AZABICYCLIC COMPOUNDS DERIVED FROM CYCLOHEPTANONE

by

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To

Mom and Dad

and

Irene

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Professor F. F. Blicke who suggested this problem and supervised the investigation.

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Rupert A. Covey

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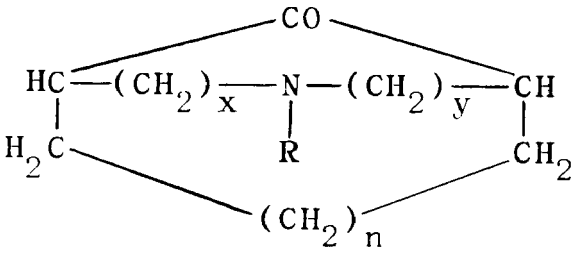
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GENERAL INTRODUCTION

A number of types of azabicyclic compounds have been reported in the literature. These cyclic systems really consist of three rings: an "outer" ring and two "inner" rings. Since it was the azabicyclic ketones which were the key intermediates in this investigation, the introduction is limited to a discussion of saturated azabicyclic compounds which contain a keto group and to systems which are characterized by the following four features: (1) a ring which contains a carbonyl group, but not a nitrogen atom; (2) a ring which contains a nitrogen atom, but not a carbonyl group; (3) a ring which contains both a carbonyl group and a nitrogen atom; (4) no two rings which have less than three ring atoms in common (Types A-E, page 2). In other words, this discussion includes all saturated azabicyclic ketones except lactams (nitrogen adjacent to the carbonyl group), 1-azabicyclic ketones (nitrogen at a bridgehead), and those in which the fused rings have only one or two ring atoms in common.

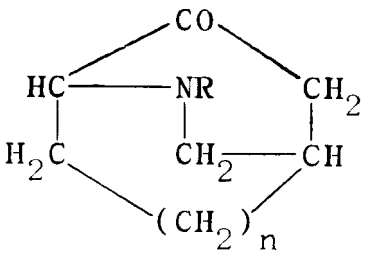
Another group of compounds discussed are the bispidines, which can be represented by Type F (page 2).

Considerable work has been done on the synthesis of azabicyclic ketones with respect to finding new analogs of morphine; in general, reduction of the carbonyl to the methylene group gave compounds which have considerable analgesic activity.



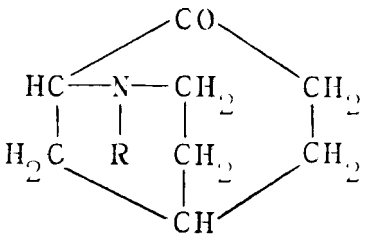
Type A

n = 0; x = 1; y = 1
n = 1; x = 0; y = 2,3
n = 2; x = 0,1; y = 1

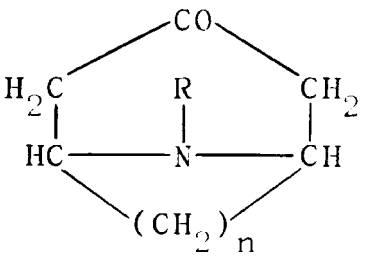


Type B

n = 1,2

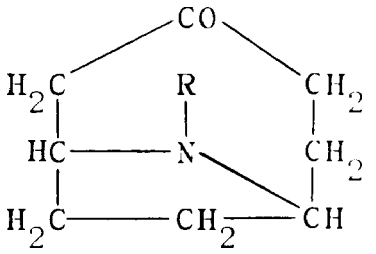


Type C

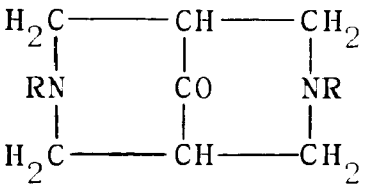


Type D

n = 2,3,4



Type E

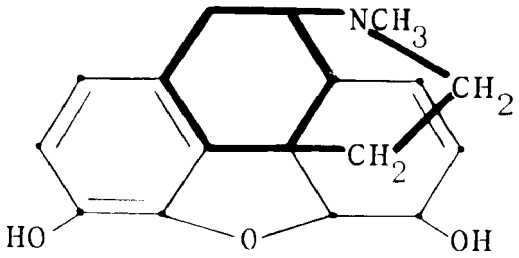


Type F

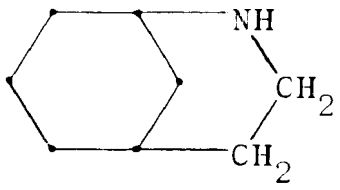
Many azabicyclic ketones have also been prepared as analogs of tropinone. Reduction of these compounds to the corresponding alcohols and the subsequent formation of esters, in general, produced compounds which have local anaesthetic or antispasmodic activity.

Type A Compounds

Barltrop (1) has synthesized a compound which contains a previously unreported ring system - a 2-azabicyclo[3.3.1]-nonane system - to which he has assigned the name "morphan", since this structure is found in the morphine molecule. His

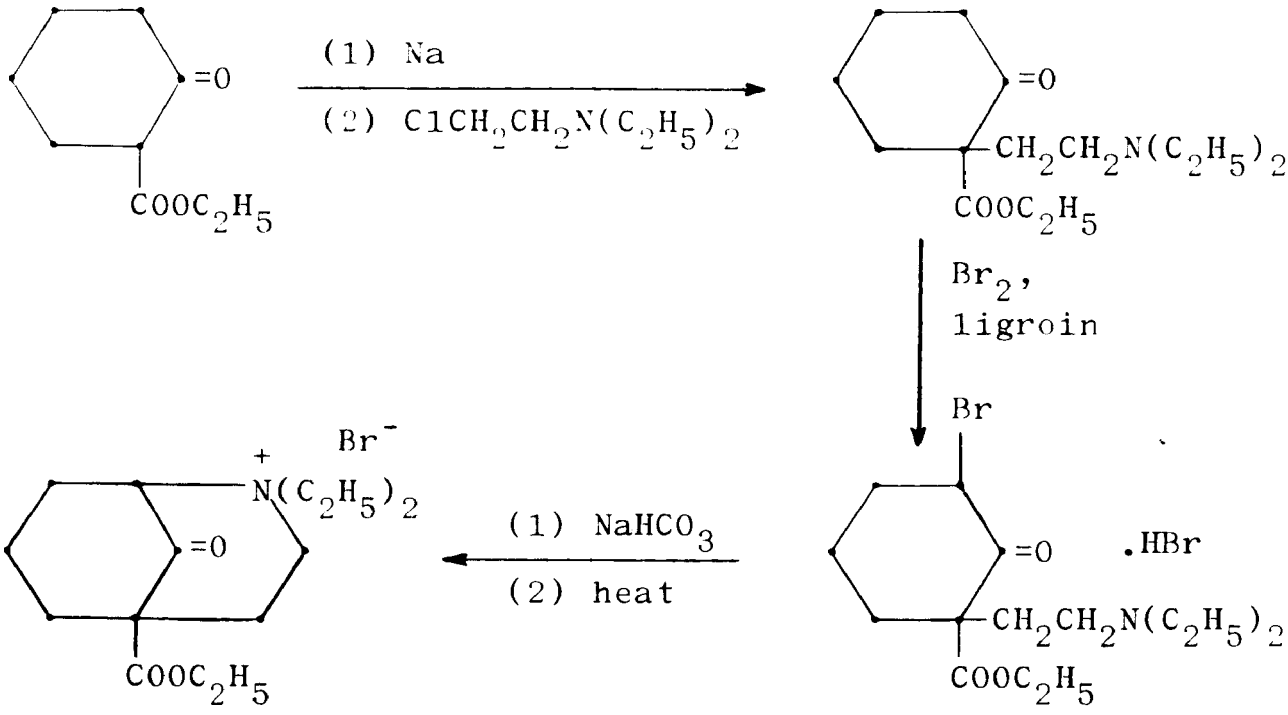


Morphine



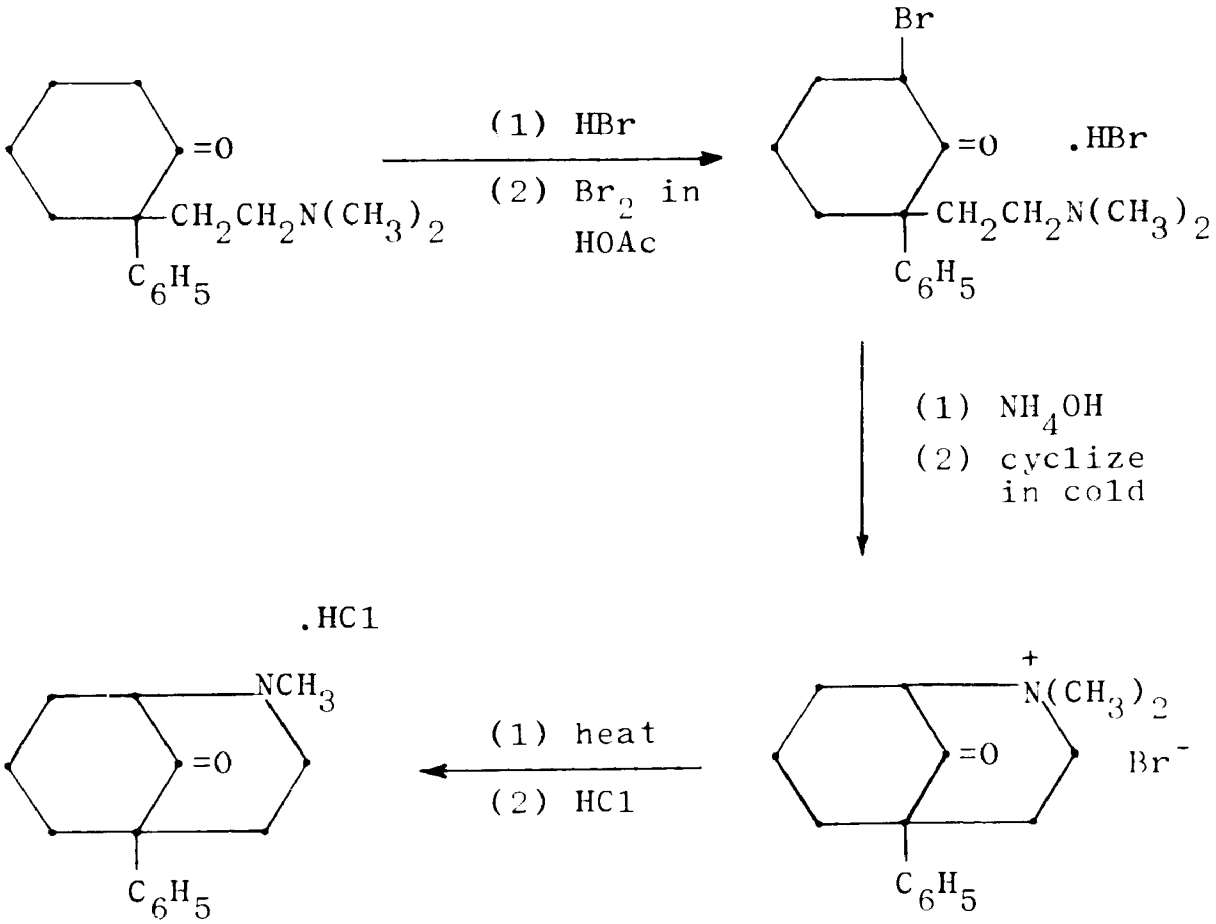
Morphan

synthesis was accomplished by the following sequence of reactions:



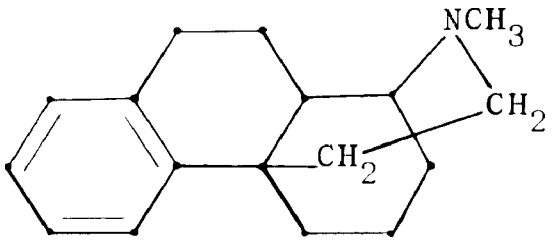
The overall yield in the bromination and subsequent cyclization was less than 1%.

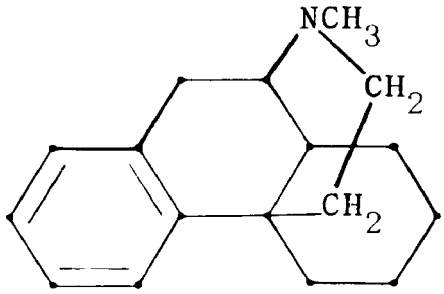
May and Murphy (2) have prepared a similar compound which has the same basic morphan ring system. This synthesis is



similar to the one described above (1), but the yields of the azabicyclic ketones are not comparable. May and Murphy reported an overall yield of 80% in the bromination and cyclization steps. A dry distillation of the quaternary compound to give the corresponding tertiary amine and subsequent formation of the hydrochloride were accomplished in 88% yield.

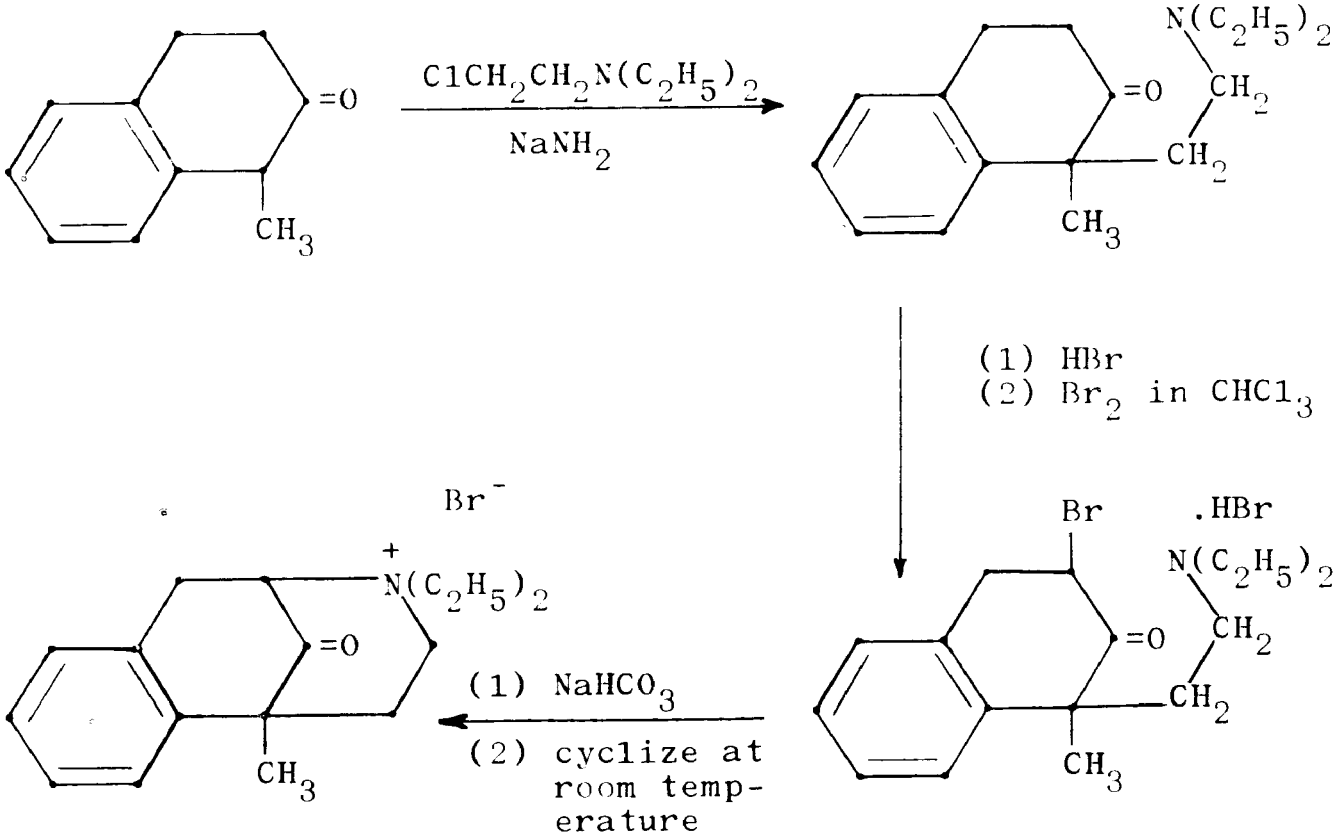
May and Murphy went on to synthesize the compound formulated below, which is an isomer of N-methylmorphinan.



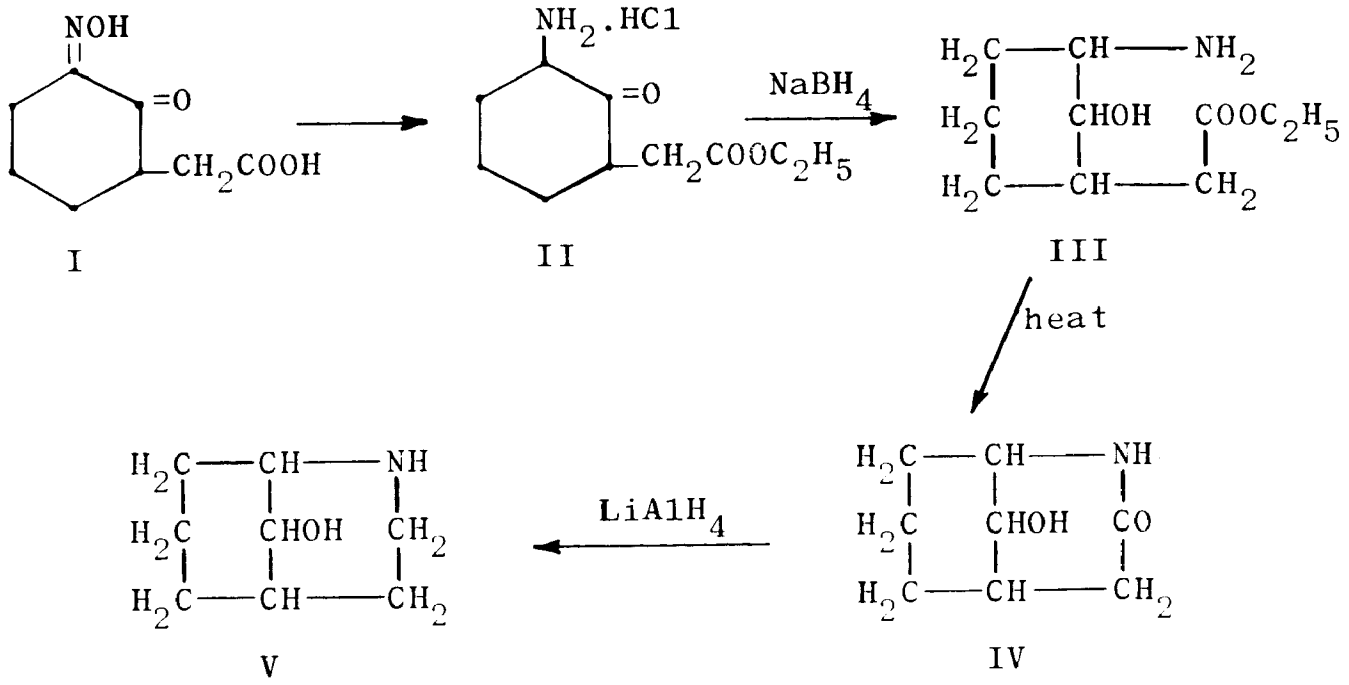


N-Methylmorphinan

Barltrop (1) synthesized another compound having this same basic ring system. The bromination and cyclization were carried out more easily in this case, but only a 9% yield could be obtained.

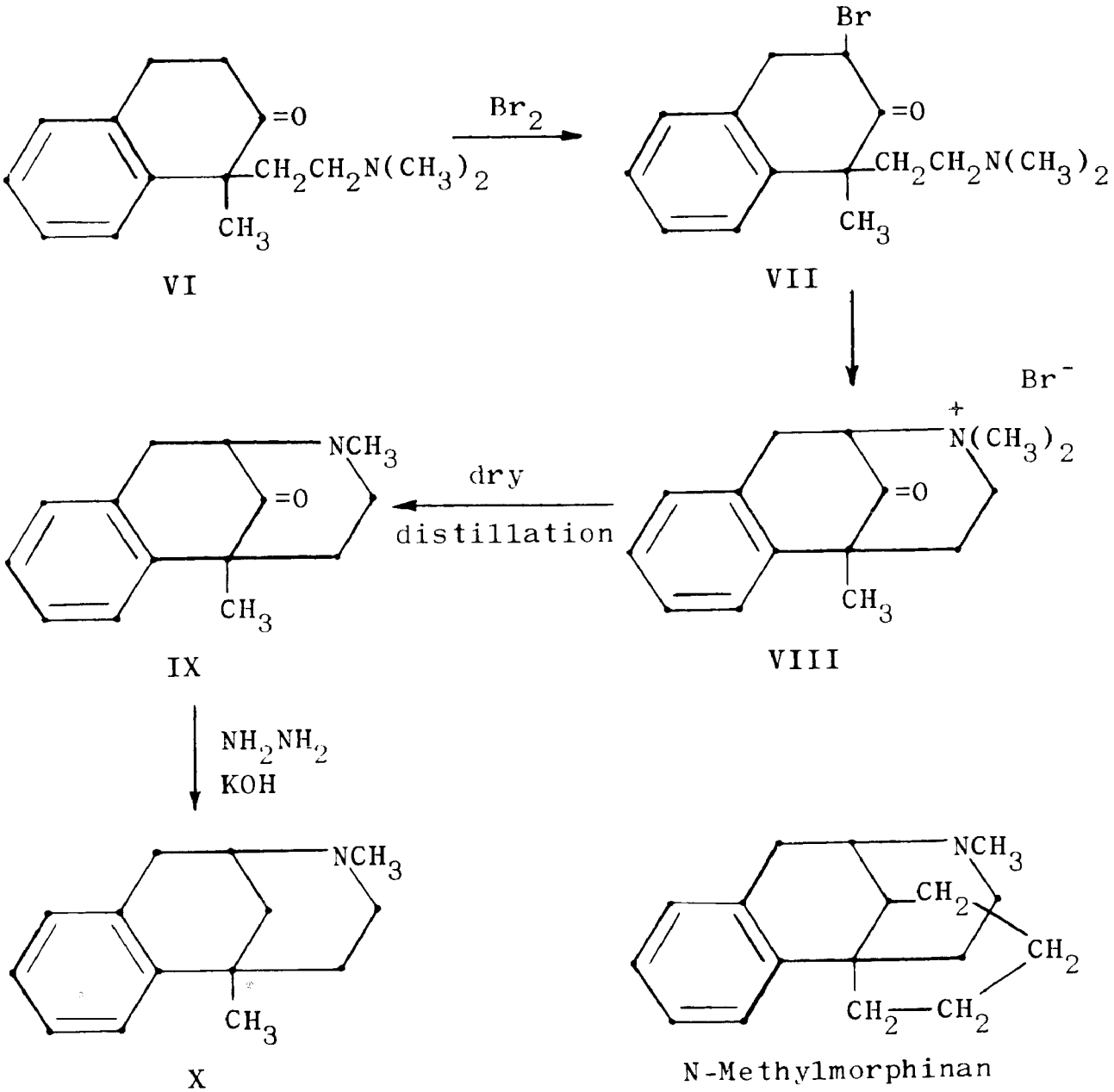


One of the stereoisomers of 9-hydroxymorphan (2-azabicyclo[3.3.1]nonan-9-ol, V) has been prepared by Ramirez and Sargent (3) by a somewhat different method of ring closure.



