Syntheses of Benzomorphan and Related Compounds. Part III (1). An Alternate Synthesis of 3-Substituted-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine (2).

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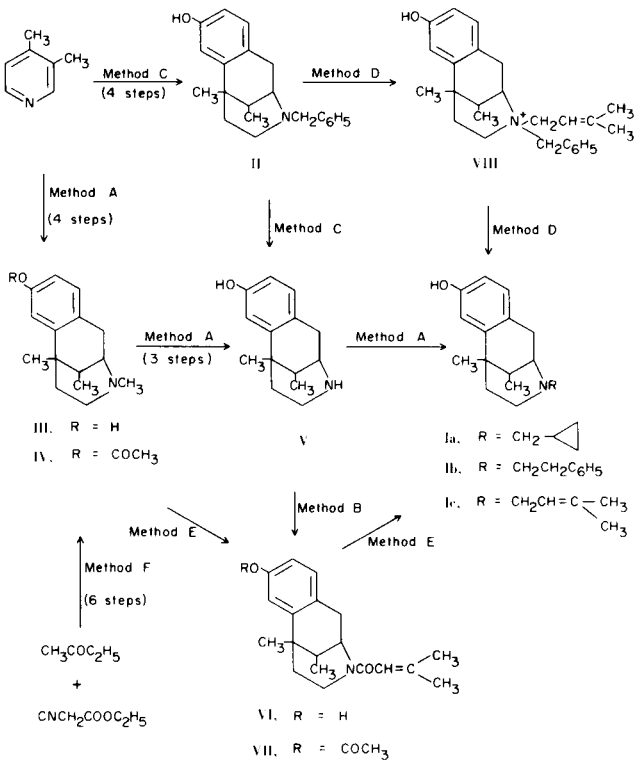
Reduction of the appropriate Schiff bases gave 5-benzylamino-3-methyl-2-pentene (XVII) and 1-benzylamino-3-methylpentane (XVIII), the condensation of which with methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate afforded a mixture of the isomeric 1-benzyl-2-(4-methoxybenzyl)-3,4-dimethyl-4-hydroxypiperidines (XIXa and XIXb). The piperidinols were heated with hydrobromic acid, respectively, to afford 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine (II). Since the conversion of II to pentazocine (Ic) had already been accomplished, an alternate synthesis of Ic was achieved.

The synthesis of a number of benzomorphan derivatives, among which cycloazocine (Ia), phenazocine (Ib), and pentazocine (Ic) (3,4), are all well known as analgesic agents, have been reported. In particular, the last compound, 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocine (Ic), has been widely used as an effective analgesic agent without addiction properties. The synthesis of pentazocine (Ic) using 3,4-lutidine as a starting material has been reported by many investigators. These various methods are shown in Scheme I as Methods A and B (4), C (5), E (6), and the present authors' Methods C and D (1,8). These methods for the synthesis of Ic have some defects from an industrial point of view, and, furthermore, the synthesis of the compound III has already been reported by Bayer's group (8). Therefore we have successively investigated a modified synthesis of Ic, and now wish to report these results.

The heating of ethyl 1-methylpropylidenecyanoacetate (IX) (9) with pyridine hydrochloride gave 4-cyano-3-methyl-2-butene (X) together with the 1-butene isomer XI in the ratio of 1:1 (10). The nitriles X and XI were also obtained by the thermal decarboxylation of XII, which was prepared by the condensation of ethyl methyl ketone with cyanoacetic acid, in the ratio of 6:4 (10), respectively. Since purification of the above products was difficult, this mixture of X and XI was used for the following reaction. Condensation of the hydrogenation products (XIII and XIV) of the nitriles (X and XI) with benzaldehyde, followed by the reduciton of the Schiff bases (XV and XVI) with sodium borohydride, afforded 5-benzylamino-3-methyl-2-pentene (XVII) and 1-benzylamino-3-methylpentane (XVIII). The treatment of the

