THE USE OF MORPHOLINE FOR THE PRODUCTION OF "MANNICH" BASES.

By Rita H. Harradence, M.Sc.,
and Francis Lions, B.Sc., Ph.D.

(Manuscript received, November 23, 1938. Read, December 7, 1938.)

Mannich and his co-workers, in a long series of researches (published mainly in the Archiv. der Pharmazie and the Berichte der deutschen chemischen Gesellschaft during the last two decades) have closely studied the reactions between ketones containing a reactive methylene group, formaldehyde and ammonium chloride, primary aliphatic amine hydrochlorides or secondary aliphatic amine hydrochlorides. Much careful work has shown that, whereas ammonium chloride and primary aliphatic amine hydrochlorides usually give rise to several different reaction products, secondary aliphatic amine hydrochlorides, on the other hand, usually react with formaldehyde and reactive keto-methylene compounds in a straightforward way, and that the reactions can be expressed by the general equation

\[
\begin{align*}
R - \text{CO} & + \text{R'} - \text{CH}_2 & \xrightarrow{\text{HCl-NH}} & \text{R''} - \text{CO} \\
\text{R''} - \text{CH}_2 - \text{CH}_2 & & \xrightarrow{\text{R'''}-\text{HCl}} & \text{R'''} - \text{CH}_2 - \text{CH}_2 \text{N} \text{HCl}
\end{align*}
\]

The resultant ketonic tertiary base hydrochlorides are readily obtainable in excellent yields, and usually afford the bases themselves in the pure condition without difficulty, although rigid purification of these is sometimes not easy. The general chemical character of these "Mannich" bases has been fairly completely elucidated, and their great usefulness as synthetic reagents for certain purposes is now well established. The present paper describes the use of the saturated heterocyclic base morpholine in the preparation of "Mannich" ketonic tertiary bases. Morpholine has recently become one of the cheapest and most accessible tertiary bases, and has the power of conferring high crystallising power on its

When acetone is reacted in alcoholic solution with morpholine hydrochloride and paraformaldehyde it readily forms the crystalline 1-morpholinobutan-3-one hydrochloride, and from this salt the base (I) is easily obtained as a colourless oil with alkali.

\[
\begin{align*}
\text{CH}_3\text{CO-CH}_2\text{CH}_2\text{N} & \text{CH}_2\text{-CH}_2\text{O} \\
\text{I.} \\
\text{CH}_3\text{CHOH-CH}_2\text{CH}_2\text{N} & \text{CH}_2\text{-CH}_2\text{O} \\
\text{II.}
\end{align*}
\]

It can be distilled in vacuo, but some decomposition occurs during the distillation. When (I) is reduced with aluminium amalgam and moist ether it affords 1-morpholinobutan-3-ol (II), an oily amino alcohol. Because the esters of amino alcohols are frequently local anaesthetics, it was deemed of value to prepare the benzoate and also the p-nitrobenzoate of (II).

The observation of du Feu, McQuillin, and Robinson (J.C.S., 1937, 53) that the quaternary halides derived from Mannich bases with alkyl halides will react readily with the sodio derivatives of such substances as β-ketonic esters, suggested that a useful method for the synthesis of dihydroresorcyclic ester (IV) would consist in the condensation of the methiodide of (I) with sodio diethyl malonate in presence of sodium ethoxide, according to the scheme:

\[
\begin{align*}
\text{CH}_3 & \text{CH}_2 \text{CH}_2 \text{N} \text{CH}_2 \text{CH}_2 \text{O} \\
\text{III.} \\
\text{CH}_3 \text{CH}_2 \text{CH}_2 \text{N} \text{CH}_2 \text{CH}_2 \text{O} & \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{O} \\
\text{IV.}
\end{align*}
\]

The methiodide of (I) condensed readily with sodio malonic ester to ethyl α-carbethoxy-δ-keto caproate, but the further cyclisation to (IV) was not observed to occur. III was characterised by formation of a semicarbazone and dinitrophenylhydrazone, and by its hydrolysis to the
Condensation of cyclohexanone and 4-methylcyclohexanone with morpholine hydrochloride and aqueous formaldehyde solution to the hydrochlorides of the bases (V) and (VI) was readily effected by a method similar to that described by Mannich and Braun (Berichte, 1920, 53, 1875). Each of these ketonic bases could be reduced to the corresponding alcohol by application of Poudorff's method — treatment with aluminium isopropylate in absolute isopropyl alcohol. Both products were oily, being probably mixtures of stereoisomers, but from each crystalline hydrochlorides of the benzoic and p-nitrobenzoic esters could be readily prepared.