The formation of the lactam (IV) was also accomplished by the cyclization of the acetic acid salt of III, and by the cyclization of the acid obtained by the hydrolysis of III. The work of Ramirez and Sargent was directed toward a stereospecific synthesis of 9-hydroxymorphan.

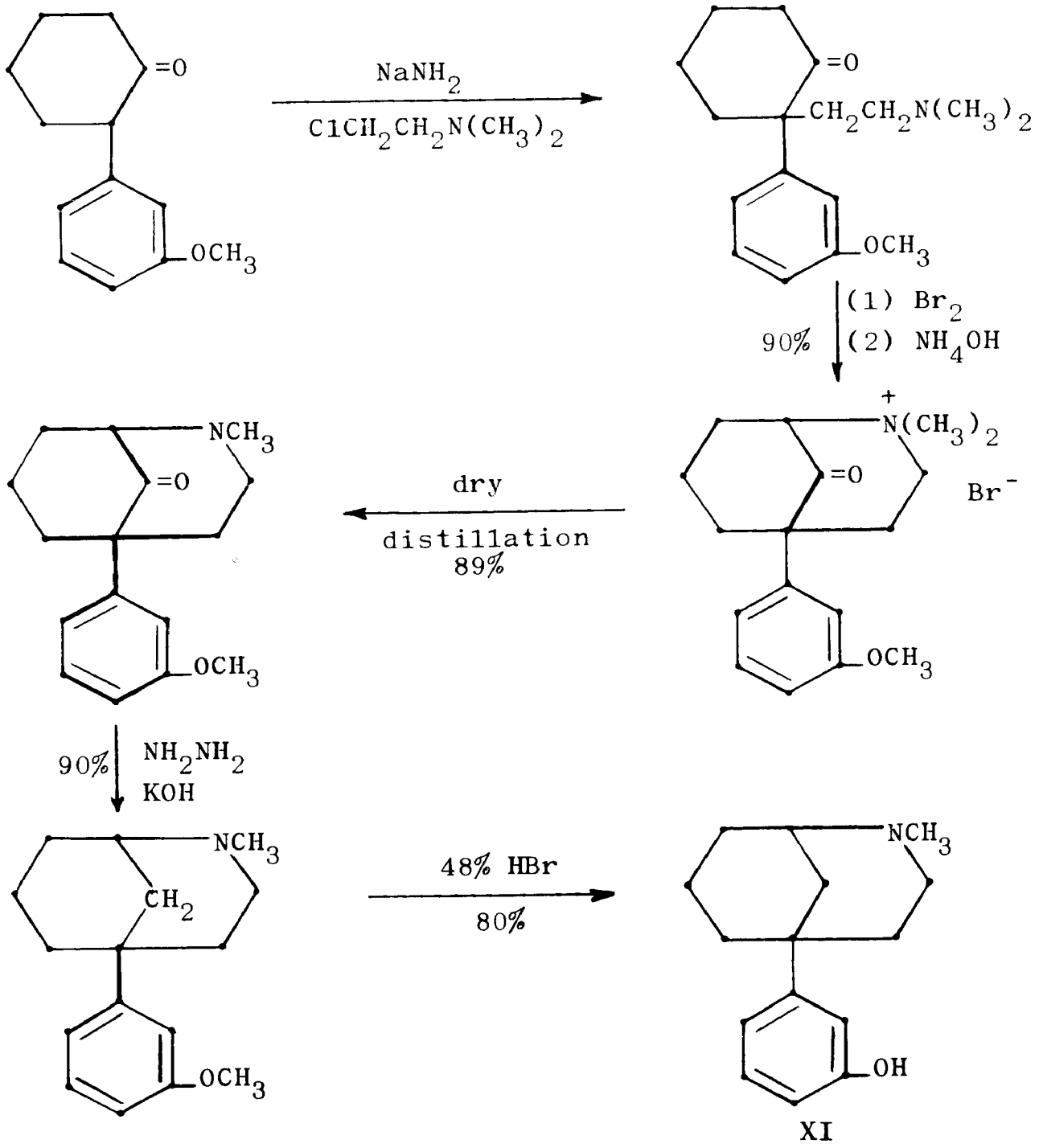
Since N-methylmorphinan, which lacks some of the peripheral groups of morphine, shows considerable analgesic activity, May and Murphy (4) sought to determine if more of the ring structure of the morphine molecule could be eliminated without decreasing the activity. 2,5-Dimethyl-6,7-benzo-2-azabicyclo[3.3.1]non-6-ene (X) was prepared by a procedure which involves the formation of a 9-ketomorphan which is nearly identical to a compound prepared by Barltrop.(1)



May and Murphy were able to obtain a 58% overall yield in the bromination and cyclization steps (VI-VIII) whereas Barltrop obtained only a 9% yield, using the diethylamino derivative (page 5). The subsequent two steps presented more difficulty, however, and compound X was obtained in only 16% yield from the quaternary compound. It was the opinion of these investigators that this series of reactions was unsatisfactory as a method of synthesis.

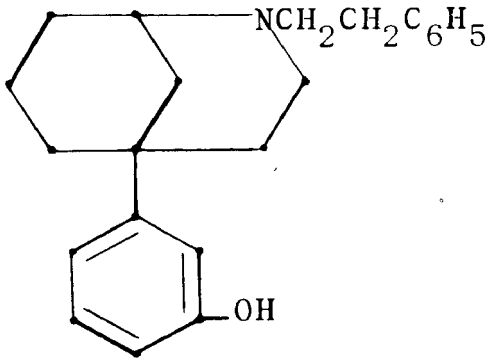
Another synthesis of compound X was developed which gave better yields. This is described under Type C compounds, page 13.

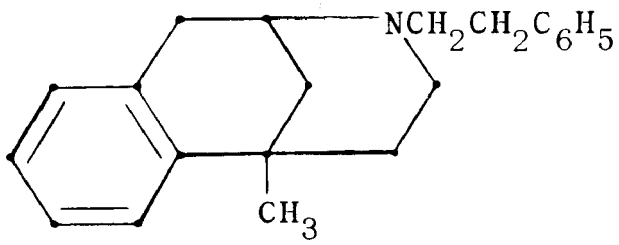
May and Murphy (5) hoped that, by introducing a hydroxyl group into the meta position of the phenyl ring in compounds previously prepared by them (page 4), analgesic activity would be increased.



Compound XI was actually found to be more potent than the corresponding deoxy compound and is comparable to morphine when administered subcutaneously.

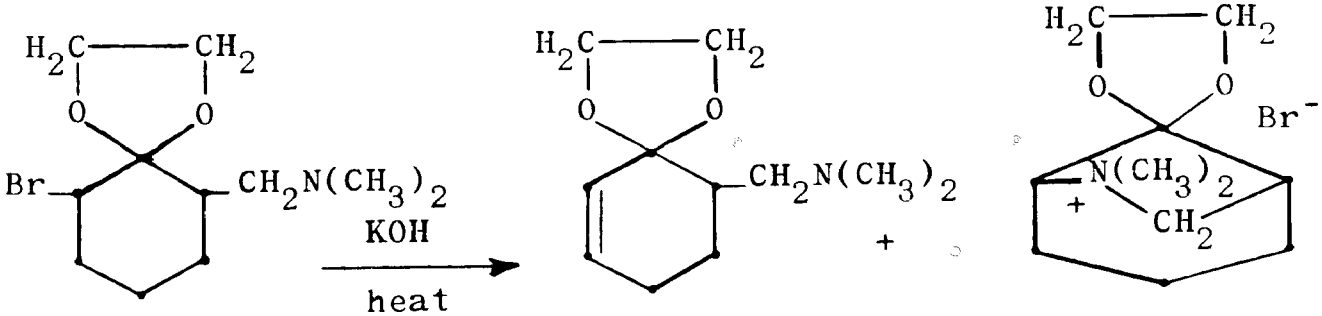
Derivatives of compounds XI and X (page 7) have been prepared by May.(6) The N-methyl groups were replaced with beta-phenylethyl radicals, giving the following compounds:





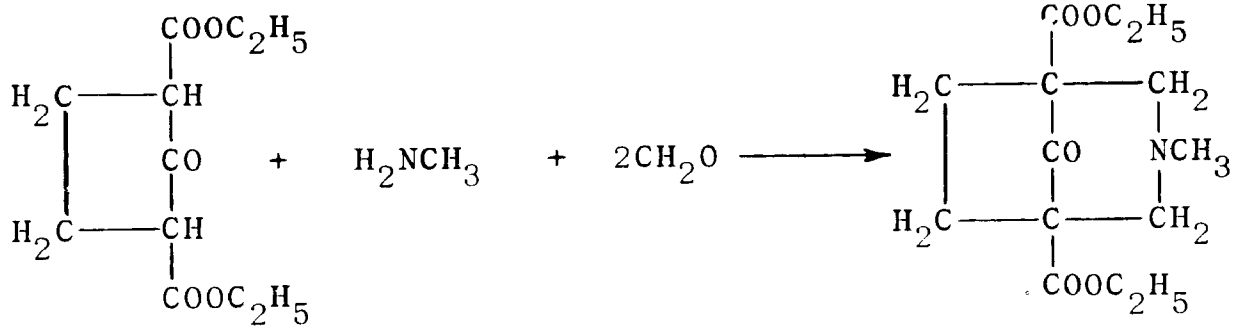
These compounds were found to be less potent analgesics than the corresponding N-methyl compounds.

Sullivan (Ref. 7, p. 46) obtained a compound in small amount as a by-product in the dehydrobromination of 2-dimethylaminomethyl-6-bromocyclohexanone ethylene ketal (XII). The analytical data corresponded to that calculated for 6-methyl-6-azabicyclo[3.2.1]octan-8-one ethylene ketal methobromide (XIII).



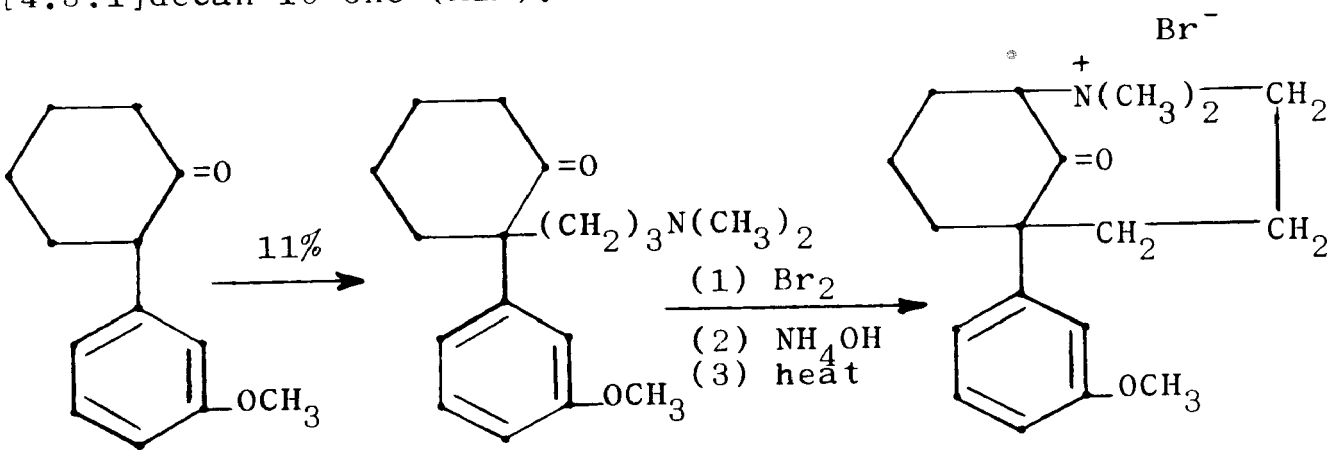
XII XIII

1,5-Dicarbethoxy-3-methyl-3-azabicyclo[3.2.1]octan-8-one (XV) was prepared by Anet et al. (8) by condensing 2,5-dicarbethoxycyclopentanone (XIV) with methylamine and formaldehyde in aqueous solution. A 50% yield was obtained.

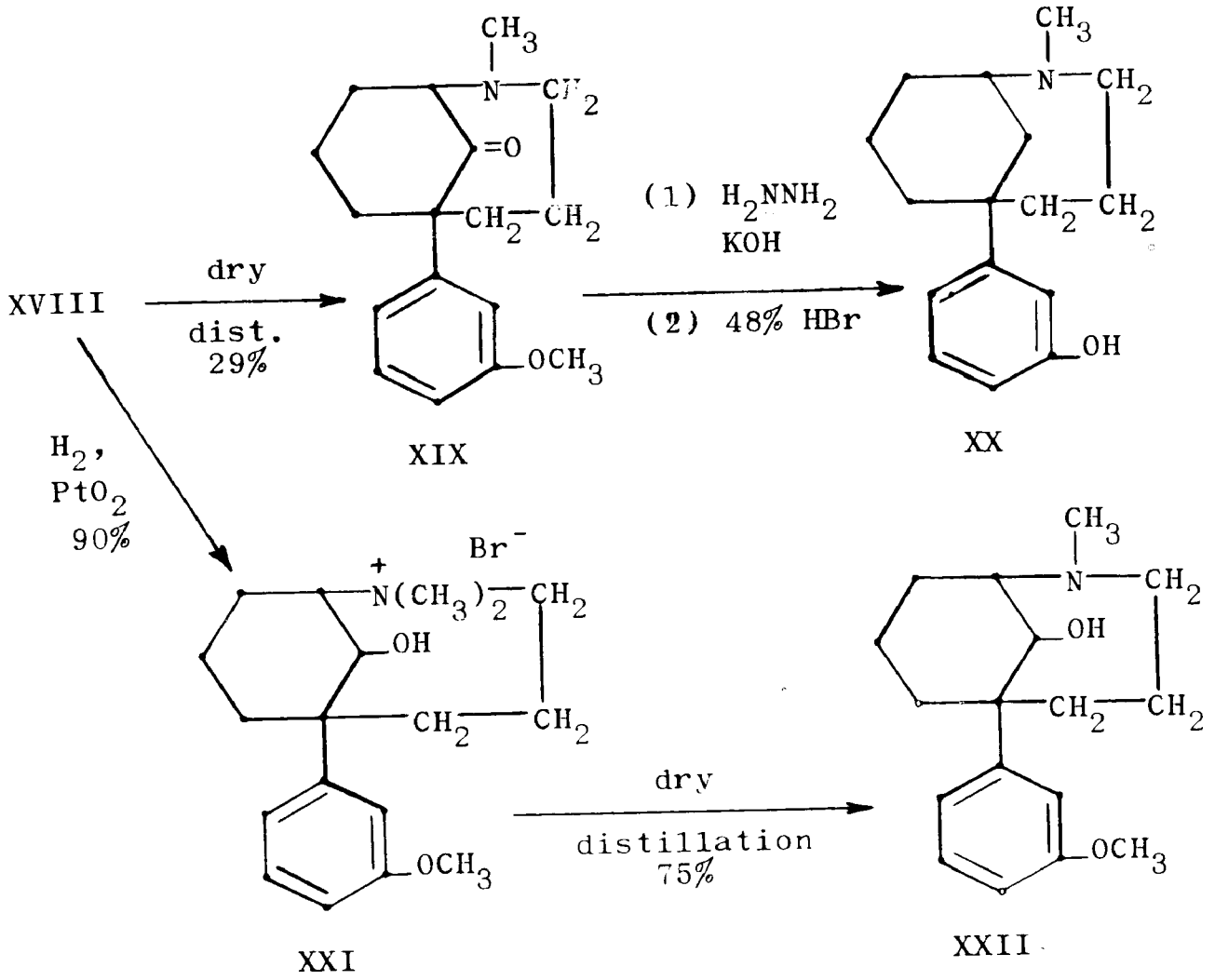


XIV XV

Since compound XI (page 8) was found to be comparable to morphine in analgesic activity, May (9) synthesized the next higher homolog (XX) in order to determine its activity. His synthesis, involving the same type of reactions as in the preparation of the lower homolog, produced a 2-azabicyclo-[4.3.1]decan-10-one (XIX).



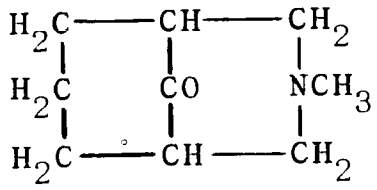
XVI XVII XVIII



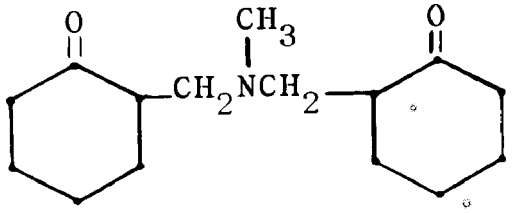
The bromination and cyclization proceeded in an overall yield of 65%. The cyclization occurred only under quite vigorous conditions (propanol at 100° for 24 hours) in contrast to the six-membered ring closure, which took place rapidly at room temperature. A salt of XX could not be isolated in crystalline form and therefore XX was not tested pharmacologically. Compound XVIII was reduced in 90% yield to the corresponding secondary alcohol (XXI), which was dry-distilled to give XXII. Compounds XVIII, XXI and XXII had no analgesic activity in mice.

Attempts have been made by Weatherbee et al. (10) to

prepare 3-methyl-3-azabicyclo[3.3.1]nonan-9-one (XXIII) by condensing methylamine, formaldehyde, cyclohexanone and HCl in a 1:2:1:1 molar ratio in methanol. When relatively



XXIII

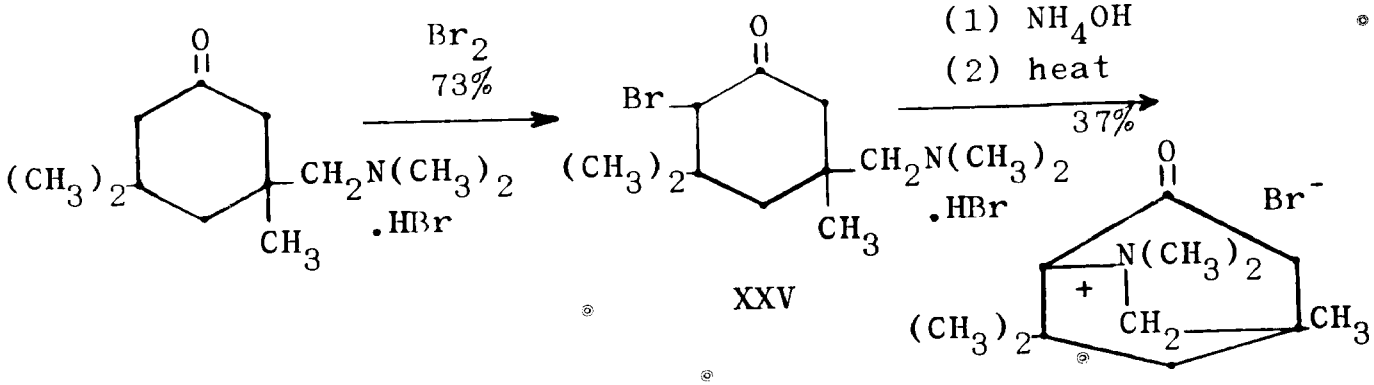


XXIV

concentrated solutions were used, a compound (XXIV) other than the expected one was obtained. In dilute solutions no crystalline compounds could be isolated. When 3-methyl- or 4-methylcyclohexanone was used in place of cyclohexanone, a product corresponding to XXIV was obtained.

Type B Compounds

Sullivan (Ref. 7, p. 57) obtained 2,4,7,7-tetramethyl-2-azabicyclo[2.2.2] octan-6-one methobromide (XXVI) in 37% yield by the cyclization of the base obtained from 3-dimethylaminomethyl-3,5,5-trimethyl-6-bromocyclohexanone hydrobromide (XXV).

