[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

THE CHEMISTRY OF THE BENZYLPYRIDINES. III. 4-BENZYLPYRIDYL- AND 4-BENZYL-N-METHYL-PIPERIDYL-CARBINOLS AND ESTERS

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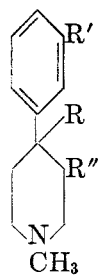
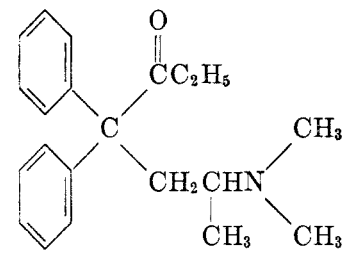
A comparison of the structures of several potent analgesics reveals that these





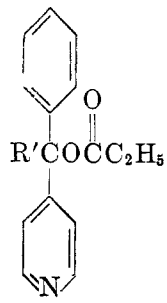
I R = $COOC_2H_5$; R′, R″ = H
II R = COC_2H_5; R′ = OH; R″ = H
III R = $OOCC_2H_5$; R′ = H; R″ = CH_3

IV

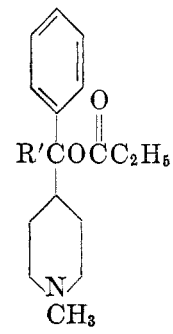
types of compounds possess a tertiary (III) or a quaternary (I, II, IV) carbon atom and a tertiary nitrogen system.[1] It has been suggested that the spatial arrangement of these two moieties resembles the configuration of these groups in morphine (1) and may account for the pronounced analgesic action of these drugs. These two structural units are part of the N-methylpiperidine group (in compounds I–III), but not in Amidone (IV).

While investigating the chemistry of the benzylpyridines (2), we have prepared for pharmacological evaluation as analgesics a limited number of propionate esters of substituted 4-benzylpyridyl- and 4-benzyl-N-methylpiperidylcarbinols of formulas V and VI respectively. The latter compounds are intermediate in structure between the analgesics of types I–III and type IV in that the quaternary carbon of IV and the tertiary carbon of VI are similarly substituted and the tertiary nitrogen of I–III and VI as part of the piperidine ring. However, it is to be noted that in morphine and in the synthetic compounds I–IV, the tertiary nitrogen atom is two carbon atoms removed from the tertiary or the quaternary carbon atom, whereas in the esters VI, three carbon atoms separate these two apparently important moieties. The esters of formula V were prepared for comparative purposes and as possible intermediates for the esters VI.

[1] Compound I is ethyl-1-methyl-4-phenylpiperidine-4-carboxylate, "Demerol," of Winthrop-Sterling; II is 1-methyl-4-(3-hydroxyphenyl)-4-piperidyl ethyl ketone, "Cliradon," of Ciba Pharmaceutical, or "Ketobemidone", WIN 1539, of Winthrop-Sterling; and III is 3-methyl-4-phenyl-4-propionoxy-N-methylpiperidine, "Nisentil," of Hoffmann-La Roche.

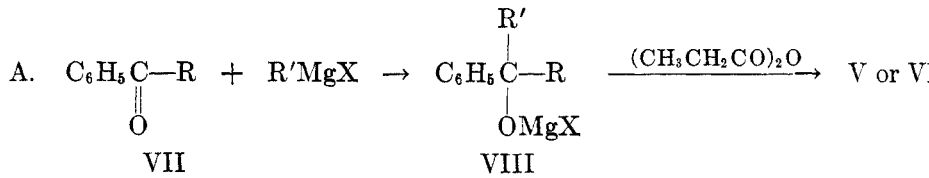


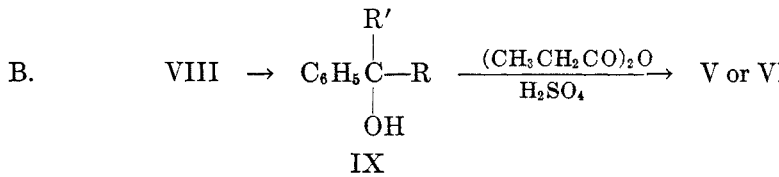
V



VI

The esters V and VI were prepared by the following sequence of reactions:





R being pyridyl or N-methylpiperidyl and R′ methyl or phenyl. Method A, was satisfactory for those compounds wherein R is methyl; whereas, when R is phenyl, method A gave only the carbinols IX. With an excess of propionic anhydride containing a few drops of sulfuric acid (method B), the carbinols IX (R = phenyl) were readily converted to the esters V and VI. Methylphenyl-4-pyridylcarbinol gave, by method B, 1-phenyl-1-(4-pyridyl)ethylene in 55–60% yield and only 10–12% of the desired ester.

The intermediate keto compounds VII were secured by the conventional Friedel-Crafts reaction of a pyridine or piperidine carboxylic acid chloride and, as reported,[2] the reaction proceeds best in the presence of small amounts of thionyl chloride. The 2-, 3- and 4-benzoylpyridines were obtained in 72–91% yields and the 3- and 4-benzoyl-N-methylpiperidines in 54 and 59% over-all yields.[3] For the two latter piperidine derivatives, the intermediates, N-methyl-3- and 4-piperidine carboxylic acids, were obtained from the corresponding pyridine-carboxylic acids by catalytic reduction and subsequent methylation with formic acid and formaldehyde.

[2] Wolffenstein and Hartwich, *Ber.*, **48**, 2047 (1915), described the preparation of 2-benzoylpyridine by this synthesis.

[3] For further synthetic studies with these compounds see Sperber, Villani, Sherlock, and Papa, *J. Amer. Chem. Soc.*, **73**, 5010 (1951).

For 4-benzoyl-N-methylpiperidine, an alternate synthesis was studied. Reduction of 4-benzylpyridine with sodium and alcohol gave 4-benzylpiperidine, which was smoothly methylated with formic acid and formaldehyde to yield the N-methyl derivative. However, the latter substance could not be oxidized with alkaline permanganate,[4] and with chromic acid only 18.5% of the desired keto compound was obtained. This approach to either the benzoylpyridines or benzoyl-N-methylpiperidines was not further investigated in view of the poor yields in the oxidation and the difficulties in securing pure 2- and 4-benzylpyridines.[5]

The direct conversion of the 4-pyridylcarbinols and propionate esters (V) to the corresponding piperidine compounds by catalytic reduction was also studied. Although methylphenyl-2(2-pyridyl)- and 1,1-diphenyl-(2-pyridyl)-carbinols are reported (3) to yield the corresponding piperidine compounds on reduction with platinum oxide catalyst at 70–80°, the compounds V were not reduced under these conditions. High pressure hydrogenation resulted in hydrogenolysis of these compounds.

In order to retain the relative position of the tertiary carbon and the tertiary nitrogen groups characteristic of analgesic III, we prepared 1,1-diphenyl-2-(N-piperidyl)-1-propionoxyethane from phenacylpiperidine and phenylmagnesium bromide by method A.

None of the compounds described in this paper showed analgesic activity when given orally or subcutaneously, compounds I and IV being used as standards.

EXPERIMENTAL

All melting points are corrected. The yields reported represent for the most part single experimental runs.

4-Benzoylpyridine. In a two liter, three-necked flask equipped with reflux condenser, stirrer and dropping funnel, there was placed 85.5 g. (0.7 mole) of isonicotinic acid (4). Thionyl chloride (500 ml.) was added through the dropping-funnel with stirring and the mixture was refluxed for 1½ hours on the steam-bath. Most of the thionyl chloride (80%) was removed *in vacuo*; and, to the residue, 500 ml. of benzene was added. The mixture was cooled in an ice-salt-bath and 348 g. of anhydrous granular aluminum chloride was added over a period of one-half hour. The red reaction mixture was allowed to warm to room temperature, then refluxed for six hours with stirring and decomposed by pouring on ice and hydrochloric acid. The benzene layer was separated, the acid solution extracted with ether,[6] and the benzene and ether solutions discarded. The acid solution was made strongly basic with an excess of concentrated sodium hydroxide sufficient to dissolve the aluminum hydroxide and extracted several times with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and, after removing the solvent, the residue was distilled. The 4-benzoylpyridine was obtained as a light yellow oil, b.p. 170–172° (10 mm.), which solidified on cooling. Recrystallized from ethanol, it melted at 70–71°, literature m.p. 71.5–72.5°, yield 115 g. (91%). The hydrochloride was prepared by

