[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XIX. Esters of Substituted 4-Piperidinols

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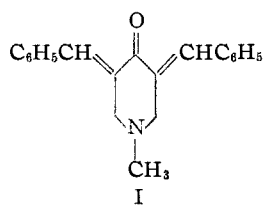
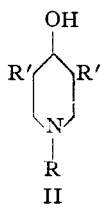
In the seventh paper of this series the benzoates and *p*-aminobenzoates of a series of 1-alkyl-4-piperidinols (II, R′ = H) were described.[2] The piperidinols were not isolated but were directly acylated in the form of their hydrochlorides, which were obtained by the hydrogenation of the corresponding 1-alkyl-4-piperidone hydrochlorides over Adams platinum oxide catalyst. In the present paper the preparation of 1-methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidinol and the three inactive stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols and certain of their esters are described.

The 1-alkyl-4-piperidinols were obtained in excellent yields by the hydrogenation of the corresponding piperidones over Raney nickel. These piperidinols were converted to the diphenylacetates and 1-methyl-4-piperidinol to the N-phenylcarbamate for pharmacological testing. The benzilic esters could not be prepared either by the direct interaction of benzilic acid with the piperidinol or with the corresponding 4-chloropiperidine according to the procedure of Horenstein and Pählicke.[3]



I



II

There are four theoretically possible stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols (II, R = CH_3; R′ = $C_6H_5CH_2$): *d*, *l*, and two *meso* forms. The hydrogenation of 1-methyl-3,5-dibenzal-4-piperidone[4] (I) under various conditions with platinum, nickel and copper chromite catalysts has yielded three different dibenzylpiperidinols, corresponding to the racemic and the two meso forms, as well as a product in which both benzene nuclei are hydrogenated. The separation of these hydrogenation products was difficult and recrystallization losses were high. The proportion of products from any one hydrogenation varied with the temperature, but in no case was the yield of any one more than 68% of the theoretical. The melting points and analyses of these piperidinols together with the catalysts and conditions under which they were produced are summarized in Table I.

TABLE I

HYDROGENATION PRODUCTS OF 1-METHYL-3,5-DIBENZAL-4-PIPERIDONE (I)

Compound	M. p., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H	Catalyst
1-Methyl-3,5-dibenzyl 4-piperidinol	155–157	$C_{20}H_{25}NO$	81.31	8.33	81.30	8.60	Ni,[a] $CuCrO_3$[b]
	183–184	$C_{20}H_{25}NO$	81.31	8.33	81.21	8.12	Pt,[c] Ni[d]
	177–178	$C_{20}H_{25}NO$	81.31	8.33	80.97	8.35	$CuCrO_3$[e]
1-Methyl-3,5-di-(hexahydrobenzyl)-4-piperidinol	176–178	$C_{20}H_{37}NO$	78.11	12.13	78.36	12.03	Ni[f]

[a] At 80° under 160 atmospheres of hydrogen for 5 hours. [b] At 200° under 160 atmospheres for 2.5 hours. [c] At 20–25° under 1 atmosphere for 1.5 hours. [d] At 60° under 105 atmospheres for 1 hour. [e] At 215° under 145 atmospheres for 5 hours. [f] At 80° under 160 atmospheres for 5 hours, followed by 180° for 3.5 hours.

With the platinum catalyst the carbon to carbon double bonds were hydrogenated in ten to fifteen minutes; the carbonyl group required an additional one to two hours. Hydrogenation over platinum was never very satisfactory, however, because a colored, oily product resulted and from this oily material pure crystalline compounds were obtained only with considerable difficulty. The nickel and copper chromite catalysts, on the other hand, gave white products that readily crystallized.

The diphenylacetate was prepared from the most abundant 1-methyl-3,5-dibenzyl-4-piperidinol (m. p. 177–178°). The salts of this ester are remarkably insoluble in water; in fact, none were found with sufficient solubility to permit pharmacological testing.

The properties and analyses of the hydrochlorides of the substituted piperidinol esters prepared in this work are summarized in Table II.

The 1-methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidyl diphenylacetate hydrochlorides were tested for antispasmodic activity by Dr. K. K. Chen and associates of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. On the isolated guinea pig ileum, the 1-methyl-4-piperidyl ester showed about 50% of the activity of atropine sulfate; the higher homologs showed only about 1% of this activity.