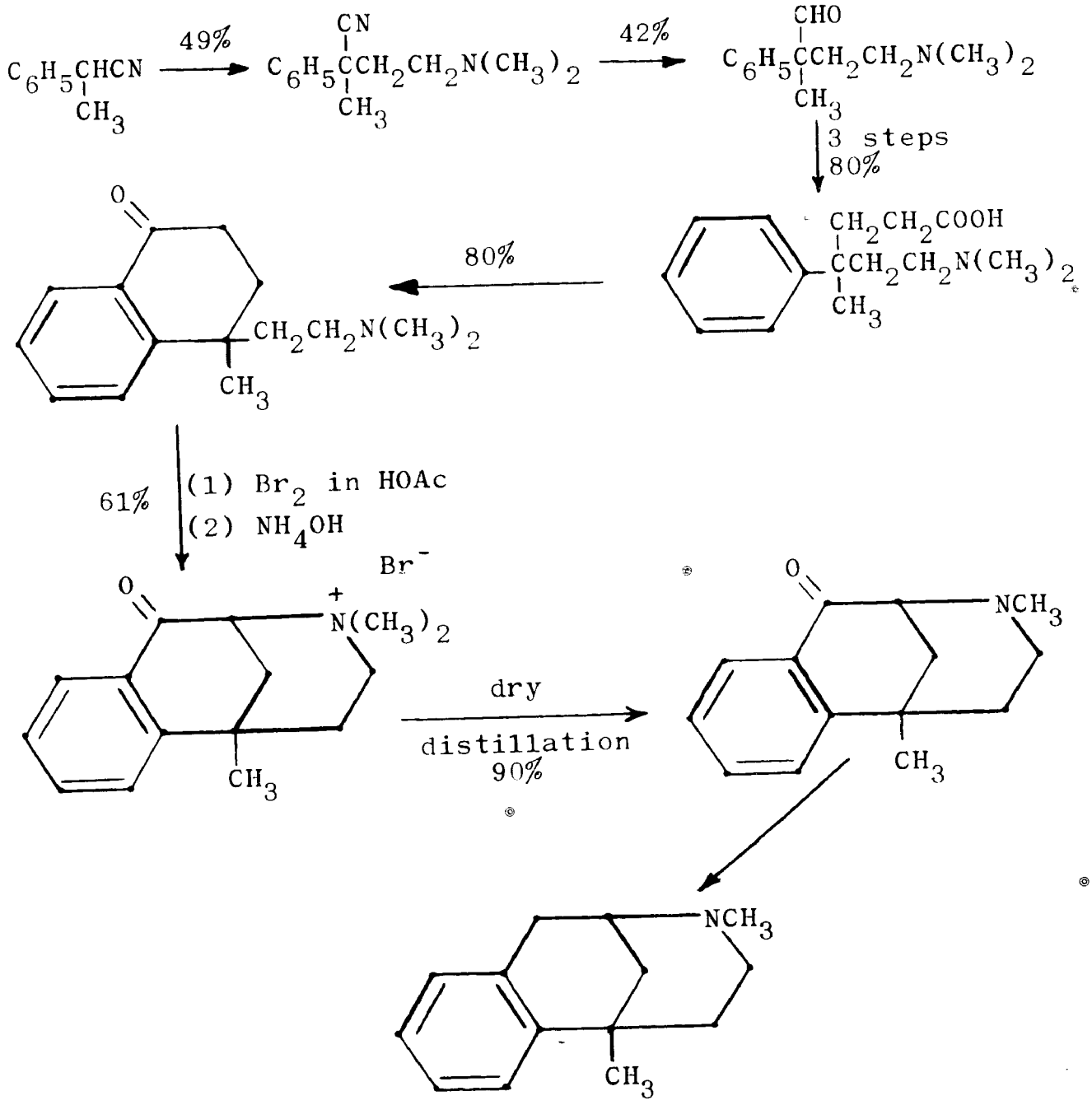


XXV

XXVI

Type C Compounds

May and Murphy (4) have prepared compound X employing a 9-ketomorphan as an intermediate in the manner which has been described (page 7). However, they obtained compound X in better yields using the corresponding 8-ketomorphan as an intermediate.



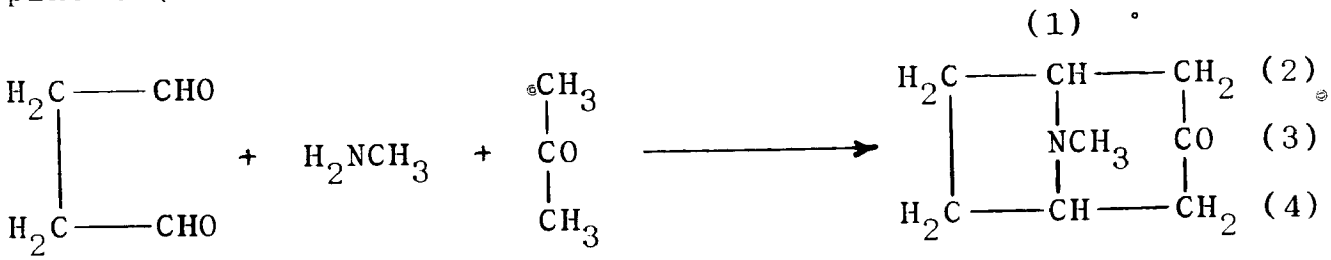
X

According to May and Murphy, compound X was "found to be one-half to one-third as active, analgesically, as N-methylmorphinan and Demerol in mice, but much less toxic than either by subcutaneous route of administration. Orally, X was also fairly effective, more so than Demerol."

Type D Compounds

Tropinone* was first synthesized in 1901 by Willstätter (11) starting from suberone. This method of preparation was a masterpiece of classical synthetic work, but was too long to be of any preparative value.

The importance of tropinone in the preparation of products of therapeutic value led Robinson (12) to seek a practical synthesis of tropinone. He found that a mixture of succindialdehyde, methylamine and acetone in water, when allowed to stand for a short time produced a very small amount of tropinone (XXVII):



XXVII

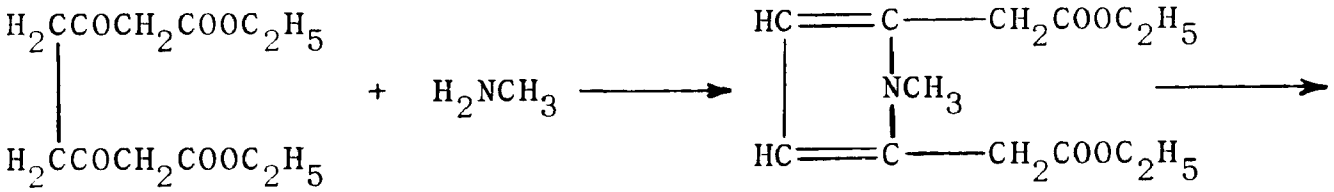
Better yields were obtained when calcium acetonedicarboxylate was used in place of acetone, producing the calcium salt of

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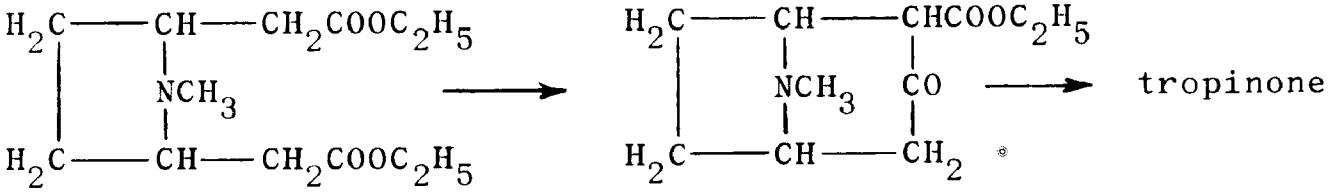
* Of all of the azabicyclic ketones known, tropinone has been the most widely studied. Extensive reviews of tropinone and tropane chemistry have been published, and no attempt has been made in this dissertation to compile a complete list of references. However, a summary of some of the most significant work in the field is presented here. More detailed information can be obtained from standard books on alkaloids.(14, 15, 16)

tropinonedicarboxylic acid. When heated in acidic solution, this compound decarboxylated yielding tropinone.

This work was later taken up in Germany and a number of procedures have been developed for the preparation of tropinone and closely related compounds. Willstätter and Pfannenstiel (13) and Willstätter and Bommer (13a) found that ethyl succinyldiacetate (XXVIII) reacted with methylamine to give ethyl N-methylpyrrole-2,5-diacetate (XXIX), which was reduced to



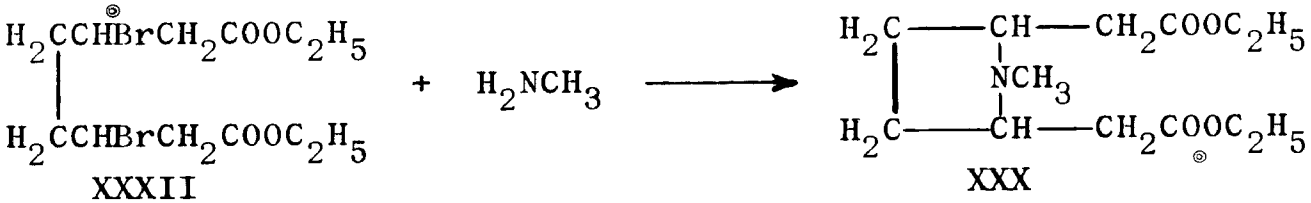
XXVIII XXIX



XXX XXXI

the corresponding pyrrolidine ester. This compound then underwent a Dieckmann-type ring closure (17)* giving the carbethoxy derivative of tropinone (XXXI), which was decarboxylated to yield tropinone.

Karrer and Alagil (18) prepared the pyrrolidine ester (XXX) by condensing the diethyl ester of β,β'-dibromosuberic acid (XXXII) with methylamine.

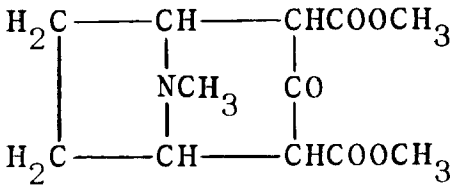


XXXII XXX

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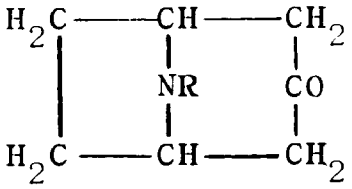
* This reaction is described by C. R. Hauser and B. E. Hudson, Jr. in Organic Reactions, Vol. I, p. 274 (1942).

Mannich and Veit (19) prepared dimethyl tropanone-2,4-dicarboxylate (XXXIII) in a 60% yield by condensing succindialdehyde with methylamine hydrochloride and dimethyl acetonedicarboxylate.



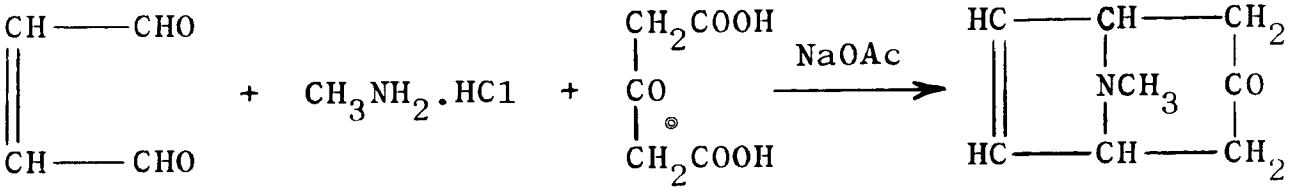
XXXIII

Schöpf and Lehmann (20) studied the effect of pH and temperature on the yields of tropinone formed by Robinson's synthesis. Further investigations of this type have been carried out by Keagle and Hartung (21), who found that the best yields are obtained under neutral or slightly basic conditions. They have prepared the following N-analogs of tropinone:



R	yield
ethyl	71.9%
benzyl	30.0%
isopropyl	51.6%
β-hydroxyethyl	63.6%

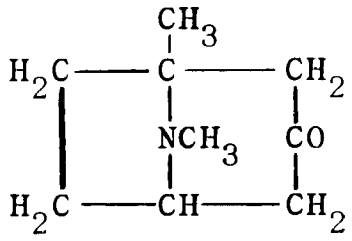
Preobrazhenskii et al. (22) have prepared tropenone (XXXIV) by the following procedure:



XXXIV

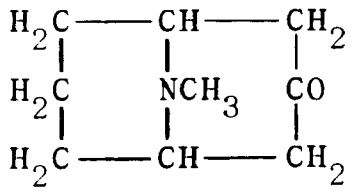
Although Blount and Robinson (23) could not obtain this type of reaction when a diketone replaced the dialdehyde,

they have been able to obtain 1-methyltropinone (XXXV) by using the ketoaldehyde, laevulinaldehyde, $CH_3COCH_2CH_2CHO$.



XXXV

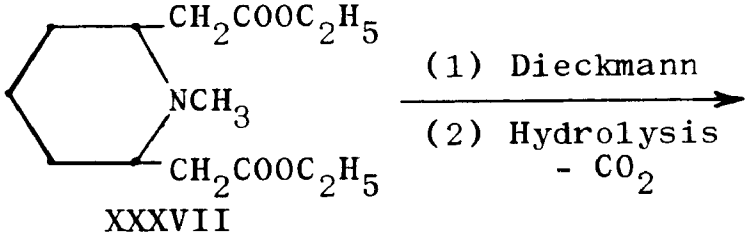
Pseudopelletierine (XXXVI) is the next higher homolog of tropinone. It is the best known of the pomegranate bark alkaloids. It was first synthesized by Menzies and Robinson (24) using a procedure similar to that of Robinson (12) for the preparation of tropinone. Glutaraldehyde, methylamine, and calcium acetonedicarboxylate were condensed to give a small amount of pseudopelletierine but glutaraldehyde was hard to obtain. Schöpf and Lehmann (20) found that yields of



XXXVI

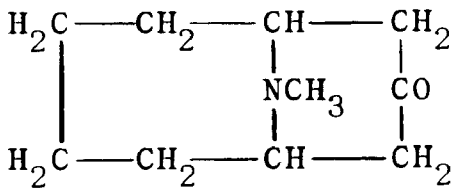
62-72% could be obtained by using a pH of 3 to 7 in the reaction. Cope et al. (25) obtained comparable yields.

Putney and Soine (26) prepared pseudopelletierine using a Dieckmann-type ring closure on diethyl N-methylpiperidine-2,6-diacetate (XXXVII).



XXXVII

N-Methylhomogranatanine (XXXVIII), the next higher homolog of pseudopelletierine, was prepared by Blount and Robinson (27), according to the original Robinson synthesis of tropinone.

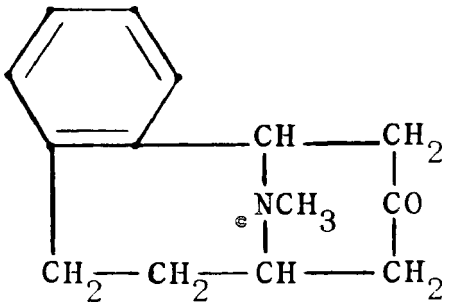


XXXVIII

The ketone was reduced to the secondary alcohol, and a benzoate was prepared. This ester showed marked local anaesthetic action.

Alder and Dortmann (28) recently prepared N-methylhomogranatanine by a similar procedure in 45-50% yield, as an intermediate in the preparation of cyclic polyolefins.

8,9-Benz-$\Delta^{8,9}$-homogranatene-3-one (XXXIX) has been pre-

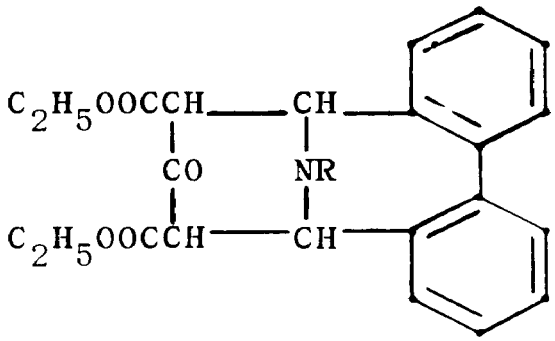


XXXIX

pared by the same procedure by Blount (29), starting with beta-(o-formylphenyl)propionaldehyde. He reduced the ketone to the secondary alcohol, and prepared a benzoate which showed local anaesthetic properties.

Anet et al. (8) have prepared 4-piperidones bridged across the 2,6 positions. When diphenyl-2,2'-dialdehyde was condensed with diethyl acetonedicarboxylate and methylamine,

a nearly pure product, diethyl 10-methyl-2,3,4,5-dibenzo-10-azabicyclo[4.3.1]deca-2,4-dien-8-one-7,9-dicarboxylate (XL, R = CH_3), crystallized out of the reaction mixture almost immediately in nearly a quantitative yield. Similar products

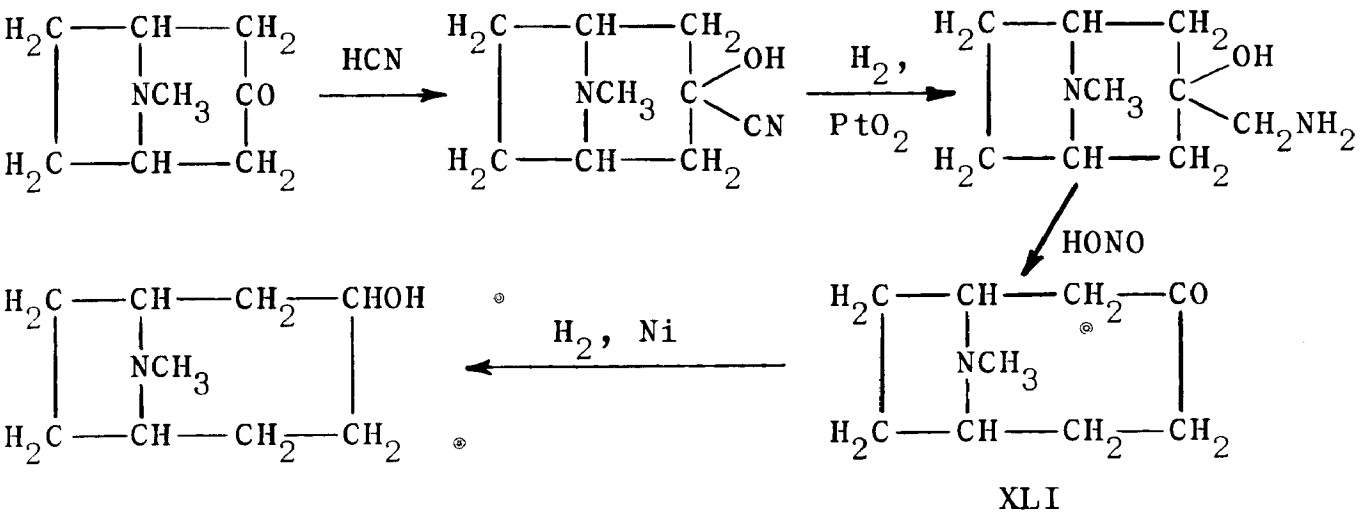


XL

were easily prepared by replacing methylamine with ethylamine, allylamine, β-hydroxyethylamine, benzylamine, or ethylene diamine. In fact, the reaction is so readily carried out that it is suggested as a test for primary aliphatic amines. All of these compounds gave positive ferric chloride tests.

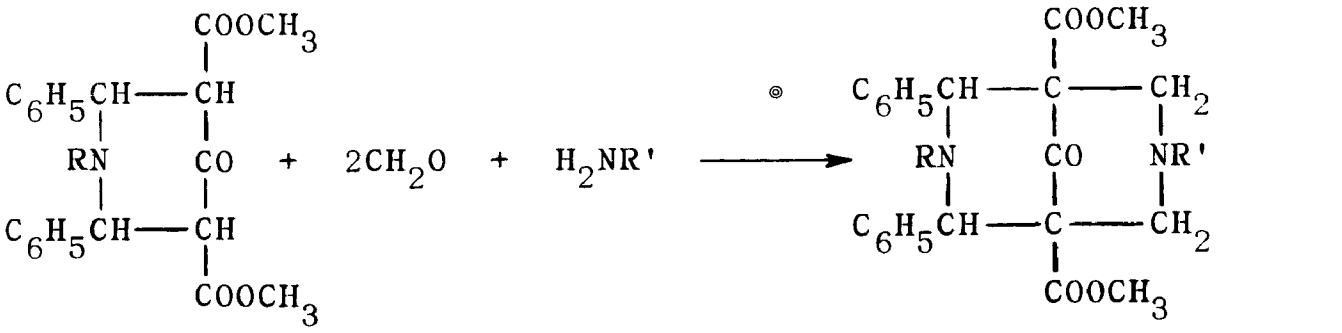
Type E Compounds

Cope, Nace and Estes (30) have prepared 9-methyl-9-azabicyclo[4.2.1]nonan-3-one (XLI), which they refer to as R-homotropinone, from tropinone in 43% yield using the Tiffeneau (31) method of ring expansion.



Type F Compounds

Mannich and Mohs (32) have synthesized diazabicyclic systems which they called "bispidines" by condensing a piperidone with formaldehyde and a primary amine. The following compounds were prepared by this method: 1,5-dicarbomethoxy-3,7-dimethyl-6,8-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (XLIIIa), 1,5-dicarbomethoxy-3-methyl-7-allyl-6,8-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (XLIIIb), and 1,5-dicarbomethoxy-3-allyl-7-methyl-6,8-diphenyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (XLIIIc). The bispidine free base was found to



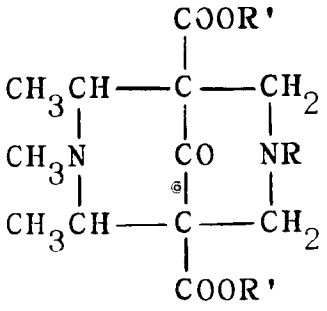
XLII

XLIIIa, R = R' = methyl
XLIIIb, R = allyl, R'=methyl
XLIIIc, R = methyl, R'=allyl

decompose when heated with alkali or with methyl iodide. The

yield of XLIIIb was 75%; other yields were not reported.

Bispidines of the type XLIV have been prepared by Mannich and Veit (19) following a procedure similar to that of Mannich and Mohs.(32) A yield of 70% was obtained in the preparation

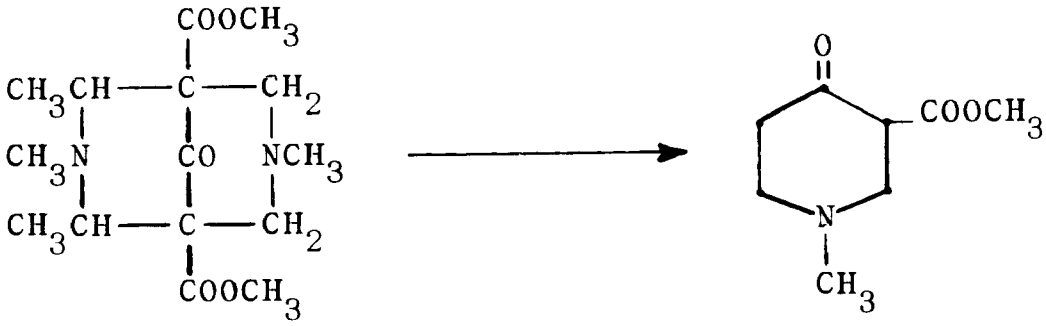


XLIV

	R	R'
XLIVa	methyl	methyl
XLIVb	methyl	ethyl
XLIVc	allyl	methyl
XLIVd	β-phenylethyl	methyl
XLIVe	β-chloroethyl	methyl

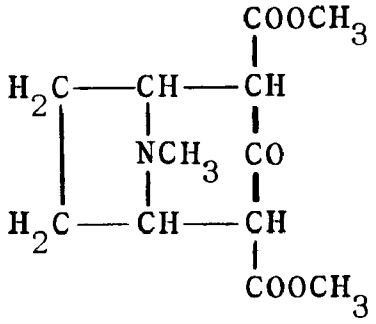
of XLIVa. Other yields were not reported.