2-Methylcyclohexanone was induced to react with morpholine hydrochloride and paraformaldehyde by heating at 110° for two hours in cyclohexanol. The resulting hydrochloride of 2-methyl-6-morpholinomethylcyclohexanone (VII) was a colourless crystalline hygroscopic substance. The free base could be distilled undecomposed.

* After the work described in this paper had been completed there appeared a paper by Mannich and Fourneau in the Berichte der deutschen chemischen Gesellschaft in which were described almost exactly similar experiments, starting, however, from the free base dimethylamino-butane and malonic ester, and cyclisation to dihydroresorcinol was effected with sodium ethoxide under mild conditions (Ber., 1938, 71, 2090).
in vacuo, and crystallised in needles melting at 50°. It could be readily reduced by Ponndorff’s method to the corresponding alcohol, from which the hydrochloride of the p-nitrobenzoic ester could be obtained crystalline.

When cyclopentanone was heated in alcoholic solution with morpholine hydrochloride and paraformaldehyde the main product of the reaction was the dihydrochloride of 2:5-dimorpholinomethylcyclopentanone (VIII) together with a small amount of the hydrochloride of 2-morpholinomethylcyclopentanone (IX).

![Chemical structure VIII and IX](image)

The hydrochloride of (IX) was the main product of reaction when cyclopentanone was reacted with morpholine hydrochloride and aqueous formaldehyde solution. Attempts to reduce (IX) to the corresponding alcohol by Ponndorff’s method proved abortive.

The formation of “Mannich” ketonic bases from aryl alkyl ketones such as acetophenone has been described by Mannich and Lammering (Berichte, 1922, 55, 3510). We have found that under similar conditions, acetophenone, acetoacetronone, and α-acetothienone react readily with morpholine hydrochloride and paraformaldehyde to yield the hydrochlorides of the bases (X), (XI), and (XII) respectively.

![Chemical structures X and XI](image)

Each of these bases reacts readily with phenylhydrazine to give a crystalline pyrazoline of the type described previously by Mannich and Bauroth (Berichte, 1924, 57, 1108) and by Jacob and Madinaveitia (J.C.S., 1937,
Addition of alcoholic picric acid to an alcoholic solution of this hydrochloride led to precipitation of a yellow oily picrate which was induced to crystallise by long standing in contact with alcohol, from which solvent it was then recrystallised. It formed yellow prisms melting at 114°. Found: N=14.1%; calculated for C14H18O9N4, N=14.5%.

The free base, 1-morpholinobutan-3-one was prepared from the crude hydrochloride after removal of excess acetone by making strongly alkaline and extracting with ether. After drying and removal of the solvent, the oily base was distilled in vacuo. It came over as a colourless oil (38 g.) with a strong "amine" odour at 116°/20 mm. Considerable decomposition occurred during the distillation and a pale yellow residual resin was left in the flask. The base itself was not analysed.

1-Morpholinobutan-3-one (I).

Acetone (60 c.c.), morpholine hydrochloride (42 g.), paraformaldehyde (16.8 g.) and absolute alcohol (10 ml.) were heated together under reflux for six hours. The solid gradually disappeared and eventually a homogeneous solution was obtained. On shaking this set to a solid crystalline mass whilst still hot. The mass was cooled, and the crystals freed from excess acetone on a porous tile. Recrystallised from absolute alcohol, this 1-morpholinobutan-3-one hydrochloride was obtained in pearly white plates which melted at 149°.

Found: C=49.0, H=8.6, N=7.3%; calculated for C8H16O2NCl, C=49.3, H=8.3, N=7.2%.

Finally, it should be noted that several of the substances described in the experimental section show definite local anaesthetic action. Of these, the most powerful effect was observed with the hydrochloride of the benzoate of morpholinobutanol. The hydrochloride of the p-nitrobenzoate of the same base was also definitely active though not so powerfully. A fairly strong action was also observed with the hydrochloride of β-morphinoethylphenyl ketone. The hydrochlorides of the benzoates and p-nitrobenzoates of morpholinomethylcyelohexanol and the morphinomethylmethylecylolhexanols showed only mild local anaesthetic action.