Experimental

Alkyl-di-(β-carbethoxyethyl)-amines.—These tertiary amines were prepared by the addition of the appropriate primary amine to ethyl acrylate. Methylamine adds to the acrylate in six hours at 65° to give an 80% yield of the

(1) Eli Lilly and Company Fellow, 1945–1947.
(2) Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929).
(3) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).
(4) McElvain and Rorig, THIS JOURNAL, **70**, 1820 (1948).

TABLE II

HYDROCHLORIDES OF SUBSTITUTED-4-PIPERIDINOL ESTERS

$RNCH_2CHR'CHOCOR''CHR'CH_2$ (bridged)

R is	R' is	R'' is	Formula	M. p., °C.	Analyses, % Cl Calcd.	Found
CH_3	H	$(C_6H_5)_2CH$	$C_{20}H_{24}ClNO_2$	115–120[a]	10.2	10.3
$(CH_3)_2CH$	H	$(C_6H_5)_2CH$	$C_{22}H_{28}ClNO_2$	174–176	9.5	9.8
n-C_4H_9	H	$(C_6H_5)_2CH$	$C_{23}H_{30}ClNO_2$	181–184	9.2	9.3
CH_3	H	C_6H_5NH	$C_{13}H_{19}ClN_2O_2$	228–229	13.1	13.5
CH_3	$C_6H_5CH_2$[b]	$(C_6H_5)_2CH$	$C_{34}H_{36}ClNO$	205–207	6.8	6.8

[a] Burtner and Cusic, THIS JOURNAL, **65**, 263 (1943), report this compound to be too hygroscopic for a melting point determination. [b] The piperidinol isomer melting at 177–178° was used to prepare this ester.

TABLE III

1-ALKYL-4-PIPERIDONES

Alkyl	Formula	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl[4]	.....	67–69	19	....	....	...	...	...	...
Isopropyl	$C_8H_{15}NO$	100–101	27	1.4627	0.9495	68.04	10.71	67.98	10.83
n-Butyl	$C_{19}H_{17}NO$	106–108	22	1.4595	0.9292	69.63	11.04	69.37	11.04

TABLE IV

1-ALKYL-4-PIPERIDINOLS

Alkyl	Formula	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl	.....	95–98	16[a]	....	....	...	...	...	...
Isopropyl	$C_8H_{17}NO$	113–114	23	1.4750	0.9529	67.09	11.97	67.14	12.11
n-Butyl	$C_9H_{19}NO$	127–129	22	1.4734	0.9411	68.72	12.18	68.42	12.00

[a] M. p. 24–27°; this compound has been prepared from chelidonic acid and reported to melt at 28° [Mills, Parkin and Ward, *J. Chem. Soc.*, 2622 (1927)]; its preparation from chelidonic acid also has been reported by Emmert, German Patent 292,871 [*Chem. Zentr.*, **87**, II, 116 (1916)]; Riegel and Reinhard, THIS JOURNAL, **48**, 1344 (1926); Burtner and Cusic, *ibid.*, **65**, 266 (1943).

tertiary amine[4]; isopropylamine requires ten hours at 175° to produce a 56% yield[5]; and *n*-butylamine requires ten hours at 125° to give a 73% yield of the tertiary amine. The properties of these tertiary amines corresponds to those previously reported.[6]

1-Alkyl-4-piperidones.—These piperidones were obtained by decarboxylation of the 1-alkyl-3-carbethoxy-4-piperidones, resulting from the Dieckmann cyclization of the above tertiary amino-esters, in the same manner as described for 1-methyl-4-piperidone.[4] The properties of these piperidones are listed in Table III.

1-Alkyl-4-piperidinols.—These compounds were obtained in 80–95% yields by the hydrogenation of the 1-alkyl-4-piperidones over Raney nickel at 140 atmospheres and 125° for two hours. The properties and analyses of these piperidinols are summarized in Table IV.