1,5-Dicarbomethoxy-3,6,7,8-tetramethyl-3,7-diazabicyclo-[3.3.1]nonan-9-one (XLIVa) was also prepared by Ugryumov.(33) Upon heating this compound with dilute hydrochloric acid, 1-methyl-3-carbomethoxy-4-piperidone (XLV) was obtained.

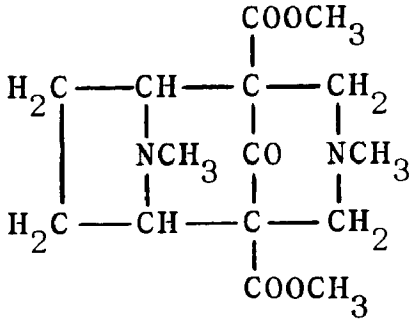


XLIVa XLV

Mannich and Veit also condensed 2,4-dicarbomethoxy-tropanone (XXXIII), prepared by a Robinson-type synthesis, with methylamine and formaldehyde to give a 45-50% yield of a tricyclic compound (XLVI).

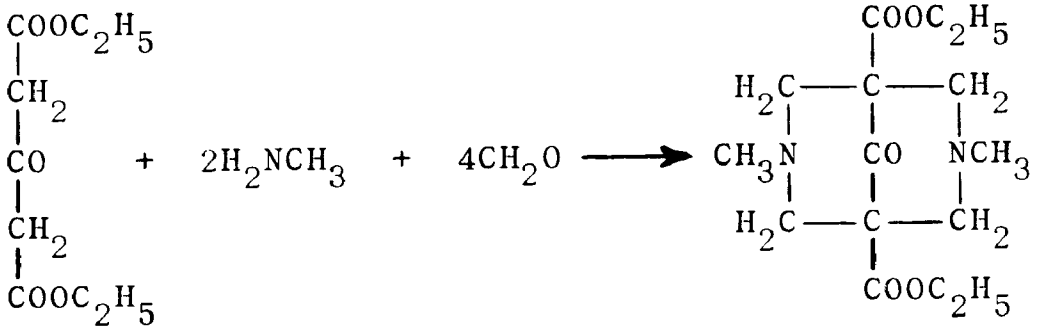


XXXIII



XLVI

Anet et al. (8) carried out a similar reaction, using diethyl acetonedicarboxylate, from which they obtained 1,5-

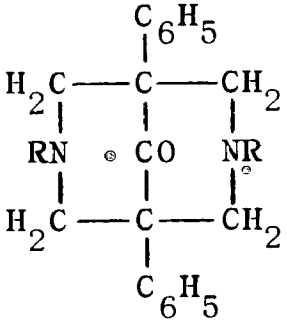


XLVII

dicarbethoxy-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (XLVII). The reaction was studied at room temperature, varying the pH from 1.4 to 6. The maximum yield obtained was 7.4% at a pH of 3.

Anet and coworkers were attempting to prepare γ-piperidones but the only compounds to be isolated were bispidines.

Several bicyclic compounds have been prepared by Zu-Yoong Kyi and Wilson (34) by condensing dibenzyl ketone with formaldehyde and a primary amine or ammonia:

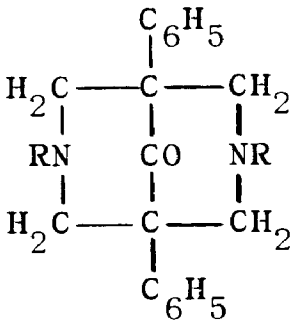


XLVIII

	R
XLVIIIa	H
XLVIIIb	CH_3CO
XLVIIIc	CH_3
XLVIIId	$CH_3CH_2CH_2$
XLVIIIe	$C_6H_5CH_2$
XLVIIIf	$HOCH_2CH_2$
XLVIIIg	$ClCH_2CH_2$

Attempts were made to prepare γ-piperidones by this procedure, but only the bispidines could be obtained. Monohydrochlorides of all compounds were made with the exception of XLVIIIb. XLVIIIa was obtained in 40% yield, whereas XLVIIIc, d, e and f were isolated in 50-65% yields. XLVIIIb was prepared from XLVIIIa with acetic anhydride, and XLVIIIg was synthesized from XLVIIIf with thionyl chloride in 80% yield. XLVIIIa and XLVIIIc would not react with phenylhydrazine, hydroxylamine, or other common carbonyl reagents. Many of these compounds showed local anaesthetic activity. The most potent (XLVIIIc) was slightly more active than procaine.

Chiavarelli et al. (35) prepared other derivatives of compound XLVIII, in addition to two of the derivatives obtained by Zu-Yoong Kyi and Wilson. All of these bispidines



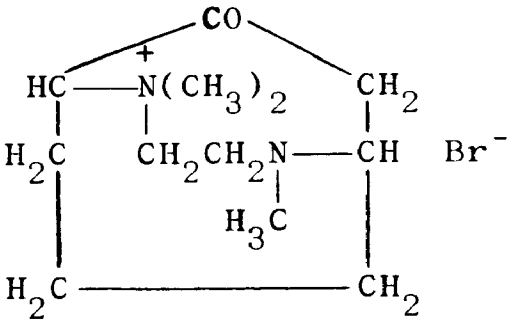
XLVIII

	R
XLVIIIa	H
XLVIIIc	CH_3
XLVIIIh	CH_3CH_2
XLVIIIi	$(CH_3)_2CH$
XLVIIIj	n-C_4H_9

were reduced to the corresponding alcohols by means of lithium aluminum hydride, except the ketone in which R represents CH_3CH_2 (XLVIIIh). This was reduced with Raney nickel. All of the ketones and alcohols were tested as anticonvulsants. Monomethyl iodide salts were prepared of all the ketones.

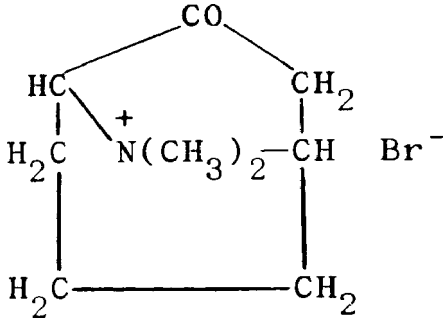
DISCUSSION OF THIS INVESTIGATION

The object of this investigation was the synthesis of azabicyclic compounds which could be prepared from cycloheptanone. Specifically, it seemed that it might be possible to obtain compounds XXXVII*, XXXVIII, XVIII, XXVIII and XXXVI.



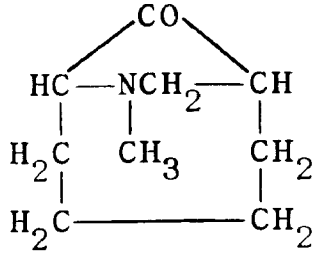
XXXVII

(Intermediates shown in Reaction Scheme A)



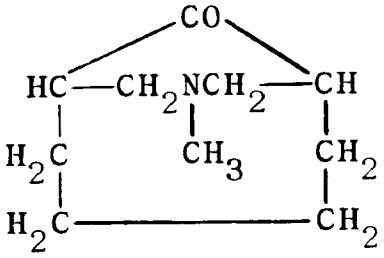
XXXVIII

(Intermediates shown in Reaction Scheme A)



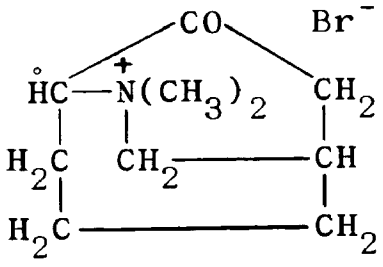
XVIII

(Reaction Scheme B)
Type A: x = 0, y = 1, n = 2



XXVIII

(Reaction Scheme C)
Type A: x = 1, y = 1, n = 2



XXXVI

(Reaction Scheme C)
Type B: n = 2

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* For certain reasons, it was necessary to use a high number, instead of I, for the first formula and to use the numbers for the formulas on this page out of numerical order.

These ketones were to be reduced to the corresponding secondary alcohols which would be esterified with appropriate acids. The esters were then to be evaluated pharmacologically.

For reasons which will be mentioned, compounds XXXVII and XXXVIII could not be synthesized. It was found possible to obtain XVIII and XXVIII. Although a product was isolated which, based on the analytical data for carbon, hydrogen, nitrogen and bromine, seemed to be XXXVI an infrared spectrum indicated the presence of an alcoholic instead of a carbonyl group.

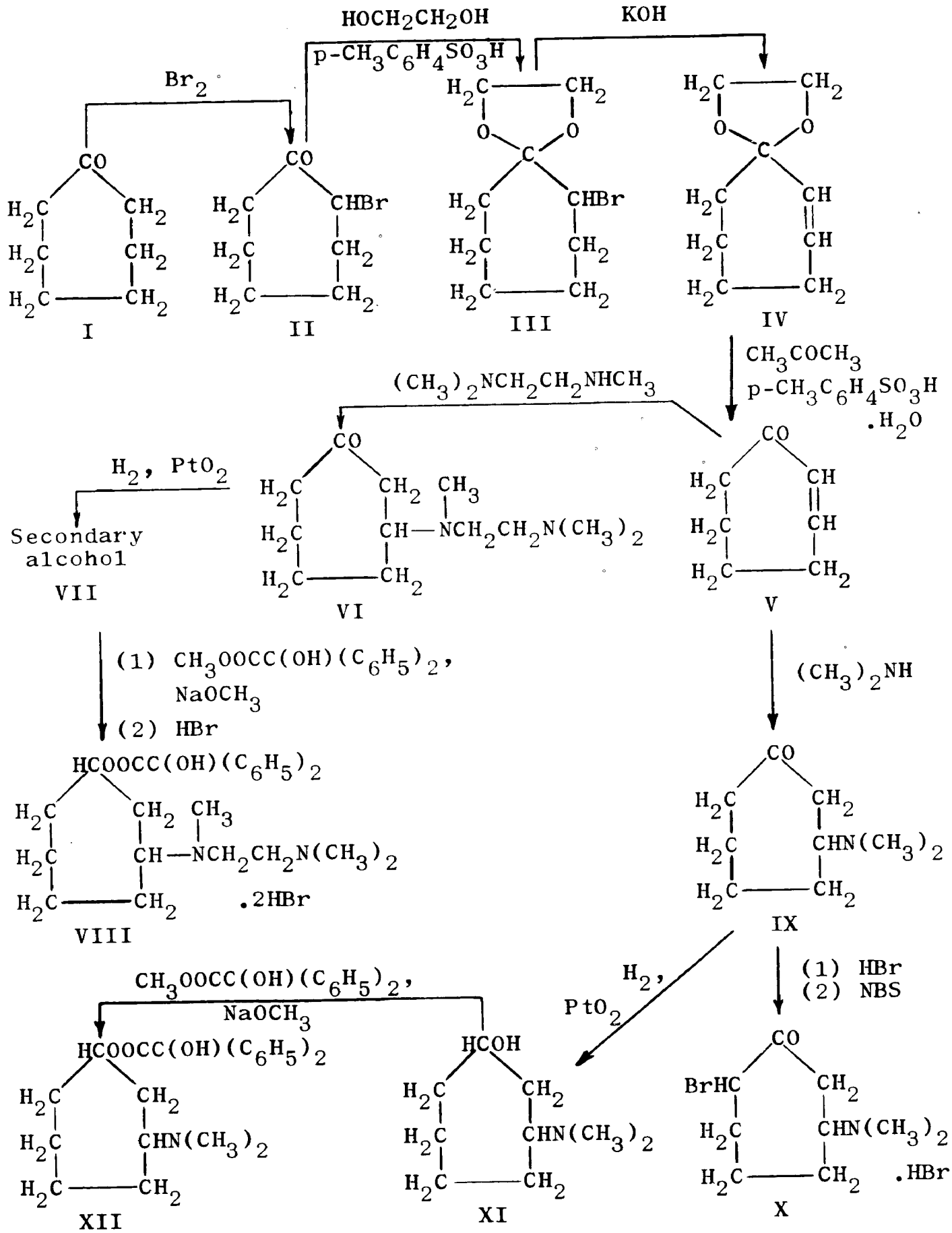
Compounds XXXVII and XXXVIII represent unknown types of azabicyclic ketones. Compounds XVIII, XXVIII and XXXVI conform to one of the general types (A or B) which were discussed in the General Introduction.

Compounds Shown in Reaction Scheme A

Compound XXXVII was to have been obtained by a seven-step synthesis from cycloheptanone. The first five steps (I-VI, Reaction Scheme A) were carried out satisfactorily in the manner described below.

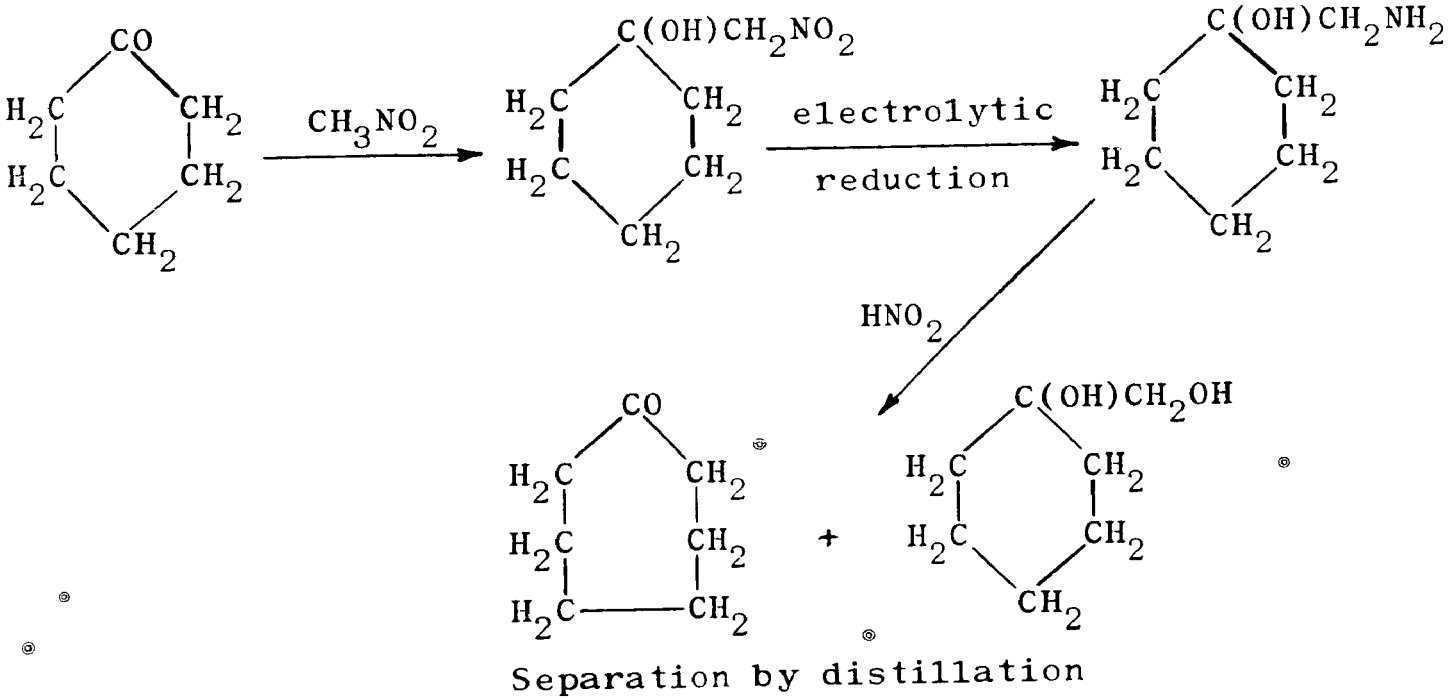
Several years ago no satisfactory process for the preparation of cycloheptanone (suberone)(I) was known. The ketone could be purchased in small amounts in this country at a prohibitive price but it is doubtful if any large amount of the material was even available. Almost simultaneously two procedures were described (36,37) by means of which cycloheptanone could be obtained in the laboratory in quite

REACTION SCHEME A



large amounts and at a reasonable cost. The three to four kilograms of cycloheptanone which were required were obtained in the following manner.

Cyclohexanone was converted into 1-(nitromethyl)cyclohexanol by the use of nitromethane. Electrolytic reduction of the nitro compound yielded 1-(aminomethyl)cyclohexanol which was treated with nitrous acid (Tiffeneau reaction) to produce cycloheptanone in 24-29% yield based on cyclohexanone. (37) About one month's work was required for the preparation

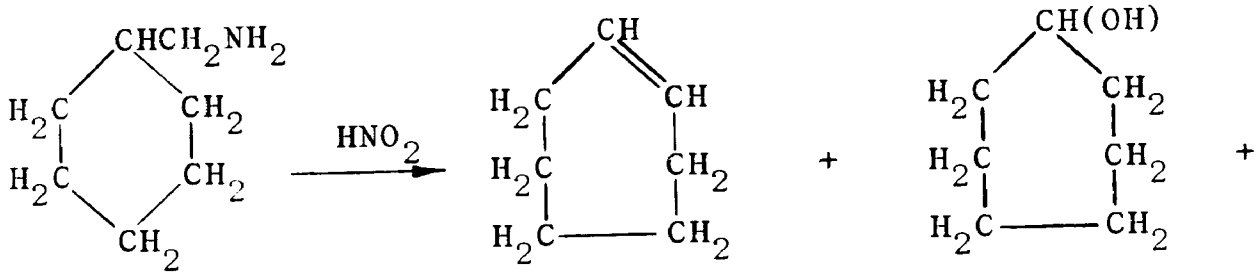


Separation by distillation

of about one and one-half kilograms of cycloheptanone by this procedure.

Since a large quantity of hexahydrobenzylamine was on hand in this laboratory, about one kilogram of cycloheptanone was prepared by a second process in order to evaluate its large scale usefulness. It may be stated at once that this process was less satisfactory than the first one.

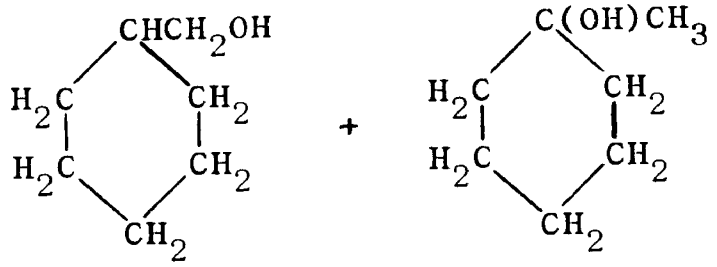
Hexahydrobenzylamine was treated with sodium nitrite in acetic acid solution (Demjanov reaction). This particular reaction has been described by Ruzicka and Brugger.(38) Upon distillation of the crude reaction product, we obtained two fractions; one fraction consisted of cycloheptene, and the other("cycloheptanol fraction") of cycloheptanol contaminated with several by-products. According to Smith and Baer (39), among the by-products are cyclohexylcarbinol, 1-methylcyclohexanol and the acetates of one or all of the alcohols. These



Hexahydrobenzylamine

Cycloheptene

Cycloheptanol



Cyclohexylcarbinol

1-Methylcyclohexanol

investigators stated that the "cycloheptanol fraction" did not contain more than 65% of cycloheptanol. The crude cycloheptanol was oxidized with sodium dichromate and sulfuric acid whereby the secondary alcohol was converted into cycloheptanone. The reaction mixture was steam-distilled and the organic layer in the distillate was treated with sodium

bisulfite. The ketone was liberated from the bisulfite addition product with alkali and then purified by distillation. The yield of pure cycloheptanone, based on hexahydrobenzylamine, was 13-19%.

It was thought that 2-cycloheptenone (V), a necessary intermediate, might be obtained by dehydration of cycloheptanol to cycloheptene and oxidation of the latter to V by a procedure, described by Whitmore and Pedlow (40) as well as by Oppenauer and Oberrauch (41), in order to convert cyclohexene into cyclohexenone. When, according to this process, cyclohexene was treated with chromium trioxide or tert.-butyl chromate in acetic acid solution, 2-cyclohexenone was obtained in 37-40% yield. When this procedure was tried with cycloheptene and the use of either chromium trioxide or tert.-butyl chromate, a 10-20% yield of a product was obtained which boiled at 70-90° (15 mm.); 2-cycloheptenone boils at 71-80° (10 mm.).(42) It is not certain that the product which we obtained was actually 2-cycloheptenone. The attempted addition of dimethylamine to this compound failed completely but when 2-cycloheptenone, prepared by a process to be described was employed, the addition compound (IX) was isolated in about 80% yield.

The successful synthesis of 2-cycloheptenone (V) involved the preparation of II, III and IV.

The conversion of 2-bromocyclohexanone into 2-cyclohexenone by the use of intermediates analogous to III and IV has been described by Wanzlick et al. (43), and the prepar-

ation of V by the use of intermediates II, III and IV has been reported in a dissertation by Ringold.(42)* This dissertation came to our attention only after compound IV had been prepared. In order to obtain II**, bromine vapor was introduced into a stirred mixture of cycloheptanone and water; the bromo compound was isolated in 60% yield.

Attempts were made to convert II directly into V by dehydrobromination. For this purpose, triethylamine (and also tributylamine) was employed in the same manner as that described by Sullivan (7) who dehydrobrominated 2-bromocyclohexanone successfully. By this procedure, we obtained V in an impure state in less than 10% yield.

Faworskii (44)*** has shown that treatment of 2-chlorocycloheptanone with potassium hydroxide yields cyclohexanecarboxylic acid, rather than 2-cycloheptenone; therefore, dehydrobromination of II by the use of alkali was not attempted.

Wanzlick et al. (43) reported that after conversion of 2-chloro- and also 2-bromocyclohexanone into the ethylene ketal, dehydrohalogenation could be effected readily by the use of potassium hydroxide in diethylene glycol; these investigators also dehydrohalogenated the ethylene ketal of 2-chlorocyclopentanone.

