above oxidation, the crude product (isolated by ether extraction of the neutralized reaction mixture) contained not only the liquid 3-nitro-2-picoline but also a solid which slowly crystallized out of the mixture. The solid was collected and recrystallized from benzene–petroleum ether yielding colorless halogen-free crystals, m.p. 112–114°; picrate, m.p. 232–234° (dec.), mixed m.p. with a sample of 3-amino-2-picoline, prepared by the method of Dornow,[9] was not depressed.

A second preparation of 3-nitro-2-picoline utilized the replacement of the 3-amino group of 3-amino-2-picoline[15] by the diazonium procedure of Hodgson, Mahadevan and Ward,[11] which was followed closely. Thus, when the bright orange diazonium sulfate (from 1.08 g. (0.01 mole) of 3-amino-2-picoline, 1.8 g. (0.025 mole) of sodium nitrite, 15 ml. of concentrated sulfuric acid, 20 ml. of glacial acetic acid and 140 ml. of ether) was added to a slurry of cupro–cupri sulfite (from 10 g. of sodium sulfite and 10 g. of copper sulfate) and sodium nitrite (20 g., 0.26 mole) in 80 ml. of water, the solution was neutralized with 6 *N* sodium hydroxide and steam distilled, and the product was extracted from the distillate with petroleum ether, 0.2 g. (15%) of 3-nitro-2-picoline was obtained. When the diazonium cobaltinitrile procedure of Hodgson and Marsden[16] was used with 3-amino-2-picoline, none of the desired 3-nitro-2-picoline could be isolated from the tarry reaction product.

(15) Although the 3-amino-2-picoline used in these experiments was prepared according to the directions of Dornow,[9] the compound may be prepared by the reduction of X in 37% yield.[2]

(16) H. H. Hodgson and E. Marsden, *J. Chem. Soc.*, 22 (1944).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE][1]

2-, 3- and 4-(1-Methylpiperidyl)-carbinols and Derivatives

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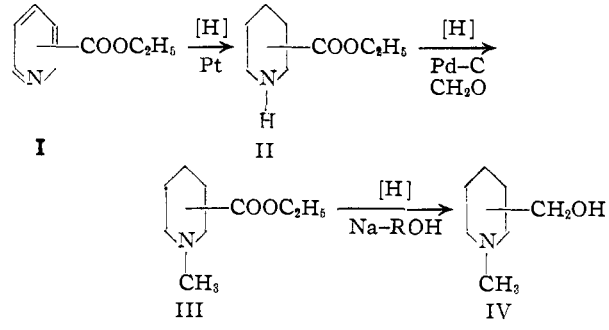
As part of an extended program to find new antispasmodic agents, an investigation of the 2-, 3- and 4-(1-methylpiperidyl)-carbinols was undertaken. Of these, the 2- and 3-alcohols had previously been described but, when the physical data reported could not be confirmed, a new general synthesis was devised which gave excellent yields of hexahydropyridine derivatives and consistent physical data. From these new carbinols some of the reported derivatives were remade and the discrepancies described.

In our study of basic esters possessing spasmolytic properties, we became interested in 3-(1-methylpiperidyl)-carbinol which was first prepared by Sandborn and Marvel[3] in connection with their work on local anesthetics. Later Renshaw, *et al.*,[4] prepared the 2-(1-methylpiperidyl)-carbinol as well as the 3-carbinol by the same method, as intermediates in their study of heterocyclics analogous to acetylcholine. Ford-Moore and Ing[5] also prepared the 3-carbinol in their study of synthetic mydriatics. The 4-carbinol is apparently new although the unmethylated 4-piperidylcarbinol was described by Clemo and Metcalfe.[6] The method of synthesis employed by each of these workers, following the publication by Sandborn and Marvel, was essentially the same. Either ethyl isonicotinate, ethyl nicotinate or ethyl picolinate was reduced by a sodium–alcohol type reduction to the corresponding 2-, 3- or 4-piperidylcarbinols. This method appeared to be very advantageous because each paper reported that both the pyridine ring and the carboethoxy group were reduced simultaneously. Methylation was accomplished either by means of methyl iodide or with formaldehyde and formic acid.

