THE SYNTHESIS, STEREOCHEMISTRY, AND ANTIMICROBIAL PROPERTIES OF SOME SUBSTITUTED CYCLOHEXANE DERIVATIVES AND RELATED ACYCLIC ANALOGUES

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfilment of the Requirements

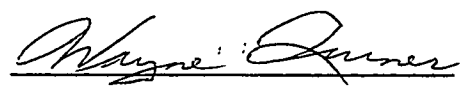
for the Degree of

Master of Science

in the College of Pharmacy

University of Saskatchewan

by



Wayne Arnold Turner

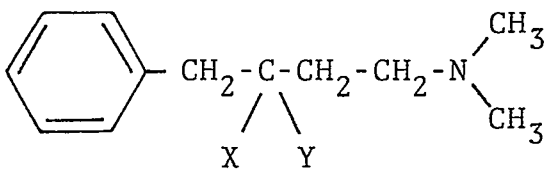
Saskatoon, Saskatchewan

September, 1970

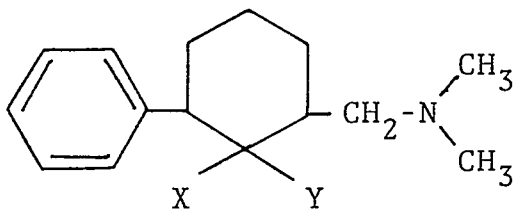
SUMMARY

This thesis consists of the synthesis of two β-amino ketones, a class of compounds known to possess a wide range of pharmacological properties, and also an investigation into the stereochemistry and antimicrobial properties of certain ketone derivatives which have been synthesized.

Two series of compounds, (A) and (B), were prepared to examine the relationship between chemical structure and antimicrobial activity. Comparison of their antimicrobial properties should indicate whether flexibility or rigidity is favored for optimum biological activity in these compounds.



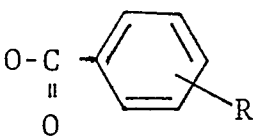
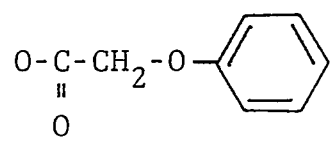
(A)

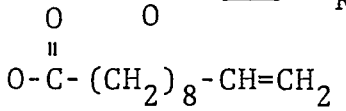


(B)

a) X = Y = O

b) X = H

Y = OH,  ,  ,



R = H, 3-Cl, 4-Cl, 4-OCH_3, 4-NO_2, 3,5-$(NO_2)_2$

It was considered that if the alcohols were biologically active, then utilization of the concept of latentiation may yield compounds with enhanced potency. Esterification would enable the alcohols to be released at different rates. In the case of the cyclic alcohol (Series B, X=H, Y=OH) two geometrical isomers are possible and a comparison of the antimicrobial activity of these compounds and the related esters may give information regarding the stereochemical requirements for high activity.

A comparison of the antimicrobial activities of the compounds in series (A) and (B) indicates that the flexible analogues (A) generally have greater activity than the rigid analogues (B). This suggests that compounds in series (A) do not favour the limiting conformations represented by series (B) for high antimicrobial activity.

Since screening results are not available for both geometrical isomers of the alcohol or for the esters of series (B), it is not possible at this stage to state whether one stereochemistry is favoured over the other in producing greater antimicrobial activity.

On the basis of present screening results some conclusions may be made as follows:

1. Both of the ketones show activity as antimicrobial agents.
2. All of the alcohols screened to date are inactive as antimicrobial agents.
3. The presence of chlorine atoms in the 3- and 4-position of the aromatic ring of the esters in series (A) and in

the 3-position of the aromatic ring of the ester in series (B) give a high level of activity.

ACKNOWLEDGEMENTS

The author wishes to thank his Associate Professor, Dr. Jonathon R. Dimmock, for his suggestion of the project, aid and criticism during the course of the investigation, and his assistance during the preparation of the manuscript. The author would also like to thank the Medical Research Council of Canada for the award of two Studentships, and Smith Kline and French Laboratories, Philadelphia, U.S.A., for carrying out the antimicrobial testing.

To

Sandra

Without whose love and understanding
this could not have been.

TABLE OF CONTENTS

LIST OF TABLES

I. THE AIMS OF THE PRESENT INVESTIGATION

1.1 Flexibility and rigidity of drug molecules

It is generally considered that drug molecules become associated at receptor surfaces by the alignment of active sites of the receptor with complementary functions of the molecule. A fixed distance between active sites requires a corresponding specific disposition of complementary groups on the molecule if effective drug-receptor site interaction is to occur.

Most effective drug adsorption would be anticipated for rigid molecules in which the distance between functions important for adsorption at the receptor surface is identical with, or does not deviate greatly from, that of the distance between the complementary active sites on the surface. A rigid molecule that does not possess the correct molecular dimensions cannot, however, associate at the receptor surface under any circumstances since it has little or no capacity for changing to a more favourable shape.

In contrast, a less rigid molecule is capable of adopting a wide range of conformations, one of which may possess molecular dimensions that enable the molecule to fit the receptor surface, even if this particular conformation does not correspond to that which is of lowest energy under ordinary conditions.

Thus examination of structure-activity relationships should yield information relevent to an understanding of the binding sites of the receptor. In the absence of evidence

concerning the conformation of receptor-bound molecules, analysis of structure-activity relationships in terms of the relative geometry of binding sites becomes uncertain.

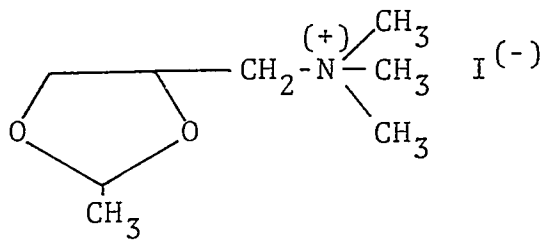
A partial solution to this problem may be obtained through the use of conformationally rigid analogs of active molecules where the distances between potentially important binding groups are fixed.

Flexibility favoured

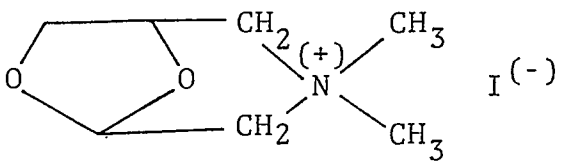
A number of workers have used this approach in attempts to define more precisely the structure of the cholinergic receptor. May and Triggle (1968) designed semirigid and rigid analogs of acetylcholine in an attempt to meet the requirements of minimum conformational flexibility without the incorporation of additional potential binding groups. They synthesized and investigated the cholinomimetic activity of two bicyclic compounds (2) and (3) which are related to cis-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (1) whose high muscarinic activity was first reported by Triggle and Belleau (1962). There is a close structural resemblance of (1) to both acetylcholine and muscarine.

The bicyclic analogs, (2) and (3), were found to have negligible activities at both muscarinic and nicotinic receptors. This clearly suggests that (1), and by analogy, acetylcholine, acetyl-β-methyl-choline, and muscarine, do not adopt, when bound at the muscarinic receptor, any of the limiting conformations represented by (2) and (3). Whether this is related to the inactivity of (2) and (3) remains to be

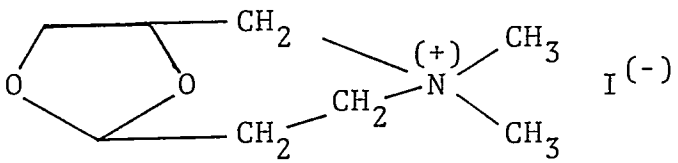
established through the synthesis of further bicyclic analogs of this type.



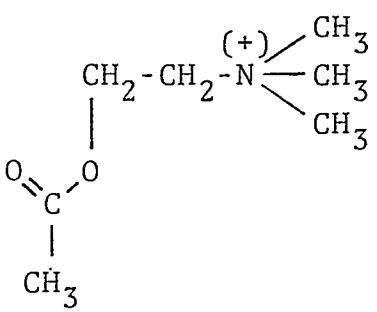
(1)



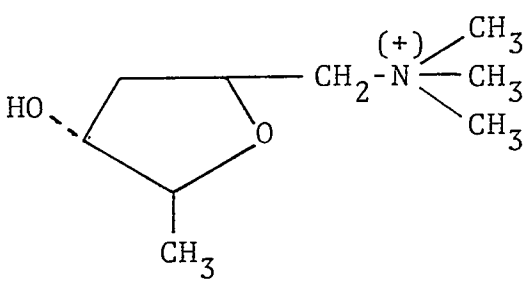
(2)



(3)

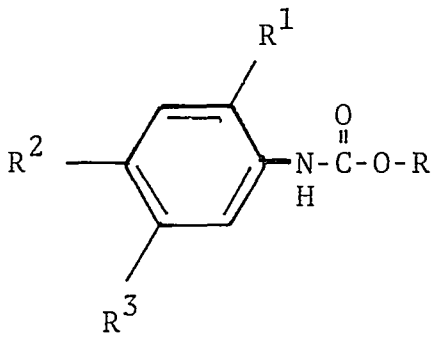


Acetylcholine

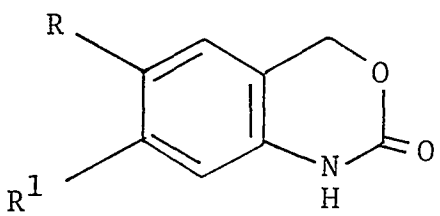


Muscarine

A series of linear carbamates (4) and cyclic carbamates (5) were prepared and investigated by Boots (1969) as inhibitors of the Hill reaction in isolated chloroplasts. These were chosen to investigate the conformational requirements of the carbamate group during binding to the receptor. The cyclic compounds were inactive while the linear carbamates exhibited activity. An effort was made to keep the electronic and hydrophobic bonding effects constant so that the inhibition would be a function of the molecular geometry of the inhibitor.



(4)



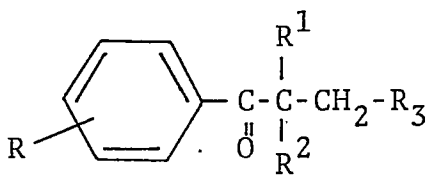
(5)

a) $R=CH_3$; $R^1=R^2=H$; $R^3=Cl$
b) $R=CH_3$; $R^1=R^3=H$; $R^2=Cl$
c) $R=R^1=CH_3$; $R^2=H$; $R^3=Cl$
d) $R=R^1=CH_3$; $R^2=Cl$; $R^3=H$

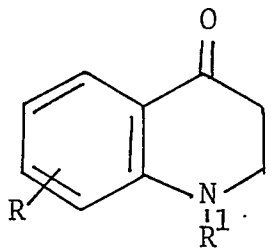
a) $R=H$; $R^1=H$
b) $R=Cl$; $R^1=H$
c) $R=H$; $R^1=Cl$

Atwal et al. (1969) synthesized a series of β-aminopropiophenones (6) which may be considered as open-chain analogs of the 2,3-dihydro-4-quinolones (7) which are known to possess analgesic activity. It was hoped that these β-aminopropiophenones might achieve a better fit on the

analgesic receptor site than the quinolones which possess a rigid ring system. These compounds contain the ketone function, the benzene ring, and the amino group which are also present in the active 2,3-dihydro-4-quinolones, but because of free rotation, the amino group can assume any number of spatial relationships with respect to the carbonyl group and the benzene ring. The importance of these groups to analgesic activity was established by evaluating the analgesic activity of a number of compounds analogous to the 2,3-dihydro-4-quinolones (7) but lacking in each case one of the groups which was assumed to be necessary for analgesic activity.



(6)



(7)

a) R=4-OCH_3; R^1=R^2=H; R^3=$N(CH_3)_2$

b) R=4-OCH_3; R^1=R^2=H; R^3=$N(CH_2)_5$

c) R=4-OCH_3; R^1=R^2=H; R^3=$NHCH_2C_6H_5$

d) R=2-OH; R^1=R^2=H; R^3=NHC_2H_5

a) R=7-OCH_3; R^1=H

b) R=H; R^1=CH_3

c) R=8-OCH_3; R^1=CH_3

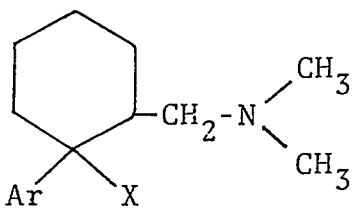
d) R=7-OCH_3; R^1=CH_3

A number of the open-chain β-amino ketones (6) were found to possess analgesic activity considerably greater than the 2,3-dihydro-4-quinolones (7). This gives credence to the hypothesis that the rigid ring systems of the 2,3-dihydro-quinolones do not permit an optimal fit on a receptor site.

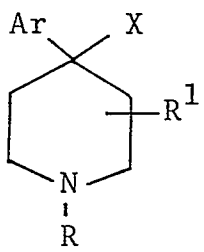
Rigidity favoured

The previous examples all illustrate cases where flexibility gives higher biological activity than the corresponding rigid compounds. In other instances, a rigid molecule possesses higher activity than a corresponding flexible molecule.

As part of a study of the relation of molecular rigidity to pharmacological activity, Casy et al. (1964) synthesized compounds (8) representing less rigid analogs of 4-aryl-piperidinols and related compounds (9), many of which possess marked pharmacological properties. Comparison of structures (8) and (9) indicates that in both series the basic nitrogen atom and the carbon bearing the substituents Ar and X are separated by two carbon atoms. However the series (8) allows for greater variation in this intergrouping distance as a consequence of free rotation about the bonds of the basic side-chain.



(8)



(9)

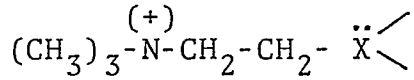
X=OH, OCOR

Ar=aryl

$R=R^1$=Alkyl

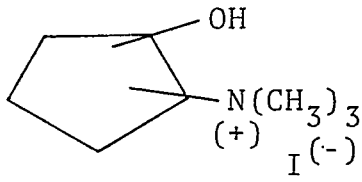
The less rigid analogs which were screened for analgesic, anti-amphetamine, and anti-reserpine activity were all inactive.

Friess and co-workers (Friess and Baldridge, 1956; Friess and McCarville, 1954) established that the structural features required for one class of potent inhibitors of acetylcholinesterase was the unit (10) in which X represents a locus of high electron density, e.g. tertiary nitrogen or halogen atom.

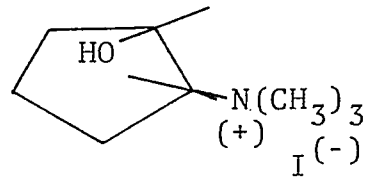


(10)

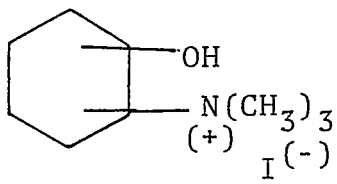
In an attempt to obtain more precise information concerning the distance between the two important sites, they used substrates and inhibitors with known distances between the important functional groups. The substituents on the planar cyclopentane ring are at fixed distances, and the nitrogen-oxygen distances can be calculated accurately in compounds (11) and (12). In the corresponding six-membered ring system (13) and (14), the various conformations of ring and substituents lead to uncertainty in group distances. The cis-alcohols (11) and (13) were better inhibitors of acetylcholinesterase than the corresponding trans-isomers (12) and (14) or acetylcholine itself. Thus the distance between the oxygen and nitrogen atoms in the cis-isomers is more favourable for attack by acetylcholinesterase than the trans-isomers or by acetylcholine itself.



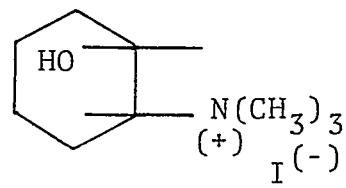
(11)



(12)

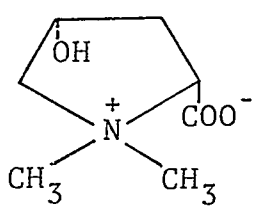


(13)

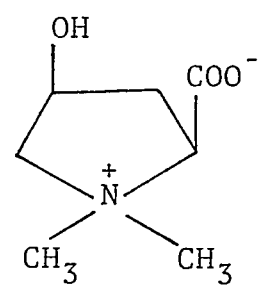


(14)

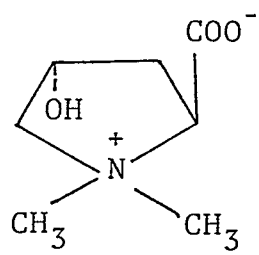
The inhibition of acetylcholinesterase by the betaine amino alcohols (15), (16), and (17) indicates that the relative spatial orientation of the carboxylate ion and hydroxyl group is important for inhibition. (Friess et al., 1957). When trans to one another as in (17) some inhibition occurs, while in the cis-compounds (15) and (16) no inhibition was observed even at concentrations 100 times higher.



(15)



(16)

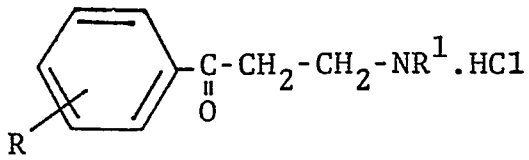


(17)

1.2 Pharmacological activities of β-amino ketones and related compounds

Recorded in the literature are numerous β-amino ketones, prepared for pharmacological testing as antispasmodics, analgesics, local anesthetics, and antibacterial agents.

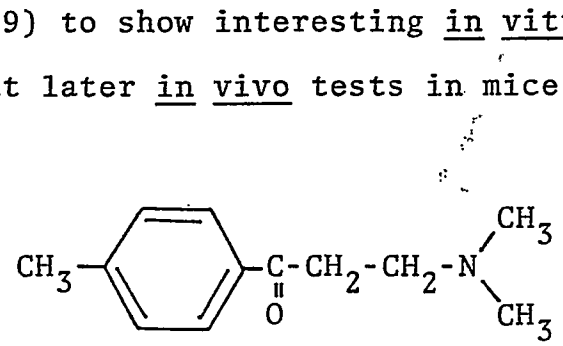
Taylor and Nobles (1960) prepared Mannich bases of the general structure (18). Several of these compounds demonstrated *in vitro* activity against various organisms, but none was promising in the *in vivo* tests.



(18) R=4-F , 4-I, 4-Cl, 4-OCH_3, 2-OH

NR^1=$N(CH_3)_2$, $N(Bu)_2$, $N(CH_2)_5$

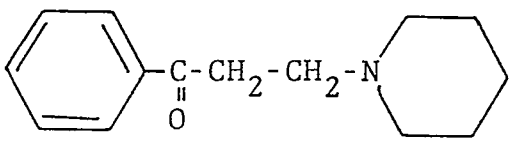
Nobles and Burckhalter (1958) tested a number of β-amino ketones for chemotherapeutic activity and found compound (19) to show interesting *in vitro* antituberculous activity but later *in vivo* tests in mice were negative.



(19)

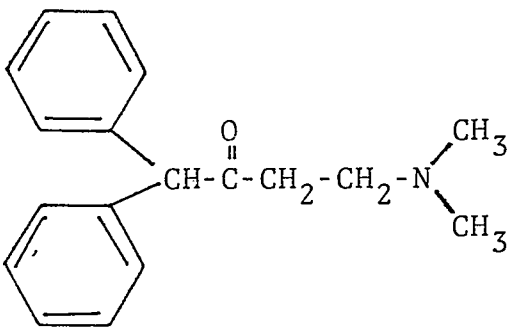
Many other Mannich bases have been reported to show *in vitro* antimicrobial activity, but no *in vivo* activity.

Mannich and Lammering (1922) prepared a series of β-amino ketones and found that β-N-piperidinoethyl phenyl ketone (20) possessed local anesthetic activity.

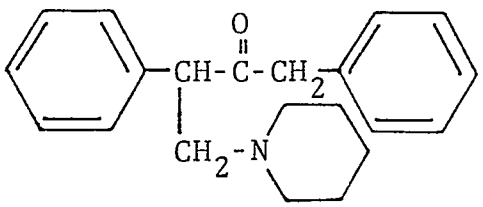


(20)

Wilson and Kyi (1952) showed that compounds of structure (21) and (22) were found to be from four to five times as active as procaine as local anesthetics. They were devoid of analgesic activity.

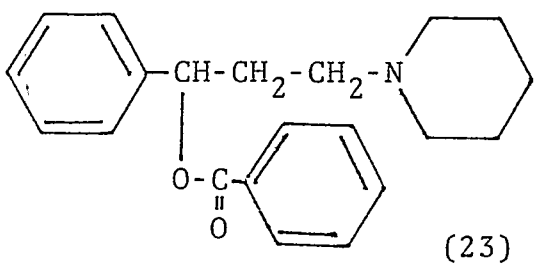


(21)

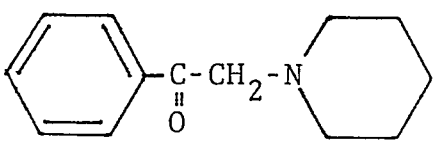


(22)

Furthermore Blicke and Blake (1930) had shown that the benzoyl ester of the corresponding secondary carbinol (23) was a strong local anesthetic, as well as the lower homolog of (20), N-piperidinomethyl phenyl ketone (24).

