

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

Anal. Calcd. for $C_{14}H_{26}O_6N_2$: 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 hydrochloride⁴; 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 acetonedicarboxylate¹⁶ 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

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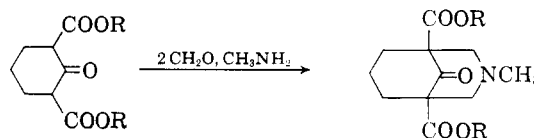
Received April 30, 1959

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

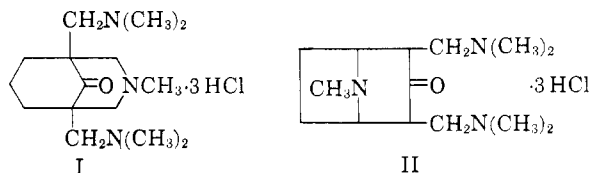
(1) E. F. L. J. Anet, G. K. Hughes, D. Marmion, and E. Ritchie, *Australian J. Sci. Research, Ser. A*, 3, 330 (1950).

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 shown² 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.



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-dicarboxylate² 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 $C_{13}H_{19}O_3N$: 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 $C_{12}H_{20}O_3NCl$: 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

(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).

warmed until a solution was obtained. The solution was stirred at 35° for 25 hr. During this time the product separated as an oily upper layer. The mixture was extracted with ether, the extract was dried over magnesium sulfate and the ether was removed. The oily base was dissolved in acetone and the solution was treated with hydrogen chloride. The solution was concentrated and cooled; the precipitated hydrochloride weighed 16.9 g.; m.p. 177–178° (dec.). After the filtrate had been concentrated and cooled, a further amount (2.5 g.) of product was obtained; total yield 66%; m.p. 176–177° (dec.).

Anal. Calcd. for C₁₅H₂₄ONCl: C, 53.98; H, 7.25; Cl, 10.62. Found: C, 53.86; H, 7.31; Cl, 10.51.

A solution of 3.2 g. (0.01 mole) of the oily base and 3 ml. (0.05 mole) of methyl bromide in 35 ml. of absolute ethanol was heated at 65° for 36 hr. in a pressure bottle. Ether was added; the precipitated methobromide weighed 3.0 g. (77%); m.p. 197–198° (dec.) after two recrystallizations from ethanol-ether.

Anal. Calcd. for C₁₅H₂₆ONBr: C, 48.99; H, 6.68; Br,

3-Methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylic acid hydrochloride dihydrate. A solution of 1.0 g. of dimethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate hydrochloride in 5 ml. of 25% hydrochloric acid was refluxed for 1 hr. The solid which separated during this time weighed 0.6 g. (67%); m.p. 190–192° (dec.). After two recrystallizations from methanol, the product melted at 190–191° (dec.).

Anal. Calcd. for C₁₇H₁₆O₅NCl₂H₂O: C, 42.10; H, 6.43. Found: C, 42.04; H, 6.60.

In order to obtain the base, a solution of 1.5 g. of the hydrochloride dihydrate in 15 ml. of water which contained 10 drops of methanol was neutralized with 0.25 g. of sodium carbonate. The solution was cooled; the precipitate weighed 0.9 g. (72%); m.p. 136–137° (dec.). A sample, recrystallized from water, melted at 137° (dec.).

Anal. Calcd. for C₁₁H₁₅O₅NCH₂O: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.73; H, 6.43; N, 5.22.

1,5-Bis(dimethylaminomethyl)-3-methyl-3-azabicyclo[3.3.1]nonan-9-one trihydrochloride (I). To a stirred solution of 2.1 g. (0.031 mol.) of methylamine hydrochloride, 5.0 g. (0.062 mol.) of 37% formalin and 10 ml. of water there was added, dropwise, a solution of 2,6(bis(dimethylaminomethyl)-cyclohexanone dihydrochloride² in 15 ml. of water during a period of 15 min. The mixture was stirred for an additional 15 min., made alkaline with sodium hydroxide solution, and the base was extracted with ether. The solvent was removed from the dried extract and the residue was distilled; b.p. 80–82° (0.07 mm.); yield 2.0 g. (27%). The base, dissolved in ether, was treated with hydrogen chloride. The precipitated hygroscopic trihydrochloride, after recrystallization from methanol-ether, melted at 221–222° (dec.).

Anal. Calcd. for C₁₂H₃₂ON₃Cl₃: C, 47.81; H, 8.56; N, 11.16; Cl, 28.23. Found: C, 47.65; H, 8.30; N, 10.78; Cl, 27.90.

2,4-Bis(dimethylaminomethyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one trihydrochloride (II). A mixture of 3.0 g. (0.013 mole) of tropinone hydrobromide,⁴ 2.2 g. (0.027 mole) of dimethylamine hydrochloride, 0.82 g. (0.027 mole) of para-formaldehyde and 15 ml. of acetic acid was heated at 60–75° for 2 hr. The solvent was removed under reduced pressure, the oily residue was dissolved in water, and the solution was made alkaline with sodium hydroxide. After extraction with ether, the dried extract was treated with hydrogen chloride. The precipitate crystallized when it was heated with isopropyl alcohol; crude yield 1.4 g. (28%); m.p. 196–197° (dec.) after recrystallization from methanol ether.

(4) Purchased from Winthrop Laboratories, New York, N. Y.

Anal. Calcd. for C₁₄H₃₀ON₃Cl₃: C, 45.59; H, 8.20; N, 11.40, Cl, 28.84. Found: C, 45.95, H, 8.09; N, 11.25; Cl, 28.98.

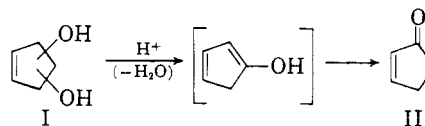
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A Simple Large Scale Synthesis of Cyclopentenone

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Received April 13, 1959

Although unsubstituted, cyclic, α - β -unsaturated ketones are among the most attractive starting materials for a variety of syntheses, they are not generally available in large quantities because of difficulties in their preparation. Cyclopentenone (II) is especially poor in this respect, the current methods of preparation involve allylic oxidation,¹ halogenation and dehydrohalogenation,² or pyrolysis of its cyclopentadiene adduct.³ All of these methods are tedious and unsatisfactory for large scale synthesis.



We wish to report a one step preparation of cyclopentenone by the distillation of the commercially available 3,4- and 3,5-cyclopentenediols^{4,5} from a trace of *p*-toluenesulfonic acid. The distillate, a mixture of cyclopentenone and water, gives, after drying and redistillation, yields on the order of 60% and the product is free from impurities. This sequence makes cyclopentenone the most readily available of all cyclic enones and will make it an attractive starting material for further investigation of five-membered ring chemistry.

EXPERIMENTAL

In a vacuum distilling apparatus equipped with a short-path distilling head was placed 100 g. (1.0 mole) of the cyclopentenediol mixture and 0.2 g. of *p*-toluenesulfonic acid. The pressure was reduced to 10 mm., the receiver was cooled in a Dry Ice-acetone bath, and the diol mixture was heated. When the temperature of the oil bath reached about

(1) W. Triebs, B. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

(2) E. J. Corey and K. Osugi, *Pharm. Bull. Japan*, **1**, 99 (1953).

(3) M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957).

(4) Columbia Southern Chemical Co., One Gateway Center, Pittsburgh, Pa.

(5) In our experience the commercial material is 60–70% 3,5- and 40–30% 3,4- diol. Either of the pure diols or the mixture is converted to cyclopentenone under the conditions of the reaction.