bonate, was added to 2 g. of wet Raney nickel paste[23] and the mixture was hydrogenated at 55–60° under an initial pressure of 52 pounds until the calculated amount of hydrogen had been absorbed (20 hr.). After removal of the catalyst by filtration, the cooled filtrate was acidified with concentrated hydrochloric acid. The precipitated 4-methyl-2-carboxyphenol weighed 0.75 g. (76%); m.p. 152–153°.

Structure proof of 6-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (54C). This procedure, with the use of 54C, was carried out in the manner mentioned above. The product, 6-methyl-2-carboxyphenol, weighed 0.3 g. (30%); m.p. 165–166°; reported[24] m.p. 167°; mixed m.p. with an authentic sample, 165–166°.

Reaction of 4,6-bis(dimethylaminomethyl)-2-carboxyphenol dihydrochloride (56C) with formaldehyde and dimethylamine. A mixture of 3.3 g. (0.01 mole) of 56C, 5.0 g. (0.06 mole) of formalin and 11.0 g. (0.06 mole) of 25% aqueous dimethylamine was heated on a steam bath for 3 hr. The mixture was made alkaline with potassium carbonate and then concentrated until most of the water had been removed. The residue was extracted with ether and the dried extract was treated with hydrogen chloride. The precipitated 2,4,6-tris(dimethylaminomethyl)phenol trihydrochloride (0.5 g.) was recrystallized from methanol; m.p. 276–277° (dec.); mixed m.p. with an authentic sample (33A), 276–277° (dec.).

2,6-Bis(dimethylaminomethyl)-4-hydroxyphenol dihydrochloride (76C). A mixture of 3.9 g. of 2,6-bis(dimethylaminomethyl)-4-benzyloxyphenol dihydrochloride (73C), 50 ml. of acetic acid and 2.5 g. of palladium on carbon[25] was hydrogenated under an initial pressure of 14 pounds for 15 min. The mixture was filtered and the solvent was removed under reduced pressure. The oily residue was crystallized from hot isopropyl alcohol; yield 2.5 g. (85%); m.p. 205–206° (dec.) after recrystallization from methanol-ether.

2,6-Bis(morpholinomethyl)-4-hydroxyphenol dihydrochloride (77C). A solution of 2.0 g. of 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol dihydrochloride (74C) in 30 ml. of 18% hydrochloric acid was heated for 3 hr. on a steam bath. The mixture was cooled and filtered to remove benzoic acid (0.45 g.). The water and hydrochloric acid were removed under reduced pressure and the residue was recrystallized from methanol-ether; yield 1.4 g. (91%); m.p. 115–116° (dec.). After the product had been dried at 65° (0.1 mm.) for 24 hr., it melted at 193–194° (dec.).

ANN ARBOR, MICH.

---

[23] Sponge Nickel Catalyst which was obtained from the Davison Chemical Company, Division of W. R. Grace and Company, Department T, Baltimore 3, Md.

[24] N. V. Sidgwick, *J. Chem. Soc.*, **117**, 396 (1920).

[25] Obtained from Baker and Company, Newark, N. J.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Disubstitution of Cycloalkanones in the Mannich Reaction

F. F. BLICKE AND F. J. McCARTY[1,2]

Received January 21, 1959

Ten bis(aminomethyl)cycloalkanones were prepared by the simultaneous introduction of two aminomethyl groups into a cycloalkanone by the use of a Mannich reaction. It was definitely established that the reaction product obtained from cyclohexanone, paraformaldehyde and dimethylamine hydrochloride was 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride and not the salt of the isomeric 2,2-disubstitution product.

The introduction of one aminomethyl group into a ketone by the use of a Mannich reaction has been reported in many instances but only a relatively few examples are known in which two aminomethyl groups have been introduced into a ketone either intentionally or fortuitously.

It was reported that acetone reacts with formaldehyde and dimethylamine[3,4] or diethylamine,[4,5] under certain conditions, with the formation of a 1,1-bis(dialkylaminomethyl)acetone, and the structures of these products have been definitely established.

From acetone, formaldehyde, and hexahydroazepine hydrochloride the disubstituted acetone 2-acetylpropane-1,3-bis(hexahydro-1-azepine) dihydrochloride has been obtained.[6]

1,1,1-Trifluoroacetone reacted with the methylols of piperidine, morpholine, and diisobutylamine to form products which appeared to be hydrates of the bis(aminomethyl)ketone.[7]

A disubstitution product obtained from methyl ethyl ketone, formaldehyde, and dimethylamine hydrochloride has been stated to be either 1-dimethylamino-4-(dimethylaminomethyl)-3-pentanone or 3,3-bis(dimethylaminomethyl)-2-butanone by Cardwell[4] but according to Barrett and Chambers[8] the product is the former compound; Haeussler and Schacht[9] claim that the product is the latter substance.

From propiophenone and from 3-acetylpyridine, β,β'-bis(1-piperidyl)pivalophenone and bis(1-piperidylmethyl)methyl-3-pyridyl ketone, respectively, were obtained by Mannich reactions.[10]

---

[1] This paper represents part of a dissertation submitted by F. J. McCarty for the Ph.D. degree in the University of Michigan.

[2] Sterling-Winthrop Fellow.

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

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

[5] A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).

[6] R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958).

[7] G. F. Grillot, S. Aftergut, S. Marmor, and F. Carrock, *J. Org. Chem.*, **23**, 386 (1958).

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

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

[10] J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *J. Am. Chem. Soc.*, **71**, 2048 (1949).

The object of this investigation was the discovery of a satisfactory method for the preparation of bis(aminomethyl)cycloalkanones by the use of the Mannich reaction.

It had been reported[11] that the interaction of cyclopentanone, formaldehyde, and morpholine hydrochloride yielded 2,5-bis(morpholinomethyl)-cyclopentanone dihydrochloride but the structure of the product was not proven.

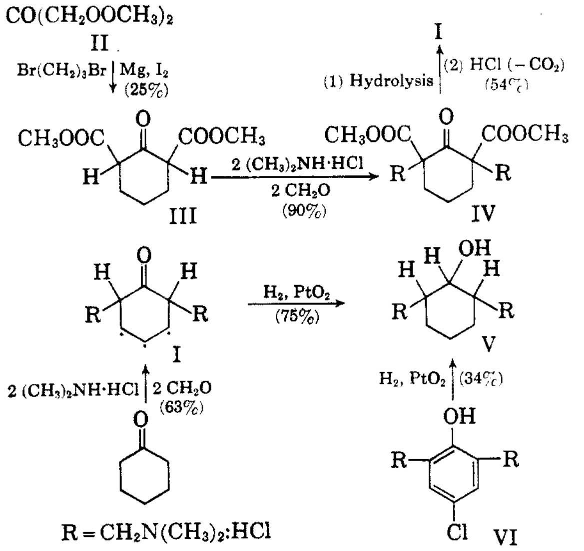
Compounds which were described[8] as 2,5-bis-(dimethylaminomethyl)cyclopentanone, 2,6-bis-(dimethylaminomethyl)cyclohexanone,[12] and 2,7-bis(dimethylaminomethyl)cycloheptanone have been obtained by the Mannich reaction but it was stated that "The possibility that the bis(dimethylaminomethyl)cycloalkanones are α,α-disubstituted cycloalkanones has not been rigorously disproved."