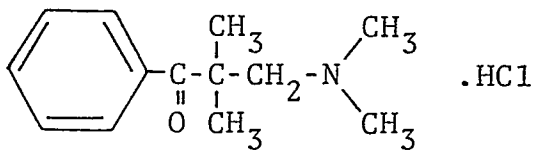


(23)



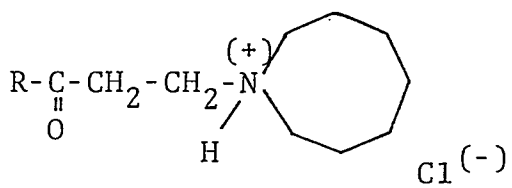
(24)

Atwal and co-workers (1969) tested a series of β-amino-propiophenones for analgesic activity and found several to possess significant analgesic activity. Compound (25) was the most potent compound prepared in this study, with an ED_{50} approximately twice that of morphine sulphate when determined under similar conditions.

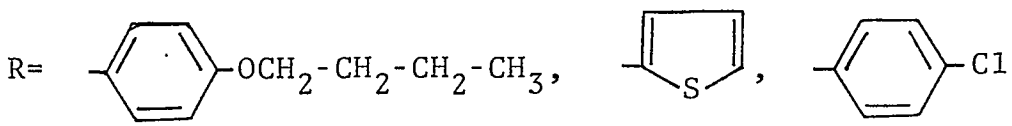


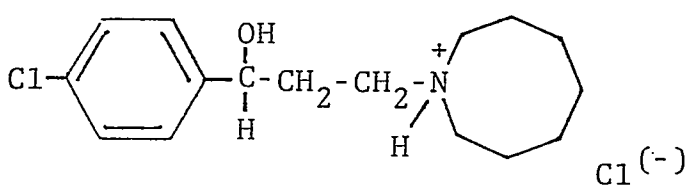
(25)

Luts and Nobles (1965) prepared derivatives of (26) and investigated their pharmacological activity. The 4-butoxyphenyl analog had anti-convulsant properties while the thiophene analog produced significant analgesia. The 4-chlorophenyl compound of the ketone had no analgesic activity, but the corresponding alcohol (27) exhibited good analgesic activity.



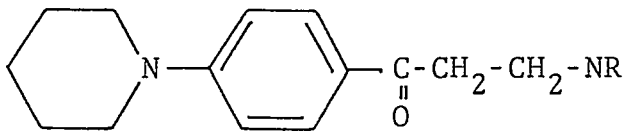
(26)



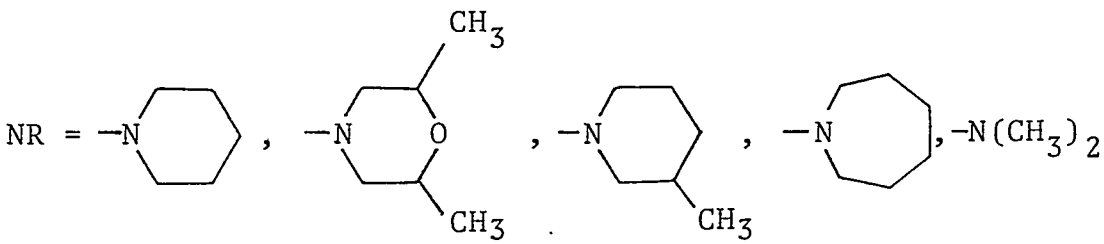


(27)

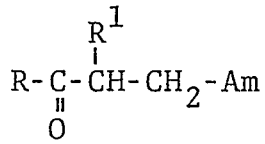
Varma et al. (1970) prepared a series of β-amino ketones (28) derived from 4-piperidinoacetophenone to investigate in vitro inhibition of respiration. They found that all the β-amino ketones prepared inhibited the oxidation of pyruvic acid, and noted the significance of the cyclic amine moiety in the inhibitory effects.



(28)



Denton et al. (1949a) showed that various β-amino ketones of the following general formula (29) have antispasmodic activity.



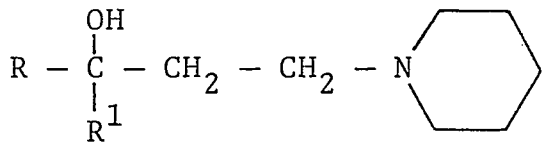
(29)

R = aryl or heterocyclic

R^1 = hydrogen or phenyl

Am = substituted amino group

Denton et al. (1949b) have shown that some tertiary alcohols (30) prepared by the addition of a Grignard reagent to β-amino ketones exhibited greater antispasmodic activity than the parent ketone from which they were derived. Introduction of simple substituents into the 4-position of the phenyl group fails to enhance the biological activity.

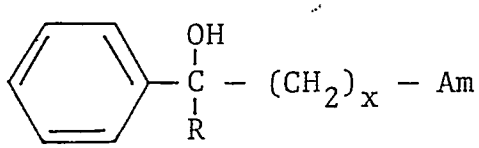


(30)

R = substituted aromatic (4-BrC_6H_4, 4-ClC_6H_4, 4-$CH_3C_6H_4$, etc.)

R^1 = alkyl (C_2H_5, n-C_4H_9)

In further experiments to determine the effect of chemical structure on the antispasmodic activity of compounds of this type, Denton and Lawson (1950) studied the lower and higher homologs of (30), namely compounds possessing the general formula (31) where x = 1 and 3. Various quaternary salts of the γ-amino alcohols, where x = 2, were also studied.



R = C_2H_5, C_6H_5

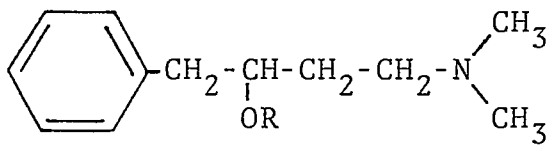
X = 1, 2, 3

Am = $N(C_2H_5)_2$, $N(CH_2)_5$

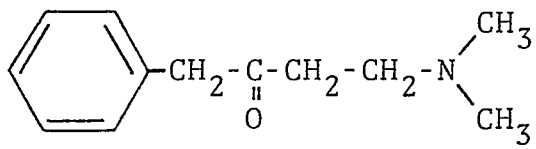
(31)

The lower homologs, where x=1, were less active than the higher homologs, where x=3, which in turn were less active than the alcohols where x=2. Thus, in this type of compound, the greatest antispasmodic activity resulted from a 1,3-relation of the hydroxyl and substituted amino group. They found no consistent relationship between the activity of quaternary salts and the corresponding hydrochlorides of series (31).

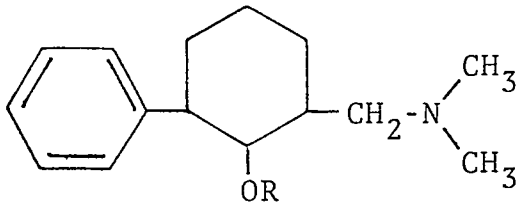
In the present investigation it was decided to prepare a series of compounds (32) derived from the acyclic β-amino ketone (33) and examine the antimicrobial activity of these compounds against nineteen species of bacteria and fungi. It was hoped that some relationship between chemical structure and antimicrobial activity could be demonstrated. Furthermore, it was decided to synthesize the related cyclic analogs (34) derived from the cyclic β-amino ketone (35), in which the flexibility between possible binding groups on the receptor surface is reduced. A comparison of the antimicrobial properties of the rigid cyclic analogs (34) and the flexible open chain analogs (32) may yield information regarding the distance between functional groups necessary for optimum biological activity.



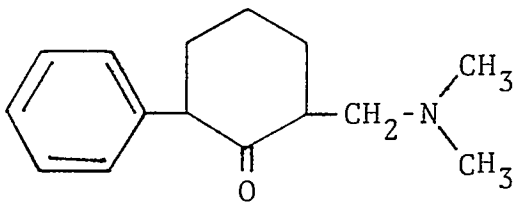
(32)



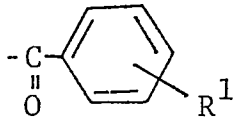
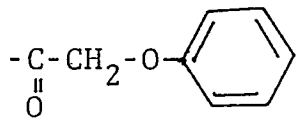
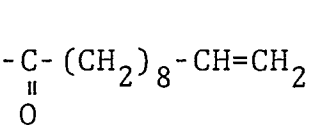
(33)



(34)



(35)

R = H,  ,  , 

R^1= H, 3-Cl, 4-Cl, 4-OCH_3, 4-NO_2, 3,5-$(NO_2)_2$

From a study of Dreiding models of the cyclic and acyclic β-amino ketones it is seen that the closest approach of oxygen-nitrogen is the same in both ketones but the acyclic ketone allows for a greater oxygen-nitrogen distance than is possible in the cyclic ketone. Thus the open chain ketone allows for more variation in the oxygen-nitrogen distance.

Dreiding models of the cyclic and acyclic γ-amino alcohols show that both the closest approach of oxygen-nitrogen and the farthest distance between oxygen-nitrogen is possible in the open-chain alcohol.

Thus, the distance between potentially important binding groups are more restricted in the cyclic analogues than in the acyclic compounds.

A number of compounds displaying significant antimicrobial properties also show antitumor activity. It appeared a

logical development to screen any of the compounds prepared in the present investigation which showed a good level of antimicrobial activity against certain neoplastic diseases, especially the L-1210 lymphoid leukemia in mice.

1.3 Utilization of latentiation in the design of drugs

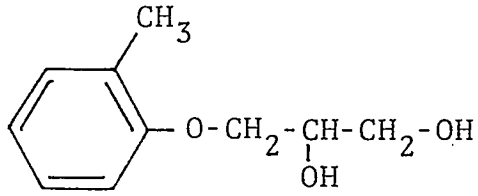
Since γ-amino alcohols have been shown to possess pharmacological activity it was decided to use the concept of latentiation by preparing esters of the cyclic and acyclic alcohols prepared in this work. Drug latentiation has been defined as the chemical modification of a biologically active compound to form an inactive transport form which upon *in vivo* enzymatic attack will liberate the parent compound (Harper, 1962).

Some differences in properties between parent drug and derivatives that may be reflected in differences in biological activities are as follows: (Kupchan *et al.*, 1965).

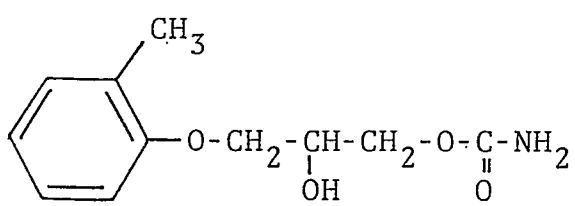
(a) Differences in rates of absorption which may result, for example, from conversion of a polar to a less polar molecule, with a consequent increase in lipid solubility and thus a more favorable transport across lipoid barriers, such as the gastrointestinal tract and the blood-brain barrier. A decrease in polarity may result also in an increase in the storage of the derivative in body fat, leading in some instances to prolongation of activity. The hydroxyl group of the alcohols is a polar group

which may inhibit passage across cell membranes. Conversion to the ester should increase the lipophilic character of the molecule, possibly facilitating transport across cell membranes.

(b) Differences in rates of metabolism. If the functional group modified is one normally involved in the metabolism of the molecule, the rate at which the drug is eliminated from the body may be reduced - hence its action prolonged, e.g., the masking of hydroxyl groups, the conjugation of which is a common metabolic pathway (Williams, 1959). The muscle relaxant, mephenesin (36), is characterized by an extremely short duration of action, due to its rapid <u>in vivo</u> oxidation to β-(o-toloxy) lactic acid (Riley and Berger, 1949). Conversion of the drug into the 1-carbamate (37) to protect the labile 1-hydroxy group prolongs the action (Berger, 1952).

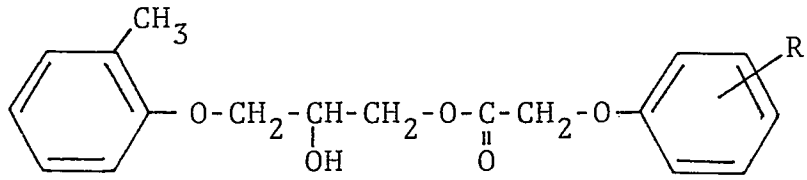


(36)



(37)

Bottari et al. (1968) found that the duration of mephenesin phenoxyacetates (38) increased from 1.5 to 3 times over that of mephenesin carbamate.



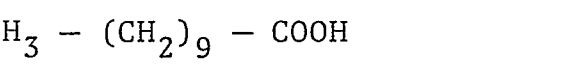
(38)

R = H, 2-OH, 4-Cl, 4-F

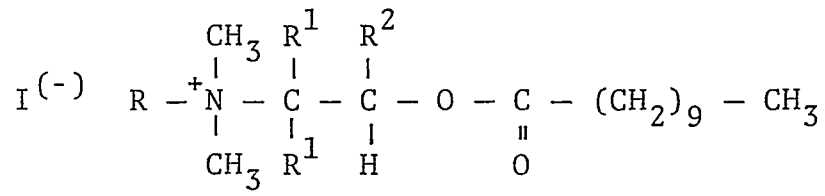
(c) Differences in time of onset and duration of action. If derivative formation involves a functional group essential for activity, the modified drug may be ineffective until the original functional group has been regenerated; the period for onset of action may therefore be longer than it is for the original drug. Duration of effect may be correspondingly greater, since metabolic processes that reduce plasma concentration of the original drug may not operate so rapidly upon the modified form.

In many cases esterification of the parent drug molecule has been used as a method of increasing the duration of action. In the case of steroids, esterification of one or more of the free hydroxyl groups with organic acids has often brought about the desired effect (Junkmann and Witzel, 1957). Dirscherl et al. (1954) reported substantially good agreement between the duration of action and the rate of hydrolysis of these esters with human or rat liver homogenates.

The completely saturated carboxylic acid, undecanoic acid (39), is an active insect repellent. Garson and Quintana (1969) formulated various undecanoic acid esters (40) designed to provide long-lasting insect-repellent efficacy by gradually releasing undecanoic acid.



(39)



(40)

R = alkyl

R^1 = H, alkyl

R^2 = H, alkyl

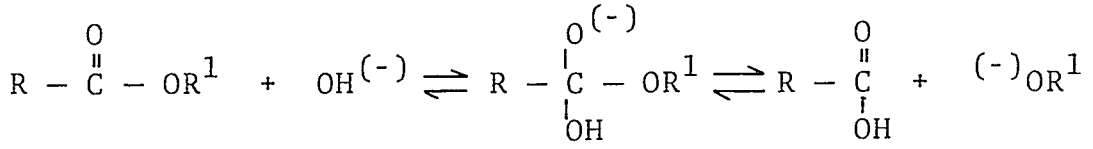
They found that the repellency was significant for several of these esters, being effective longer than undecanoic acid itself.

(d) Difference in potency. Due to more favorable transport across lipid barriers and to resistance to metabolic processes, the derivative may concentrate at the target area in a higher concentration than that of the parent. Consequently, provided conversion to the active form occurs

fairly rapidly at the site of action, enhanced potency of the derivative over the parent may result. If transformation is slow, lower potency would be expected but possibly coupled with increased duration of action.

(e) Differences in rates of excretion. Excretion and metabolic processes are closely interrelated. If the compound is converted to a less polar form it will be more difficult to excrete since a delay occurs before the original functional group has been unmasked. The elimination of the derivative from the body would be expected to be slower than that of the parent.

The anticipated facile *in vivo* conversion of such derivatives into the parent compound rests upon both *in vitro* and *in vivo* chemical evidence. For instance, esters of acids possessing electron-withdrawing groups are known to be subject to facile *in vitro* hydrolysis. Bimolecular base-catalyzed hydrolysis of esters is believed to proceed through a tetrahedral addition intermediate (41). This intermediate is negatively charged, and it is anticipated that electron-releasing substituents in the acid moiety would retard and electron-withdrawing substituents accelerate hydrolysis of esters by this mechanism.



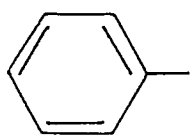
(41)

The rate of release of the active alcohol from the ester depends upon the electronic, steric, or configurational characteristics of the carrier group. In the esters synthesized from the open chain alcohol under investigation, the electronic characteristics of the carrier group should be of prime interest. The rate of release of the alcohol from the various esters can be predicted from the Hammett sigma values since the Hammett sigma value for substituents in the 3- and 4-positions of the aromatic ring of the acid moiety gives a quantitative estimate of the reactivity of the side-chain. Thus if the alcohol is found to be biologically active, a direct correlation between hydrolysis rates of the esters and biological activity may be possible.

Though the preceding comments emphasize the possibilities for base-catalyzed hydrolytic cleavage, it is recognized that enzyme-mediated cleavage of the esters <u>in vivo</u> is also highly probable. Body enzymes possess configurations which may complement the geometry and polarization of certain more simple molecules or functional groups. If the substrate and the enzyme at some sites are complementary, this will facilitate their proper orientation with regard to each other. This is a necessary prelude to modification of the substrate although this does not assure it.

When a reaction is mediated through enzymes within the body, the activation energy may be reduced appreciably, and the speed of the reaction may be far in excess of that of the uncatalyzed reaction. It is reasonable to assume that some of the alcohol derivatives may exhibit a degree of susceptibility to enzymatic cleavage processes.

The esters synthesized by reacting the alcohols with phenoxyacetyl chloride and 10-undecenoyl chloride should be of special interest. These esters would release phenoxyacetic acid (42) and 10-undecenoic acid (43) respectively, both known antifungal agents. If the alcohols released from the hydrolysis are also active, then synergistic effects are possible in these esters.



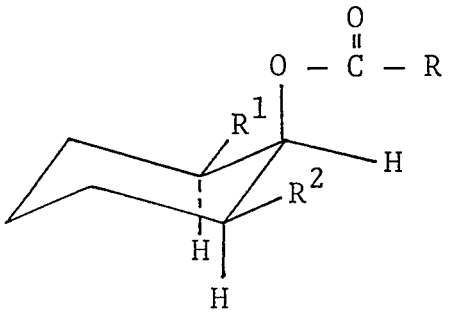
$O - CH_2 - COOH$

(42)

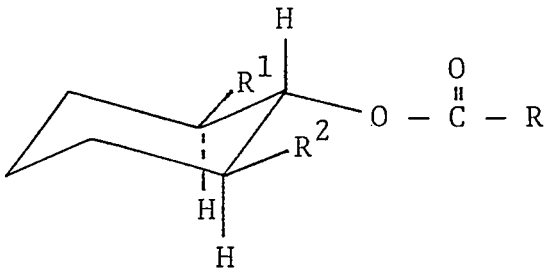
$CH_2 = CH - (CH_2)_8 - COOH$

(43)

Since there are two geometrical isomers possible in the cyclic alcohol, conformational aspects may also play a part in influencing the biological activity. If a pharmacologically active cyclic alcohol is formulated as an ester, the enzymic release of the active alcohol might well be affected by the conformation of the ester carrier group. The ester grouping can exist in an axial (44) or equatorial (45) position.



(44)



(45)

R = aryl

$R^1 = C_6H_5$

$R^2 = CH_2\text{-}N(CH_3)_2$

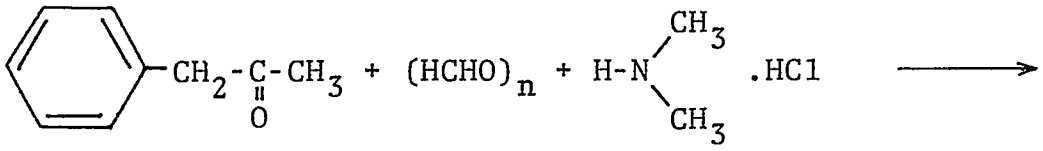
When the ester grouping is held in the axial conformation it should be more subject to steric hindrance (by the axial hydrogens in the 3- and 5-position of the cyclohexanol ring) than would be the case with an equatorial ester group. By analogy with chemical hydrolysis one would expect the equatorial ester group to be hydrolyzed more readily than the axial ester group. Thus the conformational effects here may influence biological activity, making the equatorial ester more active, or conversely, by making the axial ester have a longer duration of action.

