

Studies on the Syntheses of Analgesics. Part XXXI (1).
 Synthesis of 1,2,3,4,5,6-Hexahydro-3-methyl-6-phenyl-2,6-methano-2,3-benzo[g] diazocine
 [Studies on the Syntheses of Heterocyclic Compounds. Part CDLXXIX (2)]

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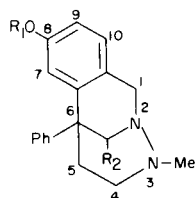
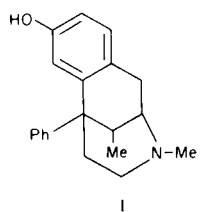
1,2,3,4,5,6-Hexahydro-8-methoxy-3-methyl-6-phenyl-2,6-methano-2,3-benzo[g]diazocine (IIa) was synthesized from 1-(3-methoxyphenyl)phenylacetonitrile (III), readily available by the benzyne reaction of *o*-chloroanisole with phenylacetonitrile, through several steps. Treatment of IIa with 47% hydrobromic acid afforded 1,2,3,4,5,6-hexahydro-8-hydroxy-3-methyl-6-phenyl-2,6-methano-2,3-benzo[g]diazocine (IIb).

In the previous paper (4-9) in order to get an effective analgesic we reported the synthesis of several kinds of azabenzomorphan and related compounds in which one carbon was replaced by a nitrogen atom on the benzomorphan ring. Previously a number of 2,6-methano-3-benzazocines possessing a phenyl group at the C₆-position (10) had been synthesized, one of which, 1,2,3,4,5,6-hexahydro-8-hydroxy-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocine (I) (11) was proved in the hot plate test to be more potent than morphine as an analgesic when given intraperitoneally. Therefore, we have investigated the synthesis of 1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-2,3-benzo[g]diazocines (IIa and IIb),

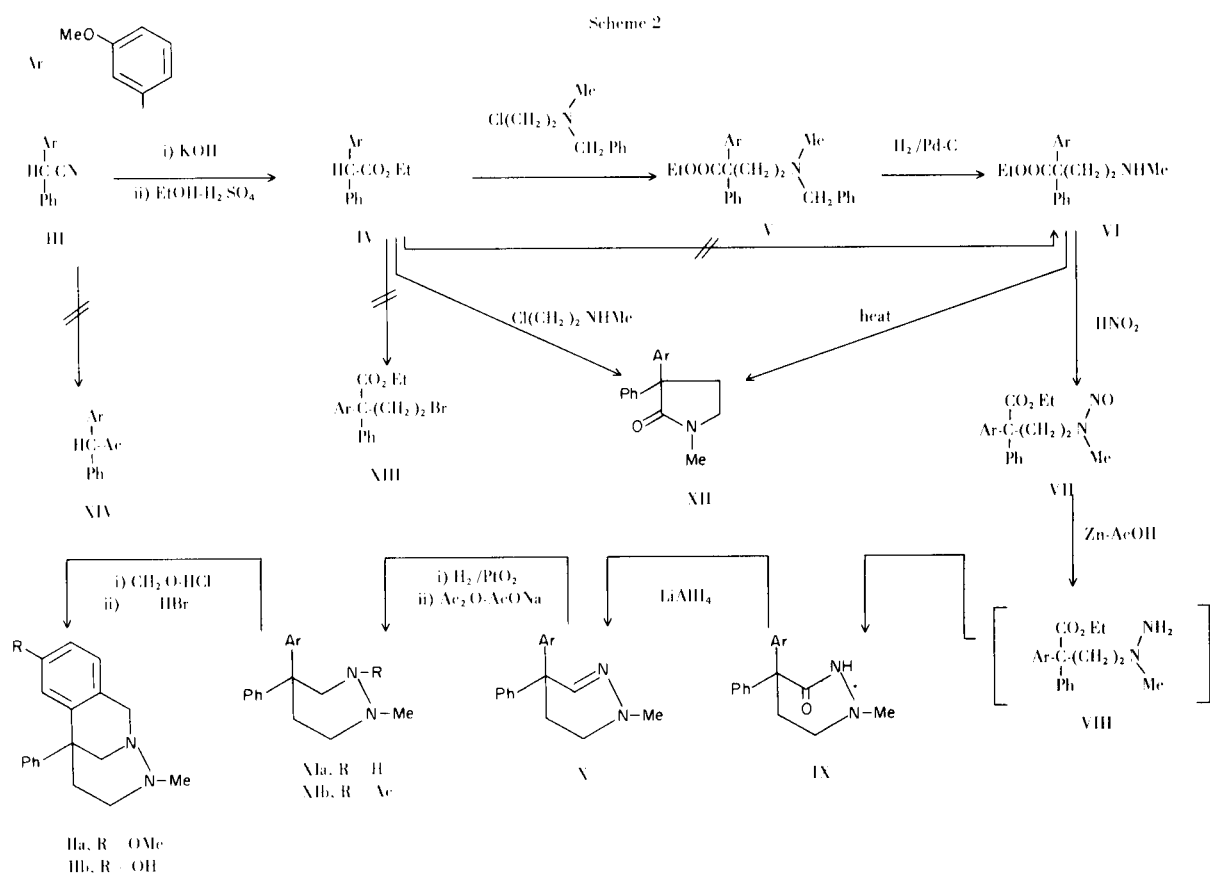
in which a nitrogen atom replaced the C₂-carbon of benzomorphan ring (I), using 1-(3-methoxyphenyl)phenylacetonitrile (III) (12) as a starting material. Herein we wish to report these results.