[4] Crook and McElvain, *J. Amer. Chem. Soc.*, **52**, 4009 (1930), reported the oxidation of 2- and 4-benzylpyridines with alkaline permanganate to the respective benzoylpyridines in good yield.

[5] At the present time, pure 2- and 4-benzylpyridine is available from Reilly Tar and Chemical Corporation.

[6] The ether extraction removed any residual diphenylsulfoxide, which is a product of the reaction of thionyl chloride and benzene.

saturating an anhydrous ethereal solution with dry hydrogen chloride; m.p. 195–199°, reported (5) 195–197°.

The 2-benzoyl- and the 3-benzoyl-pyridines were prepared by the same procedure from picolinic and nicotinic acids respectively; 2-benzoylpyridine, yield 87%, b.p. 170–175° (10 mm.), reported (5) b.p. 170–172° (10 mm.); 3-benzoylpyridine, yield 72%, b.p. 138–140° (1 mm.), picrate m.p. 164–166°, reported (6) picrate, m.p. 161°.

4-Benzoyl-N-methylpiperidine. Ethyl isonicotinate (7) was prepared in 70% yield, b.p. 88–90° (7 mm.), n_D^{21} 1.4975. The ester, dissolved in anhydrous dioxane, was reduced catalytically using a Raney nickel catalyst at 165° and 1,600 lbs. hydrogen pressure as described (8), b.p. 95–98° (7 mm.), n_D^{23} 1.4569. To a mixture of 53 g. (0.34 mole) of ethyl isonipecotate and 86 g. of 90% formic acid, 75 ml. of 37% formalin was added slowly with cooling and stirring. After the initial evolution of carbon dioxide subsided, the mixture was warmed on the steam-bath for eight hours. Then 100 ml. of 10% hydrochloric acid was added and the mixture was concentrated to dryness on the steam-bath *in vacuo*. The residue was dissolved in water, the solution made alkaline with sodium hydroxide, and then extracted with ether. The aqueous solution was buffered with acetic acid and concentrated *in vacuo*. The crude white solid was dried over phosphorus pentoxide in a vacuum desiccator.

The crude N-methylisonipecotic acid was converted to the acid chloride with 450 ml. of redistilled thionyl chloride as described. The clear yellow solution was concentrated *in vacuo* until most of the thionyl chloride was removed. Anhydrous benzene (500 ml.) was added, the mixture cooled in an ice-water-bath, and 275 g. of aluminum chloride added with stirring over a period of 1–1½ hours. The reaction mixture was slowly raised to reflux temperature, and after refluxing 18 hours, was poured into a mixture of ice and hydrochloric acid. The benzene was removed by steam-distillation and the residue, after cooling, was extracted with ether. The aqueous layer was made strongly basic and extracted with chloroform. The chloroform extracts were washed with water, dried over sodium sulfate, and distilled, yield 40 g. (59%); b.p. 130–137° (2 mm.), n_D^{23} 1.5430.

Anal. Calc'd for $C_{13}H_{17}NO$: N, 6.89. Found: N, 6.75.

The *oxime* prepared in the usual way melted at 186–187° after recrystallization from dilute ethanol.

Alternate synthesis of 4-benzoyl-N-methylpiperidine. 4-Benzylpyridine was reduced with sodium and ethanol (9) and the resulting 4-benzylpiperidine methylated in 74% yield using formic acid and formaldehyde. The N-methyl-4-benzylpiperidine was obtained as an oil, b.p. 129–130° (8 mm.), n_D^{26} 1.5295.

