methylhexahydro-*s*-triazine and sulfur gave carbon disulfide and 1,3-dimethylthiourea. 1,3-Di-*n*-dodecylthiourea was obtained from the reaction of sulfur and 1,3,5-tri-*n*-dodecylhexahydro-*s*-triazine.

EXPERIMENTAL

t-Octyl iosthiocyanate. To 48 g. (1.5 moles) of sulfur heated to 165° was added dropwise during 45 min. a mixture of 25.8 g. (0.2 mole) of *t*-octylazomethine and 25.8 g. (0.2 mole) of *t*-octylamine while the temperature was maintained at 145–155° and the mixture was constantly stirred. A solid material which collected in the condenser was periodically pushed back into the flask. The mixture was then heated to 163° during another 5 min., cooled, diluted with heptane, chilled, and filtered free of 35 g. (1.1 moles) of sulfur. The filtrate was distilled at reduced pressure and then redistilled to give 21 g. (61%) of *t*-octyl isothiocyanate,[9,10] b.p. 44–46°/0.5 mm.

Anal. Calcd. for $C_9H_{17}NS$: C, 63.10; H, 10.01; N, 8.18; S, 18.71. Found: C, 63.20; H, 9.84; N, 8.21; S, 18.48.

A mixture of 17.1 g. (0.1 mole) of *t*-octyl isothiocyanate prepared in this manner, 13 g. (0.1 mole) of *t*-octylamine, and 50 ml. of hexane was refluxed for 8 hr., allowed to stand prepared in this manner, 13 g. (0.1 mole) of *t*-octylamine, and 50 ml. of hexane was refluxed for 8 hr., allowed to stand overnight, chilled, and filtered free of 15 g. (50%) of 1,3-di-*t*-octylthiourea[9] which melted at 109–111° after recrystallization from hexane.

Anal. Calcd. for $C_{17}H_{36}N_2S$: C, 67.93; H, 12.08; N, 9.32; S, 10.67. Found: C, 68.12; H, 12.16; N, 9.21; S, 10.92.

Primene 81-R isothiocyanate. To 48 g. (1.5 moles) of stirred sulfur at 180–190° was added dropwise during 15 min. a mixture of 22 g. (0.1 mole) of Primene 81-R–azomethine and 21 g. (0.1 mole) of Primene 81-R while there was a steady evolution of gas. The mixture was then stirred another 5 min. while the temperature was raised to 200°, cooled rapidly, diluted with heptane, and filtered free of 41 g. (1.3 moles) of sulfur. The filtrate was fractionated and the material distilling at 80–95°/0.35 mm. (17 g.) was redistilled to give 14 g. (56%) of Primene 81-R isothiocyanate, b.p. 80–90°/0.35 mm.

Anal. Calcd. for $C_{12-15}H_{23-29}NS$: C, 67.54–70.52; H, 10.86–11.44; N, 5.49–6.57; S, 12.55–15.03. Found: C, 69.35; H, 10.97; N, 6.23; S, 13.39.

1,3-Dimethylthiourea. To 48 g. (1.5 moles) of sulfur heated to 150° was added dropwise with stirring 20 g. (0.16 mole) of 1,3,5-trimethylhexahydro-*s*-triazine during 0.5 hr. while the temperature dropped to 110° and there was vigorous refluxing and gas evolution. The mixture was cooled and then distilled to give 12 g. (0.16 mole) of carbon disulfide, b.p. 40–50°, which was identified by preparation of a potassium xanthate from ethyl alcohol, m.p. 225–226°. Shupe[11] reported 225–226° for the melting point of the potassium xanthate of ethyl alcohol. The residue in the distillation flask was heated to 175° but no more material distilled. It was then cooled and extracted with toluene, water, and alcohol. The combined extracts were distilled free of solvents at reduced pressure and then diluted with ethyl alcohol. A precipitate of 19 g. (0.6 mole) of sulfur was filtered off and the filtrate was distilled to give 18 g. of distillate, b.p. 120–160°/0.5 mm. This was dissolved in 100 ml. of ethyl alcohol, filtered free of an additional small quantity of sulfur, and redistilled to give 10 g. (0.1 mole) of 1,3-dimethylthiourea,[12] b.p. 155°/0.9 mm.–140°/0.4 mm., which solidified. A sample for analysis was recrystallized from a toluene–isopropyl alcohol mixture and melted at 50–52°.