The key intermediate (IX) for the synthesis of IIa and IIb was synthesized as follows (see Scheme 2). Hydrolysis of III (12), followed by esterification, afforded ethyl 2-(3-methoxyphenyl)phenylacetate (IV) (13), which was condensed with *N*-benzyl-*N*-methylaminoethyl chloride to give ethyl 2-(*N*-benzyl-*N*-methylaminoethyl)-2-(3-methoxyphenyl)phenylacetate (V). This structure was confirmed on the basis of microanalysis of its oxalate salt and spectroscopic data. Its ir spectrum (liquid) showed an absorption band due to C=O group at 1720 cm⁻¹. Reductive debenzoylation of V using 10% palladium-charcoal as a catalyst afforded ethyl 2-(3-methoxyphenyl)-2-(*N*-methylaminoethyl)phenylacetate (VI). Condensation of IV with *N*-methylaminoethyl chloride in the presence of sodium hydride gave 3-(3-methoxyphenyl)-1-methyl-3-phenylpyrrolidin-2-one (XII) and no formation of VI was observed. The structure of XII was assigned by microanalysis and comparison of spectroscopic data with those of the authentic specimen prepared from VI. Nitrosation of VI, followed by the reduction of the nitroso derivative VII by Mitsuhashi's method (14) using zinc powder and acetic acid, afforded 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazin-3(2*H*)one (IX) through the hydrazine derivative VIII. Its ir spectrum showed the absorption bands due to NH at 3150 and C=O group at 1640 cm⁻¹. An alternative method for the synthesis of IX was investigated involving condensation of IV with dibromoethane and *N*-methylaminoethyl chloride to give the bromide XII, which could

Scheme 1



IIa, R₁ - Me, R₂ - H
 IIb, R₁ - R₂ - H
 XV, R₁ - H, R₂ - Me



be further converted to IX, and the ester-amine VI, respectively. However, the formation of VI and XIII in both routes was unsuccessful.