2. DISCUSSION OF THE EXPERIMENTAL WORK

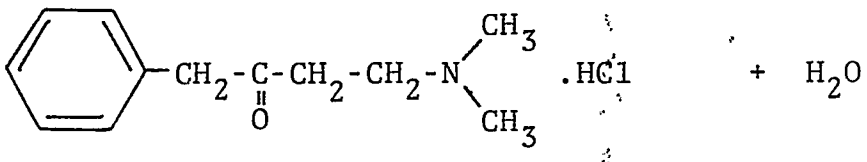
2.1 Preparation of derivatives of 1-dimethylamino-4-phenylbutane hydrochloride

2.1.1 Preparation of 4-dimethylamino-1-phenylbutan-2-one hydrochloride

The preparation of this series of compounds involves the synthesis of the β-amino ketone (47) from phenyl-2-propanone (46) by the Mannich reaction.



(46)



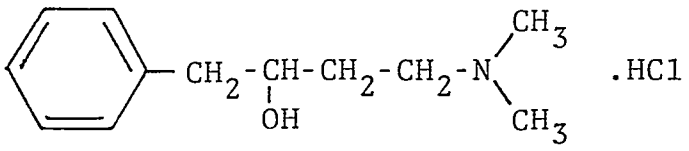
(47)

A Mannich reaction involves the condensation between an aldehyde (usually formaldehyde), ammonia or a primary or secondary amine (preferably as the hydrochloride), and a compound containing at least one active hydrogen atom. The reaction is catalyzed by small amounts of acid. When the hydrochloride of the amine (or ammonium chloride) is employed, the hydrogen chloride derived from the amine salt catalyzes the reaction (Bordwell, 1963).

Sharpe and Dohme Inc. (1953) describe a method for the preparation of 4-dimethylamino-1-phenylbutan-2-one hydrochloride (47). Phenyl-2-propanone, paraformaldehyde, dimethylamine hydrochloride, and a catalytic amount of concentrated hydrochloric acid were heated under reflux in a mixture of 5 parts methanol-100 parts 95% ethanol for 2 hours. An additional quantity of paraformaldehyde was added and the mixture heated under reflux for another hour. The addition of ether precipitated a yellow oil which was basified and extracted with ether. Dry hydrogen chloride gas was passed through the dry ether extracts, giving the desired ketone in a yield of 15.5%.

The method used in the present synthesis involved heating phenyl-2-propanone, paraformaldehyde, and dimethylamine hydrochloride together under reflux in absolute alcohol for 6 hours. The alcohol was removed, water was added, and the aqueous solution made alkaline with sodium hydroxide solution and extracted with benzene. The benzene was removed and the yellow syrup remaining was dissolved in a minimum quantity of acetone and acidified with ethanolic hydrochloric acid to yield the hydrochloride (47) in a yield of 41%.

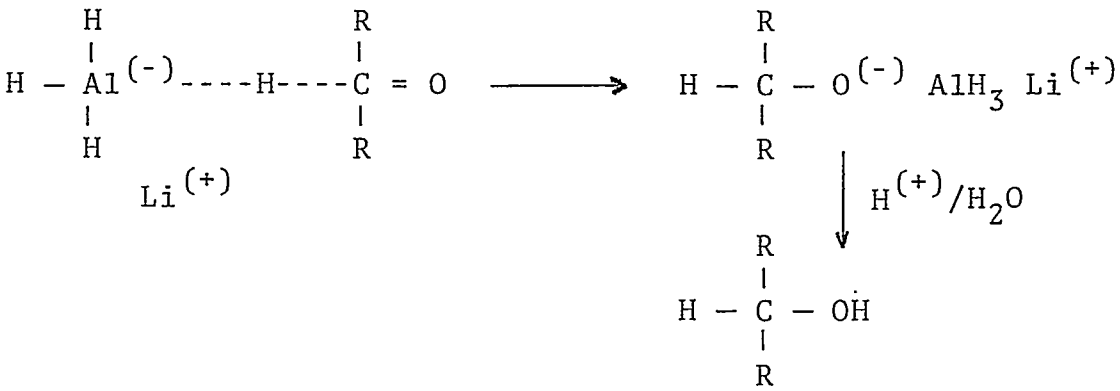
2.1.2 Preparation of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride



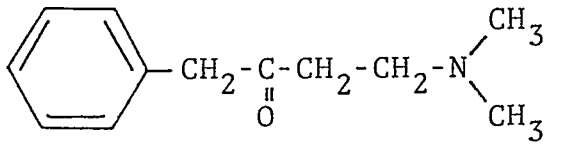
(48)

The reduction of the Mannich base (49) to the corresponding alcohol (50) can be accomplished by chemical reagents or catalysts. It has been found that β-t-amino ketone hydrochlorides of the type prepared by the Mannich reaction are deaminated by hydrogen over Raney nickel at high pressure (Schultz and Bicking, 1953). The products are an amine hydrochloride and a ketone having the same carbon skeleton as the Mannich base.

In recent years inorganic hydrides, such as lithium aluminum hydride and sodium borohydride, have become important as reducing agents of carbonyl compounds. With the metal hydrides the key step is the transfer of a hydride ion to the carbonyl carbon of the substance being reduced (Roberts and Caserio, 1964).



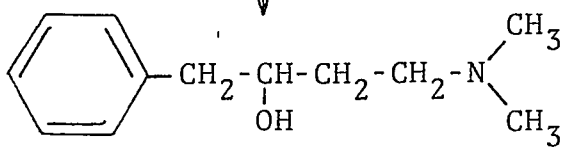
Reduction of the Mannich base (49) with lithium aluminum hydride afforded the alcohol (50) in good yield.



(49)

(1) $LiAlH_4$

(2) $H^{(+)}/H_2O$



(50)

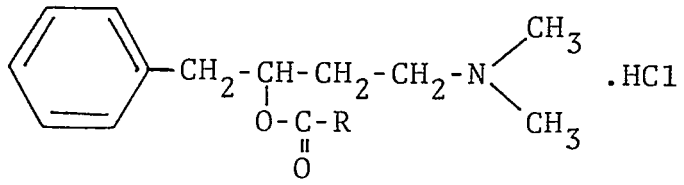
The hydrochloride salt of the alcohol (48) was formed by acidifying a solution of the alcohol (50) in dry acetone with ethanolic hydrochloric acid. The hydrochloride salt would not crystallize unless the alcohol as the free base was pure. Furthermore it was found that the ketone (49) had to be pure prior to reduction, otherwise it was impossible to crystallize the hydrochloride salt of the alcohol.

The hydrochloride salt of 4-dimethylamino-1-phenyl-butan-2-ol (48) may be a polymorph, since two batches of crystals were obtained which differed both in physical appearance and in melting points. The first fraction of crystals were colorless and granular, melting at 141-143°C. The second batch of crystals were colorless and fluffy, melting at 85-87°C.

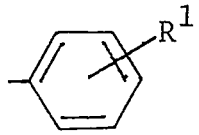
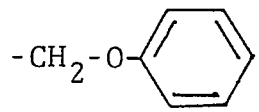
Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species (Haleblian and McCrone, 1969). Different polymorphs of a given compound are, in general, as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, etc., all vary with the polymorphic form. In general, it should be possible to obtain different crystalline forms of a drug and thus modify the pharmacological activity of the compound.

The alcohol products were not investigated thoroughly to determine whether they were polymorphs. A mixture of equal quantities of both crystals were submitted for antimicrobial examination.

2.1.3 Preparation of some esters of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride



(51)

R =  , 

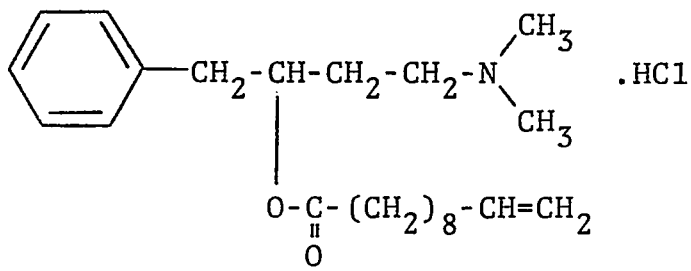
R^1 = H, 3-Cl, 4-OCH_3, 4-Cl, 4-NO_2, 3,5-$(NO_2)_2$

The formation of benzoates of aliphatic alcohols may be undertaken in a variety of ways including the Schotten-Baumann reaction in which the alcohol and acid chloride are shaken together in aqueous alkali. Pyridine can be used in place of aqueous alkali to function both as a solvent and as a base to remove the hydrogen chloride produced.

The γ-amino alcohol (50) contains a tertiary amine group and thus esterification can proceed in the absence of an external base, resulting in the formation of the ester as the hydrochloride salt (51)

Thus, a general method was used for preparing esters by reacting the alcohol with the acid chloride in the absence of any external base. The esters were prepared in yields ranging from 20% to 83%. All were confirmed by their elemental analysis, infrared spectrum, and the prominent m/e peaks of their mass spectrum.

2.1.4 Attempted preparation of the 10-undecenoyl ester of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride

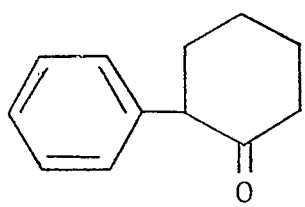


(52)

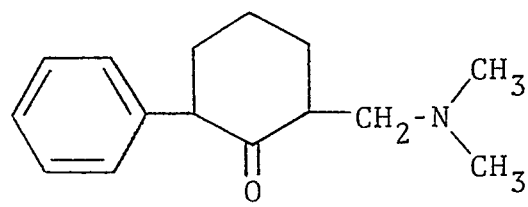
All esterifications resulted in the formation of crystalline hydrochloride salts with the exception of the reaction between 10-undecenoyl chloride and the alcohol. In this case a waxy, colorless solid resulted, showing characteristic infrared bands at ν(KBr) 1730s cm^{-1} (C=O) and ν3420s cm^{-1} (OH), indicating a mixture of the ester (52) and the alcohol (48). Repeated attempts to crystallize the reaction product failed to give a crystalline material. A second attempt to synthesize the ester by heating under reflux an ethereal solution of the alcohol in excess of the acid chloride also failed to esterify the alcohol to completion. A mixture of ester and alcohol were again indicated from the infrared spectrum.

2.2 Preparation of derivatives of 1-dimethylaminomethyl-3-phenylcyclohexane

2.2.1 Preparation of 2-phenylcyclohexanone



(53)



(54)

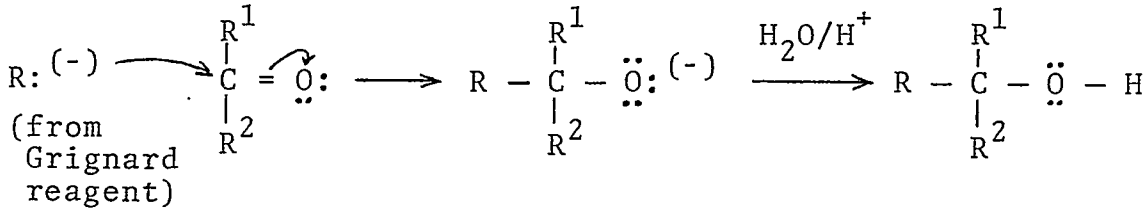
The preparation of this series of compounds involves the synthesis of 2-phenylcyclohexanone (53) as an intermediate, which may be converted into the β-amino ketone (54) by the Mannich reaction.

Newman and Farbman (1944) prepared 2-phenylcyclohexanone by adding a solution of 2-chlorocyclohexanone in ether to a solution of phenyl magnesium bromide in ether. The ether was removed by distillation, benzene was added, and the mixture was heated under reflux for 8 hours. Hydrolysis and extraction gave 2-phenylcyclohexanone as a colorless solid after vacuum distillation in a yield of 58%.

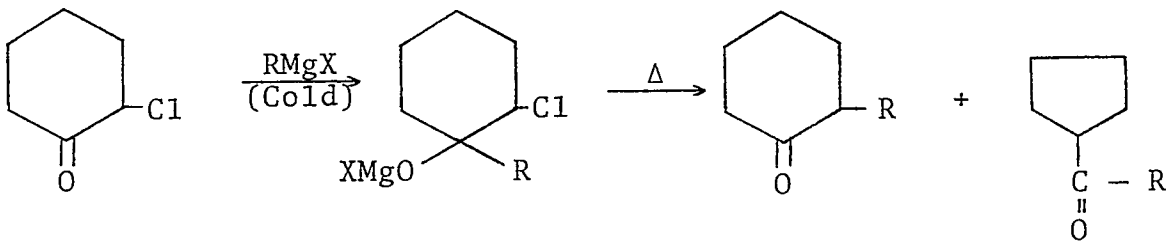
Kost and Sugrobova (1963) prepared 2-phenylcyclohexanone under the same conditions, obtaining the product by fractional distillation. No yield was quoted.

The method adopted in the present synthesis was essentially the same except benzene was not exchanged with ether for a higher reflux temperature. The heating under reflux with ether was carried out for 20 hours. The desired product, 2-phenylcyclohexanone (53) was distilled under high vacuum distillation and obtained in a yield of 56%.

Grignard reagents may be regarded as sources of anions and in this case, the phenyl anion is obtained from phenyl magnesium bromide. Such anions, with an unshared electron-pair on a carbon atom, behave as very powerful nucleophilic reagents. Normally the anion can be pictured as reacting with a ketone as shown in this simplified mechanism.



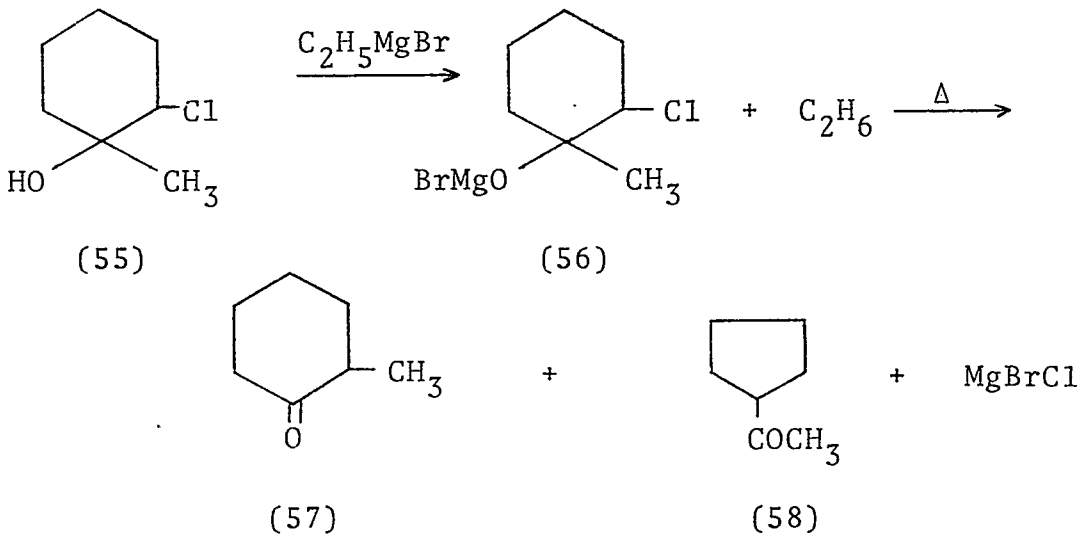
Reactions in which the halogen atom of an α-halo ketone is replaced by the organic radical of the Grignard reagents have been reported by many researchers, including Tiffeneau and Tchoubar (1934), as shown below.



$R = CH_3, C_2H_5$

X = I, Br

Tiffeneau (1907) isolated the halohydrin (55) and found that the corresponding halomagnesium halohydrinate (56), upon heating, undergoes decomposition and rearrangement to yield the α-substituted ketones (57) and (58) and magnesium halide. In the case of 2-halo cyclohexanones, the rearrangement may take, in part, a course leading to the contraction of the cyclohexane ring to a cyclopentane ring.



Newman and Farbman (1944) did not report the production of any of the cyclopentane product when they prepared 2-phenylcyclohexanone from a Grignard reagent. The gas chromatographic analysis of the product prepared in our laboratories showed only one peak, and it was assumed that the product was pure 2-phenylcyclohexanone and was not contaminated with any cyclopentane derivative.

It is expected that the phenyl substituent in 2-phenylcyclohexanone will be predominantly in the equatorial position. Eliel and Rerick (1960) found an experimental free-energy difference of 2.1 kcal/mole between an equatorial and an axial phenyl group on a cyclohexane ring. Eliel et al. (1966) quote the free-energy difference as 3.1 kcal/mole. From the free energy relationship, $\Delta F=-RT \ln K$, it can be calculated that the equatorial phenyl group will be present in a proportion greater than 97.2%, assuming a free-energy difference of 2.1 kcal/mole. If the free-energy difference is taken as 3.1 kcal/mole, then the equatorial phenyl group is calculated to be present in concentrations greater than 99.4%.

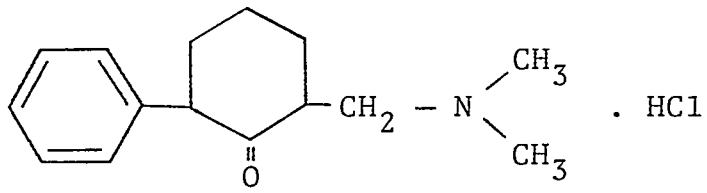
The P.M.R. spectrum shows a quartet integrating for one proton at τ6.45, corresponding to the proton attached to the 2-position of the cyclohexanone ring. This proton is deshielded by the carbonyl group and the phenyl ring, shifting it farther downfield than the other protons on the cyclohexanone ring. A broad multiplet at τ7.3-7.7 integrated for two protons and was assigned to the two protons at the 6-position

of the cyclohexanone ring. These protons are α to the carbonyl function and experience greater deshielding than the protons at the 3-, 4-, and 5-positions, which appear in a broad multiplet at τ7.7-8.8. The aromatic protons are deshielded and appear in a multiplet at τ2.7.

A valuable relationship for assigning configuration and conformation in cyclic systems is the dependence of coupling constants between protons on adjacent carbon atoms (vicinal coupling) upon the dihedral angle (ϕ) between the protons. A number of formulae have been developed to express this relationship. From Williamson and Johnson's formula (1961) the $J_{vic.}$ should have a value of about 16 c.p.s. when ϕ=180° (as in axially related protons) and 2.5 c.p.s. when ϕ=60° (as in axial/equatorial or equatorial/equatorial related protons). Smaller coupling constants are predicted from Karplus's formula (1959); the J_{aa} is about 9 c.p.s., while J_{ae} or J_{ee} is about 1.8 c.p.s.

The coupling constant for the quartet at τ6.45 was 6 c.p.s., making it difficult to assign the proton at position 2 an axial orientation with certainty. P.M.R. evidence for Isomer A of the cyclic alcohol derivative, 2-dimethylaminomethyl-6-phenylcyclohexanol (60) indicates that this proton is indeed in the axial orientation, which means that the phenyl substituent is equatorial in 2-phenyl-cyclohexanone as predicted.

2.2.2 Preparation of 2-dimethylaminomethyl-6-phenylcyclohexanone hydrochloride



(59)

This compound has been described in the literature on three occasions.

Kost and Sugrobova (1963) synthesized this compound (59) by heating 2-phenylcyclohexanone, dimethylamine hydrochloride, and paraformaldehyde together in ethanol under reflux for 16 hours. Dry hydrogen chloride gas was passed into the cooled mixture and the ethanol was evaporated under reduced pressure to give a syrup which was dissolved in a little methanol. Dry ether was added, the solution cooled, and the glassy product removed by filtration to give (59) in a yield of 61% with a melting point of 159-160°C.

A similar method was used by Bachmann and Wick (1950) who obtained the desired ketone in a yield of 62% with a higher melting point of 168-169°C. Takahashi et al. (1958) used isopropanol as the solvent and the time of heating under reflux was 2 hours. They characterized the ketone as the free base, with a melting point of 51°C. No yield was stated.

The method employed in this investigation was to heat the three starting materials together under reflux in absolute alcohol for 16 hours. The yield of compound (59), which melted at 153-154°C., was 37%. The infrared spectrum showed a carbonyl stretching frequency at 1705s cm^{-1}. Elemental analysis and mass spectrometry confirmed the structure of the product.

Noyce and Dolby (1961) found the free-energy difference between an axial and equatorial ethyl group to be 2.1 kcal/mole. Eliel *et al*. (1966) quote a free-energy difference of 2.0 kcal/mole between an axial and equatorial neopentyl group. Assuming that the dimethylaminomethyl side-chain will have an energy difference of at least 2 kcal/mole between the axial and equatorial positions, the equatorial position can be calculated to be favored in greater than 96.7% on a cyclohexane ring.