In a brief report, in which experimental procedures were not mentioned, Mühlstädt[12a] stated that he had obtained the dihydrochlorides of bis-(piperidinomethyl)cyclopentanone, bis(dimethylaminomethyl)- and bis(piperidinomethyl)cyclohexanone, bis(dimethylaminomethyl)- and bis-(piperidinomethyl)cycloheptanone. The structures of these compounds were proven by pyrolysis of the hydrochlorides of the bis(piperidinomethyl)-derivatives; the dimethylenecycloalkanones obtained were converted by hydrogenation into α,α'-dimethylcycloalkanones. This investigator reported melting points for the dihydrochlorides of the bis(dimethylaminomethyl) derivatives of cyclohexanone and cycloheptanone which are 15–25° lower than those found by Barrett and Chambers and by us.

We have found that, under proper conditions, cyclopentanone, cyclohexanone, cycloheptanone,[13] and cyclooctanone[14] will react with paraformaldehyde and a secondary amine hydrochloride in acetic acid to form salts of the bis(aminomethyl)-cycloalkanone type in 22–90% yields (Table I). In the case of the disubstitution product obtained from cyclohexanone, paraformaldehyde, and dimethylamine hydrochloride, it was proven by the two processes described below that the compound was 2,6 - bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) and not the salt of the isomeric 2,2-disubstitution product.

Diethyl acetonedicarboxylate had been shown[15] to react with 1,3-dibromopropane and magnesium to form diethyl cyclohexanone-2,6-dicarboxylate the structure of which was proven by its transformation into cyclohexanone by hydrolysis and decarboxylation.

We converted the commercially available dimethyl acetonedicarboxylate (II) into dimethyl cyclohexanone-2,6-dicarboxylate (III) and by the use of a Mannich reaction obtained dimethyl 2,6 - bis(dimethylaminomethyl)cyclohexanone - 2,6-dicarboxylate dihydrochloride (IV) from III. Samples of III and IV were converted into the corresponding secondary alcohols. After hydrolysis and decarboxylation of IV, a product was obtained which, in the form of its dihydrochloride, was identical with the product (I) prepared from cyclohexanone, paraformaldehyde and dimethylamine hydrochloride. Furthermore, two samples of the oxime dihydrochloride, one obtained from I which had been prepared by the use of cyclohexanone, the other from I which had been prepared by hydrolysis and decarboxylation of IV, proved to be identical. Consequently, compound I must be 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride.



In order to obtain further proof of the structure of I, this compound was reduced to the corresponding secondary alcohol (V). Compound V proved to be identical with the secondary alcohol which had been obtained previously[16] by simultaneous dehalogenation and ring hydrogenation of 2,6-bis-(dimethylaminomethyl)-4-chlorophenol dihydrochloride (VI). The structure of the last mentioned compound was established by its synthesis from 4-chlorophenol, formaldehyde, and dimethylamine.[16]

---

(11) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).

(12) It was stated by E. Jeney and T. Zsolnai [*Acta Microbiol. Acad. Sci. Hung.*, **2**, 249 (1955)] that 2,6-bis-(diethylaminomethyl)cyclohexanone was tested for its effect on Brucella abortus. Neither the method of preparation nor the physical properties of the product were mentioned in the abstract.

(12a) M. Mühlstädt, *Naturwissenschaften*, **45**, 240 (1958); *Chem. Abstr.*, **53**, 4274 (1959).

(13) F. F. Blicke, N. J. Doorenbos, and R. H. Cox, *J. Am. Chem. Soc.*, **74**, 2924 (1952).

(14) F. F. Blicke, J. Azuara, N. J. Doorenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).

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

(16) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1061 (1959).

The benzilate was prepared from the secondary alcohol (V), obtained from I, and from the secondary alcohol (V) prepared from VI; the two benzilates proved to be identical.

The diphenylacetyl and diphenylchloroacetyl derivatives of V were also synthesized.

The introduction of two aminomethyl groups into cyclohexanone unquestionably takes place in the 2 and 6 positions. Although this fact does not necessitate the assumption that disubstitution takes place in the same manner in the case of smaller or larger cycloalkanones, the disubstituted cycloalkanones listed in Table I have been described, arbitrarily, as compounds in which the introduced aminomethyl groups occupy positions which correspond to the 2,6 positions in cyclohexanone.

The highest yield of I (63%) was obtained by the use of the general procedure in which the cyclic ketone, paraformaldehyde, and the amine hydrochloride were heated in acetic acid solution at 95° for two and one-half hours. When changes were made in this process such as the use of absolute ethanol as a solvent instead of acetic acid, the use of more than two molecular equivalents of paraformaldehyde and dimethylamine hydrochloride, heating the reaction mixture for a longer time or at a higher or lower temperature, compound I was formed in lower yield. In a separate experiment, it was shown that I does not undergo even partial decomposition under the conditions employed in the general procedure.

2,6-Bis(diethylaminomethyl)- and 2,6-bis(dibenzylaminomethyl)cyclohexanone dihydrochloride could be obtained by the general procedure only when the reaction temperature was maintained below 80°. It was found that after the latter compound had been heated in acetic acid for two and one-half hours at 95°, dibenzylamine hydrochloride could be isolated in 88% yield. 2-(Dibenzylaminomethyl) cyclohexanone hydrochloride was prepared (reaction temperature 55–60°) and it was found that this substance also underwent decomposition when treated in the manner described above; dibenzylamine hydrochloride was obtained in 90% yield.

Although 2,6-bis(methylbenzylaminomethyl)-cyclohexanone dihydrochloride could be prepared by the general procedure (95°), we found that the monosubstitution product, 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride could be obtained in pure form only when the reaction mixture was maintained at 75–80°.

2,6 - Bis(methylbenzylaminomethyl)cyclohexanone dihydrochloride and 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride can be debenzylated by the use of hydrogen and palladium on carbon to the corresponding bis(methylaminomethyl) and the methylaminomethyl compounds, respectively. There was no reduction of the carbonyl group in these instances since both of the compounds exhibited the characteristic carbonyl infrared absorption band at 1690 cm.$^{-1}$ [17]; furthermore, an oxime was obtained from the methylaminomethyl compound.