Anal. Calcd. for $C_3H_8N_2S$: C, 34.59; H, 7.74; N, 26.90; S, 30.77. Found: C, 34.83; H, 7.84; N, 26.54; S, 30.76.

1,3-Di-n-dodecylthiourea. To a stirred refluxing mixture of 20 g. (0.63 mole) of sulfur and 100 ml. of pyridine was added dropwise during 0.5 hr. 59.1 g. (0.1 mole) of 1,3,5-tri-*n*-dodecylhexahydro-*s*-triazine. The mixture was refluxed for another 0.5 hr. and then cooled. The solid reaction product was recrystallized twice from ethyl alcohol to give 30 g. (0.07 mole) of 1,3-di-*n*-dodecylthiourea,[13] m.p. 76–78°.

Anal. Calcd. for $C_{25}H_{52}N_2S$: C, 72.74; H, 12.70; N, 6.79; S, 7.77. Found: C, 72.81; H, 12.70; N, 6.62; S, 7.66.

Acknowledgments. I am indebted to Alice Cannon for technical assistance and C. W. Nash and his associates for the elemental analyses.

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[9] N. Bortnick, L. S. Luskin, M. D. Hurwitz, and A. W. Rytina, *J. Am. Chem. Soc.*, **78**, 4358 (1956).

[10] L. S. Luskin, G. E. Gantert, and W. E. Craig, *J. Am. Chem. Soc.*, **78**, 4965 (1956).

[11] I. S. Shupe, *J. Assoc. Offic. Agr. Chemists*, **25**, 495 (1942).

[12] Beilstein, *IV*, 70.

[13] H. Z. Lecher and T. H. Chao, U. S. Patent **2,607,803**, Aug. 19, 1952; *Chem. Abstr.*, **47**, 4904 (1953).

Products Obtained from Acetone, 1-Dimethylamino-3-pentanone and Diethyl Acetonedicarboxylate in the Mannich Reaction

F. F. BLICKE AND F. J. MCCARTY

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It has been shown by Mannich and Salzmann[1] that acetone, formalin and aqueous dimethylamine react at room temperature to form 1-dimethylamino-3-butanone (I) and 1-dimethylamino-2-(dimethylaminomethyl)-3-butanone (II). The structure of II has been definitely established.[1,2]

We found that acetone, paraformaldehyde, and dimethylamine hydrochloride reacted in acetic acid at 95° to form a dihydrochloride which melted at 191–192° after one recrystallization and at 202–203° after two further recrystallizations. This product must have been either the dihydrochloride of II or III. A di(hydrogen oxalate) (m.p. 160–161°) and a dipicrate (m.p. 155–156°) were also prepared. From the comparisons of the melting points of these salts with the melting points mentioned below, it was concluded that the dihydrochloride which we obtained was III.

Cardwell[2] had allowed 1,5-dichloro-3-pentanone to react with dimethylamine and obtained 1,5-bis(dimethylamino)-3-pentanone in the form of the dihydrochloride (III) (m.p. 191–192°); he also prepared the di(hydrogen oxalate) (m.p. 155–156°).

Since the dihydrochloride of II was unknown, it was prepared and found to melt at 150–151°.

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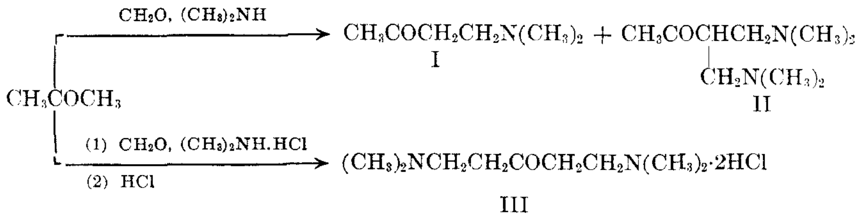
[1] C. Mannich and O. Salzmann, *Ber.*, **72**, 506 (1939).

