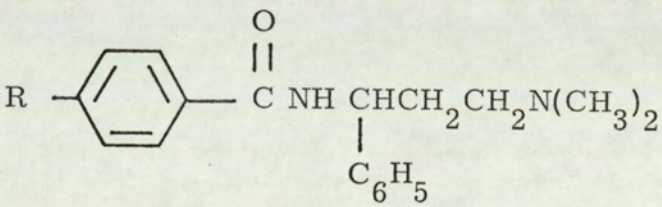


(53)

This compound was however, later prepared successfully by the reduction of the amide resulting from the treatment of the diamine with p-fluorobenzoylchloride.

(ii) Acylation.

The acylation of 3-dimethylamino-1-phenylpropylamine reported in the literature is confined to one series of benzamidopropylamines (Lilly, 1955), (54).



(54)

In the present investigation several novel amidopropylamines were synthesised which proved to be useful intermediates for further chemical modification, notably their reduction to alkylaminopropylamines.

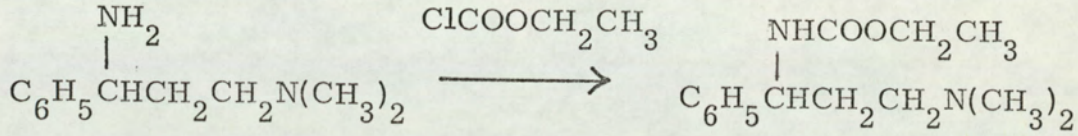
Due to their higher reactivity, acyl chlorides reacted with greater ease than their corresponding alkyl chlorides giving reaction products often of sufficient purity to be crystallised as their free bases. The general procedure adopted was to add dropwise a solution of the acyl chloride in dry benzene or 1, 2-dimethoxyethane to a vigorously stirred equimolar solution of 3-dimethylamino-1-phenylpropylamine in the same solvent in the presence of an excess of sodium hydrogen carbonate.

Two of the amido-amines thus produced were reduced efficiently by lithium aluminium hydride (Nystram and Brown, 1948) using anhydrous diethyl ether as the solvent:

$$C_6H_5\underset{\displaystyle NHCOR}{\underset{|}{C}}HCH_2CH_2N(CH_3)_2 \xrightarrow{[H]} C_6H_5\underset{\displaystyle NHCH_2R}{\underset{|}{C}}HCH_2CH_2N(CH_3)_2$$

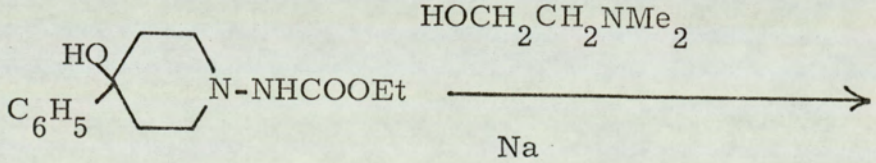
where R = benzyl (55), and p-fluorobenzyl (53).

Using a similar procedure to the acylations described above, treatment of 3-dimethylamino-1-phenylpropylamine with ethyl chloroformate gave the urethan (56).

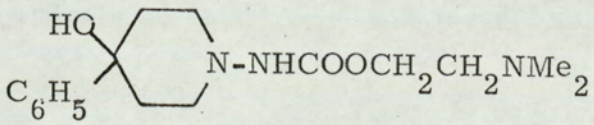


(56)

The introduction of the ester group allowed further modification to be considered, for it is well known that esters may undergo alcoholysis to give esters of higher boiling alcohols (Rehberg et al., 1955). Such a reaction was utilised by Harper et al. (1967) in the transesterification of the urethan (57) using 2-dimethylaminoethanol in the presence of the sodium alkoxide.

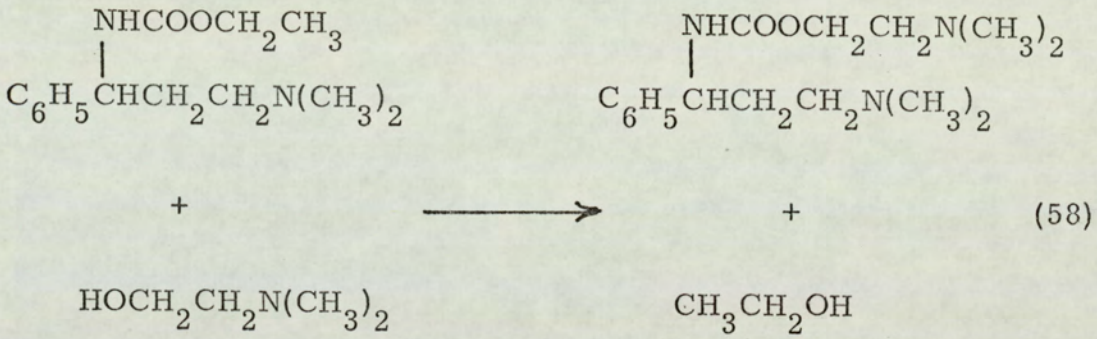


(57)



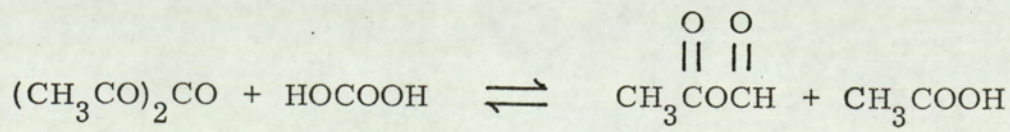
+EtOH

By this method, 3-dimethylamino-1-phenylpropylamine and a solution of sodium in excess dimethylaminoethanol were heated at 100° for 18 hours. Excess amino-alcohol was removed by distillation and aqueous extraction to give the dimethylaminoethyl ester (58).

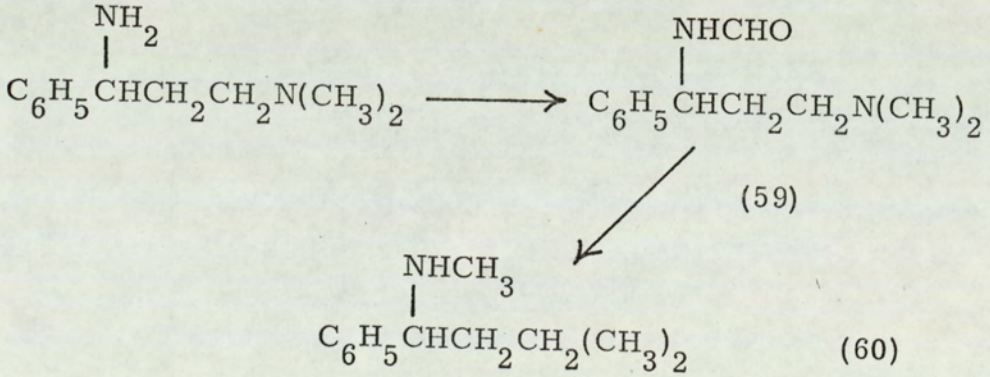


(58)

Formylation of amines to give formamides is a special case of acylation, for although formyl chloride and formic anhydride are both unstable, Huffmann (1958) showed that formylation could be accomplished by using a mixture of formic acid and acetic anhydride. It is presumed that a mixed anhydride of acetic and formic acids is the reactant and that it reacts as rapidly as it is formed.



In the present investigation 3-dimethylaminoethanol was added to a mixture of formic acid and acetic anhydride and maintained at 50° for 18 hours. The formamido-amine (59) was isolated from the reaction mixture as the free base and purified by distillation under reduced pressure. The infra-red spectrum showed the presence of amide NH at 2250 and amide carbonyl at 1630 $cm.^{-1}$ No crystalline sample could be prepared and treatment with hydrogen chloride resulted in decomposition. However, the product was reduced with lithium aluminium hydride in the usual manner to give 3-dimethylamino-1-methylamino-1-phenyl-propane (60).



(iii) Preparation of substituted ureas

Isocyanates may be regarded as acylating agents, for although not of the type R-CO-X, they react with primary and secondary amines to form products which may be looked upon as carbamoyl amides and are, of course, ureas. The reaction involves addition of the amine across the C = N bond (61). The

$$R\text{-}N{=}C{=}O + R^1NH_2 \longrightarrow R\text{-}NH\text{-}CO\text{-}NR^1 \qquad (61)$$

preparation of substituted ureas from amines and methyl and ethyl isocyanate was described by Papesche and Schroeder, (1951). This method was applied to the present investigation to prepare a novel series of ureas (62).

$$C_6H_5\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_2N(CH_3)_2 + RNCO \longrightarrow C_6H_5\underset{\displaystyle NHCONHR}{\underset{|}{C}}HCH_2CH_2N(CH_3)_2$$

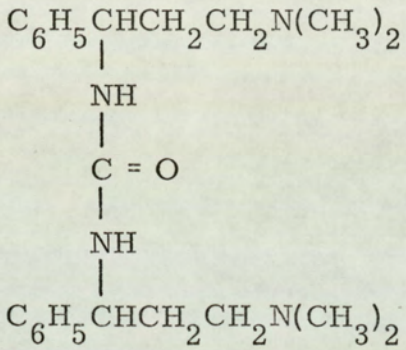
(62)

where R = CH_3; C_6H_5; C_6H_{11}. (62 a, b, c, respectively).

Taking care to exclude moisture from the reaction (isocyanates react readily with water to form symmetrically substituted ureas), a cooled solution of the isocyanate in dry benzene was added dropwise to a stirred ice-cold equimolar solution of 1-dimethylamino-1-phenyl-propylamine in dry benzene. On evaporation of the solvent, the

almost pure urea crystallised in nearly quantitative yield.

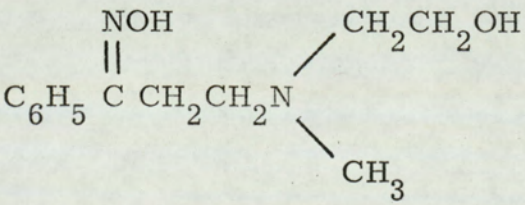
The preparation of the symmetrically disubstituted urea (63) was achieved by treating 3-dimethylamino-1-phenylpropylamine



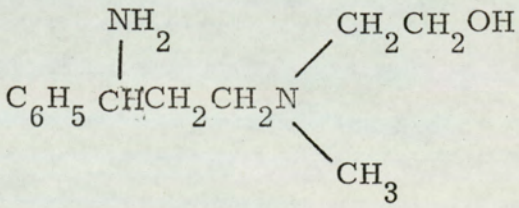
(63)

with a slight excess of phosgene in the presence of an equimolar solution of aqueous sodium hydroxide.

(c) Attempts to prepare the hydroxyethylamino analogue (65) from the corresponding oxime (64) resulted in an oil. No solid



(64)

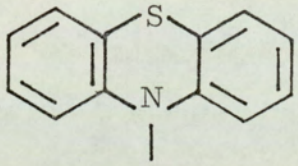


(65)

derivative could be prepared and the compound was not characterised.

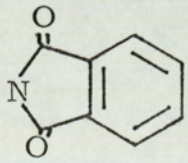
[E] PREPARATION OF PHENOTHIAZINE DERIVATIVES

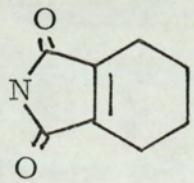
In view of the high order of antiviral activity exhibited by several 10-substituted phenothiazines, it was considered to be of interest to prepare compounds of type (66)

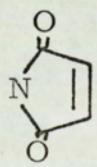


$(CH_2)_{2-3}NR'R''$ (66)

where NR'R'' is

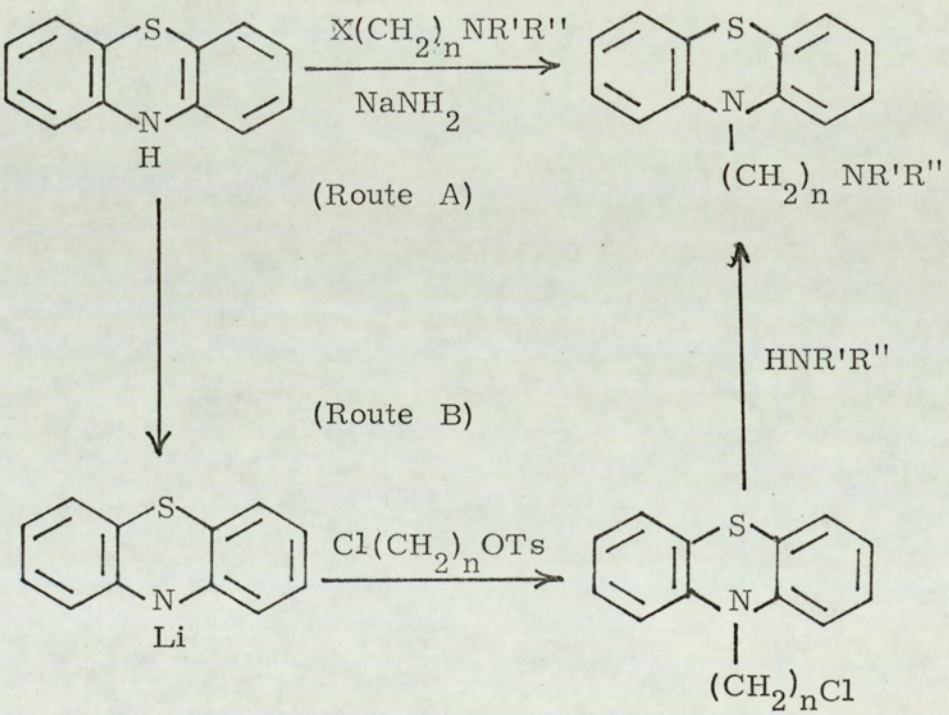






It has been shown by Schaffer et al. (1937) that the introduction of substituents in the 10-position reduces the toxicity of the phenothiazine system, a fact which led to the synthesis of a great

number of phenothiazine derivatives of biological importance. Methods available for the alkylation of the amino group have been well reviewed, Massie (1954), and is usually achieved by condensation with an alkyl halide in the presence of a basic condensing agent, sodamide being the one of choice. (Route A).



Alternatively, 10-lithiophenothiazine, prepared from butyllithium and phenothiazine can be reacted with various chloroalkyl-p-toluene sulphonates to give the corresponding

chloroalkyl phenothiazines which are useful intermediates for treatment with secondary amines, or, as in this case, with potassium phthalimide and its analogues, (Route B). This method was in fact used by Gilman and Shirley (1944) who, in search for antimalarials, prepared 10-(2-chloroethyl)- and 10-(3-chloropropyl)-phenothiazine.

A further route, the condensation of a dihalogen substituted hydrocarbon such as 1-chloro-3-bromopropane with phenothiazine itself, has been shown to be unsatisfactory (Yale and Sowinski, 1960).

Since route A necessitates the synthesis of individual chloroalkylphthalimides, which would also preclude the use of sodamide, route B is the most satisfactory.

Following the method of Gilman and Shirley (1944), ethereal solution of 3-chloroethyl-p-toluene sulphonate was added dropwise during one hour to an ice cold solution of phenothiazine lithium. After acidification of the reaction mixture, the organic layer was separated and from this 10-(2-chloroethyl)-phenothiazine was obtained.

A mixture of the latter with potassium phthalimide after refluxing in dimethylformamide for 18 hours gave 10-(2-phthalimido-ethyl)-phenothiazine.

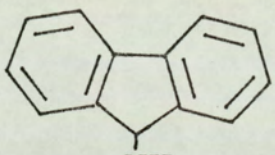
Treatment of 10-(2-chloroethyl)phenothiazine under similar conditions with potassium maleimide gave a dark brown intractable tar which could not be crystallised. The tar was purified by eluting from an alumina column with petroleum ether (b.p. 60 - 80°) and acetone mixtures. One of the fractions thus obtained gave the expected infra-red spectrum and deposited as an amorphous grey solid from ether, but on exposure to the air it reverted to a brown tar which could not be characterised.

A similar attempt using 3, 4, 5, 6-tetrahydrophthalimide also failed to produce a solid product.

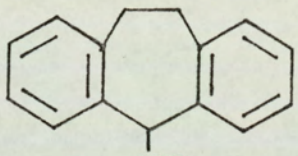
SOME THEORETICAL CONSIDERATIONS

[A] A STUDY OF REDUCTIVE AMINATION

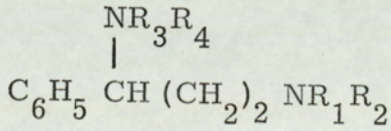
During the present investigation the possibility of synthesising such compounds as (67) and (68) by reductive amination was considered.



(67)



(68)

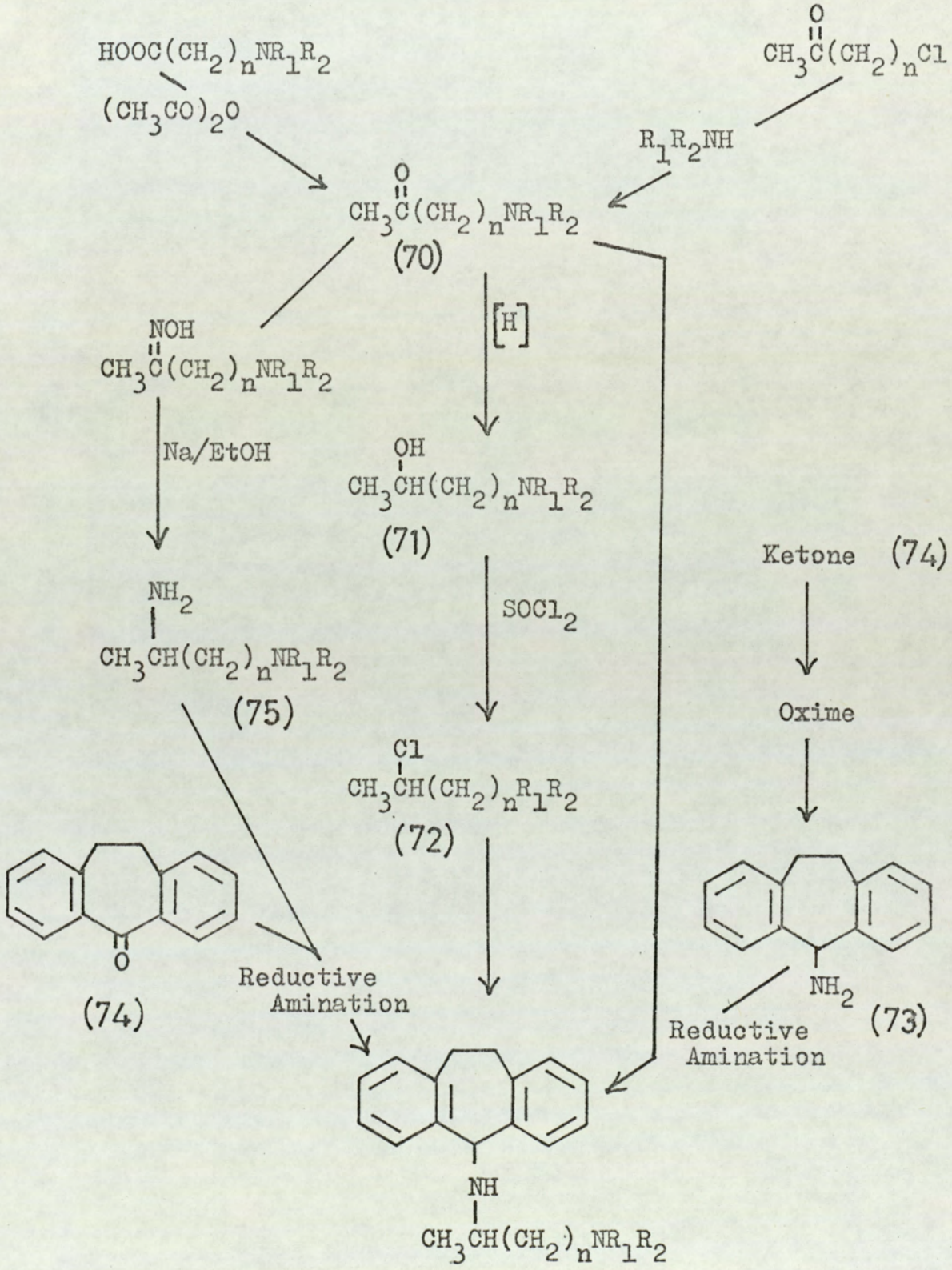


(69)

(The synthesis of compounds of type (69) by other routes has already been discussed).