**EXPERIMENTAL.**

1-Morpholinobutan-3-one (I).

Acetone (60 c.c.), morpholine hydrochloride (42 g.), paraformaldehyde (16.8 g.) and absolute alcohol (10 ml.) were heated together under reflux for six hours. The solid gradually disappeared and eventually a homogeneous solution was obtained. On shaking this set to a solid crystalline mass whilst still hot. The mass was cooled, and the crystals freed from excess acetone on a porous tile. Recrystallised from absolute alcohol, this 1-morpholinobutan-3-one hydrochloride was obtained in pearly white plates which melted at 149°.

Found: C=49.0, H=8.6, N=7.3%; calculated for C8H16O2NCl, C=49.3, H=8.3, N=7.2%.
Addition of alcoholic picric acid to an alcoholic solution of this hydrochloride led to precipitation of a yellow oily picrate which was induced to crystallise by long standing in contact with alcohol, from which solvent it was then recrystallised. It formed yellow prisms melting at 114°.

Found: N = 14.1%; calculated for \( \text{C}_{14}\text{H}_{18}\text{O}_5\text{N}_4 \), N = 14.5%.

The free base, 1-morpholinobutan-3-one was prepared from the crude hydrochloride after removal of excess acetone by making strongly alkaline and extracting with ether. After drying and removal of the solvent, the oily base was distilled in vacuo. It came over as a colourless oil (38 g.) with a strong "amine" odour at 116°/20 mm. Considerable decomposition occurred during the distillation and a pale yellow residual resin was left in the flask. The base itself was not analysed.

**I-Morpholinobutan-3-ol (II).**

A solution of 1-morpholinobutan-3-one (37 g.) in ether (500 ml.) was treated with aluminium turnings (52 g.) previously activated by immersion in 4% mercuric chloride solution, and then heated under reflux. Water (50 ml.) was added gradually to the boiling liquid over a period of five hours. Eventually the aluminium hydroxide was filtered off, well washed with ether, and these washings combined with the ethereal solution, which was then dried and the solvent removed. The residual oil was distilled in vacuo, coming over as a colourless oil (10 g.) at, 95-100°/2.5 mm. The poor yield is probably attributable to adsorption on the aluminium hydroxide and imperfect elution therefrom. The base was not analysed as such. Treatment of its alcoholic solution with alcoholic picric acid led to separation of an oily picrate, which crystallised after standing for a day. It was very soluble in alcohol, and was recrystallised from water, being thus obtained in yellow needles melting at 142-144°.

Found: N = 14.2%; calculated for \( \text{C}_{14}\text{H}_{20}\text{O}_5\text{N}_4 \), N = 14.4%.

**1-Morpholo-3-benzoyloxybutane Hydrochloride.**

To a solution of (II) (3 g.) in chloroform (5 ml.) was added a solution of benzoylchloride (3 g.) in chloroform (5 ml.). Evolution of heat occurred, and the colour deepened. After standing overnight the solvent was removed. The viscous residue crystallised on standing,
or, better, on rubbing with ether. Recrystallised twice from acetone it formed colourless prisms melting at 152°.

Found: N = 4·9%; calculated for C₁₅H₂₂O₃NCl, N = 4·7%.

The picrate, recrystallised from alcohol, formed bright yellow needles melting at 147°.

Found: N = 11·4%; calculated for C₂₁H₂₄O₁₀N₄, N = 11·4%.

1-Morpholino-3-p-Nitrobenzoyloxybutane Hydrochloride.

To a solution of (II) (3 g.) in chloroform (5 ml.) was added a solution of p-nitrobenzoylchloride (3·9 g.) in the same solvent (7 ml.). After standing overnight the solvent was removed and the residue rubbed with ether. It soon solidified, and was recrystallised twice from acetone, being thus obtained in very faintly yellow prisms melting at 199°.

Found: N = 8·6%; calculated for C₁₅H₂₁O₅N₂Cl, N = 8·2%.

The picrate, sparingly soluble in alcohol, formed yellow crystals melting at 211°.

Found: N = 12·8%; calculated for C₂₁H₂₃O₁₂N₅, N = 13·0%.

Ethyl α-Carbethoxy-δ-Keto Caproate (III).