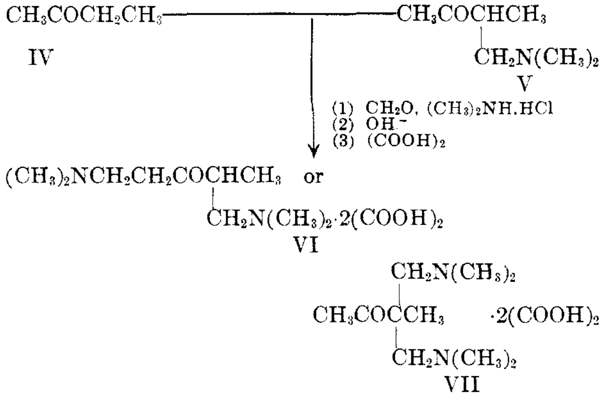
[2] H. M. E. Cardwell, *J. Chem. Soc.*, 1056 (1950).



The dipicrate of II (m.p. 136.5°) has been reported.[3] The di(hydrogen oxalate) of II is unknown; Cardwell found that the base, when treated with oxalic acid, underwent decomposition.

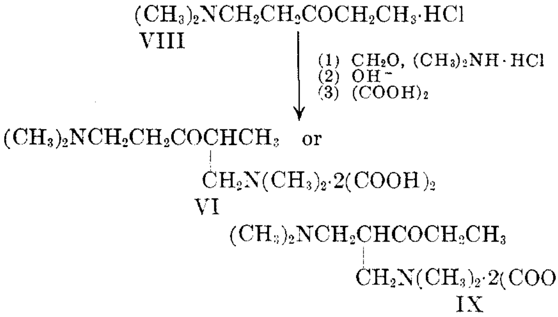
Mannich and Hof[4] isolated two bases from the interaction of methyl ethyl ketone, paraformaldehyde, and dimethylamine hydrochloride: one was reported to be a monamine, 2-(dimethylaminomethyl)-3-butanone, the other, the higher boiling product, was stated to be the isomeric monamine, 1-dimethylamino-3-pentanone.

Cardwell,[2] Haeussler, and Schacht[5] and Barrett and Chambers[6] carried out the reaction described by Mannich and Hof and studied the higher boiling product. Cardwell found that this product formed a di(hydrogen oxalate); hence it was actually a diamine and not a monamine. He showed that this di(hydrogen oxalate) (m.p. 144–145°) was identical with the di(hydrogen oxalate) (m.p. 145–146°) which he obtained from 2-(dimethylaminomethyl)-3-butanone (V) by a Mannich reaction. Since this salt was obtained from the base of the diamine formed by the use of either IV or V in a Mannich reaction, he concluded that its structure must be represented by either VI or VII.



Haeussler and Schacht stated that since the higher boiling product yielded iodoform when it was treated with sodium hypoiodite solution, it must be the base of VII. According to Barrett and Chambers, the higher boiling product must be the base of VI since they were able to convert it into a pyrrocoline; such a product could not be obtained from the base of VII.

We prepared 1-dimethylamino-3-pentanone from 1-chloro-3-pentanone and dimethylamine. The hydrochloride of this substance (VIII) was allowed to react with paraformaldehyde and dimethylamine hydrochloride. The product, isolated as the di(hydrogen oxalate) (m.p. 148–149°), must have been either VI or IX. We repeated Mannich and Hof's experiment, isolated the higher boiling product[7] and converted it into the di(hydrogen oxalate); m.p. and mixed m.p. 148–149°.



Since a common di(hydrogen oxalate) was obtained from the base of the diamine formed by interaction of IV, V, or VIII with paraformaldehyde and dimethylamine hydrochloride, this salt could be only 1-dimethylamino-4-(dimethylaminomethyl)-3-pentanone di(hydrogen oxalate) (VI), and formula VI must represent the di(hydrogen oxalate) of the higher boiling product.