Anal. Calc'd for $C_{13}H_{19}N$: N, 7.40. Found: N, 7.36.

To 20 g. (0.1 mole) of the benzyl compound dissolved in a mixture of 25 ml. of concentrated sulfuric acid and 200 ml. of glacial acetic acid, there was added 29.4 g. (0.28 mole) chromium trioxide in several small portions. The mixture was refluxed with stirring for three hours and after cooling, was filtered. The precipitate was washed with acetic acid and the filtrate and washings diluted with ice-water. The resulting solution was basified with ammonia and extracted with chloroform. The chloroform extracts were dried and distilled, yield 3.7 g. (18.5%), b.p. 120–125° (1 mm.), n_D^{25} 1.5420. The *oxime* melted at 186–187.5° and the melting point was not depressed when a sample of this oxime was mixed with the oxime of the keto compound prepared by the Friedel-Crafts reaction.

3-Benzoyl-N-methylpiperidine was prepared as described for the 4-isomer from N-methylnipecotic acid in 37% yield, b.p. 107–109° (1 mm.), n_D^{25} 1.5448.

Anal. Calc'd for $C_{13}H_{17}NO$: N, 6.89. Found: N, 6.62.

The intermediate N-methylnipecotic acid was prepared from nicotinic acid by reduction and methylation as described for isonicotinic acid, yield 54%, based on ethyl nicotinate. The hydrochloride prepared in the usual manner melted at 169–172°; literature (10) m.p. 175.1°.

Methylphenyl-4-pyridylcarbinol. To an ice-cold solution of methylmagnesium iodide (0.3 mole), a solution of 36.6 g. (0.2 mole) of 4-benzoylpyridine in 600 ml. of anhydrous benzene was added dropwise with constant stirring. The mixture was refluxed for four

hours and then kept overnight at room temperature. The Grignard complex was decomposed by the addition of a large excess of 10% ammonium chloride solution and the mixture heated to reflux temperature. The organic layer was separated and the aqueous layer extracted with benzene. The combined benzene-ether extracts were concentrated and the residue was recrystallized from benzene; yield 91%, m.p. 146–147°; literature m.p. 142–143°.

Anal. Calc'd for $C_{13}H_{13}NO$: C, 78.36; H, 6.57.

Found: C, 78.39; H, 6.80.

1,1-Diphenyl-4-pyridylcarbinol was prepared from 4-benzoylpyridine and phenylmagnesium bromide as described for the corresponding methyl compound, yield 68%, m.p. 238–238.5° after recrystallization from benzene, literature (11) m.p. 234–235°.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.73; H, 5.97.

Found: C, 82.52; H, 5.96.

1,1-Diphenyl-N-methyl-4-piperidylcarbinol was prepared in 59% yield from 4-benzoyl-N-methylpiperidine and phenylmagnesium bromide, m.p. 129–131° after recrystallization from petroleum ether. The hydrochloride prepared in the usual manner melted at 290–291°.

Anal. Calc'd for $C_{19}H_{24}ClNO$: Cl, 11.16. Found: Cl, 11.53.

1,1-Diphenyl-N-methyl-3-piperidylcarbinol prepared as described for the 4-isomer using 3-benzoyl-N-methylpiperidine and phenylmagnesium bromide, yield 66%, m.p. 145–146° after recrystallization from benzene.

Anal.. Calc'd for $C_{19}H_{23}NO$: N, 4.98. Found: N, 4.88.