The lactam IX, thus obtained, was reduced with lithium aluminum hydride to give 1,4,5,6-tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine (X) and catalytic

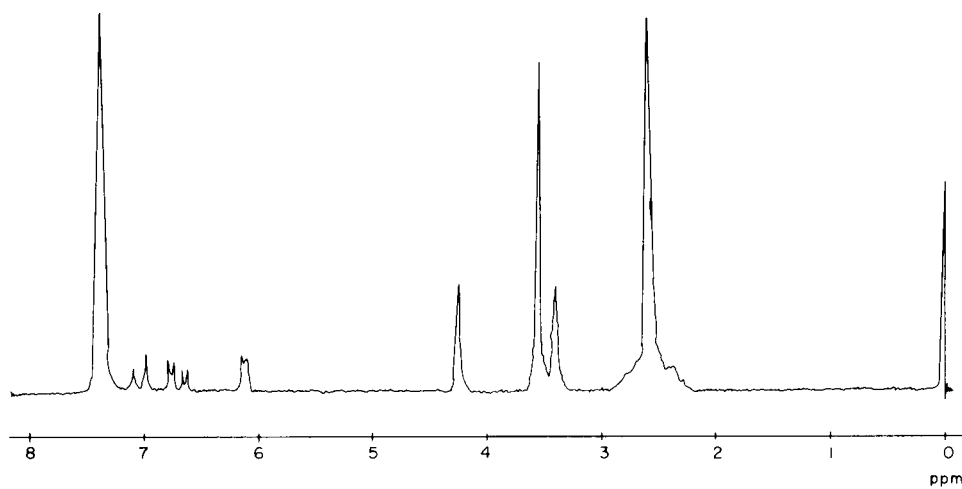


Figure 1. Nmr spectrum of IIa.

hydrogenation of X in the presence of platinum oxide gave 1,2,3,4,5,6-hexahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine (XIa), which was converted into its acetyl derivative (XIb) in order to characterize its structure.

The Pictet-Spengler reaction of XIa with formalin under acidic conditions gave 1,2,3,4,5,6-hexahydro-8-methoxy-3-methyl-6-phenyl-2,6-methano-2,3-benzo[*g*]diazocine (IIa) as expected. Its nmr spectrum (in deuteriochloroform) showed a doublet ($J = 3$ Hz) attributable to the C₇-proton at 6.11, doublet, doublet ($J = 8.2$, 3 Hz) centered at 6.71 due to the C₉-proton and a doublet ($J = 8.2$ Hz) at 7.05 ppm assigned to the C₁₀-proton. These facts indicate that the cyclization occurred at the *para* position to the methoxy group on the Pictet-Spengler reaction of XIa. Treatment of IIa with 47% hydrobromic acid afforded the desired phenolic base IIb as colorless prisms.

Finally, we examined a synthesis of 1-(3-methoxyphenyl)-1-phenylacetone (XIV), which would be a valuable intermediate for the synthesis of 11-methyl analogs (XV) of IIa from the phenylacetone nitrile (III), but resulted in failure.

EXPERIMENTAL (15)

Ethyl 2-(*N*-Benzyl-*N*-methylaminoethyl)-2-(3-methoxyphenyl)-phenylacetate (V).

A solution of 21 g. of IV (12,13) in 21 ml. of dimethylformamide was added dropwise to a solution of 4.2 g. of sodium hydride (50% suspension in mineral oil) in 80 ml. of dimethylformamide at 40°. The mixture was stirred for 1 hour and then 16 g. of *N*-benzyl-*N*-methylaminoethyl chloride was added to the above mixture at 60° with stirring. After the stirring had been continued for 3 hours, the mixture was poured into 600 ml. of ice-water and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated to give V as an oil, the oxalate of which prepared as usual was recrystallized from ethanol-ether to give 25 g. (63.5%) of a colorless powder, m.p. 101-102.5°.

Anal. Calcd. for C₂₇H₃₁NO₃·C₂H₂O₄: C, 68.62; H, 6.55; N, 2.76. Found: C, 68.63; H, 6.29; N, 2.97.

The free base (V) obtained from the oxalate with usual manner was used for the following reaction; ν max (liquid) cm⁻¹: 1720 (C=O); nmr δ (carbon tetrachloride): 1.12 (3H, triplet, CH₂CH₃), 2.13 (3H, singlet, NCH₃), 2.14 (2H, triplet, CH₂CH₂-N<), 2.58 (2H, triplet, CH₂CH₂-N<), 3.42 (2H, singlet, CH₂C₆H₅), 3.75 (3H, singlet, OCH₃), 4.13 (2H, quartet, CH₂CH₃), 6.65~7.48 (14H, multiplet, aromatic H).