SCHEME I

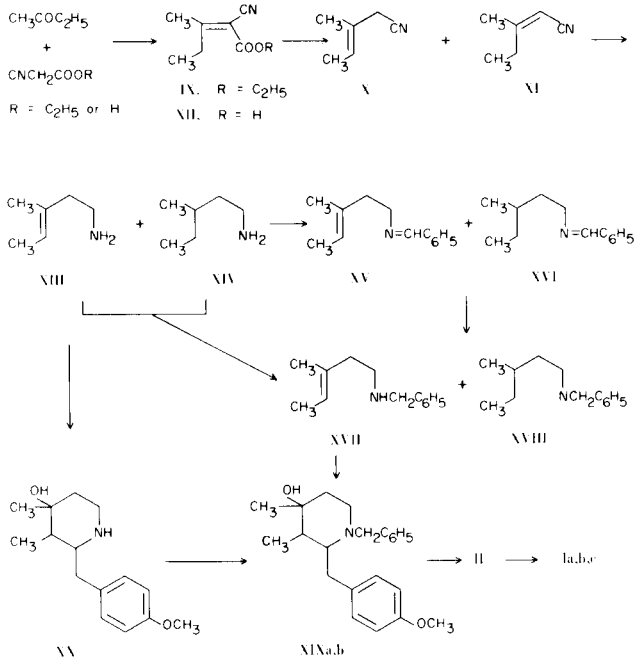


amines XIII and XIV with benzyl chloride gave the same results. A mixture of the benzylamines XVII and XVIII was heated in the presence of methyl 3-(4-methoxyphenyl)-2,3-epoxypropionate to give the diastereoisomeric piperidinols XIXa and XIXb, which were separated by alumina chromatography. Two of these diastereoisomers were characterized as picrates. The nmr spectra of the first isomer XIXa showed a doublet (J = 7 Hz) at 0.97 ppm and a singlet at 1.01 ppm attributable to the C_3-CH_3 and C_4-CH_3, respectively. The methylene signals of the benzyl group were shown at 3.04 and 4.15 ppm as a pair of doublets (J = 14 Hz). However, the second isomer XIXb exhibited the signals due to benzyl methylene protons at 3.43 and 3.94 ppm as a pair of doublets (J = 14 Hz). The second isomer XIXb was also obtained on the treatment of the piperidinol XX, obtained from the amine XIII, with benzyl bromide. Both were identical on comparison of spectroscopic and chromatographic data.

Secondly, both of the piperidinols (XIXa and XIXb) were heated with 47% hydrobromic acid, respectively, to afford 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine (II), which was identical with an authentic specimen (7), synthesized from 3,4-lutidine.

Since we had already reported the syntheses of several benzomorphans (II) from II, followed by conversion to pentazocine through methods (C and D) (1,7), this procedure was found to provide an extremely useful method from the industrial point of view for the syntheses of 3-substituted 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocines.

SCHEME II



EXPERIMENTAL (12)

4-Cyano-3-methyl-2-butene (X).

(a) A stirred mixture of 20 g. of ethyl 1-methylpropylidenecyanoacetate (IX) and 100 g. of pyridine·hydrochloride was heated at 230° for 1 hour. Hydrochloric acid (10%, 200 ml.) was added to the reaction mixture which was then extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated to give 9.5 g. (83%) of X together with 1-cyano-2-methyl-1-butene (XI) as a colorless oil, b.p. 156-157° (760 mm) [lit. (9), b.p. 156-157° (760 mm), lit. (13), 162-164° (760 mm)]. According to the nmr spectra of this mixture, X and XI were formed in a ratio of 45:55 from the integration of methine and methyl signals; nmr (carbon tetrachloride): δ 1.05 (3H, t, J = 7 Hz, CH_2-CH_3 of XI), 1.58 (3H, s, C_1-CH_3 of X), 1.65 (6H, s, 2 x C_3-CH_3 of X and XI), 2.99 (2H, s, CH_2CN of X), 5.06 (1H, broad s, >C=CH of XI), 5.25 (1H, q, >C=CH of X).

(b) A mixture of 50 g. of methyl ethyl ketone, 42.5 g. of cyanoacetic acid, 1.5 g. of ammonium acetate, and 100 ml. of benzene was refluxed until the theoretical amount of water (9 ml.) had been removed. Removal of the solvent left 80 g. of a residual oil which was distilled at 160-190° to give 38.9 g. (82%) of a mixture of X and XI (57:43) as a colorless oil, b.p. 156-157° (760 mm).

5-Benzylamino-3-methyl-2-pentene (XVII).

(a) A mixture of 11.0 g. of the amines (XIII and XIV), 11.7 g. of benzaldehyde, and 100 ml. of benzene was refluxed for 1 hour. After evaporation of the solvent, to a solution of the resulting residue in 100 ml. of methanol was added in small portions 5 g. of sodium borohydride. After the addition, the mixture was refluxed for 0.5 hour. The solvent was evaporated and 100 ml. of water was added to the above residue. This solution was extracted with ether. The extract was washed with water, dried over potassium carbonate and evaporated to leave an oil, which was distilled *in vacuo* to give 16.4 g. (78%) of a colorless oil, b.p. 113-116° (3 mm), as a mixture of XVII and XVIII (70:30), nmr (carbon tetrachloride): δ 0.95 (6H, t, 2 x CH_3 of XVIII), 1.50 (3H, d, J = 7 Hz, C_1-CH_3 of XVII), 1.50 (3H, broad s, C_3-CH_3 of XVII), 2.55 (4H, t, J = 7 Hz, 2 x CH_2CH_2NH of XVII and XVIII), 3.61 (4H, s, CH_2Ph of XVII and XVIII), 5.20 (1H, q, CH of XVII), 7.18 (10H, s, 2 x C_6H_5).

(b) A mixture of 5.7 g. of the amines (XIII and XIV) and 7.2 g. of benzyl chloride was heated for 7 hours on a water-bath. After the reaction, the mixture was acidified with 100 ml. of 10% hydrochloric acid and washed with ether. The aqueous layer was made basic with 20% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried over potassium carbonate, and evaporated to give a yellowish oil, which was distilled *in vacuo* to give 1.4 g. (11%) of a colorless oil, b.p. 113-116° (3 mm); this was identical with an oil, obtained by the method (a).