2-(Dimethylaminomethyl)cyclohexanone hydrochloride reacted with paraformaldehyde and dimethylamine hydrochloride to form 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) and with paraformaldehyde and piperidine hydrochloride to yield 2-(dimethylaminomethyl)-6-(piperidinomethyl)cyclohexanone dihydrochloride.

Compound I reacted with phenylmagnesium bromide and also with phenyllithium to form 2,6-bis(dimethylaminomethyl) - 1 - phenylcyclohexanol, and with 2-pyridyllithium to form 2,6-bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol.[8] These alcohols were converted into the corresponding propionates by the use of propionic anhydride.

The oxime of I was reduced with lithium aluminum hydride to 2,6-bis(dimethylaminomethyl)-1-aminocyclohexane.

The secondary alcohol was obtained from 2,5-bis(dimethylaminomethyl)cyclopentanone dihydrochloride by the use of sodium borohydride.

When compound IV was hydrogenated catalytically in acetic acid solution, the corresponding carbinol was obtained in 46% yield. The process was repeated with methanol as the solvent. In this instance the yield of carbinol was only 12%, and from the reaction mixture there was also isolated dimethyl cyclohexanone-2,6-dicarboxylate and trimethylamine hydrochloride. It is assumed that these last two products were obtained by a Mannich reversal reaction in which the ester and dimethylhydroxymethylamine hydrochloride may have been formed; hydrogenation of the latter would account for the formation of the trimethylamine salt. It seems probable that the reaction mixture may also have contained dimethyl cyclohexanol-2,6-dicarboxylate since, in a separate experiment, it was shown that under the conditions used in the reaction dimethyl cyclohexanone-2,6-dicarboxylate can be reduced to the corresponding alcohol.

In order to determine the extent to which IV would undergo a reversal reaction under more favorable conditions, IV has heated in aqueous solution for 3.5 hours on a steam bath.[18] The products obtained from the reaction mixture were

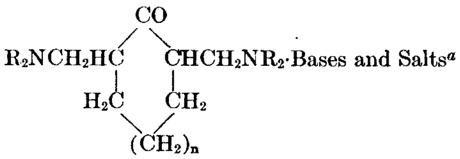
---

[17] It has been shown by R. Simonoff and W. H. Hartung (*J. Am. Pharm. Assoc. Sci. Ed.*, **35**, 306 (1946)) that in the debenzylation of α-benzylamino and α-dibenzylamino ketones with palladium on carbon either the α-amino ketone or the corresponding secondary alcohol can be obtained.

[18] An instance of the reversal of a Mannich product under similar conditions was reported by W. E. Bachmann and L. B. Wick [*J. Am. Chem. Soc.*, **72**, 3388 (1950)].

TABLE I

BIS(AMINOMETHYL)CYCLOALKANONE BASES AND SALTS



						Analyses, %							
			Yield,			Carbon		Hydrogen		Nitrogen		Halogen	
	n	· NR_2	%	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	0	$N(CH_3)_2$	32	187–188[b]	$C_{11}H_{24}ON_2Cl_2$	48.71	48.80	8.92	8.86	10.33	10.08	26.15	25.89
2	0	$N(CH_3)_2$	31	198–199	$C_{11}H_{24}ON_2Br_2$	36.67	36.91	6.71	6.57	7.78	7.86	44.38	43.95
3	0	C_4H_8ON[c]	69	202–203[d]	$C_{15}H_{28}O_3N_2Cl_2$					7.89	7.95	19.96	19.85
4	1	$NHCH_3$[e]	42	167–168	$C_{10}H_{22}ON_2Cl_2$	46.70	46.44	8.63	8.71	10.90	10.60	27.58	27.15
5	1	$N(CH_3)_2$	63	177–178[f]	$C_{12}H_{26}ON_2Cl_2$	50.51	50.55	9.19	9.17	9.82	10.12	24.85	24.56
6	1	$N(CH_3)_2$		80–81[g,h] (0.05 mm.)	$C_{12}H_{24}ON_2$	67.89	68.22	11.40	11.52				
7	1	$N(CH_3)_2$	8	188–189	$C_{12}H_{26}ON_2Br_2$	38.51	38.64	7.01	7.04	7.49	7.30	42.72	42.36
8	1	$N(C_2H_5)_2$		137–138	$C_{28}H_{38}O_{15}N_8$	46.29	46.32	5.27	5.28				
9	1	$N(C_2H_5)_2$	22	110–111[h] (0.2 mm.)	$C_{16}H_{32}ON_2$	71.59	71.52	12.02	11.80	10.44	9.85		
10	1	C_4H_8ON	57	163–164	$C_{16}H_{30}O_3N_2Cl_2$	52.04	51.63	8.19	8.17	7.59	7.66	19.20	18.80
11	1	$C_5H_{10}N$[i]		162–163	$C_{30}H_{38}O_{15}N_8$	48.00	48.08	5.10	5.20				
12	1	$C_5H_{10}N$	34	83–84[j]	$C_{18}H_{32}ON_2$	73.94	74.22	11.03	10.89				
13	1	$N(CH_3)CH_2C_6H_5$	55	169–170	$C_{24}H_{34}ON_2Cl_2$	65.89	65.79	7.83	7.99	6.40	6.43	16.21	15.97
14	1	$N(CH_2C_6H_5)_2$	90	249–250[k]	$C_{36}H_{42}ON_2Cl_2$	73.34	73.14	7.18	7.28			12.03	12.03
15	1	$N(CH_2C_6H_5)_2$		108–109[j]	$C_{36}H_{40}ON_2$	83.70	83.58	7.80	7.91	5.42	5.62		
16	2	$N(CH_3)_2$	42	168–169[l]	$C_{13}H_{28}ON_2Cl_2$	52.17	52.16	9.43	9.45	9.36	9.51	23.69	23.47
17	3	$N(CH_3)_2$	43	179–180	$C_{14}H_{30}ON_2Cl_2$	53.68	53.47	9.65	9.64	8.95	8.85	22.63	22.16

[a] Dihydrochloride, dihydrobromide, or dipicrate. [b] Ref. 8, m.p. 185–186°. [c] Morpholino. [d] Ref. 11, m.p. 195°. [e] Obtained by debenzylation of compound 13. [f] Ref. 8, m.p. 169–170°. Ref. 12a, m.p. 152–153°. [g] Ref. 8, b.p. 90–94° (0.4 mm.). [h] B.p. of base. [i] Piperidino. [j] M.p. of base. [k] Softened at 160°. [l] Ref. 8, m.p. 170–171°. Ref. 12a, m.p. 153–156°.