It was found that bis(dimethylaminomethyl)-acetic acid dihydrochloride (X) could be obtained from either diethyl acetonedicarboxylate, in 73% yield, or ethyl acetoacetate, in 2% yield, by interaction with formalin and aqueous dimethylamine at 0–25° and subsequent acidification with hydrochloric acid. This product had been prepared by Mannich and Kather,[8] in 40% yield, from malonic acid, formalin and aqueous dimethylamine after treatment of the reaction mixture with hydrochloric acid.

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[3] C. Mannich and K. Curtaz, *Arch. Pharm.*, **264**, 741 (1926).

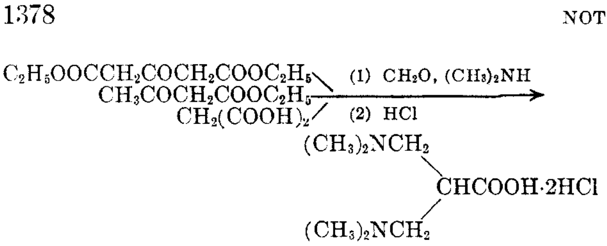
[4] C. Mannich and W. Hof, *Arch. Pharm.*, **265**, 589 (1927).

[5] H. Haeussler and W. Schacht, *Chem. Ber.*, **83**, 129 (1950).

[6] P. A. Barrett and K. A. Chambers, *J. Chem. Soc.*, 338 (1958).

[7] When we treated this product with sodium hypoiodite solution, iodoform was not produced. A positive iodoform test was obtained when V was treated in the same manner.

[8] C. Mannich and B. Kather, *Ber.*, **53**, 1368 (1920).



X

To account for the formation of X from ethyl acetoacetate, it is assumed that "acid cleavage" of some intermediate which contained dimethylaminomethyl groups, followed by hydrolysis, must have occurred. However, in the formation of X from diethyl acetonedicarboxylate, cleavage and hydrolysis of either the diester with the formation of malonic acid or cleavage and hydrolysis of an aminomethylated intermediate could have taken place.

EXPERIMENTAL

1,5-Bis(dimethylamino)-3-pentanone dihydrochloride (III). A mixture of 5.8 g. (0.1 mol.) of acetone, 6.0 g. (0.2 mol.) of paraformaldehyde, 16.4 g. (0.2 mol.) of dimethylamine hydrochloride and 40 ml. of acetic acid was heated on a steam bath for 2.5 hr. The solvent was removed under reduced pressure, the residue was heated with acetone, and the mixture was filtered; yield 8.0 g. (33%). After recrystallization from methanol ether, the product melted at 191–192° (dec.) (lit.[2] 191–192°); after two more recrystallizations from the same solvents, it melted at 202–203° (dec.); yield 3.8 g. (16%).

Anal. Calcd. for $C_9H_{22}ON_2Cl_2$: C, 44.07; H, 9.05; Cl, 28.91. Found: C, 44.00; H, 8.89; Cl, 28.72.

A sample of the dihydrochloride was converted into the base, the latter was dissolved in ethanol, and oxalic acid, dissolved in the same solvent, was added. The precipitated di(hydrogen oxalate) melted at 160–161° and at 155–156° (lit.[2] 155–156°) after recrystallization from methanol. The sample which melted at 160–161° was analyzed.

Anal. Calcd. for $C_{13}H_{24}O_9N_2$: C, 44.31, H, 6.86. Found: C, 44.39; H, 6.83.

When the dihydrochloride, dissolved in dilute ethanol, was treated with picric acid, the dipicrate precipitated; m.p. 162–163°. After recrystallization from ethanol, the salt melted at 157–158°. This sample was analyzed.

Anal. Calcd. for $C_{21}H_{26}O_{15}N_8$: C, 40.01; H, 4.16. Found: C, 40.23; H, 4.19.