The possibility of direct amination in one step presented an attractive alternative to the four stage synthesis shown on Flow Sheet IV, which would have involved the synthesis of the keto-amine (70) its reduction to the secondary alcohol (71), and

FLOW SHEET IV



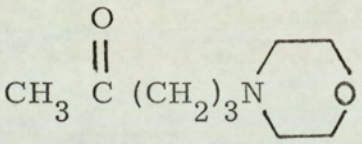
treatment with thionyl chloride to give the alkyl chloride (72), which would then have been used to alkylate a cyclic amine such as (73). In addition the cyclic amine would have had to have been synthesised from the more readily available ketones (74) by reduction of their oximes.

It can be seen that the alternative route of reductive amination could be approached in two ways, either by the amination of a cyclic ketone (74) with an aliphatic diamine (75), or conversely amination of a keto-amine (70) with a cyclic amine (73). However, it was considered that the latter method would be more suitable not only because the aliphatic ketone is hindered to a lesser extent, but also because the synthesis and isolation of the cyclic amines (73) were more convenient that that of the diamines (75).

A great variety of purely aliphatic secondary amines have been reported which have been prepared by the reductive alkylation of primary amines with ketones (Emerson, 1948). Most of the reductions have been effected with the aid of platinum catalyst although nickel and palladium have been employed. The yields obtained from simple primary amines and simple ketones are usually good (50 - 100%), but are greatly affected by steric factors, e.g. in the alkylation of cyclohexylamine with acetone, methyl ethyl ketone, diethyl ketone and cyclohexanone carried out under

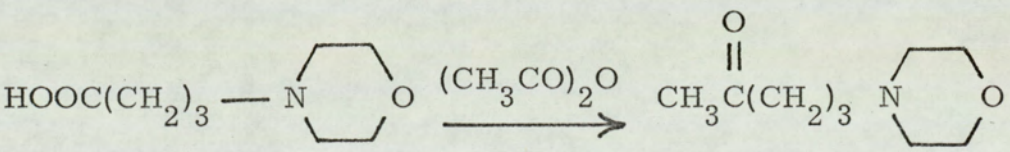
comparable conditions with hydrogen and platinum catalyst, the yields were 79%, 60%, 31% and 63% respectively (Woodruff et al., (1940).

Synthesis of the keto-amine side-chain used in the present investigation, 5-morpholinopentan-2-one (76) has



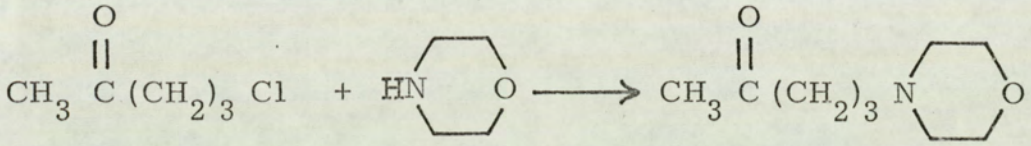
(76)

been reported by Cruickshank and Sheehan (1961) who treated 4-(4-morpholino)butyric acid (77) with acetic anhydride.



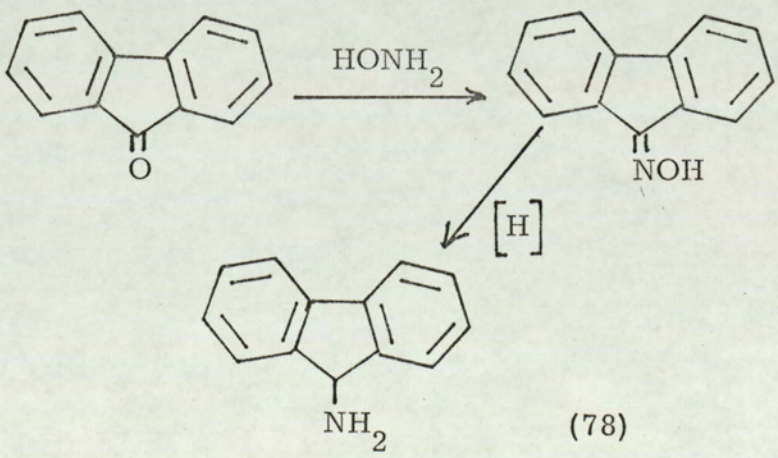
(77) (76)

However, in the present investigation it was found convenient to prepare the compound by treating morpholine with 5-chloropentan-2-one (78).



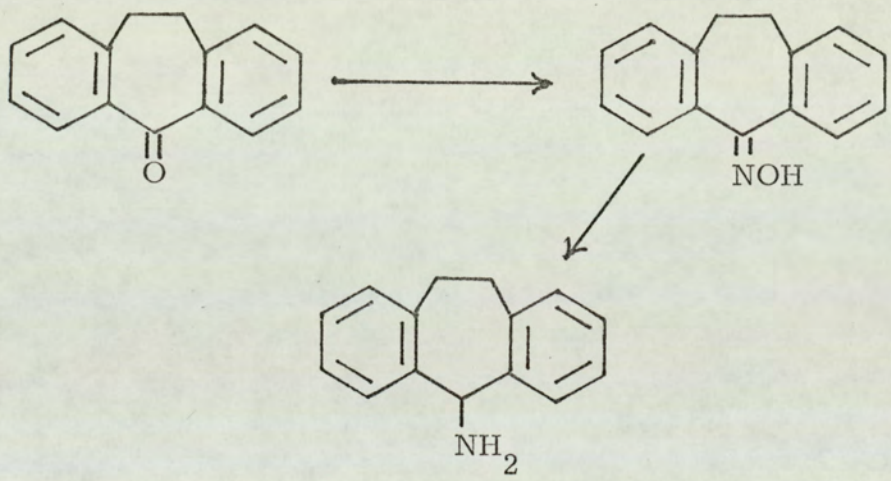
(78) (76)

The oxime of 9-fluorenone was prepared in the usual manner (Schmidt and Soll, 1907) and reduced by zinc and acetic acid (Ingold and Wilson, 1933) to give 9-aminofluorene (78).



(78)

Similarly, 10,11-dihydrodibenzo[a, d]cyclohepten-5-one (79) and hydroxylamine hydrochloride in pyridine were heated under reflux to give the corresponding oxime (Monro et al., 1963) which was reduced by sodium in ethanol to give 5-amino-10,11-dihydro-5H-dibenzo[a, d]cycloheptene.

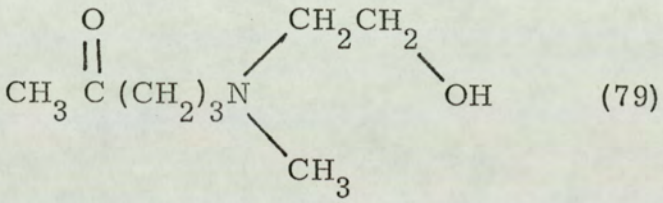


The attempted reductive amination was carried out by subjecting an equimolar mixture of 9-aminofluorene hydrochloride and 4-(4-morpholino)pentan-2-one hydrochloride in acidified ethanol to the highest pressure of hydrogen available (6 atmospheres) at an elevated temperature (80°) in the presence of Adams catalyst. Absorption of hydrogen ceased after 6 hours, and examination of the reaction products showed unchanged starting material. The observed fall in hydrogen pressure can be attributed to the reduction

of the amino-ketone to the corresponding amino-alcohol, saturation of the aromatic nuclei, or to hydrogenolysis.

A similar experiment using the same ketone and 5-amino-10, 11-dihydro-5H-dibenzo [a, d] cycloheptene under similar conditions also gave unchanged starting material.

The failure of these two experiments was undoubtedly due to the size and complexity of the reactants, and was not surprising since a comparable ketone (79) required a pressure of 1,000 lb.

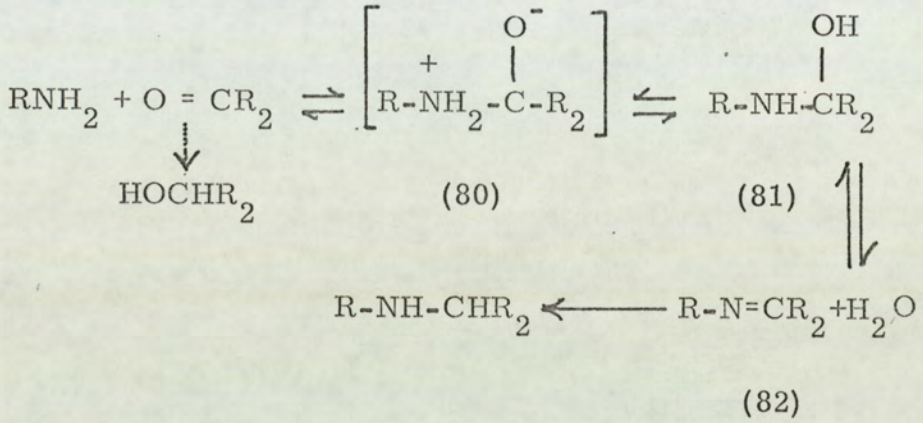


(79)

(more than ten-fold that used in the present investigation) for reductive amination with ammonia.

Consideration of the mechanism of reductive amination will reveal modifications applicable to the procedure described above.

The initial product of bond formation between carbon and nitrogen is a zwitterion (80) which rapidly undergoes proton transfer to give carbinolamine (81). However, carbinolamines derived from primary amines dehydrate readily to form ketimines or "Schiff's bases" (82). Under the conditions used in reductive amination,



(80) (81) (82)

the ketimine thus formed is reduced to a secondary amine, and eventhough the equilibrium may not favour the formation of the ketimine, its continuous removal by reduction enables the reaction to proceed. However, it is presumed that in the reactions attempted in the present investigation, the equilibrium is so little in favour of ketimine formation that reduction of the ketone occurs preferentially.

Therefore, one improvement would be to synthesise the ketimine under more favourable conditions, then either isolate it, or reduce it in situ to the secondary amine. The formation of amines is subject to general acid catalysis, but a catalyst is not customary when aliphatic amines are used. The rate-determining step in neutral solution is apparently dehydration of the intermediate carbinolamine (81), but as the acidity increases it becomes the formation of the carbinolamine. Most methods for the preparation

of imines therefore involve the removal of water, and may be summarised as,

(a) dehydration with potassium hydroxide

(b) heat treatment under pressure

(c) water azeotrope in low boiling solvent

(d) water azeotrope in high boiling solvent.

The above methods are placed in order of increasing vigor and are each useful and convenient enough within their respective limitations, but have been shown (Weingarten et al., 1967) to be insufficient to prepare ketimines in the following categories:

(i) ketimines arising from volatile or moderately volatile amines and moderately to highly substituted ketones where method (d) cannot be used owing to the low boiling point of the amine, and

(ii) ketimines from highly hindered ketones or amines where even the higher temperatures encountered with method (d) were insufficient to give a good yield.

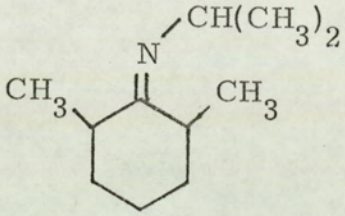
There have been reports of the use of catalysts and dehydrating agents other than potassium hydroxide and potassium

carbonate, e.g. Blanchard (1963) reported the use of granular calcium chloride in the preparation of diethylenamines from ketones, and the use of molecular sieves has also been reported (McDonagh and Smith, 1968). White and Weingarten (1967) described the use of titanium tetrachloride in the synthesis of enamines, and later applied it to ketimine synthesis too. The titanium tetrachloride is not only a more effective dehydrating agent, but also acts catalytically in the Lewis acid sense to polarise the carbonyl bond. The two main features of the mechanism are co-ordination of the carbonyl oxygen with the titanium atom, thereby preparing the carbonyl group for reaction with amines, and the transfer of the carbonyl oxygen atom from carbon to titanium. The titanium tetrachloride is not of course a catalyst in the true sense because it is used up in the reaction.

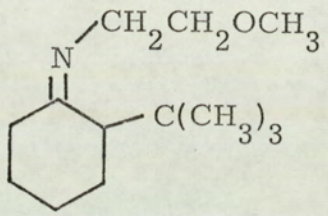
$$2 \quad \diagdown\!\!\diagup C = O \; + \; 6\ RNH_2 + \; TiCl_4 \longrightarrow 2 \quad \diagdown\!\!\diagup C = NR \; + \; 4RNH_2 \; . HCl \; + \; TiO_2$$

Slight excesses over the stoichimetric amounts of both amine and titanium tetrachloride seemed to give the best results. By this method fairly good yields were obtained even with severely hindered

ketones, for example Weingarten was able to prepare ketimine (83) in 79% yield which by



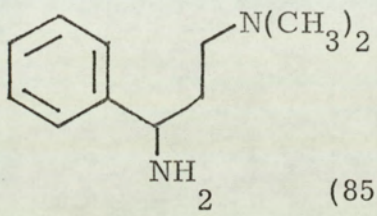
(83)



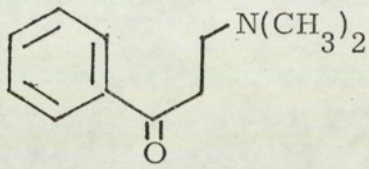
(84)

method (b) gave no imine, and also (84) in 61% yield which had proved impossible by method (d).

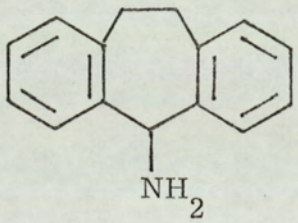
In the present investigation, some of these methods were applied to systems (85) which are analogous to the systems previously used in the reductive amination experiments e.g. (73).



(85)



(86)



(73)

Here again the choice lies between the use of (85) to aminate a cyclic ketone, or conversely, the amination of the propiophenone (86) using a cyclic amine. However, it was thought that the latter method would be the more favourable since the inductive effect of the phenyl ring would reduce the nucleophilicity of the amino group in (85) making it less reactive with carbonyl groups.

Consequently when 3-dimethylamino-1-phenyl-propylamine and cyclopentanone in benzene were treated with titanium tetrachloride and heated for 24 hours, the basic product of the reaction was an intractable dark brown tar whose infra-red spectrum still showed the presence of primary amine NH at 3450-3350 $cm.^{-1}$ The presence of a band at 1640 $cm.^{-1}$ suggested that some ketimine had been formed, but its isolation from the tar was found to be impossible. One unexpected feature of the spectrum was the disappearance of the peaks at 2800 and 2750 $cm.^{-1}$ due to dimethylamino group, suggesting that this group had been eliminated. Later experiments showed this to be the case.

A further series of experiments were carried out using 3-dimethylaminopropiophenone and cyclohexylamine to observe the relative amounts of ketimine produced under various conditions. A convenient way to assess the progress of the reaction was to note the ratio of the intensities of the C = O peak at 1680 $cm.^{-1}$ to the peak at 1630 $cm.^{-1}$ The latter peak was at first attributed solely to C = N but later investigation showed that this peak was probably a composite band due to C = N and C = C. Nevertheless, this method still proved valid for comparing the ratio of starting material to product.

In the first experiment, 3-dimethylaminopropiophenone and excess cyclohexylamine in benzene was heated under reflux beneath a Dean-Stark water separator for 24 hours. After removal of the solvent and excess cyclohexylamine under reduced pressure, the remaining oil was examined and found to be mainly starting material, for the ratio of the 1680 : 1630 $cm.^{-1}$ peaks was 4 : 1.

Repetition of the experiment using xylene as the solvent and heating under reflux for 40 hours gave a much better yield of ketimine for the intensity ratio of the above peaks was 0.7:1.

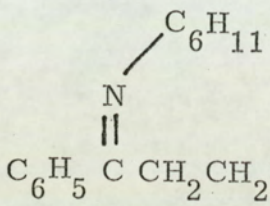
In the presence of titanium tetrachloride, refluxing in xylene for only 1 hour gave comparable results to the previous experiment with a 1680 : 1630 $cm.^{-1}$ ratio of 0.8:1.

When the previous reaction was modified by the addition of an ethereal solution of titanium tetrachloride to a solution of the ketone and amine in ether, followed by replacement of the solvent with benzene, and heating under reflux for 18 hours, the ratio of starting material to product was 1 : 5.

Replacement of the benzene by xylene and heating under reflux for a further 3 hours gave a product in which no carbonyl peak could be detected.

The physical data however, did not fit the expected structure

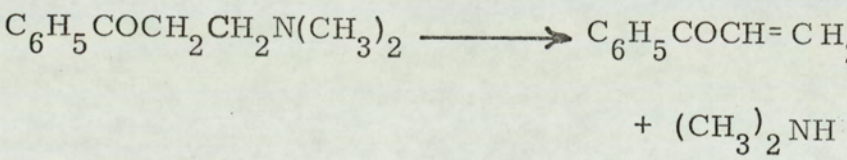
(87), for not only were the peaks due to the C - H stretch of



(87)

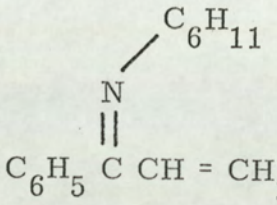
the N-dimethyl group (2800 and 2750 cm.$^{-1}$) missing, but the n.m.r. spectrum showed no singlet attributable to the N-dimethyl protons.

It is well known that under severe conditions β-aminoketones can undergo cleavage of the C - N bond to give vinyl ketones (88). In the present circumstances this elimination could have taken



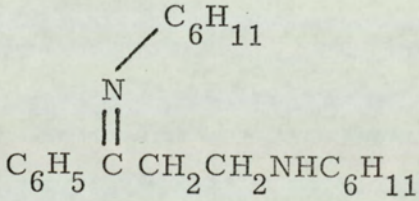
(88)

place either from the ketimine or the unreacted ketone. In any case the vinyl ketone would still be able to take part in ketimine formation, a fact which is shown by the complete disappearance of C = O absorption from the product. This would have given rise to structure (89). However, no ethylenic protons were



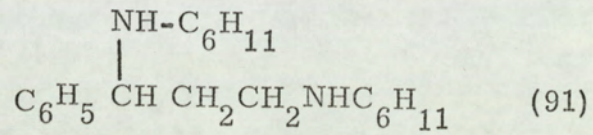
(89)

visable in the n. m. r. and integration showed more than the expected number of cyclohexyl protons. It was therefore assumed that under the conditions used, addition of cyclohexylamine across the C = C bond had taken place to give structure (90).



(90)

The compound could not be crystallised and attempts at chromatographic purification on alumina resulted in partial hydrolysis to a ketone. It was therefore hydrogenated in the presence of palladium on charcoal. The infra-red spectrum of the reduced product showed no absorption due to C = O, C = N or ethylenic C = C, but showed a sharp strong peak at 3300 $cm.^{-1}$ attributable to secondary amine N - H. The following structure (91) was therefore proposed for the product. Non aqueous titration of this base gave an equivalent of 158 which compared well



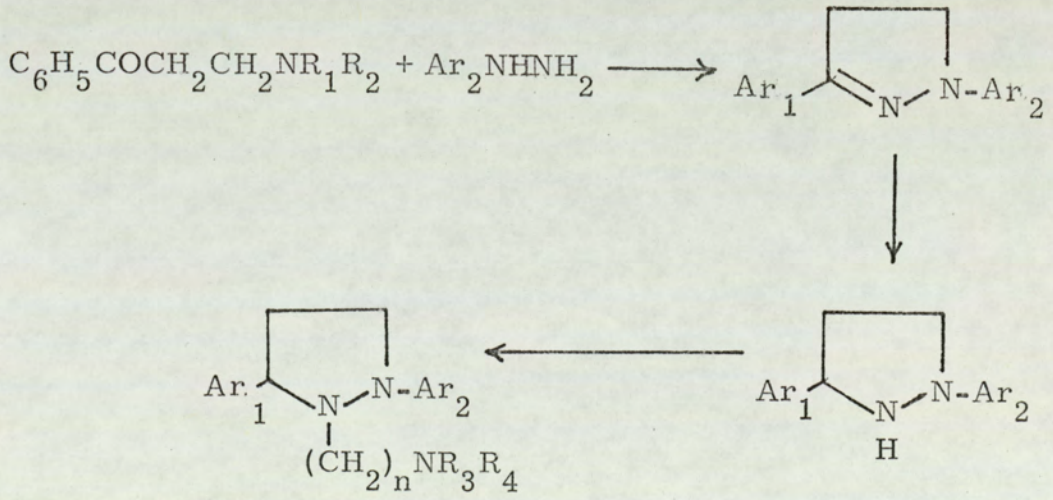
(91)

with the expected value of 157. The n.m.r. spectrum also confirmed this structure, integrating correctly for 5 phenyl protons (at 2.8 τ) and for 22 cyclohexyl protons (a multiplet extending from 8.2 - 9.1 τ). The base could not be crystallised successfully, but was converted to the dihydrochloride. The infra-red spectrum of the dried salt however, showed a peak at 3430 cm.$^{-1}$ characteristic of alcoholic -OH, and this was attributed to solvation of the salt with a mole of methanol. The salt gave an equivalent weight of 210 ($C_{21}H_{34}N_2.CH_3OH.2HCl$ required 209.5), and elemental analysis gave: C, 64.1; H, 9.5; N, 6.9%; comparing well with the calculated values of C, 63.0; H, 9.5; N, 6.7%.