It has been pointed out by Allinger and Blatter (1961) that, as a result of the trigonal geometry of the carbonyl carbon, an equatorial substituent in the 2-position is nearly eclipsed with the carbonyl oxygen, whereas an axial substituent in this position is staggered with respect to this oxygen atom. For some alkyl groups in the equatorial position next to a ketone function this eclipsing leads to an interaction energy term called the "2-alkyl ketone effect." The 2-alkyl ketone effect does play a part in the case of 2-ethyl and 2-isopropylcyclohexanone, reducing the difference between equatorial and axial ethyl groups to 1.1 kcal/mole

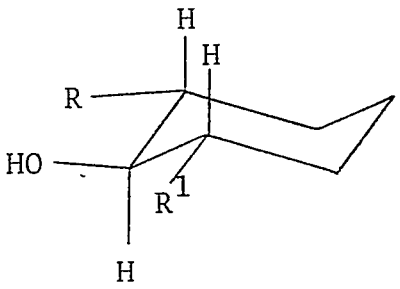
from 2.1 kcal/mole. Thus if this type of effect is present in the ketone (59), the equatorial position for the side-chain may not be favored as greatly. Assuming a free-energy difference of only 1 kcal/mole between equatorial and axial orientation of the dimethylaminomethyl side-chain would reduce the preference of the equatorial position to 84.4%.

A sample of the free base of (59) injected into the gas chromatograph resulted in only one peak so the two side-chains are both assumed to be exclusively in the equatorial position.

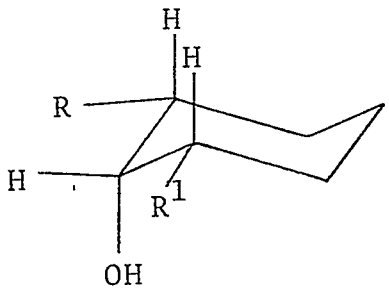
The P.M.R. spectrum shows a multiplet at τ6.3, integrating for one proton, assigned to the proton at the 6-position of the cyclohexanone ring. There are two tertiary hydrogens in this compound, both deshielded by the carbonyl function, but the hydrogen at position 6 is further deshielded by the phenyl substituent so this proton will be the one at position 6. The tertiary proton at position 2 comes out in the area encompassed by the other hydrogens on the cyclohexanone ring. In 2-phenylcyclohexanone there was a peak integrating for two protons at τ7.3-7.7, assigned to the 2 α-protons in the 6-position. In the spectrum of 2-dimethylaminomethyl-6-phenylcyclohexanone this peak has collapsed to what appears could be a multiplet in the same range integrating for one proton, the tertiary proton in the 2-position. This confirms that the Mannich reaction has occured at the desired carbon atom alpha to the carbonyl group.

2.2.3 Preparation and separation of the geometrical isomers of 2-dimethylaminomethyl-6-phenyl-cyclohexanol

Two geometrically isomeric alcohols are possible from the reduction of 2-dimethylaminomethyl-6-phenylcyclohexanone (59), one alcohol with an equatorial hydroxyl (60) and the other alcohol with an axial hydroxyl (61).



(60)



(61)

$R = Ph$

$R^1 = CH_2\text{-}N(CH_3)_2$

Takahashi *et al.* (1958) reported the reduction of the ketone (59) with lithium aluminum hydride. One mole of the amino ketone in ether was added dropwise to 0.25 mole of lithium aluminum hydride in ether at 0°C. The reaction mixture was heated under reflux for 3 hours, and treated with ice and hydrochloric acid. The acid layer was made alkaline and extracted with ether to give the amino alcohol which boiled at 156°C at 0.04 mm. No mention was made of the possibility of geometrical amino alcohols or of their separation.

In the present work, the product resulting from reduction of the ketone (59) with lithium aluminum hydride was investigated by gas chromatography. Two peaks were revealed which were thought to correspond to the two possible isomeric alcohols.

The reduction product was separated into two compounds by column chromatography on alumina, eluting with ether/Skelly F solvent of increasing ether content. All fractions were run through the gas chromatograph. Early fractions yielded one peak, intermediate fractions showed two peaks, and late fractions again contained one peak. It was observed that the first compound to come off the alumina was the second compound to come off the gas chromatograph. The first compound to elute from the alumina was designated Isomer A, the second compound to elute from the alumina was designated Isomer B.

Early fractions which appeared pure in one constituent were combined as were the late fractions which contained only one constituent. These two combined fractions were separately converted to the hydrochloride salt. Recrystallization resulted in colorless crystals in each case. The elemental analysis and mass spectrum of each hydrochloride salt corresponded to that expected for the alcohol, but the melting points were significantly different from each other and from that of the hydrochloride salt of the alcohol mixture not separated on the alumina. A mixed melting point of the two salts was below that of either salt. The infrared

spectrum of each compound was the same except for slight shifting of some functional group bands, such as the hydroxyl absorption band.

Factors controlling stereochemistry of reduction

The variation in the stereoisomeric composition of the products of reduction of 2-dimethylaminomethyl-6-phenyl-cyclohexanone (59) using various reagents and conditions is explicable in terms of thermodynamic and kinetic contributions in the reaction.

Jackman et al. (1949) considered that steric hindrance about the carbonyl group was the chief factor determining the relative amount of isomers obtained in the reduction of alkylcyclohexanones. Nace et al. (1951) emphasized the size of the reducing agent in the reduction of cholestanone; both groups mentioned the importance of the relative thermodynamic stability of the isomers in certain cases. Barton (1953) emphasized the thermodynamic factor in pointing out that the equatorial isomer was predominant in the product of reduction of alicyclic unhindered ketones. Dauben et al. (1956) stated that an increase in the effective size of the reducing agent resulted in "steric approach control" assuming an increasingly important role compared with the molecular energetics of product formation, "product development control."

(a) Thermodynamic factor

A method of allocation of the relative thermodynamic stabilities of epimeric alcohols involves the measurement of their percentages in the mixture obtained under equilibrating conditions, usually sodium/alcohol equilibration. Equilibration is assumed to proceed via dehydrogenation to an intermediate ketone (or aldehyde) and subsequent reduction (Wagner-Jauregg, 1932). In work by Beckett et al. (1959) the ketone (tropinone) was proved to be present in the products of equilibration of tropine and ψ-tropine using sodium/n-pentanol as the equilibrating reagent.

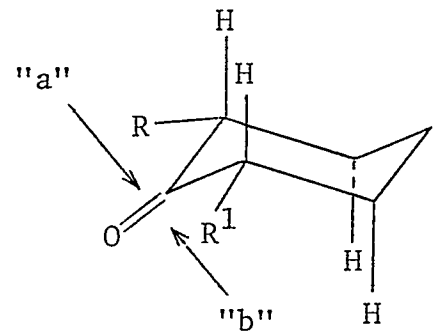
In the present investigation the product from the reduction of 2-dimethylaminomethyl-6-phenylcyclohexanone (59) with lithium aluminum hydride was equilibrated with sodium/n-pentanol. The percentage composition of Isomer A/Isomer B changed from 75%/25% to 89%/11%, indicating that Isomer A is the most thermodynamically stable isomer. Isomer A is thought to be the equatorial alcohol from the equilibration results.

(b) Kinetic factor

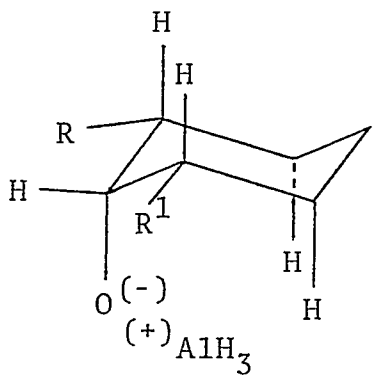
The solvent and its effect on the size of the reducing species, and the type of reagent and its mechanism of reaction with the ketone may be considered as potential contributors to the kinetic factor in the reduction. Although full clarification of the mechanism of reduction by complex metal hydrides and alkoxides has not yet been established, there is general agreement that the rate-

controlling step in reduction is attack by an H^- on the carbonyl carbon.

In the reduction of 2-dimethylaminomethyl-6-phenyl-cyclohexanone (62), steric factors will result in attack from side "a" being less hindered than that from side "b". The axial protons at positions 3 and 5 will interfere with approach of an attacking species from side "b", especially if the reducing species is bulky. However, attack from side "a" will require a higher activation energy since the resulting anionic complex (63) will be developed in the thermodynamically less stable axial conformation, interacting with the β-diaxial protons. If the carbonyl oxygen is co-ordinated to a moiety of the reducing agent, i.e. BR_3 of $NaBHR_3$ or AlH_3 of $LiAlH_4$, increasing the size of the co-ordinated group will favor anion formation in the more stable conformation. Work by Beckett *et al.* (1959) indicates that the steric control of the direct attack upon the carbonyl carbon plays a much more important role than carbonyl oxygen co-ordination in the reduction of tropinone, as R is changed from H to OCH_3 in $NaBHR_3$.



(62)



(63)

$R = C_6H_5$

$R^1 = CH_2\text{-}N(CH_3)_2$

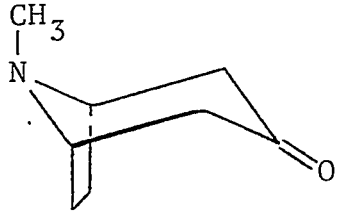
Increasing the size of the reducing species will therefore favor addition to side "a" to yield the axial alcohol, if the differences in the activation energies of the two sides of attack upon the carbonyl group are approximately represented by the differences in the energy levels obtained during equilibration.

Since the effective reducing species size is the controlling kinetic factor, interaction (either physical or chemical) between the solvent and the reducing agent becomes important. The formation of etherates of lithium aluminum hydride has been established by Gaylord (1956), while sodium borohydride can be solvated as stated by Brown et al. (1957).

In an investigation by Beckett et al. (1959) it was established that the solvent affected the isomeric composition of the reduction product to the greatest extent where chemical reaction between reagent and solvent occurs to produce a new reducing species.

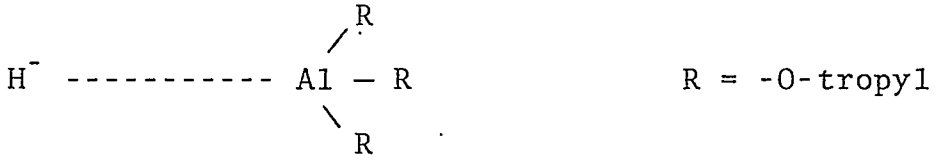
Lithium aluminum hydride

Beckett et al. (1959) state that 1/4 mole of lithium aluminum hydride reduces tropinone (64) completely and gives the same isomeric ratio as reduction with 4 moles of lithium aluminum hydride. This indicates that all the



(64)

hydrogen atoms of the reagent can be used in the reduction, excess lithium aluminum hydride playing a negligible part in the reaction. Since the size of the reducing reagent increases as the reaction proceeds (as the hydrogen atoms of lithium aluminum hydride become replaced by -O-tropyl groups), one might expect the final reducing species to constitute a very large steric factor, but their results suggest that this is not the case. Brown et al. (1956) stated that in the transfer complex, the more highly substituted aluminohydride constitutes a smaller steric factor than that which its bulk suggests due to the greater ease with which the hydride particle can be transferred to the carbonyl carbon. This may be envisaged as the "B strain" in (65) leading to a facile hydride ion separation which leads to virtual non-participation of the aluminocomplex in the stereochemistry of reduction (Beckett et al., 1959).



(65)

Borohydride in various solvents

The actual effective size of the reducing species using a borohydride reagent will depend upon the nature of the solvent since chemical interaction between the reagent and various solvents is known. Sodium borohydride dissolves in cold water without extensive evolution of hydrogen. At

room temperature and above, the hydrolysis (Eq. 1) proceeds more rapidly although the material is fairly stable in basic solution.

$$NaBH_4 + 2H_2O \longrightarrow NaBO_2 + 4H_2 \qquad \text{(Eq. 1)}$$

No appreciable reaction occurs with water at room temperature above pH 11.5 (Gaylord, 1956). Thus, solution of the borohydride in a slightly basic solution permits the use of this reagent as a reducing agent in aqueous solution.

In contrast to the slow reaction of the borohydride with water at room temperature, it reacts at an appreciable rate at -40°C. with methanol (Eq. 2).

$$NaBH_4 + CH_3OH \longrightarrow NaBH_3(OCH_3) + CH_3OH$$

$$\longrightarrow NaBH_2(OCH_3)_2 + CH_3OH \longrightarrow NaBH(OCH_3)_3 + CH_3OH$$

$$\longrightarrow NaB(OCH_3)_4 \quad \text{(Gaylord, 1956)} \qquad \text{(Eq. 2)}$$

Beckett et al. (1959) found that, in an aqueous methanol system, an increase in the methanol content gave an increase in the tropine content of the product, indicating the participation of a larger reducing species, presumably the methoxyborohydrides. The products of reduction will depend on the ratio of the various borohydride species present and their relative rates of reaction. Increase in the methanol content will yield more of the larger and more reactive trimethoxyborohydride.

In the present study, reduction of 2-dimethylaminomethyl-6-phenylcyclohexanone (59) with a sodium borohydride/methanol system changed the ratio of reduction products drastically. The percentage composition of Isomer A/Isomer B changed from 75%/25% to 31%/69%, indicating a larger reducing species as expected. There must be considerable steric hindrance to attack from side "b" in this system. Dauben et al. (1956) state that in the reduction of alkylcyclohexanones, a change to sodium borohydride in methanol from lithium aluminum hydride decreases the percentage of the stable isomer but the predominant product is still the more stable isomer with an equatorial hydroxyl.

Increasing the methanol content of the system and reducing the excess of sodium borohydride by half increased the percentage of Isomer B from 69% to 79% in the present study, indicating participation of more of the larger reducing species.

The use of borohydride in ethanol might be expected to give an even larger ethoxyborohydride reducing species, resulting in a greater percentage of Isomer B, but this was not so. This is explained by the slower rate of reaction between sodium borohydride and ethanol and therefore the greater participation of the smaller BH_4^- species (Brown et al., 1955). In the present work, no significant difference was found between the sodium borohydride/ethanol system and the sodium borohydride/methanol system where there was a large excess of sodium borohydride. The ratio of Isomer A/

Isomer B in the ethanol system was 29%/71% as compared to 31%/69% in the methanol system.

Brown et al. (1956) have shown that sodium borohydride reacts with lower straight chain but not branched chain alcohols such as isopropanol and t-butanol. Thus the similarity of the isomeric ratios obtained using borohydride in water, tetrahydrofuran, and isopropanol is not unexpected (Beckett et al., 1959). The small reducing species, BH_4^-, is again indicated and one would expect more of the more stable alcohol to be formed since attack from side "b" should be less hindered than with the alkoxyborohydride reducing species. In the present reduction with a sodium borohydride/isopropanol system the ratio of isomers was the same as that obtained with the excess of the sodium borohydride/methanol system. A smaller reducing species is not indicated.

When sodium borohydride powder was dropped into a solution of the ketone in excess methanol at room temperature, the percentage of Isomer B was again high. Increasing the methanol content of the system, reducing the excess of sodium borohydride, and the absence of cooling allow for greater participation of the larger reducing species.

2.2.4 Proof of the structure of the geometrical isomers of 2-dimethylaminomethyl-6-phenylcyclohexanol

(1) Reduction with lithium aluminum hydride

Dauben and his co-workers (1956) predicted that the products from lithium aluminum hydride reductions should contain a preponderance of the more stable equatorial alcohol. Thus Isomer A, the predominant alcohol from the lithium aluminum hydride reduction, is likely to be the equatorial alcohol.

(2) Equilibration with sodium/n-pentanol

The percentage of Isomer A increased from 75% to 89% upon equilibration, which indicates that Isomer A is the thermodynamically more stable alcohol. Equatorial alcohols are usually of lower energy than the corresponding axial alcohols.

(3) Reduction with sodium borohydride

As the size of the reducing species is effectively increased, such as with sodium borohydride in methanol, consideration must be given to steric interactions between the beta-axial hydrogen atoms of the ketone and the reducing moiety approaching in the axial position. This axial-axial type of interaction results in an increasing proportion of equatorial approach with the resultant formation of more of the less stable isomer with an axial hydroxyl group (Dauben *et al.*, 1956).

In all reductions carried out with sodium borohydride systems, Isomer B was predominant. This indicates that Isomer B is probably the axial alcohol.

(4) Separation of the geometrical isomers on alumina and by gas chromatography

When a polar group, e.g. a hydroxyl function, is in the equatorial configuration rather than the axial configuration, it is less shielded by the surrounding groups on the alicyclic ring. The equatorial hydroxyl group is therefore able to associate more easily with other polar groups.

Winstein and Holness (1955) have stated that isomers having equatorial hydroxyl groups can be expected to be adsorbed more strongly on chromatography and therefore would be more difficult to elute than the isomers having the more hindered axial hydroxyl. This was demonstrated by the chromatography of a mixture of cis- and trans-4-t-butylcyclohexanol, and later works have supported this statement as the isomers assigned axial hydroxyl groups were eluted first in each instance (Hennion and O'Shea, 1958).

The predominant isomer from the lithium aluminum hydride reduction is thought to be the equatorial alcohol, but this was the first compound to be eluted from an alumina column in our work. This result is in direct contradiction to Winstein's findings.

In simple cases the more polar isomer has a longer retention time when subjected to gas phase chromatography (Eliel and Ro, 1957). Isomer A was found to have a longer retention time than Isomer B when subjected to gas chromatography which is in accord with their findings. This indicates that Isomer A is the equatorial isomer.

(5) Infrared spectra

An equatorial group (X) attached directly to a cyclohexane ring will usually show a (C-X) stretching vibration at a higher frequency than the corresponding axial group. (When X=O-H it is the C-O not the O-H band). It has been suggested that the reason for this consistent difference is that when the C-X bond is stretched there is a small restoring force acting on the carbon when X is axial, and the vibration is essentially perpendicular to the plane of the ring. When X is equatorial the motion of the carbon forces a ring expansion, the restoring force is greater, and the frequency of the motion is therefore higher (Cole et al., 1952).

The infrared absorption bands due to carbon-oxygen stretching in equatorial and axial hydroxyl groups in cyclohexanols have been given as ν1037-1044 cm^{-1} and ν996-1036 cm^{-1} respectively (Cole et al. 1952). The infrared spectra of the hydrochloride salts of the two alcohols were compared. The first alcohol

off the alumina (Isomer A) showed ν(KBr) 1035s cm^{-1} while the second alcohol (Isomer B) showed ν995s cm^{-1}. This is in agreement with the fact that the equatorial vibration is almost always found at a higher frequency than is the axial vibration, indicating that Isomer A is the equatorial alcohol and Isomer B is the axial alcohol.

(6) Mass spectra

During an investigation of the mass spectra of epimeric cyclic alcohols, Biemann and Seibl (1959) observed that the spectra of the epimers, which were in general very similar as was expected, differed distinctly in the abundance of the molecular ion, M^+. This peak was found to be more intense in the spectrum of the less crowded epimer (equatorial hydroxyl) of secondary alcohols.

They interpreted this effect as a consequence of a different rate of decomposition into fragments of the molecular ion, M+, formed on electron impact, which is slower in the case of the more stable ion, M+.

A secondary, cyclic alcohol with the hydroxyl group in the more crowded position will therefore yield a molecular ion which has a greater tendency to decompose (and show a less intense M+ peak) than its less crowded epimer. The spectra of the acetates of the secondary alcohols also showed the same effect, enhanced due to the larger size of the acetoxy group compared with the hydroxyl group.

The mass spectra of Isomer A and Isomer B were run under the same experimental conditions and the spectra were compared. In each spectra, the intensity of the parent peak was compared to that of the prominent m/e 91 peak (Tropylium ion?). Isomer A had a parent peak which was 69.5% of the size of the m/e 91 peak; Isomer B had a parent peak which was only 54.5% of the size of the m/e 91 peak. This indicates that Isomer B is the more crowded isomer, namely the alcohol possessing an axial hydroxyl function.

(7) Comparison of the P.M.R. spectra

The P.M.R. spectrum of Isomer A and Isomer B as the free bases were run at the same concentration and under the same experimental conditions.

(i) Isomer A

The P.M.R. spectrum of Isomer A showed a broad peak integrating for one proton at τ3.35, thought to correspond to the hydroxyl proton. Deuterium exchange was used to identify this peak; upon addition of deuterium oxide to the probe the peak at τ3.35 collapsed, indicating that this was the hydroxyl proton.

The chemical shift of the hydroxyl proton in cyclohexanols varies with solvent and concentration. Ouellette (1964) measured the chemical shifts of the hydroxyl protons of cyclohexanols at different concentrations, in carbon tetrachloride, and then extrapolated to infinite dilution. It was found that

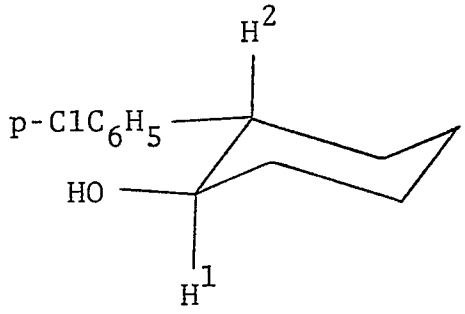
the protons of axial hydroxyl groups gave signals at higher field than protons of equatorial hydroxyl groups.