1-Dimethylamino-2-(dimethylaminomethyl)-3-butanone hydrochloride. A solution of II[1] in ether was treated with hydrogen chloride and the precipitated salt was recrystallized three times from methanol ether; m.p. 150–151°.

Anal. Calcd. for $C_9H_{22}ON_2Cl_2$: C, 44.07; H, 9.05; Cl, 28.91. Found: C, 43.87; H, 9.01; Cl, 28.40.

We found that the picrate melted at 137–138° (lit.[3] 136.5°).

1-Chloro-3-pentanone.[9] A mixture of 320 g. (2.4 mol.) of aluminum chloride,[10] 180 g. (1.92 moles) of freshly distilled propionyl chloride and 240 ml. of freshly distilled carbon disulfide was stirred vigorously and maintained at 5–8° for 4.5 hr. During this time, ethylene,[11] passed through a bubble counter in which nitrobenzene was used, was introduced at such a rate that it was just possible to count the bubbles. The mixture was allowed to remain in a refrigerator for 10 hr. and it was then poured onto ice. The product was extracted with ether, the extract was washed with sodium bicarbonate solution, then with water. The solvent was removed from the dried extract and the residue was distilled; yield 124.0 g. (53%); b.p. 67–69° (22 mm.) [lit.[9] 65° (22 mm.)].

1-Dimethylamino-3-pentanone. A stirred solution of 97 g. (2.15 mol.) of anhydrous dimethylamine in 500 ml. of ether was cooled in an ice bath and a solution of 52 g. (0.43 mol). of 1-chloro-3-pentanone in 150 ml. of ether was added, dropwise, during a period of 30 min. The mixture was stirred for 6 hr. at 5° and then for 2 hr. at room temperature, made strongly alkaline with 40% sodium hydroxide solution and the ether layer was separated and dried. After removal of the solvent, the residue was distilled; b.p. 71–73° (20 mm.); yield 47 g. (78%).

Anal. Calcd. for $C_7H_{15}ON$: C, 65.08; H, 11.70. Found: C, 65.11; H, 11.84.

The hydrogen oxalate, prepared in ether, melted at 130–131° after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{17}O_5N$: C, 49.32; H, 7.82. Found: C, 49.33; H, 7.92.

The hydrochloride (VIII), obtained by the use of ethereal hydrogen chloride, was very hygroscopic; it was dissolved in water and gold chloride solution was added. The precipitatec chloroaurate melted at 84–85° after recrystallization from ethanol.[12]

Anal. Calcd. for $C_7H_{16}ONCl_4Au$: C, 17.92; H, 3.44; Au, 42.03. Found: C, 17.86; H, 3.38; Au, 42.17.

1-Dimethylamino-4-(dimethylaminomethyl)-3-pentanone. A mixture of 4.9 g. (0.03 mol.) of VIII, 2.4 g. (0.03 mol.) of dimethylamine hydrochloride, 1.2 g. (0.04 mol.) of paraformaldehyde and 15 ml. of absolute ethanol was refluxed for 8 hr. After the addition of 0.6 g. of paraformaldehyde, the mixture was refluxed for 4 hr. The solvent was removed under reduced pressure and the oily residue was dissolved in a small amount of water, and 50% potassium hydroxide solution was then added. The product was extracted with ether and after removal of the solvent from the dried extract, the residue was distilled; b.p. 105–108° (20 mm.)[13]; yield 1.9 g. (34%).

The dihydrochloride, prepared by the use of ethereal hydrogen chloride, melted at 192–193° after recrystallization from methanol ether.

Anal. Calcd. for $C_{10}H_{24}ON_2Cl_2$: C, 46.33; H, 9.33; Cl, 27.36. Found: C, 46.30; H, 9.35; Cl, 27.62.