Compounds 1, 2 and 3 were recrystallized from methanol; 4 from isopropyl alcohol; 5, 7, 13, 14, 16, and 17 from methanol-ether; 8, 10, 11, and 15 from ethanol; 12 from petroleum ether (60–75°).

dimethyl cyclohexanone-2,6-dicarboxylate (47%), formaldehyde and dimethylamine hydrochloride.[19]

EXPERIMENTAL

Bis(aminomethyl)cycloalkanone dihydrochlorides. General procedure. (Table I, compounds 1, 5, 10, 13, 16, and 17). A mixture of 0.1 mole of the cycloalkanone, 0.2 mole of paraformaldehyde, 0.2 mole of the amine hydrochloride, and 40 ml. of acetic acid was maintained at 95° for 2.5 hr. The mixture was shaken occasionally until a solution was obtained. The solvent was removed on a steam bath under reduced pressure. The oily residue[20] was dissolved in 70 ml. of hot acetone, the solution was cooled and the precipitated dihydrochloride was recrystallized.

Instances in which compounds reported in Table I were prepared by a variation of the general procedure or by a different process are mentioned below.

Compound 12. Since the crystalline dihydrochloride could not be purified by recrystallization, it was converted into the solid base which was then purified by recrystallization from petroleum ether (60–75°). The dipicrate (11) was prepared in ethanol.

Compound 9. The reaction temperature was maintained at 75–80°, and after removal of the solvent, the residue was made alkaline and the oily product was distilled. The first fraction (9.0 g.), which boiled at 73–80° (0.4 mm.),[21] proved to be 2-(diethylaminomethyl)cyclohexanone. The picrate melted at 118–119° after recrystallization from water.

Anal. Calcd. for $C_{17}H_{24}O_8N_4$: C, 49.51; H, 5.87. Found: C, 49.50; H, 5.92.

The second fraction (6.0 g.), b.p. 110–111° (0.2 mm.), was found to be compound 9. Since the dihydro hloride was found to be very hygroscopic, a sample of the base was dissolved in ethanol and the solution was treated with picric acid whereupon the dipicrate (8) precipitated.

Compound 14. This product was prepared by the general procedure but it was necessary to maintain the temperature at 55–60°, and 160 ml. of acetic acid was employed as solvent. A portion of the dihydrochloride was converted into the base (15).

The unfavorable effect of a higher temperature in the preparation of 14 was shown by the following experiment. A mixture of 2.0 g. of 14 and 10 ml. of acetic acid was heated at 95° for 2.5 hr. and the solvent was then removed. The solid residue, after it had been purified by boiling it with acetone, was found to be dibenzylamine hydrochloride; yield 1.4 g. (88%); m.p. and mixed m.p. 257° (dec.).

Compound 2. A mixture of 8.4 g. (0.1 mole) of cyclopentanone, 31.5 g. (0.25 mole) of dimethylamine hydrobromide, 9.0 g. (0.3 mole) of paraformaldehyde and 50 ml. of absolute ethanol was refluxed for 24 hr. The precipitated product (11.0 g., 31%, m.p. 196–199°) was recrystallized from methanol.

Compound 3. This compound was synthesized in the same general manner as 2 except that 0.25 mole of morpholine hydrochloride was used and the reaction mixture was refluxed for 17 hr.; the precipitated, crude product (24.0 g.) melted at 193–194° and at 202–203° after recrystallization from methanol.

Compound 7. This compound was prepared in the same general manner as 2 except that 0.1 mole of cyclohexanone was employed. Since the product did not precipitate from the reaction mixture, the solvent was removed under reduced pressure. The oily residue became crystalline when it was triturated with isopropyl alcohol; yield 7.0 g. After several recrystallizations from methanol-ether, 2.8 g. of pure product was obtained.

Effect of solvent. The very marked difference in the yield of compound I obtained by the use of acetic acid or ethanol as a solvent is shown by the following experiments.

(a) A mixture of 98.1 g. (1 mole) of cyclohexanone, 60.0 g. (2 moles) of paraformaldehyde, 163.1 g. (2 moles) of dimethylamine hydrochloride, and 400 ml. of acetic acid was heated at 95° for 2.5 hr. The solvent was removed under reduced pressure and the solid residue was refluxed for a short time with 500 ml. of acetone. The undissolved dihydrochloride (I) was filtered; yield 175.0 g. (62%); m.p. 177–178°. Upon removal of the acetone from the filtrate, treatment of the residue with alkali and distillation, 8.5 g. of 2-(dimethylaminomethyl)cyclohexanone was obtained; b.p. 100–103° (2[illegible] mm.).[22] The hydrochloride melted at 155°.[22]

(b) The experiment described above was repeated but in place of acetic acid, 400 ml. of absolute ethanol was used. After removal of the solvent under reduced pressure, the residue was treated with alkali and then distilled. There was obtained 23.0 g. of 2-(dimethylaminomethyl)cyclohexanone, b.p. 70–75° (0.4 mm.) (the hydrochloride melted at 155–156°) and 13.5 g. (6%) of the base of I which boiled at 93–97° (0.4 mm.)[23] (compound 6) (the dihydrochloride melted at 176–177°). An analytical sample of 6 boiled at 80–81° (0.05 mm.).

In an attempt to determine whether or not the yield of the disubstitution product would be increased by the use of amounts of paraformaldehyde and dimethylamine hydrochloride greater than two molecular equivalents, a mixture of 4.9 g. (0.05 mole) of cyclohexanone, 9.0 g. (0.3 mole) of paraformaldehyde, 20.5 g. (0.25 mole) of dimethylamine hydrochloride and 20 ml. of acetic acid was heated at 95° for 2.5 hr. After removal of the solvent, treatment of the residue with alkali and distillation, only 2.8 g. (8%) of the base of I (6) was obtained.

In order to determine whether or not compound I underwent partial decomposition during its preparation by the general procedure, a solution of 28.5 g. of this substance (m.p. 178–179°) in 40 ml. of acetic acid was heated at 95° for 2.5 hr., the solvent was removed under reduced pressure and the material was purified by boiling it with acetone. The recovered salt weighed 27.8 g.; m.p. 179–180°.

2-(Dibenzylaminomethyl)cyclohexanone hydrochloride. A mixture of 9.8 g. (0.1 mole) of cyclohexanone, 1.5 g. (0.05 mole) of paraformaldehyde, 11.7 g. (0.05 mole) of dibenzylamine hydrochloride, and 50 ml. of acetic acid was heated for 2.5 hr. at 55–65°. The solvent was removed under reduced pressure at a temperature below 65°. The oily residue was dissolved in hot acetone. The crystalline product which separated from the cold solution softened at 170° and melted at 239–240° (dec.); yield 16.3 g. (95%).