Methyl iodide (34 g.) was added to an ice-cold solution of (I) (37·5 g.) in dry ether, and the mixture allowed to stand overnight. A white crystalline precipitate (47 g.), which tended to become gummy, had then separated. The supernatant liquid was poured off, and the solid washed with dry ether. This methiodide was not readily soluble in cold absolute alcohol. To it was added a solution of sodio malonic ester (prepared by adding ethyl malonate (31·4 g.) to a cooled solution of sodium (4·5 g.) in absolute alcohol (150 ml.)), and the mixture was gently warmed on the water-bath with shaking until the methiodide had separated from the walls of the flask. The mixture was then gently refluxed for three hours. Sodium iodide separated when the mixture was then cooled. Most of the solvent was removed by distillation, water was added, and the solution extracted several times with ether. The combined ethereal extracts were dried, the solvent removed and the residual oil fractionated in vacuo. Unchanged malonic ester (8·8 g.) came over first, and then a fraction
After about 10 minutes some heat was evolved and eventually a homogeneous liquid was obtained. This was heated at 100° for a further five minutes, then allowed to cool. Finally, water (50 ml.) was added, and after vigorous shaking the upper layer of excess cyclohexanone removed. After two further extractions with ether the aqueous layer was evaporated in vacuo, a colourless crystalline deposit (21 g.) being obtained. Recrystallised from ethyl alcohol, this 2-morpholinomethylcyclohexanone hydrochloride formed colourless prismatic needles melting at 128°.

Found: C = 57·2%, H = 7·5%; calculated for C₁₁H₁₈O₅NCl, C = 57·4%, H = 7·8%.

The substance is therefore, probably, the open-chain ethyl α-carbethoxy-δ-ketocaproate. When treated with aqueous-alcoholic semicarbazide acetate it readily yielded a semicarbazone, which formed flat colourless plates when recrystallised from a mixture of petroleum ether and alcohol, m.p. 118°.

Found: N = 14·7%; calculated for C₁₃H₂₁O₅N₃, N = 14·6%.

The dinitrophenylhydrazone, which came down with some difficulty owing to its ready solubility in alcohol, was recrystallised from petroleum ether and thus obtained in flat orange plates which melt at 55°.

Found: N = 13·6%; calculated for C₁₃H₂₂O₈N₄, N = 13·7%.

Attempts to effect cyclisation of this ester with alcoholic sodium ethoxide led only to formation of a viscous product which decomposed on attempted distillation in vacuo. Further proof of the constitution of the ester was obtained by its hydrolysis and decarboxylation to γ-acetylbutyric acid. When it was treated with 20% aqueous sodium hydroxide solution it went into solution, and after standing for some hours, then acidifying and exhaustively extracting with ether, there was isolated from this solution a viscous brown oil with acidic properties. When heated to 150-160° this lost carbon dioxide, leaving an oil which distilled at 150°/24 mm. There could be obtained from this oil with aqueous semicarbazide acetate a semicarbazone which crystallised in gleaming colourless needles from water and melted at 173°. This is the melting point recorded for the semicarbazone of γ-acetylbutyric acid by Bentley and Perkin (J.C.S., 1896, 69, 1511).

2-Morpholinomethyl Cyclohexanone (V).

Cyclohexanone (49 g.; 1 mol.), morpholine hydrochloride (13 g.; 1/10th mol.), and formaldehyde solution (9 g. of 40%) were gently warmed and vigorously shaken together.
After about 10 minutes some heat was evolved and eventually a homogeneous liquid was obtained. This was heated at 100° for a further five minutes, then allowed to cool. Finally, water (50 ml.) was added, and after vigorous shaking the upper layer of excess cyclohexanone removed. After two further extractions with ether the aqueous layer was evaporated in vacuo, a colourless crystalline deposit (24 g.) being obtained. Recrystallised from ethyl alcohol, this 2-morpholinomethylcyclohexanone hydrochloride formed colourless prismatic needles melting at 128°.

Found: N = 6·2%; calculated for C_{11}H_{20}O_{2}NCl, N = 6·0%.

The picrate was readily soluble in hot alcohol but only sparingly soluble in cold, and crystallised in brilliant yellow needles melting at 135°.

Found: N = 13·5%; calculated for C_{17}H_{22}O_{8}N_{4}, N = 13·7%.

The free base (V) was readily obtained from a concentrated aqueous solution of the hydrochloride by making strongly alkaline and then extracting with ether. After drying and removal of the solvent the base distilled as a colourless oil at 145-147°/5·5 mm.