We found that conversion of II into 2-bromocycloheptanone ethylene ketal (III), by the use of ethylene glycol and p-toluenesulfonic acid monohydrate, and then treatment of III

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* Details for the synthesis of II-V by Ringold are not to be found in Dissertation Abstracts, 14, 601 (1954).

** Ringold (42) prepared this compound, in 60% yield, by the use of N-bromosuccinimide.

*** For a general review of the Faworskii rearrangement see Ref. 45.

with potassium hydroxide in ethanol yielded 2-cycloheptenone ethylene ketal (IV) in 85% yield. This same procedure had been used by Ringold (42) who isolated IV in 84% yield.

Conversion of the unsaturated ketal (IV) into V was carried out by the use of acetone and p-toluenesulfonic acid monohydrate. Ringold obtained V in the same manner.

When V was treated with an aqueous solution of N,N,N'-trimethylethylenediamine at 0-5°, 3-[N-methyl-N-(β-dimethylaminoethyl)]aminocycloheptanone (VI) was formed in 34% yield. The required diamine was prepared from commercial N,N-dimethylethylenediamine by formylation and subsequent reduction of the formyl group with lithium aluminum hydride.

The amine addition with the formation of VI is analogous to the addition of N,N,N'-trimethylethylenediamine to 2-cyclohexenone which was carried out by Sullivan.(7) This investigator also obtained addition products from 2-cyclohexenone and dimethylamine, 2-cyclohexenone and N,N-dimethylethylenediamine, and isophorone and dimethylamine. We were unable to find any other references in the literature to an amine addition to 2-cyclohexenone. The addition of dimethylamine to 2-cycloheptenone (tropilene) was reported by Ladenburg.(46)

Although VI, in the form of the base, could be distilled under reduced pressure without decomposition, it was surprising to find that salts of VI could not be prepared. When alcoholic solutions of VI and picric acid were mixed, a yellow crystalline precipitate was formed. Recrystallization of the precipitate from water yielded not a picrate of VI but the

dipicrate of N,N,N'-trimethylethylenediamine. Treatment of VI in ether with hydrogen chloride or hydrogen bromide produced only gummy precipitates. Undoubtedly, 2-cycloheptenone was also formed in these experiments but no attempt was made to isolate this substance.

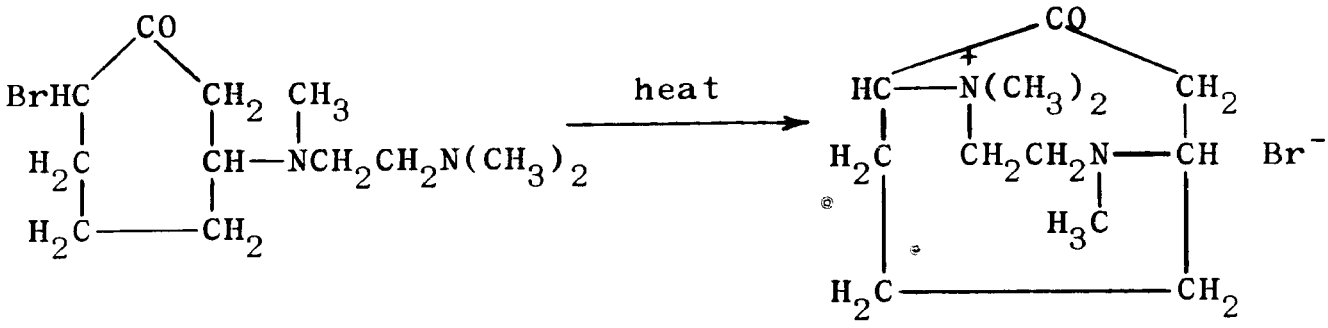
Compound VI, in the form of the base, was allowed to react with N-bromosuccinimide in the hope that the 7-bromo derivative would be obtained. The material isolated from the reaction was dissolved in ether and the solution was treated with oxalic acid in an attempt to obtain an oxalate. However, the compound isolated was the diacid oxalate of N,N,N'-trimethylethylenediamine.

Compound VI is a beta-amino ketone and hence represents the same type of compound as a Mannich base. A typical decomposition of such bases and their salts is their breakdown, sometimes spontaneous, into an amine (or amine salt) and an unsaturated ketone.(47)

In one experiment, after completion of the bromination procedure in carbon tetrachloride and removal of the precipitated succinimide* by filtration, the solution was refluxed in the hope that the 7-bromo compound, which presumably had been formed, would undergo cyclization with the production of XXXVII. A small quantity of oily product was obtained but this substance could not be crystallized.

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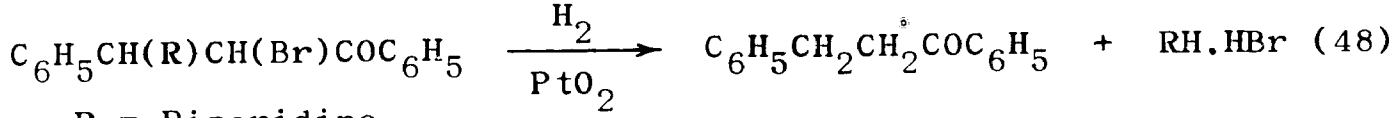
* This precipitate may have contained a small amount of the 7-bromo derivative in the form of the hydrobromide.



XXXVII

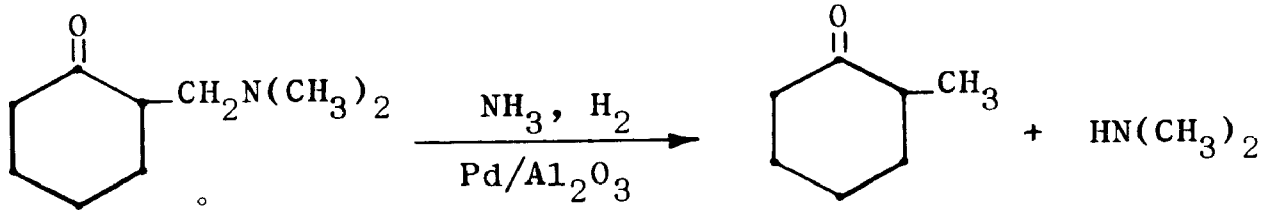
Reduction of the beta-amino ketone (VI), in the form of the base, to the corresponding alcohol (VII) was accomplished by catalytic hydrogenation. A considerable amount of low boiling material was obtained and the yield of the secondary alcohol was poor possibly due to the elimination of N,N,N'-trimethylethylenediamine.

Amine elimination from beta-amino ketones has been reported (48, 49) under similar conditions.



R = Piperidino

Attempted reductive amination of 2-dimethylaminomethylcyclohexanone yielded 2-methylcyclohexanone and dimethylamine.(49)

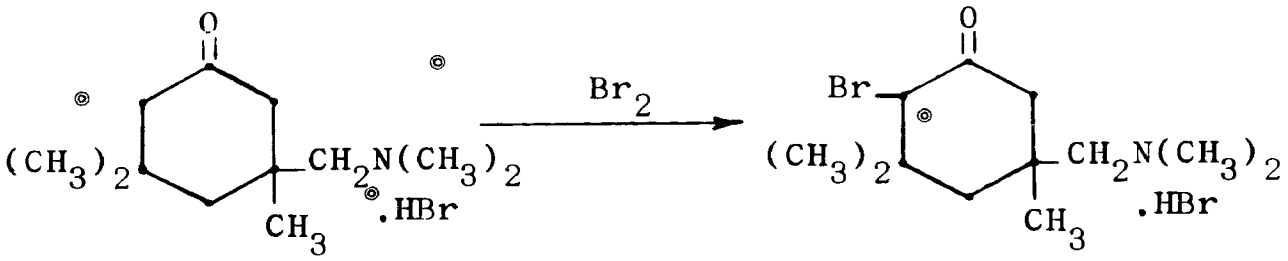


Compound VII was converted into the benzilate by transesterification. Since the dihydrochloride of the ester could

not be obtained in a pure state, the ester was isolated as the dihydrobromide for pharmacological evaluation.

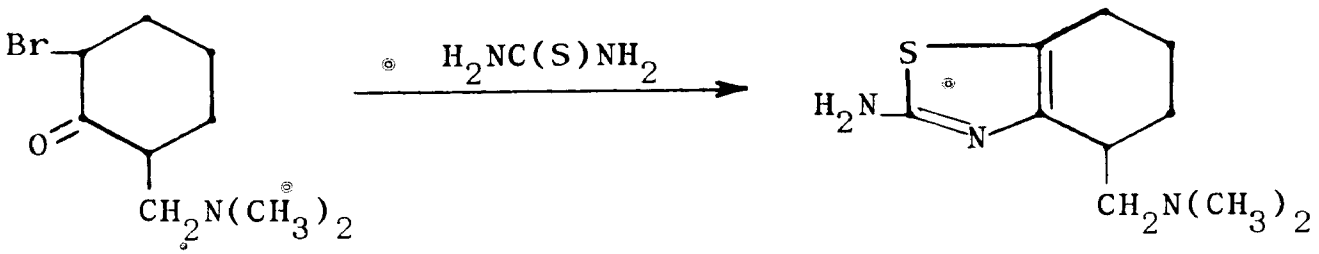
Compound V was treated with aqueous dimethylamine at 0-5° whereupon 3-dimethylaminocycloheptanone (IX) was formed in 84% yield. The hydrobromide of IX was prepared, it was suspended in chloroform, and N-bromosuccinimide was added to the ice-cold suspension. The analytical data for the reaction product corresponded to that calculated for the hydrobromide of a monobromination product of IX. Although the structure of the product was not established, it was assumed to be the 7-bromo and not the 2-bromo derivative.

The literature was searched for a similar example of the bromination of a cycloalkanone which contained a basic substituent in the 3 position but none could be found except one in which 3-dimethylaminomethyl-3,5,5-trimethylcyclohexanone hydrobromide had been brominated.(7) Since, in this instance, the base of the bromination product cyclized to a quaternary bicyclic compound, it was assumed that the bromine atom was attached to the 6 position.



The bromination of a cycloalkanone which contained a basic substituent in the 2 position has been described and the structure of the bromo derivative was determined. Land

et al. (50) brominated 2-dimethylaminomethylcyclohexanone (and also 2-piperidinomethylcyclohexanone) and then treated the bromo derivative with thiourea. The reaction product obtained was 2-amino-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole. The formation of this thiazole was possible



only if the bromine atom occupied the 6 position. In another instance (50), the structure of the thiazole compound was proven by its conversion into a known compound, and by an unequivocal synthesis.

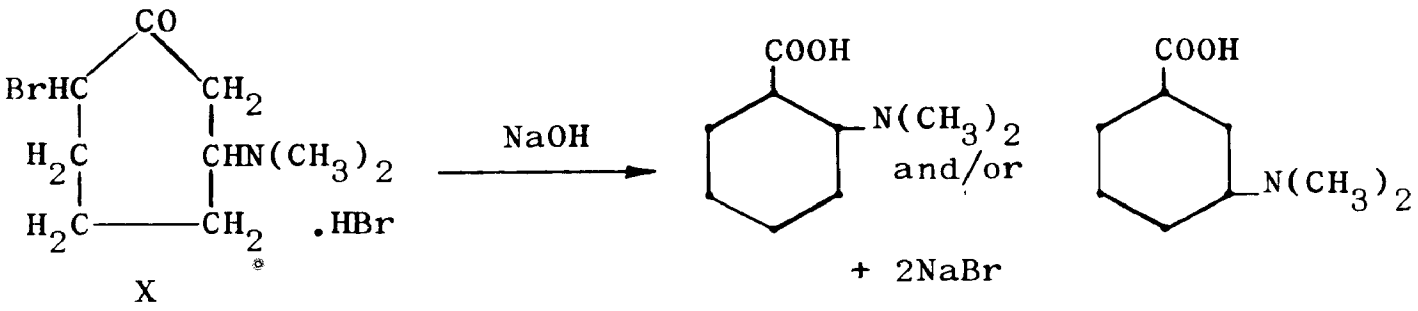
An aqueous solution of 3-dimethylamino-7(?)-bromocycloheptanone hydrobromide (X) was made basic with sodium hydroxide; only a trace of material could be extracted from the alkaline solution with ether. After removal of the ether, the residue was refluxed in benzene solution for fifteen hours in an attempt to cyclize it, but no precipitate was formed. The alkaline aqueous solution was evaporated to dryness and the gummy solid extracted with hot isopropyl alcohol. Upon cooling the alcoholic solution, two molar proportions of sodium bromide precipitated. This probably resulted from either a Faworskii rearrangement* or from cyclization of the bromo amino ketone and subsequent decomposition of the

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* For a general review of the Faworskii rearrangement see Ref. 45.

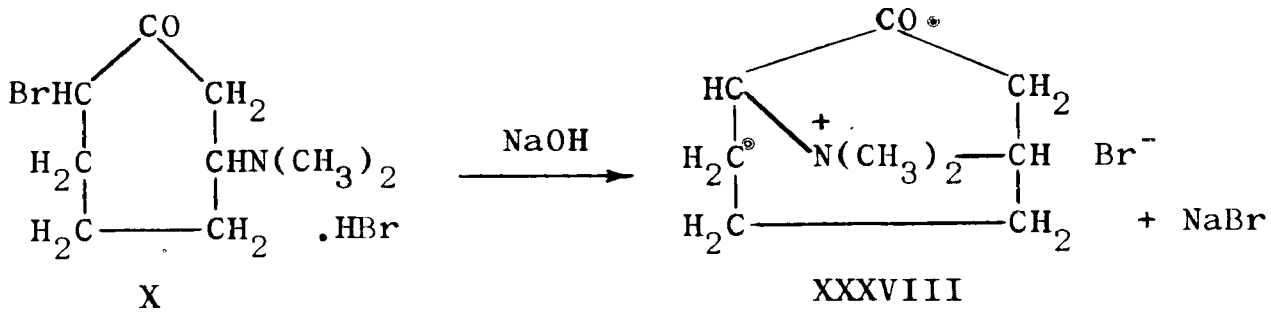
quaternary compound.

A Faworskii rearrangement would be represented as follows:

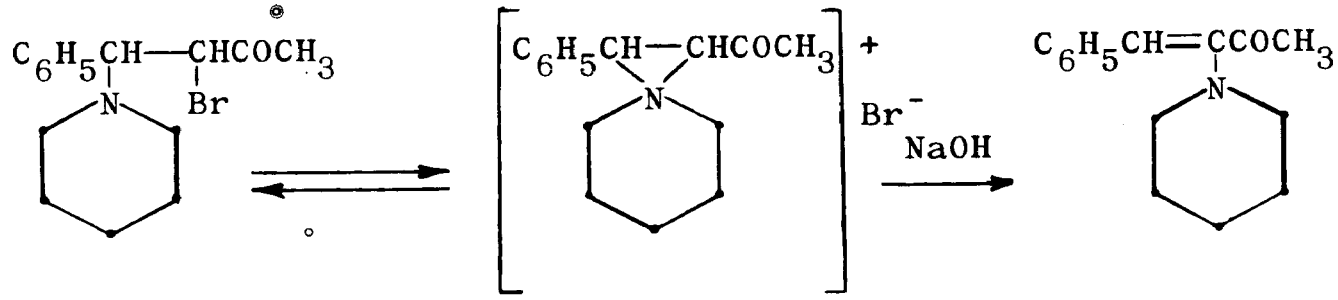


An observation of this type was reported by Sullivan (7), who isolated a picrate of an amino acid obtained by the Faworskii rearrangement of 2-dimethylaminomethyl-6-bromocyclohexanone.

A cyclization of the bromo amino ketone (base of X) would result in the formation of one of the desired azabicyclic ketones (XXXVIII).



The cyclization of a similar type of compound followed by decomposition of the quaternary compound under conditions similar to those used by us has been observed by Cromwell and Witt.(51)



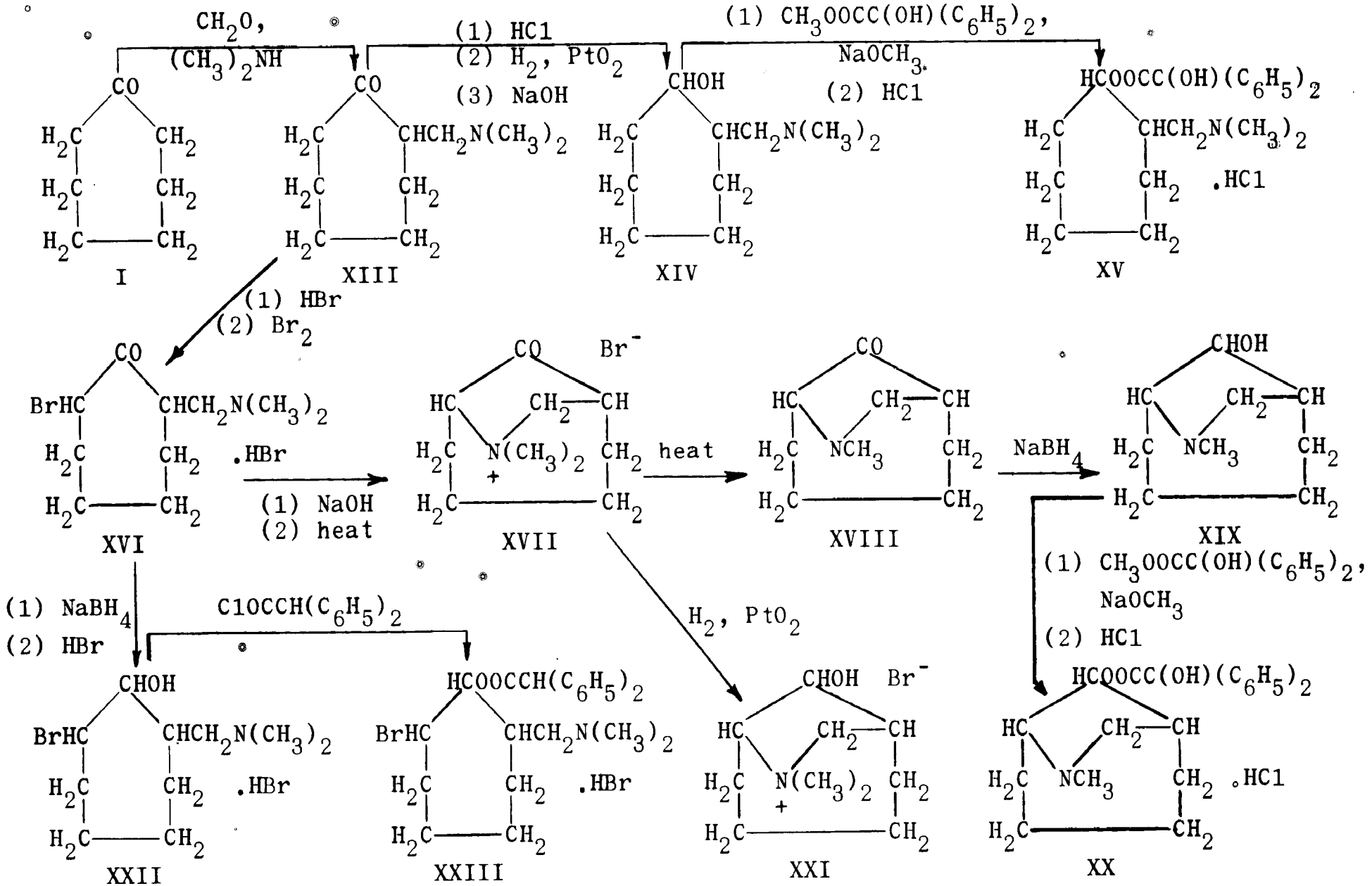
Catalytic reduction of IX with the use of platinum oxide yielded 3-dimethylaminocycloheptanol (XI) in 53% yield. The alcohol was converted by transesterification into the benzilate (XII) which was isolated as the hydrochloride and also as the methobromide.

Compounds Shown in Reaction Scheme B

Cycloheptanone (I) was converted into 2-dimethylaminomethylcycloheptanone (XIII) in a manner similar to that described by Treibs and Mühlstaedt (52) and by Sullivan.(7) Reduction of the hydrochloride of this Mannich base in the presence of platinum oxide yielded 2-dimethylaminomethylcycloheptanol (XIV) which was transesterified to form the benzilate. The ester was isolated in the form of the hydrochloride (XV).

The hydrobromide of the Mannich base (XIII) was brominated with the formation of 2-dimethylaminomethyl-7-bromocycloheptanone hydrobromide (XVI) in 82% yield. The structure of XVI is established by the following facts: the same procedure was used for the bromination of the hydrobromide of XIII as that employed by Land, Ziegler and Sprague (50) for the bromination of 2-dimethylaminomethylcyclohexanone hydrobromide; the structure of the bromination product obtained from the substituted cyclohexanone compound was definitely established by Land et al. as 6-bromo-2-dimethylaminomethylcyclohexanone in the manner which has been described (page 35). There can be no doubt that bromination of the substituted cycloheptanone yielded the 7-bromo instead of the 2-bromo derivative.

REACTION SCHEME B



The cyclization of the base of XVI produced 7-methyl-7-azabicyclo[4.2.1]nonan-9-one methobromide (XVII) in 34% yield. The analytical data obtained for carbon, hydrogen and bromine corresponded to the calculated data.

The fact that an aqueous solution of XVII gave a precipitate when treated with silver nitrate solution showed that XVII contained ionizable bromine. Since addition of concentrated ammonia water to an aqueous solution of XVII did not produce a precipitate, the ionizable bromine must have been a part of a quaternary ammonium bromide and not of a hydrobromide; addition of ammonia water to a hydrobromide would have resulted in a precipitation of a water-insoluble amine.