Ethyl 2-(3-Methoxyphenyl)-2-(*N*-methylaminoethyl)phenylacetate (VI).

A mixture of 18.5 g. of V, 200 ml. of ethanol, 4 ml. of concentrated hydrochloric acid and 5 g. of 10% palladium-charcoal was shaken in a current of hydrogen until the uptake of hydrogen ceased. After the catalyst had been filtered off, the solvent was evaporated to give 16 g. (99.3%) of the hydrochloride of VI, the crystallization of which was unsuccessful. The free base was obtained as an oil by the usual work-up; ν max (liquid) cm⁻¹:

1720 (C=O); nmr δ (carbon tetrachloride): 1.15 (3H, triplet, CH₂CH₃), 2.28 (3H, singlet, NCH₃), 2.15-2.62 (4H, multiplet, CH₂CH₂-N<), 3.75 (3H, singlet, OCH₃), 4.19 (2H, quartet, CH₂CH₃), 6.70-7.55 (9H, multiplet, aromatic H).

Ethyl 2-(*N*-methyl-*N*-nitrosoaminoethyl)-2-(3-methoxyphenyl)-phenylacetate (VII).

To a stirred solution of 14 g. of the hydrochloride of VI in 98 ml. of water was added dropwise a solution of 3.16 g. of sodium nitrite in 22 ml. of water at 70° within 1 hour. After the stirring had been continued for 1 hour at the same temperature, the mixture was extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated to afford 12.4 g. of VII as a pale yellowish oil, which was used for the following reaction without purification.

1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine-3(2H)-one (IX).

A mixture of 2.5 g. of VII, 4.5 g. of zinc powder, 30 ml. of glacial acetic acid, and 15 ml. of water was refluxed under stirring for 6 hours. After removal of the excess of zinc powder, the solvent was evaporated. The resulting residue was made basic with ammonia and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate, and evaporated. The remaining residue was triturated with ether to give 0.7 g. (33.7%) of IX as an amorphous powder; ν max (potassium bromide) cm⁻¹: 3150 (NH), 1640 (C=O); nmr δ (deuteriochloroform): 2.55 (3H, singlet, NCH₃), 2.58-3.11 (4H, multiplet, CH₂CH₂-N<), 3.76 (3H, singlet, OCH₃), 6.70-7.55 (9H, multiplet, aromatic H). The hydrochloride prepared as usual was recrystallized from ethanol-ether to give colorless needles, m.p. 208-209°.

Anal. Calcd. for C₁₈H₂₉N₂O₂·HCl: C, 64.95; H, 6.36; N, 8.42. Found: C, 65.33; H, 6.21; N, 8.52.

1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine (X).

A mixture of 1 g. of IX, 100 ml. of dry ether, and 116 mg. of lithium aluminum hydride was refluxed for 15 hours. The excess of lithium aluminum hydride was decomposed with 30% sodium hydroxide solution, and the inorganic precipitate was removed. The organic solvent was dried on magnesium sulfate and evaporated. The remaining residue was chromatographed on silica gel using chloroform as an eluant. Removal of the solvent afforded 560 mg. (59.2%) of X as colorless needles, m.p. 86-87° (from ether-petroleum ether); nmr δ (carbon tetrachloride): 2.48 (2H, triplet, CH₂CH₂-N<), 2.72 (2H, triplet, CH₂CH₂-N<), 2.78 (3H, singlet, N-CH₃), 3.63 (3H, singlet, OCH₃), 6.55-7.40 (10H, multiplet, CH=N and aromatic H).

Anal. Calcd. for C₁₈H₂₀N₂O: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.82; H, 6.98; N, 10.08.

1,2,3,4,5,6-Hexahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine (XIa).