[B] REACTIONS INVOLVING β-ELIMINATION FROM β-SUBSTITUTED KETONES AND THEIR DERIVATIVES

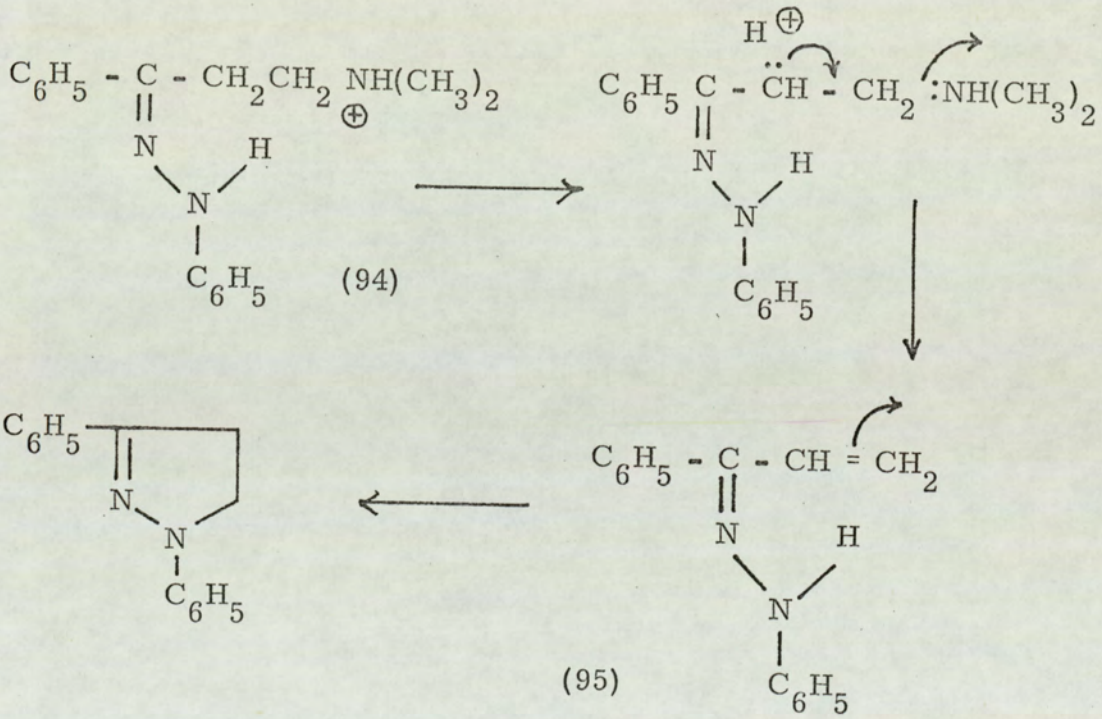
(i) The β-elimination which was seen to occur during the formation of a ketimine from 3-dimethylaminopropiophenone and cyclohexylamine has already been discussed.

(ii) From the reports that Mannich bases are useful precursors for the synthesis of 2-pyrazolines (Jarboe, 1967), the possibility of reducing such compounds to the corresponding pyrazolidines (92), followed by N-alkylation to give compounds of the type (93) was considered.



(93) (92)

The synthesis of 1,3-diphenyl-2-pyrazoline from 3-dimethylaminopropiophenone and phenylhydrazine has been reported (Auwers, 1932; Nisbett, 1945). Nisbett suggested a mechanism for this reaction which would occur under acidic conditions. It postulated the formation of a phenylhydrazone



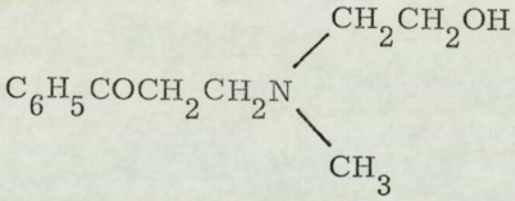
(94) (95)

intermediate (94) followed by β-elimination and subsequent addition (95) to the newly generated C = C bond.

The conditions reported for the condensation of Mannich bases with aryl-hydrazines varied greatly. In the present work it was found that simply warming an ethanolic solution of

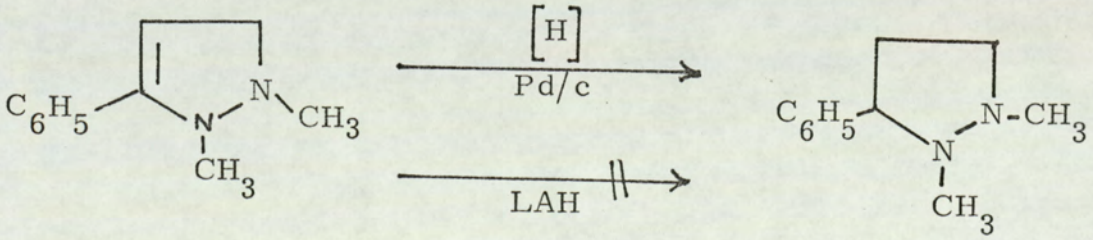
3-dimethylaminopropiophenone hydrochloride and phenylhydrazine gave 1, 3-diphenyl-2-pyrazoline in good yield.

Identical results were obtained when 3-[(2-hydroxyethyl)-methylamino]propiophenone hydrochloride (96) was treated with phenylhydrazine.



(96)

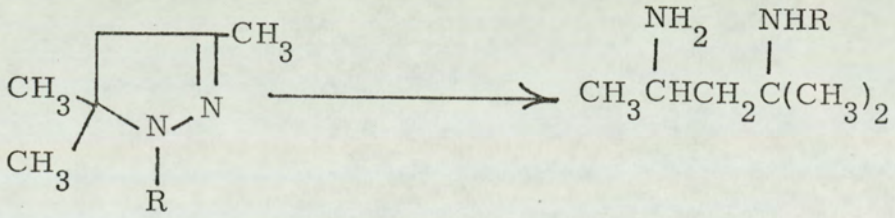
Reduction of pyrazolines, pyrazoles and pyrazolones has been achieved by several routes including sodium in ethanol, lithium aluminium hydride and catalytic hydrogenation. Hinman, 1960, reported the failure of lithium aluminium hydride to reduce 1, 2-dimethyl-3-phenyl-3-pyrazoline (97), but succeeded in its reduction by catalytic hydrogenation using palladium on carbon and acetic acid as solvent.



(97)

In the present investigation, 3,5-diphenylpyrazoline was found to be extremely resistant to reduction. Treatment with sodium in ethanol, sodium borohydride, lithium aluminium hydride and catalytic hydrogenation at 1 atmosphere with palladium on carbon all gave unchanged starting material. Hydrogenation at 4 atmospheres with Adams catalyst in acetic acid gave a dark intractable oil. Thin layer chromatography showed it to be a complex mixture which was probably the result of partial hydrogenolysis. Such fission of the pyrazoline ring has been reported by Kost (1962) who hydrogenolysed 2-pyrazolines to 1,3-diamines using Raney nickel at 100 - 120° and 80 - 140 atmospheres.

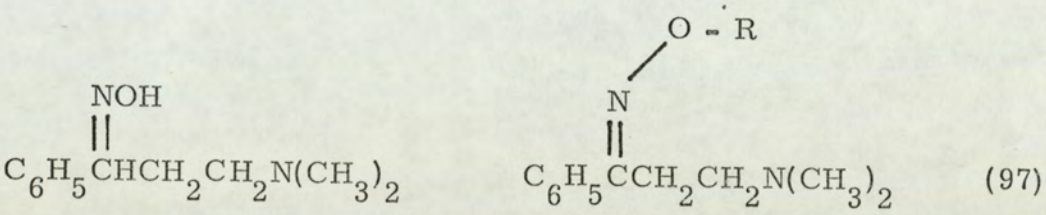
In view of these difficulties the synthesis of pyrazolidine



derivatives was not considered worthwhile.

(iii) Having synthesised 3-dimethylaminopropiophenone oxime in the course of preparing 3-dimethylaminopropylamine derivatives,

the possibility of O-alkylationof this oxime was considered in an attempt to prepare compounds of the type (97)



(97)

where R = $C_6H_5CH_2$; p - F $(C_6H_4)CH_2$.

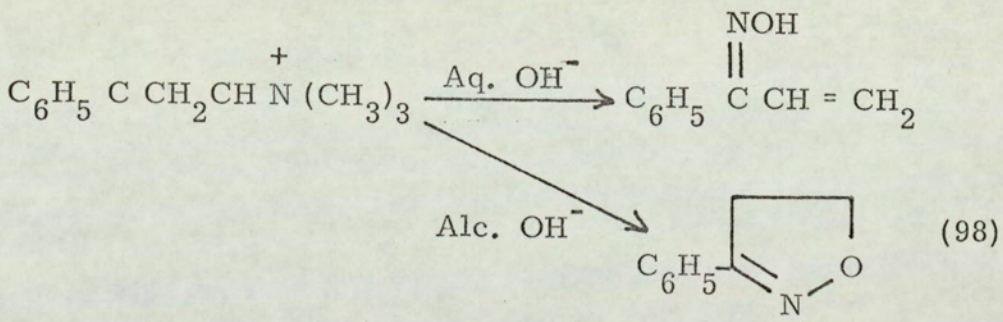
As oximes are very weak bases, they do not react in the unionised state with usual alkylating agents. It is therefore customary to prepare the sodium salt of the oxime prior to condensation with an alkyl halide. N-Alkylation to form a nitrone is usually a side reaction but is less likely when bulky alkyl groups such as benzyl are used.

The sodium salt of the oxime is invariably prepared by treating the oxime either with sodium methoxide in methanol or with sodamide in xylene (Rossi et al.). The sodium salts thus produced are treated with an alkyl halide and heated in the same solvent.

When these conditions are used for oximes of β-aminoketones however, formation of a quaternary salt is quite likely. Such salts would then be able to undergo β-elimination to form an α , β-unsaturated oxime or to ring close to form an isoxazoline,

depending on the solvent (Kyi and Wilson, 1953).

Consequently, when 3-dimethylaminopropiophenone oxime with sodamide in xylene was treated with benzyl chloride, 3-phenyl-2-isoxazoline (98) was the sole product of the reaction.



(98)

Treatment of the oxime with sodium methoxide and p-fluorobenzyl chloride however, simply gave unreacted starting material.

In view of these difficulties, the synthesis of O-alkyl derivatives of the oximes of β-aminoketones was not considered worthwhile.

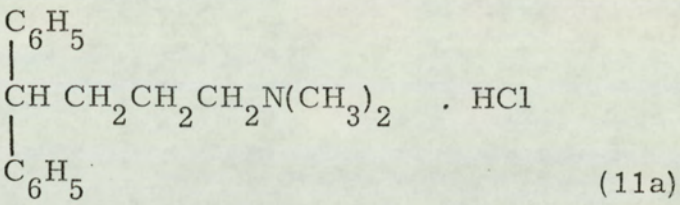
SECTION III

EXPERIMENTAL

EXPERIMENTAL

[A.] PREPARATION OF SOME DIPHENYL-AND CYCLOHEXYLPHENYLALKYLAMINES

4-Dimethylamino-1, 1-diphenylbutane hydrochloride



(11a)

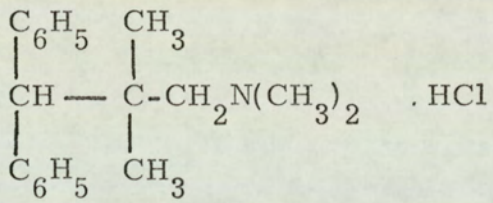
1-Cyano-4-dimethylamino-1, 1-diphenylbutane (4g.) was added to a suspension of sodamide (4g.) in toluene (20 ml.) and heated under reflux with stirring for 16 hours. The inorganic matter was filtered off, washed with ether, and the combined filtrates evaporated under reduced pressure to give a colourless oil which on subsequent treatment with ethanolic hydrogen chloride and recrystallisation from ethanol-ether gave 4-dimethylamino-1, 1-diphenylbutane hydrochloride (2.5g.) m.p. 152-153.5°.

(Seidlova et al., 1965 quote m.p. 153-154.5°).

Found: equiv., 286. $C_{18}H_{24}ClN$ requires equiv., 289.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2600, 2480 ($N^{+}H$), 1600, 1420, 1160, 760, 745, 700 and 695 (C_6H_5) $cm.^{-1}$

2,2-Dimethyl-3-dimethylamino-1,1-diphenylpropane hydrochloride



(11d)

1-Cyano-2,2-dimethyl-3-dimethylamino-1,1-diphenylpropane (2.0g.) was added to a suspension of freshly prepared sodamide (2g.) in toluene (10ml.) and heated under reflux with stirring for 18 hours. The inorganic residue was filtered off, washed with ether, and the combined filtrates evaporated under reduced pressure to give a colourless oil, which on treatment with ethanolic hydrogen chloride and subsequent recrystallisation from ethanol-ether gave 2,2-dimethyl-3-dimethylamino-1,1-diphenylpropane hydrochloride (0.94g.), m.p. 260-261°.

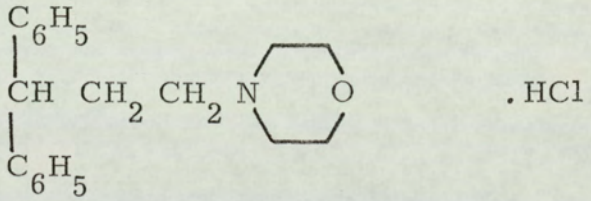
Analysis Found: C, 75.8; H, 8.7; N, 4.5%; equiv., 303.

$C_{19}H_{26}ClN$ requires C, 75.8; H, 8.7; N. 4.5%; equiv. 304.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2510, 2450 ($N^{+}H$), 1420, 990, 960, 780 745 713 and 700 (C_6H_5) $cm.^{-1}$

N. M. R.: τ (D_2O), 2.4-2.9 (m, 10H, C_6H_5); 7.1 (d, 2H, NCH_2); 7.3 (s, 6H, $2xCH_3N$); 8.6 (s, 1H, CH); 8.95 (s, 6H, $2xCH_3C$).

1,1-Diphenyl-3-morpholinobutane hydrochloride



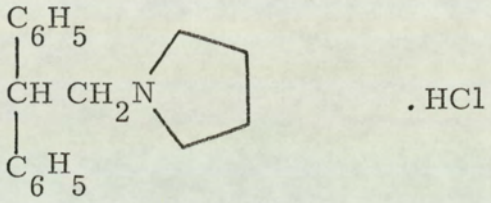
(11c)

1-Cyano-1,1-diphenyl-3-morpholinobutane (3.0g.) was added to a suspension of sodamide (3.0g.) in toluene (15ml.) and heated under reflux with stirring for 12 hours. The reaction mixture was treated in the usual manner to give a pale yellow oil which on subsequent treatment with ethanolic hydrogen chloride and recrystallisation from ethanol-ether gave 1,1-diphenyl-3- morpholinobutane hydrochloride (2.2g.), m.p. 216 - 217° (undepressed on admixture with an authentic sample).

Found: equiv., 315; $C_{19}H_{24}ClNO$ requires equiv., 317.5.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2650-2450 ($N^{+}H$), 1115, 1090, 775 745 and 700 (C_6H_5)cm.$^{-1}$

1-(2, 2-Diphenylethyl) pyrrolidine hydrochloride



. HCl

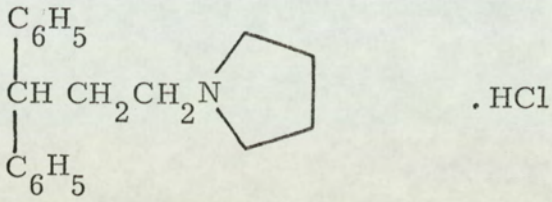
(11b)

1-(2-Cyano-2, 2-diphenylethyl)- pyrrolidine (4.0g.) was added to a suspension of sodamide (4.0g.) in toluene (20ml.) and heated under reflux for 16 hours. The reaction mixture was treated in the usual manner to give a colourless oil which on treatment with ethanolic hydrogen chloride and subsequent recrystallisation from acetone-ether gave 1-(2, 2-diphenylethyl) pyrrolidine hydrochloride (2.5g.) m.p. 181 - 182°Ide et al.(1959) quote m.p. 174-175°.

Analysis Found: C, 75.1; H, 7.7; N, 5.0%; equiv., 284. $C_{18}H_{22}ClN$ requires C, 75.1; H, 7.7; N, 4.9%; equiv. 287.

Infra-red (base): $\bar{\nu}_{max.}$ (film), 2950, 2780, 1500, 1460, 740 and 700 (C_6H_5) cm.$^{-1}$

1-(3, 3-Diphenylpropyl)pyrrolidine hydrochloride



. HCl

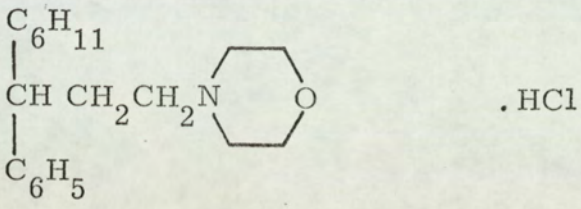
(11b)

1-(3-Cyano-3, 3-diphenylpropyl)pyrrolidine (2.0g.) was added to a suspension of sodamide (2.0g.) in toluene (10ml.), and reflux with stirring for 16 hours. The reaction mixture was treated in the usual manner to give a viscous colourless oil which on subsequent treatment with ethanolic hydrogen chloride and recrystallisation from ethanol-ether gave 1-(3, 3-diphenylpropyl)pyrrolidine hydrochloride (1.4g.), m.p. 136-137°. Treatment of an aliquot of the base with methyl iodide in ether, and recrystallisation from ethanol-ether gave 1-(3, 3-diphenylpropyl)pyrrolidine methiodide m.p. 155-156°. Ruddy (1952) quotes 156.6-157°.

Found: equiv., 304; $C_{19}H_{24}ClN$ requires equiv., 302.

Infra-red (base) $\bar{\nu}_{max.}$ (film), 2950, 2800, 1500, 1455, 755, 700 (C_6H_5) cm.$^{-1}$

1-Cyclohexyl-3-morpholino-1-phenylpropane hydrochloride



(12a)

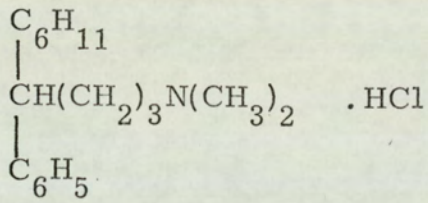
1,1-Diphenyl-3-morpholinopropane hydrochloride (1.0g.) was added to a suspension of reduced Adams catalyst (1.0g.) in acetic acid (5ml.), and shaken with hydrogen (1 atmos.) at room temperature until 240 ml. (3.4 mole) of hydrogen had been absorbed (3.25 hours). The mixture was diluted with water, the catalyst filtered off and the filtrate made alkaline with aqueous ammonia and extracted with ether. The ethereal extracts were dried (anhyd. $MgSO_4$) and evaporated to give a colourless oil. Treatment with ethanolic hydrogen chloride and subsequent fractional recrystallisations from ethanol-ether gave 1-cyclohexyl-3-morpholino-1-phenylpropane hydrochloride (0.5g.), m.p. 232-234°.

Analysis Found: C, 70.1; H, 9.4; N, 4.2%. $C_{19}H_{30}ClNO$ requires C, 70.5; H, 9.3; N, 4.3%.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2420 (N^+H), 1255, 700 (C_6H_5) $cm.^{-1}$

N.M.R.: τ (D_2O), 2.8 (s, 5H, C_6H_5); 6.1 (m, 4H, CH_2OCH_2); 6.8-7.5 (m, 6H, $CH_2N(CH_2)_2$); 7.6-7.9 (m, 3H, CH_2CH); 8.5-9.5 (m, 11H, C_6H_{11}).