The dichloroaurate precipitated when a gold chloride solution was added to the dihydrochloride dissolved in water; m.p. 147–148° after recrystallization from ethanol. After a further recrystallization from this solvent, the salt melted at 128°,[14] and after an additional recrystallization this melting point was not changed. The sample used for analysis (m.p. 147–148°) was dried for 24 hr. in a desiccator over calcium chloride.[15]

Anal. Calcd. for $C_{10}H_{24}ON_2Cl_8Au2$: C, 13.86; H, 2.79; Au, 45.52. Found: C, 14.02; H, 2.89; Au, 45.70.

Oxalic acid, dissolved in ethanol, was added to the base dissolved in the same solvent; the precipitated di(hydrogen

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(9) R. Huisger (*Ann.*, **559**, 174 (1948)) obtained this substance in 19% yield. We obtained a better yield by the described modification.

(10) Anhydrous sublimed reagent quality obtained from Baker and Adamson, General Chemical Division, Allied Chemical and Dye Corp., New York, N. Y.

(11) Matheson C.P. ethylene.

(12) After a sample of the salt had been dried for 4 hr. at 58° (0.1 mm.), the melting point was not changed but unsatisfactory analytical data was obtained when this material was analyzed.

(13) C. Mannich and W. Hof (ref. 4) obtained this compound by a different method and reported the boiling point to be 103–104° (12 mm.). They called it, incorrectly, 1-dimethylamino-3-pentanone.

(14) This is the melting point reported by C. Mannich and W. Hof (ref. 4) for this product which they called, incorrectly, the chloroaurate of 1-dimethylamino-3-pentanone; they did not report the analytical data.

(15) When the salt was dried over phosphorus pentoxide at 25° (0.3 mm.), it underwent decomposition.

oxalate) (VI) was recrystallized from methanol; m.p. 148–149° (ref. 2 144–145° and 145–146°).

Anal. Calcd. for $C_{14}H_{26}O_9N_2$: C, 45.88; H, 7.15. Found: C, 46.21; H, 7.35.

1-Dimethylamino-4-(dimethylaminomethyl)-3-pentanone was prepared also from methyl ethyl ketone, paraformaldehyde and dimethylamine hydrochloride[4]; b.p. 104–109° (20 mm.).

The dihydrochloride melted at 186–187° after recrystallization from methanol ether; mixed m.p. 189–190°.

The di(hydrogen oxalate) (IV) was prepared in ethanol; m.p. and mixed m.p. 148–149°.

Bis(dimethylaminomethyl)acetic acid dihydrochloride (X). (*a*) A mixture of 5.0 g. (0.025 mole) of diethyl acetonedicarboxylate[16] and 18.0 g. (0.1 mol.) of 25% aqueous dimethylamine was stirred, maintained at 0–5°, and treated, dropwise, with 8.1 g. (0.1 mol.) of 37% formalin during a 1.5-hr. period. The mixture was stirred for an additional 2 hr. during which time the temperature was allowed to rise gradually to 25°. After acidification with concentrated hydrochloric acid and removal of the water under reduced pressure on a steam bath, the solid residue was heated with isopropyl alcohol and the mixture was filtered; yield 4.5 g.; m.p. 180–181° (dec.). The product melted at 180–181° (dec.) after recrystallization from methanol ether; mixed m.p. with an authentic sample,[17] 178–180° (dec.).

Anal. Calcd. for $C_8H_{20}O_2N_2Cl_2$: N, 11.43; Cl, 28.70. Found: N, 11.20; Cl, 28.40.

(b) The reaction described above was repeated with the use of 13.0 g. (0.1 mole) of ethyl acetoacetate, 36.0 g. (0.2 mole) of 25% aqueous dimethylamine, and 16.2 g. (0.2 mole) of formalin; yield 0.5 g.; m.p. 175–177° (dec.) after recrystallization from methanol ether; mixed m.p. with an authentic sample,[17] 177–179° (dec.).

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[16] C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, **121**, 1638 (1922).

[17] Ref. 8, m.p. 169°. When we repeated the experiment described in the literature, the product obtained melted at 178–179° (dec.).