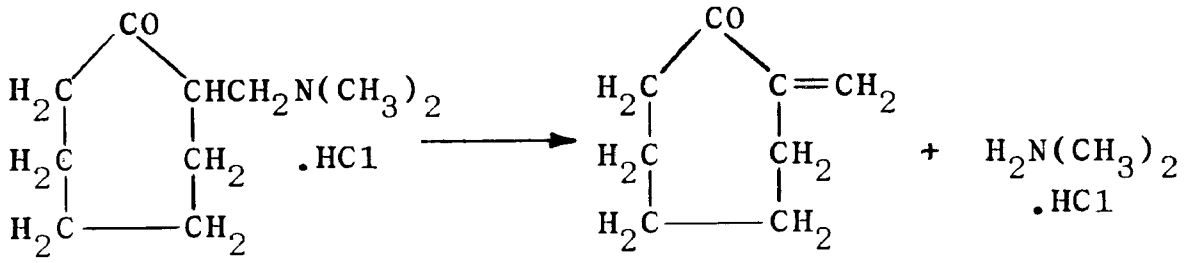
An infrared spectrum of XVII showed carbonyl absorption at 1755 $cm.^{-1}$. This is a characteristic absorption for a carbonyl group in a five-membered ring.(53)*

In order for cyclization of the base of XVI to take place, the bromine atom attached to the 7 position must be trans to the dimethylaminomethyl substituent.(54)

The low yield in the cyclization step might be explained by intermolecular quaternization which could lead to polymer formation. Another possible explanation arises from the fact that dimethylamine hydrobromide was isolated from the cyclization reaction. This could be formed by a breakdown of the Mannich base (XVI), combined with dehydrobromination. Break-

* Bellamy states that carbonyl groups in saturated five-membered rings absorb in the range of 1772-1740 $cm.^{-1}$. Six-membered rings generally absorb between 1720 and 1706 $cm.^{-1}$, while the values for seven-membered rings are generally 1699-1690 $cm.^{-1}$.

down of Mannich bases occurs readily as previously discussed (page 32). Treibs and Mühlstaedt (52) have shown that 2-dimethylaminomethylcycloheptanone hydrochloride will break down when heated to give 2-methylenecycloheptanone. We have



already shown (page 30) that dehydrobromination of 2-bromocycloheptanone can occur in the presence of triethylamine, although the yield of cycloheptenone was poor. Therefore, it is possible that either the dimethylamine from the breakdown of the Mannich base XVI, or the Mannich base itself may have been responsible for dehydrobromination. No evidence was obtained as to whether dehydrobromination occurs before or after breakdown of the Mannich base.

In one experiment the quaternary ketone (XVII) was reduced with the aid of platinum oxide to the quaternary alcohol (XXI) in 52% yield; the yield obtained in other experiments was much lower, and in some instances no reduction of the ketone took place. All attempts to prepare esters from this alcohol (XXI) by the use of diphenylacetyl chloride or diphenylchloroacetyl chloride failed.

An effort was then made to obtain an ester of XXI in a different manner. The brominated ketone hydrobromide (XVI) was reduced to the bromo alcohol with sodium borohydride, and

the alcohol was isolated as the hydrobromide (XXII). Two forms of the hydrobromide of the alcohol were obtained; one melted at 127-128°, the other at 142-142.5°. The infrared spectra of the two forms were slightly different but both showed the presence of a band in the hydroxyl region. A diphenylacetate, isolated as the hydrobromide (XXIII), was prepared from the higher melting form by the use of diphenylacetyl chloride.

Since the ester salt (XXIII) was obtained in a very small amount, the contemplated cyclization of the ester base to the diphenylacetate of XXI could not be carried out.

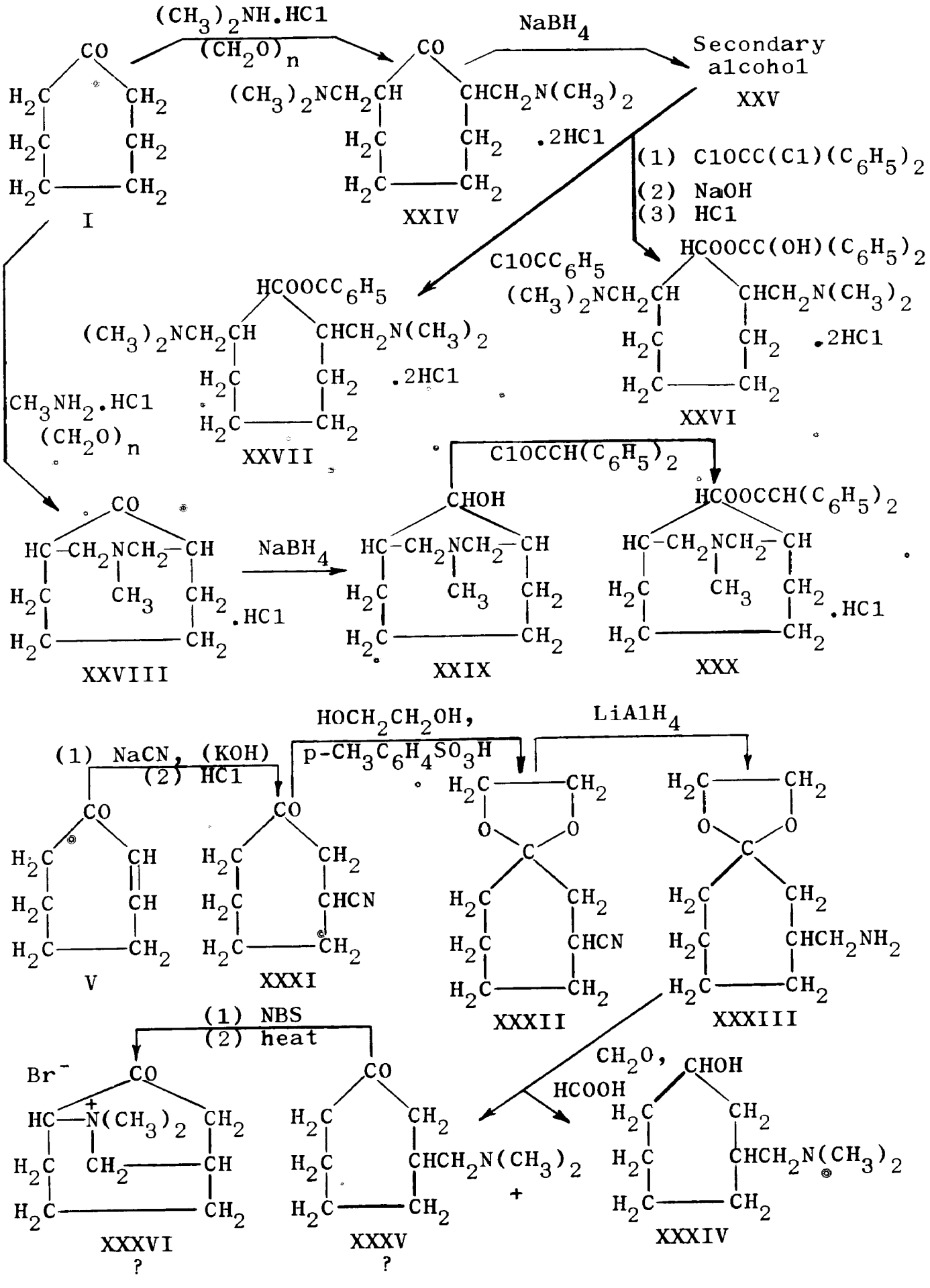
The quaternary salt (XVII) was heated to 225-235° under reduced pressure whereupon the tertiary base, 7-methyl-7-azabicyclo[4.2.1]nonan-9-one (XVIII) distilled from the reaction flask in 63% yield. The decomposition of the quaternary compound was evident from the formation of a considerable amount of white fumes, which was undoubtedly methyl bromide. The tertiary amino ketone (XVIII) was reduced with sodium borohydride to the corresponding alcohol, 7-methyl-7-azabicyclo[4.2.1]nonan-9-ol (XIX) in 76% yield. Transesterification was employed to convert the alcohol into the benzilate which was isolated as the hydrobromide (XX).

Compounds Shown in Reaction Scheme C

The first series of reactions deals with the preparation of 8-methyl-8-azabicyclo[4.3.1]decan-10-one hydrochloride (XXVIII).

During another investigation by F. J. McCarty which is in progress in this laboratory, it was found that by means of the Mannich reaction two dimethylaminomethyl groups can be introduced into cyclohexanone. When we allowed cycloheptanone to react with excess (three molecular equivalents) paraformaldehyde and excess (two and one-half molecular equivalents) dimethylamine hydrochloride in acetic acid solution, 2,7-bis-(dimethylaminomethyl)cycloheptanone dihydrochloride (XXIV) was obtained in 42% yield. It seemed that by the use of heat this substance might be made to cyclize with the formation of the desired product XXVIII. Such a reaction would be analogous to the cyclization of α,α-di(β-dimethylaminoethyl)-α-phenylacetonitrile hydrochloride to 1-methyl-4-phenyl-4-cyanopiperidine hydrochloride with the evolution of trimethylamine.(55) When XXIV was heated at 210-230°, a gas was evolved which may have been trimethylamine, dimethylamine or a mixture of both. The ether-insoluble material was dissolved in water, the solution was made basic, extracted with ether and the dried extract was treated with hydrogen chloride. No precipitation took place. From these results it seems that the initial material (XXIV) may have undergone degradation into dimethylamine, dimethylamine hydrochloride and a methylene derivative of cyclohexanone or a methylene derivative of

REACTION SCHEME C



2-dimethylaminomethylcyclohexanone. Since this type of degradation does not take place with secondary alcohols prepared from Mannich bases, XXIV was reduced with sodium borohydride to the secondary alcohol XXV. A solid hydrochloride could not be obtained, therefore the crude, oily hydrochloride of the reduction product was heated to 200-210° in the hope that cyclization of this substance might be effected. A brief but vigorous evolution of gas took place. The reaction product was dissolved in dilute hydrochloric acid, the solution was made basic and extracted with ether. Introduction of hydrogen chloride into the dried extract produced a crystalline precipitate but attempted purification of this material by repeated recrystallization from isopropyl alcohol-isopropyl ether yielded a substance which melted over quite a wide range (100-108°, dec.).

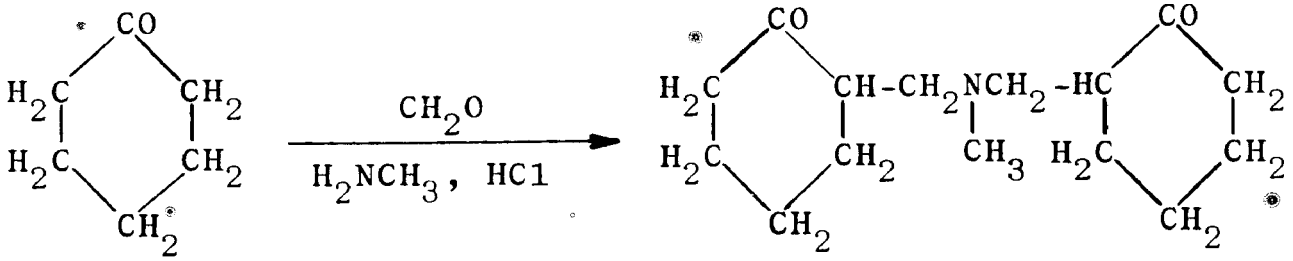
An attempt was made to prepare the benzilate of XXV by transesterification (use of methyl benzilate). A pure product could not be obtained from this reaction, however we were able to obtain the desired ester by the use of diphenylchloroacetyl chloride. The initial reaction product, the diphenylchloroacetic acid ester of XXV was not isolated but was treated with 10% sodium hydroxide solution whereby it was converted into the benzilic acid ester which was isolated as the dihydrochloride (XXVI).

The use of diphenylchloroacetyl chloride for the synthesis of esters of benzilic acid has been described by King and Holmes (56), and more recently by Hromatka (57) and by

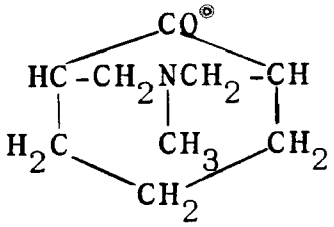
Taguchi.(58)

The benzoate of XXV was prepared by the use of benzoyl chloride; it was isolated as the dihydrochloride (XXVII).

A rather obvious method for the synthesis of XXVIII would be the interaction of cycloheptanone, formaldehyde and methylamine hydrochloride (Mannich reaction). However, since it was found by Weatherbee et al. (10) that cyclohexanone, formaldehyde, methylamine and hydrochloric acid reacted to form methylbis(2-cyclohexanonylmethyl)amine instead of the desired bicyclic compound 3-methyl-3-azabicyclo[3.3.1]nonan-9-one, it would seem that the preparation of XXVIII by means of the Mannich reaction mentioned above might not be possible.



Methylbis(2-cyclohexanonylmethyl)-amine



3-Methyl-3-azabicyclo-[3.3.1]nonan-9-one

However, before the article by Weatherbee appeared in the literature, we had found that cycloheptanone, paraformaldehyde and methylamine hydrochloride could be condensed with the formation of XXVIII. Unfortunately, the yield was

very small (5.2%) and a large amount of other material was obtained which may have been methylbis(2-cycloheptanonyl-methyl)amine. The ketone (XXVIII) was reduced to the corresponding secondary alcohol, 8-methyl-8-azabicyclo[4.3.1]decan-10-ol (XXIX), with sodium borohydride in 88% yield. The alcohol was converted into the diphenylacetate by the use of diphenylacetyl chloride, and the ester was isolated as the hydrochloride (XXX). A benzoate of XXIX was also prepared by the use of benzoyl chloride; the crude material melted at 210-213°(dec.). Since this substance was very hygroscopic, it was not purified and analyzed.

The attempted preparation of 6-methyl-6-azabicyclo[3.2.2]-nonan-9-one methobromide (XXXVI) was begun with the synthesis of 3-cyanocycloheptanone (XXXI). This substance was obtained in 58% yield by interaction of 2-cycloheptenone (V) and sodium cyanide. An analytically pure sample of the cyano derivative could not be obtained since slight decomposition always took place when the liquid product was distilled under reduced pressure.

The conversion of a number of acyclic and cyclic alpha, beta-unsaturated ketones - 2-cyclohexenone (7), isophorone and other 5,5-disubstituted-3-methyl-2-cyclohexenones (59), benzalacetophenone (60), 3-keto-5-methyl-1,4-hexadiene (61), mesitalacetomesitylene (62), mesitalacetophenone (62), mesitalacetone (62) - into 3- or beta-cyano derivatives has been described in the literature. In most instances the reaction was carried out by the addition of an aqueous solution of

sodium or potassium cyanide to the unsaturated ketone dissolved in a mixture of either methanol or ethanol and acetic acid.

In order to protect the carbonyl group from reduction during the conversion of the cyano into the aminomethyl radical, XXXI was converted, in 60% yield, into 3-cyanocycloheptanone ethylene ketal (XXXII) prior to reduction. Upon distillation of the crude ketal (XXXII), a considerable amount of 2-cycloheptenone ethylene ketal (IV) was obtained. It was not found possible to obtain an analytically pure sample of the cyano ketal by distillation.

Reduction of XXXII with lithium aluminum hydride yielded crude 3-aminomethylcycloheptanone ethylene ketal (XXXIII) in 80% yield (b.p. 100-135°, 7 mm.). A portion which boiled at 113-118° (7 mm.) proved to be analytically pure. The crude product was employed in the attempted conversion of XXXIII into XXXV.

An attempt was made to prepare the 3-dimethylaminomethyl derivative (XXXV) from the 3-aminomethyl compound (XXXIII) by an Eschweiler-Clarke methylation procedure.(63, 64) After compound XXXIII had been heated with a mixture of 37-38% aqueous formaldehyde and formic acid, the crude product which was isolated boiled at 100-115° (7 mm.)(distillate A). A portion of this material (5 g.) was dissolved in ether and the solution was treated with hydrogen bromide. The crude precipitated material weighed 5.1 g. and melted at 132-149°. After several recrystallizations, 1 g. of pure hydrobromide

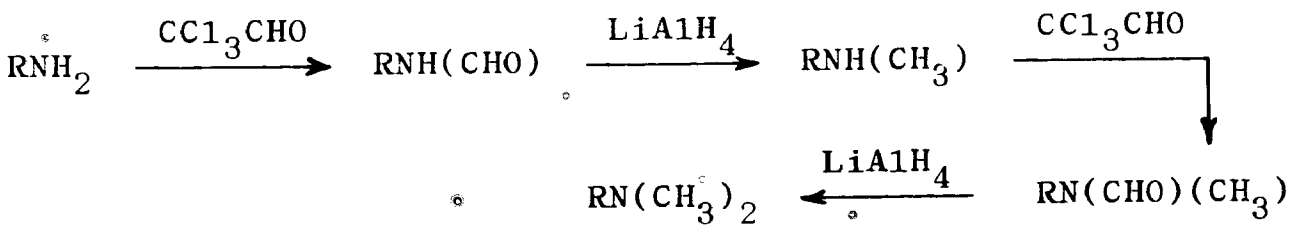
(m.p. 178-179°) was obtained. The analytical data (carbon, hydrogen and bromine analyses) found correspond to that calculated for the hydrobromide of 3-dimethylaminomethylcycloheptanol (XXXIV). The base, a liquid, prepared from the salt was also analyzed and the analytical data (carbon and hydrogen analyses) correspond to that calculated for XXXIV. The infrared spectrum of this compound showed the presence of a band in the hydroxyl region.

In view of the wide range in boiling point (15°) of the reaction product, the fact that only 1 g. of the pure hydrobromide of XXXIV could be isolated from 5 g. of the crude base (XXXIV) led us to suspect the presence of a second compound in the fraction which boiled at 100-115° (7 mm.). The experience of Sullivan (7), who treated the cyclohexane derivative corresponding to XXXIII, and also an analogous compound, with a mixture of formalin and formic acid, also suggested this possibility. From 3-aminomethylcyclohexanone ethylene ketal this investigator obtained 3-dimethylaminomethylcyclohexanol and found evidence of the presence of 3-dimethylaminomethylcyclohexanone in the reaction mixture. After the treatment of 3,5,5-trimethyl-3-aminomethylcyclohexanone ethylene ketal with formalin and formic acid this same investigator isolated 3,5,5-trimethyl-3-dimethylaminomethylcyclohexanone (72% yield) and 3,5,5-trimethyl-3-dimethylaminomethylcyclohexanol.

Since it seemed that during the Eschweiler-Clarke procedure, some product other than the desired dimethylamino

derivative (XXXV) may have been formed, it is pertinent to mention two additional instances in which other investigators encountered products foreign to the reaction. In the attempted N-methylation of mescaline by the Eschweiler-Clarke process, Reti and Castrillon (65) obtained isoquinoline derivatives, and treatment of 4-methylamino-1,2-diphenyl-3-methyl-2-butanol by Pohland et al. (66) with formaldehyde and formic acid yielded 6-benzyl-3,5-dimethyl-6-phenyl-tetrahydro-1,3-oxazine instead of the desired 4-dimethylamino derivative.

It is very probable that the difficulties encountered by the investigators mentioned above and by us could have been avoided if the methylation process outlined below had been employed.(66a)



In the belief that the distillate (distillate A) obtained by the distillation of the material formed by treatment of XXXIII with formaldehyde and formic acid might be a mixture of the alcohol XXXIV and the ketone XXXV, the mixture was treated with N-bromosuccinimide in the hope that bromination of the ketone would yield 3-dimethylaminomethyl-7-bromocycloheptanone which could be cyclized to 6-methyl-6-azabicyclo-[3.2.2]nonan-9-one methobromide (XXXVI). After treatment with N-bromosuccinimide in carbon tetrachloride, the solution was decanted from the precipitated material (presumably

succinimide) and refluxed. A very small amount of precipitate was obtained from this operation. After several recrystallizations of the precipitate, the melting point (181-181.5°) indicated that a pure substance had been obtained. An aqueous solution of the substance gave a positive test for ionic halogen with silver nitrate. When the aqueous solution was treated with ammonia water, no precipitate was formed. These two tests indicated that the product was a quaternary bromide. A complete analysis (carbon, hydrogen, nitrogen and bromine) yielded data which correspond to that calculated for the formula shown by structure XXXVI. However, since the infrared spectrum showed the presence of a hydroxyl group in the compound and the absence of a carbonyl group, we are uncertain about the structure of the substance obtained.

EXPERIMENTAL PART

2-Bromocycloheptanone (II).*--Cycloheptanone (I)(37) (224 g., 2.0 moles) and 1400 ml. of water were placed in a 3-liter, 3-necked flask fitted with an inlet tube which extended below the surface of the liquid, a reflux condenser, a stirrer and a thermometer. To the top of the condenser there was attached a tube leading to a water-trap. The mixture was stirred rapidly and heated on a steam-bath to 75°. Bromine (102 ml., 320 g., 2.0 moles)** was placed in a distilling flask and introduced into the reaction flask by means of a stream of carbon dioxide at such a rate that the reaction mixture remained nearly colorless. The mixture was maintained at a temperature of 75-80° throughout the reaction. Addition of the bromine required 2 to 2.5 hours. The colorless bromocycloheptanone was separated and distilled immediately. In this state of purity, the bromoketone turned dark almost at once and on prolonged standing became somewhat viscous. After two additional distillations, however, the product appeared relatively stable;*** b.p. 80-112° (11 mm.);**** yield 227 g. (59.5%); n_D^{24} 1.5131. A sample for analysis distilled at 96-98° (8 mm.).

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* This procedure is analogous to one used by Sullivan (7) to prepare 2-bromocyclohexanone. We found that a higher temperature than the 35-50° employed by Sullivan was necessary.

** Ref. 42. Bromination was effected with N-bromosuccinimide.

*** The analytical sample was kept in the dark for a period of two years with very little apparent decomposition.

**** Ref. 67, b.p. 103° (13 mm.).

Anal. Calcd. for $C_7H_{11}OBr$: C, 44.00; H, 5.80. Found: C, 44.11; H, 5.64.

2-Bromocycloheptanone Ethylene Ketal (III).--2-Bromocycloheptanone (227 g., 1.19 moles), 75 ml. (83.5 g., 1.35 moles) of ethylene glycol, 290 ml. of benzene, and 0.5 g. of p-toluenesulfonic acid were placed in a flask equipped with a Dean and Stark trap and a reflux condenser. The mixture was stirred with a magnetic stirrer and was refluxed until the calculated amount of water (21.4 ml.) had been removed by azeotropic distillation; the time required was about 6 hours. The benzene was removed and the residue was distilled; the fraction which boiled at 80-115° (1.7 mm.)* was collected. The crude ketal (III) weighed 255 g. (91.0%). A sample for analysis boiled at 87-88° (0.8 mm.).

Anal. Calcd. for $C_9H_{15}O_2Br$: C, 45.97; H, 6.43. Found: C, 45.92; H, 6.33.