Anal. Calcd. for $C_{21}H_{26}ONCl$: C, 73.35; H, 7.62; Cl, 10.31. Found: C, 73.24; H, 7.48; Cl, 10.62.

The picrate, prepared from the hydrochloride in ethanol, melted at 159–160° after recrystallization from ethanol.

Anal. Calcd. for $C_{27}H_{28}O_8N_4$: C, 60.43; H, 5.26. Found: C, 60.48; H, 5.25.

It was found that when 2-(dibenzylaminomethyl)cyclohexanone hydrochloride was heated at 95° in acetic acid solution for 2.5 hr. it, like the dihydrochloride of the corresponding disubstitution product, was decomposed almost completely with the formation of dibenzylamine hydrochloride in 90% yield.

2-(Methylbenzylaminomethyl)cyclohexanone hydrochloride. Cyclohexanone (15.0 g., 0.15 mole), 12.0 g. (0.076 mole) of

---

[19] This reversal also took place at room temperature and dimethyl cyclohexanone-2,6-dicarboxylate gradually precipitated from the aqueous solution.

[20] In a few instances the residue was obtained in a crystalline, acetone-insoluble form. The product was then refluxed with acetone for a short time and filtered.

[21] C. Mannich and P. Hönig (*Arch. Pharm.*, **265**, 598 (1927)), b.p. 117° (24 mm.).

[22] C. Mannich and R. Braun [*Ber.*, **53**, 1874 (1920)], b.p. 100° (13 mm.); m.p. hydrochloride, 152°.

[23] Ref. 8, b.p. 90–94° (0.4 mm.).

methylbenzylamine hydrochloride,[24] 2.3 g. (0.076 mole) of paraformaldehyde and 30 ml. of acetic acid were heated at 75–80° for 2.5 hr. After removal of the acetic acid under reduced pressure, the oily residue was dissolved in 50 ml. of acetone. The product precipitated upon the addition of ether; yield 15.0 g. (75%); m.p. 145–146°[25] after recrystallization from acetone.

Anal. Calcd. for $C_{15}H_{22}ONCl$: C, 67.28; H, 8.28; N, 5.23; Cl, 13.24. Found: C, 67.24; H, 8.32; N, 5.36; Cl, 13.02.

2,6-Bis(methylaminomethyl)cyclohexanone dihydrochloride (compound 4) by debenzylation of compound 13. A mixture of 6.5 g. of compound 13, 3.0 g. of 5% palladium on cabon[26] and 150 ml. of absolute ethanol was hydrogenated under an initial pressure of 55 pounds for 9 hr. After filtration, the solvent was removed and the oily residue was dissolved in isopropyl alcohol. Upon the addition of ether the hygroscopic product precipitated.

2-(Methylaminomethyl)cyclohexanone hydrochloride. A mixture of 7.0 g. of 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride, 3.0 g. of 5% palladium on carbon, and 150 ml. of absolute ethanol was hydrogenated under an initial pressure of 50 pounds for 15 min. The mixture was filtered and the solvent was removed under reduced pressure. The oily residue was dissolved in isopropyl alcohol and ether was added to precipitate the product; yield 3.6 g. (78%); m.p. 97–98°; m.p. 100–101° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_8H_{16}ONCl$: C, 54.08; H, 9.08; N, 7.88; Cl, 19.95. Found: C, 53.90; H, 9.02; N, 7.87; Cl, 19.55.

Oxime of 2-(methylaminomethyl)cyclohexanone hydrochloride. A solution was prepared from 1.0 g. of 2-(methylaminomethyl)cyclohexanone hydrochloride, 0.5 g. of hydroxylamine hydrochloride, 0.7 g. of potassium carbonate and 5 ml. of water. After 4 hr., the solution was saturated with potassium carbonate and extracted with ether. The ether solution was dried, treated with hydrogen chloride, and the precipitated oil was triturated with isopropyl alcohol whereupon it became crystalline; m.p. 192–193° (dec.) after recrystallization from methanol-ether; yield 0.4 g.

Anal. Calcd. for $C_8H_{17}ON_2Cl$: C, 49.87; H, 8.89; Cl, 18.40. Found: C, 49.67; H, 8.86; Cl, 18.58.

2-(Dimethylaminomethyl)cyclohexanone hydrochloride. In the preparation of this product, Mannich and Braun[22] used excess cyclohexanone as a solvent. It was found that a purer product was obtained when acetic acid was employed. A mixture of 19.6 g. (0.2 mole) of cyclohexanone, 3.0 g. (0.1 mole) of paraformaldehyde, 8.2 g. (0.1 mole) of dimethylamine hydrochloride and 40 ml. of acetic acid was heated on a steam bath for 2.5 hr. The solvent was removed, the solid residue was washed with acetone and filtered; m.p. 154–155°[27]; yield 14.5 g. (76%).

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) *from 2-(dimethylaminomethyl)cyclohexanone hydrochloride.* A mixture of 19.2 g. (0.1 mole) of 2-(dimethylaminomethyl)cyclohexanone hydrochloride, 3.0 g. (0.1 mole) of paraformaldehyde, 8.2 g. (0.1 mole) of dimethylamine hydrochloride, and 40 ml. of acetic acid was treated as described in the general procedure; yield 19.7 g. (69%); m.p. and mixed m.p. 176–177°.

2-(Dimethylaminomethyl)-6-(piperidinomethyl)cyclohexanone dihydrochloride. By the use of the general procedure, a mixture of 19.2 g. of 2-(dimethylaminomethyl)cyclohexanone hydrochloride, 3.0 g. of paraformaldehyde, 12.2 g. of piperidine hydrochloride, and 40 ml. of acetic acid yielded 15.5 g. (48%) of product; m.p. 166–167°; m.p. 168–169° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{15}H_{30}ON_2Cl_2$: C, 55.35; H, 9.30; N, 8.61; Cl, 21.80. Found: C, 55.01; H, 9.44; N, 8.22; Cl, 21.43.

Dimethyl cyclohexanone-2,6-dicarboxylate (III). A mixture of 10.0 g. (0.4 g. atom) of magnesium, 1.0 g. of iodine, and 200 ml. of absolute methanol was cooled until the reaction subsided; it was then refluxed for 1 hr. on a steam bath. The mixture was cooled in an ice bath and 70 g. of dimethyl acetonedicarboxylate[28] (II) (0.4 mole) was added. After the mixture had been shaken thoroughly, it was refluxed for 1 hr., placed in a pressure bottle, and 80.0 g. (0.4 mole) of 1,3-dibromopropane was added. The mixture was heated for 24 hr. on a steam bath, the solvent was removed, and the oily residue was mixed with 125 ml. of concentrated hydrochloric acid which had been diluted with an equal volume of water. The product was extracted with ether, the solvent was removed from the extract, and the oily residue was dissolved in 250 ml. of boiling methanol; 130 ml. of water was then added. The solution was cooled and the precipitated product (16.8 g.) was filtered; a further amount (5.8 g.) was obtained by concentration of the filtrate to one half of its original volume. After the material had been washed with 60% methanol, it was dissolved in 340 ml. of boiling methanol and 200 ml. of water was added. From the cooled mixture, 21.5 g. (25%) of product was obtained; m.p. 142–143°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.06; H, 6.59. Found: C, 56.07; H, 6.54.

