STUDIES IN SYNTHETIC ANALGESICS

by
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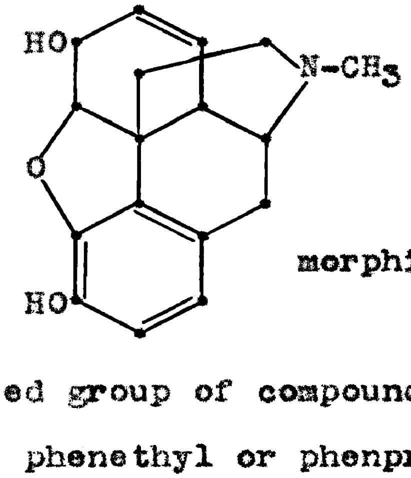
HISTORICAL

This thesis is a report on the syntheses of substances which either have been or are to be biologically tested for analgesic activity. It fits into a larger piece of work which might very ambitiously be described as an attempt to recognize those structural features of an organic molecule which either cause or lead to deadening of pain or, as probably better described, "increase of pain threshold". The historical portion of this thesis deals primarily with those investigations which have been carried out along this line and since the investigation reported in this thesis does not relate to the synthesis of morphine, as such, the chemical work on this natural product is not included.

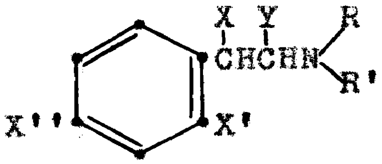
A quick examination would seem to indicate that a wide variety of unrelated compounds have been synthesized, but many of them can be related, on closer inspection, to certain features of the morphine molecule. For purposes of later reference the accepted structure of the morphine molecule is given below.



morphine

One widely studied group of compounds is the aralkylamines, primarily the phenethyl or phenpropyl derivatives. Inspection of the morphine molecule shows clearly that both of these structural units are present; the phenyl group separated from the nitrogen atom by two and by three carbon atoms.

A large number of amines have been reported which can be included in the general formula:



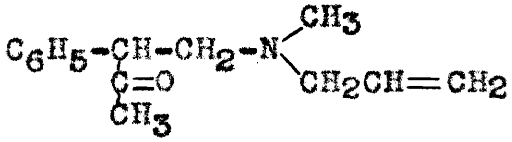
Suter (1) has reported compounds of this type where:

1) R is H or CH_3; R' is H or CH_3; Y is H; X is H or OH and X',X'' is H, OH or OCH_3
2) R is H; R' is H, CH_3; Y is CH_3 and X,X',X'' is H
3) R is H; R' is H, CH_3, C_3H_7, C_4H_9, $C_6H_5CH_2$; Y is CH_3; X,X' is H and X'' is NH_2, CH_3, CH_3O, OH, CH_3COO.

Hildebrandt (2) prepared similar compounds where R is H, alkyl or cycloalkyl, R' is alkyl with at least two carbon atoms, Y is CH_3, X and X' are H and X'' is OH by condensation of p-hydroxybenzylmethyl ketone with the alkyl or cycloalkyl amine followed by reduction to the desired compound.

Several amines exhibiting high anesthetic activity were synthesized in a similar manner by Heinzelman (3). Fourteen compounds in which R and R' were hydrogen or various alkyl groups, Y was methyl, X was hydrogen or an alkyl group, X' was methoxyl and X'' was hydrogen were reported.

A related compound possessing slight analgesic activity as the hydrochloride is the amine prepared by Avison and Morrison (4) by the reaction of benzylmethyl ketone with formaldehyde and methylallylamine.

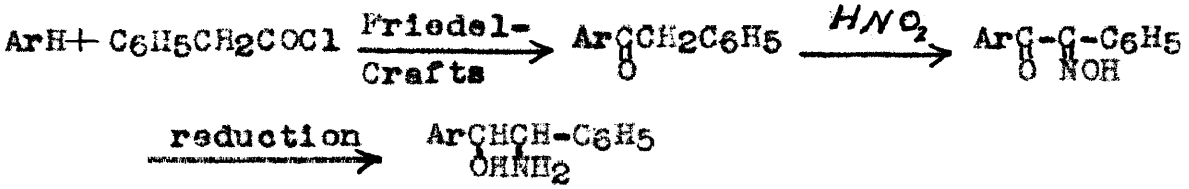


$$C_6H_5-\underset{\underset{CH_3}{|}}{\underset{C=O}{|}}{CH}-CH_2-N\begin{smallmatrix}CH_3\\ CH_2CH=CH_2\end{smallmatrix}$$

Smith et. al. (5) prepared ten α-aminophenacylpyridines and quinolines by the treatment of the α-bromophenacylheterocycle with the secondary amine. The compounds prepared were of the general formula $R_1\underset{NR_2}{CH}COR_2$ where $-NR_2$ was diethylamino, piperidyl or morpholinyl, R_1 was pyridyl or quinolyl and R_2 was phenyl or p-chlorophenyl. Two of these compounds, 4-(α-(1-piperidyl)-phenacyl)pyridine dihydrochloride and 2-(α-(1-piperidyl)-4-chlorophenyl)pyridine dihydrochloride approximate codeine in their activity.

A large number of N-substituted 1,2-diarylethylamines have been prepared by Moffett (6)(7) by the reaction of benzylmagnesium chloride with the Schiff's base resulting from the reaction of a primary amine with a substituted benzaldehyde. Vanillin, m-hydroxy-, p-hydroxy-, m-ethoxy-, 2,3-dimethoxy-, and 3,4-dimethoxybenzaldehyde are examples of the compounds used. The general formula of the resulting amines is $Ar\underset{NHR}{CH}CH_2C_6H_5$ where Ar is the substituted phenyl group. Most of these compounds exhibited weak analgesic activity and were tested as the hydrochlorides.

McPhee and Erickson (8) studied similar compounds as well as the β-hydroxy derivatives. The β-hydroxy compounds were synthesized as follows:

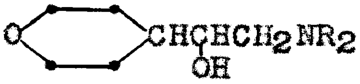


$$ArH + C_6H_5CH_2COCl \xrightarrow[\text{Crafts}]{\text{Friedel-}} Ar\underset{O}{\overset{}{\underset{\|}{C}}}CH_2C_6H_5 \xrightarrow{HNO_2} Ar\underset{O}{\underset{\|}{C}}-\underset{NOH}{\underset{\|}{C}}-C_6H_5$$

$$\xrightarrow{\text{reduction}} Ar\underset{OH}{CH}\underset{NH_2}{CH}-C_6H_5$$

The most active compounds were found to be ∝-phenyl-β-(3-methoxy-4-hydroxyphenyl)ethylamine and ∝-phenyl-β-(4-hydroxyphenyl)-β-hydroxyethylamine.

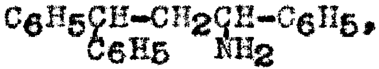
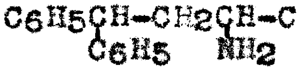
Some N-alkylated-1,2-diphenylethylamines have also been prepared by Goodson et. al. (9) by the Leuckart reaction and were found to exhibit slight analgesic activity.

Burger and coworkers (10)(11)(12) have studied several heterocyclylethylamines. For example, tetrahydropyranyl amino alcohols of the formula 

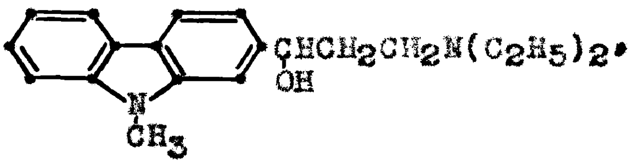
were prepared where NR_2 was diethylamino, morpholinyl or piperidyl. These compounds exhibited some analgesia. Similar compounds in which the tetrahydropyran group was replaced with a 2,3-dihydrobenzofuran group were prepared and showed mild analgesia at nearly toxic doses. A pyridine derivative, β-(6-methyl-2-pyridyl)isopropylamine, was also found to have slight activity.

Suter (1) has reported a large group of arylpropylamines, the homologues of the arylethylamines first mentioned. In addition, Geigy (13) has found analgesic activity in a group of phenoxyphenylalkylamines. An example of these compounds is 1-(4-(p-methoxyphenoxy)phenyl)-2-methyl-3-ethylaminopentane.

Good analgesic properties were exhibited in a series of 1-(p-hydroxyphenyl)-3-alkylaminobutanes prepared by Kulz (14). The alkyl group was allyl, cyclopentyl, methyl, butyl or benzyl.

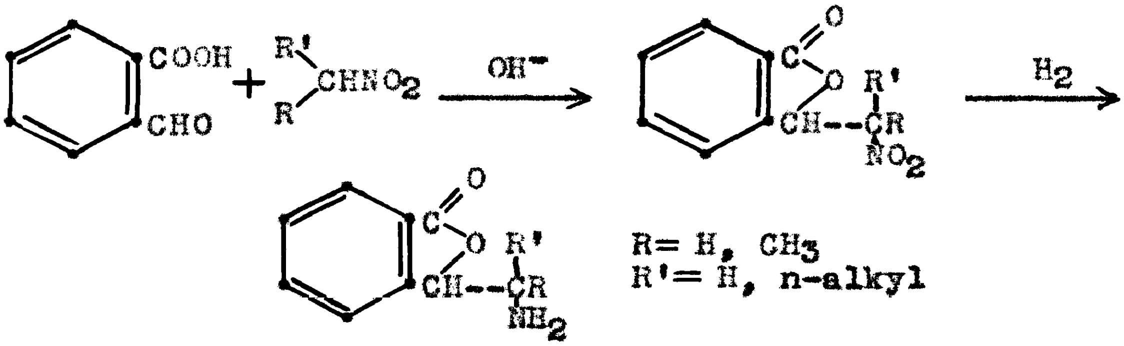
Burckhalter and Johnson (15) synthesized several γ-arylpropylamines of the following structure,  $C_6H_5\underset{R}{C}HCH_2\underset{\underset{R''}{NR'}}{C}H-R'''$, where R is H or phenyl, R' and R'' are H or alkyl and R''' is phenyl or methyl. It was their purpose to determine the effect of large space-occupying groups in the phenpropylamine skeleton which might possibly result in a spatial relationship more similar to that found in morphine. α-(Benzhydrylmethyl)benzylamine,  $C_6H_5\underset{C_6H_5}{CH}-CH_2\underset{NH_2}{CH}-C_6H_5$, was found to have an activity approaching morphine while 4,4-diphenyl-2-butylamine,  $C_6H_5\underset{C_6H_5}{CH}-CH_2\underset{NH_2}{CH}-CH_3$, was less effective. All of these amines were found to be rather toxic.

2-(3-Diethylamino-1-hydroxy-n-propyl)-9-methylcarbazole,



prepared by Ruberg and Small (16) by catalytic reduction of the aminoketone resulting from a Mannich reaction of 2-acetyl-9-methylcarbazole, approaches codeine in analgesic action but exhibits a disadvantageous convulsant effect.

An interesting group of compounds which can be considered related to the phenethylamines is the aminophthalidylalkanes synthesized by Ullyot et. al. (17). This molecule



has the aminoalcohol benzoate structure found in local anesthetics as well as the phenethylamine structure. Some of these compounds exhibited analgesic activity but no local anesthesia. If R=hydrogen there was no activity; if R=methyl the activity was slight and increasing R beyond ethyl to pentyl decreased activity and increased toxicity. No activity was present if the amino group was substituted.

Various quinoline and isoquinoline compounds have been studied. In most instances these compounds exhibit antispasmodic, rather than analgesic, activity. However, quinoline compounds with a basic side chain of adequate length in position 8 were found by Sinha (18) to exhibit anesthetic activity. 2-Alkoxy-4-aminoquinolines and 2-alkoxy-3-aminoquinolines were synthesized by Wojahn and Kramer (19) and exhibited anesthetic activity. Martin and Hanslick (20) reported that the mineral acid salts of 5,8-bis(diethylaminomethyl)quinoline are analgesics. Coates and coworkers (21) synthesized a number of monopyridyl, dipyridyl and substituted pyridylquinolines all of which were active antispasmodics.

Considerable work on the isoquinolines has been done by Külz and Hornung (22) who found antispasmodic and analgesic activity in certain of these compounds. The nitrogen-containing nucleus could be hydrogenated, non-hydrogenated, or partially hydrogenated. At least two entiroly or partially esterified or etherified hydroxyl groups in one phenyl nucleus and no hydroxyl groups, free or otherwise, in the other phenyl nucleus were necessary. Also required was aralkyl group substitution in the 1- or 2-position.

Fodor et. al. (23) found spasmolytic activity in 6,7-diethoxy-3-ethyl-, -3-propyl-, and -3-phenylisoquinoline and 6,7-diethoxy-3-phenyl-1-methylisoquinoline.

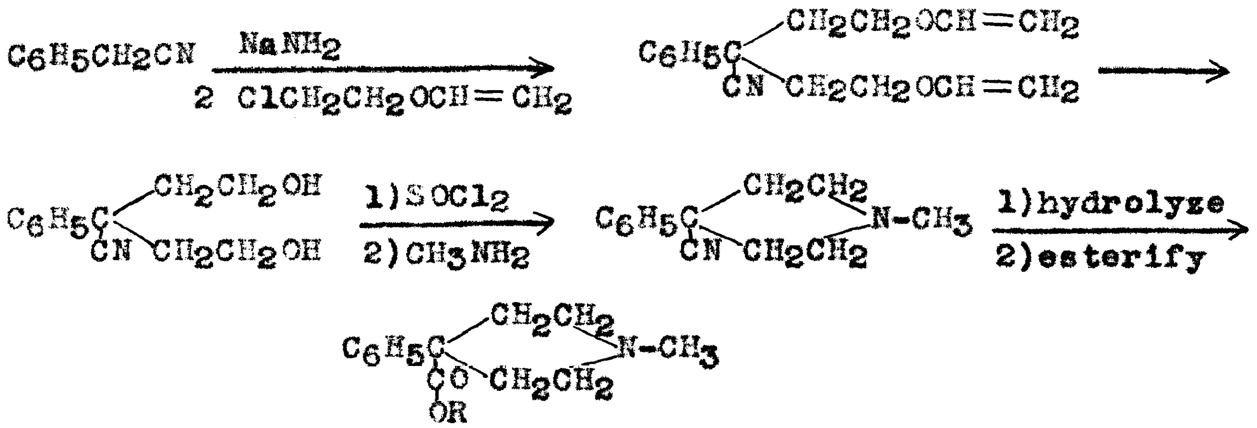
An extensive survey of the work done on phenanthrene derivatives has been reported by Small et. al. (24) and therefore will not be discussed here.

It can be seen from an inspection of the morphine molecule that there is a phenyl group situated in the 4-position of a piperidine ring. Compounds of the 4-phenylpiperidine type, usually further substituted in the 4-position, have received considerable interest.

Blicke and Krapcho (25) reported the synthesis of 1-methyl-3-keto-4,4-diphenylpiperidines and Sperber, Sherlock and Papa (26) prepared 1-methyl-4,4-diphenylpiperidine. These compounds showed no activity.

Most of the 4-phenylpiperidine compounds studied are those in which there is another group substituted in the 4-position. One of the most well-known compounds of this type is the drug "Demerol" (also known as Dolantin or pethidine), 1-methyl-4-phenyl-4-carbethoxypiperidine hydrochloride. Eisleb (27) synthesized Demerol and related piperidine compounds by the sodamide alkylation of phenylacetonitrile with the dichloroamine, $CH_3N(CH_2CH_2Cl)_2$, followed by hydrolysis of the nitrile and esterification of the acid formed.

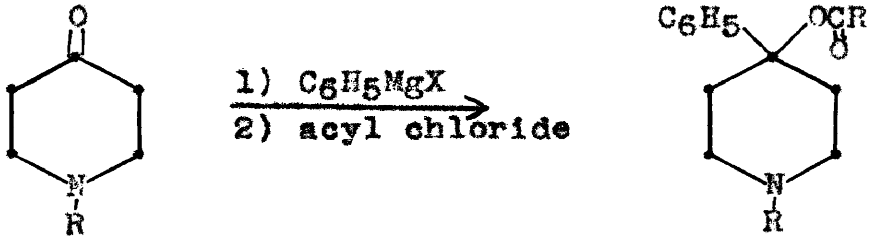
Bergel et. al. (28) synthesized Demerol and esters other than the ethyl ester by the following series of reactions:



Thorp and Walton (29) studied the effect of other alkyl groups on the nitrogen atom of Demerol. They determined that the toxicity increases with the length of the alkyl chain and analgesia increases slightly up to n-propyl.

In order to simulate the hydroxyl group in morphine, Morrison and Rinderknecht (30) prepared ethyl 4-(m-hydroxyphenyl)-1-methylpiperidine-4-carboxylate. This compound is known as "bemidone".

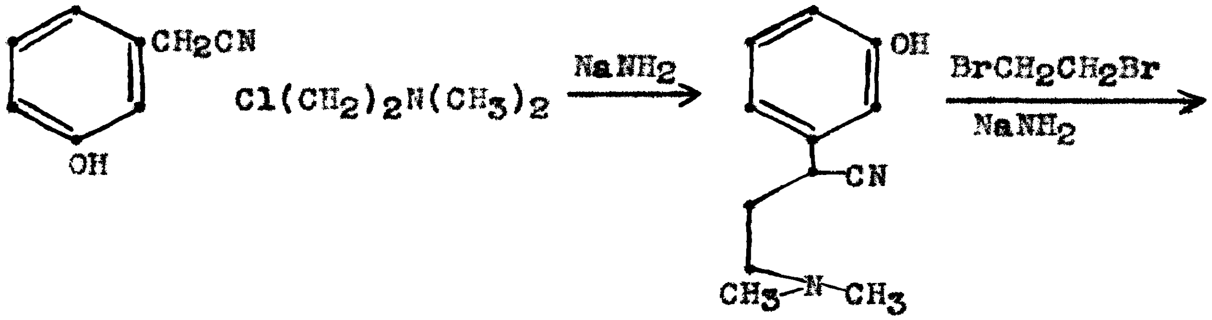
Ziering and coworkers (31)(32) prepared compounds similar to the Demerol structure in which the carbethoxy group is replaced by an acyloxy group.

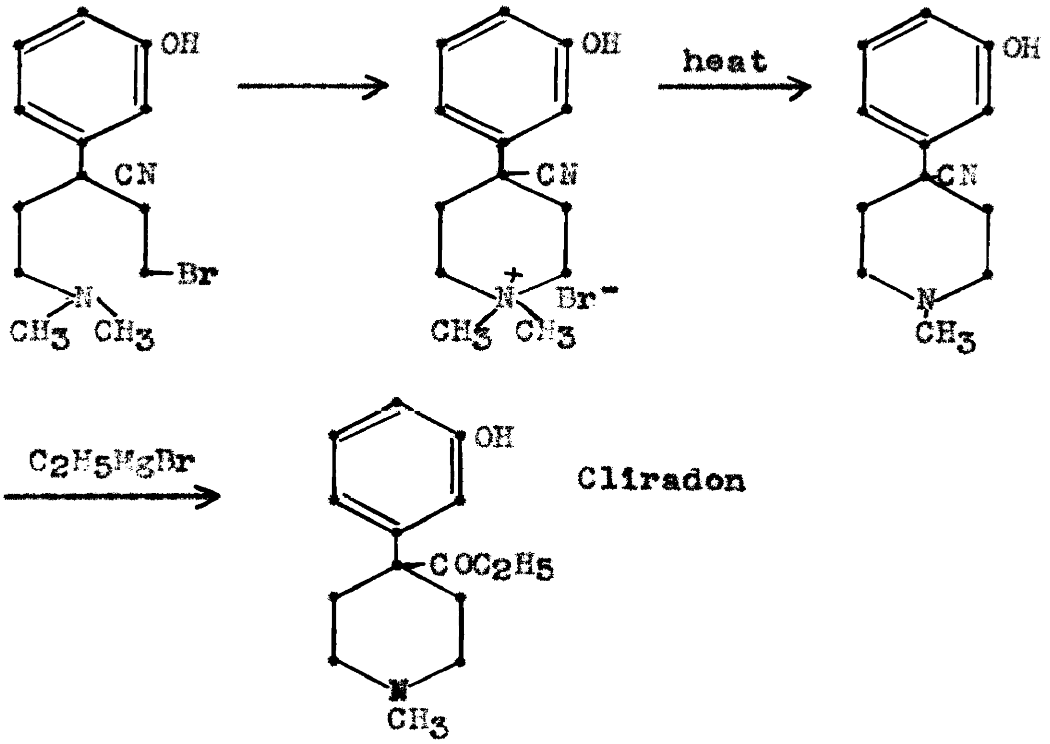


1-Methyl-4-phenyl-4-propionoxypiperidine was found to be as active at a level of 1 mg. as 25 mg. of Demerol or 3 mg. of morphine. Increase in R above methyl or substitution in the phenyl group results in a decrease in activity. These workers feel the increased activity may be due to the fact that Stuart models show the acyloxy side chain seems to simulate the cyclohexane ring in models of morphine. The 4-phenyl group was replaced with 4-alkyl, 4-cycloalkyl or 4-heterocyclyl groups and in most instances decreased activity resulted. The β-pyridyl derivative was found to have half the activity and half the toxicity of Demerol.