2-Cycloheptenone Ethylene Ketal (IV).--2-Bromocycloheptanone ethylene ketal (255 g., 1.08 moles) was added, dropwise, over a two-hour period to a refluxing solution of 302 g. (5.40 moles) of potassium hydroxide in 700 ml. of absolute ethanol. The mixture was stirred well during the addition, and was then refluxed and stirred for 7 hours. The potassium bromide which precipitated during the reaction was filtered and washed several times with ether. The filtrate and the ether washings were combined, and the solvents were removed under reduced pressure. Some external heat was

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* Ref. 42, b.p. 76-86° (0.05 mm.).

supplied in order to maintain the temperature of the mixture at approximately room temperature. Water was added to the residue to dissolve the precipitated salts, and the mixture was extracted with ether. The extract was washed with a saturated salt solution, and dried over magnesium sulfate. After the ether had been removed, the product was distilled; b.p. 82-92° (10 mm.);* yield 142 g. (85.5%). A sample for analysis distilled at 93-94° (16 mm.).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.27.

2-Cycloheptenone (Tropilene)(V).--A solution of 154 g. (1.0 mole) of 2-cycloheptenone ethylene ketal, 2 liters of acetone (reagent grade), and 0.2 g. of p-toluenesulfonic acid was refluxed for 8.5 hours. The solvent was removed in vacuo, and the residue was distilled; b.p. 62-72° (6 mm.);** yield 104 g. (94.6%).

3-[N-Methyl-N-(β-dimethylaminoethyl)]aminocycloheptanone (VI).--Cycloheptenone (V)(22 g., 0.2 mole) was added to a solution of 30 g. (0.3 mole) of N,N',N'-trimethylethylene-diamine*** in 90 ml. of water cooled to 0°. The mixture was placed in a pressure bottle in a refrigerator for 18 hours, and then was extracted with ether. The ether extracts were dried, the ether removed and the residue distilled; b.p. 155-162° (13 mm.); yield 14.5 g. (34%). A sample for analysis distilled at 162-163° (17 mm.).

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* Ref. 42, b.p. 87-91° (10 mm.).
** Ref. 42, b.p. 72-82° (10 mm.).
Ref. 68, b.p. 181-182°
*** Prepared by the method of Sullivan.(7).

Anal. Calcd. for $C_{12}H_{24}ON_2$: C, 67.87; H, 11.39. Found: C, 67.95; H, 11.27.

All attempts to prepare salts of this compound were unsuccessful. Both the hydrochloride and the hydrobromide were too hygroscopic to be characterized. An attempt to prepare the picrate resulted in a breakdown of the aminoketone, giving the dipicrate of N,N,N'-trimethylethylenediamine; m.p. 196-197° with decomposition.

Anal. Calcd. for $C_{24}H_{30}O_{15}N_8$: C, 42.99; H, 4.51. (Picrate of aminoketone).

Calcd. for $C_{17}H_{20}O_{14}N_8$: C, 36.43; H, 3.60. (Picrate of amine).

Found: C, 36.52, 36.64; H, 3.71, 3.55.

3-[N-Methyl-N-(β-dimethylaminoethyl)]aminocycloheptanol (VII) Diacid Maleate.--3-[N-Methyl-N-(β-dimethylaminoethyl)]-aminocycloheptanone (VI)(14.5 g., 0.0684 mole), dissolved in 75 ml. of absolute ethanol, was hydrogenated for 18 hours under an initial pressure of 51.8 p.s.i. using 0.2 g. of platinum oxide catalyst. Slightly more than the theoretical amount (5.9 p.s.i.) of hydrogen was taken up, possibly due to some breakdown of the product. The solution was filtered, the ethanol was evaporated, and the residue distilled; b.p. 170-185° (12 mm.); yield 4.0 g. (27%). A considerable amount of lower boiling material was obtained.

A diacid maleate was prepared in ether, and after recrystallization from ethanol-ether it melted 142-144°.

Anal. Calcd. for $C_{20}H_{34}O_9N_2$: C, 53.80; H, 7.67. Found: C, 53.78; H, 7.76.

The Dihydrobromide of the Benzilate of 3-[N-Methyl-N-(β-dimethylaminoethyl)]aminocycloheptanol (VIII).*--3-[N-Methyl-N-(β-dimethylaminoethyl)]aminocycloheptanol (VII) (4.0 g., 0.0187 mole), 4.5 g. (0.0187 mole) of methyl benzilate obtained by the procedure of Acree (70), 0.5 g. of sodium methylate, and 50 ml. of petroleum ether (b.p. 90-100°) were combined and the mixture was refluxed for 6 hours, collecting the methanol formed in the reaction in a Dean and Stark trap. Only about one-fifth of the theoretical amount of methanol was collected. The solvent was evaporated, water was added, and the oily layer was extracted into ether. The ether solution was dried, the ether was evaporated, and the remaining oil was dissolved in anhydrous ether. One-half of this solution was placed in a pressure bottle for 15 hours with excess methyl bromide. The light yellow precipitate was filtered but was very hygroscopic and could not be recrystallized.

The remaining half of the ethereal solution was treated with hydrogen bromide. The white precipitate was filtered and recrystallized from ethanol-methanol-ether; m.p. 210-210.5° with decomposition; yield 1 g. (9%).

Anal. Calcd. for $C_{26}H_{38}O_3N_2Br_2$: C, 53.26; H, 6.53; Br, 27.25. Found: C, 52.98; H, 6.51; Br, 27.27.

3-Dimethylaminocycloheptanone (IX).--2-Cycloheptenone (22.0 g., 0.2 mole) was cooled to 0-5° in a 500 ml. pressure bottle, and 60 ml. (54.0 g., 0.3 mole) of 25% aqueous dimethylamine, which had been cooled to 0-5°, was added with swirling.

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* Prepared by a general method described by Feldkamp.(69)

The bottle was sealed and cooled in an ice-bath for a few minutes, since heat was evolved in the reaction. After a short time, the mixture became homogeneous and was placed in a refrigerator for 18 hours. The pale yellow solution was saturated with sodium chloride and was extracted with ether. The extract was dried with magnesium sulfate. The ether was removed, and upon distillation of the residue a colorless product was obtained; b.p. 104-114° (13 mm.);* yield 26.1 g. (84%). The boiling point upon redistillation was 115-117° (17 mm.).

Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 70.34; H, 11.21.

A hydrobromide was prepared by treating an ethereal solution of 17.9 g. of IX with dry hydrogen bromide. The precipitated hydrobromide weighed 15.4 g. (69%); m.p. 142° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_9H_{18}ONBr$: C, 45.77; H, 7.68; Br, 33.84. Found: C, 45.77; H, 7.58; Br, 33.75.

3-Dimethylamino-7(?)-bromocycloheptanone Hydrobromide (X).--3-Dimethylaminocycloheptanone hydrobromide (IX.HBr) (24 g., 0.10 mole) was dissolved in chloroform, and the solution was added, dropwise, to a cold (0°) stirred suspension of 20.6 g. (0.12 mole) of N-bromosuccinimide in 100 ml. of chloroform. When the addition was completed, stirring was continued, and the mixture was allowed to warm to room temperature. The mixture was evaporated under reduced pressure to about one-half of its original volume and was then filtered

* Ref. 46, b.p. 198-205°.

to remove 6.6 g. of crystalline succinimide. The evaporation was continued until a thick oil remained, whereupon ethanol was added to effect crystallization. The crude brominated product was recrystallized from isopropyl alcohol; m.p. 153-154° with decomposition; yield 5.1 g. (16%).

Anal. Calcd. for $C_9H_{17}ONBr_2$: C, 34.31; H, 5.44; Br^-, 25.37. Found: C, 34.43; H, 5.57; Br^-, 25.27.

3-Dimethylaminocycloheptanol (XI) Hydrochloride.--3-Dimethylaminocycloheptanone (15.5 g., 0.1 mole), dissolved in 100 ml. of absolute ethanol, was reduced at room temperature using 0.2 g. of platinum oxide catalyst and an initial pressure of 51.0 p.s.i. After 4 hours, the theoretical amount of hydrogen (8.6 p.s.i.) had been taken up. The solution was filtered to remove the catalyst, the solvent was removed, and the crude product was distilled; b.p. 130-135° (11 mm.); yield 8.3 g. (52.8%).

A hydrochloride was prepared in ether and was recrystallized from isopropyl alcohol-isopropyl ether; m.p. 158-160°.

Anal. Calcd. for $C_9H_{20}ONCl$: C, 55.80; H, 10.41. Found: C, 55.95; H, 10.38.

3-Dimethylaminocycloheptyl Benzilate (XII) Hydrochloride and Methobromide.--The benzilate of 3-dimethylaminocycloheptanol was prepared according to the general procedure (page 55), using 5.0 g. (0.0318 mole) of the amino alcohol and 7.7 g. (0.0318 mole) of methyl benzilate. The crude product was obtained as an oil, which solidified after some time. The crude solid melted at 85-95°. About one-half of the crude

solid was dissolved in anhydrous ether and the hydrochloride was precipitated with hydrogen chloride. After recrystallization from ethanol-ether the salt (XII.HCl) melted at 201-202° with decomposition; yield 3.2 g. (about 50% from the amino alcohol).

Anal. Calcd. for $C_{23}H_{30}O_3NCl$: C, 68.38; H, 7.49; Cl, 8.78. Found: C, 68.10; H, 7.53; Cl, 8.74.

The other half of the crude ester (XII) was dissolved in ether, placed in a pressure bottle, and the solution cooled to 0°. Excess liquid methyl bromide (about 6 ml.) was added, and the bottle was sealed and allowed to stand for 24 hours at room temperature. The precipitated salt was filtered and recrystallized several times from ethanol-ether; m.p. 201-202° with decomposition; yield 2.4 g. (about 33% from the amino alcohol).

Anal. Calcd. for $C_{24}H_{32}O_3NBr$: C, 62.34; H, 6.97; Br, 17.28. Found: C, 62.06; H, 7.16; Br, 17.13.

2-Dimethylaminomethylcycloheptanone (XIII) Hydrobromide and Acid Maleate.--Cycloheptanone (56 g., 0.5 mole), 90 g. (0.5 mole) of 25% aqueous dimethylamine, and 40.5 g. (0.5 mole) of 37% formalin solution were combined in a flask equipped with reflux condenser. The solution was cleared by the addition of ethanol and was refluxed for 3 hours on a steam-bath. After cooling, the solution was acidified (solution A) and was extracted with ether. The ether extracts were dried over magnesium sulfate. The ether was removed and the unreacted cycloheptanone was distilled; b.p. 70-78°

(15 mm.); weight 14 g. (25% recovery).

The aqueous acidic solution (A) was made basic and was extracted with ether. The ether extracts were dried with magnesium sulfate. After removal of the ether, the residue was distilled; b.p. 115-125° (15 mm.); yield 40.2 g. (47.5%).

A hydrobromide was prepared by treating an ethereal solution of 25 g. of XIII with anhydrous hydrogen bromide. The hydrobromide was filtered and recrystallized from isopropyl alcohol; m.p. 156-157°; yield 30.1 g. (81.3%).

Anal. Calcd. for $C_{10}H_{20}ONBr$: C, 48.01; H, 8.06; Br, 31.94. Found: C, 47.72; H, 7.79; Br, 31.72.

A small amount of XIII in ethanol solution was treated with a saturated ethanol solution of maleic acid. The precipitated acid maleate was filtered and recrystallized from isopropyl alcohol; m.p. 101-102°.

Anal. Calcd. for $C_{14}H_{23}O_5N$: C, 58.93; H, 8.13. Found: C, 58.79; H, 7.97.

The hydrochloride of XIII was prepared by adding anhydrous hydrogen chloride to an ethereal solution of 40.8 g. of XIII. The precipitated hydrochloride was filtered and recrystallized from isopropyl alcohol-isopropyl ether; m.p. 131-132°,* yield 33.5 g. (67.5%).

2,7-Bis(dimethylaminomethyl)cycloheptanone Diacid Maleate and Dihydrobromide(?).--The residue from the distillation of XIII contained about 10 g. of liquid boiling 145-155° (15 mm.) with some decomposition. A small amount of this liquid was

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* Ref. 7, m.p. 125-126°.
Ref. 52, m.p. 127°.

dissolved in ethanol, and a saturated ethanol solution of maleic acid was added to precipitate the acid maleate salt. After two recrystallizations from isopropyl alcohol, it melted at 110.5-111°. A good analysis for the diacid maleate of this compound could not be obtained.

Anal. Calcd. for $C_{21}H_{34}O_9N_2$: C, 55.01; H, 7.47; N, 6.11. Found: C, 59.54; H, 7.57; N, 5.29.

A dihydrobromide was prepared by dissolving a small amount of the distillate in ether and introducing dry hydrogen bromide. The precipitated dihydrobromide was recrystallized from isopropyl alcohol-ethanol; m.p. 170-170.5°.

Anal. Calcd. for $C_{13}H_{28}ON_2Br_2$: C, 40.22; H, 7.27; Br, 41.17. Found: C, 39.74; H, 7.09; Br, 42.76.

2-Dimethylaminomethylcycloheptanol (XIV) Hydrochloride.--2-Dimethylaminomethylcycloheptanone (XIII) hydrochloride (10.3 g., 0.05 mole), dissolved in 100 ml. of absolute ethanol, was hydrogenated at 60-70° for 16 hours under an initial pressure of 49 p.s.i. using 0.2 g. of platinum oxide catalyst. During the hydrogenation the mixture took up only about one-half of the calculated amount of hydrogen. The addition of fresh catalyst and subsequent heating for 20 hours longer completed the uptake of hydrogen (calculated = 4.3 p.s.i.). After removal of the catalyst and evaporation of the ethanol, the crude product was recrystallized from isopropyl alcohol-isopropyl ether; m.p. 174-176°; yield 7.1 g. (68.3%).

Anal. Calcd. for $C_{10}H_{22}ONCl$: C, 57.81; H, 10.68. Found: C, 57.94; H, 10.57.

2-Dimethylaminomethylcycloheptyl Benzilate Hydrochloride (XV).--2-Dimethylaminomethylcycloheptanol (XIV) hydrochloride (5.0 g., 0.024 mole) was dissolved in water and the solution was made basic with dilute sodium hydroxide solution. The free amino alcohol was taken up in ether and the ether solution was dried with magnesium sulfate. The ether was removed and the crude free base (weight 4.1 g.) was transesterified according to the general procedure (page 55), using 5.8 g. (0.024 mole) of methyl benzilate. The crude product was obtained as an oil. This was dissolved in anhydrous ether and the hydrochloride was precipitated by the addition of hydrogen chloride to the ethereal solution. After three recrystallizations from ethanol-ether the product melted at 200-201° with decomposition; yield 3.0 g. (30%).

Anal. Calcd. for $C_{24}H_{32}O_3NCl$: C, 68.95; H, 7.72; Cl, 8.49. Found: C, 68.85; H, 7.56; Cl, 8.51.

2-Dimethylaminomethyl-7-bromocycloheptanone Hydrobromide (XVI).--A stirred solution of 50.0 g. (0.2 mole) of 2-dimethylaminomethylcycloheptanone hydrobromide in 100 ml. of glacial acetic acid was heated to the boiling point and was illuminated with a 100 watt bulb while 32 g. (0.2 mole) of bromine in 50 ml. of acetic acid was added, dropwise, over a period of 10-15 minutes. Hydrogen bromide was evolved during the addition, and the stirring and illumination were continued for 20-30 minutes after the addition was completed. The solution was allowed to cool, and 300 ml. of isopropyl ether was added. A dark oil separated and after stirring and scratching,

the oil crystallized into a finely divided brown solid. This was filtered, washed twice with isopropyl ether, dried, and recrystallized from isopropyl alcohol; m.p. 145.5-146° with decomposition; yield 54.2 g. (82.4%).

Anal. Calcd. for $C_{10}H_{19}ONBr_2$: C, 36.49; H, 5.82. Found: C, 36.17; H, 5.57.

7-Methyl-7-azabicyclo[4.2.1]nonan-9-one Methobromide (XVII).--7-Bromo-2-dimethylaminomethylcycloheptanone hydrobromide (XVI)(19.7 g., 0.06 mole) was dissolved in about 100 ml. of water and the solution was cooled to 0-5°. Ether was added and the mixture was stirred with a magnetic stirrer. Dilute sodium hydroxide solution was added until the aqueous layer was strongly basic. The ether layer was separated and the aqueous layer was extracted with two more portions of ether. The ether extracts were combined and dried with magnesium sulfate. The ether was evaporated under a jet of air and the residual oil was dissolved in 700 ml. of isopropyl alcohol. The solution was refluxed for 5.5 hours and the isopropyl alcohol was removed under reduced pressure. The solid residue was recrystallized from isopropyl alcohol; m.p. 224-224.5° with decomposition; yield 5.0 g. (33.6%).

Anal. Calcd. for $C_{10}H_{18}ONBr$: C, 48.40; H, 7.31; Br, 32.21. Found: C, 48.40; H, 7.14; Br, 32.05.

From a second crop there was obtained crystalline material which melted at 134-135°. An authentic sample of dimethylamine hydrobromide melts at 134-136°. An analysis indicated that this substance was not pure.

Anal. Calcd. for C_2H_8NBr: C, 19.06; H, 6.40. Found: C, 20.05; H, 6.37.

7-Methyl-7-azabicyclo[4.2.1]nonan-9-one (XVIII) Acid Maleate.--7-Methyl-7-azabicyclo[4.2.1]nonan-9-one methobromide (XVII)(7.4 g., 0.03 mole) was placed in a 10 ml. distilling flask the side arm of which was attached to a small water-cooled condenser and a small suction flask which served as a receiver. The system was evacuated to a pressure of 15 mm. and the distilling flask was heated for 45 minutes at 225-235° by means of a Woods' metal bath. The quaternary compound decomposed into methyl bromide which was evolved as white fumes, and the amino ketone (XVIII) which distilled as a light yellow oil. The oil was dissolved in anhydrous ether, the solution was filtered, the ether was removed, and the product distilled;* b.p. 107° (19 mm.); yield 2.9 g. (63%).

A small amount of the distillate was dissolved in ether and the acid maleate was precipitated. The white solid was recrystallized from isopropyl alcohol; m.p. 119-121°.

Anal. Calcd. for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.12. Found: C, 58.03; H, 7.41.

7-Methyl-7-azabicyclo[4.2.1]nonan-9-ol (XIX) Hydrochloride.--7-Methyl-7-azabicyclo[4.2.1]nonan-9-one (XVIII)(2.5 g., 0.0163 mole) was dissolved in 15 ml. of methanol and the solution was added, dropwise, to a stirred solution of 0.4 g. of

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* In a later run, of 0.04 mole, the yellow oil was not distilled at this point but was reduced directly with sodium borohydride. The reduction product was distilled; b.p. 124° (13 mm.); yield 2.8 g. (45% based on the quaternary compound).

sodium borohydride in 15 ml. of methanol, while the mixture was maintained at room temperature. The solution was stirred for one hour and 8 ml. of 10% sodium hydroxide solution was added. The solution was evaporated on a steam-bath to approximately one-half of its original volume, water was added and the solution was extracted with ether. The ether extract was dried over magnesium sulfate. The ether was removed and the residue was distilled; the colorless, very viscous oil boiled at 123-127° (18 mm.), yield 1.9 g. (76%).

A small amount of the distillate was dissolved in ether and the hydrochloride was precipitated with hydrogen chloride. The crude salt was recrystallized from isopropyl alcohol-isopropyl ether; m.p. 210-211° with decomposition.

Anal. Calcd. for $C_9H_{18}ONCl$: C, 56.39; H, 9.46. Found: C, 56.36; H, 9.44.

The infrared spectrum of this compound has a band at 3200 $cm.^{-1}$, indicating the presence of a hydroxyl group.

The Hydrochloride of the Benzilate of 7-Methyl-7-azabicyclo[4.2.1]nonan-9-ol (XX).--The benzilate of 7-methyl-7-azabicyclo[4.2.1]nonan-9-ol (XIX) was prepared according to the general procedure (page 55) using 2.8 g. (0.0181 mole) of the amino alcohol and 4.7 g. (0.0193 mole) of methyl benzilate. During the reflux period, two 0.3 g. portions of sodium methylate were added; additional methanol was formed after each addition. When the theoretical amount (0.7 ml.) of methanol had been obtained (5 hours), the petroleum ether was removed by means of a water aspirator. Water was added, and

the oily layer was extracted with ether. The ether extracts were dried and the ether removed. The resulting oil was dissolved in anhydrous ether and the hydrochloride was precipitated with hydrogen chloride. The crude salt was recrystallized from isopropyl alcohol; m.p. 221-223° with decomposition; yield 1.8 g. (25%).

Anal. Calcd. for $C_{23}H_{28}O_3NCl$: C, 68.73; H, 7.02; Cl, 8.82. Found: C, 68.98; H, 7.27; Cl, 8.93.

7-Methyl-7-azabicyclo[4.2.1]nonan-9-ol Methobromide (XXI).--7-Methyl-7-azabicyclo[4.2.1]nonan-9-one methobromide (XVII)(5.0 g., 0.02 mole) was dissolved in 75 ml. of absolute ethanol and was reduced using 0.05 g. of platinum oxide, an initial pressure of 46 p.s.i., and a temperature of 60-70°. After heating the solution for 18 hours, it was filtered, and the filtrate was evaporated to a thick oil which crystallized upon the addition of isopropyl ether. The crude solid was recrystallized from isopropyl alcohol; m.p. 221-223° with decomposition; yield 2.6 g. (52%).

Anal. Calcd. for $C_{10}H_{20}ONBr$: C, 48.01; H, 8.06. Found: C, 47.87; H, 7.97.

The infrared spectrum of this compound showed absorption in the hydroxyl region at about 3200 $cm.^{-1}$ and showed no carbonyl absorption.

2-Dimethylaminomethyl-7-bromocycloheptanol Hydrobromide (XXII), α and β Forms.--A solution of 32.9 g. (0.1 mole) of 2-dimethylamino-7-bromocycloheptanone hydrobromide (XVI) in 75 ml. of water was added, dropwise, to a solution of 4.2 g.