1-Cyclohexyl-4-dimethylamino-1-phenyl-butane hydrochloride



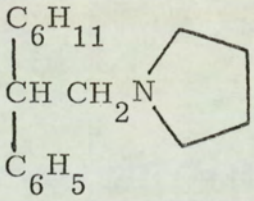
(12b)

4-Dimethylamino-1,1-diphenylbutane hydrochloride (1.0g.) was added to a suspension of reduced Adams catalyst (0.6g.) in acetic acid (5ml.) and shaken with hydrogen (1 atmos.) at room temperature until 3.4 moles (282ml. at 20° C) of hydrogen had been absorbed (3 hours). The reaction mixture was treated in the usual manner to give a pale yellow oil which on treatment with ethanolic hydrogen chloride and subsequent fractional recrystallisations from ethanol-ether gave 1-cyclohexyl-4-dimethylamino-1-phenyl-butane hydrochloride (0.5g.), m.p. 158.5-160°.

Analysis Found: C, 73.4; H, 11.1; N, 4.6%. $C_{18}H_{30}ClN$ requires C, 73.1; H, 10.2; N, 4.7%

N.M.R.: τ (D_2O), 2.8 (s, 5H, C_6H_5); 6.9-7.1 (m, 2H, CH_2N); 7.2 (s, 6H, $N(CH_3)_2$); 7.5-7.7 (m, 1H, CH); 8.2-9.4 (m, 15H, C_6H_{11}, CH_2CH_2).

1-(2-Cyclohexyl-2-phenylethyl)pyrrolidine hydrochloride



.HCl

(12c)

1-(2,2-Diphenylethyl)pyrrolidine hydrochloride (2.0g.) was added to a suspension of reduced Adams catalyst (1.0g.) in acetic acid (10ml.) and shaken with hydrogen (1 atmos.) at room temperature until 578 ml. (3.4 mole) of hydrogen had been absorbed. The reaction mixture was treated in the usual manner to give a colourless oil which upon treatment with ethanolic hydrogen chloride and subsequent recrystallisations from ethanol-ether gave 1-(2-cyclohexyl-2-phenylethyl)pyrrolidine hydrochloride (0.5g.), m.p. 217.5-218.5°.

Analysis Found: C, 73.5; H, 9.6; N, 4.9% $C_{18}H_{28}ClN$ requires C, 73.6; H, 9.5; N, 4.8%.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 2930, 1455, 705 and 680 (C_6H_5) $cm.^{-1}$

Two attempted preparations of 1-cyclohexyl-2, 2-dimethyl-3-dimethylaminopropane

[A] 2, 2-Dimethyl-3-dimethylamino-1, 1-diphenylpropane hydrochloride (1.0 g.) was added to a suspension of reduced Adams catalyst (0.5 g.) in a mixture of acetic acid (25 ml.) and dilute hydrochloric acid (10 ml.). This was treated in the usual manner to give unchanged 2, 2-dimethyl-3-dimethylamino-1, 1-diphenylpropane hydrochloride (0.97 g.).

[B] 2, 2-Dimethyl-3-dimethylamino-1, 1-diphenyl-propane hydrochloride (1.0 g.) added to a suspension of reduced Adams catalyst (1.0 g.) in acetic acid (10 ml.) was shaken with hydrogen (6 atmos.) for 102 hours. The reaction mixture was treated in the usual manner to give unchanged starting material (0.95 g.).

[B] PREPARATION OF β-AMINOKETONES

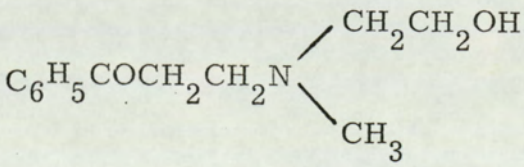
3-Dimethylaminopropiophenone hydrochloride

$$C_6H_5COCH_2CH_2N(CH_3)_2 \quad .HCl \qquad (21)$$

A mixture of acetophenone (58.5 ml.), dimethylamine hydrochloride (52.7g.) and paraformaldehyde (19.8g.) in 95% ethanol (80 ml.) and hydrochloric acid (1 ml.) was heated under reflux for 2 hours. The reaction mixture was diluted with acetone (400 ml.) and cooled slowly to give 3-dimethylaminopropiophenone hydrochloride (75.0g.) 153-154°. Maxwell (1955), quotes 152-153°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2700-2500 (N^+H), 1680 (C = O), 1345, 1230, 970, 765 and 700 (C_6H_5) $cm.^{-1}$

3-[(2-hydroxyethyl)methylamino] propiophenone hydrochloride



(22)

. HCl

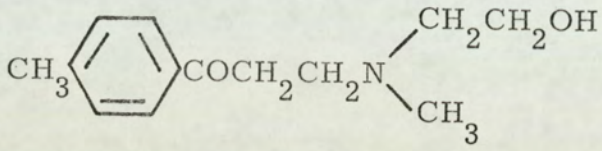
Acetophenone (12.0g.), 2-methylaminoethanol hydrochloride (11.2 g.), paraformaldehyde (4.5g.) and ethanolic

hydrochloric acid (10 ml.) in ethanol (30 ml.) was heated under reflux for 2 hours. Further paraformaldehyde (3.0 g.) was added and refluxing continued for 4 hours. A major portion of ethanol was removed under reduced pressure on the steam bath, the residue diluted with water (200 ml.) and washed with two portions of ether. The aqueous layer was made alkaline with concentrated aqueous ammonia and extracted with ether. The ethereal extracts were dried (anhyd. $MgSO_4$) and evaporated to give a pale yellow mobile oil. Treatment with ethanolic hydrogen chloride and subsequent recrystallisations from ethanol-ether gave 3-[(2-hydroxyethyl) methylamino]-propiophenone hydrochloride (8.0 g.) m.p. 147-149°. Yun-Sung Chough (1959) quotes 145-147°, and Walker (1962) quotes 149-152°.

Found: equiv. 240. $C_{12}H_{18}ClNO_2$ requires equiv. 243

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3400 (OH), 2910, 2810, 2790, 1680 (C = O), 1600, 1580, 1455, 1210, 1040, 745 and 690 (C_6H_5)cm.$^{-1}$

3-[(2-Hydroxyethyl)methylamino]-4'-methylpropiophenone hydrochloride



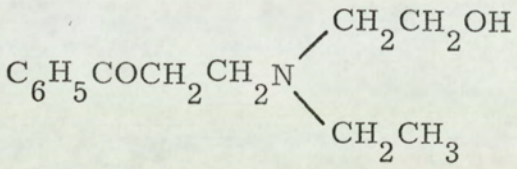
(25)

A cooled solution of 2-methylaminoethanol (37.5 g.) in ethanol (200 ml.) was acidified with hydrogen chloride. p-Methyl-acetophenone (67g.) and paraformaldehyde (20 g.) were added and the mixture heated under reflux with stirring for 18 hours. The ethanol was removed under reduced pressure, the residue dissolved in water (200 ml.) and washed with ether (2 x 50 ml.). The aqueous layer was basified with aqueous ammonia and extracted with ether (3 x 150 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a golden-brown oil (31.5 g.) which upon treatment with hydrogen chloride and subsequent recrystallisation from ethanol-ether gave 3-[(2-hydroxyethyl)methylamino]-4'-methylpropiophenone hydrochloride m.p. 90 - 91°.

Analysis Found: C, 60.8; H, 7.9; N, 5.3%; equiv., 263 $C_{13}H_{20}ClNO_2$ requires C, 60.6; H, 7.8; N, 5.4%; equiv., 258.

Infra-red: $\tilde{\nu}_{max.}$ (base, film), 3400 (OH), 2900, 1675 (C = O), 1610, 1185 and 1045 $cm.^{-1}$

3-[(2, Hydroxyethyl)ethylamino]-propiophenone hydrochloride



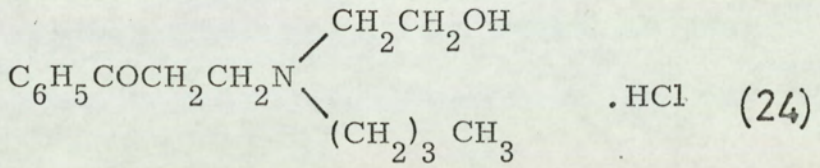
(23)

A cooled solution of 2-ethylaminoethanol (8.9 g.) in ethanol (100 ml.) was acidified with hydrogen chloride. Acetophenone (12 g.) and paraformaldehyde (4 g.) was added and the mixture heated under reflux with stirring for 18 hours. Treatment in a similar manner to the preparation of 3-[(2-hydroxyethyl)methylamino] -4'-methylpropiophenone hydrochloride gave a pale brown oil (12.0 g.) which upon treatment with hydrogen chloride and recrystallisation from ethanol-ether gave 3-[(2-hydroxyethyl)ethylamino] propiophenone hydrochloride, m.p. 101-102°. Yung-Sung Chough (1959) quotes m.p. 104-105°.

Found: equiv., 260. $C_{13}H_{20}ClNO_2$ requires equiv., 258.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3450 (OH), 2950, 1680 (C = O), 1450, 1205, 1040, 740 and 680 (C_6H_5) $cm.^{-1}$

3-[(2-Hydroxyethyl)-n-butylamino]propiophenone hydrochloride



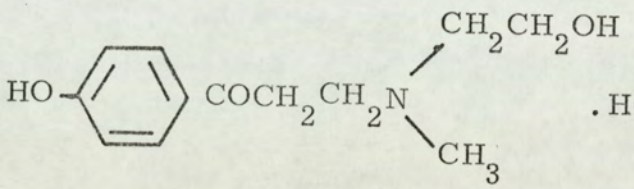
(24)

A cooled solution of N-n-butylethanolamine (23.4 g.) in ethanol (200 ml.) was acidified with hydrogen chloride. Acetophenone (24.0 g.) and paraformaldehyde (8 g.) was added and the mixture heated under reflux with stirring for 18 hours. Treatment in a similar manner to the preparation of 3-[(2-hydroxyethyl)methylamino]-4'-methylpropiophenone hydrochloride gave 3-[(2-hydroxyethyl)-n-butylamino]propiophenone hydrochloride (15.2 g.), m.p. 92-93°.

Analysis Found: C, 63.2; H, 8.5; N, 4.8%; equiv., 287. $C_{15}H_{24}ClNO_2$ requires C, 63.1; H, 8.4; N, 4.9%; equiv., 286.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 (OH), 2650 - 2750 (N^+H), 1685 (C=O), 1410, 1080, 770 and 705 (C_6H_5) $cm.^{-1}$

4'-Hydroxy-3-[(2-hydroxyethyl)methylamino]propiophenone hydrochloride



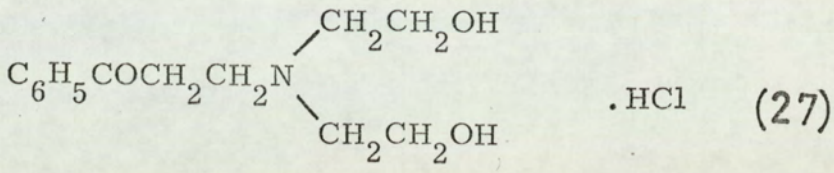
(26)

A cooled solution of 2-methylamino ethanol (37.5 g.) in ethanol (200 ml.) was acidified with hydrogen chloride. p-Hydroxyacetophenone (68 g.) and paraformaldehyde (20 g.) was added and the mixture heated under reflux with stirring for 18 hours. The ethanol was removed under reduced pressure, the residue washed with ether and subsequently crystallised from acetone with scratching to give a white crystalline solid (103 g.). Recrystallisation from ethanol gave 4'-hydroxy-3-[(2-hydroxyethyl)-methylamino]propiophenone hydrochloride, m.p. 125-126°.

Analysis Found: C, 55.7; H, 7.1; N, 5.3%; equiv., 259. $C_{12}H_{18}ClNO_3$ requires C, 55.9; H, 6.9; N, 5.4%; equiv., 260.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 (aliphatic OH); 3050 (phenolic OH), 2700 (N^+H), 1660 (C = O), 1610, 1345, 1285, 720 (C_6H_4) $cm.^{-1}$

3-[Di-(2-hydroxyethyl)amino]propiophenone hydrochloride



.HCl (27)

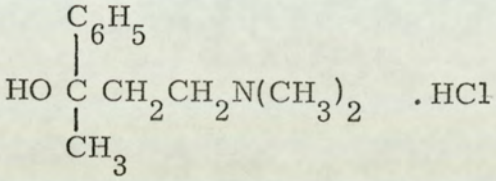
A cooled solution of diethanolamine (10.5g.) in ethanol (10 ml.) was acidified with hydrogen chloride. Acetophenone (12.0 g.) and paraformaldehyde (4.0 g.) was added and the mixture heated under reflux with stirring for 18 hours. The ethanol was removed under reduced pressure and the residue triturated with ether to give a white crystalline solid (15 g.). Recrystallisation from ethanol-ether gave 3-[di-(2-hydroxyethyl)amino]propiophenone hydrochloride, m.p. 97-98°.

Analysis Found: C, 56.9; H, 7.4; N, 5.3%; equiv., 274. $C_{13}H_{20}ClNO_3$ requires C, 57.0; H, 7.3; N, 5.1%; equiv., 275.

Infra-red: $\bar{\nu}_{max.}$ (Hexachlorbutadiene), 2400 - 3200 (OH), 2700 (N^+H), 1680 (C = O), 760 and 690 (C_6H_5) $cm.^{-1}$

[C.] PREPARATION OF ALKYLAMINOPROPANOLS

4-Dimethylamino-2-phenyl-2-butanol hydrochloride



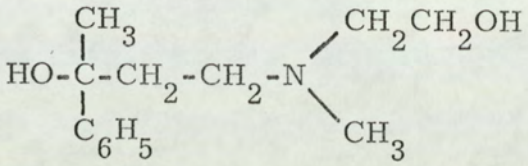
(29)

To a stirred solution of methyl-lithium, prepared from lithium (3.8 g.) in anhyd. ether (75 ml.) and methyl iodide (35.5 g.) in anhyd. ether (75 ml.), was added 3-dimethylamino-propiophenone hydrochloride (10.0 g.) in small portions. After heating under reflux for 20 hours the reaction mixture was acidified with dilute hydrochloric acid and the aqueous layer washed with ether (3 x 50 ml.), and made alkaline by the addition of aqueous ammonia. The aqueous suspension was extracted with ether (3 x 100 ml.), and the extracts dried (anhyd. Na_2SO_4), and evaporated to give a pale yellow oil which on treatment with hydrogen chloride and recrystallisation from ethanol-ether gave 4-dimethylamino-2-phenyl-2-butanol hydrochloride (2.7 g.), m.p. 165-167°. Adamson (1951) quotes m.p. 165-166°.

Found: equiv., 225. $C_{12}H_{20}ClNO$ requires 229.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 (OH), 2650-2450 (N^+H), 1255, 1165, 1065, 965, 760 and 690 (C_6H_5) $cm.^{-1}$

4-[(2-Hydroxyethyl)methylamino]-2-phenyl-2-butanol hydrochloride



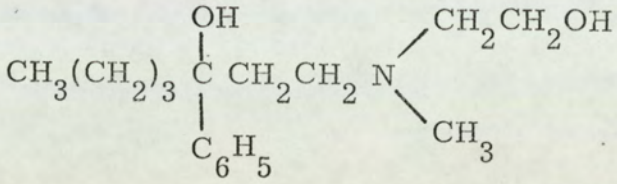
.HCl (32)

To a solution of methyl-lithium prepared from methyl iodide (71 g.) and lithium (7.6 g.) in anhyd. ether (300 ml.), a solution of 3-[(2-hydroxyethyl)methylamino]propiophenone (24 g.) in anhyd. ether (150 ml.) was added dropwise with stirring. The reaction mixture was heated under reflux for 66 hours and treated in a similar manner to the preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a straw-coloured oil. Treatment with hydrogen chloride and subsequent recrystallisation from ethanol-ether gave 4-[(2-hydroxyethyl)methylamino]-2-phenyl-2-butanol hydrochloride m.p. 94-95°.

Analysis Found: C, 59.9; H, 8.4; N, 5.6%; equiv., 264. $C_{13}H_{22}ClNO_2$ requires C, 60.1; H, 8.5; N, 5.4%; equiv., 260.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3500 - 3200 (OH), 3000, 2850, 1480, 1460, 1080, 1050, 780 and 705 (C_6H_5) $cm.^{-1}$

1-[(2-Hydroxyethyl)methylamino]-3-phenyl-3-heptanol



(33)

A solution of n-butyl chloride (5 g.) in anhyd. ether (100 ml.) was added to magnesium turnings (54.7 g.) under an atmosphere of dry nitrogen. The reaction was initiated by the addition of a solution of ethyl bromide (1 ml.) in anhyd. ether (100 ml.) and stirring was commenced. The remaining n-butyl chloride (180 g.) in anhyd. ether (600 ml.) was added at such a rate that gentle refluxing was maintained. Stirring was continued for a further 2 hours and the reaction was completed by allowing to stand overnight. A solution of 3-[(2-hydroxyethyl)methylamino]propiophenone (20 g.) in anhyd. ether (200 ml.) was added dropwise and refluxed for 24 hours. A small aliquot was treated in a similar manner to the preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a pale brown mobile oil. Infra-red spectroscopy indicated a high proportion of ketone in the product. The reaction was therefore allowed to proceed further by the addition of anhyd. xylene (400 ml.) followed by removal of the ether. Heating under reflux was continued for a

further 24 hours and the reaction mixture was worked up in the usual manner to give a pale brown oil which later crystallised from petroleum ether (b.p. 60 - 80°). Recrystallisation from the same solvent gave 1-[(2-hydroxyethyl)methylamino]-3-phenyl-3-heptanol, m.p. 46 - 47°.

Analysis Found: C, 72.4; H, 10.1; N, 5.3%; equiv. 264. $C_{16}H_{27}NO_2$ requires C, 72.5; H, 10.2; N, 5.3%. equiv. 265. Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3200 - 2400 (OH), 1600, 1580, 1080, 1045, 880, 765 and 700 (C_6H_5) $cm.^{-1}$

1-Dimethylamino-3-phenyl-3-heptanol.

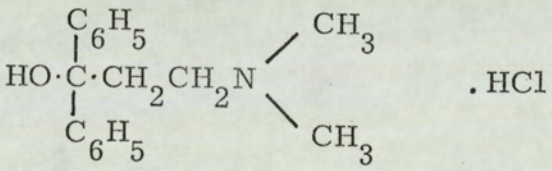
$$CH_3(CH_2)_3\,\underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{C}}(OH)CH_2CH_2N(CH_3)_2 \qquad (30)$$

To a solution of n-butylmagnesium chloride prepared in a similar manner to the previous experiment (from magnesium turnings (54.7 g.) and n-butyl chloride in anhyd. ether), a solution of 3-dimethylaminopropiophenone (20 g.) in anhyd. ether (200 ml.) was added with stirring. After heating under reflux for 3 hours the ether was replaced by xylene and refluxing was continued for 24 hours. The reaction mixture was treated in a similar manner to the

preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a viscous golden oil which crystallised as prisms from petroleum ether (b.p. 60 - 80°). Recrystallisation from the same solvent gave 1-dimethylamino-3-phenyl-3-heptanol, m.p. 51-52°, b.p. 134°/4mm..

Analysis Found: C, 75.9; H, 10.6; N, 5.9%; equiv., 234. $C_{15}H_{25}NO$ requires C, 76.6; H, 10.6; N, 5.9%; equiv., 235. Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3170 (OH), 1320; 1190; 1065; 1040; 760 and 700 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1,1-diphenyl-1-propanol hydrochloride.



(31)

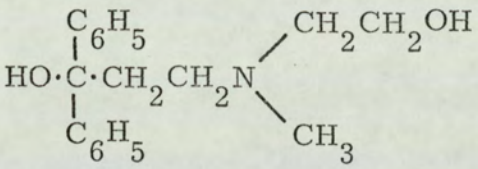
To a stirred solution of phenyl-lithium prepared from lithium (7.6 g.) and bromobenzene (78.5 g.) in anhyd. ether (250 ml.), 3-dimethylaminopropiophenone hydrochloride (21.0 g.) was added in small portions. After heating under reflux for 24 hours the reaction mixture was treated in a similar manner to the preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a viscous golden oil. Treatment of the oil in ether with hydrogen chloride

and subsequent recrystallisations from ethanol-ether gave 3-dimethylamino-1,1-diphenyl-1-propanol hydrochloride, m.p. 200-202°. Morrison (1949) quotes 205°).