Lemieux *et al.* (1958) investigated the conformation and P.M.R. spectra of *trans*- and *cis*-4-t-butylcyclohexyl alcohols and their acetates. They did not quote τ values for the hydroxyl protons of the two alcohols but the hydroxyl proton of the *trans*-compound (equatorial alcohol) was farther downfield than the hydroxyl proton of the *cis*-alcohol (axial alcohol).

The P.M.R. spectrum of Isomer B showed a broad peak integrating for one proton at τ6.35 which was identified as the hydroxyl proton by deuterium exchange. This is upfield from the hydroxyl proton of Isomer A which indicates that Isomer A is the less shielded equatorial alcohol.

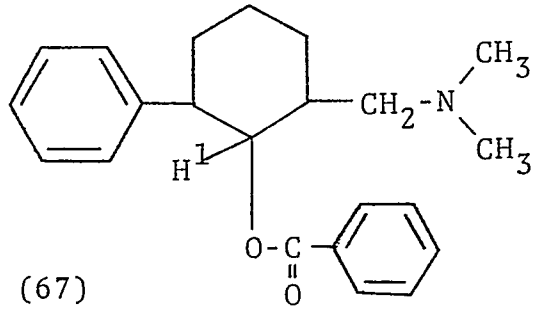
The P.M.R. spectrum of Isomer A shows a pair of doublets overlapping at τ6.4 which integrate for one proton. This is thought to be the proton at position 1 of the cyclohexanol ring. The P.M.R. spectrum of the corresponding cyclohexanone showed a multiplet at τ6.3 assigned to the proton at position 6 of the cyclohexanone ring. Reduction to the cyclohexanol is expected to reduce the deshielding of this proton, with a corresponding shift upfield into the broad envelope of the methylene protons at position 3, 4, and 5 of the cyclohexanol ring.

In an investigation of trans-2-(p-chlorophenyl) cyclohexanol (66) by Staiff et al. (1964) the signal of the 1-proton was identified by the large downfield shift upon acetylation, shifting from τ6.73 to τ5.12, since the carbonyl function in the acetate further deshields the proton at position 1. The broad unresolved multiplets in the case of the 1- and 2-protons (τ6.73 and τ7.42 respectively) are consistent with their trans configuration, both being axial.



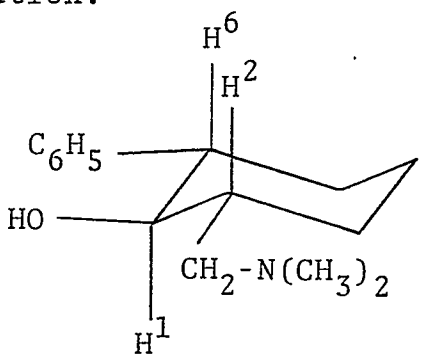
(66)

In the present study, the proton at τ6.4 in Isomer A shifted downfield to τ4.85 upon esterification with benzoyl chloride to produce the unsubstituted benzoyl ester (67). The chemical shift indicates that the proton at τ6.4 is the proton at the 1-position of the cyclohexanol ring.



(67)

The coupling constant for the pair of doublets centered at τ6.4 was 9 c.p.s., indicating diaxial coupling between the proton at position 1 and two adjacent axial protons. This indicates that the proton at position 1, 2, and 6 must all be in the axial configuration. This means that Isomer A is the equatorial alcohol (68), with the hydroxyl, phenyl, and dimethylaminomethyl groups all in the equatorial configuration.



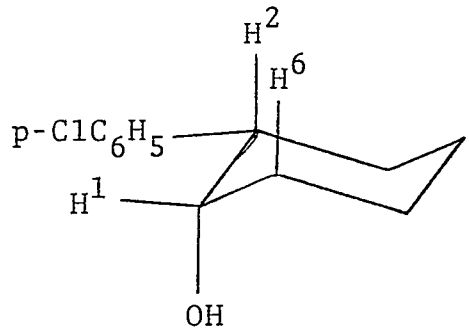
(68)

(ii) Isomer B

The P.M.R. spectrum of Isomer B showed a broad peak integrating for one proton at τ6.35, thought to correspond to the hydroxyl proton. Deuterium exchange resulted in the collapse of this peak, indicating that this was the hydroxyl proton.

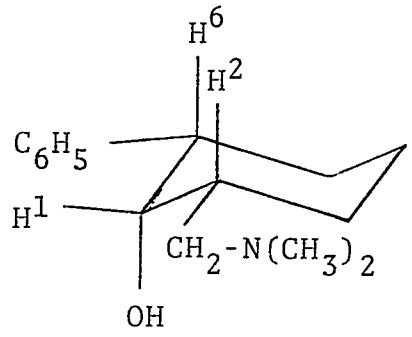
A singlet at τ6.0 integrated for one proton and was suspected to be the 1-proton. If this proton is equatorial, it has little spin-spin coupling with the adjacent axial hydrogens and can result in an approximate singlet.

Staiff et al. (1964) found that the 1-proton was an approximate singlet at τ6.23 in the P.M.R. spectrum of cis-2-(p-chlorophenyl) cyclohexanol (69). Since this hydrogen was equatorial, there was little coupling with the adjacent axial protons.



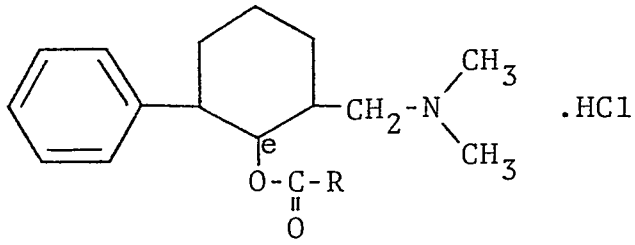
(69)

Therefore, Isomer B is the axial alcohol (70) with the hydroxyl group in the axial position and the phenyl and dimethylaminomethyl groups in the equatorial position.

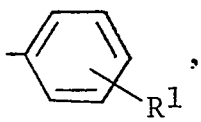
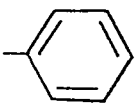


(70)

2.2.5 Preparation of some esters of 2-dimethylamino-methyl-6-phenylcyclohexanol hydrochloride (Isomer A)



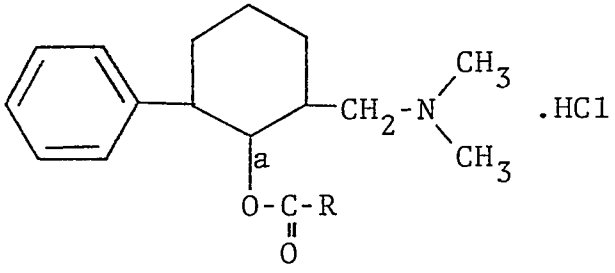
(71)

R =  , $-CH_2-O-$  , $-(CH_2)_8-CH=CH_2$

R^1 = H, 3-Cl, 4-Cl, 4-OCH_3, 4-NO_2, 3,5-$(NO_2)_2$

All esterifications resulted in crystalline hydrochloride salts of the ester (71). The esters were prepared in a similar manner to the acyclic esters (51) by reacting the alcohol with the acid chloride in the absence of any external base. The yields ranged from 61% to 89%. Surprisingly, the 10-undecenoyl ester formed in good yield with this cyclic alcohol compared to the acyclic analogue where only a mixture of ester and alcohol was obtained. All esters were confirmed by their elemental analysis, infrared spectrum, and the prominent m/e peaks of their mass spectrum.

2.2.6 Preparation of some esters of 2-dimethylaminomethyl-6-phenylcyclohexanol hydrochloride (Isomer B)



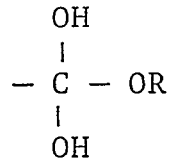
(72)

Axial substituents are in a more crowded environment than equatorial substituents, and this, in general, gives rise to differences in reactivity between the two types. In many reactions, the steric requirements of the transition state are greater than the steric requirements of the ground state. In such reactions, the crowding around the axial substituent produces steric hindrance, and the axial substituent reacts more slowly than the equatorial substituent.

Examples in which the axial substituent reacts more slowly are found in the saponification of esters of cyclohexanols. Eliel *et al*. (1961) found a considerably greater rate of saponification of ethyl *trans*-4-t-butylcyclohexane carboxylate (equatorial carboethoxy group) as compared to the *cis* isomer (axial isomer) - by a factor of 20. This is in keeping with other examples recorded in the literature.

It is known that these reactions involve not merely transition states but discrete intermediates (Bender, 1951) of the type (73) in which the carbonyl carbon has become

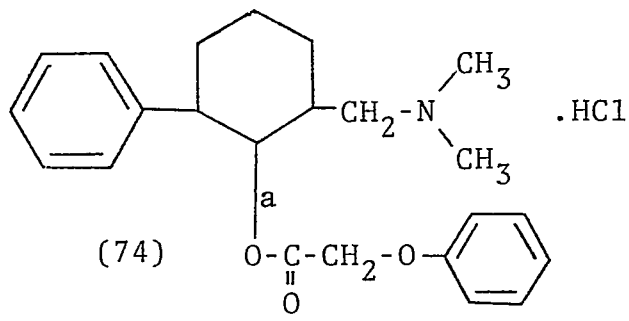
tetrahedral and has therefore increased in bulk from its original trigonal state. The effect on rate is greater when the cyclohexyl substituent is in the acid part of the ester



(73)

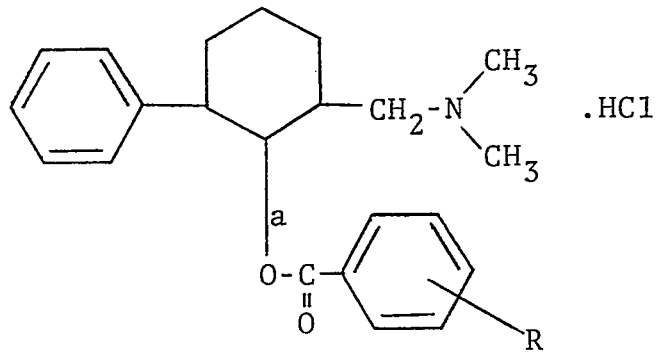
than when it is in the alcohol part. This is to be expected, since the site of crowding - the carbonyl group - is closer to the ring in the former case than in the latter. The ratio of saponification rates of trans- and cis-4-t-butylcyclohexyl acetates in 50% aqueous dioxane at 40°C. is 6.65 (Chapman et al., 1960); the ratio for the corresponding p-nitrobenzoates in 80% acetone at 25°C. is 2.5 (Hennion and O'Shea, 1958).

Thus, it is not surprising that difficulties were encountered in esterifications of Isomer B with its axial hydroxyl group. In nearly every case the product of esterification was a mixture of the ester and the alcohol hydrochloride salts. The only esterification which was completely successful was in the formation of the phenoxyacetyl ester (74).



(74)

Less steric crowding would be expected in the transition state leading to the phenoxyacetyl ester (74) because of the greater distance between the phenyl ring and the carbonyl function of the acid chloride, separation by a methylene group and an oxygen atom instead of being adjacent as in the benzoyl esters (75).



(75)

R = H, 3-Cl, 4-Cl, 4-OCH_3, 4-NO_2, 3,5-$(NO_2)_2$

The lithium salt of Isomer B was formed in an attempt to make the esterification with 4-nitro benzoyl chloride go to completion. The alcohol anion should be a more powerful nucleophile than the hydroxyl group and it was hoped that this would facilitate reaction. However, the product of this esterification was again a mixture of ester and alcohol.

Some success at separation of the ester-alcohol mixtures occured with alumina columns. In each case the ester was eluted before the more polar alcohol. The 3-chloro- and the 4-methoxybenzoyl esters were separated from unreacted alcohol on alumina. The 4-chloro benzoyl ester was also separated

from unreacted alcohol on alumina but the hydrochloride salt could not be crystallized.

The unsubstituted benzoyl ester and the 10-undecenoyl ester also were contaminated with unreacted alcohol. Esterification of the alcohol with 3,5-dinitrobenzoyl chloride did not work at all. Steric hindrance would be expected to be greatest in this esterification, due to the two bulky nitro groups.

3. DISCUSSION OF THE SCREENING RESULTS

The compounds for which screening data is available have been screened by Smith Kline and French laboratories of Philadelphia, U.S.A. The research management of this firm have recently decided to phase out most of the antimicrobial screen, and those compounds for which there is a lack of screening data have also been submitted to Ayerst Laboratories of Montreal, Quebec, Canada.

The structures of the compounds, with the relevant code numbers, for which screening results are available are given in Table I and Table II.

A comparison of the compounds in Table III indicates that the flexible analogues (Series 1) generally have greater activity than the rigid analogues (Series 2). In each series the β-amino ketone has the greatest activity and the corresponding alcohols are completely inactive at the highest concentrations used in the screen. Since some of the esters show activity, it may be that passage across the cell membrane is facilitated in the ester or, alternatively, substituents on the acid portion of the ester cause the enhanced activity over the alcohols.

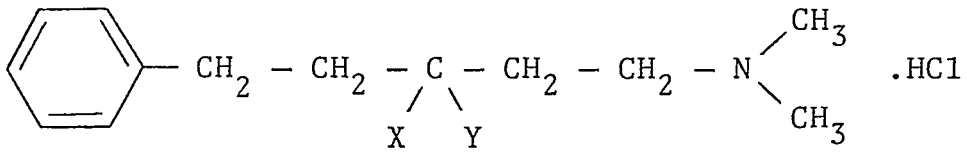
In each series the phenoxyacetyl ester had no activity at the highest concentrations used in the screen, which suggests that these esters are not being transported into the fungal cell and then hydrolysed. Hydrolysis should result in the release of phenoxyacetic acid, an established anti-

fungal agent, which should result in some activity even if the alcohol moiety is inactive.

In the acyclic series (Series 1) the most active esters with the broadest spectra are the 3- and 4-chlorobenzoyl esters. The antibacterial and antiseptic activity of halogenated compounds is well known, and the activity here is attributed to the chlorine atom. A 4-nitro substituent (σ = 0.778) and a 3,5-dinitro substituent (σ = 2 X 0.710 = 1.420) have a larger Hammett σ value than a 4-chloro substituent (σ = 0.226) or a 3-chloro substituent (σ = 0.373). If activity of the esters depended upon hydrolysis of the ester to the alcohol, the nitro esters would be expected to have greater activity. The nitro esters are inactive.

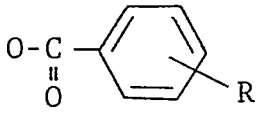
In the cyclic series (Series 2) the most active ester with the broadest spectrum is the 3-chlorobenzoyl ester. The 4-chlorobenzoyl ester is totally inactive, unexpected since the other chloro esters of both series have some activity.

In related work carried out in our Department, the following series of compounds (Series 3) has been prepared (Qureshi, 1970). In this series the chlorinated esters have the highest activity and the alcohol is completely inactive.



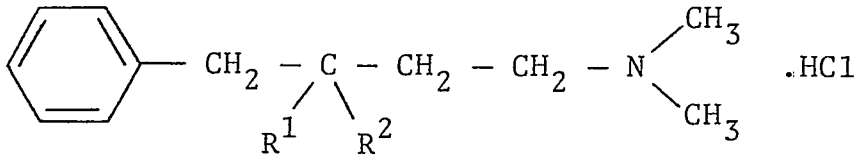
(Series 3)

X = H

Y = OH; 

R = H, 2-Cl, 4-Cl, 4-CH_3, 4-NO_2

Table I. Structures of compounds for which screening results are available (Series 1)



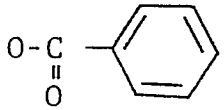
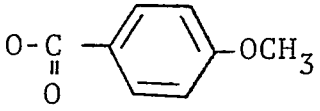
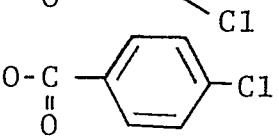
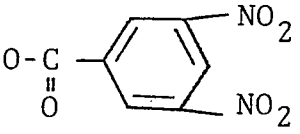
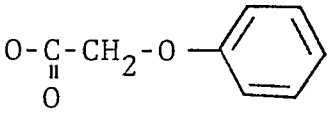
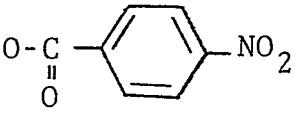
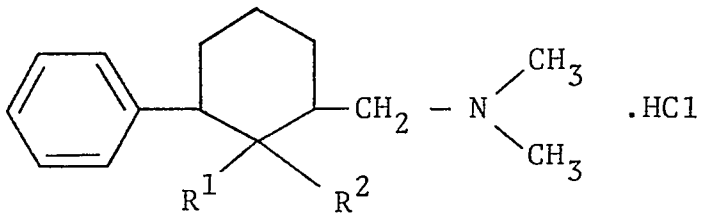
N.C. Number	R^1	R^2
16	-	=O
17	H	OH
18	"	
19	"	
20	"	
21	"	
22	"	
23	"	
43	"	

Table II. Structures of compounds for which screening results are available (Series 2)



(Isomer A)

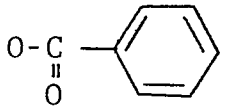
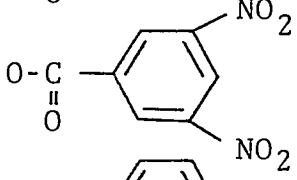
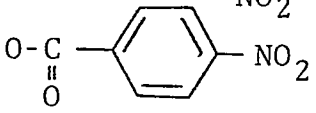
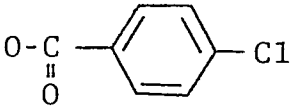
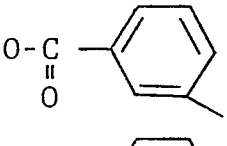
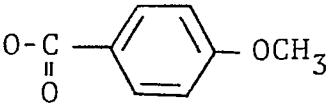
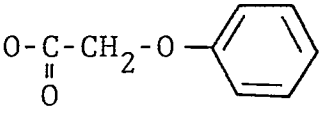
N.C. Number	R^1	R^2
24	-	=O
51	H	OH
44	"	
45	"	
46	"	
47	"	
48	"	
49	"	
50	"	

Table III. Antimicrobial screening results

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
N.C Number	S. faecalis	S. aureus (R)	S. aureus (S)	K. pneumoniae	Ps. aeruginosa	E. coli	S. typhimurium	T. mentagrophytes	M. smegmatis	C. albicans	B. subtilis	F. oxysporum	P. citrinum	A. niger	C. neoformans	B. dermatitidis	Xanthomonas v.	S. pyogenes	Sarc. lutea
16	1	1	1	1	-	1	1	16	4	1	1	16	16	16	16	16	1	1	1
17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	1	1	-	-	1	1	1	1	1	-	-	-
20	-	-	-	-	-	-	-	4	4	-	1	1	1	1	1	1	1	-	1
21	-	-	-	-	-	-	-	4	4	1	1	1	1	1	1	1	1	-	1
22	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	16	4	1	1	4	4	4	4	-	-	-	-
43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	1	-	1	1	-	-	-	-	-	-	1	1
45	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48	1	1	1	-	-	-	-	1	1	1	4	1	1	1	1	1	1	4	4
49	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
51	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Screening method for antimicrobial results

The compounds were tested against the species of bacteria listed in Table III initially at a dose of 200 µg./ml. If activity was found, the dose range was reduced. The system of assessing activity is as follows:

Activity at 200 µg./ml.		= 1
Activity at 50 µg./ml.		= 4
Activity at 12.5 µg./ml.	or less	= 16
Inactivity at 200 µg./ml.		= -

A compound showing inhibitory action at a concentration of 6 µg./ml. is generally considered as a useful lead for subsequent *in vivo* experiments.

Four of the compounds prepared in this work were screened for antiviral activity against rhinoviruses 1A, 2, 14, and 17. There was no plaque inhibition observed, as shown in Table IV.

