Snytheses of Analgesics. Part XXXVII (1). An Alternative Synthesis of 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine [Studies on the Syntheses of Heterocyclic Compounds. Part DXXI (2)]

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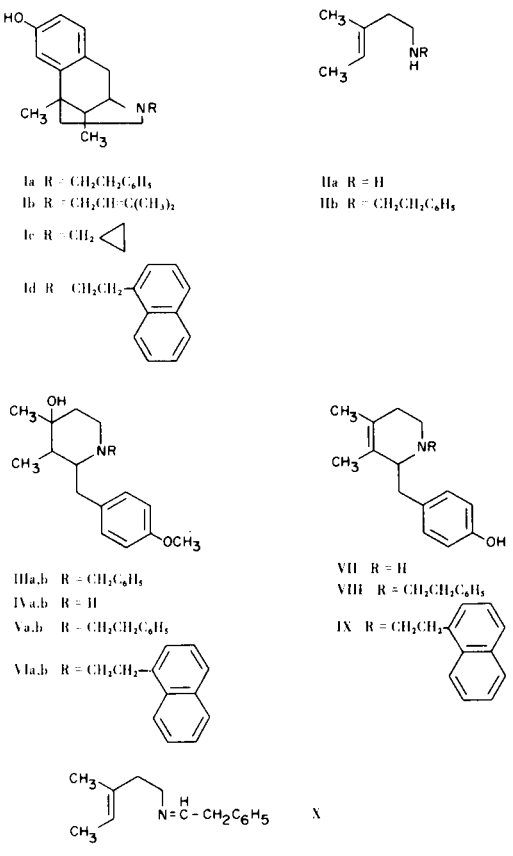
Acid treatment of the alkylated products of (Va, Vb, and VIII) of piperidinols IVa and IVb, and tetrahydropyridine VII with β-bromoethylbenzene, afforded 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine (Ia) in good yield. Piperidinols Va and Vb were also obtained from the reaction of *N*-(3-methyl-3-pentenyl)-β-phenethylamine (IIb) with methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate.

Phenazocine (Ia) as well as pentazocine (Ib) and cyclazocine (Ic) having a skeleton of 2,6-methano-3-benzazocine are well known as potential analgesics. The synthesis of phenazocine (Ia) using 3,4-lutidine as a starting material has been reported (4-6). Previously we reported the synthesis of pentazocine (Ib) and related compounds, among which the synthetic method (7,8) using 3-methyl-3-pentenylamine (IIa), obtained easily by condensation of cyanoacetic acid with ethyl methyl ketone, as a starting material has been found to be advantageous from the industrial point of view. Since we have synthesized 1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine (phenazocine) (Ia) and 3-naphthylethyl derivative Id, we wish to report these results.

1-Benzyl-4-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (IIIa and IIIb), prepared from the amine IIa, was hydrogenated and the reaction mixture was fractionally recrystallized to give piperidinols IVa and IVb. Treatment of piperidinol IVa and IVb and tetrahydropyridine VII (8) with β-bromoethylbenzene or 1-(2-bromoethyl)-naphthalene gave piperidinols Va, b and VIa, b and tetrahydropyridines VIII and IX. The reaction of *N*-(3-methyl-3-pentenyl)-β-phenethylamine (IIb), obtained by condensation of amine IIa with phenylacetaldehyde, followed by reduction with sodium borohydride of X, with methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate also gave piperidinols Va and Vb.

Treatment of the compounds, Va, Vb, and VIII with 48% hydrobromic acid afforded 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine (Ia) in good yield. Similarly the reaction of VIa, VIb and IX with 48% hydrobromic acid also gave 3-[2-(1-naphthyl)ethyl]-3-benzazocine (Id) in good yield. The compounds Ia and Id were identical with authentic samples on mixed melting point determination and spectral comparisons.

CHART I



EXPERIMENTAL (9)

N-(3-Methyl-3-pentenyl)-β-phenethylamine (IIb).