Hydrogenation of I to the 1-Methyl-3,5-dibenzyl-4-piperidinols. (a) **Adams Platinum Oxide Catalyst.**—A 2.00-g. sample of 1-methyl-3,5-dibenzal-4-piperidone hydrochloride in 33 ml. of 95% ethanol was hydrogenated over 0.20 g. of Adams platinum oxide catalyst. The amount of hydrogen necessary for saturation of the olefinic bonds was taken up in ten minutes. However, hydrogenation of the carbonyl group was so much slower that ninety-two minutes were required for completion. The free basic product was obtained by neutralization and crystallized from an aqueous ethanolic medium. The first crop of crystals, weighing 0.29 g., melted at 176.5–178.0°. Three lower-melting crops, totaling 0.20 g., were obtained by diluting the ethanolic mother liquors.

The first crop was recrystallized once from aqueous ethanol and twice from benzene–petroleum ether (b. p. 60–68°) solvent to give an analytical sample melting at 183.5–184.0°.

(b) **Raney Nickel Catalyst.**—The 183.5–184° isomer was also obtained by high pressure hydrogenation over Raney nickel. To 2.57 g. of 1-methyl-3,5-dibenzal-4-piperidone and 40 ml. of ethanol in a 270-ml. steel hydrogenation bomb was added 0.4 g. of Raney nickel catalyst prepared according to the directions of Pavlic and Adkins.[7] The bomb was filled with hydrogen to an initial pressure of 105 atmospheres and hydrogenated at 60° for fifty minutes. After filtering off the catalyst and removing the ethanol, the residue was taken up in hot petroleum ether (b. p. 60–68°). On cooling this solution 0.30 g. of material melting at 160–167° was obtained. Three recrystallizations from benzene–petroleum ether mixture raised the melting point to 182–183°. There was no depression of melting point when this sample was mixed with the one previously obtained by hydrogenation over Adams platinum oxide catalyst.

The above hydrogenation was repeated with 7 g. of I in 25 ml. of ethanol over 3 g. of the nickel catalyst at 80° and 160 atmospheres for five hours. After removal of the catalyst and solvent, the product was crystallized from a mixture of two volumes petroleum ether (b. p. 60–68°) and one volume benzene to give 2.4 g. of crude product melting 153–159°. This was recrystallized three times from the benzene–petroleum ether solvent to remove a higher melting impurity. The analytical sample thus obtained melted 155.0–156.0°.

(c) **Copper-Chromite Catalyst.**—The lower melting 1-methyl-3,5-dibenzyl-4-piperidinol was also obtained by the hydrogenation of a 2.0-g. sample of the dibenzal-piperidone over 1.0 g. of copper–chromite catalyst which

(5) Ziering, Berger, Heineman and Lee, *J. Org. Chem.*, **12**, 901 (1947), recently reported the preparation of this tertiary amine by allowing the reactants to stand in alcohol solution for one week at room temperature.

(6) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926).

(7) Adkins and Pavlic, *ibid*, **68**, 1471 (1946).

was prepared according to Adkins' directions.[8] The bomb was filled initially to a hydrogen pressure of 160 atmospheres, and the hydrogenation run at 200° for two and one-half hours. The recrystallized product (1.36 g.) melted 155–157°. A mixture of this product with that obtained from the Raney nickel hydrogenation melted at 154.5–157°.

When 5.0 g. of 1-methyl-3,5-dibenzal-4-piperidone in ethanol and 2.0 g. of copper chromite catalyst in a bomb containing 145 atmospheres of hydrogen were heated for five hours at 215°, 1.76 g. of white crystals melting at 175–177° was obtained by allowing the hydrogenation product to crystallize from a benzene–petroleum ether (b. p. 60–68°) mixture. This product then was recrystallized from the same solvent mixture to give an analytical sample of 1-methyl-3,5-dibenzyl-4-piperidinol melting at 177.0–178.5°. A mixture of a sample of this material with the 1-methyl-3,5-dibenzyl-4-piperidinol, m. p. 183.5–184.0°, was 153–170°.