(0.11 mole) of sodium borohydride in 50 ml. of water. The mixture was stirred for 1 hour after the addition was completed, and was made basic with 10% sodium hydroxide solution. The oily layer was extracted with ether and the extracts were dried with magnesium sulfate. The ether was removed, and the residual oil (weight 18.1 g.) was dissolved in anhydrous ether. Hydrogen bromide was introduced, and the white gummy precipitate was recrystallized from isopropyl alcohol; m.p. 142-142.5° with decomposition (α-form); yield 10.0 g. (30.2%).

Anal. Calcd. for $C_{10}H_{21}ONBr_2$: C, 36.27; H, 6.40. Found: C, 36.33; H, 6.38.

From the filtrate was obtained a small amount of lower melting material which was recrystallized from isopropyl alcohol-isopropyl ether; m.p. 127.5-128°(β-form); yield 1.3 g. (3.4%).

Anal. Calcd. for $C_{10}H_{21}ONBr_2$: C, 36.27; H, 6.40. Found: C, 36.70; H, 6.32.

The infrared spectra of these two compounds are somewhat different, but both show the presence of a hydroxyl band and the absence of a carbonyl band.

2-Dimethylaminomethyl-7-bromocycloheptyl Diphenylacetate Hydrobromide (XXIII).--A small amount (about 0.1 g.) of 2-dimethylaminomethyl-7-bromocycloheptanol hydrobromide (XXII) (α-form) was heated with a small amount of diphenylacetyl chloride* at 140-145° for 30 minutes. Acidic fumes were evolved during the heating. The gummy reaction mixture was

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* Prepared by the procedure of Pierce et al. (71); m.p. 53-55°; yield 93.0%.

dissolved in isopropyl alcohol, and, upon standing, a white precipitate appeared. After recrystallization from methanol-ether, it melted at 191.5-192° with decomposition. The analysis indicated that the sample may not have been entirely pure.

Anal. Calcd. for $C_{24}H_{31}O_2NBr_2$: C, 54.87; H, 5.95. Found: C, 55.58; H, 5.92.

2,7-Bis(dimethylaminomethyl)cycloheptanone Dihydrochloride (XXIV).* --A mixture of 11.2 g. (0.10 mole) of cycloheptanone, 20.4 g. (0.25 mole) of dimethylamine hydrochloride, 9.0 g. (0.3 mole) of paraformaldehyde, and 40 ml. of glacial acetic acid was heated on a steam-bath for 2.5 hours. Most of the acetic acid was distilled under reduced pressure (0.5 hour) and the light yellow, viscous residue was dissolved in 35 ml. of isopropyl alcohol. Ether (50-60 ml.) was added until the mixture became cloudy. Crystallization was started by heating and scratching the sides of the flask with a stirring rod. The mixture was cooled in a refrigerator until precipitation was completed, and was then filtered; the material was washed with a 1:1 mixture of acetone-isopropyl alcohol, and then with ether. The product was recrystallized from ethanol-ether; m.p. 168-168.5°; yield 12.5 g. (42%).

Anal. Calcd. for $C_{13}H_{28}ON_2Cl_2$: C, 52.17; H, 9.43; N, 9.36; Cl, 23.69. Found: C, 52.16; H, 9.45; N, 9.51; Cl, 23.47.

2,7-Bis(dimethylaminomethyl)cycloheptanol (XXV) Dipicrate. --2,7-Bis(dimethylaminomethyl)cycloheptanone dihydrochloride

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* Prepared according to a general method developed in this laboratory by F. J. McCarty.

(9.5 g., 0.0317 mole), dissolved in 30 ml. of water, was added, dropwise, to a cold stirred solution of 2.0 g. (0.053 mole) of sodium borohydride in 30 ml. of water. The solution was stirred for one hour and then allowed to warm to room temperature. Ten per cent sodium hydroxide solution (50 ml.) was added and the resulting oily layer was taken up in ether. The aqueous layer was extracted once more with ether and the extracts were combined and dried over magnesium sulfate. The ether was removed and an oil* (6.4 g., 89% crude yield) was obtained.

A small amount of the oil was dissolved in ether, and an ethereal solution of picric acid was added. The yellow precipitate was filtered, and was recrystallized from ethanol-water; m.p. 214-214.5° with decomposition.

Anal. Calcd. for $C_{25}H_{34}O_{15}N_8$: C, 43.73; H, 4.99. Found: C, 43.92; H, 5.12.

The hydrochloride and the hydrobromide were prepared in ether, but were too hygroscopic to be characterized.

2,7-Bis(dimethylaminomethyl)cycloheptyl Benzilate Dihydrochloride (XXVI).--2,7-Bis(dimethylaminomethyl)cycloheptanol (3.4 g., 0.015 mole) was added, dropwise, with cooling and stirring to 5.3 g. (0.020 mole) of diphenylchloroacetyl chloride** which had been heated above its melting point. The mixture became very thick and after a half hour, water was added and the mixture was made strongly acidic with dilute

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* In another run the product was distilled; b.p. 151-157° (10 mm.); yield 78%.

** Obtained by the procedure of King and Holmes (56), m.p. 42-47°.

hydrochloric acid. The mixture was extracted with ether, the ether extract was discarded and the aqueous layer was made basic with 10% sodium hydroxide solution. The oily layer was taken up in ether, and the aqueous layer was extracted with ether. The extracts were combined and dried over magnesium sulfate. The solution was filtered and the dihydrochloride was precipitated and recrystallized from ethanol-methanol-ether; m.p. 189-191° with decomposition; yield 3.3 g. (43%).

Anal. Calcd. for $C_{27}H_{40}O_3N_2Cl_2$: C, 63.40; H, 7.88; N, 5.48; Cl, 13.86. Found: C, 63.09; H, 7.99; N, 5.36; Cl, 13.53.

2,7-Bis(dimethylaminomethyl)cycloheptyl Benzoate Dihydrochloride (XXVII).--To a small amount (about 0.1 g.) of the oil, obtained from the reduction of 2,7-bis(dimethylaminomethyl)cycloheptanone dihydrochloride, there was added a small amount of benzoyl chloride. Heat was evolved and a solid was obtained which was washed with ether and recrystallized from isopropyl alcohol-isopropyl ether; m.p. 228-229° with decomposition. This compound analyzed as a hydrate. The presence of water in the molecule was further indicated by an infrared spectrum which showed an absorption band in the hydroxyl region at 3480 $cm.^{-1}$.

Anal. Calcd. for $C_{20}H_{34}O_2N_2Cl_2.H_2O$: C, 56.74; H, 8.57. Found: C, 56.40; H, 8.78.

8-Methyl-8-azabicyclo[4.3.1]decan-10-one Hydrochloride (XXVIII).--A solution of 22.4 g. (0.20 mole) of cycloheptanone, 13.6 g. (0.20 mole) of methylamine hydrochloride,

60 ml. of glacial acetic acid, and 10 ml. of water was added, dropwise, during one hour to a stirred suspension of 18 g. (0.60 mole) of paraformaldehyde in 60 ml. of glacial acetic acid, which was heated on a steam-bath. Heating and stirring were continued for 1.5 hours after the addition was completed. The solution was concentrated under reduced pressure (water aspirator) until most of the acetic acid had been removed. The viscous, yellow residue was made basic with dilute sodium hydroxide solution and was then extracted with ether. The ether solution was extracted with dilute hydrochloric acid.* The aqueous acidic layer was made basic and was extracted with ether. The ether solution was dried, the ether was evaporated and the residue distilled; b.p. 115-130° (16 mm.).**

The distillate was dissolved in ether and the hydrochloride was precipitated with hydrogen chloride. The salt was filtered and was recrystallized from isopropyl alcohol; m.p. 209-210° with decomposition; yield 2.1 g. (5.2%).

Anal. Calcd. for $C_{10}H_{18}ONCl$: C, 58.96; H, 8.91; Cl, 17.40. Found: C, 58.89; H, 8.84; Cl, 17.04.

8-Methyl-8-azabicyclo[4.3.1]decan-10-ol (XXIX).--A solution of 3.0 g. (0.015 mole) of 8-methyl-8-azabicyclo[4.3.1]-decan-10-one hydrochloride (XXVIII) in 10 ml. of water was added, dropwise, to a cooled, stirred solution of 0.6 g. (0.015 mole) of sodium borohydride in 10 ml. of water. Methanol (10 ml.) was added and during one hour the mixture was

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* The ether solution at this point contained about 2 g. of neutral oils and it was discarded.

** Only about one-third of the oil distilled; the rest remained as a very viscous, yellow residue.

allowed to warm to room temperature. A solution of 10% sodium hydroxide (10 ml.) was added whereupon a white solid appeared on top of the water-methanol layer. After one hour, the mixture was filtered, and the solid was washed several times with water. The solid was dried; m.p. 76-78°; yield 2.2 g. (88%). After recrystallization of a small amount from methanol-water, the product melted 78-79°. The product was pure enough, without recrystallization, to be used in further reactions.

Anal. Calcd. for $C_{10}H_{19}ON$: C, 70.95; H, 11.32. Found: C, 70.81; H, 11.42.

The Hydrochloride of the Diphenylacetate of 8-Methyl-8-azabicyclo[4.3.1]decan-10-ol (XXX).--8-Methyl-8-azabicyclo-[4.3.1]decan-10-ol (XXIX)(0.3 g., 0.00177 mole) and 1.0 g. (0.0043 mole) of diphenylacetyl chloride* were combined and heated on a steam-bath for 15 minutes. Ether was added and the insoluble white precipitate was filtered and washed several times with ether. It was recrystallized from isopropyl alcohol-isopropyl ether; m.p. 199-200°; yield 0.6 g. (85%).

Anal. Calcd. for $C_{24}H_{30}O_2NCl$: C, 72.07; H, 7.56; Cl, 8.87. Found: C, 71.91; H, 7.76; Cl, 9.02.

A benzoate of XXIX was prepared by the above procedure with the use of benzoyl chloride but it appeared to be hygroscopic, and formed a hydrate; m.p. 210-213° with decomposition. The infrared spectrum of this compound showed absorption in the hydroxyl region at 3280 $cm.^{-1}$. This compound was not analyzed.

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* See footnote, page 66.

3-Cyanocycloheptanone (XXXI).--2-Cycloheptenone (55.0 g., 0.5 mole) dissolved in 250 ml. of methanol was cooled to 0°, and the solution was added, in one portion, to a cold solution (0°) of 49.0 g. (1.0 mole) of sodium cyanide, 150 ml. of water, and 5 drops of 15% potassium hydroxide* solution. The mixture was allowed to react for one hour, while the temperature was maintained at 0°. Concentrated hydrochloric acid was added until the reaction mixture became acidic, and it was then extracted with ether. After drying the extracts over magnesium sulfate, the ether was removed and the residue was distilled; b.p. 105-125° (0.8 mm.) with some decomposition; yield 39.8 g. (58%). Two further distillations produced a sample boiling at 95-97° (0.5 mm.) with some decomposition. A good analysis could not be obtained on this compound.

Anal. Calcd. for $C_8H_{11}ON$: C, 70.04; H, 8.08. Found: C, 69.46; H, 9.28.

A forerun was obtained from the distillation of XXXI which yielded 6.1 g. (11%) of unreacted cycloheptenone after redistillation.

3-Cyanocycloheptanone Ethylene Ketal (XXXII).--A mixture of 47.2 g.(0.344 mole) of 3-cyanocycloheptanone, 25 ml. (28 g., 0.44 mole) of ethylene glycol, 100 ml. of benzene, and 0.2 g. of p-toluenesulfonic acid was refluxed and stirred for 5.5 hours until the theoretical amount of water (6.2 ml.) had been collected in a Dean and Stark trap. The benzene was removed and the residue was distilled; b.p. 90-110° (0.5 mm.);

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* It is not certain if the catalytic amount of potassium hydroxide is necessary for this reaction.

yield 33.9 g.

A lower boiling fraction was obtained, which upon redistillation gave 9.2 g. of 2-cycloheptenone ethylene ketal (IV); b.p. 80-90° (7 mm.) and 3.3 g. of the cyano ketal (XXXII).

The total yield of XXXII was 37.2 g. (60%). A sample for analysis distilled at 89-94° (0.3 mm.). The analysis indicated that the sample was not entirely pure.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34. Found: C, 66.89; H, 8.75.

3-Aminomethylcycloheptanone Ethylene Ketal (XXXIII) and Hydrobromide.--A solution of 36.3 g. (0.20 mole) of 3-cyanocycloheptanone ethylene ketal (XXXII), dissolved in 90 ml. of ether, was added, dropwise, during 45 minutes to a stirred suspension of 11.4 g. (0.30 mole) of lithium aluminum hydride in 450 ml. of ether. An intermediate complex precipitated which, when stirred, formed a large ball. The ball was broken up with a stirring rod and more ether was added. The mixture was stirred for 6 hours without external heating and was then allowed to stand for 15 hours. Water (34 ml.) was added to hydrolyze the complex and the mixture was then stirred for 6 hours and allowed to stand for an additional 15 hours. The white precipitate was filtered and the ether was removed from the solution. The residual oil was distilled; it boiled from 100 to 135° (7 mm.). The yield of the crude amino ketal was 29.5 g. (80%). This was used without further purification in the Eschweiler-Clarke reaction. However, in another experiment, redistillation yielded a center cut, b.p.

113-118° (7 mm.), which was used for analysis.

Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34. Found: C, 64.53; H, 10.54.

A hydrobromide of the amino ketal (XXXIII) was prepared by adding dry hydrogen bromide to an ethereal solution of 5.0 g. of the amino ketal. The precipitated hydrobromide was filtered and recrystallized twice from ethanol-ether; m.p. 161-161.5°, yield 1.8 g. (25%).

Anal. Calcd. for $C_{10}H_{20}O_2NBr$: C, 45.12; H, 7.57; Br, 30.02. Found: C, 44.81; H, 7.29; Br, 30.33.

The Eschweiler-Clarke Reaction with the Use of 3-Aminomethylcycloheptanone Ethylene Ketal. 3-Dimethylaminomethylcycloheptanol (XXXIV) and Hydrobromide.--3-Aminomethylcycloheptanone ethylene ketal (18.6 g., 0.1 mole) was added to 25.6 g. (0.5 mole) of 90% formic acid which had been cooled to 0°. Formalin (20.6 g., 0.24 mole of formaldehyde) was added and the solution was heated for 9 hours on a steam-bath. A solution of 11 ml. of concentrated hydrochloric acid in 11 ml. of water was added, and the solution was evaporated to a thick oil on a steam-bath under a jet of air. Dilute sodium hydroxide solution was added to the oil and the oily undissolved material was extracted with ether. The ether solution was dried, the ether was removed, and the residue was distilled; b.p. 100-115° (7 mm.);* weight 11.3 g.

Five grams of this oil was dissolved in ether and the hydrobromide was precipitated. Repeated recrystallizations

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* This distillate was not pure. It apparently contained 3-dimethylaminomethylcycloheptanol (XXXIV) and other material.

from ethanol-ether gave about 1 g. of a pure compound, m.p. 178-179°. Analysis showed that this material was the hydrobromide of XXXIV.

Anal. Calcd. for $C_{10}H_{22}ONBr$: C, 47.62; H, 8.79; Br, 31.69. Found: C, 47.69; H, 8.71; Br, 31.78, 31.67.

Some of the hydrobromide was converted to the free base, and the base (XXXIV) was distilled; b.p. 90-91° (7 mm.).

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36. Found: C, 69.92; H, 12.09.

The infrared spectrum of the free base shows the absence of a band in the carbonyl region.

Attempted Preparation of 6-Methyl-6-azabicyclo[3.2.2]-nonan-9-one Methobromide (XXXVI).--The distillate from the Eschweiler-Clarke reaction (5.1 g.) was dissolved in 75 ml. of carbon tetrachloride and the solution was cooled to 0°. N-Bromosuccinimide (5.3 g.) was added slowly during 45 minutes, while the cold mixture was stirred. When the addition was completed, the mixture was allowed to warm to room temperature very slowly, and stirring was continued for six hours. The carbon tetrachloride solution was filtered, and the filtrate was heated for an hour on a steam-bath. A small amount of dark-red oil was formed, which crystallized after standing at room temperature for several hours. The solid was filtered and recrystallized several times from acetone-isopropyl alcohol; m.p. 181-181.5°; wt. about 0.2 g.

Anal. Calcd. for $C_{10}H_{18}ONBr$ (XXXVI): C, 48.39; H, 7.31; N, 5.65; Br, 32.20. Found: C, 48.32; H, 7.34; N, 5.85;

Br, 32.52.

Although the analytical data for this compound corresponded with that calculated for XXXVI, the infrared spectrum showed the presence of a hydroxyl band and the absence of a carbonyl band.

Compounds Submitted for Pharmacological Evaluation

	RAC code No.
2-Dimethylaminomethylcycloheptyl Benzilate Hydrochloride	243
3-Dimethylaminocycloheptyl Benzilate Hydrochloride	245
3-Dimethylaminocycloheptyl Benzilate Methobromide	247
The Hydrochloride of the Benzilate of 7-Methyl-7-azabicyclo[4.2.1]nonan-9-ol	251
2,7-Bis(dimethylaminomethyl)cycloheptyl Benzilate Dihydrochloride	256
The Hydrochloride of the Diphenylacetate of 8-Methyl-8-azabicyclo[4.3.1]decan-10-ol	260
The Dihydrobromide of the Benzilate of 3-[N-Methyl-N-(β-dimethylaminoethyl)]aminocycloheptanol	261

SUMMARY

Salts of two azabicyclic ketones, 7-methyl-7-azabicyclo-[4.2.1]nonan-9-one (I) and 8-methyl-8-azabicyclo[4.3.1]decan-10-one (II), were obtained during this investigation. Both ketones were reduced with sodium borohydride to the corresponding secondary alcohols. The alcohol obtained from I was converted into a benzilate, that prepared from II into a diphenylacetate.

The synthesis of I is indicated by the following scheme: cycloheptanone $\xrightarrow[HN(CH_3)_2]{CH_2O}$ 2-dimethylaminomethylcycloheptanone (III) $\xrightarrow[(2)\ Br_2]{(1)\ HBr}$ 2-dimethylaminomethyl-7-bromocycloheptanone hydrobromide (IV) $\xrightarrow[(2)\ heat]{(1)\ NaOH}$ 7-methyl-7-azabicyclo[4.2.1]nonan-9-one methobromide (V) $\xrightarrow{heat}$ 7-methyl-7-azabicyclo[4.2.1]nonan-9-one (I).

The azabicyclic ketone II was prepared in the following manner: cycloheptanone $\xrightarrow[\text{excess } CH_2O]{CH_3NH_2.HCl}$ 8-methyl-8-azabicyclo-[4.3.1]decan-10-one hydrochloride (II).

Unsuccessful attempts were made to obtain 2,5-dimethyl-2,5-diazabicyclo[4.3.2]undecan-10-one monomethobromide by treatment of 3-[N-methyl-N-(β-dimethylaminoethyl)]aminocycloheptanone (VI) with N-bromosuccinimide followed by attempted cyclization. After the bromination procedure had been carried out the material obtained, presumably the 7-bromo derivative, was subjected to an elevated temperature whereupon cyclization was expected to take place. Only an oil of an unknown nature

was obtained.

In order to obtain VI, the following series of reactions was carried out: cycloheptanone $\xrightarrow{Br_2}$ 2-bromocycloheptanone $\xrightarrow[p\text{-}CH_3C_6H_4SO_3H]{HOCH_2CH_2OH}$ 2-bromocycloheptanone ethylene ketal $\xrightarrow{KOH}$ 2-cycloheptenone ethylene ketal $\xrightarrow[p\text{-}CH_3C_6H_4SO_3H]{CH_3COCH_3}$ 2-cycloheptenone $\xrightarrow{(CH_3)_2NCH_2CH_2NHCH_3}$ 3-[N-methyl-N-(β-dimethylaminoethyl)]aminocycloheptanone (VI).

Also unsuccessful were efforts to synthesize 8-methyl-8-azabicyclo[3.2.1]octan-6-one methobromide from 3-dimethylamino-7-bromocycloheptanone (VII). The manner in which VII was obtained is illustrated by the following scheme: cycloheptenone $\xrightarrow{(CH_3)_2NH}$ 3-dimethylaminocycloheptanone (VIII) $\xrightarrow[(2)\ NBS]{(1)\ HBr}$ 3-dimethylamino-7-bromocycloheptanone (VII).

It was expected that 6-methyl-6-azabicyclo[3.2.2]nonan-9-one methobromide might be obtained by the following series of reactions: 2-cycloheptenone $\xrightarrow[(2)\ H^+]{(1)\ NaCN}$ 3-cyanocycloheptanone $\xrightarrow[p\text{-}CH_3C_6H_4SO_3H]{HOCH_2CH_2OH}$ 3-cyanocycloheptanone ethylene ketal $\xrightarrow{LiAlH_4}$ 3-aminomethylcycloheptanone ethylene ketal (IX) $\xrightarrow[HCOOH]{CH_2O}$ 3-dimethylaminomethylcycloheptanone (X) $\xrightarrow[(2)\ heat]{(1)\ NBS}$ 6-methyl-6-azabicyclo[3.2.2]nonan-9-one methobromide (XI). Interaction of IX with formaldehyde and formic acid yielded a mixture of products which included 3-dimethylaminomethylcycloheptanol and possibly the desired ketone X. The mixture was treated with N-bromosuccinimide in the hope that the 7-bromo derivative of X would be formed. After bromination

and subjection of the crude reaction mixture to heat, a product was obtained which, according to a complete analysis, was the ketone XI. However, its infrared spectrum showed absorption in the hydroxyl and not in the carbonyl region.

The ketones III, V, VI and VIII were reduced with hydrogen and platinum oxide to the corresponding secondary alcohols. The alcohols prepared from III, VI and VIII were converted into benzilates. Esters of the alcohol prepared from V could not be obtained. The bromo ketone IV was reduced with sodium borohydride to the bromo alcohol, which was converted into a diphenylacetate.

Attempts to form the bicyclic ketone II by the cyclization of 2,7-bis(dimethylaminomethyl)cycloheptanone dihydrochloride (XII) were unsuccessful. Compound XII was prepared from cycloheptanone by the action of dimethylamine hydrochloride and paraformaldehyde. The ketone XII was reduced with sodium borohydride to the corresponding alcohol, and both a benzilate and benzoate were obtained.

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