Ziering and Lee (33) in an effort to determine to what extent the remaining parts of the cyclohexane ring in morphine contribute to the analgesic effect substituted a methyl group in the 3-position of 1-methyl-4-propionoxypiperidine. As was expected two forms were obtained, one much more active than the other and probably spatially related to dihydrodesoxymorphine.

A very extensive study of compounds containing a keto side chain in the 4-position of the 4-phenylpiperidines was carried out by Kagi and Miescher (34). The drug known as "Cliradon", 1-methyl-4-(m-hydroxyphenyl)-4-piperidylethyl ketone, was the result of this work. This material exhibits more analgesic activity than morphine.

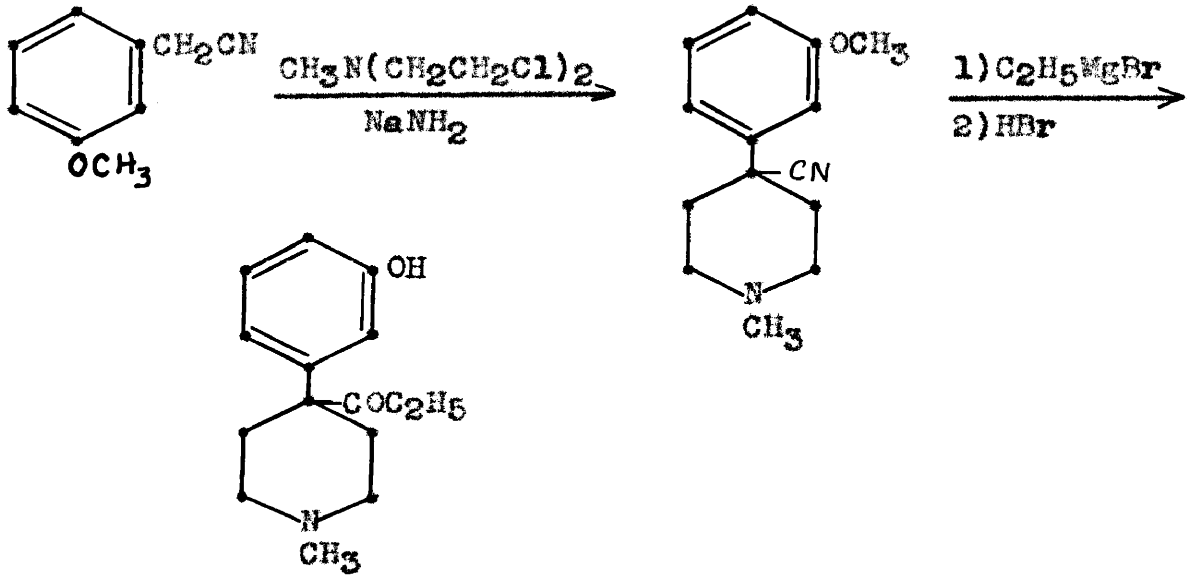




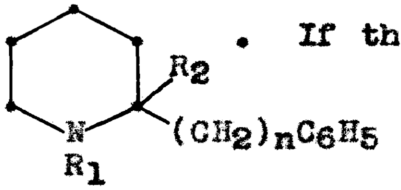
Cliradon

A large number of related compounds were prepared to study the effect of lengthening the keto side chain, of moving the hydroxyl group to the ortho position, and of acetylation or methylation of the hydroxyl group. It was found that the compound containing the ethyl ketone and the free meta hydroxyl group was the most effective one.

Cliradon (also known as ketobemidone) was later prepared by Avison and Morrison (35).

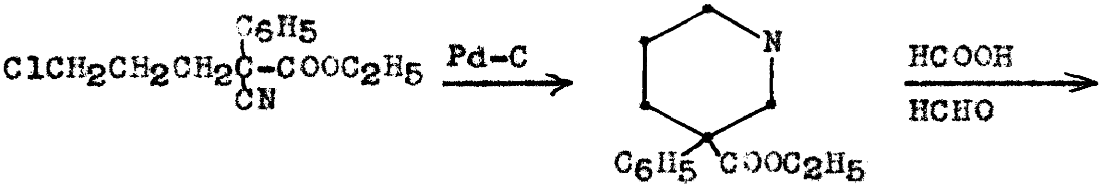


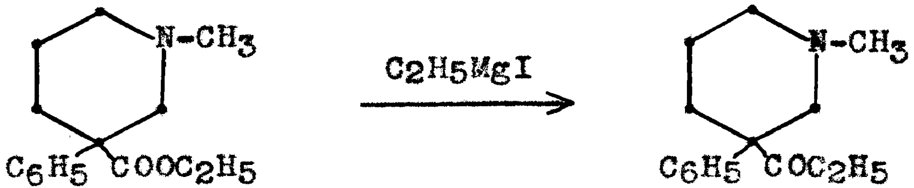
Spielman (36) has reported analgesic activity in 4-phenyl-1-alkylpiperidine acid lactones. The 1-methyl-4-substitutedphenyl-4-cyanopiperidine was prepared and treated with hydrogen bromide to form the lactones. The phenyl group in these compounds was substituted in the 3 or 6 position with hydroxyl, methoxyl or alkyl groups.

The morphine molecule also contains a 2-benzylpiperidine structure. Anker et. al. (37) synthesized 2-benzylpiperidine, 1-β-methoxyethyl- and 1-β-ethoxyethyl-2-benzylpiperidine. Lee et. al. (38) prepared a group of compounds with the general formula 

. If the phenyl group was attached directly to the piperidine nucleus ($R_1 = CH_3$, $R_2 = H$, $n = 0$) the compound was inactive. If the phenyl group was linked to the piperidine ring by a $-CH_2-$ group the compound was still inactive. Low activity was exhibited when the side chain was increased to two carbon atoms.

The 3-phenyl derivatives were synthesized in order to compare them with the 2- and 4-phenylpiperidines. Avison and Morrison (39) prepared ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (metadine) and related compounds.

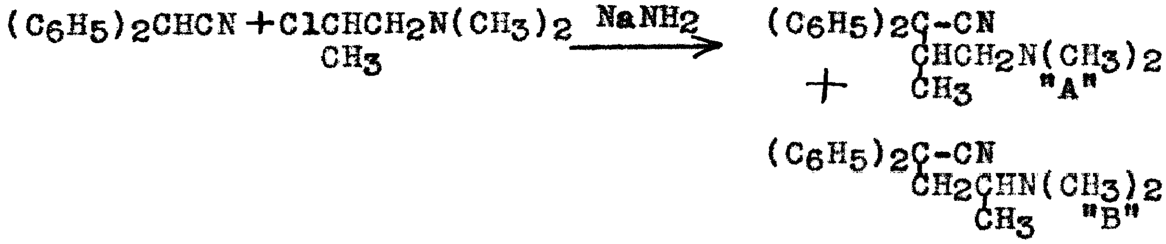




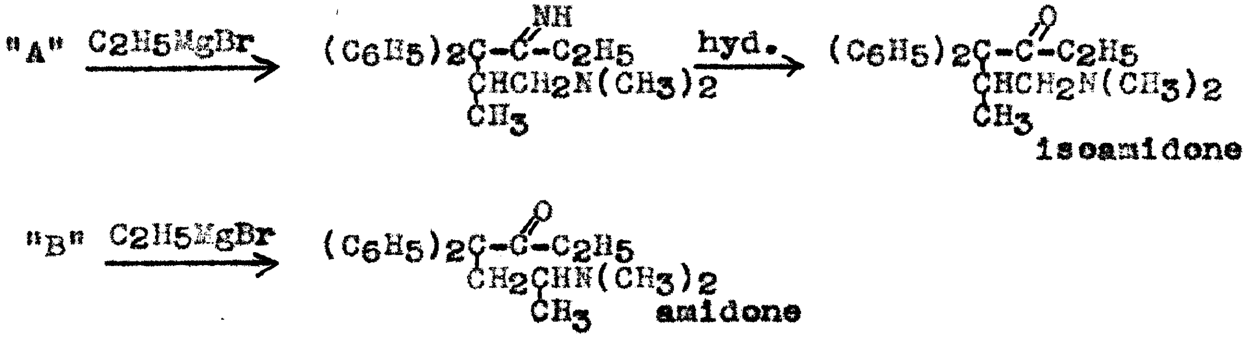
metadine

In view of the activity of metadine, the 3-acyloxy-3-phenylpiperidines were prepared for comparison with the highly active related 4-phenyl compounds. Both the 3-propionoxy and the 3-ethyl ketone compounds were less active then metadine itself. The relation between structure and activity does not follow parallel paths in the 3- and 4-phenylpiperidine series. Apparently the analgesic action of metadine is exerted through a different mechanism than the morphine-like drugs since it stimulates respiration and antagonizes the morphine-induced Straub reaction.

The open-chain analogues of the 4-phenylpiperidine compounds are of considerable importance as analgesics. The most widely known drug of this type is "Amidone"(Methadon). The reaction of diphenylacetonitrile with 2-chloro-1-dimethylaminopropane results in two nitriles which, in turn, yield two isomeric ketones on treatment with a Grignard reagent. The structures of the two nitriles and the two ketones have been established (40)(41)(42).



$$(C_6H_5)_2CHCN + \underset{CH_3}{ClCH}CH_2N(CH_3)_2 \xrightarrow{NaNH_2} (C_6H_5)_2C\text{-}CN\,\underset{CH_3}{CH}CH_2N(CH_3)_2 \text{ "A"} + (C_6H_5)_2C\text{-}CN\,CH_2\underset{CH_3}{CH}N(CH_3)_2 \text{ "B"}$$



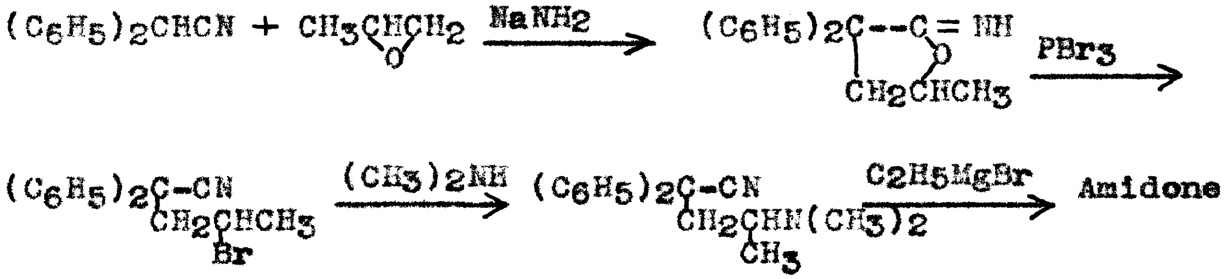
$$\text{"A"} \xrightarrow{C_2H_5MgBr} (C_6H_5)_2\underset{\substack{CHCH_2N(CH_3)_2\\ CH_3}}{C}-\overset{NH}{\overset{\|}{C}}-C_2H_5 \xrightarrow{hyd.} (C_6H_5)_2\underset{\substack{CHCH_2N(CH_3)_2\\ CH_3}}{C}-\overset{O}{\overset{\|}{C}}-C_2H_5$$

isoamidone

$$\text{"B"} \xrightarrow{C_2H_5MgBr} (C_6H_5)_2\underset{\substack{CH_2CHN(CH_3)_2\\ CH_3}}{C}-\overset{O}{\overset{\|}{C}}-C_2H_5$$

amidone

A synthesis of amidone which gives a very poor yield but only one isomer has been reported and confirms the structure given above.



$$(C_6H_5)_2CHCN + CH_3\underset{O}{CHCH_2} \xrightarrow{NaNH_2} (C_6H_5)_2\underset{\substack{|\\ CH_2CHCH_3}}{C}--\underset{O}{C}=NH \xrightarrow{PBr_3}$$

$$(C_6H_5)_2\underset{\substack{CH_2CHCH_3\\ Br}}{C}-CN \xrightarrow{(CH_3)_2NH} (C_6H_5)_2\underset{\substack{CH_2CHN(CH_3)_2\\ CH_3}}{C}-CN \xrightarrow{C_2H_5MgBr} \text{Amidone}$$

Sletzinger and Tishler (43) have reported that isoamidone is less toxic and more active than the isomer amidone.

In view of the activity of amidone, a large number of related compounds have been synthesized. Ofner, Thorp and Walton (44) prepared the piperidyl analogues of amidone and isoamidone. The analgesia was found to be similar in duration to that of amidone and with a small degree of undesirable side effects. Attenburrow et. al. (45) synthesized the morpholinyl analogues and found high activity.

Ofner and Walton (46) studied the effect of variations in the basic side chain of amidone by using the following groups; 2-piperidinopropyl, 3-piperidinopropyl, 2-diethylaminoethyl and 2-diethylaminopropyl. They concluded that methyl branching in the basic side chain, particularly β to the quaternary carbon, is an important factor. Small variations in the basic group have a minor effect; the 2-aminopropyl group exhibits the maximum effect.

Walton, Ofner and Thorp (47) varied the keto side chain in both amidone and isoamidone by employing various Grignard reagents. The methyl, ethyl, propyl, iso-propyl, butyl, phenyl and benzyl ketones were prepared. In both series the activity was a maximum with the ethyl ketone and much less in the higher and lower analogues.

König and Magyar (48) prepared 1-(1-piperidyl)-3,3-diphenyl-4-hexanone hydrobromide (Hexalgon) as well as a number of other compounds related to the amidone structure and concluded that the following correlations exist between structure and analgesic effect: 1) any changes in aryl ring or exchange with heterocyclic chain may diminish or eliminate analgesic effect; 2) changes in basic group had less effect; the nitrogen was most effective when located at a distance of two carbons from the central carbon and a methyl group on the carbon next to the nitrogen atom increased activity whereas methyls further away diminished the effect; 3) the strongest analgesia was found in compounds with the ketone side chain, the ethyl ketone being the most effective.

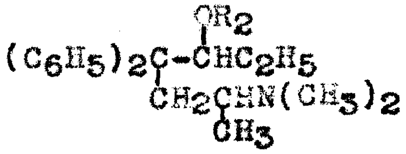
Shapiro (49) prepared amidone derivatives in which one phenyl group was substituted with a bromo, methoxyl or methyl group and where one phenyl group was replaced with a benzyl group and found no activity.

Cheney et. al. (50) prepared ketimines and acylketimines related to amidone and isoamidone. In both series the order of decreasing toxicity and increasing activity index is ketone: ketimine: acylketimine.

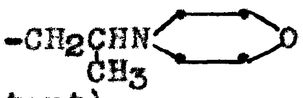
Lithium aluminum hydride reduction of amidone and isoamidone was studied by May and Mosettig (51). Reduction to the carbinol reduced analgesia and acetylation nearly restored it. Dehydration of the alcohol to an ethylenic compound had little effect. An attempt to reduce the carbonyl group in a Wolff-Kishner reaction resulted in cleavage of the molecule to form $(C_6H_5)_2CHCH_2CH(CH_3)N(CH_3)_2$ which was inactive.

Speeter et. al. (52) also studied the effect of reduction of amidone to the corresponding carbinol and found that the alcohol was less toxic than the corresponding ketone but the analgesic activity was unpredictable. The acetate esters were more active but also more toxic than the ketones.

Pohland, Marshall and Carney (53) resolved methadon and the related carbinols and esters. l-Methadon was found to be twice as active as dl-methadon, the l form of the alcohol was more active than the d, and the d form of the ester was the most active. Speeter, Cheney and Binkley (54) prepared halogen-containing esters related to methadon. It was found that the activities of these compounds were considerable higher than the activity of methadon.



$$(C_6H_5)_2\underset{CH_2\underset{CH_3}{CH}N(CH_3)_2}{C}-\overset{OR_2}{C}HC_2H_5 \qquad R_2 = ClCH_2CO,\ BrCH_2CO$$

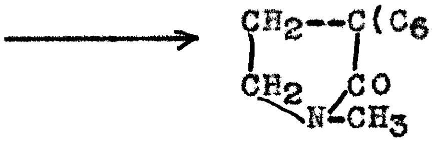
Bockmühl and Ehrhart (55) synthesized compounds of the general formula $R_2C{<}^{X}_{Y}$ where X was a ketone, ester or amide group, Y was various basic side chains and R was a phenyl or substituted phenyl group. If X was an ester or amide group the activity was poor regardless of the rest of the molecule. If X was a ketone other than ethyl or if one phenyl group was substituted the activity was low. If X was $-COC_2H_5$, the most effective Y group was $-CH_2\underset{CH_3}{CH}N(CH_3)_2$ or  (the branched methyl group was very important).

Dupré et. al. (56) synthesized a number of compounds related to amidone.

$$Br(CH_2)_2Br + (C_6H_5)_2CHCN \xrightarrow{NaNH_2} Br(CH_2)_2C(C_6H_5)_2CN$$

$$\xrightarrow{(CH_3)_2NH} (CH_3)_2N(CH_2)_2C(C_6H_5)_2CN \xrightarrow[2)\,Grignard]{1)\,ROH,\ H} \begin{matrix}1)\ ester\\ 2)\ ketone\end{matrix}$$

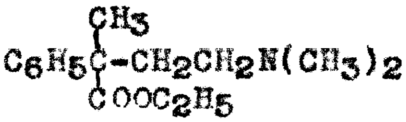
$$(CH_3)_2N(CH_2)_2C(C_6H_5)_2COOH \xrightarrow{SOCl_2} (CH_3)_2N(CH_2)_2C(C_6H_5)_2COCl$$



3,3-diphenyl-1-methylpyrrolidone-2

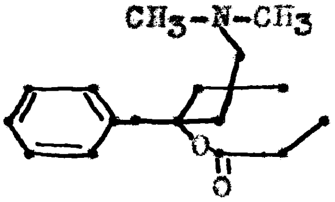
Burckhalter and Johnson (57) prepared ketones similar to amidone in which one phenyl group was replaced by a methyl group. The analgesic activity was very low and it is possible that the phenyl group of amidone locks the aliphatic group into a morphine-like spatial arrangement thus establishing the apparently requisite rigidity. The methyl group appears to lack the necessary size for this steric hindrance.

Anker and Cook (58) found a similar low degree of activity in the related esters.



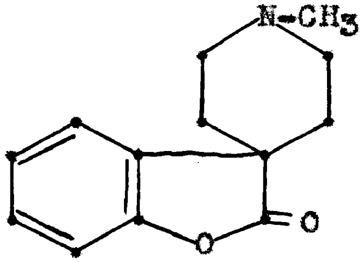
$$C_6H_5\overset{CH_3}{\underset{COOC_2H_5}{C}}-CH_2CH_2N(CH_3)_2$$

A number of esters of α-(2-dialkylaminoethyl)benzyl alcohols were synthesized by Burckhalter and Johnson (59). The structure of these compounds can be written to simulate portions of the morphine skeleton. No important analgesic activity was found in these esters and this was attributed

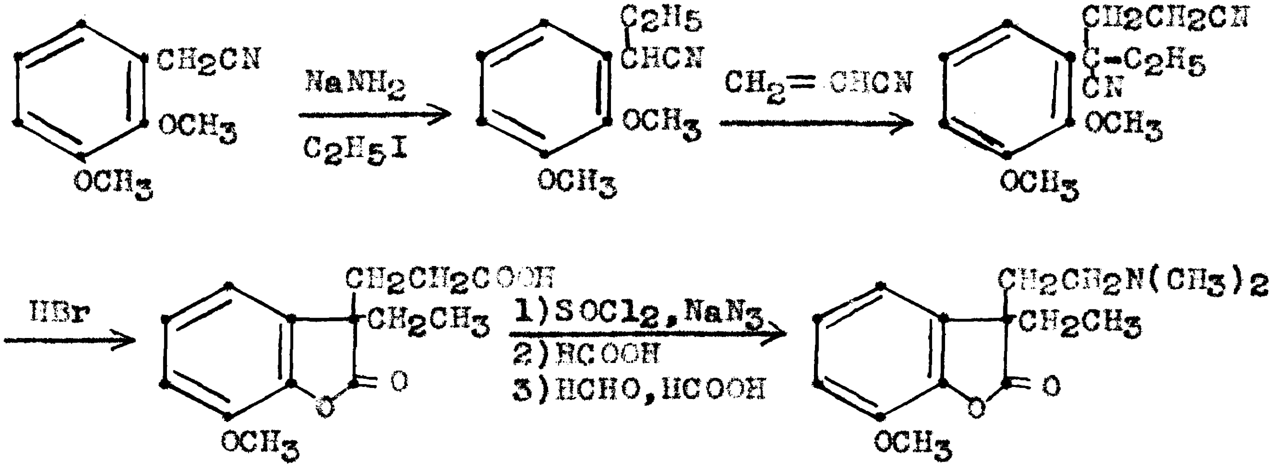


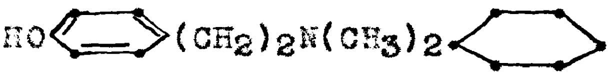
to the probable lack of the necessary rigidity in the molecule.

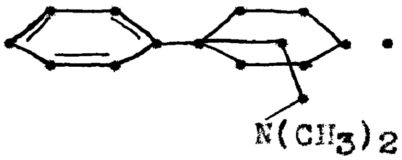
Bergel et. al. (60) prepared a 2,3-dihydrobenzofuran derivative with the following formula:



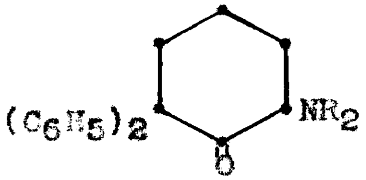
2-Keto-3-ethyl-3-(β-dimethylaminoethyl)-7-methoxy-2,3-dihydrobenzofuran was synthesized by Horning and Shock (61).