2-Morpholinomethylcyclohexanol (Va).

2-Morpholinomethylcyclohexanone (16 g.) was dissolved in absolute isopropyl alcohol (50 ml.) in a distilling flask and a solution of aluminium isopropyl oxide (12·5 g.) in isopropyl alcohol (75 ml.) added. This solution was kept gently boiling for five hours, the acetone formed in the reaction distilling over with some isopropyl alcohol. More isopropyl alcohol was added as required during the reaction. The presence of acetone in the distillate was shown by the formation of its D.N.P. When reduction was apparently complete, the isopropyl alcohol was removed as completely as possible by distillation, and the residue was treated with sodium hydroxide solution. The liberated base was taken up and dried in ether. After removal of the solvent it was distilled in vacuo, coming over between 120° and 128° at 1·8 mm. (8 g.).

This product was, most probably, a mixture of stereoisomers. It gave an oily picrate which could not be induced to crystallise.

Q—December 7, 1938.
2-Morpholinomethyl-1-Benzoyloxy-cyclohexane Hydrochloride.

A solution of the benzoylchloride (1 g.) in a little chloroform was added to a solution of the base (Va) (1 g.) in chloroform (5 ml.). The solution turned brown and heat was evolved. After standing overnight the chloroform was evaporated and the residue induced to crystallise by rubbing with ether. Recrystallised from acetone, it came out in colourless prisms melting at 211°.

Found: N = 4.0%; calculated for C₁₉H₂₇O₅NCl, N = 4.1%.

2 - Morpholinomethyl - 1 - p - Nitrobenzoyloxy-cyclohexane Hydrochloride.

Prepared from (Va) and p-nitrobenzoyl chloride in a manner similar to that described for the benzoic ester, this ester hydrochloride was recrystallised from a mixture of acetone and alcohol and was obtained in colourless prisms melting at 233°.

Found: C = 55.5, H = 6.7, N = 7.1%; calculated for C₁₉H₂₈O₅N₂Cl, C = 56.2, H = 6.9, N = 7.3%.

2-Morpholinomethyl-4-Methyl Cyclohexanone (VI).

A mixture of morpholine hydrochloride (12.4 g.), formaldehyde solution (9 g. of 40%), and 4-methylcyclohexanone (56 g.; excess) was warmed on the water-bath, and shaken for about 10 minutes until reaction commenced. Reaction proceeded with evolution of heat, and was finally completed by warming on the water-bath for a further 10 minutes. The homogeneous solution separated into two layers on cooling. The mixture was shaken out with water (50 ml.) and the aqueous extract freed from traces of methyl cyclohexanone with ether. The aqueous extract was then evaporated to dryness in a vacuum desiccator, a crystalline mass of 2-morpholinomethyl-4-methylcyclohexanone hydrochloride being left. This was recrystallised from acetone, and then from a mixture of acetone and alcohol, and thus obtained in colourless prisms melting at 145°.

Found: C = 58.4, H = 9.3%; calculated for C₁₂H₂₂O₂NCl, C = 58.2, H = 8.9%.

The free base, liberated from a solution of the hydrochloride with alkali, washed and dried in ether and then distilled in vacuo came over at 131-132°/2.2 mm. as a colourless oil.
The picrate, thrice recrystallised from alcohol, formed bright yellow needles melting at 139°.

Found: $N = 12.9\%$; calculated for $C_{18}H_{24}O_9N_4$, $N = 12.7\%$.

2-Morpholinomethyl-4-methyl Cyclohexanol (VIa).

The keto base (VI) (9 g.) was reduced by the Ponndorff method with aluminium isopropylxide (6 g.) in isopropyl alcohol, the distillation being continued for three hours. Isolated by the method described for (Va) it was obtained as a colourless fairly viscous oil (7.5 g.) boiling at 135-137°/2 mm. A crystalline picrate could not be obtained from it.

2-Morpholinomethyl - 4 - Methyl - 1 - Benzoyloxy cyclohexane Hydrochloride.

Obtained by a method similar to that described for the benzoic ester hydrochloride of (Va) this substance was obtained, after two recrystallisations from acetone, in colourless crystals melting at 228-230°.

Found: $N = 3.6\%$; calculated for $C_{19}H_{28}O_9NCl$, $N = 4.0\%$.