1-Benzyl-2-(4-methoxybenzyl)-3,4-dimethyl-4-hydroxypiperidines (XIXa and XIXb).

(a) A suspension of 5.0 g. of the above mixture (XVII and XVIII) in 50 ml. of water was adjusted to pH 3.0 with 10% hydrochloric acid, and 5.5 g. of methyl 3-(4-methoxyphenyl)-

2,3-epoxypropionate was added. The mixture was heated at 80-90° under vigorous stirring for 3 days. After removal of an insoluble substance, the mixture was washed with ether. The aqueous layer was made basic with 20% sodium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to leave 6.2 g. of a brownish oil, which was chromatographed on 190 g. of alumina using benzene as an eluant. The initial elution afforded the amine XVIII as an oil, which was characterized as its hydrochloride (1.18 g., 20%), m.p. 208-209° (from 2-propanol).

Anal. Calcd. for $C_{13}H_{21}N$·HCl: N, 6.21. Found: N, 6.35.

The successive eluate gave 0.6 g. of the first piperidinol (XIXa), nmr (carbon tetrachloride): δ 0.97 (3H, d, J = 7 Hz, C_3-CH_3), 1.01 (3H, s, C_4-CH_3), 3.04, 4.15 (2H, 2 x d, J = 14 Hz, N-CH_2Ph), 3.70 (3H, s, OCH_3), 6.80, 7.15 (4H, 2 x d, J = 8 Hz, ArH), 7.31 (5H, s, ArH). Recrystallization of the picrate from 2-propanol yielded yellowish needles, m.p. 172-173°.

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot C_6H_3N_3O_7$: C, 59.14; H, 5.67; N, 9.85. Found: C, 58.92; H, 5.74; N, 9.73.

Further elution gave 3.0 g. of a mixture of the isomeric piperidinols (XIXa and XIXb), and the final elution gave 1.0 g. of second piperidinol (XIXb), nmr (carbon tetrachloride): δ 0.91 (3H, d, J = 7 Hz, C_3-CH_3), 1.04 (3H, s, C_4-CH_3), 3.43, 3.94 (2H, 2 x d, J = 14 Hz, NCH_2Ph), 3.70 (3H, s, OCH_3), 6.75, 7.16 (4H, 2 x d, J = 8 Hz, ArH), 7.30 (5H, s, ArH), the picrate of which was recrystallized from ethanol to give yellow needles, m.p. 159-160°.

Anal. Calcd. for $C_{22}H_{29}NO_2 \cdot C_6H_3N_3O_7$: C, 59.14; H, 5.67; N, 9.85. Found: C, 59.45; H, 5.86; N, 9.87.

(b) A suspension of 2.0 g. of the above mixture (XVII and XVIII) in 40 ml. of water was adjusted to *p*H 3.0 with 10% hydrochloric acid. 4-Methoxyphenylacetaldehyde (2.0 g.) was added and the mixture was heated at 80-90° under vigorous stirring for 3 days. After removal of insoluble substance, the mixture was washed with ether and the aqueous layer was made basic with 20% sodium hydroxide solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to leave 1.3 g. of a brownish oil, which was chromatographed on alumina, as in method (a) to give 35 mg. of the first piperidinol (XIXa), 150 mg. of a mixture of the isomers (XIXa and XIXb), and 50 mg. of the second piperidinol (XIXb). The spectroscopic data of XIXa and XIXb, obtained by this method, were identical with those of the compounds obtained by method (a).

1-Benzyl-2-(4-methoxybenzyl)-3,4-dimethyl-4-hydroxypiperidine (XIXb).

A suspension of 3 g. of the piperidinol (XX), 2.06 g. of benzyl bromide, 3.0 g. of potassium carbonate, and 60 ml. of dimethylformamide was refluxed for 5 hours. After removal of the solvent, the residue was poured into 150 ml. of ice-water and extracted with ether. The organic layer was extracted with 10% hydrochloric acid. The acidic extract was basified with 20% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried over potassium carbonate and evaporated to leave 3.35 g. (83%) of XIXb as a pale yellowish oil, the ir and nmr data of which were identical with those of XIXb, obtained as above.

3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocine (II).

(a) A mixture of 0.5 g. of the piperidinol (XIXa), 10 ml. of 47% hydrobromic acid, and 2 ml. of acetic acid was refluxed for 50 hours. The mixture was basified with 28% ammonium hydroxide and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to leave II as a brownish oil. Recrystallization of II·HCl from 2-propanol gave 230 mg. (46%) of colorless prisms, m.p. 268-270° dec. [lit. (7) m.p. 268-270° dec.] which were identified by comparison of spectroscopic data and a mixed melting point test.

(b) A mixture of 3.35 g. of the piperidinol XIXb, 40 ml. of 47% hydrobromic acid, and 8 ml. of acetic acid was refluxed for 50 hours, and the mixture was worked up in the case of method (a) to give 1.5 g. (43%) of II·HCl, which was identical with the authentic specimen by comparison of spectroscopic data and mixed melting point test.

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