To a solution of 2 g. of a mixture of 3-methyl-3-pentenylamine (IIa) and 3-methylpentylamine (7) in 50 ml. of methanol, 6 g. of phenylacetaldehyde (40-50% in diethyl phthalate) in 50 ml. of methanol was added at room temperature, and then the mixture was warmed for 10 minutes. After 1 g. of sodium borohydride had been added to the above mixture in portions with stirring, the stirring was continued for 30 minutes at room temperature. After evaporation of the solvent, the residue was poured into water. The resulting solution was acidified with 10% hydrochloric acid and the oil which separated was removed by extraction with ether. The acidic layer was extracted with chloroform. The chloroform extract was washed with water and dried over sodium sulfate. Evaporation of the solvent afforded 2.1 g. of a pale yellow solid, whose recrystallization from methanol-ether gave the hydrochloride of the mixture of IIb and *N*-(3-methylpentyl)-β-phenethylamine as colorless prisms, m.p. 215-225° dec.; nmr δ (free base): 0.90 (6H, multiplet, 2 x C-C-C*H*$_3$), 1.12 (2H, singlet, NH), 1.58 (6H, broad singlet, 2 x C=C-C*H*$_3$), 2.28 (8H, singlet, *N*-(C*H*$_2$)$_2$-C$_6$H$_5$), 5.34 (1H, broad singlet, -C*H*=C), 7.38 (10H, singlet, -C$_6$H$_5$).

4-Hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidines (IVa) and (IVb).

A solution of 10 g. of the hydrochloride of 1-benzyl-4-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (7) (IIIa,b) in 150 ml. of ethanol was hydrogenated in the presence of 2 g. of 10% palladium-charcoal until hydrogen uptake ceased. The mixture was filtered and the filtrate was evaporated to dryness. The residue was basified with 10% sodium hydroxide solution and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 4.5 g. of a solid, whose recrystallization from ether afforded 1.5 g. of IVa as colorless needles, m.p. 140-141° [lit. (10), m.p. 140-141°]. Concentration of the ethereal mother liquor gave 1.8 g. of IVb as colorless needles, m.p. 134-136° [lit. (10), m.p. 134-136°].

4-Hydroxy-2-(4-methoxybenzyl)-3,4-dimethyl-1-phenethylpiperidine (Va).

A mixture of 0.4 g. of the piperidinol IVa, 0.4 g. of β-bromoethylbenzene, 0.4 g. of sodium bicarbonate, and 15 ml. of dimethylformamide was refluxed for 5 hours with stirring. After evaporation of the solvent, the residue was admixed with water and extracted with ether. The ethereal extract was again extracted with 10% hydrochloric acid, and the acidic solution was basified with 10% sodium hydroxide and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to afford 0.5 g. of a pale yellowish syrup. Purification on silica gel column chromatography, followed by distillation *in vacuo*, gave 0.15 g. of Va as a pale yellow oil, b.p. 180-185° (0.8 mm), nmr δ: 0.85 (3H, doublet, J = 6.7 Hz, C$_3$-CH$_3$), 1.08 (3H, singlet, C$_4$-CH$_3$), 3.75 (3H, singlet, OCH$_3$), 6.80, 7.20 (each 2H, A$_2$B$_2$ type quartet, J = 9 Hz, -O-C$_6$*H*$_4$-), 7.20 (5H, singlet, C$_6$*H*$_5$).

Anal. Calcd. for C$_{23}$H$_{31}$NO$_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 77.96; H, 8.50; N, 4.01.

4-Hydroxy-2-(4-methoxybenzyl)-3,4-dimethyl-1-phenethylpiperidine (Vb).

a) A mixture of 1 g. of piperidinol IVb, 1 g. of β-bromoethylbenzene, 1 g. of sodium bicarbonate and 30 ml. of dimethylformamide was refluxed for 5 hours with stirring. The mixture was worked up as in the case of Va to give a reddish syrup, which was chromatographed on silica gel using ether as eluant. After evaporation of the ethereal eluate, recrystallization from ether gave 0.8 g. of Vb as colorless needles, m.p. 95-96°, nmr δ: 0.87 (3H, doublet, J = 6 Hz, C$_3$-CH$_3$), 1.05 (3H, singlet, C$_4$-CH$_3$), 3.75 (3H, singlet, OCH$_3$), 6.60, 6.91 (each 2H, A$_2$B$_2$ type quartet, J = 9 Hz, -O-C$_6$*H*$_4$-), 7.18 (5H, singlet, C$_6$*H*$_5$).