Our primary concern was the preparation of the 3-carbinol which we first prepared by the original method. We were very disappointed with our yields but more so with our inability to either confirm the physical data of Sandborn and Marvel or repeat our own on various runs. Subsequent experiments led us to a general synthesis which applied equally well to each of the three homologs and gave good yields of the true piperidine products.



We started with the same pyridine esters (I) which we prepared in excellent yields from the corresponding acids by means of thionyl chloride and ethyl alcohol. These pyridine esters were readily reduced to their piperidine analogs by catalytic reduction with platinum in aqueous acetic solutions. Isolation of the piperidine derivatives (II) could be done at this stage but was not found to be necessary because N-methylation proceeded rapidly by exchanging the catalyst for palladium-on-charcoal and hydrogenating in the presence of a slight excess of aqueous formaldehyde. This latter step was most advantageous for two reasons. Whereas we were unable to methylate these esters by means of formic acid and formaldehyde, reductive methylation gave excellent yields. Also we found that all attempts to reduce the carboethoxy groups prior to N-methylation resulted in side reactions and very low yields.

The ethyl 1-methylpiperidylcarboxylates (III) were isolated and characterized as quaternary salts. Preparation of the carbinols (IV) from the piperidine esters was easily accomplished by means

(1) Preliminary work done at Frederick Stearns Scientific Laboratories, Detroit, Michigan.

(2) Present address: Smith–Dorsey, Lincoln, Nebraska.

(3) L. T. Sandborn and C. S. Marvel, THIS JOURNAL, **50**, 563 (1928).

(4) R. R. Renshaw, M. Ziff, B. B. Brodie and N. Kornblum, *ibid.*, **61**, 638 (1939).

(5) A. H. Ford-Moore and H. R. Ing, *J. Chem. Soc.*, 55 (1947).

(6) G. R. Clemo and T. P. Metcalfe, *ibid.*, 1523 (1937).

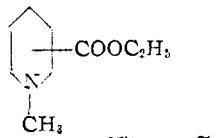
of the modified Bouveault and Blanc reaction of Hansley.[7] Not only did this synthesis consistently give better yields but we were able to repeatedly check the physical constants of different runs.

Since the physical data reported for the 3-carbinol were most inclusive we repeated the preparation by the original sodium and ethyl alcohol method. The high index of refraction reported, which was also obtained quantitatively, indicated partial unsaturation. This was shown by the absorption of bromine when the high index oil was treated with acidified bromine water and by absorption of hydrogen in the presence of palladium-on-charcoal. The hydrogenated carbinol had about the same index as the alcohol made by the above synthesis and did not absorb bromine. Apparently, therefore, the sodium and ethyl alcohol reductions originally used did not completely reduce the pyridine ring, resulting in varying mixtures of partially hydrogenated pyridine derivatives that could not be readily detected by ordinary methods and in particular carbon, hydrogen and nitrogen analyses.

In the case of the 1-methyl-3-piperidylmethyl 4-aminobenzoate hydrochloride reported by Sandborn and Marvel, no outstanding discrepancy was found because they had prepared this derivative by the catalytic reduction of the corresponding 4-nitrobenzoate. This step would hydrogenate any unsaturation present at the same time. We did, however, find a 45° difference in the melting point of our nitro derivative.