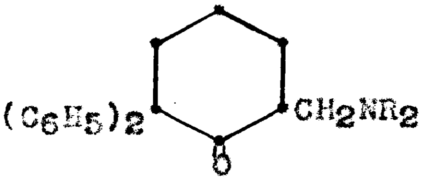


Other compounds, structures of which can be related to the morphine molecule, have been prepared. For example, Suter (1) reported the synthesis of phenylalkyl-β-cyclohexylethylmethylamines, . These compounds are slightly active but it is unlikely that the activity is due to any similarity to morphine.

Barltrop and Nicholson (62) synthesized 1-dimethylaminoethyl-1-phenylcyclohexane . 1-Phenyl-2-dialkylaminoalkylcyclohexanes have been reported by Suter (1) to exhibit negligible analgesic activity.

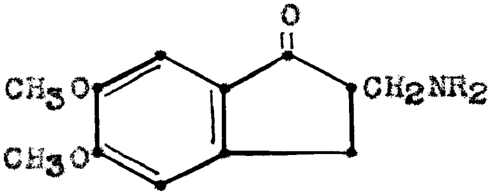
Zaugg, Freifelder and Horrom (63) felt that the important features of amidone are the quaternary carbon atom to which are attached two phenyl groups, a carbonyl group and a basic side chain and attempted to determine whether a different arrangement of these groups around the quaternary carbon would still result in activity. The following amino derivatives of 2,2-diphenylcyclohexanone were prepared. Both of these compounds exhibited a low order of



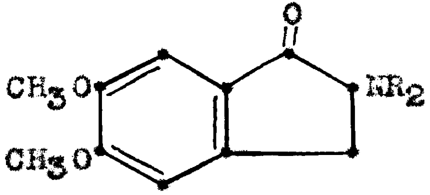


analgesia. Burger and Bennet (64)(65) prepared the same compounds as well as the 5-dimethylamino substituted compound.

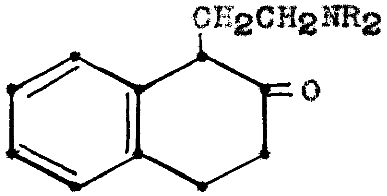
Barltrop (66) synthesized the following compounds which can be related in structure to some portion of the morphine molecule and found they exhibited slight analgesic activity.



2-dialkylaminomethyl-5,6-
dimethoxyindanone-1

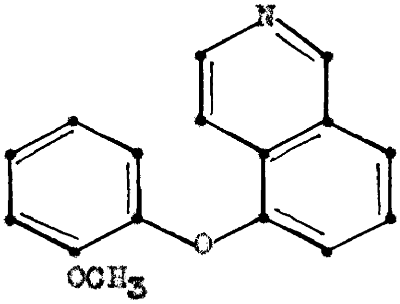


2-dialkylamino-5,6-
dimethoxyindanone-1



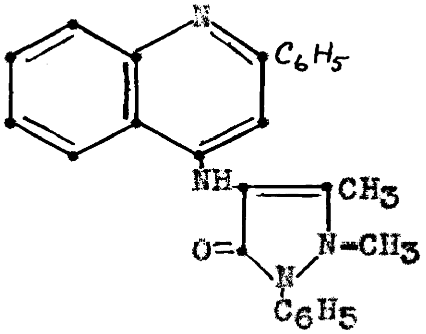
R= piperidyl, morpholinyl

1-dialkylaminoethyltetralone-2



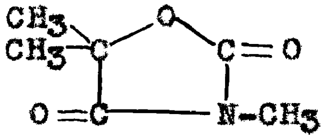
5-(o-methoxyphenoxy)-
isoquinoline

Several interesting types of heterocyclic compounds have been prepared as potential analgesics. Hanna (67) prepared 1-phenyl-2,3-dimethyl-4-(2'-phenylquinolyl-4')-amino-5-pyrazolone and found it and related compounds

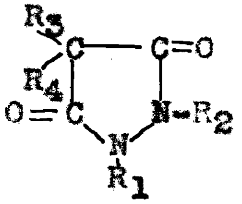


useful as analgesics.

Spielman (68) reported analgesic activity in the aspirin range and low toxicity for 3,5,5-trimethyloxazolidine-2,4-dione.



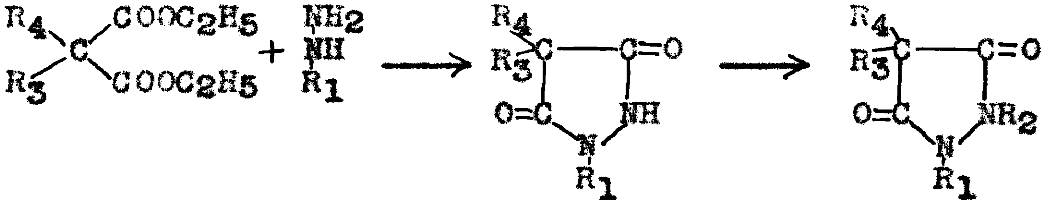
Buchi et. al. (69) synthesized a large number of 3,5-dioxopyrazolidines with the following general formula:



$R_3, R_4 = H$, alkyl

$R_1 = C_6H_5,\ C_6H_5CH_2$

$R_2 = H,\ C_6H_5,\ C_6H_5CH_2$



Many of these compounds exhibited analgesic activity but were very toxic.

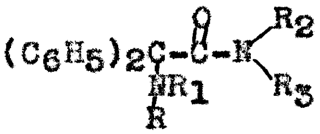
A brief glance at the types of compounds which exhibit antispasmodic activity is of interest to show the differences in these structures and those that show analgesic activity.

One large group of antispasmodics is the amino alcohol ester type. Some representative examples of active compounds of this type are the diethylaminoethanol esters of α-phenylvaleric acid (70)(71), benzilic acid (72), diphenylacetic acid and alkyldiphenylacetic acid (73), 1-indanylphenylacetic acid (74) and the benzylmethylaminoethanol ester of dibenzylacetic acid (75).

Other esters which are useful as antispasmodics are those in which the basic residue is in the acidic portion of the ester. Examples of this type are the esters prepared by Bockmühl and Ehrhart (76) with the general formula $R_1R_2R_3CCOOR_4$ where R_1 and R_2 are aryl groups, R_3 is a tertiary aminoalkyl group and R_4 is an alkyl or aralkyl group.

The alkyl amides and phenylsubstituted acetamides are active as antispasmodics. Many of them are hypnotics and a few have exhibited analgesic activity. Tertiary saturated alkylsubstituted acetamides of five to seventeen carbons are good antispasmodics (77)(78). Certain tertiary butyl aliphatic amides such as the methylamide, allylamide and cyclohexylamide of α-bromo-t-butylacetic acid show hypnotic effects (79).

Papa et. al. (80) synthesized N,N-dialkylamides with the structure $RCH=CR'CON(R'')_2$ where R is aryl, heterocyclic, R' is hydrogen, alkyl, aryl or alicyclic and R'' is hydrogen or lower alkyl. These compounds exhibited an analgesic activity comparable to aspirin.

N,N'-Substituted α-aminodiphenylacetamides of the formula  $(C_6H_5)_2C(NRR_1)-C(=O)-N(R_2)(R_3)$ where all the R's are hydrogen or alkyl have been prepared and are active antispasmodics (81) (82).

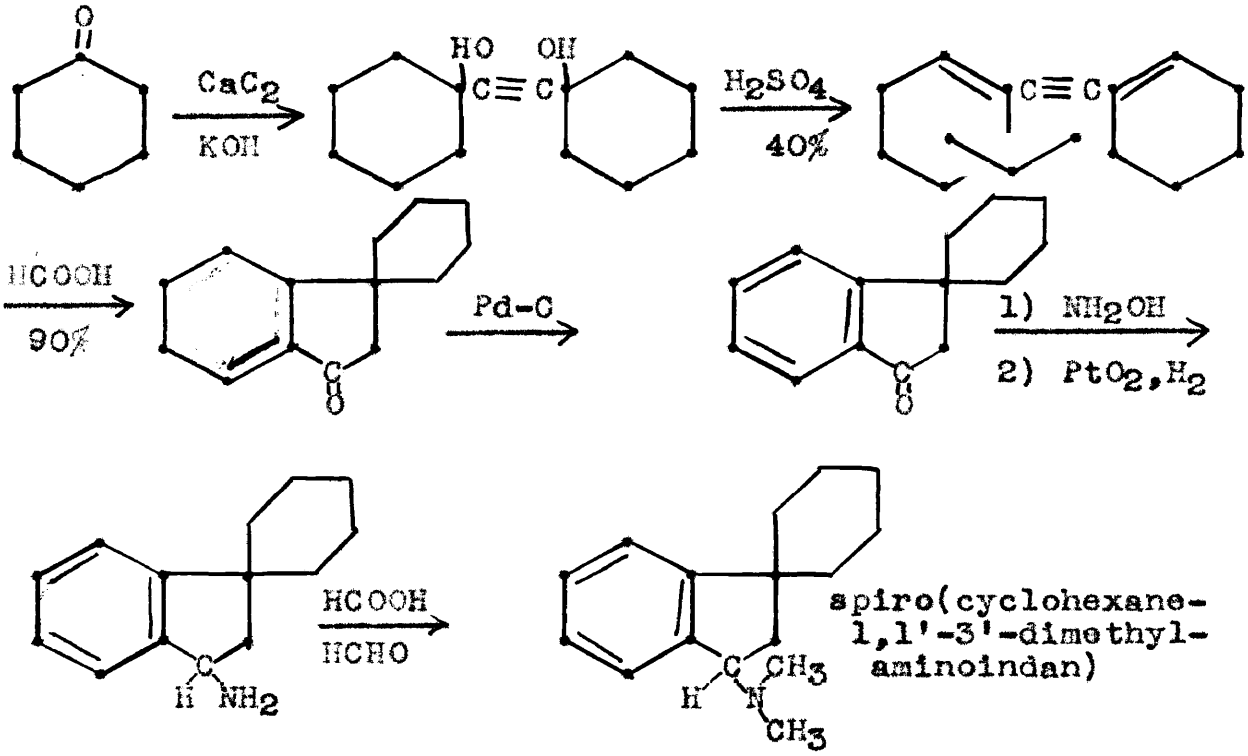
Trialkylacetic acids containing a total of fifteen to twenty carbon atoms show antispasmodic activity (83). A large group of alkylamines have been synthesized and found to be antispasmodics. Examples of these are; methyldi-β-cyclohexylethylamine (84), methyldi-n-octylamine and methyldi-β-3-methylcyclohexylethylamine (85), β-di and tri-alkylethylamines containing eleven to eighteen carbons (86), 2-methyl-iso-amylaminooctane (87) and unsaturated ethylamines such as 5-benzylamino-1-hexene (88).

Külz and coworkers (89)(90) prepared a large group of amines of the type $(RCH_2CH_2)_2NH$ where R is phenyl, dimethoxysubstituted phenyl or an alkylsubstituted phenyl. Alkylation of the benzene rings resulted in an increase in activity whereas alkylation of the nitrogen atom produced an irregular effect. A methyl group on the nitrogen caused a marked weakening of activity and increasing the number of carbon atoms gradually increased activity.

DISCUSSION

Several types of compounds with structures indicating the possibility of analgesic activity, or the study of which is necessary in an attempt to correlate structure with this biological activity, have been of interest to this laboratory.

Schwartzman (91) synthesized a series of spiro(cyclohexane-1,1'-3'-aminoindans) in order to study their analgesic activities. Of particular interest in the structure of these compounds is the quaternary carbon atom and the tertiary amine group; both structural units found in the morphine molecule. Spiro(cyclohexane-1,1'-3'-dimethylaminoindan) was prepared by the following series of reactions:

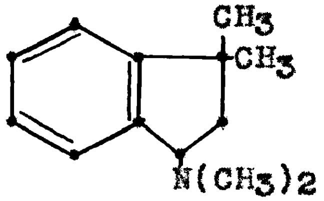


An extension of this work (92) was the study of the effect of substitution in the aromatic ring. Spiro(cyclohexane-1,1'-3'-dimethylaminoindan) was nitrated and the nitro compound reduced catalytically to the diamime, spiro-(cyclohexane-1,1'-x'-amino-3'-dimethylaminoindan). The position of the nitro group in the benzene ring was not established. The diazonium compound prepared from the diamine was converted to the phenolic compound. The diamine was acetylated and the amide reduced with lithium aluminum hydride to spiro(cyclohexane-1,1'-3'-dimethylamino-x'-ethylaminoindan).

It was found that spiro(cyclohexane-1,1'-3'-dimethylaminoindan) gave reasonable yields of the corresponding ketoamine in a Friedel-Crafts reaction with acetic anhydride, propionic anhydride or n-butyryl chloride. Reduction of the ketoamines with lithium aluminum hydride produced the aminoalcohols.

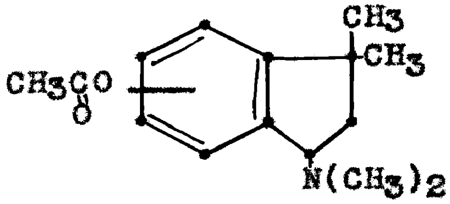
A similar group of compounds, 3,3-dimethylindanamines, in which two methyl groups occupy the position of the cyclohexane ring was prepared in this laboratory by Goo-On (93). The parent compound for these syntheses was 3,3-dimethylindanone-1 prepared by the cyclization of the acid obtained by a hypochlorite oxidation of the methyl ketone resulting from a Friedel-Crafts reaction of mesityl oxide with benzene.

The oxime of 3,3-dimethylindanone-1 was prepared in the usual fashion and reduced catalytically to 3,3-dimethyl-1-aminoindane. This amine was readily converted to the dimethylamino derivative by treatment with formaldehyde and formic acid.



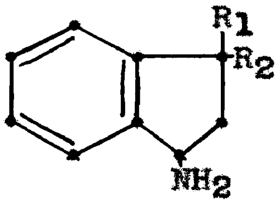
3,3-dimethyl-1-dimethylaminoindane

This amine was nitrated and the nitro group reduced catalytically to the corresponding diamine. The diamine was converted to the acetoxy-indanamine using standard reactions.



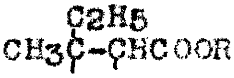
3,3-dimethyl-x-acetoxy-1-indanamine

In order to determine the effect of varying the groups on the quaternary carbon atom it was desired to synthesize indanamines with the following general formula:



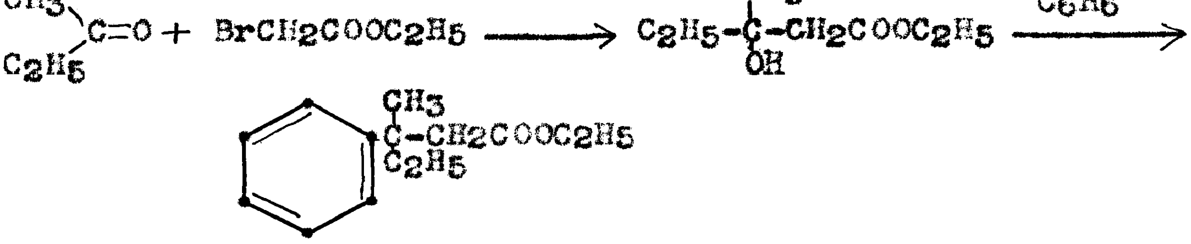
R_1 and R_2 would be similar or different alkyl groups with one or more carbon atoms.

The first member of this series is 3,3-dimethyl-1-aminoindane, the compound prepared by Goo-On. The second member of the series, the molecule in which R_1 is methyl and R_2 is ethyl, is the compound synthesis of which was attempted in the course of this research.

Investigation of the possible methods of synthesis of the desired parent compound, 3-ethyl-3-methylindanone-1, indicated the most fruitful avenue of approach should be a Friedel-Crafts reaction between benzene and a molecule with the structure  $CH_3\overset{C_2H_5}{C}-CHCOOR$ where R could be H or an alkyl group, followed by cyclization of the acid formed to the desired 3,3-disubstituted indanone.

One possible route to the molecule of the structure just shown was a Reformatsky reaction with ethyl methyl ketone and ethyl bromoacetate, followed by dehydration of the β-hydroxy acid to the α,β-unsaturated acid. This method was not considered applicable for two reasons; 1) in many instances dehydration of a molecule of this type results in the β,γ-unsaturated acid (94) and 2) an attempted Friedel-Crafts reaction carried out by Goo-On (93), with benzene and β,β-dimethylacrylic acid, to synthesize the desired intermediate for the preparation of 3,3-dimethylindanone-1 was completely unsuccessful.

In view of the many instances of successful Friedel-Crafts reactions with tertiary alcohols (95) it was decided to use the product from the Reformatsky reaction, the β-hydroxy ester, in the Friedel-Crafts reaction. If the reaction proceeded as desired the necessary acid intermediate (β-methyl-β-phenylvaleric acid) needed for the preparation of the desired indanone would be obtained by hydrolysis of the ester.



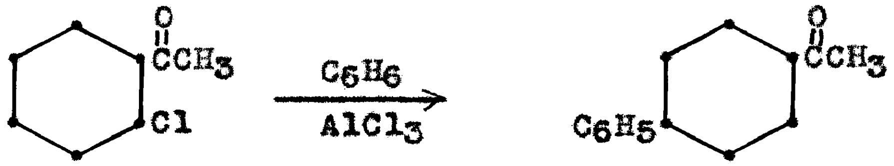
The Reformatsky reaction was carried out in good yield (60%) to obtain ethyl β-hydroxy-β-methylvalerate. The hydroxy ester was subjected to a Friedel-Crafts reaction with benzene and anhydrous aluminum chloride. The reaction was carried out at 0-5°C. and gave a good yield (82%) of an ester which was presumed to be ethyl β-methyl-β-phenylvalerate.

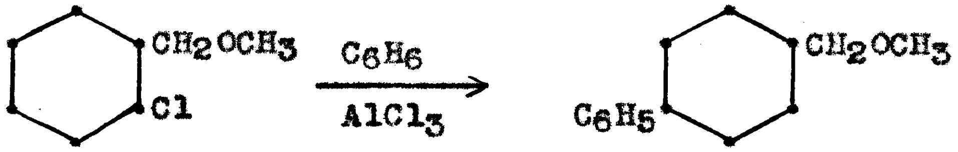
The product from the Friedel-Crafts reaction was hydrolyzed readily with methanolic potassium hydroxide. The resulting acid was cyclized by either of two methods; 1) treatment of the acid chloride with anhydrous aluminum chloride or 2) treatment of the free acid with concentrated sulfuric acid. In either instance the yield was 40-50%.

The product of these reactions was a ketone as indicated by the formation of a 2,4-dinitrophenylhydrazone and a semicarbazone. Analysis indicated the ketone was either the desired indanone or an isomer.

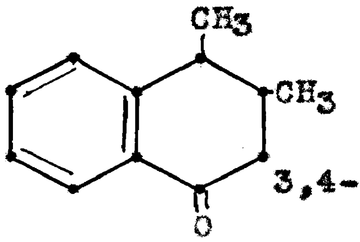
Some doubt as to the structure of this cyclic ketone arose as a result of work done by Lederle (96) of this laboratory. In an attempt to prepare 1-phenylcyclohexaneacetic acid which could then be converted by means of reduction of the amide to the amine, 1-(2-aminoethyl)-1-phenylcyclohexane, Lederle carried out a Reformatsky reaction on cyclohexanone followed by a Friedel-Crafts reaction on the hydroxy ester. Instead of the desired 1-phenylcyclohexaneacetic acid, the product obtained was 4-phenylcyclohexaneacetic acid. If the Friedel-Crafts reaction was carried out at room temperature hydrolysis of the product yielded an acid melting at 112-114°C. If the reaction was carried out in boiling benzene an acid melting at 86-88°C. was obtained. Both acids resulted in the same amide, 4-phenylcyclohexaneacetamide, indicating the possibility of cis-trans isomers.

Other examples of similar rearrangements in the Friedel-Crafts reaction have been reported. Nenitzescu and coworkers (97)(98) carried out an investigation of this type of rearrangement. In the study of the cyclohexane compound the unsaturated acid was used instead of the hydroxy ester with similar results. A similar reaction takes place with various chloro compounds as illustrated by the following examples:





In view of the rather extensive evidence of rearrangement in the Friedel-Crafts reaction it was necessary to determine the structure of the cyclic ketone, synthesis of which involved a Friedel-Crafts reaction of a hydroxy ester where rearrangement could easily occur. The product to be expected from a rearrangement is 3,4-dimethyltetralone-1 (IV).



3,4-dimethyltetralone-1

It seemed probable that a determination of the ultraviolet absorption spectrum of the cyclic ketone would differentiate between the 5-membered ring indanone and the 6-membered ring tetralone structure. For comparison purposes the ultraviolet spectra of indanone-1 and 3,3-dimethylindanone-1 were determined along with that of the ketone in question. Inspection of the curves (Fig. I) indicates definite agreement in the spectra of indanone-1 and 3,3-dimethylindanone-1 and certain aspects of similarity in the spectrum of the ketone being studied. Comparison of these spectra with a spectrum for tetralone-1 as determined by Biquard (99) indicated that this method of differentiation between the tetralone and indanone structure was not feasible since the spectra are very similar.