2-Morpholinomethyl - 4 - Methyl - 1 - p - Nitrobenzoyloxy cyclohexane Hydrochloride.

Obtained in chloroform solution by interaction of (VIa) (1 g.) and p-nitrobenzoylchloride (1 g.), this substance was isolated as a syrup by removal of the solvent but crystallised after long contact with ether. After recrystallisation from a mixture of acetone and alcohol, a colourless crystalline solid melting at 242-244° was obtained.

Found: $N = 7.3\%$; calculated for $C_{19}H_{27}O_5N_2Cl$, $N = 7.0\%$.

2-Methyl-6-Morpholinomethyl Cyclohexanone (VII).

2-Methylcyclohexanone (40 g.; 2 mols.), morpholine hydrochloride (20 g.; 1 mol.) and paraformaldehyde (6.5 g.; 1.2 mols.) were heated together in cyclohexanol (100 g.) at 110° for two hours. After cooling the mixture was shaken out with water, and the aqueous extract freed from traces of methyl cyclohexanone and cyclohexanol with ether. It was then made alkaline with sodium hydroxide solution and the base collected with ether and eventually distilled in vacuo. It came over undecomposed
at 130°/1.8 mm., and after standing overnight crystallised out in colourless needles melting at 48-50°. The picrate, twice recrystallised from alcohol, formed long yellow needles melting at 118°.

Found: N = 12.6%; calculated for C_{18}H_{24}O_{6}N_{4}, N = 12.7%.

2-Methyl-6-Morpholinomethyl Cyclohexanol (VIIa).

The keto base (VII) (7 g.) was reduced with aluminium isopropylxide (4 g.) according to Ponndorff's method, as described for (V). The base was obtained as a colourless viscous oil boiling at 137-138°/2.3 mm. It gave an oily picrate. The hydrochloride of the benzoic ester, obtained in the usual manner, was an uncrystallisable oil. However, 2-methyl-6-morpholinomethyl-1-p-nitrobenzoyloxy-cyclohexane hydrochloride was obtained in colourless needles melting at 237° after several crystallisations from a mixture of acetone and alcohol.

Found: N = 7.0%; calculated for C_{19}H_{27}O_{5}N_{2}Cl, N = 7.0%.

Condensation of Cyclopentanone with Formaldehyde and Morpholine Hydrochloride.

(A) 2-Morpholinomethylcyclopentanone (IX). Morpholine hydrochloride (12.4 g.; 0.1 mol.), formaldehyde solution (8 g. of 40%; 0.1 mol.), and cyclopentanone (42 g.; 0.5 mol.) were warmed together on the water-bath, with shaking until reaction commenced (five to ten minutes). Heating was discontinued and the reaction proceeded to completion of its own accord, a small amount of crystalline material separating towards the end. After cooling the mixture was shaken out with water (50 ml.), and the hydrochloride of 2-morpholinomethylcyclopentanone recovered from the aqueous extract by the usual method. The crude solid (19.5 g.) was taken up in boiling alcohol, the solution being filtered from a small amount (2 g.) of insoluble material (A), and allowed to crystallise after concentrating and cooling. It formed colourless prisms, melting at 137°.

Found: C = 54.5, H = 8.2%; calculated for C_{16}H_{16}O_{2}NCl, C = 54.7, H = 8.2%.

The picrate of the base (X), precipitated from an alcoholic solution of the hydrochloride by saturated alcoholic picric acid, after recrystallisation from alcohol formed yellow needles melting at 130°.
Found: \( N = 13.6\% \); calculated for \( C_{16}H_{20}O_9N_4; N = 13.6\% \).

The free base (IX) was recovered from the hydrochloride in the usual way and was obtained as a colourless oil boiling at 115-118°/2 mm. An attempt to reduce it to 2-morpholinomethylcyclopentan-1-ol by Ponndorff’s method led to formation of an oil which broke down on distillation in vacuo, giving off morpholine.

(B) 2:5-Dimorpholinomethylcyclopentanone (VIII). Re-fluxing together cyclopentanone (21 g.), morpholine hydrochloride (31 g.), paraformaldehyde (9 g.) and absolute alcohol (20 ml.) for several hours led to the gradual separation of a white crystalline substance. After cooling this was collected and boiled with alcohol, in which it was very sparingly soluble. It was found to be insoluble in such solvents as benzene, dioxane, ethyl acetate, acetone and chloroform, but was readily soluble in water. Recrystallised from aqueous alcohol, it formed colourless needles melting at 195°, identical with the product (A) obtained as a by-product in the preparation of (IX).