Dimethylcyclohexanol-2,6-dicarboxylate. A mixture of 13.0 g. (0.06 mole) of dimethyl cyclohexanone-2,6-dicarboxylate, 0.3 g. of platinum dioxide, and 300 ml. of absolute methanol was hydrogenated for 1 hr. under an initial pressure of 50 pounds. After filtration of the mixture the solvent was removed from the filtrate. The oily residue was crystallized from petroleum ether (60–75°) and then recrystallized from the same solvent; m.p. 65–66°; yield 10.2 g. (78%).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.60; H, 7.51.

Dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride (IV). A mixture of 16.0 g. (0.074 mole) of dimethyl cyclohexanone-2,6-dicarboxylate, 12.0 g. (0.148 mole) of dimethylamine hydrochloride, 15.0 g. (0.185 mole) of 37% formalin, and 80 ml. of methanol was refluxed for 2 hr. The methanol and water were removed and the solid residue was refluxed with 60 ml. of acetone for 10 min. The cooled suspension was filtered and the product was washed with acetone; yield 26.8 g. (90%); m.p. 185–186°; m.p. 186–187° after recrystallization from methanol-ethyl acetate.

Anal. Calcd. for $C_{16}H_{30}O_5N_2Cl_2$: C, 47.89; H, 7.54; N, 6.98; Cl, 17.67. Found: C, 47.97; H, 7.66; N, 6.82; Cl, 17.75.

Dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanol-2,6-dicarboxylate dihydrochloride. A mixture of 3.5 g. of dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride (IV), 0.2 g. of platinum dioxide, and 50 ml. of acetic acid was hydrogenated at 60° under an initial pressure of 56 pounds for 5 hr. After removal of the catalyst and solvent, the oily residue was dissolved in hot isopropyl alcohol. The product, which precipitated from the cold solution, weighed 1.6 g. (46%); m.p. 205–206° (dec.) after recrystallization from methanol-ethyl acetate.

Anal. Calcd. for $C_{16}H_{32}O_5N_2Cl_2$: C, 47.64; H, 8.00; Cl, 17.58. Found: C, 47.75; H, 7.86; Cl, 17.30.

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I). *Formation by hydrolysis and decarboxylation of* IV. A mixture of 3.0 g. (0.0075 mole) of IV and 27 ml. of 5% aqueous sodium hydroxide solution (0.034 mole) was stirred for 7 hr. Concentrated hydrochloric acid (4.0 g., 0.04 mole) was added, dropwise, whereupon carbon dioxide was evolved. The mixture was then made basic with sodium hydroxide solution, saturated with sodium chloride, and extracted with ether. The dried ether solution was treated with hydrogen chloride. The ether was decanted from the pre-

---

(24) F. F. Blicke and Chi-Jung Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(25) A. L. Morrison and H. Rinderknecht [*J. Chem. Soc.*, 1510 (1950)] obtained the product in 54% yield by the use of alcohol as a solvent; m.p. 144–146°.

(26) Obtained from Baker and Company, Newark, N. J.

(27) Ref. 22, m.p. 152°.

(28) Purchased from Chas. Pfizer and Company.

cipitated oil and the latter was triturated with 20 ml. of isopropyl alcohol whereupon it crystallized; after filtration, 0.9 g. of product was isolated; m.p. 179–180°. A further amount (0.25 g.) of product was obtained by addition of ether to the isopropyl alcohol filtrate; total yield 54%. A mixture of the product and 2,6-bis(dimethylaminomethyl) cyclohexanone dihydrochloride, obtained from cyclohexanone, melted at 179–180°.

Anal. Calcd. for $C_{12}H_{26}ON_2Cl_2$: Cl, 24.85. Found: Cl, 24.50.

Oxime of 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride. Two samples of 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I), one obtained by the use of cyclohexanone, the other prepared by hydrolysis and decarboxylation of IV, were converted into oximes in the manner described below; both oxime salts, after recrystallization from methanol, melted at 221–222° (dec.); mixed m.p. 221–222° (dec.).

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (20.0 g., 0.07 mole), 20.0 g. (0.29 mole) of hydroxylamine hydrochloride, 30 ml. of pyridine, and 200 ml. of absolute ethanol were refluxed for 4 hr. The solvents were removed under reduced pressure, the residue was dissolved in a small amount of water, and the solution was made basic with sodium hydroxide. After saturation with sodium chloride, the mixture was extracted with ether. The dried ether solution was treated with hydrogen chloride; an oil precipitated. After decantation of the ether, the oil was heated with isopropyl alcohol whereupon it crystallized. After recrystallization from methanol-ether, the oxime dihydrochloride melted at 221–222° (dec.); yield 14.0 g. (67%).

Anal. Calcd. for $C_{12}H_{27}ON_3Cl_2$: C, 48.00; H, 9.07; Cl, 23.61. Found: C, 48.14; H, 8.98; Cl, 23.23.

2,6-Bis(dimethylaminomethyl)cyclohexanol dihydrochloride (V). A mixture of 25.0 g. of compound I, 225 ml. of methanol, and 0.25 g. of platinum dioxide was hydrogenated until the calculated amount of hydrogen was absorbed (4 hr.). The catalyst was removed and the solution was concentrated to one half of its original volume. Ether was added until the solution became cloudy. It was then cooled whereupon 19.0 g. (75%) of product precipitated; m.p. 229–230° (dec.); m.p. and mixed m.p. 231–232° (dec.)[16] after recrystallization from methanol-ether. The product was very hygroscopic.

The dipicrate, prepared in ethanol, melted at 198–199° after recrystallization from water; mixed m.p. 197–198°.[16]

Diphenylacetate of V. A mixture of the base, obtained from 5.0 g. of V, 40 ml. of methyl ethyl ketone, and 4.0 g. of diphenylacetyl chloride[29] was heated on a steam bath for 15 min. The precipitated product (3.5 g.) was filtered. Treatment of the filtrate with hydrogen chloride yielded an additional 3.0 g. After two recrystallizations from methanol-ether, the material melted at 246–247° (dec.); yield 3.8 g. (46%).