Acylation of carbinols, Method A: 1-Phenyl-1-(N-methyl-4-piperidyl)-1-propionoxyethane. To a solution of methylmagnesium iodide (0.22 mole) in 200 ml. of ether, there was added dropwise a solution of 28 g. (0.14 mole) of 4-benzoyl-N-methylpiperidine in 100 ml. of anhydrous benzene. The mixture was refluxed and stirred for four hours, then 39 g. of propionic anhydride added, and, after heating for two hours, the mixture was decomposed with ammonium chloride. The organic layer was separated and the aqueous phase extracted twice with ether. The ether-benzene solution was washed, dried and after removing the solvent, the residue was distilled, yield 37%, b.p. 155–157° (3 mm.), n_D^{20} 1.5185.

Anal. Calc'd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15.

Found: C, 74.40; H, 9.19.

Using the same procedure, there was prepared 1-phenyl-1-(4-pyridyl)-1-propionoxyethane from 4-benzoylpyridine in 24% yield, b.p. 147–151° (1 mm.), n_D^{20} 1.5620.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71.

Found: C, 74.97; H, 6.97.

The 1,1-diphenyl-2-(N-piperidyl)-1-propionoxyethane was prepared by this method from phenylmagnesium bromide and phenacylpiperidine (12) in 33% yield. The ester was extracted with chloroform and the residue, after removal of the chloroform, was recrystallized from methanol, m.p. 101.5–102°.

Anal. Calc'd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06.

Found: C, 77.92; H, 8.05.

Method B. A solution of 10 g. (0.035 mole) of 1,1-diphenyl-N-methyl-4-piperidylcarbinol and 100 ml. of propionic anhydride containing 10 drops of concentrated sulfuric acid was refluxed on the steam-bath for seven hours. The deep red solution was kept overnight at room temperature and the propionic anhydride was then removed *in vacuo*. The residue was dissolved in water and the solution made alkaline with sodium carbonate and extracted with chloroform. The chloroform extracts were washed with water, dried with sodium sulfate, and the solvent removed. The residue, a pale yellow, low-melting solid, was recrystallized from petroleum ether to give a 25% yield of 1,1-diphenyl-1-(N-methyl-4-piperidyl)-propionoxymethane as the hydrate, m.p. 115–116°.

Anal. Calc'd for $C_{22}H_{27}NO_2 \cdot H_2O$: C, 74.36; H, 8.22; N, 4.00.

Found: C, 74.48; H, 8.24; N, 4.13.

Similarly, 1,1-diphenyl-1-(4-pyridyl)propionoxymethane was prepared from 1,1-diphenyl-4-pyridylcarbinol in 50% yield, b.p. 189–190° (1 mm.), n_D^{24} 1.5974.

Anal. Calc'd for $C_{21}H_{19}NO_2$: C, 79.46; H, 6.03.

Found: C, 79.51; H, 6.03.

By the same procedure, 1,1-diphenyl-1-(N-methyl-3-piperidyl)propionoxymethane was prepared from 1,1-diphenyl-N-methyl-3-piperidylcarbinol in 80% yield, b.p. 170–173° (1 mm.).

Anal. Calc'd for $C_{22}H_{27}NO_2$: N, 4.15. Found: N, 4.28.

1-Phenyl-1-(4-pyridyl)ethylene. Methylphenyl-4-pyridylcarbinol (10 g., 0.05 mole) was treated with a mixture of 100 ml. of propionic anhydride and 10 drops of concentrated sulfuric acid. The reaction mixture was worked up as described and on fractional distillation using a 30-cm. Vigreux column there was obtained 4.9 g. (54%) of the ethylene compound as a colorless liquid, b.p. 113–114° (1 mm.), n_D^{22} 1.6100, literature (13) b.p. 300–305° dec.

Anal. Calc'd for $C_{13}H_{11}N$: C, 86.70; H, 6.11.

Found: C, 86.43; H, 5.96.

A second fraction was obtained, yield 1.5 g. (12%), b.p. 147–150° (1 mm.), n_D^{25} 1.5616, which corresponds in physical properties with the ester, phenyl-(4 - pyridyl) propionoxyethane.

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SUMMARY

A series of 4-benzylpyridyl- and 4-benzyl-N-methylpiperidyl-carbinols and esters has been described.

BLOOMFIELD, N. J.

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