In order to definitely establish the structure of the product from the Friedel-Crafts reaction it was necessary to carry out a degradation to a known compound. A Barbier-Wieland degradation of the desired ester would give α-methyl-α-phenylbutyric acid (lit m.p. 60°C.) whereas degradation of the rearranged product would give α-methyl-β-phenylbutyric acid (lit m.p. 130-132°C).

The ester was treated with phenylmagnesium bromide and the product distilled from a trace of acid to yield the

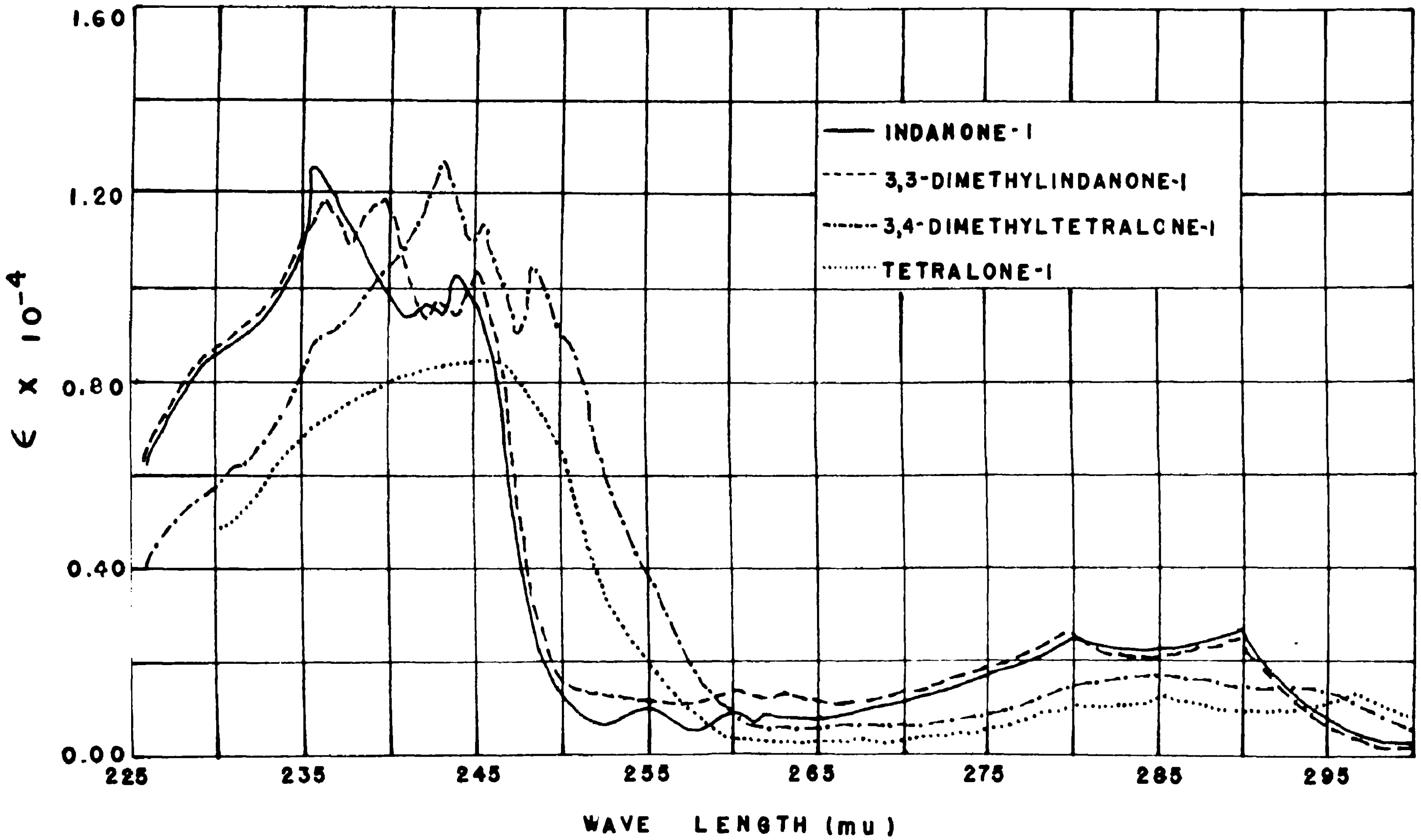


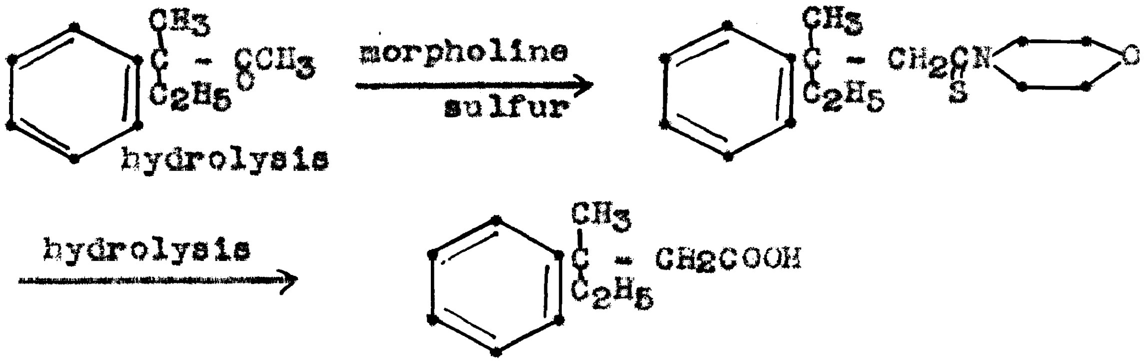
Fig. I ULTRAVIOLET ABSORPTION SPECTRA

ethylenic compound (V). This was oxidised with chromic acid and the acid (VI) obtained melted at 130-131°C., indicating rearrangement in the Friedel-Crafts reaction had occurred.

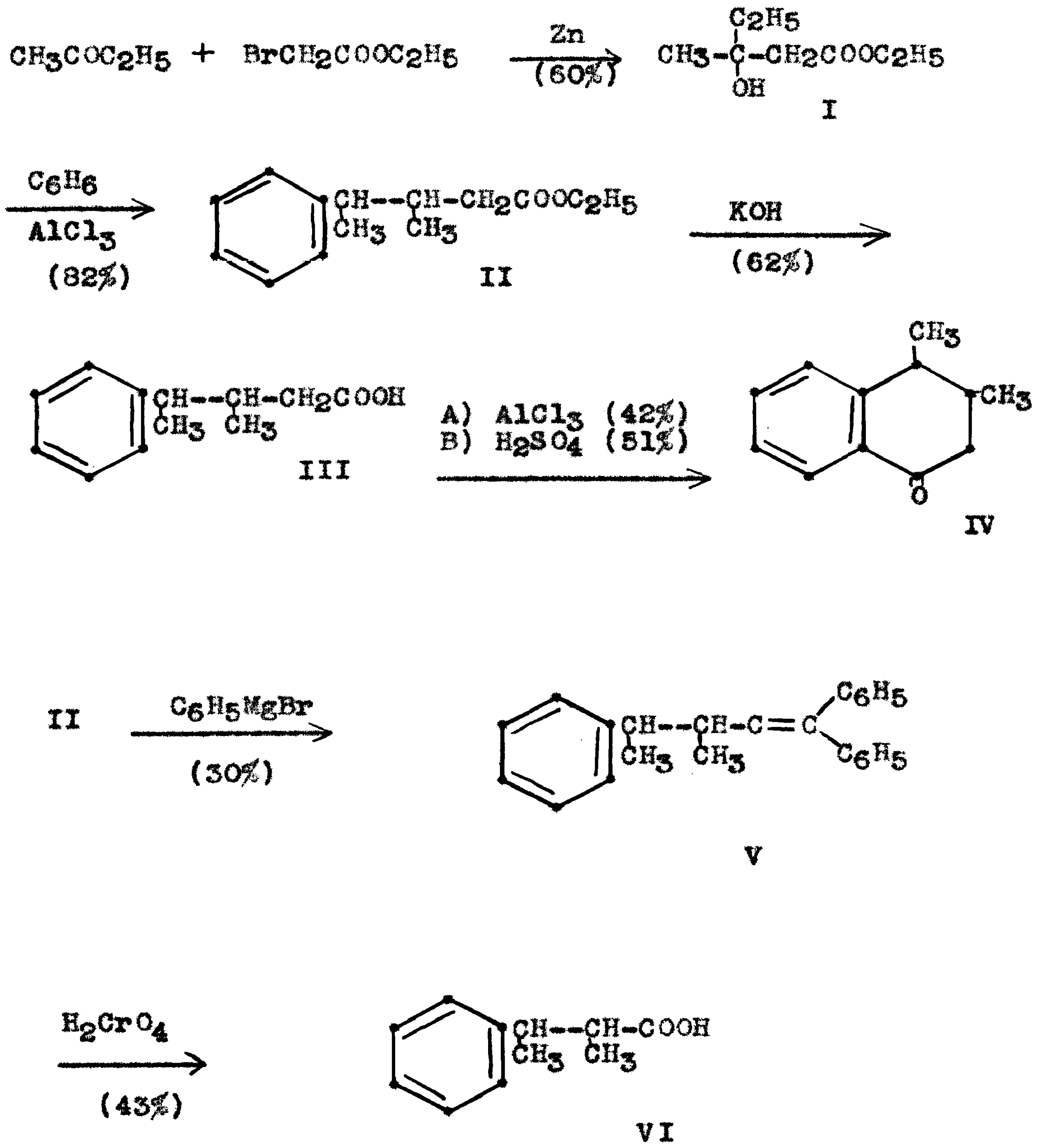
A further indication of the structure of the product from the Friedel-Crafts reaction was obtained by a permanganate oxidation of the ester (II). The acid obtained from the oxidation melted at 119-121°C. and gave no depression in a mixed melting point with an authentic sample of benzoic acid. If the ester had contained a quaternary carbon atom adjacent to the benzene ring, oxidation could not have produced benzoic acid.

The sequence of reactions used in the synthesis of 3,4-dimethyltetralone-1 and in the determination of the structure of the ester, ethyl β-methyl-γ-phenylvalerate, is shown in Fig. II.

Another possible synthetic approach to the desired acid, β-methyl-β-phenylvaleric acid was through the use of 3-methyl-3-phenylpentanone-2 in a Willgerodt reaction. The postulated series of reactions is as follows:



An attempt was made to prepare 3-methyl-3-phenylpent-



$CH_3COC_2H_5$ + $BrCH_2COOC_2H_5$ $\xrightarrow[(60\%)]{Zn}$ $CH_3-C(C_2H_5)(OH)-CH_2COOC_2H_5$
I
$\xrightarrow[AlCl_3\ (82\%)]{C_6H_6}$ $C_6H_5-CH(CH_3)-CH(CH_3)-CH_2COOC_2H_5$
II
$\xrightarrow[(62\%)]{KOH}$
$C_6H_5-CH(CH_3)-CH(CH_3)-CH_2COOH$
III
A) $AlCl_3$ (42%)
B) H_2SO_4 (51%)
CH_3
CH_3
O
IV
II $\xrightarrow[(30\%)]{C_6H_5MgBr}$ $C_6H_5-CH(CH_3)-CH(CH_3)-CH=C(C_6H_5)_2$
V
$\xrightarrow[(43\%)]{H_2CrO_4}$ $C_6H_5-CH(CH_3)-CH(CH_3)-COOH$
VI

Fig. II

anone-2 by the reaction of methylmagnesium bromide with α-methyl-α-phenylbutyronitrile. No ketone was obtained from this reaction; the starting material was recovered in good yield as evidenced by hydrolysis of a portion of the product to α-methyl-α-phenylbutyric acid.

In view of the increased reactivity of the alkyllithium over the alkylmagnesium halide reagent an attempt was made to convert the nitrile to the methyl ketone by means of reaction with methyllithium.

If this reaction was carried out at the reflux temperature of ether only undistillable viscous material was obtained; if the nitrile was added to the methyllithium reagent at 0°C. and the mixture allowed to stir at room temperature, a good recovery of product was possible but the properties of the material indicated a mixture of ketone and nitrile. The two compounds, α-methyl-α-phenylbutyronitrile and 3-methyl-3-phenylpentanone-2, cannot be separated by normal distillation techniques due to the proximity of their boiling points.

The product from the methyllithium reaction formed a 2,4-dinitrophenylhydrazone derivative with difficulty and it seemed advisable to attempt to separate the ketone from the starting material in order to determine the yield obtained in the reaction. It was also deemed advisable to have pure ketone for use in the Willgerodt reaction.

An attempt to separate the ketone from the nitrile by chromatographic absorption of the ketone on an alumina column proved to be quite successful. For instance, from 20 g.

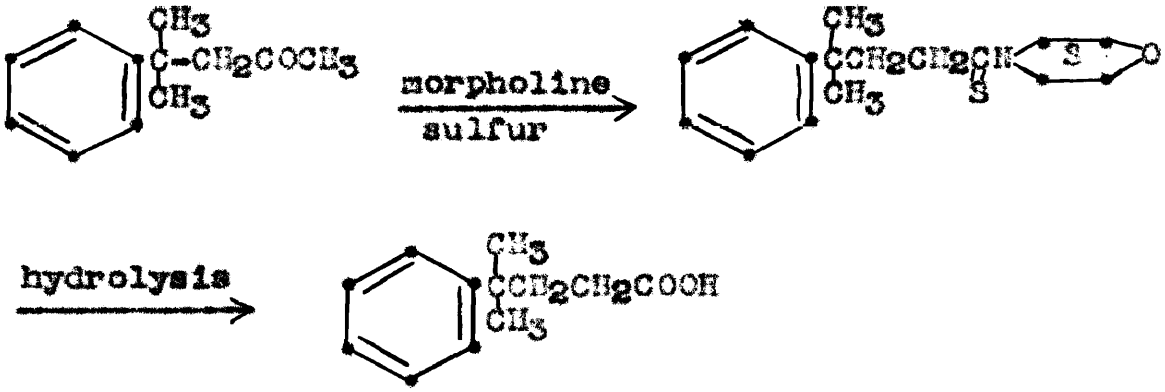
of the material from the methyllithium reaction 4 g. of ketonic material which gave a positive test with 2,4-dinitrophenylhydrazine reagent was separated with a recovery of 16 g. of a material which did not give a positive test with 2,4-dinitrophenylhydrazine reagent. The results of this separation procedure indicated a yield of 3-methyl-3-phenylpentanone-2 from the methyllithium reaction too small to make this method feasible.

An attempt to make 3-methyl-3-phenylpentanone-2 by the reaction of methyllithium with α-methyl-α-phenylbutyric acid, obtained from the hydrolysis of α-methyl-α-phenylbutyronitrile, was also unsuccessful. In this instance the problem of separation of the ketone from the starting material was eliminated but only a negligible amount of product was obtained and it gave no positive test for a ketone with any of the common reagents.

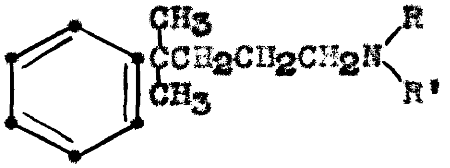
In view of the difficulties encountered in attempting to synthesize 3-ethyl-3-methylindanone-1, it was decided to discontinue this phase of the research.

A large group of compounds which have received considerable attention as potential analgesics are the aralkylamines, primarily the phenethyl or phenpropyl types which for the purpose of this investigation can be considered as similar in structure to a portion of the morphine molecule.

Rowe (100) of this laboratory prepared some 4,4-dimethylphenbutyl amines. 4-Methyl-4-phenylpentanone-2 was prepared in a Friedel-Crafts reaction from mesityl oxide and benzene. This ketone was subjected to a Kindler modification of the Willgerodt reaction and the thiomorpholide hydrolyzed to 4-methyl-4-phenylvaleric acid.



Three amides were prepared by treatment of the acid chloride with ammonia, methylamine, and dimethylamine. The amides were reduced to the corresponding amines with lithium aluminum hydride. The three amines obtained are shown below.

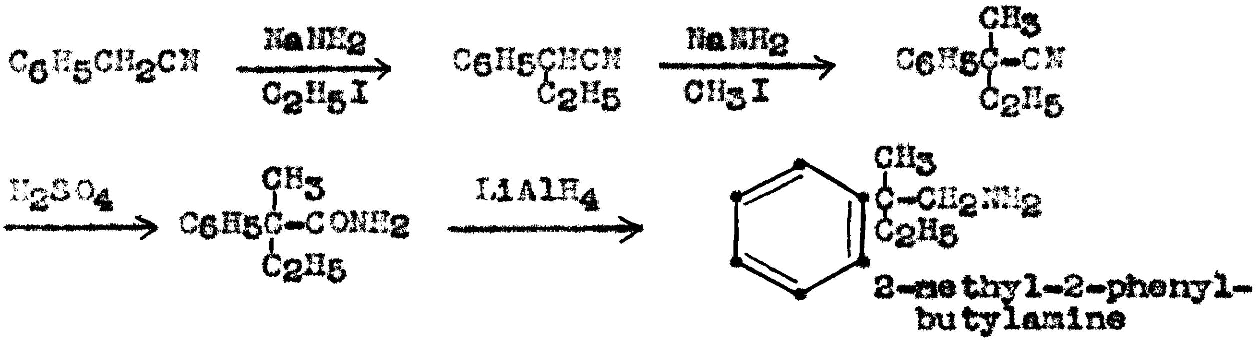


$R = R' = H$

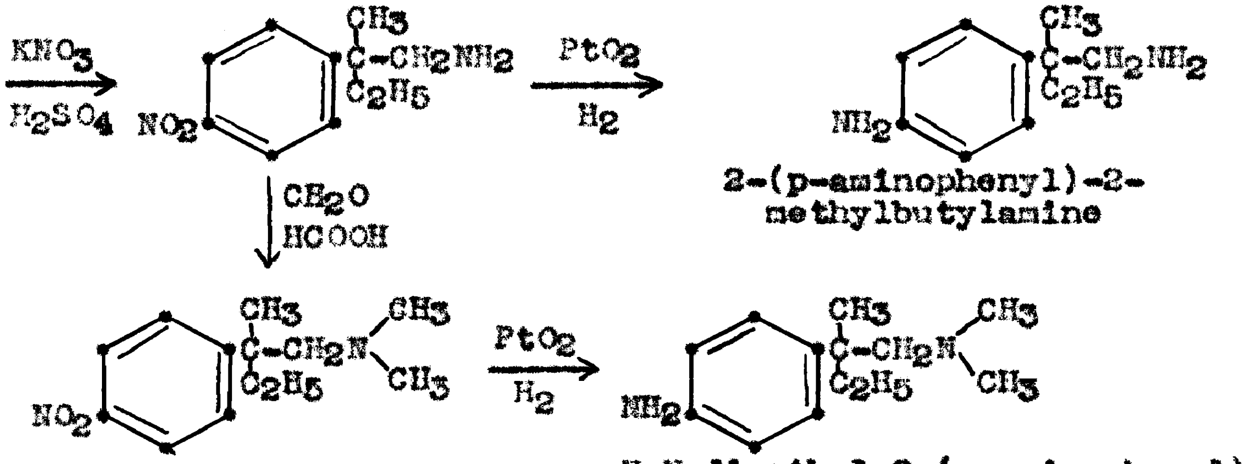
$R = CH_3,\ R' = H$

$R = R' = CH_3$

The synthesis of several 2-ethyl-2-methylphenethyl amines or 2-methyl-2-phenylbutylamines was carried out by Gasser (101) of this laboratory. The series of reactions resulting in these amines is given below.



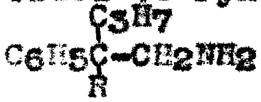
2-methyl-2-phenylbutylamine



2-(p-aminophenyl)-2-methylbutylamine

N,N-dimethyl-2-(p-aminophenyl)-2-methylbutylamine

It seemed desirable to synthesize compounds related to the phenethylamine types synthesized by Gasser for the purpose of testing their analgesic activity. It was decided to synthesize compounds of the general formula



$C_6H_5\overset{C_3H_7}{\underset{R}{C}}-CH_2NH_2$ in which R would be various alkyl groups. Substitution in the phenyl ring as well as substitution on the amino group was carried out.

The first compounds prepared were those in which the R group is methyl. A schematic outline of the reactions carried out is given in Fig. III.

The sodio derivative of phenylacetonitrile was prepared by the dropwise addition of phenylacetonitrile to sodamide in anhydrous ether solution. The alkylation of this sodio derivative was carried out by the addition of n-propyl bromide in the usual manner. After decomposition of the reaction mixture α-phenylvaleronitrile (VIII) was obtained in 79% yield.

In the same fashion the sodio derivative of α-phenylvaleronitrile was formed and alkylated with methyl iodide.