Found: equiv., 307; $C_{17}H_{22}ClNO$ requires 292.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 (OH), 2700 - 2500 ($N^{+}H$), 1070, 795, 765, and 710 - 730 (C_6H_5) $cm.^{-1}$

1,1-Diphenyl-3[(2-hydroxyethyl)methylamino]-1-propanol



(34)

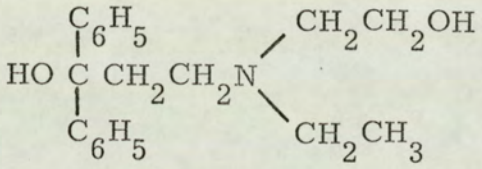
To a solution of phenyl-lithium prepared from lithium (7.6 g.) in anhyd. ether (100 ml.) and bromobenzene (76.5 g.) in anhyd. ether (250 ml.), a solution of 3-[(2-hydroxyethyl)-methylamino]propiophenone (17.0 g.) in anhyd. ether (50 ml.) was added dropwise with stirring. The mixture was heated under reflux for 66 hours, and treated in a similar manner to the preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a pale brown oil which crystallised upon standing. Recrystallisation from benzene-petroleum ether (60 - 80°) gave 1,1-diphenyl-3[(2-hydroxyethyl)methylamino]-1-propanol, m.p. 83 - 85°.

Analysis Found: C, 75.3; H, 8.3; N, 4.7%; equiv., 286.

$C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%; equiv., 285.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3430 (OH); 1080; 1050; 1000; 775, 760, 740, 700 (C_6H_5) $cm.^{-1}$

3-[(2-Hydroxyethyl)ethylamino]-1,1-diphenyl-1-propanol hydrochloride



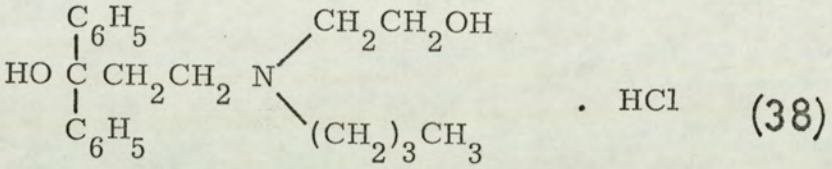
.HCl (37)

To a stirred solution of phenyl-lithium prepared from lithium (3.8 g.) and bromobenzene (39.3 g.) in anhyd. ether (200 ml.), 3-[(2-hydroxyethyl)ethylamino]propiophenone hydrochloride (12.0 g.) was added in small portions. After heating under reflux for 18 hours the reaction mixture was treated in a similar manner to the preparation of 4-dimethylamino-2-phenyl-2-butanol hydrochloride to give a yellow oil which crystallised as long needles, m.p. 75 - 76° from petroleum ether (b.p. 60 - 80°), but in poor yield. Treatment in ether with hydrogen chloride and subsequent recrystallisations from ethanol-ether gave 3-[(2-hydroxyethyl)ethylamino]-1,1-diphenyl-1-propanol hydrochloride (7.9 g.), m.p. 161.5 - 162.5°.

Analysis Found: C, 67.9; H, 7.9; N, 4.2%; equiv., (base), 300. $C_{19}H_{26}ClNO_2$ requires C, 70.0; H, 7.9; N, 4.2%; equiv. (base), 299.

Infra-red: $\bar{\nu}_{max.}$ (Base, Nujol), 3380 (OH), 1075, 1050, 765 740 and 690 (C_6H_5) $cm.^{-1}$

3-[(2-Hydroxyethyl)-n-butylamino]-1,1-diphenyl-1-propanol hydrochloride



. HCl (38)

3-[(2-Hydroxyethyl)-n-butylamino]propiophenone hydrochloride (10.0 g.) was added in small portions to a stirred solution of phenyl-lithium, prepared from bromobenzene (39.3 g.) and lithium (3.8 g.), in anhyd. ether (300 ml.). The reaction mixture was heated under reflux for 18 hours, acidified with dilute aqueous hydrochloric acid (250 ml.), and the ethereal layer washed with further portions of acid (3 x 50 ml.). The aqueous layer, upon standing, yielded a copious flocculent precipitate which was filtered off, dried and recrystallised from acetone-ether to give 3-[(2-hydroxyethyl)-n-butylamino]-1,1-diphenyl-1-propanol hydrochloride (4.2 g.), m.p. 95 - 96°. An additional small yield of product was obtained by basifying the aqueous layer with aqueous ammonia and extracting with chloroform (3 x 80 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a golden oil which upon treatment in ethereal solution with hydrogen chloride

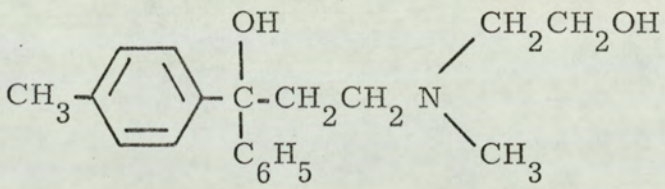
gave the desired product.

Analysis Found: C, 69.4; H, 8.1; N, 3.8%; equiv., 365.

$C_{21}H_{30}ClNO_2$ requires C, 69.3; H, 8.2; N, 3.8%; equiv., 363.5.

Infra-red: $\tilde{\nu}_{max.}$ (Nujol), 3250 (OH); 2650, 2580 (N^+H); 1070; 1040; 760, 690 (C_6H_5) cm.$^{-1}$

3-[(2-Hydroxyethyl)methylamino]-1-phenyl-1-p-tolyl-1-propanol.



(36)

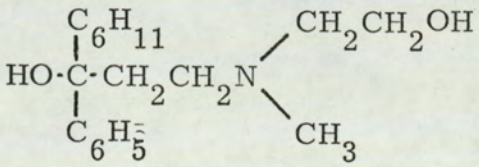
To a stirred solution of phenyl-lithium prepared from lithium (3.8g.) and bromobenzene (39.3g.) in anhyd. ether (200 ml.), 3-[(2-hydroxyethyl)methylamino]-p-methylpropiophenone hydrochloride (10.0g.) was added in small portions, and heated under reflux with stirring for 24 hours. The reaction mixture was acidified with dilute hydrochloric acid and the aqueous layer washed with ether (3 x 100 ml.). An oily layer, insoluble in water or ether separated, was collected, and subsequently crystallised from acetone to give 3-[(2-hydroxyethyl)methylamino]-1-phenyl-1-p-tolyl-1-propanol hydrochloride m.p. 259 - 260°. The remaining aqueous layer was

basified with aqueous ammonia and extracted with ether. The dried (anhyd. Na_2SO_4) extracts were evaporated to give a pale brown viscous oil (10.8 g.) which did not crystallise and showed two major spots on a thin-layer chromatography plate. Purification by chromatography on alumina (150 g.) using as eluants petroleum ether (b.p. 60 - 80°), diethyl ether, and acetone consecutively, gave a pale yellow oil which crystalli sed upon standing. Recrystallisation from petroleum ether (b.p. 60 - 80°) gave 3-[(2-hydroxyethyl)methylamino]-1-phenyl-1-p-tolyl-1-propanol (5 g.), m.p.83.0 - 83.5°, as colourless needles.

Analysis. Found: C, 76.4; H, 8.4; N, 4.8% equiv., 296. $C_{19}H_{25}NO_2$ requires C, 76.3; H, 8.4; N, 4.7%; equiv. 299.

Infra-red: $\bar{\nu}_{max.}$ (Base, film), 3350 (OH), 3000, 2900, 2800, 1460 - 1440, 1060 - 1020, 810 755 710 690 and 670 (C_6H_5, C_6H_4) $cm.^{-1}$

1-Cyclohexyl-3-[(2 hydroxyethyl)methylamino]-1-phenyl-1-propanol hydrochloride



.HCl (35)

Cyclohexyl chloride (3 ml.) was added to magnesium turnings (5.3 g.) in anhyd. ether (20 ml.). A crystal of iodine was added to

initiate the reaction and gentle heat was applied until 10 minutes after the iodine colour had disappeared. Further anhyd. ether (25 ml.) was added and stirring commenced, then a solution of cyclohexyl chloride (24 ml.) in anhyd. ether (45 ml.) was added over a period of 15 minutes. After stirring for a further 30 minutes, a solution of 3-[(2-hydroxyethylamino]propiophenone (2 g.) in anhyd. ether (20 ml.) was added dropwise, and heating under reflux continued for 24 hours. A small aliquot was taken, poured into a mixture of ice and hydrochloric acid, and washed with two portions of ether. The aqueous layer was made alkaline with concentrated aqueous ammonia and extracted exhaustively with ether. The ethereal extracts were dried (anhyd. $MgSO_4$) and evaporated to give a mobile golden oil. Infra-red spectroscopy indicated a high proportion of ketone in the product; the reaction was therefore allowed to proceed further by the addition of anhyd. xylene (50 ml.), and removal of the ether by distillation. Heating was continued for 40 hours, and the reaction was treated as before to give a pale brown oil. Treatment with ethanolic hydrogen chloride and subsequent recrystallisations from ethanol-ether gave 1-cyclohexyl-3-[(2-hydroxyethyl)methylamino]-1-phenyl-1-propanol hydrochloride, m.p. 168 - 168.5°.

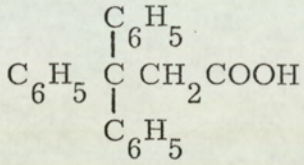
Analysis: Found: C, 65.8; H, 9.3; N, 4.5%; equiv., 330.

$C_{18}H_{30}ClNO_2$ requires C, 66.0; H, 9.2; N, 4.3%; equiv., 327.5.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3200 - 3100, 1170, 1085, 1000, 760 755 715 and 705 (C_6H_5) $cm.^{-1}$

[D.] PREPARATION OF A TRIPHENYALKYLAMINE

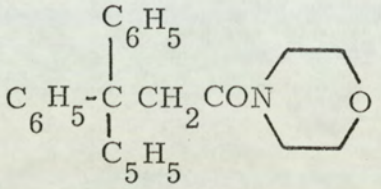
3,3,3-Triphenylpropionic acid



Triphenylcarbinol (2.0 g.) and malonic acid (8.0 g.) were mixed thoroughly, placed in a large tube and heated in an oil bath at 165 - 170°. When effervescence had ceased (0.75 hours) the molten product was dissolved in a hot aqueous solution of sodium carbonate and filtered while still warm. The cooled solution was treated with hydrochloric acid to give a voluminous precipitate which hardened on stirring. Recrystallisation from ethanol gave triphenyl propionic acid, m.p. 166 - 167° (2.1 g.). (Fosse 1931, quotes m.p. 177 - 178°).

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3400 (OH), 1710 (C = O), 1500, 1230, 750, 700 (C_6H_5) $cm.^{-1}$

N-(3, 3, 3-Triphenylpropionyl)morpholine



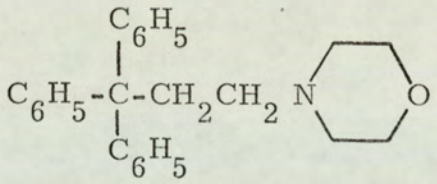
(41)

A mixture of triphenylpropionic acid (2.9 g.) and thionyl chloride (5 ml) was refluxed for 1 hour. Excess thionyl chloride was removed under reduced pressure and the residue dissolved in 1, 2-dimethoxyethane (20 ml.). A solution of morpholine (1 ml.) in 1, 2-dimethoxyethane (20 ml.) was added dropwise with vigorous stirring in the presence of anhyd. sodium carbonate (2 g.), the mixture refluxed with stirring for 15 minutes, then filtered whilst hot. The inorganic residue was further extracted with warm chloroform, and the combined filtrates evaporated to give a white amorphous solid which was redissolved in chloroform (80 ml.), and washed successively with 10% sodium carbonate solution (15 ml.), dilute hydrochloric acid (15 ml.) and water (15 ml.). The dried (anhyd. Na_2SO_4) chloroform layer was evaporated to give a white amorphous solid (3.6 g.) which was recrystallised from ethanol to give N-(3, 3, 3-triphenylpropionyl)morpholine, as white needles m.p. 187 - 188°.

Analysis Found: C, 80.8; H, 6.9; N, 3.7%. $C_{25}H_{25}NO_2$ requires C, 80.8; H, 6.7; N, 3.8%.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1635 (C = O), 1230, 1115, 1050, 1035, 775 705 695 (C_6H_5) $cm.^{-1}$

N-(3, 3, 3-Triphenylpropyl)-morpholine



(42)

A solution of N-(3, 3, 3-triphenylpropionyl)morpholine (6.0 g.) in anhyd. tetrahydrofuran (80 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (2.0 g.) in tetrahydrofuran (40 ml.). The mixture was stirred for 2 hours, then refluxed for a further 4 hours. 30% Sodium hydroxide solution was added dropwise, the organic layer separated, dried (anhyd. $MgSO_4$), and evaporated to give a white amorphous solid (5.7 g.) m.p. 162 - 166°. Recrystallisation from benzene-petroleum ether (b.p. 60 - 80°) gave N-(3, 3, 3-triphenylpropyl)morpholine, m.p. 166 - 168°. (Martensson and Nilsson, 1965, quote 165 - 167°). Treatment with ethanolic hydrogen chloride gave N-(3, 3, 3-triphenylpropyl)-morpholine hydrochloride m.p. 279 - 280°. (Martensson and Nilsson

quote m.p. 267 - 270°).

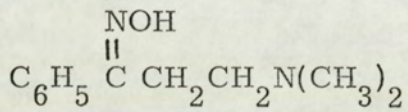
Analysis Found: C, 76.1; H, 7.0; N, 3.6%; equiv., 396.

$C_{25}H_{28}ClNO$ requires C, 76.2; H, 7.1; N, 3.6%; equiv., 394.

Infra-red: $\bar{\nu}_{max.}$ (base, Nujol), 1500 cm.$^{-1}$, 1115, 1010, 865, 770 - 750 and 710 - 690 (C_6H_5) cm.$^{-1}$

[E.] PREPARATION OF 3-DIALKYLAMINO-1-PHENYLPROPYLAMINE DERIVATIVES

3-Dimethylaminopropiophenone oxime

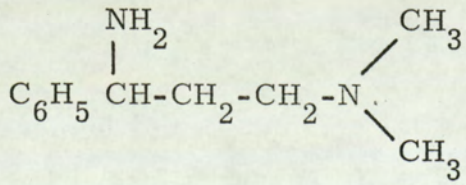


A solution of 3-dimethylaminopropiophenone hydrochloride (22 g.) and hydroxylamine hydrochloride (21 g.) in water (50 ml.) was made alkaline by the addition of a solution of sodium carbonate (20 g.) in water (50 ml.). The mixture was heated on a steam bath for 18 hours. On cooling, the crystalline cake was filtered off, washed with water and recrystallised from ethanol to give 3-dimethylaminopropiophenone oxime, m.p. 105°. Mannich and Heilner (1922) quote m.p. 108°.

Found: equiv. 196. $C_{11}H_{16}N_2O$ requires 192.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3150 (OH), 1615 (C = N); 1030, 960, 870, 770 700 (C_6H_5)cm.$^{-1}$

3-Dimethylamino-1-phenylpropylamine



(50)

3-Dimethylaminopropiophenone oxime (417 g.) in anhydrous

ethanol (4 l.) (Vogel p. 167) was heated to boiling. The source of heat was removed and sodium metal (500 g.) added in small lumps at a rate which maintained vigorous refluxing. When all the sodium metal had dissolved, the reaction mixture was cooled and water (5 l.) was added. About 6 litres of the ethanol-water mixture was removed under reduced pressure and the residue exhaustively extracted with ether. The dried (anhyd. Na_2SO_4) ethereal extracts were evaporated to give a pale golden oil which distilled at 106°/3mm. to give 3-dimethylamino-1-phenylpropylamine (240 g.). Terent'ev and Gusar (1965) quote b.p. 117°/8mm. A portion treated with ethanolic hydrogen chloride and recrystallised from ethanol-ether gave 3-dimethylamino-1-phenylpropylamine dihydrochloride, m.p. 243 - 244°.

Analysis (dihydrochloride) Found: C, 53.0; H, 8.0; N, 11.0%; equiv., 130. $C_{11}H_{20}Cl_2N_2$ requires C, 52.6; H, 8.0; N, 11.1%; equiv., 126.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3350 - 3150 (NH_2), 2950, 2750, 1600, 1460, 1040, 765 and 700 (C_6H_5); (dihydrochloride, Nujol), 2680, 2006 (N^+H), 1590, 1500, 765 and 695 (C_6H_5).

Attempted preparation of 1-dimethylallylamino-3-dimethylamino-1-phenylpropane dihydrochloride

(52)

(i) A mixture of 3-dimethylamino-1-phenylpropylamine (1.78 g.), dimethylallyl chloride (1.05 g.) and sodium hydrogen carbonate (1 g.) in xylene (12 ml.) was heated under reflux with stirring for 20 hours. The inorganic matter was filtered off and washed with ether. The filtrates were combined and extracted with 4N-hydrochloric acid (3 x 20 ml.). The extracts were basified with ether (3 x 50 ml.). The ethereal extracts were dried (anhyd. $MgSO_4$) and evaporated to give a brown mobile oil (1.9 g.). The infra-red spectrum gave the following peaks:-

$\tilde{\nu}_{max.}$ (film), 3250 (NH), 1665 (C=C), 1600 (C_6H_5) $cm.^{-1}$

Treatment of an ethereal solution of the oil with hydrogen chloride and crystallisation from ethanol-ether gave the starting material dihydrochloride, m.p. 235 - 240°. A further crystalline product could not be obtained from the mother liquor.

(ii) The experiment was repeated using dimethylformamide as solvent and heating under reflux with stirring for 24 hours. The inorganic matter was filtered off, washed with chloroform and the combined filtrates evaporated under reduced pressure. The residue was redissolved in ether and extracted in the usual manner to give a brown

oil (1.5 g.) with the following infra-red spectrum:-

$\bar{\nu}_{max.}$ (film), 3200 (NH), 1655 (C=C), 1445 and 695 (C_6H_5);

and the following n.m.r. spectrum:-

τ (CCl_4), 3.0 (s, 5H, C_6H_5), 4.9 (t, 1H, CH=C), 6.4 (t, 1H, NCH), 7.2 (m, 4H, CH_2N, NCH_2), 7.95 (s, 6H, $N(CH_3)_2$), 8.2 - 8.6 (m, 2H, CH_2), 8.4 (s, 6H, $C(CH_3)_2$), 8.6 (s, 1H, NH).

Treatment of an aliquot of the oil in ethereal solution with hydrogen chloride gave a hygroscopic gum which could not be crystallised.

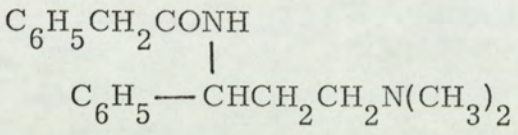
The oil gave two major spots on a t.l.c. plate, and was purified by column chromatography on alumina (50 g.) using petroleum ether (b.p. 60 - 80°) and diethyl ether as eluants to give the following fractions:-

Wt of crude oil applied, 1.55 g.

Fraction	Eluant	Volume of eluant (ml.)	Wt. solute (g.)	Aggregate wt. (g.)
(1)	Pet. ether (b.p. 60-80°)	20	0.393	0.393
(2)	"	"	0.319	0.712
(3)	"	"	0.132	0.844
(4)	"	"	0.208	0.052
(5)	"	40	0.206	1.258
(6)	"	50	0.013	1.271
(7)	"	"	0.012	1.283
(8)	Diethyl ether	"	0.247	1.530

The infra-red spectra of fractions (1) - (5) showed absorption at 3250 (NH), 1665 (C = C), 1460 and 700 (C_6H_5) cm.$^{-1}$ and was considered to be 1-dimethylallylamino-3-dimethylamino-1-phenylpropane. Treatment of fraction (2) in ethereal solution with hydrogen chloride and crystallisation from ethanol-ether gave an amorphous solid in very small yield m.p. 206 - 208°. Fraction (8) was considered to be mainly starting material.