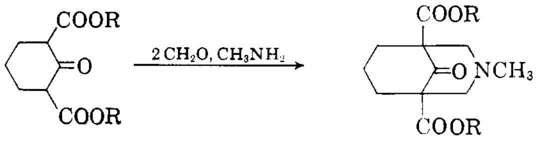
Use of 2,6-Disubstituted Cyclohexanones and of Tropinone in the Mannich Reaction

F. F. Blicke and F. J. McCarty

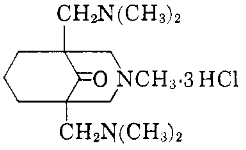
Received April 30, 1959

It has been reported by Anet et al.[1] that diethyl cyclopentanone-2,5-dicarboxylate condensed with formalin and aqueous methylamine in alcohol at room temperature to yield diethyl 3-methyl-3-aza-bicyclo[3.2.1]octan-8-one-1,5-dicarboxylate in 50% yield.

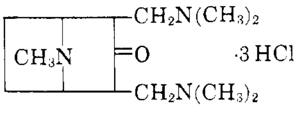
We found that dimethyl cyclohexanone-2,6-dicarboxylate reacted with formalin and aqueous methylamine in methanol at room temperature to form dimethyl 3-methyl-3-azabicyclo[3.3.1]-nonan-9-one-1,5-dicarboxylate in 80% yield. The corresponding diethyl ester was obtained from diethyl cyclohexanone-2,6-dicarboxylate under the same conditions except that ethanol was used as a solvent; it was isolated as the hydrochloride in 66% yield. Hydrolysis of the dimethyl ester hydrochloride with hydrochloric acid yielded 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylic acid hydrochloride.



It has been shown[2] that cyclohexanone, paraformaldehyde and dimethylamine hydrochloride react to form 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride. When this substance was allowed to react with formalin and methylamine hydrochloride, 1,5-bis(dimethylaminomethyl) - 3 - methyl - 3 - azabicyclo[3.3.1]nonan-9-one trihydrochloride (I) was obtained.



I



II

By the interaction of tropinone hydrobromide, paraformaldehyde and dimethylamine hydrochloride, a product was formed which was isolated as a trihydrochloride. In view of the behavior of cyclohexanone with paraformaldehyde and dimethylamine hydrochloride, we believe that this reaction product is 2,4-bis(dimethylaminomethyl)-8-methyl-8 - azabicyclo[3.2.1]octan - 3 - one trihydrochloride (II).

EXPERIMENTAL

Dimethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate. A solution of 6.0 g. (0.028 mol.) of dimethyl cyclohexanone-2,6-dicarboxylate[2] in 200 ml. of methanol was stirred and 3.5 g. of 25% aqueous methylamine (0.028 mole) and 4.5 g. of 37% formalin (0.056 mole) were added. The mixture was stirred for 24 hr. and the methanol and water were then removed under reduced pressure; yield 6.0 g. (80%); m.p. 76–78°. After two more recrystallizations from methanol, the product melted at 80–81°.

Anal. Calcd. for $C_{13}H_{19}O_5N$ C, 57.97; H, 7.11. Found: C, 57.84; H, 7.24.

The base, dissolved in acetone, was treated with hydrogen chloride; the precipitate, after two recrystallizations from acetone, melted at 201–202° (dec.). After it had been dried at 65° (0.3 mm.) for 24 hr., the hygroscopic solid melted at 207–208° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_5NCl$: C, 51.06; H, 6.59; Cl, 11.60. Found: C, 51.08; H, 6.62; Cl, 11.52.

Diethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate hydrochloride and methobromide. A mixture of 21.0 g. (0.087 mole) of diethyl cyclohexanone-2,6-dicarboxylate,[3] 10.5 g. (0.087 mole) of 25% aqueous methylamine, 14.0 (0.174 mole) of 37% formalin and 28 ml. of ethanol was

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[1] E. F. L. J. Anet, G. K. Hughes, D. Marmion, and E. Ritchie, *Australian J. Sci. Research, Ser. A*, **3**, 330 (1950).

[2] F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).

[3] P. C. Guha and N. K. Seshadriengar, *Ber.*, **69**, 1207 (1936).