TABLE I

ETHYL X-(1-METHYLPIPERIDYL)-CARBOXYLATES



X	B.p., °C.	Mm.	$n^{25}D$	M.p., HCl, °C.	M.p., CH_3Br, °C.	Nitrogen, % Calcd. for $C_9H_{17}NO_2$: N, 8.21 Found
2	93–95	16	1.4487			8.20
3	98–99.5	17	1.4474	141–142[a]	155.3–157.4[b]	8.08
4	94–95	12	1.4470			8.19

[a] *Anal.* Calcd. for $C_9H_{17}NO_2$·HCl: C, 52.1; H, 8.74; Cl, 17.08. Found: C, 52.39; H, 8.72; Cl, 17.07. [b] *Anal.* Calcd. for $C_{10}H_{20}BrNO_2$: C, 45.12; H, 7.57; Br, 30.02. Found: C, 45.28; H, 7.39; Br, 29.80.

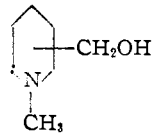
Experimental[8]

General methods are illustrated throughout by preparations of derivatives of the 3-homolog. Tables I, II and III give the complete data for each of the isomers and derivatives prepared.

Ethyl 3-(1-Methylpiperidyl)-carboxylate (III).—Ethyl nicotinate (453.5 g., 3.0 moles) was suspended in 500 cc. of water and treated with 343 cc. (6.0 moles) of glacial acetic acid. The solution was diluted to 1500 cc. with water and placed in an American Instrument Co. rocking bomb hydrogenator with 7.5 g. of Adams platinum oxide catalyst. Slightly over the theoretical amount of hydrogen was absorbed in four hours at room temperature at an initial hydrogen pressure of 1200 lb. per sq. in. The catalyst was removed by filtration and the filtrate returned to the hydrogenator with 300 cc. of 36% formaldehyde solution (3.60 moles) and 30 g. of 10% palladium catalyst freshly prepared from 3 g. of palladium chloride and 27 g. of Darco D-3 charcoal. Absorption of hydrogen proceeded very rapidly at room temperature and was complete in two hours. The catalyst was removed by filtration and the clear filtrate covered with ether, cooled to 15° and slowly made basic with about 630 cc. of cold 35% sodium hydroxide solution. The ether layer containing the liberated basic ester was separated and, after the aqueous layer was completely extracted with the same solvent, the combined extract was dried over anhydrous magnesium sulfate. After filtration and removal of solvent by distillation, the residual oil was distilled under reduced pressure; yield 389.7 g. (76%).

TABLE II

X-(1-METHYLPIPERIDYL)-CARBINOLS

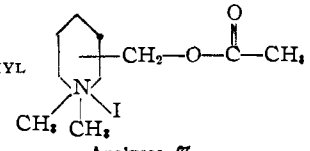


X	B.p., °C.	Mm.	$n^{25}D$	M.p., HCl, °C.	M.p., CH_3I, °C.	Analyses, % Calcd. for $C_7H_{15}NO$: C, 65.0; H, 11.70; N, 10.82 Carbon	Hydrogen	Nitrogen
2	90–92	15	1.4764	Hygroscopic	Over 300[b]	64.71	11.79	10.83
3	114	20	1.4765	135.6–139.4[c]	215.4–216.6[c]	64.74	11.48	10.90
4	116	16	1.4761	143–145[c]	204.7–205.4[d]	64.86	11.76	10.73

[a] *Anal.* Calcd. for $C_7H_{15}NO$·HCl: C, 50.75; H, 9.74; Cl, 21.45. Found: C, 50.80; H, 9.56; Cl, 21.58. [b] *Anal.* Calcd. for $C_8H_{18}INO$: C, 35.5; H, 6.70; I, 46.8. Found: C, 35.46; H, 6.71; I, 46.45. Reference (4), m.p. 275–280°. [c] *Anal.* Found[4]: C, 35.45; H, 6.56; I, 46.80. Reference (4) 140.5–142°. [d] *Anal.* Found[4]: C, 35.55; H, 6.59; I, 46.6. [e] Uncorrected; too hygroscopic for analysis.