3-Dimethylamino-1-phenyl-1-phenylacetamidopropane hydrochloride



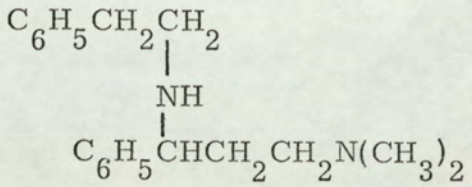
(54)

A solution of phenylacetyl chloride (10.0 g.) in benzene (100 ml.) was added dropwise to a stirred solution of 3-dimethylamino-1-phenylpropylamine (7.0 g.) in benzene (50 ml.) in the presence of sodium hydrogen carbonate (10.0 g.). The mixture was refluxed gently for 30 minutes, then poured into dilute aqueous ammonia (100 ml.). The benzene layer was removed and the aqueous layer extracted further with ether (3 x 30 ml.). The combined extracts were dried (anhyd. Na_2SO_4) to give a golden brown oil (7.0 g.) which crystallised from petroleum ether (b.p. 60 - 80°) to give colourless crystals, m.p. 81 - 83½. Treatment with ethanolic hydrogen chloride and recrystallisation from ethanol-ether gave 3-dimethylamino-1-phenyl-1-phenylacetamido propane hydrochloride m.p. 198 - 199°.

Analysis (hydrochloride). Found: C, 68.6; H, 7.6; N, 8.4%; equiv., (base), 300. $C_{19}H_{25}ClN_2O$ requires C, 68.6; H, 7.5; N, 8.4%; equiv. (base), 296.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3320 (NH), 1645 (amide I), 1545 (amide II), 1270, 780 740 and 700 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1-phenyl-1-(2-phenyl)ethylaminopropane dihydrochloride



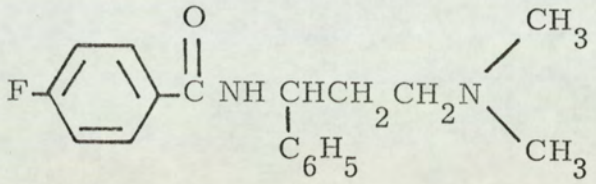
(55)

3-Dimethylamino-1-phenyl-1-phenylacetamidopropane hydrochloride (4.3 g.) was added in small portions to a stirred suspension of lithium aluminium hydride (1.5 g.) in anhyd. ether (200 ml.). The mixture was stirred with gentle heating for 18 hours. Water (1 ml.) was cautiously added to the ice-cold vigorously stirred mixture, followed by 30% sodium hydroxide solution (10 ml.). Water was again added dropwise until a clear supernatant ethereal layer was obtained, which was dried (anhyd. Na_2SO_4), filtered and evaporated to give a colourless oil. Treatment with ethanolic hydrogen chloride and recrystallisation from ethanol-ether gave 3-dimethylamino-1-phenyl-1-(2-phenyl)-ethylaminopropane dihydrochloride, m.p. 269 - 270°.

Analysis (dihydrochloride), Found: C, 63.8; H, 7.8; N, 7.8%; equiv., 178. $C_{19}H_{30}ClN_2$ requires C, 64.2; H, 7.8; N, 7.9%; equiv., 183.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 2920, 2800, 2750 (N^+H), 1455, 745 700 and 675 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1-(4'-fluorobenzamido)-1-phenylpropane



(53)

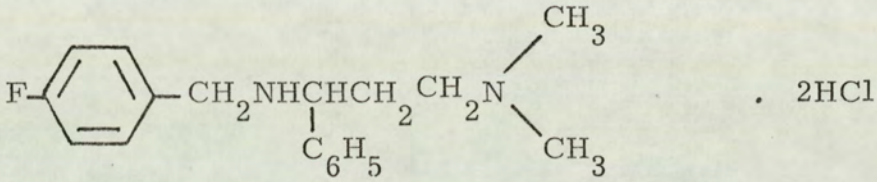
A solution of 4'-fluorobenzoyl chloride (8.0 g.) in 1,2-dimethoxyethane (20 ml.) was added dropwise to a stirred solution of 3-dimethylamino-1-phenylpropylamine (8.9 g.) in 1,2-dimethoxyethane (20 ml.) in the presence of sodium hydrogen carbonate (15 g.). The mixture was refluxed gently for 30 minutes then diluted with water (100 ml.) and extracted with chloroform (2 x 30 ml.). The dried (anhyd. Na_2SO_4) extracts on evaporation gave a pale yellow oil (11.5 g.) which crystallised from petroleum ether (b.p. 30 - 40°) as colourless prisms. Recrystallisation from petroleum ether (b.p. 80 - 100°) gave 3-dimethylamino-1-(4'-fluorobenzamido)-1-phenylpropane, m.p. 96 - 97°.

Analysis Found: C, 71.9; H, 7.1; N, 9.2%; equiv., 310 $C_{18}H_{21}FN_2O$ requires C, 72.0; H, 7.0; N, 9.2%; equiv., 300

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300, (NH), 1640 (amide I), 1605, 1560 (amide II), 1520, 1240, 1170, 870, 770, 710 and 680 (C_6H_5) $cm.^{-1}$

Two methods were used to prepare the following compound, one of which was successful.

3-Dimethylamino-1-(4'fluorobenzylamino)-1-phenylpropane dihydrochloride



(53)H

Method A

A mixture of 3-dimethylamino-1-phenylpropylamine (1.78 g.), 4-fluorobenzyl chloride (1.27 g.) and sodium carbonate (2 g.) in dimethylformamide (20 ml.) was heated under reflux with stirring for 24 hours. The inorganic matter was filtered off, washed with chloroform, and the combined filtrates evaporated under reduced pressure. The residue was redissolved in chloroform (80 ml.), washed with water (3 x 20 ml.), dried (anhyd. Na_2SO_4) and evaporated to give a pale yellow oil (1.5 g.). The infra-red spectrum showed the following peaks, $\bar{\nu}_{max.}$ (film), 3250 (NH), 1215 (C - N), 820 760 700 and 675 (C_6H_4 and C_6H_5) cm.$^{-1}$ Treatment of the oil in ethereal solution with hydrogen chloride gave a hygroscopic gum which could not be crystallised.

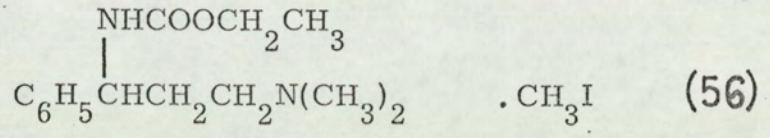
Method B

3-Dimethylamino-1-(4'-fluorobenzamido)-1-phenylpropane (5.7 g.) was added in small portions to a stirred suspension of lithium aluminium hydride (1.0 g.) in anhyd. ether (150 ml.). The mixture was gently heated under reflux with stirring for 18 hours and treated in a similar manner to the preparation of 3-dimethylamino-1-phenyl-1-(2-phenyl)ethylaminopropane dihydrochloride to give a colourless oil (5.4 g.). Treatment of the oil in ethereal solution with hydrogen chloride gave an amorphous hygroscopic solid which upon reprecipitation from ethanol-ether gave 3-dimethylamino-1-(4'fluorobenzylamino)-1-phenylpropane dihydrochloride, m.p. 160 - 161°.

Analysis (dihydrochloride) Found: C, 60.0; H, 6.9; N, 7.8%; equiv., 187. $C_{18}H_{24}ClFN_2$ requires C, 60.2; H, 7.0; N, 7.8% equiv., 180.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3270 (NH), 2900, 2780, 1510, 1215, 815, 760 700 and 675 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1-ethoxycarbonylamino-1-phenylpropane methiodide



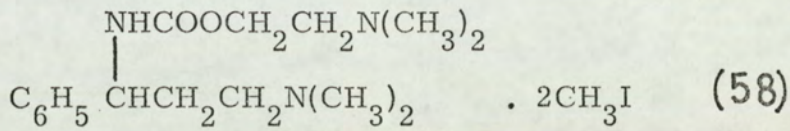
(56)

A solution of ethyl chloroformate (1 ml.) in acetone (10 ml.) was added dropwise to a vigorously stirred solution of 3-dimethylamino-1-phenylpropylamine (1.78 g.) in acetone (10 ml.) in the presence of sodium carbonate (2 g.). The mixture was refluxed for 15 minutes, cooled, filtered and the solvent removed to give a pale yellow oil (0.8 g.) b.p. 150 - 160°/3.5 mm. Treatment of an ethereal solution of the oil with methyl iodide and subsequent recrystallisation from ethanol-ether gave 3-dimethylamino-1-ethoxycarbonylamino-1-phenylpropane methiodide, m.p. 166 - 168°.

Analysis (methiodide); Found: C, 46.1; H, 6.4; N, 7.2%; equiv., 397. $C_{15}H_{25}IN_2O_2$ requires C, 45.9; H, 6.4; N, 7.1%; equiv., 392.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3350 (NH), 1710 - 1690 (C = O), 770, 700 and 680 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1-(dimethylaminoethoxycarbonylamino)-1-phenylpropane dimethiodide



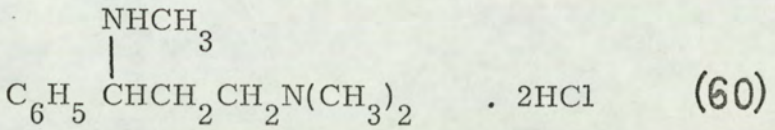
(58)

Sodium metal (0.1 g.) was dissolved in 2-dimethylaminoethanol (20 ml.). 3-Dimethylamino-1-ethoxycarbonylamino-1-phenylpropane (2.5 g.) was added and the reaction mixture placed in an open flask on the steam-bath for 18 hours. Most of the excess amino-alcohol was removed under reduced pressure, and the residue poured into water (ca. 30 ml.) and extracted with ether (3 x 30 ml.). The extracts were washed with water (2 x 10 ml.), dried (anhyd. Na_2SO_4), and evaporated to give a pale brown oil. Treatment of an ethereal solution of the oil with methyl iodide and subsequent recrystallisation from methanol-ethanol gave 3-dimethylamino-1-(dimethylaminoethoxycarbonylamino)-1-phenylpropane dimethiodide, m.p. 261 - 262°.

Analysis (dimethiodide); Found: C, 37.6; H, 5.5; N, 6.9%. $C_{18}H_{33}I_2N_3O_2$ requires C, 37.4; H, 5.7; N, 7.3%.

Infra-red: $\bar{\nu}_{max.}$ (base, film), 3250 (NH), 1690 (C = O), 700 and 680 (C_6H_5) $cm.^{-1}$

3-Dimethylamino-1-methylamino-1-phenylpropane dihydrochloride



(60)

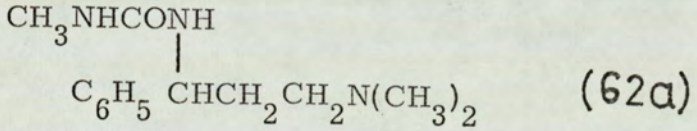
Formic acid (50 ml.) was added, with external cooling, to 3-dimethylamino-1-phenylpropylamine (8.9 g.). Acetic anhydride (16 ml.) was added dropwise, and the reaction mixture maintained at 50° for 18 hours. The mixture was basified with dilute sodium hydroxide solution and extracted with ether (3 x 40 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a pale yellow viscous oil (8.5 g.), b.p. 172°/3 mm.
An infra-red spectrum showed the following peaks: $\bar{\nu}_{max.}$ (film), 3250 (NH), 2920, 1670 (C = O), 1540, 1470, 1390, 785 and 700 (C_6H_5) cm.$^{-1}$ and the oil was considered to be 3-dimethylamino-1-formamido-1-phenylpropane. Treatment of an aliquot in ethereal solution with hydrogen chloride failed to yield a solid salt.

Impure 3-dimethylamino-1-formamido-1-phenylpropane (6.4 g.) in anhyd. ether (40 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (2.0 g.) in anhyd. ether (100 ml.). The mixture was refluxed with stirring for 18 hours and the complex decomposed with water and 30% sodium hydroxide solution. The

ethereal layer was dried (anhyd. Na_2SO_4) and evaporated to give a colourless oil (5.2 g.), which upon treatment in ethereal solution with hydrogen chloride and subsequent recrystallisation from ethanol-ether gave 3-dimethylamino-1-methylamino-1-phenylpropane dihydrochloride, m.p. 229 - 231°.

Analysis Found: C, 54.5; H, 8.4; N, 10.4%; equiv., 137. $C_{12}H_{22}Cl_2N_2$ requires: C, 54.4; H, 8.3; N, 10.6%; equiv., 133. Infra-red: $\bar{\nu}_{max.}$ (base, film), 3300 (NH), 2930, 2770, 1430, 700 and 680 (C_6H_5) cm.$^{-1}$

N-(3-Dimethylamino-1-phenylpropyl)-N'-methylurea

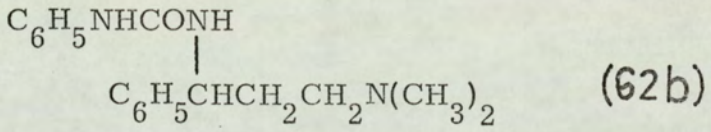


(62a)

A solution of methyl isocyanate (1.14 ml.) in anhyd. benzene (10 ml.) was added dropwise to an ice-cold stirred solution of 3-dimethylamino-1-phenylpropylamine (3.56 g.) in anhyd. benzene (10 ml.). The solvent was removed under reduced pressure on a steam bath to give a pale yellow oil which crystallised from petroleum-ether (b.p. 60 - 80°). Recrystallisation from acetone-ether gave N-(3-dimethylamino-1-phenylpropyl)-N'-methylurea (4.3 g.), m.p. 101 - 102°

Analysis Found: C, 66.3; H, 9.0; N, 17.8%; equiv., 234. $C_{13}H_{21}N_3O$ requires C, 66.4; H, 8.9; N, 17.9%; equiv., 235. Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3320 - 3250 (NH), 1630 (amide I), 1570 (amide II), 760 700 (C_6H_5) cm.$^{-1}$

N-(3-Dimethylamino-1-phenylpropyl)-N'-phenylurea

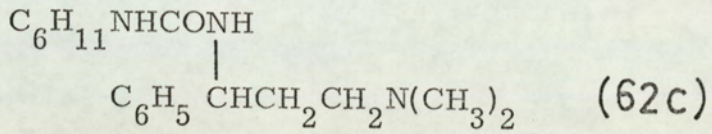


(62b)

A solution of phenyl isocyanate (3.57 g.) in anhyd. benzene (20 ml.) was added dropwise to an ice-cold stirred solution of 3-dimethylamino-1-phenylpropylamine (5.34 g.) in anhyd. benzene (20 ml.). The solvent was evaporated under reduced pressure on a steam bath to give a pale brown viscous oil which crystallised as long needles upon standing. Recrystallisation from acetone-ether gave N-(3-dimethylamino-1-phenylpropyl)-N'-phenylurea (7.8 g.), m.p. 100 - 101°.

Analysis Found: C, 72.6; H, 7.8; N, 14.0; equiv., 298. $C_{18}H_{23}N_3O$ requires C, 72.7; H, 7.7; N, 14.1%; equiv. 297. Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3350 (NH), 1650 (amide I), 1600, 1580 (amide II), 1320, 755 and 700 (C_6H_5) cm.$^{-1}$

N-Cyclohexyl-N'-(3-dimethylamino-1-phenylpropyl)urea



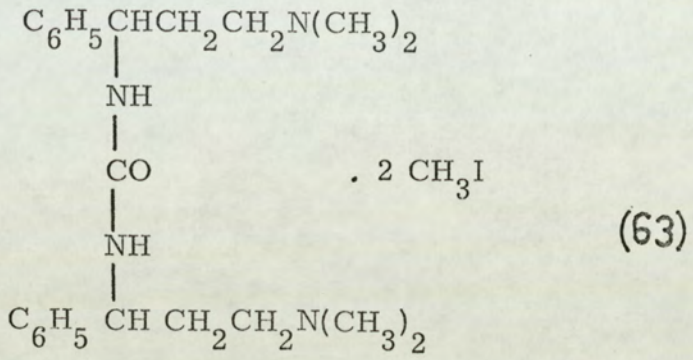
(62c)

A solution of cyclohexyl isocyanate (5.0 g.) in anhyd. benzene (20 ml.) was added dropwise to an ice-cold stirred solution of 3-dimethylamino-1-phenylpropylamine (7.12 g.) in anhyd. benzene (20 ml.). The solvent was evaporated under reduced pressure on a steam-bath to give a brown viscous oil which crystallised from acetone-ether to give N-cyclohexyl-N'-(3-dimethylamino-1-phenylpropyl)urea (9.6 g.), as colourless needles, m.p. 105 - 107°.

Analysis Found: C, 71.2; H, 9.7; N, 13.9%; equiv., 299. $C_{18}H_{29}N_3O$ requires C, 71.3; H, 9.6; N, 13.9%; equiv., 303.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 (NH), 1615 (amide I), 1570 (amide II), 750 and 700 (C_6H_5) $cm.^{-1}$

N,N'-Bis(3-dimethylamino-1-phenylpropyl)urea dimethiodide



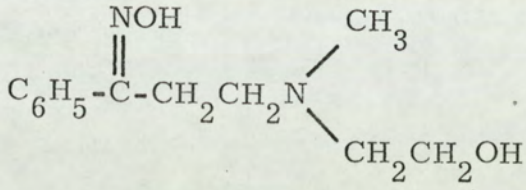
(63)

A 12½% w/v solution of phosgene in benzene (8.7 ml.) was added dropwise to a cooled, stirred suspension of 3-dimethylamino-1-phenylpropylamine (1.78 g.) in a solution of sodium hydroxide (0.4 g.) in water (3 ml.). The reaction mixture was stirred at room temperature for 1 hour and the benzene layer separated, and dried (anhyd. Na_2SO_4). Evaporation of the solvent gave a golden oil (1.9 g.). Treatment of an ethereal solution of the oil with hydrogen chloride gave a very deliquescent solid. The oil was characterised by formation of the methiodide, and recrystallisation from ethanol gave N,N'-Bis(3-dimethylamino-1-phenylpropyl)urea dimethiodide, m.p. 238 - 239°.

Analysis Found: C, 44.9; H, 6.0; N, 8.2%; equiv., 330. $C_{25}H_{40}I_2N_4O$ requires C, 45.0; H, 6.0; N, 8.4%; equiv., 333.

Infra-red: (base) $\bar{\nu}_{max.}$ (film), 3350 (NH), 1640 (amide I), 1560 (amideII), 765 and 705 (C_6H_5) $cm.^{-1}$

3-[(2-Hydroxyethyl)methylamino]propiophenone oxime



(64)

A solution of anhyd. sodium carbonate (2 g.) in water (5 ml.) was added slowly to a solution of 3-[(2-hydroxyethyl)methylamino]propiophenone hydrochloride (2.3 g.) in water (5 ml.). The mixture was maintained at about 50° for 18 hours on a steam bath. On cooling, the semi-crystalline mass was filtered off, washed with water, dried and recrystallised from petroleum ether (b.p. 60 - 80°) to give 3-[(2-hydroxyethyl)methylamino]propiophenone oxime (1.5 g.) m.p. 68 - 69°.

Analysis Found: C, 65.0; H, 8.1; N, 12.6%. $C_{12}H_{18}N_2O_2$ requires C, 64.9; H, 8.1; N, 12.6%.