Anal. Calcd. for C$_{23}$H$_{31}$NO$_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.13; H, 9.05; N, 4.13.

b) To a solution of 2.2 g. of the hydrochloride of IIb in 50 ml. of water, 3.5 g. of methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate was added to *p*H 3. The mixture was vigorously stirred for 100 hours at 90-95°. After cooling, the reaction mixture was filtered, and the filtrate was washed with ether, basified with sodium bicarbonate and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate. Evaporation of the solvent gave a brown gum which was acetylated to remove the starting amine. The reaction product which could not be acetylated was chromatographed on silica gel using chloroform as eluant. The first chloroform eluant gave 400 mg. of Vb as colorless needles, m.p. 95-96°, whose nmr spectrum was superimposable with that of Vb obtained by procedure (a). The second eluant gave 0.2 g. of the mixture of Vb and Va, which could not be separated.

4-Hydroxy-2-(4-methoxybenzyl)-3,4-dimethyl-1-[2-(1-naphthyl)-ethyl]piperidine (VIa).

A mixture of 1.5 g. of IVa, 1.6 g. of 1-(2-bromoethyl)naphthalene, 1 g. of sodium bicarbonate and 15 ml. of dimethylformamide was refluxed for 5 hours. The reaction mixture was worked up as in the case of Va to give 2.1 g. of VIa as a reddish oil, which was chromatographed on silica gel. The ethereal eluant gave 1.0 g. of a yellowish oil, nmr δ: 0.88 (3H, doublet, J = 6 Hz, C$_3$-CH$_3$), 1.15 (3H, singlet, C$_4$-CH$_3$), 3.75 (3H, singlet, OCH$_3$), 6.70-8.20 (11H, multiplet, aromatic protons). Recrystallization of the hydrochloride of VIa from ethanol-ether gave colorless needles, m.p. 213-214° dec.

Anal. Calcd. for C$_{27}$H$_{33}$NO$_2$·HCl: C, 73.70; H, 7.79; N, 3.18. Found: C, 73.91; H, 7.88; N, 3.04.

4-Hydroxy-2-(4-methoxybenzyl)-3,4-dimethyl-1-[2-(1-naphthyl)-ethyl]piperidine (VIb).

A mixture of 2.5 g. of IVb, 2.7 g. of 1-(2-bromoethyl)-naphthalene, 2.0 g. of sodium bicarbonate and 30 ml. of dimethylformamide was refluxed for 5 hours. The reaction mixture was worked up as in the case of VIa to give a reddish oil, which was purified by silica gel column chromatography. Recrystallization from *n*-hexane afforded 1.8 g. of VIb as colorless needles, m.p. 118-119°, nmr δ: 0.95 (3H, doublet, J = 7.5 Hz, C$_3$-CH$_3$), 1.15 (3H, singlet, C$_4$-CH$_3$), 3.75 (3H, singlet, OCH$_3$), 6.70-8.20 (11H, multiplet, aromatic protons).

Anal. Calcd. for C$_{27}$H$_{33}$NO$_2$: C, 80.36; H, 8.24; N, 3.47. Found: C, 80.56; H, 8.20; N, 3.54.

1,2,5,6-Tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethyl-1-phenethylpyridine (VIII).

A mixture of 2.0 g. of tetrahydropyridine VII, 2.0 g. of β-bromoethylbenzene, 2.0 g. of sodium bicarbonate and 50 ml. of dimethylformamide was heated for 4 hours at 110-120°. After cooling, the reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated to afford 1.5 g. of VIII

as a colorless gum, nmr δ: 1.55 (6H, singlet, 3-CH_3, 4-CH_3), 2.67 (4H, singlet, N-(CH_2)$_2$$C_6H_5$), 6.63, 7.05 (each 2H, A_2B_2 type quartet, -C_6H_4-O-), 7.15 (5H, singlet, -C_6H_5).