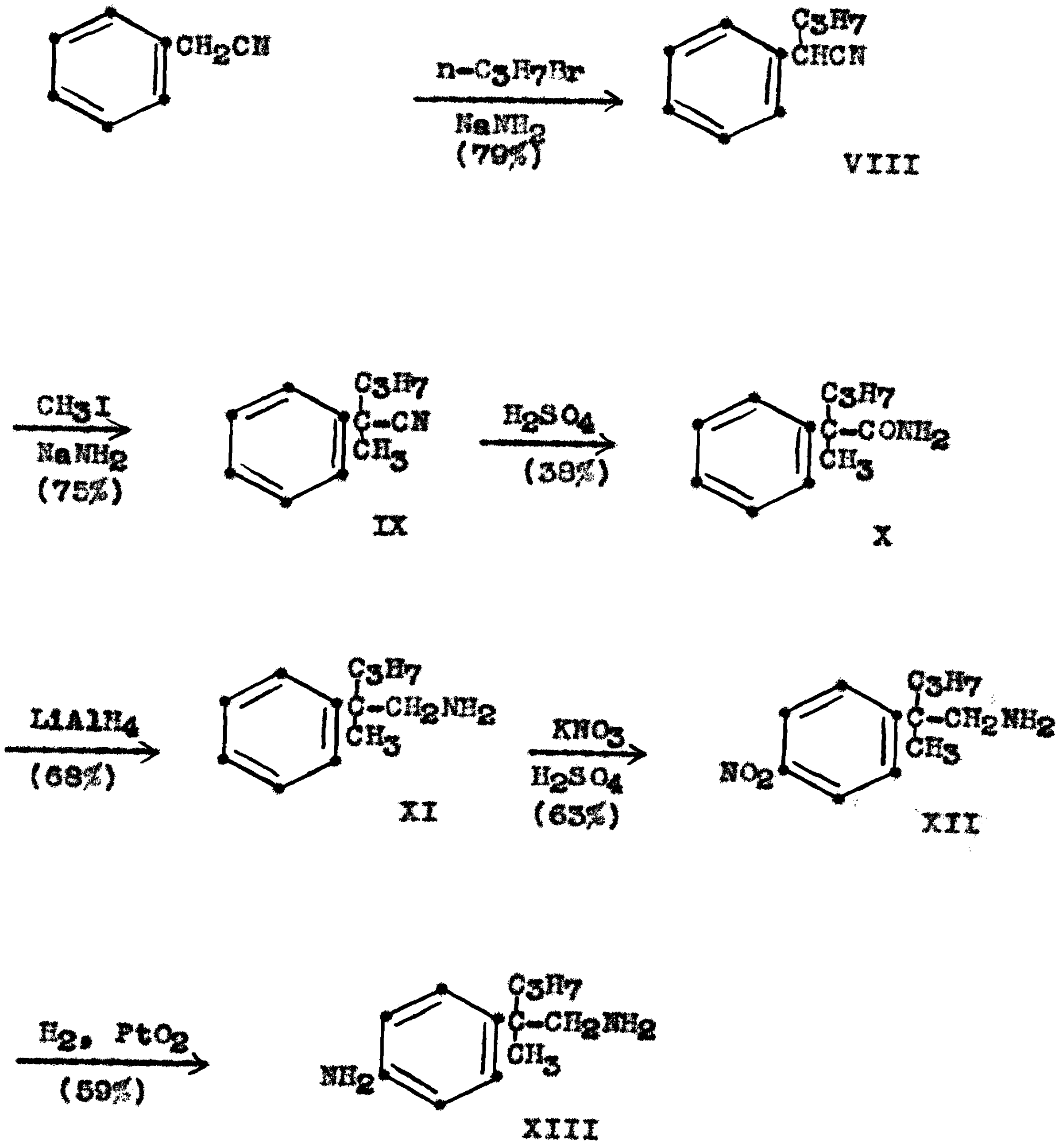

CH2CN
n-C3H7Br
NaNH2
(79%)
C3H7
CHCN
VIII
CH3I
NaNH2
(75%)
C3H7
C-CN
CH3
IX
H2SO4
(38%)
C3H7
C-CONH2
CH3
X
LiAlH4
(68%)
C3H7
C-CH2NH2
CH3
XI
KNO3
H2SO4
(63%)
NO2
C3H7
C-CH2NH2
CH3
XII
H2, PtO2
(59%)
NH2
C3H7
C-CH2NH2
CH3
XIII

Fig. III

The nitrile was converted to the corresponding amide (X) by sulfuric acid hydrolysis. On distillation the amide, an extremely viscous material, was obtained in only a 38% yield. The crystallization of α-methyl-α-phenylvaleramide could not be accomplished in spite of the extreme viscosity of the material. The results of the analysis of the amide were slightly high in the percentage of carbon. It was presumed that the sample could be impure due to the high viscosity of the amide which made complete removal of unhydrolyzed nitrile or other impurities very difficult.

α-Methyl-α-phenylvaleramide was converted to 2-methyl-2-phenylamylamine (XI) in high yield by lithium aluminum hydride reduction. The hydrochloride of 2-methyl-2-phenylamylamine was prepared by bubbling dry hydrogen chloride gas into an anhydrous ether solution of the amine. After recrystallization a white, stable solid was obtained.

Nitration of the amine with potassium nitrate and sulfuric acid to yield 2-methyl-2-(p-nitrophenyl)amylamine (XII) was achieved in 63% yield. The nitroamine was obtained as an orange liquid upon distillation. The hydrochloride of 2-methyl-2-(p-nitrophenyl)amylamine was prepared in the usual manner. The material turned into an oil after filtration and was recrystallized with difficulty to give a hard yellow powder.

Catalytic reduction at low pressure of the nitroamine gave a 59% yield of 2-methyl-2-(p-aminophenyl)amylamine (XIII). The diamine was a light yellow, viscous liquid. The dihydrochloride of 2-methyl-2-(p-aminophenyl)amylamine was prepared in the usual manner. A white solid formed which turned yellow and seemed to oil slightly after filtration. Recrystallization gave a white crystalline solid.

The second group of compounds was synthesized in which the R group of the general formula given previously was ethyl. A more extensive series of compounds was prepared than was prepared in the first group. A schematic outline of the reactions carried out in this series of syntheses is given in Fig. IV.

α-Phenylvaleronitrile was alkylated by forming the sodio derivative and adding ethyl iodide in the same manner as in the previous case. A 64% yield of α-ethyl-α-phenylvaleronitrile (XIV) was obtained. The nitrile was converted to α-ethyl-α-phenylvaleramide (XV) by acid hydrolysis. Extremely poor yields were obtained in the usual method and attempts to improve the yield by a slight reduction in the concentration of the sulfuric acid which, it was hoped, should retard sulfonation gave only slightly improved results. The α-ethyl-α-phenylvaleramide was an extremely viscous material which would not solidify but formed a glass when cooled. As in the case of 2-methyl-2-phenylvaleramide the results of the analysis of the amide were high in the percentage of carbon.

Lithium aluminum hydride reduction of the amide gave 2-ethyl-2-phenylamylamine (XVI) in very good yield (80%). The hydrochloride of 2-ethyl-2-phenylamylamine was prepared

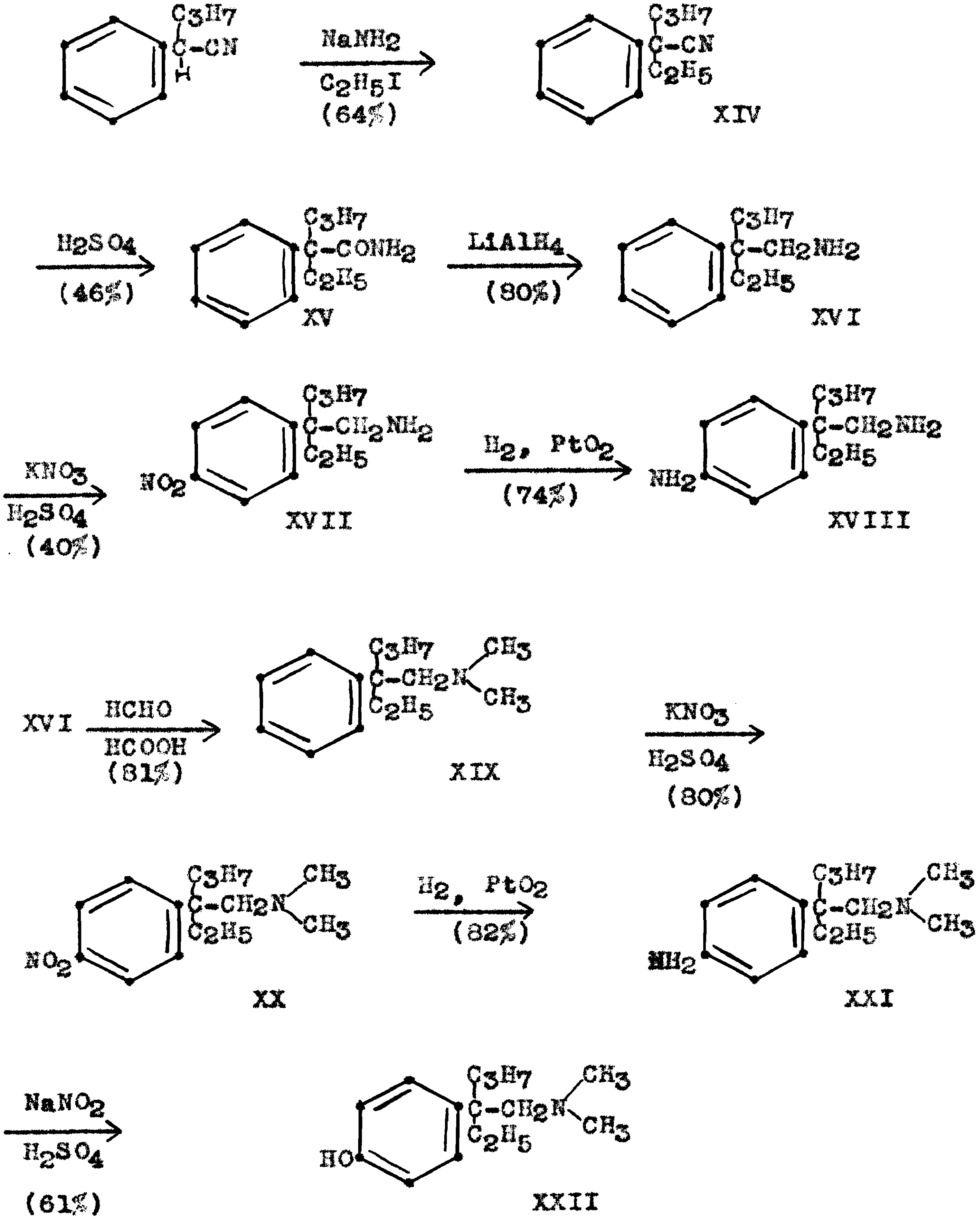

C3H7
C-CN
H
NaNH2
C2H5I
(64%)
C3H7
C-CN
C2H5
XIV
H2SO4
(46%)
C3H7
C-CONH2
C2H5
XV
LiAlH4
(80%)
C3H7
C-CH2NH2
C2H5
XVI
KNO3
H2SO4
(40%)
NO2
C3H7
C-CH2NH2
C2H5
XVII
H2, PtO2
(74%)
NH2
C3H7
C-CH2NH2
C2H5
XVIII
XVI
HCHO
HCOOH
(81%)
C3H7
C-CH2N
CH3
CH3
C2H5
XIX
KNO3
H2SO4
(80%)
NO2
C3H7
C-CH2N
CH3
CH3
C2H5
XX
H2, PtO2
(82%)
NH2
C3H7
C-CH2N
CH3
CH3
C2H5
XXI
NaNO2
H2SO4
(61%)
HO
C3H7
C-CH2N
CH3
CH3
C2H5
XXII

Fig. IV

by the usual procedure but was soluble in anhydrous ether. The ether was replaced with petroleum ether (90-100°) and the hydrochloride obtained as a white crystalline solid.

The nitration of 2-ethyl-2-phenylamylamine to 2-ethyl-2-(p-nitrophenyl)amylamine (XVII) was carried out using the same method as employed previously; potassium nitrate and sulfuric acid.

The nitroamine was obtained as an orange liquid in 40% yield upon distillation. Difficulty was encountered in carrying out the distillation due to the excessively high temperature required. Because of this a considerable amount of product was not distilled. The hydrochloride of the nitroamine was prepared in the usual manner and was obtained as a white powdery solid after recrystallization.

Catalytic reduction of the nitroamine gave a good yield (74%) of the diamine, 2-ethyl-2-(p-aminophenyl)amylamine (XVIII), a bright yellow liquid, The dihydrochloride of 2-ethyl-2-(p-aminophenyl)amylamine was prepared in the usual manner. The first precipitate obtained could not be recrystallized, forming an oil in each attempt, and an analysis of the unrecrystallized material corresponded to the monohydrochloride. This was readily converted to the dihydrochloride which recrystallized easily to give a creamy-white, stable solid.

The tertiary amine, N,N-dimethyl-2-ethyl-2-phenylamylamine (XIX), was prepared in good yield (81%) from 2-ethyl-2-phenylamylamine. The primary amine was refluxed with a mixture of formaldehyde and formic acid. After isolation of the product from the reaction mixture the tertiary amine was obtained as a colorless liquid with a fishy, amine-like odor. The hydrochloride of N,N-dimethyl-2-ethyl-2-phenylamylamine was prepared in the usual manner and yielded a white, crystalline solid after recrystallization.

The nitration of N,N-dimethyl-2-ethyl-2-phenylamylamine was carried out using potassium nitrate and sulfuric acid. A good yield (80%) of the nitroamine, N,N-dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine (XX), an amber-colored liquid, was obtained. The hydrochloride of N,N-dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine was prepared in the usual manner to yield a creamy-white solid after recrystallization.

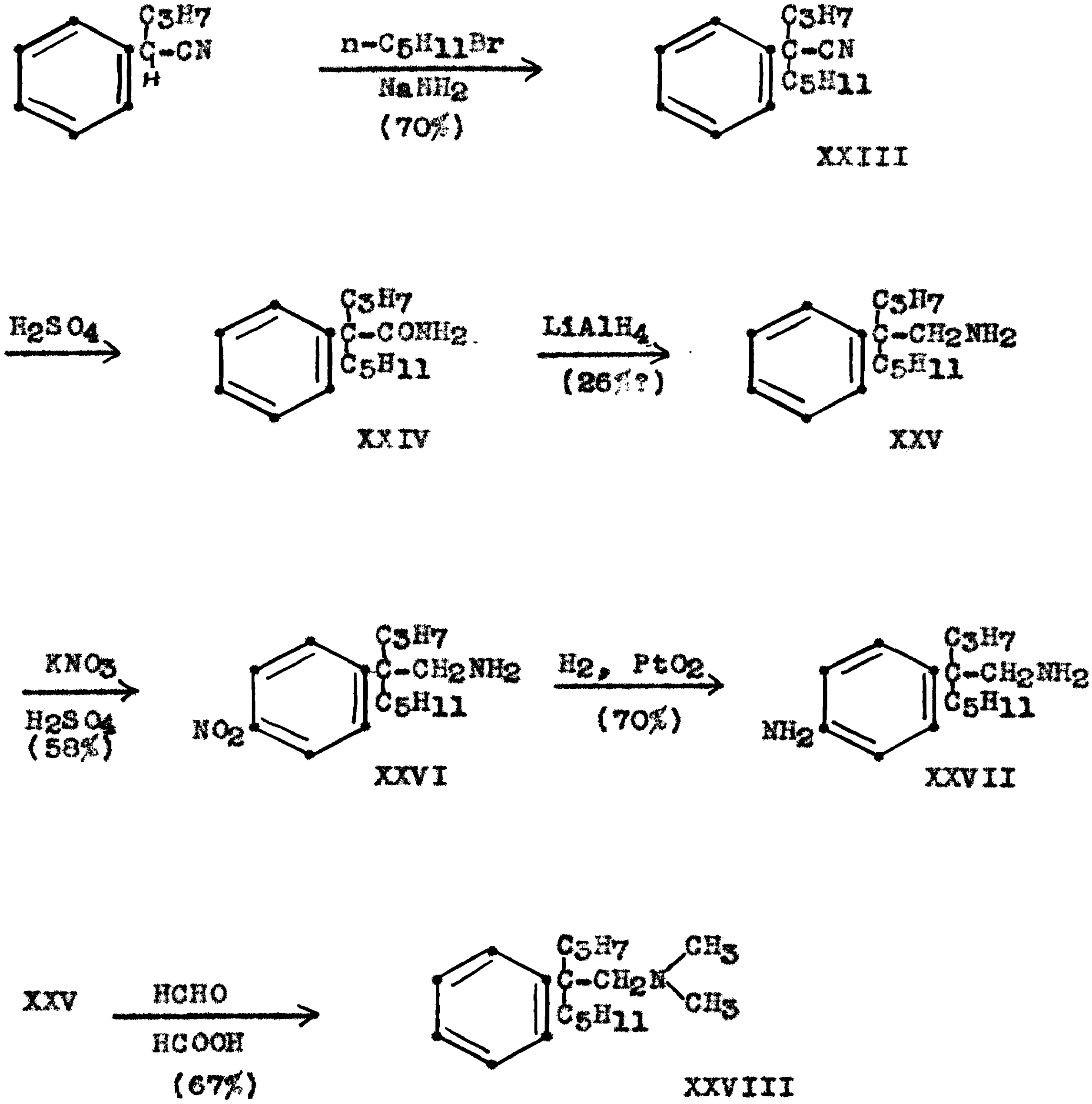
N,N-Dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine was reduced catalytically to the diamine, N*,N*-dimethyl-2-ethyl-2-(p-aminophenyl)amylamine* (XXI) in 82% yield. The dihydrochloride of N*,N*-dimethyl-2-ethyl-2-(p-aminophenyl)-amylamine* was prepared in the usual manner but formed a yellow, taffy-like material after filtration. The dihydrochloride was recrystallized with difficulty to yield a creamy-white solid which was extremely hygroscopic. Due to the hygroscopic nature of the compound good results could not be obtained on analysis.

The diamine was converted to the hydroxy compound, N,N-dimethyl-2-ethyl-2-(p-hydroxyphenyl)amylamine (XXII) through the use of a diazotization reaction. N*,N*-Dimethyl-2-ethyl-2-(p-aminophenyl)amylamine* dissolved in a cold solution of sulfuric acid and water was treated with solid sodium nitrite and the excess nitrite ion destroyed with urea. After isolation from the reaction mixture, the phenol solidified and was recrystallized from petroleum ether (60-80°). A creamy-white, powdery solid (61% yield after recrystallization) was obtained.

The hydrochloride of N,N-dimethyl-2-ethyl-2-(p-hydroxyphenyl)amylamine was prepared in the usual manner and formed a pinkish-white solid which oiled on standing. After recrystallization a creamy-white, stable solid was obtained.

A third series of compounds in which R in the general formula is n-amyl was prepared. The n-amyl compound was chosen because it was felt necessary to determine the effect of a five carbon alkyl group since a number of instances are known where a four carbon group produces the maximum biological effect and this effect falls off with the introduction of a five carbon group. It seemed advisable to ascertain wheter the same effect occurs in this group of compounds. The schematic outline of the reactions involved is given in Fig. V.

α-Phenyl-α-n-propylheptonitrile (XXIII) was prepared in 70% yield by the alkylation of α-phenylvaleronitrile with n-amyl bromide in the manner described previously. The nitrile was converted to the amide, α-phenyl-α-n-propylheptamide (XXIV), by acid hydrolysis. In the isolation of the amide the acidification of the basic extracts yielded an appreciable yellow layer which separated from



C3H7
C-CN
H
n-C5H11Br
NaNH2
(70%)
C3H7
C-CN
C5H11
XXIII
H2SO4
C3H7
C-CONH2
C5H11
XXIV
LiAlH4
(26%?)
C3H7
C-CH2NH2
C5H11
XXV
KNO3
H2SO4
(58%)
NO2
C3H7
C-CH2NH2
C5H11
XXVI
H2, PtO2
(70%)
NH2
C3H7
C-CH2NH2
C5H11
XXVII
XXV
HCHO
HCOOH
(67%)
C3H7
C-CH2N
CH3
CH3
C5H11
XXVIII

Fig. V

the strongly acid solution. This yellow material was insoluble in ether and soluble in water which would seem to indicate that it was the product of a sulfonation reaction which occurred during the hydrolysis.

Distillation of a small portion of the amide was attempted. The material was so viscous that distillation was extremely difficult. In the small portion distilled only a small amount of nitrile was recovered so the crude amide, without distillation, was used for the reduction. It was felt that a trace of nitrile should have no effect on the lithium aluminum hydride reduction. In transferring the α-phenyl-α-n-propylheptamide from one container to another, evidence of a white solid was noted. Several grams of the crude amide, a yellow liquid, was dissolved in petroleum ether (60-80°) and on cooling a white solid was obtained.

Even though it would seem likely that this amide, being a solid, could be more easily purified than the previous ones which were viscous liquids, the results of the analysis were still high in the percentage of carbon after several recrystallizations. No explanation for the inability to obtain pure samples of these amides has been discovered.