Infra-red: $\bar{\nu}_{max.}$ (film), 3400 - 3200 (OH), 1635 (C = N), 1450, 1050, 770 and 700 (C_6H_5) $cm.^{-1}$

A portion treated with ethanolic hydrogen chloride and recrystallised from ethanol-ether gave 3-[(2-hydroxyethyl)methylamino]-propiophenone oxime hydrochloride, m.p. 149 - 152° (decomp.), equiv., 259. $C_{12}H_{19}ClN_2O_2$ requires equiv., 259.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3340 (OH), 3170 (OH), 2710 (N^+H), 1610 (C = N), 940, 770 755 715 and 695 (C_6H_5) $cm.^{-1}$

Attempted preparation of 3-[(2-hydroxyethyl)methylamino]-1-phenyl-propylamine (65)

a) A solution of 3-[(2-hydroxyethyl)methylamino]propiophenone hydrochloride (5 g.) and ammonium formate (5 g.) in dimethylformamide (15 ml.) was heated under reflux for 20 hours. Hydrochloric acid (10 ml.) in water (10 ml.) was added and heating continued for 1 hour. On cooling, the aqueous layer was washed with ether (3 x 50 ml.), basified with a 30% w/v aqueous solution of sodium hydroxide and extracted with chloroform (3 x 50 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a brown oil (2 g.). The infra-red spectrum was indicative of the starting material. No solid hydrochloride could be obtained.

b) A solution of 3-[(2-hydroxyethyl)methylamino]-propiophenone oxime (4 g.) in anhyd. ether (100 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (2 g.) in anhyd. ether (100 ml.). The mixture was heated under reflux for 4 hours then stirred at room temperature for 18 hours. The complex was decomposed with water and 30% sodium hydroxide, and the dried (anhyd. Na_2SO_4) ethereal extract evaporated to give an almost colourless oil (2.0 g.) which darkened upon standing. The infra-red

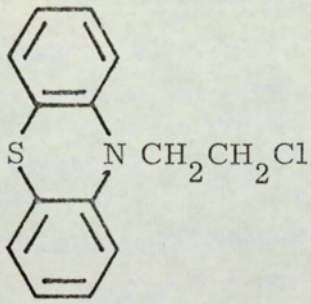
spectrum showed a broad band at 3400 - 3200 cm.$^{-1}$ (OH, NH_2). Treatment with ethanolic hydrogen chloride did not give a solid salt. The oil was not characterised.

c) Sodium Metal (2.75 g.) was added in small pieces to a refluxing solution of 3-[(2-hydroxyethyl)methylamino]-propiophenone oxime hydrochloride (2.6 g.) in anhyd. ethanol (20 ml.). When all the sodium had dissolved, the mixture was cooled, and water (25 ml.) added. The ethanol was distilled off under reduced pressure and the residue extracted with ether (3 x 50 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a pale yellow oil (1.5 g.), b.p. 140-160°/2mm. The infra-red spectrum of the distilled product showed a broad band at 3350 - 3150 cm.$^{-1}$ (OH and primary NH). Although thin layer chromatography indicated the presence of only one major constituent, the oil could not be crystallised, neither was any attempt at producing a solid hydrochloride, methiodide or picrate salt successful. The preparation of the mono-acetyl derivative was attempted by refluxing a portion of the oil (0.87 g.) in a mixture of hydrochloric acid (2 ml.) and acetic acid (8 ml.) for 20 minutes. The cooled reaction mixture was basified and extracted with ether. The dried (anhyd. Na_2SO_4) extracts were evaporated to give an oil (0.5 g.) which could not be induced to crystallise.

Infra-red: $\bar{\nu}_{max.}$ (film), 3350 - 3250 (primary NH), 2900, 1725 (ester C = O), 1235, 1020, 760 700 and 680 (C_6H_5) $cm.^{-1}$

Treatment with ethanolic hydrogen chloride did not produce a solid salt.

10-(2-Chloroethyl)phenothiazine

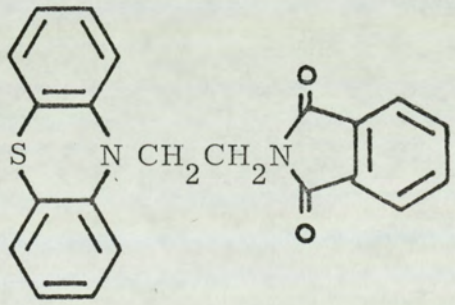


Lithium (4.26 g.), cut into small pieces was added to anhyd. ether contained in a suitably equipped flask under an atmosphere of dry nitrogen. After cooling to -25°, n-butyl bromide (7.5 ml.) was added and the mixture stirred for 15 minutes. A solution of n-butyl bromide (21 ml.) in ether (50 ml.) was added dropwise, the reaction mixture stirred for 2 hours, then allowed to reach room temperature. Phenothiazine (39.8 g.) was added in small portions and the solution stirred for 5 minutes. The

stream of nitrogen was discontinued, the solution cooled in an ice-bath and a solution of 2-chloroethyl-p-toluene sulphonate (46.9 g.) in ether (40 ml.) added dropwise during one hour. The reaction mixture was acidified with dilute hydrochloric acid and the ethereal layer washed several times with water. The dried (anhyd. Na_2SO_4) ethereal layer was evaporated to give a dark brown oil (51.0 g.). Recrystallisation from ethanol gave 10-(2-chloroethyl)phenothiazine as yellow needles m.p. 93-96°. Gilman and Shirley (1944) quote m.p. 97-98°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1590, 1570, 1330, 1255, 755 and 745 (C_6H_4)cm.$^{-1}$

10-(2-Phthalimidoethyl)phenothiazine



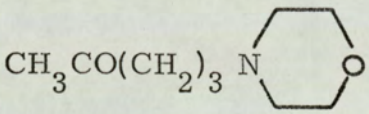
(66)

A mixture of 10-(2-chloroethyl)-phenothiazine (2.20 g.) and potassium phthalimide (1.54 g.) in dimethylformamide (25 ml.) was heated under reflux with stirring for 18 hours. The cooled reaction mixture was poured into water (100 ml.) and extracted with chloroform

(4 x 40 ml.). The chloroform extracts were washed with water (2 x 20 ml.), dried (anhyd. Na_2SO_4) and evaporated to give a pale brown oil which crystallised upon standing. Recrystallisation from acetone gave 10-(2-phthalimidoethyl)phenothiazine (1.85 g.), m.p. 175 - 177°. Societe des Usines Chimiques Rhone-Poulenc (1955) quote 173 - 174°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1760 and 1700 (C = O), 1400, 1360, 1140, 1020, 780 745 737 and 715 (C_6H_4) $cm.^{-1}$

5-(4-Morpholino)pentan-2-one



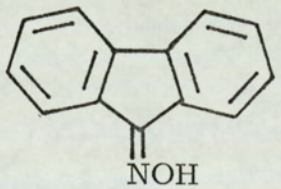
(76)

A mixture of 5-chloro-pentan-2-one (12.0 g.) and morpholine (17.4 g.) in xylene (40 ml.) was heated under reflux for 2.5 hours. On cooling, the supernatant liquor was removed and evaporated to give a brown oil, which was dissolved in dilute hydrochloric acid and washed with ether. The aqueous layer was basified with aqueous ammonia and extracted with ether. The dried (anhyd. $MgSO_4$) ethereal extracts were evaporated to give 5-(4-morpholino)-pentan-2-one (8.1 g.) as a golden oil.

Infra-red: $\bar{\nu}_{max.}$ (film), 2950 - 2800, 1715 (C = O), 1365, 1140 and 1120 $cm.^{-1}$

A mixture of the above product (1 ml.), semicarbazide hydrochloride (1 g.), and sodium acetate (0.9 g.) in 95% ethanol (5 ml.) was heated under reflux for 1 hour. The reaction mixture was diluted with water (20 ml.) and extracted with methylene chloride (3 x 20 ml.). The dried (anhyd. $MgSO_4$) extracts were evaporated to give a solid residue which was recrystallised from tetrahydrofuran-petroleum ether (b.p. 80 - 100°) to give 5-(4-morpholino)pentan-2-one semicarbazone m.p. 143 - 145°. Cruickshank and Sheehan (1961) quote m.p. 145 - 146°.

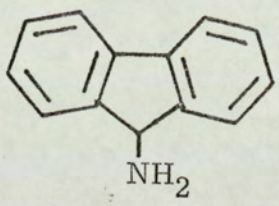
9-Fluorenone oxime



A solution of sodium hydrogen carbonate (6.3 g.) in water (20 ml.) was added to a solution of hydroxylamine hydrochloride (3.5 g.) in water (10 ml.) and the mixture added immediately to a stirred solution of 9-fluorenone (9.0 g.) in dioxan. After heating

under reflux for 5 hours, the solvents were removed under reduced pressure to give a yellow solid which was redissolved in hot ethanol, filtered, and crystallised to give 9-fluorenone oxime (8.0 g.) m.p. 192 - 194°. Schmidt and Soll (1907), quote m.p. 193 - 194°. Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 - 3100 (OH), 1640 (weak C = N), 1000, 935, 780 and 730 (C_6H_4)cm.$^{-1}$

9-Aminofluorene



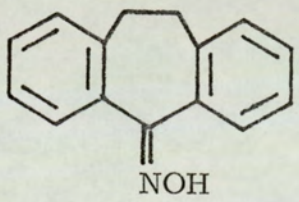
(78)

Zinc dust (7.0 g.) was added in small portions to a stirred solution of 9-fluorenone oxime (4.0 g.) in acetic acid (26.7 ml.) and water (1.3 ml.), at a rate which maintained gentle boiling. The reaction was heated under reflux for a further hour, then water (40 ml.) was added. The mixture was filtered and the residue extracted with hot 5% acetic acid (20 ml.). The combined filtrates on cooling gave a small yield of aceto-9-fluorenamide which was filtered off. Addition of an equal volume of hydrochloric acid to the filtrate and storage at 0° for 18 hours gave 9-aminofluorene hydrochloride as white

fibrous needles. The precipitate was removed, washed with cold hydrochloric acid, basified with aqueous ammonia and extracted with chloroform. The dried (anhyd. Na_2SO_4) extracts were evaporated to give a white solid which was recrystallised from benzene-petroleum ether (b.p. 60 - 80°) to give 9-aminofluorene (4.3 g.), m.p. 60 - 62°. Ingold and Wilson (1933), quote m.p. 62 - 63°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3300 - 3150 (NH_2), 940, 760 and 730 (C_6H_4)cm.$^{-1}$

10, 11-Dihydro-5H-dibenzo[a, d]cyclohepten-5-one oxime

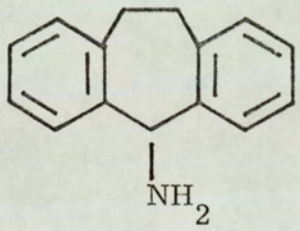


A solution of 10, 11-dihydro-5H-dibenzo-[a, d]cyclohepten-5-one (15 g.) and hydroxylamine hydrochloride (15 g.) in pyridine (200 ml.) was heated under reflux for 24 hours. The bulk of the pyridine was removed under reduced pressure and the residue poured into water and extracted with ether (3 x 80 ml.). The ethereal extracts were washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water respectively. The dried (anhyd. $MgSO_4$) extracts were

evaporated to give a white solid (14g.). Recrystallisation from benzene-petroleum ether (b.p. 60 - 80°), gave 10,11-dihydrodibenzo[a,d]cyclohepten-5-one oxime m.p. 167 - 169° undepressed on admixture with an authentic sample.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3200 (OH), 1000, 930, 770 740 and 710 (C_6H_4)cm.$^{-1}$

5-Amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

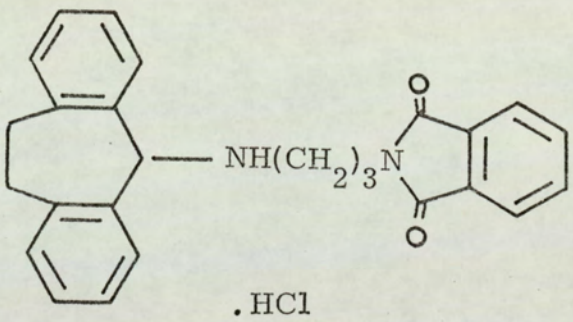


(73)

Sodium (12 g.) was added in small portions over 1.5 hours to a refluxing solution of 10,11-dihydro-5Hdibenzo[a,d]-cyclohepten-5-one oxime (2.0 g.) in anhyd. ethanol (100 ml.). When all the sodium had dissolved, water (300 ml.) was added and the mixture extracted with ether. The dried (anhyd. Na_2SO_4) extracts were evaporated to give a white solid (1.7 g.). Recrystallisation from ethanol gave 5-Amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene m.p. 90 - 92°. Monro et al.(1963) quote m.p. 91 - 93°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3350 - 3280 (NH_2), 1350, 1050, 960, 935, 810 775 750 and 720 (C_6H_4) $cm.^{-1}$

10, 11-Dihydro-5-(3-phthalimidopropylamino)-5H-dibenzo[a, d] cycloheptene hydrochloride



A mixture of 5-amino-10, 11-dihydro-5H-dibenzo[a, d] cycloheptene (1.04 g.), 3-bromopropylphthalimide (1.34 g.) and sodium hydrogen carbonate (1.0 g.) in ethanol (20 ml.) was heated under reflux with stirring for 24 hours. The reaction mixture was poured into water (80 ml.), made more alkaline with aqueous ammonia (1.0 ml.) and extracted with ether (3 x 50 ml.). The dried (anhyd. $MgSO_4$) extracts were evaporated to give a pale yellow oil which upon treatment with ethanolic hydrogen chloride and

recrystallisation from ethanol-ether gave 10,11-dihydro-5-(3-phthalimidopropylamino)-5H-dibenzo[a,d]cycloheptene hydrochloride (1.05 g.), m.p. 210 - 211°.

Analysis Found: C, 72.4; H, 5.9; N, 6.4%; equiv., 429. $C_{26}H_{25}ClN_2O_2$ requires C, 72.1; H, 5.8; N, 6.5%; equiv. 432.5.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 2700 - 2600 (N^+H), 1765 and 1710 (C = O); 1400, 1315, 1140, 1035, 950, 770 750 and 720 (C_6H_5)cm.$^{-1}$

Attempted preparation of 2-(9-fluorenylamino)-5-(4-morpholino)-butane dihydrochloride.

A solution of 9-aminofluorene hydrochloride (2.17 g.) and 5-morpholinopentan-2-one hydrochloride (2.08 g.) in ethanol (30 ml.) was shaken with hydrogen (6 atmos.) at 80° in the presence of Adams catalyst. After 6 hours the catalyst was filtered off and the solvent evaporated to give the starting materials.

Attempted preparation of 10,11-dihydro-5H-5-[1-methyl-4-(4-morpholino)-propylamino]-dibenzo[a,d]cycloheptene.

A solution of 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene hydrochloride (2.45 g.) and 5-morpholinopentan-2-one hydrochloride

(2.08 g.) in ethanol (40 ml.) to which ethanolic hydrogen chloride (10 ml.) had been added, was shaken with hydrogen (6 atmos.) at 80° in the presence of Adams catalyst. After 48 hours the catalyst was filtered off and the solvent evaporated to give the starting materials.

Methods used for the preparation of a ketimine from cyclohexylamine and 3-dimethylaminopropiophenone.

(i) A solution of cyclohexylamine (6.0 g.) and 3-dimethylamino-propiophenone (4.0 g.) in benzene (100 ml.) was heated under reflux beneath a Dean-Stark water separator for 24 hours. Removal of the solvent and excess cyclohexylamine under reduced pressure gave a mobile straw-coloured oil. The infra-red spectrum showed that it was mainly starting material, for the ratio of the 1680 : 1630 $cm.^{-1}$ peaks was 4 : 1.

(ii) The experiment was repeated using xylene as the solvent and heating under reflux for 40 hours after which time 1 ml. of water had collected. The mixture was treated in the usual manner to give an oil with 1680 : 1630 $cm.^{-1}$ peak absorbance ratio of 0.7 : 1.

(iii) A solution of titanium tetrachloride (1.9 g.) in dry xylene (10 ml.) was added dropwise to a vigorously stirred solution of 3-dimethyl-aminopropiophenone (5.3 g.) and cyclohexylamine (10.0 g.) in dry

xylene (50 ml.). The mixture was heated under reflux for 1 hour, a slight excess of water added, and the inorganic matter filtered off and washed with ether. The combined filtrates were dried (anhyd. $MgSO_4$) and evaporated under reduced pressure to give a viscous brown oil with a 1680 : 1630 $cm.^{-1}$ absorbance ratio of 0.8 : 1.

(iv) A solution of titanium tetrachloride (1.25 ml.) in anhyd. ether was added dropwise to a stirred solution of 3-dimethylamino-propiophenone (5.3 g.) and cyclohexylamine (20.0 g.) in anhyd. ether (100 ml.). The ether was replaced with dry benzene (200 ml.) and heated under reflux for 18 hours. An aliquot was treated with sodium hydrogen carbonate solution and extracted with ether. The dried extracts were evaporated under reduced pressure to give an oil with a 1680 : 1630 $cm.^{-1}$ absorbance ratio of 1 : 5. The solvent in the remainder of the reaction was replaced by dry xylene (150 ml.) and the mixture heated under reflux for a further 3 hours. The reaction was treated in a similar manner to give an oil in which no carbonyl group could be detected.

Infra-red: $\bar{\nu}_{max.}$ (film), 2940, 2870, 1635, 1455, 1280, 900, 765, 705 and 700 $cm.^{-1}$

N.m.r.: τ (CCl_4), 2.7 (m, 5H, C_6H_5), 6.3 - 7.8 (m, 5H), 8.0 - 9.0 (m, 22H, 2 x C_6H_{11}). The compound was considered to be 3-cyclohexylamino-1-cyclohexylimino-1-phenylpropane.

1,3-dicyclohexylamino-1-phenylpropane dihydrochloride

(91) $C_6H_5CH(NHC_6H_{11})CH_2CH_2NHC_6H_{11}$ .2HCl

A solution of impure 3-cyclohexylamino-1-cyclohexylimino-1-phenylpropane (7.5 g.) in ethanol (30 ml.) was shaken with hydrogen (1 atmos.) in the presence of palladium on carbon (1.0 g.). After the theoretical quantity of hydrogen had been absorbed, the catalyst was filtered off and the solvent evaporated to give a pale yellow oil (6.7 g.).

Infra-red: $\bar{\nu}_{max.}$ (film), 3300 (NH), 2950, 2850, 1460, 1130, 900, 760, 700.

N.m.r.: τ, (CCl_4), 2.8 (m, 5H, C_6H_5), 6.2 (t, 1H, CH), 7.2 - 8.0 (m, 6H), 8.0 - 9.2 (m, 22H, 2 x C_6H_{11}).

Found: Equiv., 158; $C_{21}H_{34}N_2$ requires equiv., 157.

An ethereal solution of the oil was treated with hydrogen chloride. Recrystallisation from methanol gave 1,3-dicyclohexylamino-1-phenylpropane dihydrochloride, m.p. 301°, solvated with one mole of methanol.

Analysis Found: C, 64.1; H, 9.5; N, 6.9%; equiv., 210.

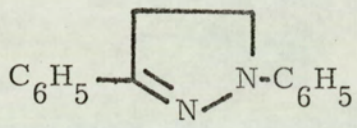
$C_{21}H_{36}N_2Cl_2CH_3OH$ requires C, 63.0; H, 9.5; N, 6.7%; equiv., 209.5.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3430 (OH, solvated), 1585 (C_6H_5), 1290,

1055, 755 and 705 (C_6H_5) cm.$^{-1}$

N.m.r. : τ (D_2O), 2.4 (s, 5H, C_6H_5), 6.2 - 7.8 (m, 7H), 7.8 - 9.4 (m, 22H, 2 x C_6H_{11}).

1,3-Diphenyl-2-pyrazoline



(95)

(a) A solution of 3-dimethylaminopropiophenone (4.0 g.) and phenylhydrazine (5 ml.) in ethanol (15 ml.) was heated on a steam bath for 30 minutes. On cooling, yellow plates were deposited which were recrystallised from ethanol to give 1,3-diphenyl-2-pyrazoline (3.2 g.), m.p. 155 - 155.5° (Auwers, 1932 quotes m.p. 158°, [152°]).

Solutions in ether and benzene showed a blue fluorescence.

Analysis Found: C, 81.0; H, 6.5; N, 12.7%.

$C_{15}H_{14}N_2$ requires C, 81.1; H, 6.3; N, 12.6%.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1590 - 1580 (C = N, C_6H_5), 1505, 1495, 1130, 755 740 685 and 660 (C_6H_5) cm.$^{-1}$

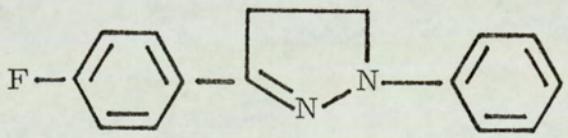
(b) A solution of 3-[(2-hydroxyethyl)methylamino]propiophenone (5 g.) and phenylhydrazine (5 ml.) in ethanol (20 ml.) was heated under reflux for 30 minutes. On cooling, yellow crystals were obtained which were recrystallised from ethanol to give 1,3-diphenyl-2-pyrazoline (3.7 g.), m.p. 154 - 155°, undepressed by admixture of an authentic sample, and having an identical infra-red spectrum.