1-Methyl-3,5-di-(hexahydrobenzyl)-4-piperidinol.—When the 1-methyl-3,5-dibenzyl-4-piperidinol, melting at 155–157°, was prepared by hydrogenation over Raney nickel the yields were low. A substantial portion of the crude product was much more soluble in petroleum ether (b. p. 60–68°) than the 155–157° melting product. The solubility suggested that the benzene rings had been hydrogenated in the reaction. However, no such product could be isolated from the crude mixture. Accordingly this petroleum ether soluble residue (4.20 g.) was rehydrogenated over fresh Raney nickel (4 g.) for three and one-half hours at 180° and 165 atmospheres hydrogen pressure. After removal of catalyst and solvent, the oily residue was caused to crystallize by rubbing with a few drops of petroleum ether. The resultant semi-crystalline mass then was dissolved in 25 ml. of petroleum ether (b. p. 60–68°) and cooled to −10° to precipitate a crop (1.08 g.) of white, fluffy needles melting 160–167°. These were recrystallized from 50 ml. of petroleum ether to give 0.80 g. of analytically pure product melting at 176.5–178.0°.

The analytical data for these 3,5-substituted N-methylpiperidinols are listed in Table I.

1-Methyl-4-chloropiperidine.—A solution of 7.0 g. of thionyl chloride in 25 ml. of dry benzene was added slowly to 4.15 g. of 1-methyl-4-piperidinol in 25 ml. of dry benzene. An oily precipitate formed almost immediately. This mixture was refluxed for one hour and cooled overnight. The solid, when filtered and dried, weighed 5.5 g., melted at 145–155°, and contained 42.7% chlorine (calcd. for $C_6H_{13}Cl_2N$: Cl, 41.7). When this salt was twice recrystallized from isopropanol and ether, the melting point was raised to 163–165°.

A solution of 4.65 g. of 1-methyl-4-chloropiperidine hydrochloride in 15 ml. of water was neutralized with an excess of potassium carbonate to salt out the free base. This was taken up in ether, dried, and distilled to give 2.81 g. of a liquid with a pungent, ammoniacal odor, b. p. 160–162° (733 mm.). Elementary analyses gave consistent but slightly high results for carbon and hydrogen. This may well be due to the presence of a small amount of the tetrahydropyridine, formed by dehydrohalogenation of the chloropiperidine during distillation. Accordingly the 1-methyl-4-chloropiperidine was redistilled at reduced pressure and three fractions collected. The middle cut, on analysis was found to contain less carbon and hydrogen than before but more than required by theory. There was insufficient material to redistil further.

Anal. Calcd. for $C_6H_{12}ClN$: C, 53.93; H, 9.06. Found: C, 54.87; H, 9.18.

After several days of standing, a brown gum began to deposit from this redistilled 1-methyl-4-chloropiperidine.

Hydrochlorides of Certain 1-Alkyl-4-piperidinol Esters.—The hydrochlorides of the various piperidyl diphenylacetates were obtained from the reaction of diphenylacetyl chloride with the piperidinol in refluxing benzene solution. On cooling the salt separated and was further purified by recrystallization from benzene. 1-Methyl-4-piperidyl N-phenylcarbamate was prepared from the piperidinol and phenyl isocyanate. The free base melted at 125–126°[9]; the hydrochloride was prepared by treatment of an ether solution of the free base with hydrogen chloride. The melting points and analyses of these hydrochlorides are listed in Table II.

In an attempt to prepare 1-methyl-4-piperidylbenzilate by the method of Horenstein and Pählicke,[3] 1.13 g. of freshly distilled 1-methyl-4-chloropiperidine was added to 1.94 g. of benzilic acid in 20 ml. of anhydrous isopropanol. After refluxing for thirteen hours, the solvent was removed by distillation *in vacuo*, and the residue was extracted with ether. From this ethereal extract 1.10 g. of benzilic acid was recovered. The ether-insoluble residue, which should have contained the 1-methyl-4-piperidyl-benzilate hydrochloride, was a water insoluble, brown gum from which no pure product could be isolated.

Summary

All of the possible inactive stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols and one of the 1-methyl-3,5-dihexahydrobenzyl-4-piperidinols have been isolated from the hydrogenation of 1-methyl-3,5-dibenzal-4-piperidone.

1-Methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidinol have been prepared by the hydrogenation of the corresponding 4-piperidones.

Certain esters of these piperidinols have been prepared for pharmacological testing.

Madison, Wisconsin Received January 2, 1948

(8) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wis., 1937, p. 13.

(9) Emmert, German Patent 292,871 [*Chem. Zentr.*, **87**, II, 116 (1916)] reported this compound to melt at 120°.