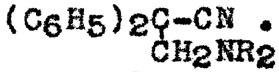
The amide was reduced to 2-phenyl-2-n-propylheptylamine (XXV) in a very poor yield (26% based on the crude amide; purity of which was unknown). The lithium aluminum hydride reduction was carried out as described previously. In this instance the reaction was very slow and external heating during the addition of the benzene solution of the amide was necessary to maintain reflux. The hydrochloride of 2-phenyl-2-n-propylheptylamine was prepared in the usual manner but was soluble in anhydrous ether. After removal of the ether and the addition of petroleum ether (40-60°) a white solid crystallized. The results of the analysis were poor even after three recrystallizations.

2-(p-Nitrophenyl)-2-n-propylheptylamine (XXVI) was prepared by nitration of 2-phenyl-2-n-propylheptylamine in the usual manner using potassium nitrate and sulfuric acid. The nitroamine was obtained in 58% yield as an orange-red, viscous liquid. The hydrochloride of 2-(p-nitrophenyl)-2-n-propylheptylamine was prepared with difficulty. It was obtained as a cream-colored solid after precipitation from anhydrous ether with petroleum ether (60-80°).

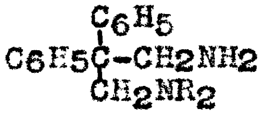
The nitroamine was reduced catalytically to the diamine, 2-(p-aminophenyl)-2-n-propylheptylamine (XXVII) in 70% yield. In all cases, the diamines were difficult to distill. Therefore, the product from this reduction was converted directly to the dihydrochloride by the standard method. On analysis, a small residue was observed. Several recrystallizations of the dihydrochloride did not eliminate this residue. The limited amount of material available made it impractical to attempt to obtain a purer sample of 2-(p-aminophenyl)-2-n-propylheptylamine.

The tertiary amine, N,N-dimethyl-2-phenyl-2-n-propylheptylamine (XXVIII), was prepared from 2-phenyl-2-n-propylheptylamine by the formic acid-formaldehyde method described previously. A 67% yield of the tertiary amine was obtained. The dihydrochloride of the tertiary amine was prepared in the usual manner and was obtained as a white, crystalline solid after recrystallization.

In order to study the effect of variations in the structures of compounds of this general type it was desired to synthesize a diamine with both amino groups in the alkyl residue instead of one in the benzene ring.

The synthesis of several 2,2-diphenyl-1,3-propanediamines has been reported recently (102)(103). Diphenylacetonitrile was reacted with dimethylamine, diethylamine, piperidine and morpholine under the conditions of the Mannich reaction to yield amino nitriles with the general formula  $(C_6H_5)_2C(CN)CH_2NR_2$.

Lithium aluminum hydride reduction of these nitriles yielded the 2,2-diphenyl-1,3-propanediamines.

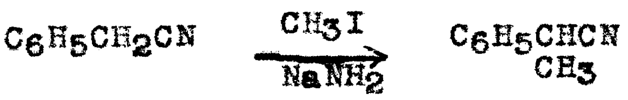


$C_6H_5C(C_6H_5)(CH_2NH_2)CH_2NR_2$

$-NR_2 = N(CH_3)_2$, piperidine and morpholine

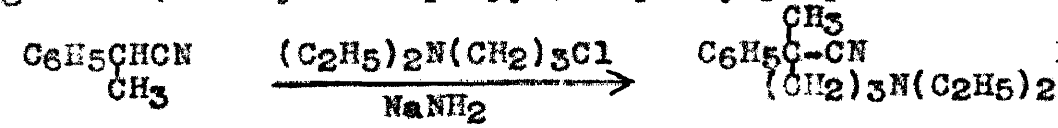
In the compounds prepared in this investigation one phenyl group was replaced by a methyl group and the basic side chain introduced was the diethylaminopropyl group.

α-Phenylpropionitrile (XXIX) was prepared in 78% yield by the alkylation of phenylacetonitrile using the method described previously.



$C_6H_5CH_2CN \xrightarrow[NaNH_2]{CH_3I} C_6H_5CH(CH_3)CN$ XXIX

In a similar manner α-phenylpropionitrile was alkylated with 3-diethylaminopropyl chloride in 47% yield to give α-(diethy$(C_2H_5)_2N(CH_2)_3Cl$-phenylpropionitrile (XXX).



$$C_6H_5\underset{CH_3}{C}HCN \xrightarrow[NaNH_2]{(C_2H_5)_2N(CH_2)_3Cl} C_6H_5\overset{CH_3}{\underset{(CH_2)_3N(C_2H_5)_2}{C}}-CN$$

XXX

The hydrochloride of α-(diethylaminopropyl)-α-phenylpropionitrile was prepared in the usual manner. After recrystallization a white, extremely hygroscopic solid was obtained. Good results in the analysis were not possible because of the hygroscopic nature of the material.

The aminonitrile was reduced to 2-(diethylaminopropyl)-2-phenylpropylamine (XXXI) in 60% yield using lithium aluminum hydride.

XXXI

All attempts to prepare the dihydrochloride of 2-(diethylaminopropyl)-2-phenylpropylamine were unsuccessful. The solid which formed on the addition of hydrogen chloride to the ether solution of the diamine was extremely hygroscopic and could not be retained as a solid after filtration.

Sublimation yielded a white solid which turned liquid before it could be removed from the sublimation apparatus.

The disulfate could only be obtained as an oil. Since the results of the analysis on the diamine were very good it was decided not to attempt the preparation of any other derivatives.

EXPERIMENTAL

Ethyl β-hydroxy-β-methylvalerate (I). The procedure of Bohnsack (104) was used. In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 250 ml. of anhydrous benzene and 150 g. of zinc-copper alloy turnings (8% copper). Several crystals of iodine were added and the benzene heated to reflux temperature.

A mixture of ethyl bromoacetate (250 g., 1.5 moles) and ethyl methyl ketone (108 g., 1.5 moles) dissolved in 200 ml. of anhydrous benzene was added from the dropping funnel at a rate to maintain gentle reflux. Heating of the benzene to reflux temperature before the addition of the reacting materials was very essential. If this was not done, a large portion of the reactants had to be added before the reaction was initiated and then the reaction occurred violently with a considerable evolution of heat. If the benzene was at reflux temperature, the reaction took place immediately.

The addition required two hours. External heating was not necessary during the addition. After the addition, the mixture was heated under reflux for one hour.

The reaction mixture, after cooling, was decomposed by pouring into one liter of dilute (10%) sulfuric acid. The benzene layer was separated and the aqueous layer extracted with two 100-ml. portions of benzene. The combined benzene extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and the benzene removed under reduced pressure.

Distillation yielded 142 g. (60%) of the hydroxy ester boiling at 87-93°/25 mm.[1] (Lit. b.p. 88-100°/20 mm.(104))

Ethyl β-methyl-γ-phenylvalerate (II). In a 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 125-ml. dropping funnel and a reflux condenser with an outlet for evolved hydrogen chloride, were placed 300 ml. of anhydrous, thiophene-free benzene and 220 g. (1.7 moles) of anhydrous aluminum chloride.

Ethyl β-hydroxy-β-methylvalerate (70 g., 0.44 mole) was added over a period of one hour while the mixture was cooled by means of an ice bath. During the addition the color changed to a yellowish-green and hydrogen chloride was evolved. Stirring was continued for one hour with cooling and then the mixture was allowed to warm to room temperature with stirring. Stirring at room temperature was continued for fifteen hours.

The reaction mixture was decomposed by pouring into an ice-hydrochloric acid mixture. The benzene layer was separated and the aqueous layer extracted with two 50-ml. portions of benzene. The combined benzene extracts were washed once with water and then washed with dilute (2%) sodium bicarbonate solution until the washings were basic.

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[1] All boiling points are uncorrected.

The benzene solution was washed with water until neutral, dried over anhydrous magnesium sulfate and the benzene removed under reduced pressure.

Distillation yielded 79 g. (82%) of ethyl β-methyl-δ-phenylvalerate boiling at 125-135°/2 mm.

<u>β-Methyl-δ-phenylvaleric acid</u> (III). In a 500-ml. one-necked round-bottomed flask were mixed 65 g. (0.29 mole) of ethyl β-methyl-δ-phenylvalerate and 20 g. of potassium hydroxide dissolved in 250 ml. of methanol. The mixture was heated under reflux for eight hours. The color of the mixture was a deep red.

The major portion of the methanol was removed under reduced pressure and the residue poured into water. The unsaponified ester was removed by extraction with three 50-ml. portions of ether. The aqueous layer was acidified with dilute (20%) sulfuric acid and extracted with four 50-ml. portions of ether. The ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

Distillation yielded 41 g. (62%) of β-methyl-δ-phenylvaleric acid which boiled at 108-110°/0.1 mm. The product was very viscous and slightly yellow in color. (Lit. b.p. 175°/13 mm.(105))

Removal of the ether from the unsaponified ester yielded 19.5 g. (30%) of starting material.

<u>3,4-Dimethyltetralone-1</u> (IV). Two methods for the cyclization of β-methyl-δ-phenylvaleric acid to the ketone,

3,4-dimethyltetralone-1, were used.

1. Cyclization of the acid chloride with aluminum chloride.

In a 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a reflux condenser fitted with a calcium chloride drying tube, and an addition flask for solids, were placed 200 ml. of anhydrous benzene and 27 g. (0.14 mole) of β-methyl-γ-phenylvaleric acid. Phosphorus pentachloride (50 g., 0.24 mole) was added over a period of one hour. The mixture was then heated under reflux for two hours on the steam bath. Anhydrous aluminum chloride (30 g., 0.23 mole) was added slowly; the mixture becoming very dark red during the addition. Refluxing was continued for three and one-half hours.

The complex was decomposed by pouring into a mixture of ice and concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer extracted with two 50-ml. portions of benzene. The combined benzene extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and the benzene removed under reduced pressure.

Distillation yielded 11.5 g. (42%) of the cyclic ketone which boiled at 97-99°/1.5 mm.

2. Cyclization of the free acid with concentrated sulfuric acid.

β-Methyl-γ-phenylvaleric acid (37 g., 0.2 mole) was added dropwise to 500 ml. of concentrated sulfuric acid contained in a 1-l. Erlenmeyer flask equipped with a mechanical glass stirrer. During the addition the mixture was stirred and cooled in an ice bath to 0°C. The addition was carried out at such a rate as to keep the temperature around 0°C. After the addition of the β-methyl-γ-phenylvaleric acid, the mixture was warmed to 50°C. on the steam bath and immediately poured onto ice.

The acid solution was extracted with five 100-ml. portions of ether. The ether extracts were washed with dilute (10%) potassium hydroxide until the washings were basic and then with water until neutral. The ether solution was dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

Distillation yielded 18.5 g. (51%) of 3,4-dimethyltetralone-1: b.p. 108-112°/3 mm.; n_D^{25}1.5500[2]. (Lit. b.p. 142-143°/13 mm.; n_D^{15}1.5524 (105))

Analysis[3] Calculated for $C_{12}H_{14}O$: C, 82.72; H, 8.10.
Found: C, 82.47; H, 8.00.

The *2,4-dinitrophenylhydrazone* of 3,4-dimethyltetralone-1 was prepared in the usual manner and melted at 189-190° after several recrystallizations from an ethanol-ethyl acetate mixture.

Analysis Calculated for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12.
Found: C, 61.18; H, 5.00.

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[2] Refractive indices were taken with an Abbe refractometer.

[3] All analyses were carried out by Professor Mary Aldridge and Miss Kathyrn Gerdeman.

The semicarbazone of 3,4-dimethyltetralone-1 was prepared in the usual manner and melted at 174-175° after two recrystallizations from an ethanol-water mixture. v. Braun reported a melting point of 177° for this derivative.

The ultraviolet absorption spectra of indanone-1, 3,3-dimethylindanone-1, and 3,4-dimethyltetralone-1 were determined. A Beckman spectrophotometer, with cells of 1.000 cm. length was used. All of the spectra were determined using spectro grade isooctane as the solvent. The data for these spectra are given in Tables 1-4.

3-Methyl-1,1,4-triphenylpentene-1 (V). A 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube, was dried by flaming under an atmosphere of nitrogen. Magnesium turnings (3.7 g., 0.15 g. atom) and 50 ml. of anhydrous ether were placed in the flask and several crystals of iodine added. Freshly distilled bromobenzene (25.5 g., 0.15 mole) dissolved in 100 ml. of anhydrous ether was added dropwise at a rate to maintain gentle reflux. The addition required one hour. The mixture was heated under reflux for an additional hour. Ethyl β-methyl-δ-phenylvalerate (10 g., 0.046 mole) dissolved in 100 ml. of anhydrous ether was added over a period of one hour. Mild external heating was required to maintain reflux temperature. The mixture was then heated under reflux for one hour.

The reaction mixture was decomposed by pouring onto

Table 1. Ultraviolet Absorption Spectrum of Indanone-1 (concentration, 1.28 x 10^{-4} moles/liter)

mu	% T	ϵ	mu	% T	ϵ
226	15.9	6.23 x 10^3	252	82.8	6.4 x 10^2
228	10.8	7.54	253	84.1	5.9
230	7.8	8.66	254	82.2	6.7
232	5.9	9.59	255	81.6	6.9
233	5.8	9.66	256	83.1	6.3
234	4.9	1.02 x 10^4	257	85.0	5.5
235	4.1	1.08	258	84.9	5.6
236	2.6	1.24	259	84.9	5.6
238	3.2	1.17	260	77.0	8.9
240	5.3	9.97 x 10^3	261	80.8	7.2
241	5.7	9.76	262	77.2	8.8
242	5.4	9.88	263	79.3	7.9
243	5.5	9.82	264	79.0	8.0
244	5.0	1.02 x 10^4	265	78.2	8.3
245	5.8	9.66 x 10^3	270	70.3	1.19 x 10^3
246	9.4	8.03	275	61.0	1.68
247	18.3	5.76	280	50.5	2.31
248	32.8	3.78	285	53.1	2.14
249	50.6	2.31	290	47.9	2.50
250	63.9	1.52	295	81.0	7.1 x 10^2
251	76.2	9.2 x 10^2	300	96.0	1.4

Table 2. Ultraviolet Absorption Spectrum of 3,3-Dimethyl-indanone-1
(concentration, 1.27 x 10^{-4} moles/liter)

mu	% T	∈	mu	% T	∈
226	14.2	6.67 x 10^3	251	66.0	1.42 x 10^3
227	12.9	6.98	252	73.5	1.05
228	10.5	7.70	253	76.1	9.3 x 10^2
229	9.2	8.15	254	78.8	8.2
230	8.2	8.55	255	79.3	7.9
231	6.8	9.18	256	78.8	8.2
232	6.2	9.50	257	77.8	8.6
233	5.6	9.87	258	77.2	8.9
234	4.8	1.04 x 10^4	259	76.1	9.3
235	4.3	1.07	260	75.0	9.8
236	3.4	1.15	261	74.3	1.02 x 10^3
237	3.2	1.18	262	74.0	1.03
238	4.0	1.10	263	74.9	9.9 x 10^2
239	3.8	1.12	264	70.9	1.18 x 10^3
240	3.2	1.18	265	72.1	1.12
241	5.2	1.01	266	68.2	1.31
242	5.5	9.90 x 10^3	268	67.2	1.36
243	5.4	9.96	270	65.2	1.46
244	7.0	9.10	272	60.2	1.61
245	4.9	1.03 x 10^4	275	58.9	1.81
246	7.1	9.02 x 10^3	280	50.4	2.34
247	12.9	7.00	285	54.8	2.06
248	23.9	4.90	290	49.8	2.38
249	39.5	3.17	295	82.8	6.4 x 10^2
250	54.1	2.11	300	95.2	1.7

Table 3. Ultraviolet Absorption Spectrum of 3,4-Dimethyltetralone-1
(concentration, 1.14 x 10^{-4}moles/liter)

mu	% T	ϵ	mu	% T	ϵ
226	35.0	4.00 x 10^3	253	19.9	6.15 x 10^3
227	30.2	4.56	254	24.3	5.38
228	29.0	4.71	255	31.4	4.42
229	25.8	5.15	256	44.2	3.11
230	23.2	5.56	257	54.0	2.34
231	20.6	6.02	258	65.3	1.62
232	20.2	6.10	259	72.8	1.21
233	14.8	7.26	260	76.6	1.02
234	12.5	7.92	261	80.6	8.2 x 10^2
235	11.2	8.36	262	81.8	7.7
236	8.8	9.25	263	82.4	7.4
237	8.6	9.35	264	81.8	7.7
238	7.8	9.72	265	81.2	7.9
239	6.9	1.03 x 10^4	266	81.0	8.0
240	6.2	1.06	267	80.1	8.5
241	5.6	1.10	268	79.6	8.7
242	4.2	1.21	269	78.8	9.1
243	3.5	1.28	270	77.6	9.7
244	5.2	1.13	272	76.8	1.05 x 10^3
245	6.3	1.05	275	73.2	1.19
246	5.3	1.12	280	67.6	1.49
247	8.8	9.25 x 10^3	285	63.6	1.72
248	6.2	1.06 x 10^4	290	65.2	1.63
249	8.8	9.25 x 10^3	295	67.6	1.49
250	9.8	8.84	300	85.3	6.1 x 10^2
251	11.1	8.37	305	95.6	1.7
252	13.8	7.55			

Table 4. Ultraviolet Absorption Spectrum of Tetralone-1
(Data taken from curve reported by D. Biquard)

mu	ϵ	mu	ϵ
231	5.0 x 10^3	265	7.0 x 10^2
235	7.1	270	7.0
240	8.0	275	1.0 x 10^3
244	8.3	280	1.3
246	8.1	285	1.5
249	7.0	286	1.6
250	6.6	290	1.3
253	4.0	293	1.2
254	2.5	296	1.2
255	1.7	297	1.1
260	6.0 x 10^2	300	8.0 x 10^2
261	5.0	305	3.0

ice and 100 ml. of dilute (20%) sulfuric acid was added to dissolve the precipitated magnesium hydroxide. The acid solution was subjected to steam distillation to remove impurities. Approximately three liters of distillate were collected and discarded.

The residue from the steam distillation was extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The ether extracts were not washed to remove the trace of acid present since this was desirable to aid in the dehydration of the hydroxy compound to the ethylenic compound during distillation.

Distillation yielded 4 g. (30%) of a very viscous yellow oil boiling at 165-170°/0.2 mm. This material readily decolorized a dilute permanganate solution.

<u>α-Methyl-β-phenylbutyric acid</u> (VI). In a 250-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 50-ml. dropping funnel, and a thermometer dipping below the surface of the liquid, was placed 35 ml. of acetic acid. 3-Methyl-1,1,4-triphenylpentene-1 (4 g., 0.013 mole) was dissolved in 10 ml. of isooctane and added to the flask. Chromic acid (4.5 g., 0.038 mole) dissolved in 4 ml. of water and 25 ml. of acetic acid was added dropwise while the temperature was kept below 50°C. by external cooling with an ice bath. After addition of the chromic acid solution, the mixture was warmed to 50°C. for thirty minutes. The mixture was then cooled and 10 ml. of

methanol added dropwise to destroy the excess chromium trioxide. The mixture was concentrated under reduced pressure to a volume of about 20 ml. and then poured into 150 ml. of cold water. No solid acid was obtained.

The aqueous solution was extracted with three 50-ml. portions of ether. The ether extracts were extracted with three 20-ml. portions of dilute (10%) potassium hydroxide. The basic extracts were combined and acidified with dilute sulfuric acid, with the formation of a yellow oil. The acid solution was extracted with three 50-ml. portions of ether, the ether solution decolorized with charcoal, and extracted with dilute (10%) potassium hydroxide. The basic extracts were acidified with dilute sulfuric acid and extracted with three 50-ml. portions of ether. After removal of the ether, a light-yellow, viscous oil was obtained.

An attempt to purify the acid by distillation under reduced pressure ~~sublimation~~ was unsuccessful. No distillation occurred on heating to 180°/20 mm. On cooling, the material partially solidified. After recrystallization from petroleum ether (60-80°), 1 g. (43%) of a white crystalline solid melting at 129-131° was obtained. H. Rupe et. al. reported a melting point of 130-130.5° for α-methyl-β-phenylbutyric acid (106).

Oxidation of ethyl β-methyl-γ-phenylvalerate to benzoic acid. An alkaline permanganate oxidation of ethyl β-methyl-γ-phenylvalerate was carried out in the usual fashion. Four grams of ester, 5 g. of potassium permanganate and 2 ml. of 10% potassium hydroxide in 250 ml. of water were heated under reflux in a 500-ml. round-bottomed flask. Four additional 5-g. portions of potassium permanganate were added over a period of two hours. An additional hour of heating under reflux did not decolorize the solution. The manganese dioxide was filtered from the basic solution, the excess permanganate removed by the addition of several crystals of sodium sulfite and the solution acidified with dilute sulfuric acid. The acid was isolated by ether extraction and recrystallized from water.

The product obtained was a white crystalline solid melting at 119-121°. This material gave no depression in a mixed melting point with an authentic sample of benzoic acid.

3-Methyl-3-phenylpentanone-2 (VII). Three methods, the reaction of α-methyl-α-phenylbutyronitrile with methyl Grignard reagent and with methyllithium, and the reaction of α-methyl-α-phenylbutyric acid with methyllithium, were attempted to prepare 3-methyl-3-phenylpentanone-2.

1. The reaction of α-methyl-α-phenylbutyronitrile with methylmagnesium bromide.

In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a reflux condenser fitted with a calcium chloride drying tube, and an inlet tube for methyl bromide, were placed 300 ml. of anhydrous ether and 10 g. of magnesium turnings.