Table IV. *In vitro* antiviral testing results

N.C. Number	Rhino Virus 1A		Rhino Virus 2		Rhino Virus 14		Rhino Virus 17	
	T	A	T	A	T	A	T	A
17	0	0	0	0	0	0	0	0
20	1	0	1	0	1	0	1	0
22	0	0	0	0	0	0	0	0
24	2	0	2	0	2	0	2	0

T = Cell toxicity

A = Plaque inhibition

0 = No plaque inhibition

1 = <10 mm. radius zone

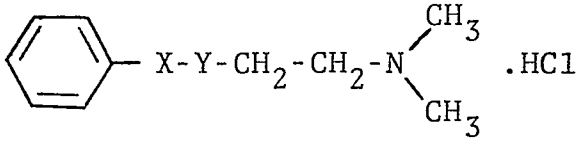
2 = >10 mm. radius zone

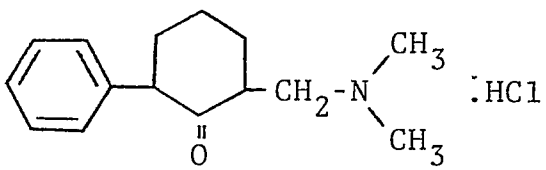
Anti-Trichinella spiralis screen

Four of the compounds prepared in this work were screened against Trichinella spiralis in mice. Trichinella spiralis is the worm involved in trichinosis, and it is used as the test organism in the primary screen for anthelmintic agents by the Animal Health group of Smith Kline and French Laboratories. The results are given in Table V. The structurally related compound, N.C. 15, has also been assessed against this worm and is included in the table.

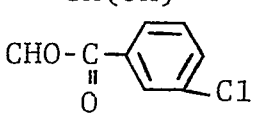
These compounds show consistent activity against the causative organism of trichinosis. However, this is of a rather low order, as a reduction of at least fifty percent in the worm count is required in order for the activity to be classified as significant.

Table V. Anti-Trichinella spiralis screening results





N.C. 24

N.C. Number	X	Y	% Reduction in Worm Count
15	CH = CH	C = O	29.6
16	CH_2	"	30.1
17	"	CH(OH)	18.6
20	"		22.5
24	-	-	24.4

Screening Method

Male Charles River CD_1 mice weighing between 18 and 20 g. are inoculated *per os* with 200 larvae/0.5 c.c. and are given food and water *ad lib.* for the rest of the study. After 24 hours each test mouse is treated with both 25 mg./Kg./0.25 c.c. P.O. and 25 mg./Kg./ 0.25 c.c. S.C. of test compound dissolved or suspended in carboxymethyl cellulose solution. There are 10 mice in both the test and control groups. After 3 days, the animals are killed and the number of intestinal parasites are counted and compared with the controls.

CNS Pharmacology Screen

One of the compounds prepared in this work, N.C. 51, was screened for possible tetrabenazine antagonism in mice. Male CF_1S mice weighing between 20 and 26 g. were administered *per os* with N.C. 51 (173 mg./kg.) suspended or dissolved in tragacanth once on the first day of the study. Approximately 3 hours after dosing, the mice were injected intraperitoneally with tetrabenazine (20 mg./kg.), a tranquillizer which resembles reserpine in action but with less profound sedation. No tetrabenazine antagonism was observed. No apparent pharmacological effects due to N.C. 51 were observed; the animals appeared normal on the day of administration, 24 hours later, and 7 days later.

Anti-cancer screen

Several of the compounds listed in Table I and II will be dispatched to the Cancer Chemotherapy National Service Center at the National Cancer Institute in Bethesda, Maryland. The primary screen currently under way is against the L-1210 lymphoid leukemia although other screens have been employed in previous years, and other tumour systems such as the Lewis lung carcinoma and the B-16 melanocarcinoma are currently being explored.

One of the compounds prepared in the present investigation, 4-dimethylamino-1-phenylbutan-2-one hydrochloride (N.C. 16) was screened in 1960 and in 1961 against three forms of cancer. The results of these screens are summarized in Table VI. In each case the compound was dissolved or suspended in methylcellulose and administered to the appropriate animal by intraperitoneal injection. In the case of the screens against Sarcoma 180 the injections of 125 mg./kg. were made twice daily, while in the other two tumour systems, injections of 100 mg./kg. were made daily. An increase in the mean survival time of 25% and a low level of mammalian toxicity is necessary before a compound approaches an interesting level of activity. Table VI indicates that administration of N.C. 16 at the dose level used decreased the growth of the Sarcoma 180 tumour by 21% in the test animals, but resulted in an increase in growth of 22% for the Adenocarcinoma 755 tumour in the test animals. N.C 16 therapy against lymphoid leukemia L-1210 decreased the mean survival time of the test animals by 2.4%.

Table VI. In vivo anti-cancer testing results for N.C. 16

Cancer	Host	No. of Injections	Day of Sacrifice	Survivors ( ) of ( )		Tumour weight Survival (days) Test	Control	Percent C - T / C
SA	01	14	8	5	6	590	747	21.0%
CA	03	11	12	10	10	740	605	-22.3%
LE	02	Z	Z	6	6	8.0	8.2	- 2.4%

Z = until death

Cancer:

SA = Sarcoma 180

CA = Adenocarcinoma 755

LE = Lymphoid leukemia L-1210

Host:

01 = Swiss (Non-inbred Albino mice)

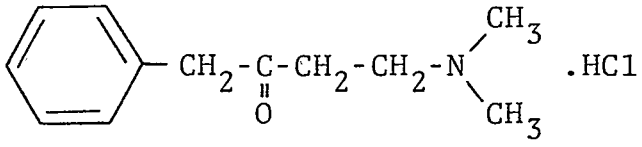
02 = BDF_1 mice

03 = C57BL/6 mice

4. DESCRIPTION OF THE EXPERIMENTAL WORK

4.1 Preparation of derivatives of 1-dimethylamino-4-phenylbutane

4.1.1 Preparation of 4-dimethylamino-1-phenylbutan-2-one hydrochloride

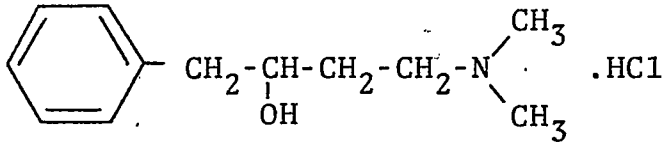


(76)

Phenyl-2-propanone (200 g., 1.495 moles), dimethylamine hydrochloride (93.3 g., 1.145 moles), and paraformaldehyde (34.8 g., 0.387 moles) were dissolved in absolute alcohol (500 c.c.) and heated under reflux with stirring for 6 hours. Removal of the alcohol under reduced pressure gave a thick, orange liquid which was dissolved in water and extracted with benzene to remove unreacted phenyl-2-propanone and paraformaldehyde. The aqueous solution was basified with aqueous sodium hydroxide solution (50% w/v) and extracted with benzene. The combined benzene extracts were washed with aqueous sodium carbonate solution (10% w/v), then with water, and dried over anhydrous magnesium sulphate. Removal of the benzene under reduced pressure gave a pale yellow syrup (149.3 g.) which was dissolved in the minimum quantity of dry acetone, acidified with ethanolic hydrochloric acid (20% w/v), and refrigerated overnight. The colourless crystals (126.7 g.) which deposited were removed by filtration and

repeated crystallization from ether-ethanol gave 4-dimethylamino-1-phenylbutan-2-one hydrochloride (106.4 g, 41% yield) m. pt. 137-138°C. (Sharpe and Dohme Inc., 1953, quote m. pt. 145-146°C. Found C: 63.00%; H: 8.12%; $C_{12}H_{17}NO.HCl$ requires C: 63.29%; H: 7.97%). ν(KBr) 1705s cm^{-1} (C=O). Mass spectrum: prominent m/e peak: 191 (parent peak).

4.1.2 Preparation of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride

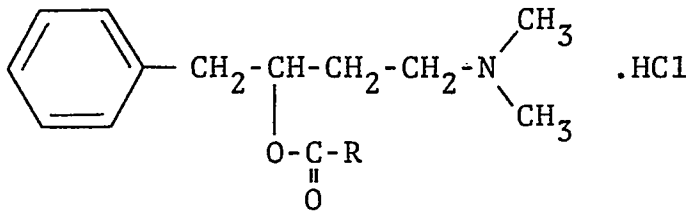


(77)

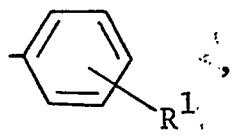
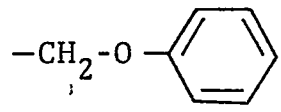
4-Dimethylamino-1-phenylbutan-2-one (94.4 g., 0.493 moles) in dry ether (200 c.c.) was added dropwise to a stirring suspension of lithium aluminum hydride (9.40 g., 0.247 moles) in dry ether (300 c.c.) at such a rate that the ether refluxed gently. The reaction mixture was heated under reflux for 4 hours. On cooling, water (25 c.c.) was added dropwise to decompose the reduction complex at a rate whereby the ether refluxed gently. The inorganic white precipitate was removed by filtration. The ether solution was washed with water and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a pale yellow syrup (76.7 g., 80.5% yield) ν(smear) 3400s cm^{-1} (OH), ν1705s cm^{-1} (C=O) absent.

A small quantity of the reduction product (3.6 g.) was dissolved in the minimum amount of dry acetone, acidified with ethanolic hydrochloric acid (20% w/v), and refrigerated overnight. The colourless, granular crystals which deposited (1.57 g.) were recrystallized from ether-ethanol to give the desired alcohol hydrochloride (1.17 g., 27.4%) m. pt. 141-143°C. The addition of more ether to the original ether-ethanol mother liquor gave colourless, fluffy crystals (2.21g.) which were recrystallized from ether-ethanol to give 4-dimethylamino-1-phenylbutan-2-ol hydrochloride (1.87 g., 43.7%) m. pt. 85-87°C. Both fractions of crystals had identical infrared spectra with ν(KBr) 3310s cm^{-1} (OH), ν1705s cm^{-1} (C=O) absent. (Found: C: 62.60%; H: 8.98%; $C_{12}H_{19}NO.HCl$ requires C: 62.73%; H: 8.77%). Mass spectrum: prominent m/e peak: 193 (parent peak).

4.1.3 Preparation of some esters of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride



(78)

R =  , 

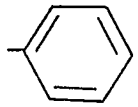
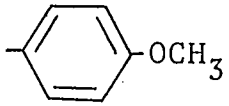
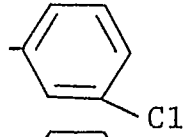
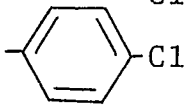
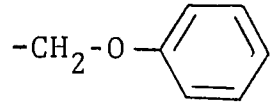
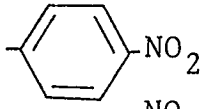
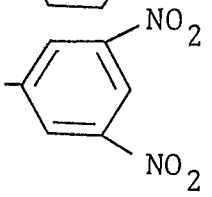
R^1 = H, 4-OCH_3, 3-Cl, 4-Cl, 4-NO_2, 3,5$(NO_2)_2$

A general method for preparing the various esters is as follows:

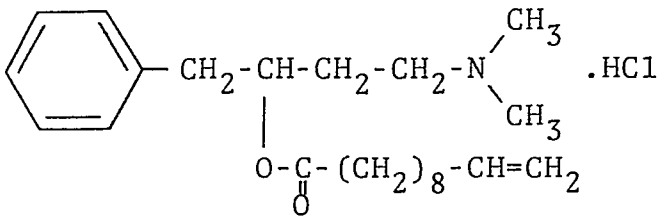
A solution of the acid chloride (0.025 moles) in dry ether (35 c.c.) was added dropwise to a stirring solution of 4-dimethylamino-1-phenylbutan-2-ol (0.025 moles) in dry ether (35 c.c.). The temperature of the reaction was maintained at 0-5°C. during this addition process. The resulting mixture was stirred at room temperature for at least 8 hours. The colourless or pale yellowish-white precipitate (78) was removed by filtration and recrystallized from ether-ethanol to give colourless crystals except for the nitro esters which were pale yellow-white in colour.

The results are summarized in Table VII.

Table VII. Esters of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride

No.	R	Yield (%)	m. pt. (°C)	Analysis Found: C%	Analysis Found: H%	Analysis Calc.: C%	Analysis Calc.: H%	I.R. Spectrum C=O Stretching Frequency	Mass Spectrum P. found	Mass Spectrum P. Calc.
1		40	145-147	68.40	7.47	68.35	7.25	ν1715s cm^{-1} (C=O)	297	297
2		69	204-205(d)	65.80	7.40	66.01	7.20	ν1700s cm^{-1} (C=O)	327	327
3		78	192-193	61.70	6.59	61.96	6.29	ν1725s cm^{-1} (C=O)	331	331
4		65	200-201	61.60	6.62	61.96	6.29	ν1720s cm^{-1} (C=O)	331	331
5		20	170-172	65.50	7.47	66.01	7.20	ν1755s cm^{-1} (C=O)	327	327
6		83	179-180	60.30	6.29	60.23	6.12	ν1725s cm^{-1} (C=O)	342	342
7		81	207-209(d)	53.50	5.52	53.84	5.23	ν1730s cm^{-1} (C=O)	387	387

4.1.4 Attempted preparation of the 10-undecenoyl ester of 4-dimethylamino-1-phenylbutan-2-ol hydrochloride



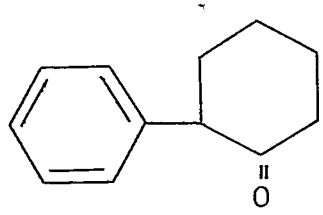
(79)

10-Undecenoyl chloride (5.32 g., 0.0261 moles) in dry ether (35 c.c.) was added dropwise to a stirring solution of 4-dimethylamino-1-phenylbutan-2-ol (5.05 g., 0.0261 moles) in dry ether (35 c.c.), during which time the reaction mixture was kept at 0-5°C. The reaction mixture was stirred at room temperature for 8 hours and the colourless precipitate removed by filtration. The precipitate (2.35 g.) was a waxy, colourless solid. Repeated attempts to recrystallize this product from ether-ethanol or from ether-acetone failed to produce a crystalline salt. Drying in a dessicator over concentrated sulfuric acid also failed to result in a crystalline compound. The infrared spectrum showed ν(smear) 1730s cm^{-1} (C=O) and ν3420s cm^{-1} (OH), indicating a mixture of the ester (79) and alcohol (77).

A second attempt to synthesize the ester, (79) by heating under reflux an ethereal solution of the alcohol in excess of the acid chloride, also failed to produce a crystalline hydrochloride salt. A mixture of alcohol and ester were again indicated from the infrared spectrum.

4.2 Preparation of derivatives of 1-dimethylaminomethyl-3-phenylcyclohexane

4.2.1 Preparation of 2-phenylcyclohexanone



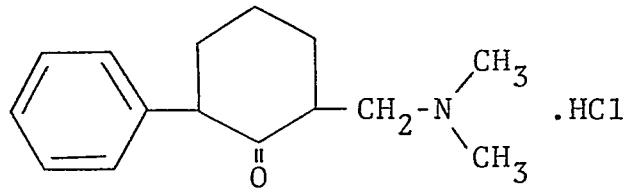
(80)

2-Chlorocyclohexanone (143.7 g., 1.084 moles) was dissolved in dry ether (200 c.c.) and added dropwise to a stirring solution of phenyl magnesium bromide in dry ether (600 c.c.) prepared from bromobenzene (200 g., 1.274 moles) and magnesium shavings (33.1 g., 1.362 moles) by Grignard reaction. The ketone was added at such a rate that the ether refluxed gently. The reaction mixture was heated under reflux for 20 hours with stirring. On cooling, the reaction mixture was decomposed by pouring onto a mixture of crushed ice (600 g.) and concentrated hydrochloric acid (30 c.c.). The ether layer was separated, washed with aqueous sodium carbonate solution (10% w/v), then with water, and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a thick, brownish-black syrup (375 g.).

Fractional distillation of the crude product at 155°C. and 0.5 mm. gave a pink oil in the early fractions (42.3 g.) and a colourless oil in the later fractions (63.1 g.). Upon standing these fractions (80) solidified, giving a pink

solid and a bluish-white solid respectively (total 105.4 g., 56% yield) m. pt. 48-50°C. for both fractions (Newman and Farbman, 1944, quote m. pt. 53-54°C.; Kost and Sugrobova, 1963, quote m. pt. 59-60°C.). The infrared spectra for both fractions was identical with ν(smear) 1715s cm^{-1} (C=O). P.M.R. spectrum: τ2.7 (5H, multiplet, C_6H_5), 6.45 (1H, quartet, J=6 c.p.s., H at 2-position of cyclohexanone ring), 7.3-7.7 (2H, broad multiplet, CH_2 at 6-position of cyclohexanone ring), 7.7-8.8 (6H, broad multiplet, 3 X CH_2 at 3-, 4-, and 5-position of cyclohexanone ring).

4.2.2 Preparation of 2-dimethylaminomethyl-6-phenylcyclohexanone hydrochloride

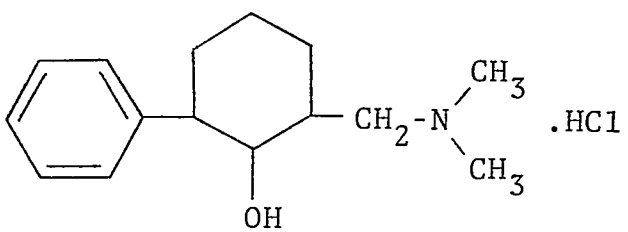


(81)

2-Phenylcyclohexanone (122.9 g., 0.714 moles), paraformaldehyde (72.2 g., 0.802 moles), and dimethylamine hydrochloride (72.2 g., 0.885 moles) were dissolved in absolute alcohol (250 c.c.) and heated under reflux with stirring for 16 hours. The alcohol was evaporated under reduced pressure to give a thick, yellow syrup which was dissolved in water and extracted with ether to remove unreacted ketone and paraformaldehyde. The aqueous solution was basified with aqueous sodium hydroxide solution (50% w/v)

and extracted with benzene. The combined benzene extracts were washed with aqueous sodium carbonate solution (10% w/v), water, and dried over anhydrous magnesium sulphate. The benzene was removed under reduced pressure to give a pale yellow oil, which was dissolved in the minimum of dry acetone and acidified with ethanolic hydrochloric acid (20% w/v). On refrigerating overnight a colourless precipitate (76.7 g.) deposited which was removed by filtration. Repeated recrystallizations from ether-ethanol gave feathery, colourless crystals of 2-dimethylaminomethyl-6-phenylcyclohexanone hydrochloride (71.5 g., 37% yield) m. pt. 153-154°C. (Kost and Sugrobova, 1963,quote m. pt. 159-160°C.; Bachmann and Wick, 1950, quote m. pt. 168-169°C. Found: C: 67.25%; H: 8.70%; $C_{15}H_{21}NO.HCl$ requires C: 67.27%; H: 8.28%). ν(KBr) 1705s cm^{-1} (C=O). Mass spectrum: prominent m/e peak: 231 (parent peak). P.M.R. spectrum: τ2.7 (5H, multiplet, C_6H_5), 6.3 (1H, multiplet, proton at position 6 of cyclohexanone ring), 8.0 (singlet, 2 X CH_3 of $N(CH_3)_2$), 7.1-8.9 (broad multiplet, proton at position 2 and 3 X CH_2 of cyclohexanone ring).

4.2.3 Preparation of 2-dimethylaminomethyl-6-phenylcyclohexanol hydrochloride



(82)

Different reduction systems were employed to find the optimum conditions to produce one or the other of the two geometrical isomers in predominance. In each case the reduction product was analyzed by gas chromatography to determine the percentage of each isomer present. The following general method was used.

The gas chromatographic separations were performed by means of a Microtek Model MT-220 gas chromatograph equipped with a flame ionization detector, and 6 ft. X 3/16 in. glass columns packed with 3% SE-52 adsorbed onto Silanized Chromosorb W (70/80 mesh). The method used nitrogen as the carrier gas at 80 ml./min.; injection temperature 220°C.; column temperature 130°C.; detector temperature 245°C. 1 to 4 µl. of a 1% w/v solution of the reduction product in chloroform was injected into the chromatograph. In each reduction product analyzed, two peaks were found on the recorder chart, corresponding to the two geometrical alcohol isomers. The peaks were integrated to determine the percentage composition of each isomer. In each case Isomer A designates the second isomer to come off the gas chromatograph and Isomer B designates the first isomer to appear. Optimum resolution was achieved with isothermal runs at 130°C, with an average retention time of 30 minutes for Isomer B and an average retention time of 35 minutes for Isomer A.

(a) Reduction with lithium aluminum hydride

A solution of 2-dimethylaminomethyl-6-phenylcyclohexanone (59.6 g., 0.258 moles) in dry ether (250 c.c.) was added dropwise to a stirring suspension of lithium aluminum hydride (4.91 g., 0.129 moles) in dry ether (250 c.c.) at such a rate that the ether refluxed gently. The reaction mixture was heated under reflux with stirring for 4 hours. On cooling, the reduction complex was decomposed by adding water dropwise at a rate to gently reflux the ether. The ether layer was separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a pale yellow syrup (54.0 g., 90% yield) which solidified upon standing. ν(smear) 3240s cm^{-1} (OH), ν1705s cm^{-1} (C=O) absent. Gas chromatographic analysis showed the percentage composition of Isomer A-Isomer B to be 75% - 25%.