Found: \( C = 50.8, \ H = 8.1\% \); calculated for \( C_{15}H_{25}O_3N_2Cl_2; C = 50.7, \ H = 7.9\% \).

The substance was thus the dihydrochloride of 2:5-dimorpholinomethylcyclopentanone.

The picrate, precipitated from alcohol solution, in which it is very sparingly soluble, was recrystallised from a large volume of alcohol. It formed bright yellow crystals melting at 152°.

Found: \( N = 14.9\% \); calculated for \( C_{27}H_{32}O_{17}N_8, N = 15.1\% \).

β-Morpholinoethylphenyl Ketone (X).

During the course of 30 minutes, acetophenone (24 g.) was gradually added to a boiling mixture of morpholine hydrochloride (26 g.), paraformaldehyde (9 g.) and absolute alcohol (60 ml.). A further quantity of paraformaldehyde (6 g.) was then added and the heating continued for a further 20 minutes. After filtration whilst still hot, the liquid separated into two layers on cooling. Eventually crystallisation commenced and it was possible to recover the hydrochloride of (X) (14 g.) by filtration. Heating of the mother liquor (still in two layers) until most of the alcohol had evaporated, followed by cooling and seeding led to separation of much more of the hydrochloride of
I-Phenyl-3-oL-Thienyl-Pyrazoline (XIII), p-Morpholinoethyl a-thienyl ketone (XII; 3 g.) and phenylhydrazine (1.5 g.) were refluxed with ethyl alcohol (10 ml.) for two hours. The oil obtained by pouring into water was rubbed with dilute acetic acid, washed with water and then rubbed with alcohol, when it solidified. Recrystallised from alcohol it was obtained in pale yellow needles melting at 103°.

Found: N = 12.3%; calculated for C_{13}H_{18}O_{2}NCl, N = 12.3%.

The free base could readily be recovered as an oil from an aqueous solution of the hydrochloride, but it was not distilled, owing to the marked tendency observed by Mannich (Berichte, 1922, 55, 3510) of similar bases to decompose on attempted distillation. An attempt to reduce it by Ponndorff's method led to no isolable amino alcohol.

Heating of the base (X) with phenylhydrazine at 100° for several hours, or refluxing it with excess phenylhydrazine in alcoholic solution led to ready formation of the 1:3-diphenylpyrazoline melting at 153° previously described by Jacob and Madinaveitia (J.C.S., 1937, 1929).

β-Morpholinoethyl-2-Thienyl Ketone (XII).

2-Acetylthiophene (30 g.) was added gradually over 30 minutes to a boiling mixture of morpholine hydrochloride (30 g.), paraformaldehyde (12 g.) and absolute alcohol (40 ml.) and then concentrated hydrochloric acid (0.5 ml.) was added and boiling continued under reflux for 20 minutes. Paraformaldehyde (3 g.) was added and refluxing continued for a further 15 minutes, when the contents of the flask solidified. After cooling, the solid was collected and recrystallised from alcohol, being thus obtained in naeuous plates (30 g.) melting at 194°.

Found: N = 5.2%; calculated for C_{11}H_{16}O_{2}NSCl, N = 5.0%.

It was thus the hydrochloride of β-morpholinoethyl-2-thienyl ketone. The picrate of XII was readily obtained from an alcoholic solution of the hydrochloride with alcoholic picric acid. Recrystallised from a mixture of alcohol and nitrobenzene it formed fine bright yellow needles melting at 189-190°.

Found: N = 12.4%; calculated for C_{17}H_{18}O_{6}N_{4}S, N = 12.3%.

The base (XII) was readily obtained as an oil which was not distilled.
1-Phenyl-3-α-Thienyl-Pyrazoline (XIII).

β-Morpholinoethyl α-thienyl ketone (XII; 3 g.) and phenylhydrazine (1.5 g.) were refluxed with ethyl alcohol (10 ml.) for two hours. The oil obtained by pouring into water was rubbed with dilute acetic acid, washed with water and then rubbed with alcohol, when it solidified. Recrystallised from alcohol it was obtained in pale yellow needles melting at 103°.