TABLE III

1-METHYL-X-PIPERIDYLMETHYL ACETATE METHIODIDES



X	M.p., °C.	Analyses, % Calcd. for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; I, 40.53 Carbon	Hydrogen	Iodine
2	145.1–146.3[a]	38.33	6.32	40.15
3	130.0–130.9[b]	38.58	6.56	40.35
4	149.4–151.5	38.30	6.36	40.30

[a] Reference (4), 126.5–128.5°. [b] *Ibid.*, 134–135°.

3-(1-Methylpiperidyl)-carbinol (IV).—Freshly cut sodium metal (214.5 g., 9.33 moles) was placed in a 5-liter flask fitted with a stirrer, dropping funnel, condenser and calcium chloride tube. The sodium was covered with a sufficient part of 1900 cc. of dry toluene and the mixture heated to refluxing. The molten sodium and toluene were efficiently stirred and heated at a low reflux rate while a solution of 389.7 g. (2.275 moles) of ethyl 3-(1-methylpiperidyl)-carboxylate (III) in 482 g. (4.66 moles) of 4-methylpentanol-2[9] and the remaining toluene was added slowly. The addition was made over a period of four hours with just sufficient external heating to maintain refluxing. When complete, the reaction mixture was stirred and refluxed for one-half

(7) V. L. Hansley, *Ind. Eng. Chem.*, **39**, 55 (1947).

(8) All melting points reported are corrected.

(9) Methyl amyl alcohol, Carbide and Carbon Chemicals Corporation.

hour longer and then allowed to cool to about 80°. A small amount of dispersed sodium was disregarded and the mixture hydrolyzed by the slow addition of 600 cc. of water. Care should be taken during this process to prevent overheating and excessive foaming. The warm hydrolysis mixture was immediately transferred to a separatory funnel, the toluene layer removed and the aqueous layer further extracted with the same solvent. The combined extract was dried over anhydrous magnesium sulfate. After filtration, the toluene was removed by distillation at atmospheric pressure, and the 4-methylpentanol-2 at partially reduced pressure. The residual oil distilled at 112–114° at 15 mm. pressure; yield 237.1 g. (82.8%).

We repeated the preparation of **3-piperidylcarbinol** precisely as to the quantities and procedure described by Sandborn and Marvel[3]; yield 6.40 g. (18.5%), b.p. 111–114° at 5 mm., $n^{20}D$ 1.5088 (reported[3]: 14–15 g. (40–43%), b.p. 106–107° at 3.5 mm., $n^{20}D$ 1.4964).

Methylation was accomplished by refluxing this product with 1.8 g. (5 cc., 0.06 mole) of 36% formaldehyde and 5.5 g. (0.12 mole) of formic acid. About 15 cc. of 36% hydrochloric acid was added to the reaction product and the mixture concentrated *in vacuo*. The free base was isolated by alkalizing with 40% potassium hydroxide and extracting with benzene; yield 4.74 g. (66%), b.p. 77–79° at 3 mm., $n^{25}D$ 1.4874. Another similar experiment gave a product that distilled at 90–95° at 5–6 mm., $n^{20}D$ 1.4918 (reported[3]: b.p. 110–112° at 7 mm., $n^{20}D$ 1.4988). The residual unsaturation of these methylated carbinols was shown by the absorption of bromine and hydrogen. An alcoholic solution, acidified with hydrochloric acid to congo red, readily decolorized bromine water. A similar alcoholic solution (50 cc.) containing 4.70 g. (0.0364 mole) of product absorbed 63% of the theoretical amount of hydrogen for one double bond at three atmospheres pressure in the presence of 0.50 g. of 5% palladium-on-charcoal. The hydrogenated product was isolated by filtration, evaporation of solvent and precipitation from an aqueous solution as above; yield 2.35 g., b.p. 84° at 4 mm., $n^{25}D$ 1.4766.

3-(1-Methylpiperidyl)-carbinol Hydrochloride.—A solution of 2.58 g. (0.02 mole) of 3-(1-methylpiperidyl)-carbinol in 75 cc. of anhydrous ether was saturated with hydrogen chloride. The insoluble hydrochloride salt was collected, washed with ether and recrystallized from a mixture of ethanol and ethyl ether; yield 2.75 g. (83%).