(b) Reduction with sodium borohydride

(1) water/ethanol as solvent

Sodium borohydride (0.87 g., 0.0232 moles) was dissolved in cold water (5 c.c.) basified with aqueous sodium hydroxide solution (50% w/v) and added dropwise to a stirring solution of 2-dimethylaminomethyl-6-phenylcyclohexanone (4.33 g., 0.0187 moles) in ethanol (18 c.c.) basified with aqueous sodium hydroxide solution (50% w/v). The reaction mixture was cooled in an ice bath during the addition, after which stirring was continued at room temperature for 20 hours. Glacial acetic acid (5 c.c.) was added dropwise to decompose

the reduction complex and to decompose any unreacted sodium borohydride. The ethanol was removed under reduced pressure, and the residual aqueous solution was basified with aqueous sodium hydroxide solution (50% w/v) and extracted with ether. The ether extracts were combined, washed with aqueous sodium carbonate solution (10% w/v), then with water, and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a colourless syrup (3.76 g., 86% yield) which solidified upon standing. Gas chromatographic analysis gave the percentage composition of Isomer A-Isomer B as 29% - 71%.

(2) water/methanol as solvent

Sodium borohydride (0.49 g., 0.0128 moles) was dissolved in cold water (3 c.c.) basified with aqueous sodium hydroxide solution (50% w/v) and added dropwise to a stirring solution of 2-dimethylaminomethyl-6-phenylcyclohexanone (2.39 g., 0.0103 moles) in methanol (10 c.c.) basified with aqueous sodium hydroxide solution (50% w/v). The reaction mixture was cooled in an ice bath during the addition. The reaction mixture was stirred at room temperature for 18 hours, then decomposed and extracted as described for the preceding experiment to give a colourless syrup (1.95 g., 81% yield) which solidified upon standing. Analysis by gas chromatography gave the percentage composition of Isomer A-Isomer B to be 31% - 69%.

This reduction procedure was repeated using one-half molar quantity of sodium borohydride (0.26 g., 0.00705 moles) with the ketone (3.11 g., 0.0135 moles) giving a colourless solid reduction product (2.97 g., 94.5% yield). Gas chromatographic analysis showed that the product had increased in the percentage of Isomer B, giving a percentage composition of Isomer A-Isomer B of 21% - 79%.

(3) methanol as solvent

Sodium borohydride (0.32 g., 0.00845 moles) as the dry powder was slowly dropped into a stirring solution of the ketone (3.21 g., 0.0139 moles) in methanol (40 c.c.). No cooling was used during the addition. The reaction mixture was stirred at room temperature for 18 hours, then decomposed and extracted as described previously to give a colourless syrup (2.97 g., 91.5% yield) which solidified upon cooling. Gas chromatographic analysis gave the percentage composition of Isomer A-Isomer B as 22% - 78%.

(4) water/isopropanol as solvent

Sodium borohydride (0.43 g., 0.0113 moles) was dissolved in cold water (3 c.c.) basified with aqueous sodium hydroxide solution (50% w/v) and added dropwise to a stirring solution of the ketone (2.08 g., 0.0090 moles) in isopropanol (10 c.c.) basified with aqueous sodium hydroxide solution (50% w/v) and cooled in an ice bath during the addition. The reaction mixture was stirred at room temperature for 18 hours, then decomposed and extracted as before to give a colourless

syrup (1.78 g., 84.5% yield) which solidified upon standing. Analysis of the reduction product by gas chromatography showed the percentage composition of Isomer A-Isomer B to be 31% - 69%.

4.2.4 Separation of the geometrical isomers of 2-dimethylaminomethyl-6-phenylcyclohexanol (82)

The reduction product was separated into the two geometrical isomers by column chromatography on alumina. A general method is described below.

Approximately 35 g. of alumina was used for each gram of reduction product to be chromatographed, a packed column being about 3/4 in. wide and 14 in. long when 3 g. of material were to be separated. The product was eluted with pure Skelly F, followed by 10% ether/Skelly F, 20% ether/Skelly F, and finally 30% ether/Skelly F. The solvents from the individual fractions were removed under reduced pressure and the residue of each fraction was analyzed by gas chromatography. Early fractions yielded one peak, intermediate fractions showed two peaks, and the late fractions again contained one peak. It was observed that the first compound to be eluted from the alumina was the second compound to come off the 3% SE-52 column in the gas chromatograph. Early fractions which were pure in one isomer were combined as were late fractions which were pure in the other isomer. The first compound to be eluted was designated Isomer A; the second compound to be eluted was designated Isomer B.

A typical procedure for the separation of the geometrical isomers is as follows:

The first alumina column run employed the alcohol mixture (1.51 g.) from the lithium aluminum hydride reduction. This material was dissolved in Skelly F (10 c.c.) and chromatographed on adsorption alumina (50.1 g.) wetted with Skelly F. The column was eluted with Skelly F (300 c.c.), 10% ether/Skelly F (300 c.c.), 20% ether/Skelly F (300 c.c.). The eluate was collected in 50 c.c. portions.

Fractions 10 - 13 showed one peak on the gas chromatograph; fractions 14 - 15 appeared as a mixture of the two isomers, and fractions 16 - 18 appeared pure in the other isomer. The pure isomers were converted to their hydrochloride salts.

Preparation of the hydrochloride salt of Isomer A

Fractions 10 - 13 inclusive (0.63 g.) were combined, dissolved in the minimum of dry acetone, and acidified with ethanolic hydrochloric acid (20% w/v). Ether was added until the solution first started to cloud, and the solution was cooled overnight. The colourless solid (0.53 g.) which precipitated was removed by filtration. Repeated recrystallizations from ether-acetone gave colourless crystals (0.49 g.) m. pt. 227-228°C. ν(KBr) 3430s cm^{-1} (OH). (Found: C: 66.30%; H: 9.02%; $C_{15}H_{23}NO.HCl$ requires C: 66.77%; H: 8.96%). Mass spectrum: prominent m/e peak: 233 (parent peak).

Preparation of the hydrochloride salt of Isomer B

Fractions 16 - 18 (0.31 g.) were combined, dissolved in the minimum of dry acetone, and acidified with ethanolic hydrochloric acid (20% w/v). Ether was added as before and upon cooling overnight, a colourless solid (0.17 g.) precipitated out of solution and was removed by filtration. Recrystallization from ether-acetone gave colourless crystals (0.14 g.) m. pt. 200-201°C. ν(KBr) 3410s cm^{-1} (OH). (Found: C: 66.55%; H: 9.04%; $C_{15}H_{23}NO.HCl$ requires C: 66.77%; H: 8.96%). Mass spectrum: prominent m/e peak: 233 (parent peak).

Equal quantities of the hydrochloride salts of Isomer A and Isomer B were mixed together. The mixed melting point was 181-183°C, below that of either Isomer A or Isomer B.

4.2.5 Proof of the structure of the geometrical isomers of 2-dimethylaminomethyl-6-phenylcyclohexanol

(a) Equilibration with sodium/n-pentanol

A solution of the reduction product from the lithium aluminum hydride reduction (2.93 g., 0.026 moles) in dry n-pentanol (10 c.c.) was added to sodium n-pentoxide prepared from sodium (4.01 g., 0.0175 moles) and dry n-pentanol (40 c.c.) and the mixture refluxed for 24 hours. After cooling and decomposing with water, dilute hydrochloric acid (10% w/v) was added and the aqueous layer separated. This was made alkaline with aqueous sodium hydroxide solution (50% w/v) and extracted with ether. The ether extracts were washed with aqueous sodium carbonate solution (10% w/v),

water, and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a colourless syrup (2.65 g., 90.5% yield). Gas chromatography showed that the percentage composition of Isomer A-Isomer B had changed from 75% - 25% to 89% - 11%.

(b) Comparison of the infrared spectra

The infrared spectrum of the hydrochloride salt of Isomer A and Isomer B were both run on potassium bromide discs and the C - O stretching frequencies and the O - H stretching frequencies were compared. The C - O stretching frequency of Isomer A was ν1035s cm^{-1}; Isomer B showed ν995s cm^{-1}. The O - H stretching frequency of Isomer A was ν3430s cm^{-1}; Isomer B showed ν3410s cm^{-1}.

(c) Comparison of the mass spectra

The mass spectra of Isomer A and Isomer B were run under the same conditions and the spectra were compared. In each case, the intensity of the parent peak was compared to that of the prominent m/e 91 peak (tropylium ion?). Isomer A had a parent peak which was 69.5% of the size of the m/e 91 peak; Isomer B had a parent peak which was only 54.5% of the size of the m/e 91 peak.

(d) Comparison of the P.M.R. spectra

The P.M.R. spectra of Isomer A and Isomer B were run at the same concentration (55 mg./0.5 c.c. $CDCl_3$) and under the same experimental conditions.

(i) Isomer A

P.M.R. spectrum on the free base:

τ2.7 (5H, multiplet, C_6H_5), 3.35 (1H, broad hump, hydroxyl proton), 6.4 (1H, 2 overlapping doublets, J=9 c.p.s., proton at 1-position of cyclohexanol ring), 7.8 (6H, singlet, 2 X CH_3 of $N(CH_3)_2$), 7.1-9.3 (10H, broad multiplets, other protons on the cyclohexanol ring and the α-protons in the side-chain at position 2 of the cyclohexanol ring).

Deuterium exchange was used to identify the peak at τ3.35. Two drops of D_2O were added to the probe, followed by vigorous shaking. The spectrum was run at the same experimental conditions again. The peak at τ3.35 had collapsed.

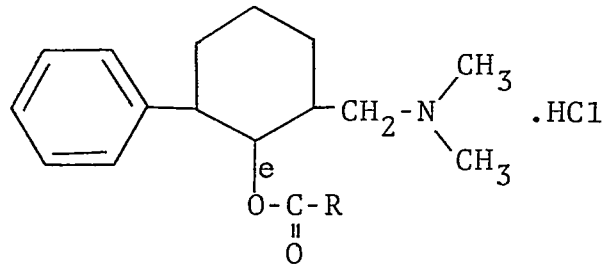
(ii) Isomer B

P.M.R. spectrum on the free base:

τ2.7 (5H, multiplet, C_6H_5), 6.0 (1H, singlet, proton at 1-position of cyclohexanol ring), 6.35 (1H, broad hump, hydroxyl proton), 7.8 (6H, singlet, 2 X CH_3 of $N(CH_3)_2$), 7.1-9.3 (10H, broad multiplets, other 8 protons on cyclohexanol ring, CH_2 of dimethylaminomethyl side-chain).

Deuterium exchange was used to identify the peak at τ6.35. Two drops of D_2O were added to the probe, followed by vigorous shaking. The spectrum was rerun at the same experimental conditions. The peak at τ6.35 had collapsed.

4.2.6 Preparation of some esters of 2-dimethylamino-methyl-6-phenylcyclohexanol hydrochloride (Isomer A)



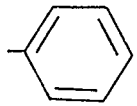
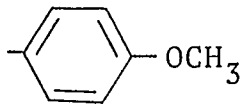
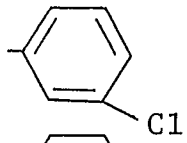
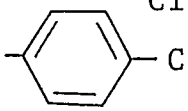
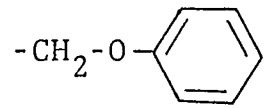
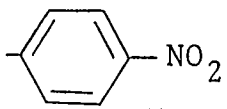
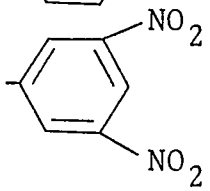
(83)

A general method for preparing the esters is as follows:

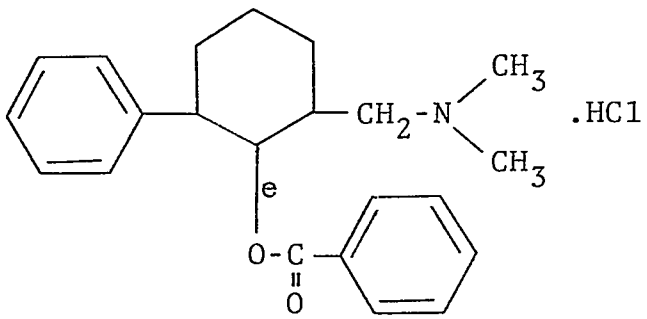
A solution of the acid chloride (0.0069 moles) in dry ether (40 c.c.) was added dropwise to a stirring solution of Isomer A (0.0065 moles) in dry ether (40 c.c.). The temperature of the reaction was maintained at 0-5°C. during the addition process. The resultant mixture was stirred at room temperature for 20 hours. The colourless to pale yellowish-white precipitate was removed by filtration and recrystallized from ether-ethanol to give colourless crystals, except for the nitro esters which were pale yellow-white in colour.

The results are summarized in Table VIII.

Table VIII. Esters of 2-dimethylaminomethyl-6-phenylcyclohexanol hydrochloride (Isomer A)

No.	R	Yield (%)	m. pt. (°C)	Analysis Found: C%	Analysis Found: H%	Analysis Calc.: C%	Analysis Calc.: H%	I.R. Spectrum C=O Stretching Frequency	Mass Spectrum P. found	Mass Spectrum P. Calc.
1		88	272-273	70.50	7.45	70.67	7.55	ν1710s cm^{-1} (C=O)	337	337
2		62	202-205	68.00	7.49	68.39	7.45	ν1730s cm^{-1} (C=O)	367	367
3		61	198-199	64.50	6.78	64.70	6.66	ν1715s cm^{-1} (C=O)	371	371
4		80	202-204	64.80	6.83	64.70	6.66	ν1720s cm^{-1} (C=O)	371	371
5		86	239-241	68.30	7.49	68.39	7.49	ν1755s cm^{-1} (C=O)	367	367
6		89	227-230	63.00	6.63	63.08	6.50	ν1715s cm^{-1} (C=O)	382	382
7		83	135-137	56.77	5.51	56.96	5.65	ν1730s cm^{-1} (C=O)	427	427
8	$-(CH_2)_8-CH=CH_2$	70	193-195	71.10	9.65	71.62	9.71	ν1725s cm^{-1} (C=O)	399	399

P.M.R. spectrum of the benzoyl ester of 2-dimethylaminomethyl-6-phenylcyclohexanol hydrochloride (Isomer A)



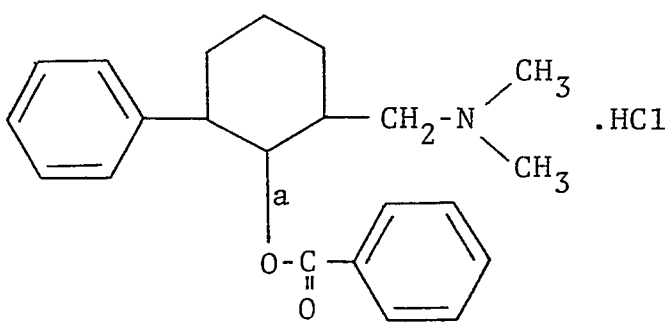
(84)

P.M.R. on free base.

τ2.2 (2H, multiplet, the 2 ortho-protons on the phenyl ring of the benzoyl function), 2.7 (8H, multiplet, all the other aromatic protons of the 2 phenyl rings), 4.85 (1H, 2 overlapping doublets, J=9 c.p.s., proton at position 1 of the cyclohexanol ring), 7.8 (6H, singlet, 2 X CH_3 of $N(CH_3)_2$), 7.1-9.3 (10H, broad multiplets, other protons on the cyclohexanol ring and the CH_2 of the dimethylaminomethyl side-chain).

4.2.7 Preparation of some esters of 2-dimethylaminomethyl-6-phenylcyclohexanol hydrochloride (Isomer B)

Attempted preparation of the benzoyl ester of Isomer B hydrochloride

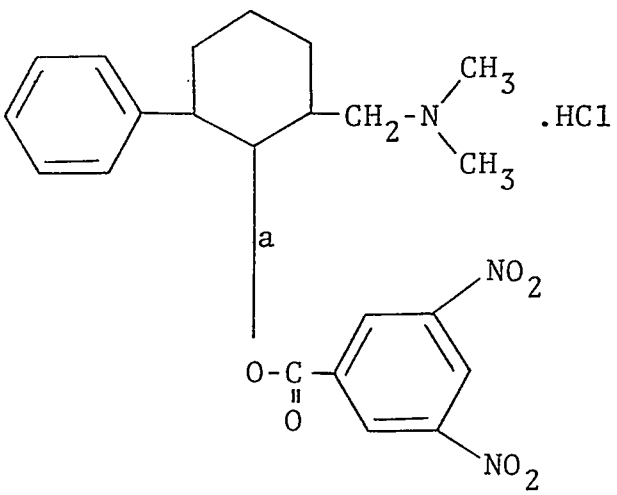


(85)

A solution of benzoyl chloride (0.52 g., 0.00374 moles) in dry ether (25 c.c.) was added dropwise to a stirring solution of Isomer B (0.76 g., 0.00327 moles) in dry ether (20 c.c.). The temperature of the reaction was maintained at 0-4°C. during the addition process. The resulting mixture was stirred at room temperature for 24 hours. The colourless precipitate (0.63 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1705s cm^{-1} (C=O) and ν3330s cm^{-1} (OH), indicating a mixture of the ester (85) and alcohol (82), Isomer B.

This product was refluxed with excess benzoyl chloride (0.71 g.) in dry benzene (50 c.c.) for 48 hours. The brownish-coloured precipitate (0.41 g.) was removed by filtration. The infrared spectrum showed that ν(KBr) 1705s cm^{-1} (C=O) had almost disappeared, leaving the prominent ν3330s cm^{-1} (OH). It appears that the ester (85) had been hydrolyzed to the alcohol (82), Isomer B.

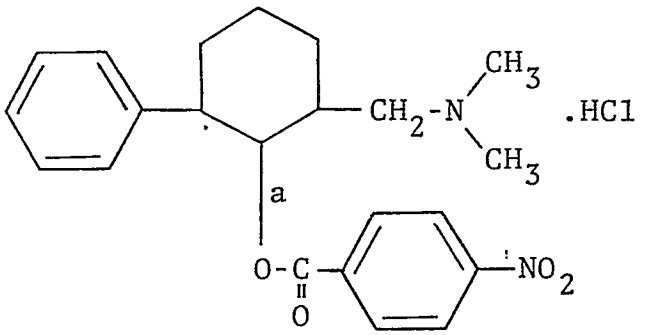
Attempted preparation of the 3,5-dinitro benzoyl ester of Isomer B hydrochloride



(86)

A solution of 3,5-dinitrobenzoyl chloride (0.28 g., 0.00121 moles) in dry acetone (20 c.c.) was added dropwise to a stirring solution of Isomer B (0.28 g., 0.00104 moles) in dry acetone (20 c.c.), maintained at room temperature. The resulting reaction mixture was stirred at room temperature for 8 hours. Part of the acetone was removed under reduced pressure, and ether was added. After cooling overnight, the colourless precipitate (0.22 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 3420s cm^{-1} (OH), with (C=O) absent, indicating that the esterification did not work at all.

Attempted preparation of the 4-nitrobenzoyl ester of Isomer B hydrochloride

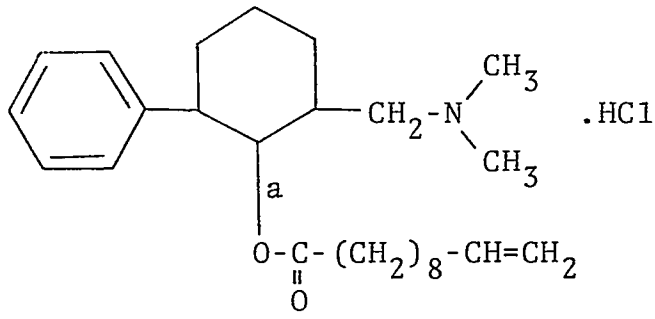


(87)

A solution of Isomer B (0.33 g., 0.00141 moles) in dry ether (10 c.c.) was added dropwise to a stirring solution of phenyl-lithium, prepared from 0.0199 g. of lithium metal and 0.225 g. of bromobenzene by the method of Vogel (1967). A solution of 4-nitrobenzoyl chloride (0.316 g., 0.00170 moles) in dry ether (10 c.c.) was added dropwise to the

resulting solution with stirring, maintaining a temperature of 0-4°C. during the addition process. The reaction mixture was stirred at room temperature for 8 hours. Water (10 c.c.) was added dropwise to decompose any residual lithium metal and to dissolve the lithium salts present. The ether layer was separated, washed with water, and dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave a pale yellow syrup (0.21 g., 30% yield). ν(smear) 1720s cm^{-1} (C=O), ν3410s cm^{-1} (OH), indicating a mixture of the ester (87) and the alcohol (82), Isomer B.