Methyl bromide was bubbled into the ether over a period of one and one-half hours until all of the magnesium had dissolved. α-Methyl-α-phenylbutyronitrile (50 g., 0.31 mole) dissolved in 300 ml. of anhydrous ether was added dropwise over a period of one and one-half hours. The reaction mixture was allowed to stir overnight following which it was heated under reflux on the steam bath for two hours.

The reaction mixture was decomposed by pouring into dilute (10%) sulfuric acid and was extracted with four 100-ml. portions of ether. The ether extracts were washed with water until neutral.

Since it was possible for the Grignard reaction to result in imine formation, steam distillation from the acid medium was indicated. Steam distillation was carried out and the distillate extracted with two 100-ml. portions of ether and these ether ectracts combined with the original ether extracts. Only a very small amount of material was obtained from the steam distillation.

The ether solution was dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. Distillation yielded 46.3 g. of product: b.p. 73-76°/0.8-1 mm.

Attempts to prepare ketone derivatives from the product failed completely. Refluxing of 10 g. of the product for seventeen hours with 150 ml. of water and 100 ml. of concentrated sulfuric acid yielded 9 g. of α-methyl-α-phenylbutyric acid which melted at 56-58°. (Lit. m.p. 60° (107)) This indicated the material obtained from the Grignard reaction was essentially α-methyl-α-phenylbutyronitrile, the starting material.

2. The reaction of α-methyl-α-phenylbutyronitrile with methyllithium.

In a 2-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a reflux condenser fitted with a calcium chloride drying tube, and a gas inlet tube for methyl bromide, were placed 400 ml. of anhydrous ether and 7 g. (1 g. atom) of lithium ribbon cut in one-half inch pieces. Methyl bromide was bubbled into the ether over a period of three and one-half hours at which time all the lithium had dissolved.

α-Methyl-α-phenylbutyronitrile (80 g., 0.5 mole) dissolved in 400 ml. of anhydrous ether was added dropwise over a period of two hours. During the addition the mixture was cooled in an ice bath. The mixture became light green in color as the reaction proceeded. At the end of the addition stirring was stopped, the mixture allowed to warm to room temperature, and stand for a further three hours.

Ice water (25 ml.) was added dropwise over a period of thirty minutes. The color changed to yellow, and then white with the precipitation of lithium hydroxide. Thirty-five milliliters of concentrated sulfuric acid in 200 ml. of ice water was added dropwise over a period of thirty minutes. At the end of the addition, the precipitate had dissolved and the ether layer had a faint yellow color.

Steam distillation was carried out from the original reaction flask. About four liters of distillate was collected. The steam distillate was extracted with four 250-ml.

portions of ether, the ether layer dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. Distillation yielded 69.5 g. of product which boiled at 108-110°/12 mm.

The 2,4-dinitrophenylhydrazone of the product was prepared in the usual manner and formed with difficulty; requiring standing overnight before crystallization occurred. After recrystallization from an alcohol-water mixture a yellow-orange crystalline solid melting at 102-104° was obtained.

The semicarbazone of the product was prepared in the usual manner and, after recrystallization from an alcohol-water mixture, melted at 192-193°.

The behavior of the product indicated the presence of a mixture of α-methyl-α-phenylbutyronitrile and 3-methyl-3-phenylpentanone-2 which could not be separated by fractional distillation due to the proximity of their boiling points.

A separation of the ketone and nitrile by chromatographic absorption on an alumina column was attempted with 20 g. of the product from the methyllithium reaction. Petroleum ether (40-60°) was used as the solvent. Sixteen and one-half grams of the material was not absorbed and this material did not form any ketone derivatives.

The ketone was eluted from the column with methanol. After removal of the methanol and distillation, a colorless liquid (3 g.) boiling at 130-135°/30 mm. was obtained. (Lit. b.p. 112-116°/13 mm. (108))

Analysis Calculated for $C_{12}H_{16}O$: C, 81.77; H, 9.15.

Found: C, 81.50; H, 8.83.

3. The reaction of α-methyl-α-phenylbutyric acid with methyllithium.

In a 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 125-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 150 ml. of anhydrous ether and 3.5 g. (0.5 g. atom) of lithium ribbon. Methyl iodide (35 g., 0.25 mole), dissolved in 100 ml. of anhydrous ether, was added dropwise at a rate to maintain gentle reflux.

α-Methyl-α-phenylbutyric acid (10 g., 0.06 mole) dissolved in 50 ml. of anhydrous ether was then added dropwise at a rate to maintain reflux. The mixture was heated under reflux for one and one-half hours and then poured onto ice. The ether layer was removed and the basic aqueous layer extracted with two 50-ml. portions of ether. The combined ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

A yellow liquid (1 g.) was obtained which gave no positive test with 2,4-dinitrophenylhydrazone reagent.

α-Phenylvaleronitrile (VIII). In a 3-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 500-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 450 ml. of anhydrous ether and 172 g. (10% excess) of sodamide. Phenylacetonitrile (468 g., 4 moles) was slowly added with stirring at a rate to maintain constant reflux. The addition required about two hours. As the nitrile was added, the color changed to a dark red-brown and at the end of the addition all of the sodamide had reacted. After the addition of the nitrile the mixture was heated under reflux overnight to ensure removal of all the ammonia.

n-Propyl bromide (492 g., 4 moles) dissolved in 600 ml. of anhydrous ether was added dropwise at a rate to maintain steady reflux. Three hours were required for this addition. As the halide was added a heavy creamy-white precipitate of sodium bromide was formed. The mixture was heated under reflux for one hour after the addition and then allowed to cool. Water was added slowly, with external cooling, to decompose the mixture. The precipitated sodium bromide dissolved with the addition of water.

The ether layer was separated and the aqueous layer extracted with two 100-ml. portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding a colorless liquid (496.8 g., 78.5%): b.p. 140-148°/20-24 mm.; n_D^{24}1.5030. (Lit. b.p. 255-61°/760 mm. (109))

<u>α-Methyl-α-phenylvaleronitrile</u> (IX). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 150 ml. of anhydrous ether and 46 g. (10% excess) of sodamide. α-Phenylvaleronitrile (160 g., 1 mole) was added from

the dropping funnel at a rate to maintain reflux, requiring about one hour. As in the previous reaction, a dark red-brown color appeared as the reaction progressed, After the addition, refluxing was continued for one-half hour.

Methyl iodide (142 g., 1 mole) was added, with cooling, to maintain reflux. The addition was slow requiring about three hours for completion since the reaction took place very readily with a considerable evolution of heat. A heavy precipitation of sodium iodide occurred until, at the end of the addition, the mixture was completely white and very thick. After the addition the mixture was heated under reflux for eighteen hours. The mixture was decomposed by pouring into water. The ether layer was separated and the aqueous layer extracted with two 100-ml. portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding a colorless liquid (130 g., 75%) boiling at 135-145°/20-25 mm., n_D^{24}1.5028.

Analysis Calculated for $C_{12}H_{15}N$: C, 83.18; H, 8.73;
Found: C, 82.93; H, 8.96.

α-Methyl-α-phenylvaleramide (X). α-Methyl-α-phenylvaleronitrile (116 g., 0.67 mole) was added with stirring to 250 ml. of concentrated sulfuric acid contained in a 1-l. Erlenmeyer flask. The mixture turned deep red and stirring was continued for twenty-four hours. The mixture was then allowed to stand for thirty-six hours.

The sulfuric acid solution was dropped with stirring onto crushed ice. A yellow, taffy-like material was obtained. The acid solution was extracted with six 200-ml. portions of ether. The taffy-like material was not extremely soluble in ether which necessitated the use of such a large volume of ether for the extraction. The ether extracts were washed with four 100-ml. portions of dilute (2%) sodium hydroxide to remove any acid which might have formed during the hydrolysis. All of the yellow coloration was removed in the basic extraction. Subsequent acidification of the basic extracts gave no appreciable amount of ether-soluble material. The yellow coloration remained in the aqueous layer.

The ether solution was washed with water until neutral, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The residue gave no indication of being a solid.

In the distillation of the product a forerun (10 g.) was obtained boiling at 75-95°/1.5 mm. The major portion of the material (48 g., 37.5%) boiled at 125-145°/1.5 mm. and was extremely viscous. The product formed a glass on cooling, but did not crystallize.

Analysis Calculated for $C_{12}H_{17}NO$: C, 75.35; H, 8.96.

Found: C, 77.67, 77.29; H, 9.27, 8.99.

2-Methyl-2-phenylamylamine (XI). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube, were placed 400 ml. of anhydrous ether and 18 g. (0.48 mole) of lithium aluminum hydride. α-Methyl-α-phenylvaleramide (48 g., 0.25 mole) dissolved in 250 ml. of anhydrous benzene was added dropwise at a rate to maintain constant reflux. The addition required about one hour. After addition of the amide, the upright condenser was removed, a side-arm containing a thermometer was inserted, condenser attached, and the ether removed by distillation until the temperature reached 70-75°C. After removal of the ether, the reflux condenser was again inserted and the mixture heated under reflux for seventeen hours.

The mixture was decomposed by very slowly adding as little water as possible. Very slow addition was necessary due to the considerable evolution of heat. Cooling was used sparingly but could not be employed to the best advantage since freezing of the benzene occurred which, combined with the precipitation of aluminum hydroxide, made the necessary efficient stirring practically impossible. The precipitated aluminum hydroxide was removed by filtration and washed with ether. The combined ether and benzene layers were extracted with three 100-ml. portions of dilute hydrochloric acid (30 ml. of concentrated acid diluted to 300 ml.). The acid solution was neutralized with concentrated ammonium hydroxide and then extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The amine was distilled yielding a colorless liquid

(30 g., 68%) which boiled at 75-80°/1.5 mm., n_D^{24}1.5152.

Analysis Calculated for $C_{12}H_{19}N$: C, 81.39; H, 10.81.

Found: C, 81.65; H, 10.74.

The hydrochloride of 2-methyl-2-phenylamylamine was prepared by dissolving 3 g. of the amine in 300 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white precipitate formed immediately. The amine hydrochloride was recrystallized from an absolute ethanol-anhydrous ether mixture. A white, stable, crystalline solid melting at 146-148° was obtained.

Analysis Calculated for $C_{12}H_{20}NCl$: C, 67.43; H, 9.48.

Found: C, 67.83; H, 9.31.

2-Methyl-2-(p-nitrophenyl)amylamine (XII). In a 500-ml. wide-mouthed Erlenmeyer flask, equipped with a glass stirrer and a long-stemmed thermometer dipping below the surface of the liquid, was placed 250 ml. of concentrated sulfuric acid. The acid was cooled to 0°C. by means of an ice-salt bath.

2-Methyl-2-phenylamylamine (27.5 g., 0.16 mole) was added slowly with the temperature maintained below 5°C. During the addition of the amine the color changed to a light orange. Powdered potassium nitrate (18 g., 10% excess) was added slowly, keeping the temperature below 5°C. The mixture was heated to 50°C. by means of a hot-water bath and then allowed to cool, with stirring, to room temperature. At the end of this time, the solution was orange-brown in color.

The reaction mixture was poured onto ice and neutralized with concentrated ammonium hydroxide. A dark red oil separated which was extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The nitroamine was distilled yielding an orange liquid (22 g., 62.5%): b.p. 145-155°/1.5 mm.

The hydrochloride of 2-methyl-2-(p-nitrophenyl)amylamine was prepared by dissolving 8 g. of the amine in 400 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A fine, powdery material precipitated which was very difficult to filter. On standing overnight the material seemed to oil and then solidify into a hard, brown material. This brown material was dissolved in absolute ethanol and on the addition of anhydrous ether a heavy yellow precipitate was formed. After filtration and drying, a hard yellow powder melting at 184-188° was obtained.

Analysis Calculated for $C_{12}H_{19}N_2O_2Cl$: C, 55.70; H, 7.40.
Found: C, 55.49; H, 7.25.

2-Methyl-2-(p-aminophenyl)amylamine (XIII). 2-Methyl-2-(p-nitrophenyl)amylamine (13.5 g., 0.06 mole) was dissolved in 50 ml. of 95% ethanol and a small amount of platinum oxide catalyst added. Hydrogenation was carried out at a starting pressure of eighteen p.s.i. and a pressure drop of thirteen pounds took place over a period of forty minutes. The hydrogenation apparatus was calibrated so that a hydrogen uptake of 0.1 mole resulted in a pressure drop of seven pounds. On this basis, the theoretical drop for this reaction was calculated as 12.6 pounds. During the hydrogenation an appreciable amount of heat was evolved.

The solution was filtered to remove the catalyst and the alcohol removed under reduced pressure. The diamine was distilled yielding a light yellow, viscous liquid (6.9 g., 59%) boiling at 145-150°/2.8 mm., n_D^{24}1.5570.

The dihydrochloride of 2-methyl-2-(p-aminophenyl)amylamine was prepared by dissolving 2 g. of the diamine in 200 ml. of anhydrous ether and passing in dry hydrogen chloride gas. A white precipitate formed which turned yellow and seemed to oil slightly after filtration. After standing overnight the material had turned hard and yellow and was recrystallized from an absolute ethanol-anhydrous ether mixture. A stable, white, crystalline solid melting at 206-209° was obtained.

Analysis Calculated for $C_{12}H_{22}N_2Cl_2$: C, 54.34; H, 8.36.
Found: C, 54.66; H, 8.28.

α-Ethyl-α-phenylvaleronitrile (XIV). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube, were placed 250 ml. of anhydrous ether and 46 g. (10% excess) of sodamide. α-Phenylvaleronitrile (160 g., 1 mole) was added dropwise at a rate to maintain reflux, requiring about one hour for the addition. After the addition, the mixture was heated under reflux for one hour. Ethyl iodide (156 g., 1 mole) was added dropwise, over a period of two hours, at a rate to maintain constant reflux. After the addition the mixture was heated under reflux for eighteen hours.

The reaction mixture was poured into water, the ether layer separated, and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding a colorless liquid (119.2 g., 63.6%) which boiled at 98-102°/4.5 mm., n_D^{24}1.5001.

Analysis Calculated for $C_{13}H_{17}N$: C, 83.37; H, 9.15.

Found: C, 83.46; H, 9.12.

α-Ethyl-α-phenylvaleramide (XV). α-Ethyl-α-phenylvaleronitrile (119 g., 0.63 mole) was mixed with 250 ml. of concentrated sulfuric acid contained in a 500-ml. Erlenmeyer flask equipped with a glass stirrer. The mixture was stirred for twenty-four hours and then allowed to stand for twelve hours. At the end of this time, the reaction mixture was dark red in color.

The acid solution was dropped with stirring onto ice and a yellow, taffy-like material separated. The mixture was extracted with five 200-ml. portions of ether and the ether extracts washed with four 100-ml. portions of dilute (2%) sodium hydroxide to remove any acid which might have formed during the hydrolysis. As in the case of the hydrolysis of α-methyl-α-phenylvaleronitrile, no acid was obtained on acidification of these basic extracts. The ether solution was washed with water until neutral, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

The product was distilled yielding an extremely viscous, colorless liquid (27.5 g.) boiling at 122-125°/1 mm. after a large forerun (58.1 g.) of starting nitrile which boiled at 80-85°/1 mm.

The recovered nitrile was mixed with concentrated sulfuric acid (150 ml.) and 15 ml. of water was added. Stirring was continued for four days. The amide was isolated as before and on distillation 30.4 g. of unreacted nitrile was recovered and 17.7 g. of amide obtained.

The nitrile recovered from the second hydrolysis (30.4 g.) was added to 150 ml. of concentrated sulfuric acid and water was added until the mixture became cloudy. Stirring was begun with the mixture heated on the steam bath to 70-80°C. Stirring was continued for two and one-half hours with the temperature maintained at 60-70°C. During this heating period the mixture became homogeneous and a very dark red-brown color. After isolation of the amide, 8.8 g. of nitrile was recovered and 14.6 g. of amide obtained on distillation.

The total yield of amide from the three hydrolysis reactions was 59.8 g. (46.1%), b.p. 122-125°/1 mm. The product formed a glass on cooling but would not crystallize.

Analysis Calculated for $C_{13}H_{19}NO$: C, 76.05; H, 9.34.

Found: C, 77.19; H, 9.54.

2-Ethyl-2-phenylamylamine (XVI). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 400 ml. of anhydrous ether and 24 g. (0.63 mole) of lithium aluminum hydride. α-Ethyl-α-phenylvaleramide (59.8 g., 0.29 mole) dissolved in 200 ml. of anhydrous benzene was added dropwise to maintain constant reflux. The addition of the amide required one and one-half hours. After the addition the ether was removed by distillation and the mixture heated under reflux for eighteen hours.

A minimum amount of water was added slowly with cooling to decompose the mixture. The precipitated aluminum hydroxide was removed by filtration and washed with ether. The combined ether and benzene solution was extracted with three 100-ml. portions of dilute hydrochloric acid. The acid extracts were neutralized with concentrated ammonium hydroxide and extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding a colorless liquid (44.7 g., 80%) boiling at 82-85°/0.8 mm., n_D^{26}1.5172.

Analysis Calculated for $C_{13}H_{21}N$: C, 81.61; H, 11.07.

Found: C, 81.74; H, 11.04.

The hydrochloride of 2-ethyl-2-phenylamylamine was prepared by dissolving 3 g. of the amine in 300 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. No precipitation took place even after standing overnight in the refrigerator. It seemed probable that the amine hydrochloride was soluble in ether so the ether was replaced with high-boiling (90-100°) petroleum ether. On cooling, white crystals formed very readily. After recrystallization from petroleum ether, a white crystalline material melting at 155-160° was obtained.

Analysis Calculated for $C_{13}H_{22}NCl$: C, 68.54; H, 9.74.
Found: C, 68.83; H, 9.71.

2-Ethyl-2-(p-nitrophenyl)amylamine (XVII). To 250 ml. of concentrated sulfuric acid contained in a 500-ml. Erlenmeyer flask, equipped with a glass stirrer and a long-stemmed thermometer dipping below the surface of the liquid, and cooled by means of an ice-salt bath, was added 2-ethyl-2-phenylamylamine (20 g., 0.11 mole). The amine was added at a rate to keep the temperature between 0°C. and 10°C. Powdered potassium nitrate (12.4 g., 10% excess) was added slowly keeping the temperature below 10°C. The ice bath was removed and the mixture was heated to 50°C. by means of a hot-water bath and then allowed to cool to room temperature with stirring.

The acid mixture was poured onto ice and neutralized with concentrated ammonium hydroxide. A dark red oil separated which was extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding an orange liquid (10.4 g., 40%) which boiled at 135-140°/0.3 mm. A considerable amount was not distilled since it was necessary to heat the oil bath to 210°C. even with a pressure of 0.3 mm.

The hydrochloride of 2-ethyl-2-(p-nitrophenyl)amylamine was prepared by dissolving 1 g. of the nitroamine in 200 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white precipitate appeared immediately. On recrystallization from an absolute ethanol-anhydrous ether mixture a white powdery solid melting at 206-208° was obtained.

Analysis Calculated for $C_{13}H_{21}N_2O_2Cl$: C, 57.23; H, 7.76.

Found: C, 56.89; H, 7.61; C, 57.06; H, 7.87.

2-Ethyl-2-(p-aminophenyl)amylamine (XVIII). 2-Ethyl-2-(p-nitrophenyl)amylamine (9.4 g., 0.042 mole) was dissolved in 60 ml. of 95% ethanol and a small amount of platinum oxide catalyst added. The hydrogenation was carried out at a starting pressure of fourteen p.s.i. and at the end of twenty minutes a pressure drop of ten pounds had occurred (theoretical drop, nine pounds).

The catalyst was removed by filtration and the alcohol removed under reduced pressure. The diamine was distilled yielding a bright yellow liquid (6.5 g., 74%) boiling at 125-130°/0.09 mm.

The dihydrochloride of 2-ethyl-2-(p-aminophenyl)amylamine was prepared by dissolving 6 g. of the diamine in 300 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white precipitate formed which turned slightly yellow on standing. Attempts at recrystallization were unsuccessful since the material turned into an oil as soon as it was filtered. An analysis of this unrecrystallized material (m.p. 135-138°) indicated it was the monohydrochloride of 2-ethyl-2-(p-aminophenyl)amylamine.

<u>Analysis</u> Calculated for $C_{13}H_{23}N_2Cl$: C, 64.31; H, 9.55.

Found: C, 63.99; H, 9.49.

The monohydrochloride of the diamine was dissolved in absolute ethanol and anhydrous ether added until the mixture began to appear cloudy. This solution was then saturated with dry hydrogen chloride gas and the dihydrochloride precipitated. After recrystallization from an absolute ethanol-anhydrous ether mixture a stable, creamy-white solid melting at 234-238° was obtained.

<u>Analysis</u> Calculated for $C_{13}H_{24}N_2Cl_2$: C, 55.91; H, 8.61.

Found: C, 56.16; H, 8.57.

<u>N,N-Dimethyl-2-ethyl-2-phenylamylamine</u> (XIX). 2-Ethyl-2-phenylamylamine (20 g., 0.11 mole) was placed in a 100-ml., round-bottomed flask with 25 ml. (0.55 mole) of formic acid (concentration, 90%) and 28 ml. (0.38 mole) of formaldehyde (concentration, 40%).