3-(1-Methylpiperidyl)-carbinol Methiodide.—A solution of 2.58 g. (0.02 mole) of 3-(1-methylpiperidyl)-carbinol and 5.67 g. (0.004 mole) of methyl iodide in 25 cc. of anhydrous ethanol was allowed to stand at room temperature for 15 hours. A white solid precipitate was collected by filtration and recrystallized from ethanol; yield 4.5 g. (83%).

1-Methyl-3-piperidylmethyl Acetate Methiodide.—A mixture of 17.4 g. (0.0643 mole) of 3-(1-methylpiperidyl)-carbinol methiodide and 61 g. (0.643 mole) of acetic anhydride was refluxed for one-half hour. The excess acetic anhydride was removed by distillation *in vacuo* and the residual slurry dissolved in a small amount of ethanol. Crude crystals were readily precipitated by diluting this solution with anhydrous ether; yield 18.2 g. (90.5%) after recrystallization from a mixture of the same solvents.

1-Methyl-3-piperidylmethyl Chloride Hydrochloride.—Hydrogen chloride was bubbled into a flask containing a solution of 51.7 g. (0.40 mole) of 3-(1-methylpiperidyl)-carbinol in 350 cc. of chloroform until two layers developed. A condenser, dropping funnel, calcium chloride tube and mantle were attached to the flask and 190 g. (1.60 moles) of thionyl chloride slowly added at reflux temperature. At the end of the addition, the mixture was refluxed for one hour longer and then freed of solvent and excess thionyl chloride by distillation *in vacuo*. Two 50-cc. portions of ethanol were successively added and similarly removed by distillation. The residual slurry was then dissolved in ethanol, the solution decolorized with charcoal and the clear filtrate diluted to a fog with anhydrous ether. Crystallization was rapid and complete at room temperature; yield 67.2 g. (91.2%), m.p. 169.1–170.2°.

Anal. Calcd. for $C_7H_{14}ClN \cdot HCl$: Cl, 38.5; C, 45.66; H, 8.21. Found: Cl, 38.40; C, 45.84; H, 8.14.

1-Methyl-3-piperidylmethyl Chloride.—Eighteen and four-tenths grams (0.10 mole) of 1-methyl-3-piperidylmethyl chloride hydrochloride was dissolved in 30 cc. of 20% sodium hydroxide. The liberated base was immediately extracted with ether and the extract dried with anhydrous magnesium sulfate. After filtration and removal of solvent by distillation the residual oil was distilled at reduced pressure; yield 11.7 g. (79.5%), b.p. 61° at 7 mm., 69° at 11 mm., $n^{25}D$ 1.4700.

(a) 1-Methyl-3-piperidylmethyl 4-nitrobenzoate and (b) 1-Methyl-3-piperidylmethyl 4-Aminobenzoate Hydrochlorides.—These compounds were prepared by the same method described by Sandborn and Marvel[3] from 3-(1-methylpiperidyl)-carbinol having an index of $n^{25}D$ 1.4755.

(a) **4-Nitrobenzoate.**—M.p. 232.8–234.5°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4 \cdot HCl$: Cl, 11.28. Found: Cl, 11.08 (S and M found: m.p. 187–190°; Cl, 11.09.)

(b) **4-Aminobenzoate.**—We likewise experienced difficulty in purifying this salt. It crystallized best from isopropyl alcohol but prolonged drying in an Abderhalden drier at 100° over phosphorus pentoxide failed to remove all the water; m.p. 183.5–184.9°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2 \cdot HCl$: Cl, 12.45; N, 9.84. Found: Cl, 12.01; N, 9.35; H_2O, 2.46. Calcd. on a dry basis: Cl, 12.31; N, 9.58. (S and M found: m.p. 174–177°; Cl, 12.38.)

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