Anal. Calcd. for $C_{26}H_{38}O_2N_2Cl_2$: C, 64.86; H, 7.96; N, 5.82; Cl, 14.73. Found: C, 64.56; H, 8.11; N, 5.68; Cl, 14.40.

Diphenylchloroacetate of V. The base of V (4.4 g.), dissolved in 60 ml. of methyl ethyl ketone, was added, during a period of 1 hr., to a stirred solution of 5.5 g. of diphenylchloroacetyl chloride[30] dissolved in 60 ml. of methyl ethyl ketone. The mixture was heated for 15 min. on a steam bath. The precipitate (V) was removed by filtration. When the filtrate was treated with ethereal hydrogen chloride, an oil precipitated. The solvents were decanted and the oil was heated with isopropyl alcohol whereupon it became crystalline; yield 1.3 g.; m.p. 241–242° (dec.) after recrystallization from methanol-ether.

Anal. Calcd. for $C_{26}H_{37}O_2N_2Cl_3$: C, 60.52; H, 7.23; N, 5.43; Cl, 20.62. Found: C, 60.38; H, 7.41; N, 5.23; Cl, 20.55.

Benzilate of V. The base, obtained from 10.0 g. of V, was added with stirring, slowly and dropwise, to 9.3 g. of molten diphenylchloroacetyl chloride which was cooled in an ice bath. The mixture was then heated on a steam bath for 10 min., 25 ml. of water was added to the cooled mixture, and it was then acidified with hydrochloric acid. The oily material was extracted with ether and the ether solution was discarded. The aqueous solution was made alkaline with sodium hydroxide, the mixture was extracted with ether, and the dried extract was treated with hydrogen chloride. The precipitated, hygroscopic salt was recrystallized from methanol-ether; yield 7.0 g. (50%); m.p. 254° (dec.).

Anal. Calcd. for $C_{26}H_{38}O_3N_2Cl_2$: C, 62.76; H, 7.70; N, 5.63; Cl, 14.25. Found: C, 62.74; H, 7.82; N, 5.53; Cl, 14.02.

A sample of the base of V, which had been prepared from VI,[16] was converted into the benzilate in the manner described above; m.p. and mixed m.p. 254° (dec.).

2,6-Bis(dimethylaminomethyl)-1-phenylcyclohexanol. (a) 2,6-Bis(dimethylaminomethyl)cyclohexanone (42.4 g.) was added, dropwise, to a stirred solution of phenylmagnesium bromide which had been prepared from 63.0 g. of bromobenzene, 9.7 g. of magnesium and 1500 ml. of ether. The mixture was refluxed for 2 hr., decomposed with ammonium chloride solution, the ether layer was separated, washed with water, and the solvent was removed. The residue was distilled; b.p. 136–138° (0.1 mm.); yield 21.5 g. (37%).

Anal. Calcd. for $C_{18}H_{30}ON_2$: C, 74.44; H, 10.41. Found: C, 74.54; H, 10.36.

The dihydrochloride, obtained by the use of ethereal hydrogen chloride, melted at 269–270° (dec.) after recrystallization from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_{18}H_{32}ON_2Cl_2$: C, 59.50; H, 8.88; N, 7.71; Cl, 19.52. Found: C, 59.30; H, 8.91; N, 7.67; Cl, 19.17.

The dipicrate, prepared in ethanol, melted at 195–196° after recrystallization from ethanol.

Anal. Calcd. for $C_{30}H_{36}O_{15}N_8$: C, 48.13; H, 4.85. Found: C, 48.25; H, 4.97.

(b) A stirred solution of phenyllithium, prepared from 47.0 g. of bromobenzene, 4.2 g. of lithium, and 500 ml. of ether, was cooled to −5° and 59.3 g. of 2,6-bis(dimethylaminomethyl)cyclohexanone, dissolved in 100 ml. of ether, was added. The mixture was stirred for 1 hr., cooled and decomposed with saturated ammonium chloride solution. The ether layer was separated, washed with water, dried, and the solvent was removed. The oily residue was distilled; b.p. 128–131° (0.3 mm.); yield 45 g. (55%). The solidified product was recrystallized from petroleum ether (60–75°); m.p. 71–73°.

The dihydrochloride, prepared by the use of ethereal hydrogen chloride, melted at 276–277° (dec.) after recrystallization from isopropyl alcohol-ethyl acetate; mixed m.p. 275–277° (dec.).

The dipicrate, after recrystallization from ethanol, melted at 201–202°.

The base, dissolved in ether, was treated with excess methyl bromide. After several hours, the dimethobromide precipitated; m.p. 301–302° (dec.) after recrystallization from isopropyl alcohol and then from methanol-ether.

Anal. Calcd. for $C_{20}H_{36}ON_2Br_2$: C, 50.02; H, 7.56; Br, 33.27. Found: C, 49.99; H, 7.69; Br, 33.05.

The dimethiodide was obtained in a similar manner from the base and methyl iodide; m.p. 283–284° (dec.) after recrystallization from isopropyl alcohol and then from methanol-ether.

Anal. Calcd. for $C_{20}H_{36}ON_2I_2$: C, 41.82; H, 6.32; I, 44.19. Found: C, 41.91; H, 6.32; I, 44.40.

2,6-Bis(dimethylaminomethyl)-1-phenyl-1-propionyloxycyclohexane dihydrochloride. A mixture of 8.0 g. of 2,6-bis(dimethylaminomethyl)-1-phenylcyclohexanol dihydrochlo-

---

(29) J. S. Pierce, W. W. Haden, and R. D. Gano, *J. Am. Chem. Soc.*, **67**, 408 (1945).

(30) F. E. King and D. Holmes, *J. Chem. Soc.*, 166 (1947).

ride and 80 ml. of propionic anhydride was heated at 110–120° for 6 hr. and the excess anhydride was then removed. The oily residue was dissolved in about 100 cc. of hot acetone and the solution was cooled whereupon the product precipitated; yield 8.1 g. (88%); m.p. 228–229° after recrystallization from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_{21}H_{36}O_2N_2Cl_2$: C, 60.13; H, 8.65; N, 6.68; Cl, 16.90. Found: C, 59.95; H, 8.44; N, 7.02; Cl, 16.55.

The dimethobromide, prepared from the base in ether, melted at 220–221° (dec.) after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{23}H_{40}O_2N_2Br_2$: C, 51.50; H, 7.52; Br, 29.80. Found: C, 51.60; H, 7.59; Br, 29.85.