1,2,5,6-Tetrahydro-2-(4-hydroxybenzyl)-3,4-dimethyl-1-[2-(1-naphthyl)ethyl]pyridine (IX).

A mixture of 2.4 g. of tetrahydropyridine VII, 3.0 g. of 1-(2-bromoethyl)naphthalene, 2.5 g. of sodium bicarbonate and 50 ml. of dimethylformamide was heated for 4 hours at 130-140°. The reaction mixture was admixed with water and extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and evaporated to afford a brown syrup, which was chromatographed on silica gel. The chloroform eluant gave 2.5 g. of a colorless syrup, nmr δ: 1.54 (6H, singlet, 3-CH_3, 4-CH_3), 6.78, 7.16 (each 2H, A_2B_2 type quartet, J = 9 Hz, -C_6H_4-O-), 7.10-8.05 (7H, multiplet, aromatic protons). The hydrochloride of the compound IX was recrystallized from methanol-acetone to give colorless prisms, m.p. 137-140° dec.

Anal. Calcd. for $C_{26}H_{29}NO.0.5H_2O$: C, 74.88; H, 7.49; N, 3.36. Found: C, 75.33; H, 7.96; N, 2.98.

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine (Ia).

a) A mixture of 0.95 g. of the piperidinol Va and 10 ml. of 47% hydrobromic acid was refluxed for 13 hours. The reaction mixture was basified with 28% ammonia under cooling and extracted with chloroform. The chloroform extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 0.75 g. of a brown powder, whose recrystallization from acetone afforded 500 mg. of Ia as colorless needles, m.p. 180-182° [lit. (5), m.p. 181-182°], nmr δ: 0.86 (3H, doublet, J = 7 Hz, C_{11}-CH_3), 1.31 (3H, singlet, C_6-CH_3), 2.89 (4H, singlet, N-(CH_2)$_2$-C_6H_5), 7.25 (5H, singlet, C_6H_5), 8.22 (1H, singlet, OH).

b) A mixture of 0.3 g. of the piperidinol Vb and 4 ml. of 47% hydrobromic acid was refluxed for 13 hours. The reaction mixture was worked up as in the case of method (a) to give 0.18 g. of a brown powder, whose recrystallization from acetone afforded 120 mg. of Ia as colorless needles, m.p. 180-182°, which was identical with Ia obtained by method (a).

c) A mixture of 1.5 g. of the tetrahydropyridine VIII and 20 ml. of 47% hydrobromic acid was heated for 7 hours at 140-145°. The reaction mixture was basified with ammonia and extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated to give a pale reddish powder. Recrystallization from acetone afforded 500 mg. of Ia as colorless prisms, m.p. 181-182°, identical with the above sample Ia.

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-[2-(1-naphthyl)ethyl]-3-benzazocine (Id).

a) A mixture of 0.3 g. of the hydrochloride of the piperidinol VIa and 5 ml. of 47% hydrobromic acid was refluxed for 30 hours. The reaction mixture was worked up as usual to give a powder, whose recrystallization from ethanol afforded 100 mg. of Id as colorless needles, m.p. 180-181° [lit. (11), m.p. 180-181°], nmr δ: 0.90 (3H, doublet, J = 7 Hz, C_{11}-CH_3), 1.36 (3H, singlet, OH).

b) A mixture of 0.8 g. of the piperidinol VIb and 5 ml. of 47% hydrobromic acid was refluxed for 20 hours. The reaction mixture was treated with ammonia and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate. Evaporation of the solvent afforded 0.45 g. of Id as a yellowish powder, whose recrystallization from ethanol gave 160 mg. of colorless needles, m.p. 180-181°, which was identical with Id obtained by method (a).

c) A mixture of 2.5 g. of the hydrochloride of the tetrahydropyridine IX and 25 ml. of 47% hydrobromic acid was heated for 32 hours at 145-150°. The mixture was treated with ammonia and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 1.5 g. of a brown gum, which was chromatographed on silica gel. The chloroform-methanol (99:1) eluant gave 800 mg. of Id, which was recrystallized from acetone to afford colorless prisms, m.p. 182-184°, identical with Id obtained from the above procedure (a).

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