Found: N = 12.3%; calculated for C_{13}H_{12}N_{2}S, N = 12.3%.

Shaking of this solid substance with ether, ligroin, or petroleum ether imparted a blue fluorescence to these liquids. With concentrated sulphuric acid it gave a deep blue colour, whilst with concentrated nitric acid the colour was deep violet.

β-Morpholinoethyl-3 : 4-Dimethoxyphenyl-Ketone (XI).

Acetoveratrine (36 g.) was added during half an hour to a boiling solution of morpholine hydrochloride (24.7 g.) paraformaldehyde (10 g.) and absolute alcohol (30 ml.). Concentrated hydrochloric acid (0.75 ml.) was then added and refluxing continued for 15 minutes. Two layers soon appeared, the lower layer gradually increasing in volume until the solution was again almost homogeneous. On cooling the hydrochloride of (XI) crystallised out. After collection and recrystallisation from boiling ethyl alcohol, in which it is but sparingly soluble, it was obtained in colourless prisms (35 g.) melting at 192°.

Found: N = 4.5%; calculated for C_{15}H_{22}O_{4}N_{1}, N = 4.4%.

The picrate, precipitated from an alcoholic solution of the hydrochloride, crystallised from a mixture of alcohol and nitro-benzene in yellow needles melting at 165°.

Found: N = 11.0%; calculated for C_{21}H_{23}O_{11}N_{4}, N = 11.0%.

The free base, (XI), was obtained by basification of an aqueous solution of the hydrochloride. Recrystallised from alcohol it formed colourless prisms melting at 129°.

Found: N = 5.2%; calculated for C_{15}H_{21}O_{4}N, N = 5.0%.

1-Phenyl-3-(3': 4'-Dimethoxyphenyl)-Pyrazoline (XV).

A solution of the base (XI) (2 g.) and phenylhydrazine (1 g.) in absolute alcohol (10 ml.) was heated under reflux for an hour. On cooling the pyrazoline (XV) crystallised.
It was collected and recrystallised from alcohol, forming pale yellow needles melting at 130°.

Found: N = 9.9%; calculated for $C_{17}H_{18}O_2N_2$, N = 10.0%.

Solutions of this substance showed a characteristic blue fluorescence.

*Morpholinomethyl Antipyrine (XIV).*

Antipyrine (5 g.), morpholine hydrochloride (3.3 g.) and 40% formaldehyde solution (2.2 g.) were mixed in water and allowed to stand for 24 hours. The solution was then extracted with chloroform to remove unchanged antipyrine, made alkaline and again extracted with chloroform. After drying and removal of the solvent from this second extract, a crystalline product (6 g.) was obtained, which when recrystallised from ethyl acetate formed beautiful colourless flat prisms melting at 131°.

Found: C = 67.1, H = 7.8%; calculated for $C_{16}H_{21}O_2N_3$, C = 66.9, H = 7.3%.

The picrate, precipitated from alcohol and then recrystallised from the same solvent formed beautiful orange-yellow needles melting at 190°.

Found: N = 16.6%; calculated for $C_{21}H_{24}O_9N_6$, N = 16.3%.

ACKNOWLEDGMENTS.

One of the authors (R.H.H.) gratefully acknowledges the receipt of a Commonwealth Government Research Scholarship which has enabled her to take part in the work. The authors also desire to thank Miss D. M. Little, B.Sc., for some of the (micro) analyses recorded in this paper; and the Carbide and Carbon Chemical Corporation of America, who, through their Sydney agents, Messrs. Robert Bryce and Co. Ltd., arranged a gift of morpholine for this work.

Department of Organic Chemistry,

The University of Sydney.

View This Item Online: https://www.biodiversitylibrary.org/item/174130
DOI: https://doi.org/10.5962/p.360249
Permalink: https://www.biodiversitylibrary.org/partpdf/360249

Holding Institution
Smithsonian Libraries

Sponsored by
Biodiversity Heritage Library

Copyright & Reuse
Copyright Status: In Copyright. Digitized with the permission of the rights holder
Rights Holder: Royal Society of New South Wales
License: http://creativecommons.org/licenses/by-nc-sa/3.0/
Rights: https://www.biodiversitylibrary.org/permissions/

This document was created from content at the Biodiversity Heritage Library, the world’s largest open access digital library for biodiversity literature and archives. Visit BHL at https://www.biodiversitylibrary.org.