The flask was fitted with a reflux condenser and the mixture heated on the steam bath. A vigorous evolution of carbon dioxide took place over a period of approximately one hour; the mixture was heated on the steam bath for twenty hours.

The excess formaldehyde was removed and, after cooling, the solution was made basic with concentrated ammonium hydroxide. The basic solution was extracted with three 100-

ml. portions of ether, the ether extracts dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

The tertiary amine was distilled yielding a colorless liquid (19.5 g., 81%): b.p. 73-77°/0.5 mm., n_D^{26}1.5020.

Analysis Calculated for $C_{15}H_{25}N$: C, 82.13; H, 11.49.

Found: C, 82.35; H, 11.27.

The hydrochloride of N,N-dimethyl-2-ethyl-2-phenylamylamine was prepared by dissolving 1 g. of the amine in 250 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white precipitate formed which, on recrystallization from an absolute ethanol-anhydrous ether mixture, yielded a stable, white crystalline material melting at 184-187°.

Analysis Calculated for $C_{15}H_{26}NCl$: C, 70.42; H, 10.25.

Found: C, 70.65; H, 10.03.

N,N-Dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine (XX). N,N-Dimethyl-2-ethyl-2-phenylamylamine (18 g., 0.082 mole) was added dropwise to 250 ml. of concentrated sulfuric acid contained in a 500-ml. Erlenmeyer flask equipped with a glass stirrer and a long-stemmed thermometer dipping below the surface of the liquid, and cooled by means of an ice salt bath. During the addition of the amine the temperature was kept below 10°C. Powdered potassium nitrate (9.6 g., 10% excess) was added at a rate to keep the temperature below 10°C.

The acid solution was poured onto ice and made basic with concentrated ammonium hydroxide. A dark brown oil separated which was extracted with three 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The nitroamine was distilled yielding an amber-colored liquid (17.5 g., 80%) boiling at 123-127°/0.08 mm.

The hydrochloride of N,N-dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine was prepared by dissolving 1 g. of the nitroamine in 100 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. The amine hydrochloride precipitated nicely and, after recrystallization from an absolute ethanol-anhydrous ether mixture, was a creamy-white solid melting at 193-196°.

Analysis Calculated for $C_{15}H_{25}N_2O_2Cl$: C, 59.88; H, 8.38.

Found: C, 59.86; H, 8.32.

N*,N*-Dimethyl-2-ethyl-2-(p-aminophenyl)amylamine* (XXI). N,N-Dimethyl-2-ethyl-2-(p-nitrophenyl)amylamine (16.5 g., 0.063 mole) was dissolved in 50 ml. of 95% ethanol and a small amount of platinum oxide catalyst added. Hydrogenation was carried out at a starting pressure of sixteen p.s.i. and a drop in pressure of thirteen pounds (theoretical drop, thirteen pounds) occurred in thirty minutes.

The catalyst was removed by filtration and the alcohol removed under reduced pressure. The amine was distilled yielding an orange liquid (12 g., 82%) which boiled at 135-140°/1.5 mm.

The dihydrochloride of N*,N*-dimethyl-2-ethyl-2-(p-aminophenyl)amylamine* was prepared by dissolving 2 g. of the diamine in 200 ml. of anhydrous ether and passing dry hydrogen chloride through the solution. A white precipitate formed which turned into a yellow, taffy-like material after filtration.

The dihydrochloride was recrystallized with difficulty from an absolute ethanol-anhydrous ether mixture. A creamy-white powdery material melting at 160-163° was obtained. It was quite hygroscopic and caused considerable difficulty in the analysis.

Analysis Calculated for $C_{15}H_{28}N_2Cl_2$: C, 58.62; H, 9.18.

Found: C, 56.50, 54.22, 55.93; H, 9.53, 9.15, 9.31.

The compound was recrystallized and dried between each analysis and before the final analysis it was dissolved in an alcohol-ether mixture and the solution saturated with dry hydrogen chloride gas.

N,N-Dimethyl-2-ethyl-2-(p-hydroxyphenyl)amylamine (XXII). N*,N*-Dimethyl-2-ethyl-2-(p-aminophenyl)amylamine* (9 g., 0.038 mole) was dissolved in a solution of 9 ml. of concentrated sulfuric acid in 125 ml. of water contained in a 250-ml. Erlenmeyer flask, equipped with a glass stirrer and a long-stemmed thermometer. This mixture was cooled to 0°C. by means of an ice-salt bath and solid sodium nitrite (approximately 3 g.) was added, keeping the temperature below 2°C., until an excess of nitrite ion was present as indicated by the use of potassium iodide-starch test paper.

Solid urea was then added to destroy the excess nitrite ion. The mixture was poured into a solution of 20 ml. of concentrated sulfuric acid and 15 ml. of water and heated on the steam bath. Evolution of nitrogen began at about 65°C. and continued for approximately one hour.

The mixture was cooled and neutralized with concentrated ammonium hydroxide to a pH of approximately 6 (Alkacid test paper). On extraction with two 50-ml. portions of ether most of the color remained in the aqueous layer so the pH was adjusted to approximately 7 with concentrated ammonium hydroxide and extracted again with three 50-ml. portions of ether. With this extraction most of the color was transferred to the ether layer. The combined ether extracts were extracted four times with 50-ml. portions of dilute (5%) hydrochloric acid. The combined acid extracts were neutralized with concentrated ammonium hydroxide and extracted four times with 50-ml. portions of ether.

The ether extracts were washed once with water, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

On standing overnight after the removal of the ether, the phenol solidified and was recrystallized from petroleum ether (60-80°). The solution was decolorized with charcoal during the recrystallization. A creamy-white, powdery solid (5.5 g., after recrystallization, 61%) melting at 99-102° was obtained.

<u>Analysis</u> Calculated for $C_{12}H_{25}NO$: C, 76.54; H, 10.71.

Found: C, 76.13; H, 10.51.

The hydrochloride of N,N-dimethyl-2-ethyl-2-(p-hydroxyphenyl)amylamine was prepared by dissolving 1.5 g. of the phenolic amine in 250 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white precipitate formed which turned pink on filtration and on standing began to oil. Attempted recrystallizations from absolute ethanol-anhydrous ether mixtures gave only an oily product.

The oily material was dissolved in a minimum amount of absolute ethanol and anhydrous ether was added until the solution was faintly cloudy. The solution was allowed to stand for several days in the refrigerator and a creamy-white, stable solid melting at 138-140° was obtained.

Analysis Calculated for $C_{15}H_{26}NOCl$: C, 66.27; H, 9.64.

Found: C, 66.31; H, 9.38.

α-Phenyl-α-n-propylheptonitrile (XXIII). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube, were placed 250 ml. of anhydrous ether and 46 g. (10% excess) of sodamide. α-Phenylvaleronitrile (160 g., 1 mole) was added dropwise at a rate to maintain steady reflux. The mixture turned dark brown during the addition which took about one hour. After the addition the mixture was heated under reflux for one hour.

n-Amyl bromide (151 g., 1 mole) was added at a rate to maintain reflux; the addition required two and one-half hours. After the addition the mixture was heated under reflux for eighteen hours. The reaction mixture, after cooling, was poured into water and the ether layer separated. The aqueous layer was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The product was distilled yielding a colorless liquid (160 g., 70%) boiling at 105-115°/0.2 mm., n_D^{25}1.4959.

<u>Analysis</u> Calculated for $C_{16}H_{23}N$: C, 83.78; H, 10.11.

Found: C, 83.93; H, 9.97.

<u>α-Phenyl-α-n-propylheptamide</u> (XXIV). α-Phenyl-α-n-propylheptonitrile (160 g., 0.70 mole) was dissolved in 350 ml. of concentrated sulfuric acid contained in a 500-ml. wide-mouthed Erlenmeyer flask equipped with a glass stirrer. Twenty milliliters of water was added to the red acid solution and, with the addition of the water, the solution became quite cloudy. The solution was heated on the steam bath to a temperature of 70-80°C. and this temperature was maintained, with stirring, for four hours. At the end of this time, the mixture was homogeneous and a very dark brown color.

At the end of the four-hour heating period, it was decided to work up a portion of the reaction mixture to determine whether the hydrolysis had proceeded to a reasonable degree. One hundred milliliters of the acid solution was poured with stirring onto crushed ice. A pink, taffy-like material separated from the solution. The mixture was extracted with four 100-ml. portions of ether and the combined ether extracts washed with two 50-ml. portions of dilute (2%) sodium hydroxide. The ether solution was washed with water until neutral, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

On distillation of the product, a very small forerun (2 g.) of unhydrolyzed nitrile was obtained. A portion of the amide was distilled as an extremely viscous liquid which boiled at 120-140°/0.08 mm. Distillation of the amide was very difficult due to the high viscosity of the material. Since the forerun of unreacted nitrile was so small from this portion of the reaction mixture it was decided to use the crude amide, without distillation, in the next step in the synthesis; reduction with lithium aluminum hydride.

The remainder of the acid hydrolysis mixture was treated in the same fashion as the 100-ml. portion. The combined basic washings were acidified and a yellow oil separated from a strongly acid solution. This yellow oil was insoluble in ether and soluble in water, indicating it was probably a sulfonation product.

After removal of the ether, 100 g. of crude α-phenyl-α-n-propylheptamide, light yellow in color, was obtained. On transferring the crude amide from the flask in which it had been contained as an ether solution it was noticed that a white solid seemed to have formed a film covering the inside of the flask.

Five milliliters of the crude amide was dissolved in petroleum ether (60-80°) and on cooling a white, powdery solid melting at 81-83° was obtained.

Analysis Calculated for $C_{16}H_{25}NO$: C, 77.68; H, 10.19.

Found: C, 78.52, 78.42; H, 10.24, 9.95.

2-Phenyl-2-n-propylheptylamine (XXV). In a 2-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 500-ml. dropping funnal and a reflux condenser fitted with a calcium chloride drying tube, were placed 400 ml. of anhydrous ether and 38 g. (1 mole) of lithium aluminum hydride. The crude α-phenyl-α-n-propylheptamide (100 g., approximately 0.4 mole) dissolved in 400 ml. of anhydrous benzene was added dropwise over a period of two hours. This reaction was very slow and external heating was necessary to maintain reflux. After the addition, the apparatus was arranged for distillation and the major portion of the ether was removed. The mixture was heated under reflux overnight.

The reaction mixture was decomposed by the slow addition of a minimum amount of water. The precipitated aluminum hydroxide was filtered off and washed with ether. The combined ether and benzene solution was extracted with four 100-ml. portions of dilute hydrochloric acid. The acid extracts were neutralized with concentrated ammonium hydroxide and extracted with four 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

The amine was distilled yielding a colorless liquid

(24.5 g., 26% based on amount of crude amide): b.p. 110-112°/0.9 mm., n_D^{26} 1.5062.

Analysis Calculated for $C_{16}H_{27}N$: C, 82.33; H, 11.66.

Found: C, 82.41; H, 11.52.

The ether solution containing the acid-insoluble material from the reduction was washed with water until neutral, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. After removal of the ether, the residue was dissolved in petroleum ether (60-80°) and on cooling the unreacted amide (36.2 g.) was obtained as a white solid.

The hydrochloride of 2-phenyl-2-n-propylheptylamine was prepared with difficulty. The amine (1 g.) was dissolved in 200 ml. of anhydrous ether and dry hydrogen chloride gas was passed into the solution for five minutes. No precipitation of the amine hydrochloride occurred. The ether was removed by evaporation and 10 ml. of petroleum ether (40-60°) added. A white, apparently stable, solid crystallized. This material was recrystallized three times from petroleum ether (40-60°) and melted at 88-92°.

Analysis Calculated for $C_{16}H_{28}NCl$: C, 71.21; H, 10.46.

Found: C, 71.82, 71.81; H, 10.70, 10.50.

2-(p-Nitrophenyl)-2-n-propylheptylamine (XXVI). 2-Phenyl-2-n-propylheptylamine (15 g., 0.065 mole) was added dropwise to 200 ml. of concentrated sulfuric acid contained in a 500-ml. Erlenmeyer flask equipped with a glass stirrer and a long-stemmed thermometer, and cooled by means of an ice-salt bath. During the addition of the amine the temperature was kept below 10°C. Powdered potassium nitrate (7.5 g., 10% excess) was added in small portions to keep the temperature below 10°C. The mixture was warmed to 50°C. by means of a hot-water bath and then allowed to cool to room temperature.

The acid solution was poured onto ice and neutralized with concentrated ammonium hydroxide. A dark red oil separated which was extracted with four 100-ml. portions of ether. The ether extracts were washed with water until neutral, dried over anhydrous magnesium sulfate, and the ether removed under reduced pressure.

The nitroamine was distilled yielding an orange-red, viscous liquid (10.6 g., 58%) boiling at 175-185°/0.9 mm. A tarry residue (approximately 3 g.) remained which could not be distilled.

The <u>hydrochloride</u> of 2-(p-nitrophenyl)-2-n-propylheptylamine was prepared with considerable difficulty. The nitroamine (0.5 g.) was dissolved in 200 ml. of anhydrous ether and dry hydrogen chloride gas was passed into the solution for five minutes. A faint cloudiness appeared but no filterable precipitate.

Petroleum ether (60-80°) was added to the solution until precipitation occurred. A tan solid was obtained on filtration. This material was dissolved in a minimum amount of absolute ethanol and petroleum ether (60-80°) was added until the solution turned cloudy. After standing several days in the refrigerator, a cream-colored solid melting at 159-161° was obtained.

Analysis Calculated for $C_{16}H_{27}N_2O_2Cl$: C, 61.03; H, 8.65.

Found: C, 61.11; H, 8.52.

2-(p-Aminophenyl)-2-n-propylheptylamine (XXVII). 2-(p-Nitrophenyl)-2-n-propylheptylamine (10 g., 0.036 mole) was dissolved in 50 ml. of 95% ethanol and a small amount of platinum oxide catalyst added. Hydrogenation was carried out with a starting pressure of thirteen p.s.i. The theoretical pressure drop of seven and one-half pounds took place very slowly over a period of one hour. During the hydrogenation the mixture became slightly warm but considerably less heat was evolved than was observed in the similar hydrogenations in the preceding two series of syntheses.

The catalyst was removed by filtration, and the alcohol removed under reduced pressure. In previous instances, difficulty was encountered in distilling the diamines due to the relatively high boiling points and the necessity for heating the oil-bath to an excessively high temperature. Because of this difficulty, it was decided to convert the crude diamine to the dihydrochloride without distillation.

The dihydrochloride of 2-(p-aminophenyl)-2-n-propylheptylamine was prepared by dissolving the dark-red oil obtained from the hydrogenation in 200 ml. of anhydrous ether and passing dry hydrogen chloride gas into the solution. A dark tan solid separated which turned into an oil after filtration. Eight grams of crude dihydrochloride was obtained. This would correspond to a 70% yield in the hydrogenation.

After several recrystallizations from an absolute ethanol-anhydrous ether mixture, accompanied by decolorization with charcoal during each recrystallization, a light tan solid melting at 183-187° was obtained.

<u>Analysis</u> Calculated for $C_{16}H_{30}N_2Cl_2$: C, 59.80; H, 9.41.

Found: C, 61.35; H, 8.98; residue, 1.6.

C, 60.65; H, 9.08; --

C, 60.69; H, 9.02; residue, 0.97.

This sample was recrystallized before each analysis and all efforts to eliminate the material causing the residue failed.

<u>N,N-Dimethyl-2-phenyl-2-n-propylheptylamine</u> (XXVIII). 2-Phenyl-2-n-propylheptylamine (7 g., 0.03 mole) was placed in a 100-ml. round-bottomed flask with 8 ml. (0.18 mole) of formic acid (concentration, 90%) and 9 ml. (0.13 mole) of formaldehyde (concentration, 40%).

The flask was fitted with a reflux condenser and the mixture heated on the steam bath. A vigorous evolution of carbon dioside took place over a period of one-half hour; the mixture was heated on the steam bath for twenty hours.

The excess formaldehyde was removed and after cooling the solution was neutralized with concentrated ammonium hydroxide. The basic solution was extracted with three 50-ml. portions of ether, the ether extracts dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The product was distilled yielding a colorless liquid (5 g., 67%) which boiled at 117-119°/2 mm., n_D^{26} 1.4958.

Analysis Calculated for $C_{18}H_{31}N$: C, 82.69; H, 11.95.

Found: C, 82.51; H, 11.75.

The hydrochloride of N,N-dimethyl-2-phenyl-2-n-propylheptylamine was prepared by dissolving 2 g. of the amine in 200 ml. of anhydrous ether and passing dry hydrogen chloride gas into the solution. A white, crystalline material was formed which, after recrystallization from an absolute ethanol-anhydrous ether mixture, melted at 132-136°.

Analysis Calculated for $C_{18}H_{32}NCl$: C, 72.57; H, 10.83.

Found: C, 72.58; H, 10.79.

α-Phenylpropionitrile (XXIX). In a 1-l. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 43 g. (10% excess) of sodamide and 400 ml. of anhydrous ether.

Phenylacetonitrile (117 g., 1 mole) was added dropwise over a period of one hour. During the addition the temperature remained above the reflux temperature. After the addition the mixture was heated under reflux overnight.

Methyl iodide (136 g., 1 mole) dissolved in 200 ml. of anhydrous ether was added dropwise, with external cooling, at a rate to maintain reflux. After the addition the mixture was heated under reflux for one hour and then allowed to stand overnight.

The reaction mixture was poured into water and the ether layer separated. The aqueous layer was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. Distillation yielded 102 g. (78%) of α-phenylpropionitrile, a yellow liquid boiling at 99-101°/10 mm.

α-(Diethylaminopropyl)-α-phenylpropionitrile (XXX). In a 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 12 g. (10% excess) of sodamide and 200 ml. of anhydrous ether.

α-Phenylpropionitrile (37 g., 0.28 mole) was added dropwise over a period of one hour at a rate to amintain constant reflux. The dark reddish-brown mixture was heated under reflux for one and one-half hours.

3-Diethylaminopropyl chloride (42 g., 0.28 mole) dissolved in 100 ml. of anhydrous ether was added dropwise over a period of one hour. Precipitation of sodium chloride occurred during the addition. The mixture was heated under reflux for four hours and then allowed to stand overnight. The reaction mixture was poured into water, the ether layer removed and the aqueous layer extracted with two 100-ml. portions of ether.

The combined ether extracts were extracted with four 100-ml. portions of dilute hydrochloric acid to separate the product from any unreacted starting material. The acid solution was made basic with concentrated ammonium hydroxide and extracted with four 100-ml. portions of ether.

The ether extracts were washed once with water, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The product was a very slightly yellow liquid (35 g., 47%): b.p. 117-119°/0.5 mm., n_D^{25}1.4981.

<u>Analysis</u> Calculated for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90.

Found: C, 78.27, 78.83; H, 9.71, 9.75.

The <u>hydrochloride</u> of α-(diethylaminopropyl)-α-phenylpropionitrile was prepared by dissolving 2 g. of the amino nitrile in 200 ml. of anhydrous ether and passing dry hydrogen chloride gas through the solution. A white solid formed which could be recrystallized from an anhydrous ether-absolute ethanol mixture giving a product melting at 65-68°. The hydrochloride was extremely hygroscopic and a good analysis was not possible.

<u>Analysis</u> Calculated for $C_{16}H_{25}N_2Cl$: C, 68.42; H, 8.97.

Found: C, 66.79; H, 8.78.

<u>2-(Diethylaminopropyl)-2-phenylpropylamine</u> (XXXI). In a 500-ml. three-necked round-bottomed flask, equipped with a Hershberg stirrer, a 250-ml. dropping funnel and a reflux condenser fitted with a calcium chloride drying tube, were placed 10 g. (0.28 mole) of lithium aluminum hydride and 200 ml. of anhydrous ether. α-(Diethylaminopropyl)-α-phenylpropionitrile (33 g., 0.14 mole) dissolved in 150 ml. of anhydrous ether was added dropwise at a rate to maintain constant reflux. The addition required one hour. The mixture was heated under reflux for five hours and then allowed to stand overnight.

The reaction mixture was decomposed by adding as small an amount of water as possible, with cooling. The precipitated aluminum hydroxide was removed by filtration and washed with ether. The combined ether extracts were extracted with four 100-ml. portions of dilute (1:4) hydrochloric acid. The acid solution was made basic with concentrated ammonium hydroxide and extracted with four 100-ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether removed under reduced pressure.

Distillation yielded 21.1 g. (60%) of 2-(diethylaminopropyl)-2-phenylpropylamine, a clear, colorless liquid boiling at 128-132°/2 mm., n_D^{26}1.5092.

Analysis Calculated for $C_{16}H_{28}N_2$: C, 77.36; H, 11.36.

Found: C, 77.37; H, 11.33.

All attempts to prepare the dihydrochloride of 2-(diethylaminopropyl)-2-phenylpropylamine by the usual method were unsuccessful. The material was EXTREMELY hygroscopic and could not be retained as a solid for any reasonable length of time. All attempts to recrystallize this material resulted in the formation of an oil.

Sublimation gave a white, powdery material which turned liquid before it could be removed from the sublimation apparatus. The disulfate was also prepared but could only be obtained as an oil.

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