2,6-Bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol. A solution of butyllithium was prepared from 2.8 g. of lithium, 27.5 g. of butyl bromide, and 400 ml. of ether at −10° under nitrogen. The solution was cooled to −60°, stirred, and 28.5 g. of 2-bromopyridine, dissolved in 50 ml. of ether, was added during a period of 10 min. The stirred solution was maintained at −60° and 34 g. of 2,6-bis(dimethylaminomethyl)cyclohexanone, dissolved in 100 ml. of ether, was added during a 15-min. period. The material was stirred at −40° for 2 hr., the temperature was allowed to rise to room temperature and the mixture was decomposed with ammonium chloride solution. The ether layer was separated, dried, and the solvent was removed. The oily residue was distilled; b.p. 130–133° (0.1 mm.)[31]; yield 19.0 g. (41%). After the product became crystalline, it was recrystallized from petroleum ether (60–75°); m.p. 66–67°.

Anal. Calcd. for $C_{17}H_{29}ON_3$: C, 70.07; H, 10.03. Found: C, 70.11; H, 10.07.

When the base, dissolved in acetone, was treated with hydrogen chloride, the trihydrochloride precipitated. After recrystallization from isopropyl alcohol and then from methanol–ethyl acetate, the salt melted at 258–259° (dec.).

Anal. Calcd. for $C_{17}H_{32}ON_3Cl_3$: C, 50.94; H, 8.05; N, 10.49; Cl, 26.54. Found: C, 50.74; H, 7.96; N, 10.25; Cl, 26.95.

2,6-Bis(dimethylaminomethyl)-1-(2-pyridyl)-1-propionyloxycyclohexane dihydrochloride. A mixture of 10.0 g. of 2,6-bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol trihydrochloride and 100 ml. of propionic anhydride was heated at 110–120° for 12 hr. After filtration, the excess anhydride was removed and the residue was purified by refluxing it with 100 ml. of acetone in which the product did not dissolve. The filtered material (7.6 g., 67%) was recrystallized from methanol–ethyl acetate–ether; m.p. 249–250° (dec.).

Anal. Calcd. for $C_{20}H_{35}O_2N_3Cl_2$: C, 57.15; H, 8.39; N, 9.98; Cl, 16.87. Found: C, 57.08; H, 8.36; N, 9.71; Cl, 16.63.

2,6-Bis(dimethylaminomethyl)-1-aminocyclohexane tripicrate. The base of the oxime, obtained from 12.0 g. of the oxime of I, was dissolved in 125 ml. of ether. The solution was added, dropwise, to a stirred suspension of 6.1 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred and refluxed for 4 hr. and then stirred for 9 hr. at room temperature. Water (12 ml.) was added, dropwise, to the stirred mixture and then 6 ml. of 15% sodium hydroxide solution was added. After filtration, the dried ether filtrate was treated with hydrogen chloride. The crystalline, very hygroscopic precipitate (10.5 g.) was dissolved in ethanol and picric acid, dissolved in the same solvent, was added. The precipitated tripicrate was recrystallized from water; m.p. 230–231° (dec.).

Anal. Calcd. for $C_{30}H_{36}O_{21}N_{12}$: C, 40.01; H, 4.03. Found: C, 40.05; H, 4.28.

2,5-Bis(dimethylaminomethyl)cyclopentanol dihydrochloride. A solution of 5.0 g. of 2,5-bis(dimethylaminomethyl)-cyclopentanone dihydrochloride in 8 ml. of water was added, dropwise, during a period of 20 min. to a stirred, cooled solution of 1.6 g. of sodium borohydride in 8 ml. of water. The mixture was stirred for 2 hr., decomposed with excess sodium hydroxide solution and extracted with ether. The dried ether solution was treated with hydrogen chloride and the precipitated salt was recrystallized from ethanol; yield 4.0 g. (80%); m.p. 226–228°.

Anal. Calcd. for $C_{11}H_{26}ON_2Cl_2$: C, 48.33; H, 9.59; N, 10.25; Cl, 25.94. Found: C, 48.29; H, 9.52; N, 9.97; Cl, 25.67.

Mannich reversal of dimethyl 2,6-bis(dimethylaminomethyl)-cyclohexanone-2,6-dicarboxylate dihydrochloride (IV). (a) After 15.0 g. of IV, 0.2 g. of platinum dioxide, and 150 ml. of absolute methanol had been hydrogenated for 1 hr. under an initial pressure of 50 pounds, the mixture was filtered, about one half of the solvent was removed, ether was added, and the mixture was placed in a refrigerator for 7 days. The precipitate (5.5 g.) of crude dimethyl 2,6-bis-(dimethylaminomethyl)cyclohexanol-2,6-dicarboxylate dihydrochloride was filtered and recrystallized five times from methanol–ethyl acetate; yield 1.8 g. (12%); m.p. 201–202° (dec.); mixed m.p. 205–206° (dec.).

The filtrate was concentrated to a small volume and cooled. The filtered precipitate (0.7 g.), dimethyl cyclohexanone-2,6-dicarboxylate, melted at 142–143°; mixed m.p. 142–143°. The filtrate, when treated with ether, yielded an oil which was dissolved in hot isopropyl alcohol. When the solution was cooled, 1.5 g. of trimethylamine hydrochloride was obtained; m.p. 274–275° (dec.) after recrystallization from isopropyl alcohol; mixed m.p. 276–277° (dec.). An aqueous solution of the trimethylamine hydrochloride was treated with picric acid; the m.p. and mixed m.p. of the precipitated picrate was 217–219°.

(b) A solution of 4.0 g. of dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride in 25 ml. of water was heated on a steam bath for 3.5 hr. Throughout the experiment a stream of air, which passed through the mixture, carried the evolved formaldehyde into a solution of 2,4-dinitrophenylhydrazine.[32] At the end of 30 min., dimethyl cyclohexanone-2,6-dicarboxylate (1.0 g., 47%) (m.p. and mixed m.p. 141–142°), which had precipitated, was removed by filtration. The solvent was removed under reduced pressure and the oily residue was crystallized from isopropyl alcohol–ether and then recrystallized from isopropyl alcohol. This substance (0.3 g.) was dimethylamine hydrochloride; m.p. 167–168°; mixed m.p. 168–170°.

The precipitated 2,4-dinitrophenylhydrazone of formaldehyde (0.2 g.) was recrystallized from ethanol; m.p. and mixed m.p. 163–165°.[33,34]

ANN ARBOR, MICH.

---

[31] Ref. 8, b.p. 140–155° (0.5 mm.).

[32] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Ed. John Wiley and Sons, New York, N. Y., p. 219.

[33] N. R. Campbell [*Analyst*, **61**, 392 (1936)], m.p. 166°.

[34] In a duplicate experiment, a continuous stream of air was passed through the solution which was heated on a steam bath for 2 days. The precipitated hydrazone weighed 0.8 g.