Analysis Found: C, 81.0; H, 6.3; N, 12.7%

$C_{15}H_{14}N_2$ requires: C, 81.1; H, 6.3; N, 12.6%.

The compound did not titrate in non-aqueous media.

3-(4'Fluorophenyl)-1-phenyl-2-pyrazoline



(95a)

A mixture of 3-chloro-4'fluoropropiophenone (7.44 g.) and phenylhydrazine (1.0 ml.) in pyridine (15 ml.) was heated under reflux for 2 hours. The reaction mixture was poured into water (200 ml.) and the yellow solid which separated was filtered off, washed with water and recrystallised to give 3-(4'-fluorophenyl)-1-phenyl-2-pyrazoline

(9.9 g.) as pale yellow plates, m.p. 139 - 141°.

Analysis Found: C, 75.2; H, 5.6; N, 11.8%.

$C_{15}H_{13}FN_2$ requires: C, 75.0; H, 5.4; N, 11.7%.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1600 (C = N, C_6H_5), 1225, 1210, 840 750 and 690 (C_6H_4), (C_6H_5) $cm.^{-1}$

Attempted reduction of 1,3-diphenylpyrazoline.

(a) Sodium (10 g.) was added in small pieces to a refluxing solution of 1,3-diphenylpyrazoline (1.0 g.) in anhyd. ethanol (80 ml.). When all the sodium had dissolved, water (100 ml.) was added and the ethanol removed under reduced pressure. The residue was extracted with chloroform (3 x 40 ml.), dried (anhyd. Na_2SO_4) and evaporated to give the starting material (0.9 g.) m.p. 150 - 152°, undepressed on mixing with an authentic sample.

(b) A solution of sodium borohydride (0.10 g.) in 0.2N. aqueous sodium hydroxide solution (2 ml.) was added to a solution of 1,3-diphenylpyrazoline (0.22 g.) in methanol (40 ml.) and stirred at room temperature for 18 hours. The reaction mixture was acidified with dilute acetic acid to decompose excess hydride then excess 10% sodium hydroxide solution was added to deposit the starting material (0.13 g.).

(c) 1,3-Diphenylpyrazoline (2.5 g.) was added to a stirred suspension of lithium aluminium hydride (0.5 g.) in anhyd. ether (100 ml.). The mixture was heated under reflux for 3 hours and stirred at room temperature for 18 hours. Water and 30% sodium hydroxide was added and the dried (anhyd. Na_2SO_4) ethereal extract evaporated to give the starting material (1.5 g.).

(d) 1,3-Diphenylpyrazoline (2.5 g.) was added to a stirred suspension of lithium aluminium hydride (0.5 g.) in anhyd. tetrahydrofuran (50 ml.). The mixture was refluxed for 18 hours and treated with water and sodium hydroxide to give the starting material (1.1 g.).

(e) A solution of 1,3-diphenylpyrazoline (0.22 g.) in warm cyclohexane (50 ml.) was added to a suspension of reduced Adams catalyst (0.1 g.) in methanol (10 ml.) and shaken with hydrogen (1 atmos.) at room temperature for 20 hours. After negligible uptake of hydrogen, the catalyst was removed and the solvents evaporated to give the starting material (0.17 g.).

(f) A solution of 1,3-diphenylpyrazoline (0.22 g.) in acetic acid (20 ml.) was added to a suspension of reduced Adams catalyst (0.1 g.) in acetic acid (5 ml.) and shaken with hydrogen (4 atmos.) at room temperature for 80 hours. The catalyst was filtered off, and the solvent reduced in volume, basified with dilute aqueous ammonia, and

extracted with ether (3 x 50 ml.). The dried (anhyd. Na_2SO_4) extracts were evaporated to give a brown oil (0.15 g.) the infra-red spectrum of which showed peaks at 3350, 3250, 1600, 1500, 745 and 690 cm.$^{-1}$ suggesting a primary amine. Thin layer chromatography showed at least five major spots, and attempts to obtain a solid hydrochloride from the mixture were unsuccessful.

Two attempted preparations of O-benzyl-3-dimethylaminopropiophenone oxime.

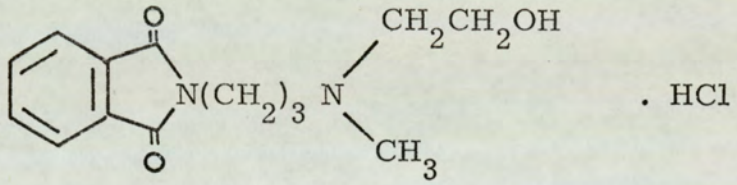
[A] 3-Dimethylaminopropiophenone oxime (2.0 g.) was added to a stirred solution of sodium (0.25 g.) in methanol (20 ml.). Benzyl chloride (5 ml.) was added and the mixture heated under reflux for 12 hours. Water (20 ml.) was added and the methanol removed under reduced pressure. The residue was acidified with dilute hydrochloric acid, washed with ether and basified with aqueous ammonia. The base was extracted with ether and evaporated to give a mobile golden oil which crystallised from petroleum ether (b.p. 60 - 80°) to give the starting material (1.3 g.), m.p. 103 - 106° undepressed on admixture with an authentic sample.

[B] 3-Dimethylaminopropiophenone oxime (5.0 g.) was added to a stirred suspension of sodamide (2.0 g.) in xylene (20 ml.). Benzyl

chloride (5 ml.) was added and the mixture heated under reflux for 1.5 hours. Water (20 ml.) was added, and the organic layer separated, dried, and evaporated under reduced pressure to give a viscous brown oil. Crystallisation from petroleum ether (b.p. 60 - 80°) gave 3-phenyl-2-isoxazoline (1.3 g.), m.p. 64 - 67°. Auwers and Muller (1933) quote m.p. 66 - 67°.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 1345, 920, 880, 845, 750, and 685 cm.$^{-1}$

3-[(2-Hydroxyethyl)methylamino]-1-phthalimidopropane hydrochloride



A mixture of 2-methylaminoethanol (7.5 g.), 3-bromopropylthalimide (2.68 g.), and sodium hydrogen carbonate (1.0 g.) in ethanol (30 ml.) was heated under reflux with stirring for 24 hours. The reaction mixture was poured into water (200 ml.), made more alkaline with aqueous ammonia (2 ml.) and extracted with ether (3 x 50 ml.). The dried (anhyd. $MgSO_4$) extracts were evaporated to give a colourless oil (1.5 g.), which upon treatment with ethanolic hydrogen chloride and subsequent recrystallisation from ethanol-ether gave

3-[(2-hydroxyethyl)methylamino]-1-phthalimidopropane hydrochloride

m.p. 154 - 155°.

Analysis Found: C, 55.9; H, 6.4; N, 9.6%; equiv., 305.

$C_{14}H_{19}ClN_2O_3$ requires C, 56.3; H, 6.4; N, 9.8%; equiv., 298.5.

Infra-red: $\bar{\nu}_{max.}$ (Nujol), 3400 - 3200 (OH), 2700 - 2400 (N^+H), 1765, 1710 - 1680 (C = O), 1300, 1185, 1070, 1035, 780 and 710 (C_6H_4) $cm.^{-1}$

1 - ANTIVIRAL RESULTS

Some of the results obtained from an antiviral screen are shown in tables III and IV. Compounds were tested by an in vitro method against Influenza PR8 (an RNA virus) and Vaccinia (a DNA virus). Whilst it is difficult to draw any positive conclusions with regard to structure-activity from these results it is interesting to note that the saturation of one of the phenyl groups of compound 11a greatly enhances its antiviral activity. However a similar cyclohexyl-phenyl structure with a slightly longer carbon chain and morpholino as the terminal amino group is devoid of activity. The results would seem to indicate that the activity is not solely dependant on a particular structural moiety but on some other parameters associated with the molecule as a whole.

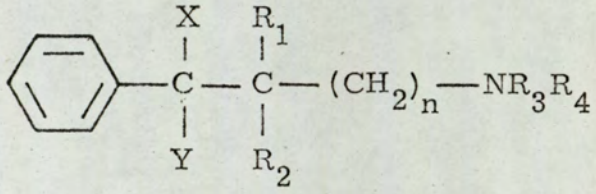
TABLE III

Compound No.	Page	PR8	Vaccinia
11a	24; 86	+	+
11d	24;27;87		+
12a	26;91	0	0
12b	26;92	+++	++
22	34;95	+	+++
34	40;107	++	+
41	43;115	0	+
42	44;116	0	0
64	58;135	+	+
66	59,139		0
73	65;144	++	+
78	67,142	0	0

KEY

0 - inactive
+ - slightly active
++ - moderately active
+++ - most active

TABLE IV



Compound No.	X	Y	R_1	R_2	n	NR_3R_4	PR8	Vaccinia
-	CN	C_6H_5	H	H	2	dimethylamino	+	++
-	CN	C_6H_5	H	CH_3	1	piperidino	+	++
-	CN	C_6H_5	H	H	0	dimethylamino		0
11a	H	C_6H_5	H	H	2	dimethylamino	+	0
11d	H	C_6H_5	CH_3	CH_3	1	dimethylamino		+
12a	H	C_6H_{11}	H	H	1	morpholino	0	0
12b	H	C_6H_{11}	H	H	2	dimethylamino	+++	++
-	OH	o-$CH_3 \cdot C_6H_4$	H	H	1	morpholino	+	++
34	OH	C_6H_5	H	H	1	hydroxyethylmethylamino	++	+

II - PHARMACOLOGICAL RESULTS

In addition to the screen for antiviral activity some of the compounds synthesised were tested in mice for potential CNS activity. The following test procedures were adopted, the results of which are shown in tables V to VIII.

(a) Convulsant activity

Activity in this test is indicative of general CNS stimulation, thus compounds such as amphetamine sulphate would be active. Anoxia also produces convulsions due to the stimulant action of carbon dioxide on the CNS.

Symbols used : 0 inactive
C convulsant
CA convulsant of anoxic origin

(b) Behavioural test.

This test is based upon visual observation of the animals following administration of the test compound. The following behavioural states were noted :

\- sedation
0 normal behaviour
\+ excitation

(c) Locomotor activity.

Similar to test (b) above; the animals being placed in an

activity cage.

Symbols used	:	−	decreased activity
		0	normal activity
		+	increased activity

(d) Rectal temperature.

Symbols used	:	−	hypothermia
		0	no effect
		+	hyperthermia

Tests (b-d) indicate whether the test compound is a CNS stimulant or depressant. Thus the psychomotor stimulants of the amphetamine type increase locomotor activity and produce hyperthermia, while CNS depressants such as chlorpromazine, chlordiazepoxide and hexobarbitone produce sedation and hypothermia.

(e) Writhing test.

The intraperitoneal injection of acetic acid elicits a characteristic writhing response in the mouse which can be abolished by even weak analgesics. To test for analgesic activity, a dose of the compound is given followed about 20 minutes later by an intraperitoneal injection of acetic acid. The number of writhes is recorded and the degree of protection calculated :

$$\% \text{ protection} = 100 - \left(\frac{\text{Experimental}}{\text{control}} \times 100\right)$$

Symbols used in tables V - VIII :

0	no protective effect
+	slight protective effect ($\leqslant 25\%$)
++	medium protective effect ($\leqslant 50\%$)
+++	protective effect ($>50\%$)

The compounds were given at three doses :

'1 dose' indicates the highest dose active

'2 doses' indicates the high and medium dose active

'3 doses' indicates the lowest dose also active

The disadvantage of this test is its lack of specificity. Not only analgesics but also other drugs such as antihistaminics, parasympathomimetics, sympathomimetics, CNS stimulants and adrenergic blocking drugs inhibit writhing. Chlorpromazine and imipramine are in fact effective in doses less than those that depress the CNS, so that in this test they would be recorded as

Imipramine	+++	(3 doses)
Chlorpromazine	+++	(3 doses)
Chlordiazepoxide	+++	(1 dose)
Hexobarbitone	+++	(1 dose)

(f) Pupil diameter.

Pupil diameter reflects the general effect of the drug on the autonomic nervous system. Such activity in a CNS acting drug would be regarded as a side effect in clinical use. Enlargement indicates either a sympathomimetic effect as in the case of amphetamine, or a parasympatholytic effect such as can be seen to a small extent by imipramine. A small pupil may indicate possible muscarinic action.

Symbols used :

0	$\leqslant$ 0.5 mm.
+	0.5 - 1.0 mm.
++	1.0 - 1.5 mm.
+++	$>$ 1.5 mm.

(g) Reserpine induced ptosis.

It is believed that reserpine depletes the stores of catecholamines in the brain leading to a state of depression which, in the rat, manifests as a passive closure of the upper eyelid (ptosis). The ability of a drug to give protection from this effect gives a good indication of anti-depressant activity. Both monoamine-oxidase inhibitors and thymoleptics with other modes of action are active in this test.

The results were assessed as :

0	no protective effect
+	slight protective effect
++	medium protective effect
+++	protective effect

(h) Weight.

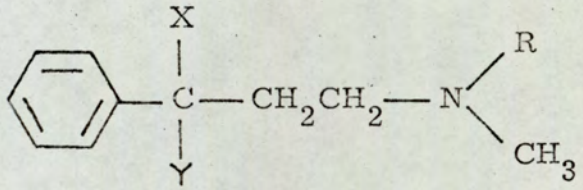
Animals were weighed before administration of the drug and again 24 hours later. A loss in weight can be attributed either to a toxic effect or to a true anorexic effect such as is found in amphetamine and other sympathomimetics.

Symbols used	:	0	no weight change
		–	weight loss

TABLE V

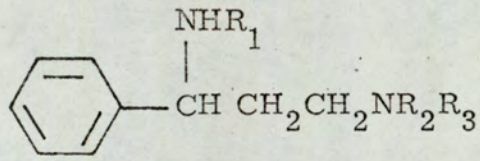
COMPOUND No.	PAGE NO.	CONVULSANT ACTIVITY	BEHAVIOUR	LOCOMOTOR ACTIVITY	RECTAL TEMP	WRITHING TEST	PUPIL DIAMETER	RESERPINE PTOSIS	WEIGHT CHANGE
22	34 95	C	0	0	-	+	+	0	0 or -
30	40 105	C	0	+	+	+++ 1 dose	+++	+++ 1 dose	No test
32	40 103	CA	0	0	0	0	0	0	0
33	40 104	C	+	+	+	+++ 2 doses	+++	++ 1 dose	No test
34	40 107	C	+	+	0	+++ 3 doses	+++	+++ 1 dose	-
41	43 115	0	0	0	0	++	0	+	0
42	44 116	0	+	+	0	++	+	0	-
53H	52 126	C	0	0	-	+++ 3 doses	+	0	0
53	52 125	CA	0 or -	0	-	+++ 1 dose	++	++ 1 dose	-
54	52 123	CA	-	-	-	+++ 3 doses	+++	++	0
55	53 124	CA	-	0	-	0	++	0	0
60	56 130	0	0 or -	0	-	++ 1 dose	0	0	0
62b	57 132	0	-	-	0	+++ 2 doses	+++	0	No test
64	58 135	0	0	0	0	+	0	+	0
91	78 149	CA	0	0	0	+++ 1 dose	0	0	0
95	81 150	0	0	-	0	+	0	0	0
95a	81 151	0	0 or -	0	0	0	0	0	0

TABLE VI



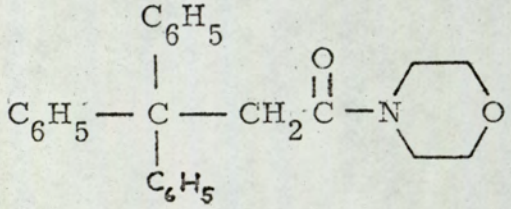
COMPOUND No.	X	Y	R	CONVULSANT ACTIVITY	BEHAVIOUR	LOCOMOTOR ACTIVITY	RECTAL TEMP	WRITHING TEST	PUPIL DIAMETER	RESERPINE PTOSIS	WEIGHT CHANGE
22	carbonyl	-	CH_2CH_2OH	C	0	0	-	+	+	0	0 or -
30	n-butyl	OH	CH_3	C	0	+	+	+++ 1 dose	+++	+++ 1 dose	No test
32	CH_3	OH	CH_2CH_2OH	CA	0	0	0	0	0	0	0
33	n-butyl	OH	CH_2CH_2OH	C	+	+	+	+++ 2 doses	+++	++ 1 dose	No test
34	C_6H_5	OH	CH_2CH_2OH	C	+	+	0	+++ 3 doses	+++	+++ 1 dose	-
64	oxime	-	CH_2CH_2OH	0	0	0	0	+	0	+	0

TABLE VII

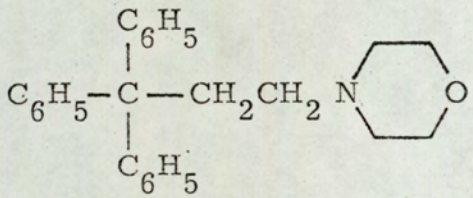


COMPOUND No.	R_1	NR_2R_3	CONVULSANT ACTIVITY	BEHAVIOUR	LOCOMOTOR ACTIVITY	RECTAL TEMP	WRITHING TEST	PUPIL DIAMETER	RESERPINE PTOSIS	WEIGHT CHANGE
53	$CO.C_6H_4.F$	dimethylamino	CA	0 or -	0	-	+++ 1 dose	++	++ 1 dose	-
53H	$CH_2.C_6H_4F$	dimethylamino	C	0	0	-	+++ 3 doses	+	0	0
54	$CO.CH_2.C_6H_5$	dimethylamino	CA	-	-	-	+++ 3 doses	+++	++	0
55	$CH_2.CH_2.C_6H_5$	dimethylamino	CA	-	0	-	0	++	0	0
60	CH_3	dimethylamino	0	0 or -	0	-	++ 1 dose	0	0	0
62b	$CO.NH.C_6H_5$	dimethylamino	0	-	-	0	+++ 2 doses	+++	0	No test
91	C_6H_{11}	NHC_6H_{11}	CA	0	0	0	+++ 1 dose	0	0	0

TABLE VIII



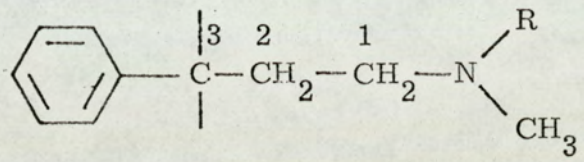
(41)



(42)

Compound No.	Convulsant Activity	Behaviour	Locomotor Activity	Rectal Temp	Writhing Test	Pupil Diameter	Reserpine Ptosis	Weight Change
41	0	0	0	0	++	0	+	0
42	0	+	+	0	++	+	0	-

III - STRUCTURE-ACTIVITY RELATIONSHIPS



(i) Substitution of the tertiary alcohol group on carbon atom 3 by an amino moiety would appear to change the spectrum of activity from CNS stimulant to CNS depressant.

(ii) In the tertiary alcohol series (table VI) it would appear that a bulky group, either aliphatic or aromatic, on carbon atom 3 is necessary for optimum CNS stimulant activity. Substitution by a methyl group abolishes any activity.

(iii) Substitution of the methyl substituent of the amino group by hydroxyethyl showed a slight enhancement in activity in these tests.

The most active compound in this series (compound 34) shows CNS stimulant and antidepressant activity. It is active in the writhing test and is possibly a sympathomimetic and anorexigenic.

(iv) In the propanediamine series (table VII) most of the compounds exhibit CNS depressant activity and are also active in the writhing test.

However, replacement of the dimethylamino group by a secondary amino one lost this activity.

(v) The size of the secondary amino substituent R_1 does not seem to affect the depressant activity for both compounds with methyl and phenethyl groups in this position have similar activity. However, in general the amides would appear to be slightly more active depressants and also exert a greater atropine-like effect.

APPENDIX

Melting-points

All quoted melting-points are uncorrected.

Elemental analyses

Elemental analyses were carried out by Alfred Bernhardt, Mulheim, W. Germany.

Determination of equivalent weights

The equivalent weights of bases were determined by titration with 0.02 N perchloric acid in acetic acid using Oracet Blue B as indicator. Titration of hydrochloride salts was performed in a similar manner in the presence of mercuric acetate.

Infra-red absorption spectra

Infra-red spectra were recorded on a Unicam S. P. 200 spectrophotometer.

N. M. R. spectra

N. M. R. spectra were recorded on a Varian A60A analytical spectrometer using trimethylsilane as internal standard.

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