Attempted preparation of the 10-undecenoyl ester of Isomer B hydrochloride

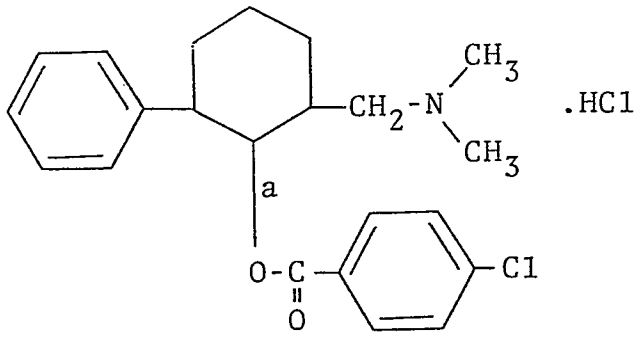


(88)

A solution of 10-undecenoyl chloride (0.26 g., 0.00128 moles) in dry ether (20 c.c.) was added dropwise to a stirring solution of Isomer B (0.14 g., 0.000601 moles) in dry ether (20 c.c.) at room temperature. The reaction mixture was stirred at room temperature for 72 hours. The colourless precipitate (0.18 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1720s cm^{-1} (C=O), ν3340s cm^{-1} (OH), indicating a mixture of the ester (88) and

alcohol (82). No separation of the products was attempted on alumina.

Preparation of the 4-chlorobenzoyl ester of Isomer B hydrochloride



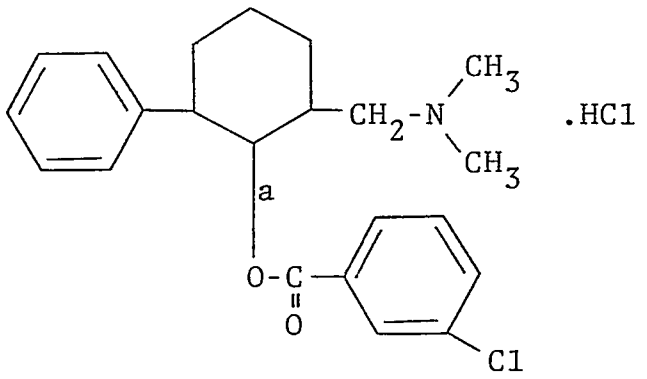
(89)

A solution of 4-chlorobenzoyl chloride (0.77 g., 0.00440 moles) in dry ether (20 c.c.) was added dropwise to a stirring solution of Isomer B (0.92 g., 0.00395 moles) in dry ether (20 c.c.), maintained at 0-4°C. during the addition process. The resulting mixture was stirred at room temperature for 22 hours. The colourless precipitate (1.01 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1720s cm^{-1} (C=O), ν3420s cm^{-1} (OH), indicating a mixture of ester (89) and alcohol (82), Isomer B.

This product was converted to the free base, and part of it (0.54 g.) was placed on a column packed with alumina (40 g.) and wetted with Skelly F. The column was eluted with Skelly F, fractions of 125 c.c. being collected. Each fraction was evaporated to dryness under reduced pressure and the infrared spectrum was run. The first fractions

appeared to be pure ester with ν(smear) 1720s cm^{-1} (C=O), ν3420s cm^{-1} (OH) absent. These fractions were combined, dissolved in the minimum of dry acetone, and acidified with ethanolic hydrochloric acid (20% w/v). Ether was added and the solution refrigerated overnight. No crystalline precipitate formed. The mother liquor was evaporated to dryness and the residue was dried over concentrated sulphuric acid in a dessicator. Again no crystalline salt formed.

Preparation of the 3-chlorobenzoyl ester of Isomer B hydrochloride



(90)

A solution of 3-chlorobenzoyl chloride (0.70 g., 0.0040 moles) in dry ether (30 c.c.) was added dropwise to a stirring solution of Isomer B (0.84 g., 0.0036 moles) in dry ether (30 c.c.). The temperature of the reaction mixture was maintained at 0-4°C. during the addition. The resulting mixture was stirred at room temperature for 22 hours. The colourless precipitate (0.73 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1710s cm^{-1} (C=O), ν3340s cm^{-1} (OH), indicating a mixture of ester (90) and alcohol (82), Isomer B.

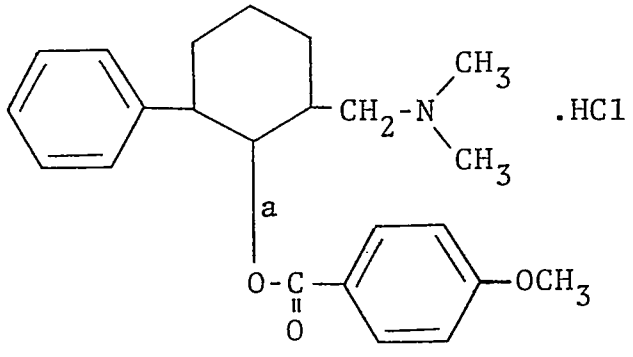
This product was refluxed with excess 3-chlorobenzoyl chloride (0.75 g.) in dry benzene (50 c.c.) for 72 hours. The brownish-coloured precipitate (0.54 g.) was removed by filtration. Recrystallization from acetone gave a colourless powder (0.41 g.) ν(KBr) 3340s cm^{-1} (OH), ν1710s cm^{-1} (C=O) absent, indicating that the ester (90) had been hydrolyzed to the alcohol (82), Isomer B.

In a second attempt to synthesize the ester, a solution of 3-chlorobenzoyl chloride (0.64 g., 0.0036 moles) in dry acetone (10 c.c.) was added dropwise to a stirring solution of Isomer B (0.63 g., 0.0027 moles) in dry acetone (30 c.c.). The temperature of the reaction mixture was maintained at 0-4°C. during the addition process. The resulting mixture was stirred at room temperature for 36 hours. The acetone volume was reduced under reduced pressure and dry ether was added. The resulting precipitate (0.52 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1710s cm^{-1} (C=O), ν3340s cm^{-1} (OH), indicating a mixture of ester (90) and alcohol (82) again.

This product was converted to the free base (0.44 g.) and placed on a column packed with alumina (50 g.), and wetted with Skelly F. The column was eluted with Skelly F, 10% ether/Skelly F, and 20% ether/Skelly F, fractions of 125 c.c. being collected. Each fraction was checked for alcohol absorption by infrared spectroscopy. Those fractions which appeared to be pure ester were combined, dissolved in dry ether, cooled to 0-5°C., and acidified with ethanolic

hydrochloric acid (20% w/v). The colourless precipitate (0.12 g.) was removed by filtration. Recrystallization from acetone gave a colourless powder (0.091 g.) m. pt. 195-197°C. (Found: C: 64.40%; H: 6.96%; $C_{22}H_{26}NO_2Cl.HCl$ requires C: 64.70%; H: 6.66%). ν(KBr) 1710s cm^{-1} (C=O), ν3340s cm^{-1} (OH) absent. Mass spectrum: prominent m/e peak: 371 (parent peak).

Preparation of the 4-anisoyl ester of Isomer B hydrochloride

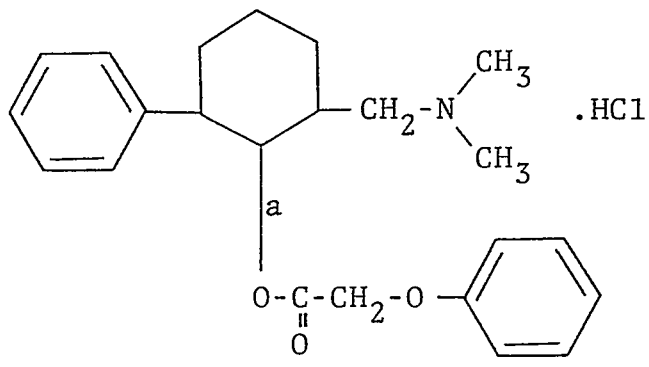


(91)

A solution of 4-anisoyl chloride (1.32 g., 0.00774 moles) in dry ether (20 c.c.) was added dropwise to a stirring solution of Isomer B (0.89 g., 0.00382 moles) in dry ether (40 c.c.) at room temperature. The reaction mixture was heated under reflux for 53 hours. The colourless precipitate (1.14 g.) was removed by filtration. The infrared spectrum showed ν(KBr) 1705s cm^{-1} (C=O), ν3380s cm^{-1} (OH), indicating a mixture of the ester (91) and alcohol (82), Isomer B.

This product was converted to the free base and a portion (0.67 g.) was placed on a column packed with alumina (47 g.) and wetted with Skelly F. The column was eluted with Skelly F, 10% ether/Skelly F, and 25% ether/Skelly F, fractions of 125 c.c. being collected. All fractions were evaporated to dryness under reduced pressure and the infrared spectrum of each fraction was run. The first fractions appeared to be pure ester with ν(smear) 1705s cm^{-1} (C=O), ν3380s cm^{-1} (OH) absent. These fractions were combined, dissolved in dry ether, and acidified with ethanolic hydrochloric acid (20% w/v). The colourless precipitate (0.153 g.) was removed by filtration and recrystallized from ether-ethanol to give colourless crystals (0.096 g.) m. pt. 228-230°C. (Found: C: 67.20%; H: 7.50%; $C_{23}H_{29}NO_3$.HCl requires C: 68.38%; H: 7.48%) ν(KBr) 1705s cm^{-1} (C=O), ν3380s cm^{-1} (OH) absent. Mass spectrum: prominent m/e peak: 367 (parent peak).

Preparation of the phenoxyacetyl ester of Isomer B hydrochloride



(92)

A solution of phenoxyacetyl chloride (0.39 g., 0.00228 moles) in dry ether (30 c.c.) was added dropwise to a stirring solution of Isomer B (0.35 g., 0.00150 moles) in dry ether (30 c.c.). The temperature of the reaction was maintained at 0-5°C. during the addition process. The resultant mixture was stirred at room temperature for 40 hours. The colourless precipitate (0.46 g.) was removed by filtration and recrystallized from acetone to give colourless crystals (0.20 g., 33% yield) m. pt. 222-224°C. (Found: C: 68.05%; H: 7.72%; $C_{23}H_{29}NO_3$.HCl requires C: 68.38%; H: 7.49%). ν(KBr) 1750s cm^{-1} (C=O), ν3410s cm^{-1} (OH) absent. Mass spectrum: prominent m/e peak: 367 (parent peak).

5. APPENDIX

1. Sodium dry ether. This solvent was prepared by placing commercial anhydrous ether over anhydrous magnesium sulphate for 24 hours. The ether was filtered into a dry bottle and sodium wire was added. The bottle was stoppered with a calcium chloride drying tube until the evolution of hydrogen ceased. After 24 hours, the ether was ready for use.
2. Dry acetone. This solvent was prepared by placing commercial anhydrous acetone over anhydrous magnesium sulphate for 24 hours. The acetone was filtered into a dry distilling apparatus and distilled. The first few mls. of distillate were discarded, and the distillation was not carried to dryness. The acetone from the distillation was kept in a tightly stoppered bottle.
3. Absolute alcohol. The commercial anhydrous product as supplied was used without further drying.
4. Extraction and drying procedure. Extractions with benzene or ether were carried out 3 times unless otherwise stated. The organic extracts were dried over anhydrous magnesium sulphate for 20-25 minutes. After filtration by gravity, the solvent was removed on a rotary film evaporator.
5. Conversion of hydrochloride salts to the free base. The hydrochloride salt was dissolved in distilled water and extracted with redistilled ether to remove any organic impurities. The aqueous solution was basified with aqueous sodium hydroxide solution (50% w/v) and extracted

3 times with redistilled ether. The ether extracts were combined, washed with aqueous sodium carbonate solution (10% w/v), distilled water, and dried over anhydrous magnesium sulphate for 20 minutes. The magnesium sulphate was removed by gravity filtration, and the ether evaporated under reduced pressure to yield the free base.

6. Recrystallization solvent systems. Ether, acetone, and ethanol used in recrystallizations were the dry solvents prepared as described in the Appendix.
7. Elemental analyses. These were carried out on a Coleman model 33 carbon-hydrogen analyzer by Mr. R. M. Smith of the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Saskatchewan, Saskatoon, Canada.
8. Infrared absorption spectra. These spectra were recorded on a Unicam SP200G spectrophotometer previously calibrated with polystyrene. Results are expressed in cm^{-1} and the abbreviations are as follows: s = strong, m = medium, w = weak.
9. P.M.R. spectra. These spectra were run on a Varian T60 operating at 35°C. Deuterochloroform solutions of about 0.2 M. were used, with tetramethylsilane as internal reference. P.M.R. spectra were run on the free bases unless otherwise stated. A spinning rate of 40 r.p.s., a sweep time of 250 seconds, and a sweep width of 500 Hz. were employed.

10. Mass spectra. Mass spectra were carried out on an AEl MS12 mass spectrometer by Mr. John Fisher of the Department of Chemistry, University of Saskatchewan, Saskatoon, Canada.

11. Melting points. Melting points were carried out on a Gallenkamp melting point apparatus. All melting points are uncorrected. (d) = decomposition at the melting point.

12. Product drying. Compounds for carbon-hydrogen analysis were dried in an Abderhalden drying pistol at 60-62°C. at 2 mm. for 4 hours.

6. REFERENCES

Allinger, N. L. and Blatter, H. M., J. Amer. Chem. Soc., 83, 994 (1961).

Allsop, I. L., Cole, A. R. H., White, D. E., and Willix, R. L. S., J. Chem. Soc., 4868 (1956).

Atwal, M. S., Bauer, L., Dixit, S. N., Gearien, J. E., Megahy, M., Morris, R., and Pokorny, C., J. Med. Chem., 12, 994 (1969).

Bachmann, W. E., and Wick, L. B., J. Amer. Chem. Soc., 72, 3388-92 (1950).

Barton, D. H. R., J. Chem. Soc., 1027 (1953).

Beckett, A. H., Harper, N. J., Balon, A. D. J., and Watts, T. H. E., Tetrahedron, 6, 319-330 (1959).

Bender, M. L., J. Amer. Chem. Soc., 73, 1626 (1951).

Berger, F. M., J. Pharmacol. Exptl. Therap., 104, 468 (1952).

Biemann, K., and Seibl, J., J. Amer, Chem. Soc., 81, 3149 (1959).

Blicke, F. F., and Blake, E. S., ibid., 52, 236 (1930).

Boots, M. R., J. Med. Chem., 12, 426-428 (1969).

Bordwell, F. G., "Organic Chemistry," The MacMillan Company, New York, 1963, p. 297.

Bottari, F., Saettone, M. F., and Serafini, M. F., J. Med. Chem., 11, 904 (1968).

Brown, H. C., Mead, E. J., and Subba Rao, B. C., J. Amer. Chem. Soc., 77, 6209 (1955).

Brown, H. C., and Subba Rao, B. C., ibid., 78, 2582 (1956).

Brown, H. C., Mead, E. J., and Sharp, C. J., ibid., 78, 3616 (1956).

Brown, H. C., Mead, E. J., and Tierney, P. A., ibid., 79, 5400 (1957).

Casy, A. F., Harper, N. J., and Dimmock, J. R., J. Chem. Soc., 3635 (1964).

Chapman, N. B., Parker, R. E., and Smith, P. J. A., ibid., 3634 (1960).

Cole, A. R. H., Jones, R. N., and Dobriner, K., J. Amer. Chem. Soc., 74, 5571 (1952).

Dauben, W. G., Fonken, G. J., and Noyce, D. S., J. Amer. Chem. Soc., 78, 2579 (1956).

Denton, J. J., Turner, R. J., Neier, W. B., Lawson, V. A., Schedl, H. P., ibid., 71, 2048 (1949a).

Denton, J. J., Lawson, V. A., Neier, W. B., and Turner, R. J., ibid., 71, 2052 (1949b).

Denton, J. J., and Lawson, V. A., ibid., 72, 3279-3795 (1950).

Dircherl, W., and Dardenne, U., Biochem. Z., 325, 195-209 (1954), c.f., C.A. 48, 7089d.

Eliel, E. L., and Ro, R. S., J. Amer. Chem. Soc., 79, 5992 (1957).

Eliel, E. L., and Rerick, M., ibid., 82, 1367 (1960).

Eliel, E. L., Allinger, N. L., Angyal, S. J., Morrison, G. A., "Conformational Analysis," Interscience Publishers, New York, 1966, p. 44.

Eliel, E. L., Haubenstock, H., and Acharya, R. V., J. Amer. Chem. Soc., 83, 2351 (1961).

Friess, S. L., and McCarville, W. J., ibid., 76, 1363, 2260 (1954).

Friess, S. L. and Baldridge, H. D., ibid., 78, 2482 (1956).

Friess, S. L., Patchett, A. A., and Witkop, B., ibid., 79, 459 (1957).

Garson, L. R., and Quintana, R. P., J. Med. Chem., 12, p. 538-540 (1969).

Gaylord, N. G., "Reduction With Complex Metal Hydrides," Interscience Publishers Inc., New York, 1956, p. 89.

Haleblian, J. K., and McCrone, W., J. Pharm. Sci., 58, 911 (1969).

Hardy, K. D., and Wicher, R. J., J. Amer. Chem. Soc., 80, 640 (1958).

Harper, N. J., 1962, "Progress in Drug Research," Jucker, E., Birkhäuser Verlag, Basel, Vol. 4, p. 223.

Hennion, G. F., and O'Shea, F. X., J. Amer. Chem. Soc., 80, 614 (1958).

Huitric, A. C., Clarke, W. G., Leigh, K., and Staiff, D. C., J. Org. Chem., 29, 3106 (1964).

Jackman, L. M., Macbeth, A. K., and Mills, J. A., J. Chem. Soc., 2641 (1949).

Junkmann, K., and Witzel, H., Z. Vitamin-, Hormon-, u. Fermentforsch, 9, 97-143 (1957), c.f., C.A. 52, 16593f.

Karplus, M., J. Chem. Phys., 30, 11 (1959).

Kost, A. N., and Sugrobova, I. P., Vestn. Mosk. Univ. Ser. 11, Khim., 18 (3), 75-9 (1963), c.f., C.A. 59, 7460a.

Kupchan, S. M., Casy, A. F., and Swintosky, J. V., J. Pharm. Sci., 54, 514 (1965).

Lemieux, R. U., Kullnig, R. K., Berstein, H. J., and Schneider, W. G., J. Amer. Chem. Soc., 80, 6098 (1958).

Luts, H. A., and Nobles, W. L., J. Pharm. Sci., 54, 67-70 (1965).

Mannich, C., and Lammering, D., Ber., 55, 3510 (1922).

May, M., and Triggle, D. J., J. Pharm. Sci., 57, 511-513 (1968).

Nace, H. R., and O'Connor, G. L., J. Amer. Chem. Soc., 73, 5824 (1951).

Newman, M. S., and Farbman, M. D., ibid., 66, 1550-2 (1944).

Nobles, W., and Burckhalter, J., J. Amer. Pharm. Assoc., 47, 80 (1958).

Noyce, D. S., and Dolby, L. J., J. Org. Chem., 26, 3619 (1961).

Ouellette, R. J., J. Amer. Chem. Soc., 86, 3089 (1964).

Qureshi, A. M., 1970, Private communication.

Riley, R. F., and Berger, F. M., Arch. Biochem, 20, 1959 (1949).

Schultz, E. M., and Bicking, J. B., J. Amer. Chem. Soc., 75, 1128 (1953).

Sharpe and Dohme Inc., Brit., 693, 128 (1953).

Takahashi, T., Hori, M., and Okamura, K., Yakugaku Zasshi, 78, 18-22 (1958), c.f., C.A. 52, 10913g.

Taylor, E. D., and Nobles, L. W., J. Amer. Pharm. Assoc. Sci., 49, 317-19 (1960).

Tiffeneau, Ann. Chim., (8), 10, 322-78 (1907).

Tiffeneau and Tchoubar, Compt. rend., 198, 941-3 (1934).

Triggle, D. J., and Belleau, B., Can. J. Chem., 40, 1201 (1962).

Varma, R. S., Ali, B., Parmar, S. S., and Nobles, W. L., J. Med. Chem., 13, 147 (1970).

Vogel, A. I., "A Text-Book of Practical Organic Chemistry," Longmans, Green and Co., Ltd., London, 3rd ed., 1967, p. 931.

Wagner-Jauregg, T., Freudenberg, Stereochemie, p. 866, Franz Deuticke, Leipzig (1932).

Williams, R. T., "Detoxification Mechanisms," John Wiley & Sons Inc., New York, N.Y., 1959, p. 46.

Williamson, K. L., and Johnson, W. S., J. Amer. Chem. Soc., 83, 4623 (1961).

Wilson, W., and Kyi, Z., J. Chem. Soc., 1321 (1952).

Winstein, S., and Holness, N., J. Amer. Chem. Soc., 77, 5562 (1955).