A mixture of 780 mg. of X, 50 ml. of ethanol, 0.6 ml. of concentrated hydrochloric acid, and platinum oxide as a catalyst was shaken in a current of hydrogen until the uptake of hydrogen ceased. After removal of the catalyst, the solvent was evaporated to leave 820 mg. (92.6%) of the hydrochloride of XIa; nmr δ (deuteriochloroform): 2.92 (3H, singlet, N-CH₃), 2.52-3.40 (4H, multiplet, CH₂CH₂-N<), 3.70 (3H, singlet, OCH₃), 3.85 (2H, singlet, CH₂NH-), 6.58-7.52 (9H, multiplet, aromatic H), which was used in the following reaction without purification because of difficult crystallization.

2-Acetyl-1,2,3,4,5,6-hexahydro-4-(3-methoxyphenyl)-1-methyl-4-phenylpyridazine (XIb).

A mixture of 230 mg. of the hydrochloride of XIa, 1 ml. of acetic anhydride, and 70 mg. of sodium acetate was refluxed for 1.5 hours. After removal of the excess of acetic anhydride *in vacuo*, the mixture was poured into water, and extracted with ether. The extract was washed with 10% potassium carbonate solution and water, and dried over magnesium sulfate. The solvent was evaporated and the remaining residue was recrystallized from ether-petroleum ether to give 150 mg. (64.1%) of XIb as colorless needles, m.p. 108-109°; ν max (potassium bromide) cm^{-1} : 1640 (C=O); nmr δ (deuteriochloroform): 2.16 (3H, singlet, COCH_3), 2.15-3.31 (6H, multiplet, $\text{CH}_2\text{CH}_2\text{N}$ and $\text{CH}_2\text{NCOCH}_3$), 2.71 (3H, singlet, NCH_3), 3.85 (3H, singlet, OCH_3), 6.73-7.56 (9H, multiplet, aromatic H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.89; H, 7.06; N, 8.65.

1,2,3,4,5,6-Hexahydro-8-methoxy-3-methyl-6-phenyl-2,6-methano-2,3-benzo[*g*]diazocine (IIa).

A mixture of 900 mg. of the hydrochloride of XIa, 5 g. of 37% formaldehyde, 5 g. of water, and 3 drops of concentrated hydrochloric acid was heated on a water-bath for 1.5 hours. After evaporation of the solvent, the remaining residue was made basic with ammonia and extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated. The resulting residue was chromatographed on silica gel using chloroform as an eluant. Removal of the solvent afforded 540 mg. (57.9%) of IIa as a pale yellowish oil; nmr δ (deuteriochloroform): 2.25-2.89 (4H, multiplet, $\text{C}_4\text{-H}_2$ and $\text{C}_5\text{-H}_2$), 2.58 (3H, singlet, NCH_3), 3.38 (2H, singlet, $\text{C}_{11}\text{-H}_2$), 3.55 (3H, singlet, OCH_3), 4.25 (2H, singlet, $\text{C}_1\text{-H}_2$), 6.11 (1H, doublet, $J = 3$ Hz, $\text{C}_7\text{-H}$), 6.71 (1H, doublet, doublet, $J = 8.2, 3$ Hz, $\text{C}_9\text{-H}$), 7.05 (1H, doublet, $J = 8.2$ Hz, $\text{C}_{10}\text{-H}$), 7.39 (5H, singlet, C_6H_5). The hydrochloride prepared as usual was recrystallized from 2-propanol-ether to give colorless prisms, m.p. 173-178° dec.

Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}\cdot\text{HCl}$: C, 68.97; H, 7.00; N, 8.46. Found: C, 68.73; H, 7.00; N, 8.32.

1,2,3,4,5,6-Hexahydro-8-hydroxy-3-methyl-6-phenyl-2,6-methano-2,3-benzo[*g*]diazocine (IIb).

The hydrochloride (550 mg.) of IIa, 4 ml. of glacial acetic acid and 4 ml. of 47% hydrobromic acid was refluxed for 1.5 hours. After evaporation of the solvent, the resulting residue was made basic with ammonia and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate, and evaporated. The remaining residue was chromatographed on silicic acid using chloroform as an eluant. Removal of the solvent afforded 120 mg. (25.8%) of IIb; ν max (potassium bromide) cm^{-1} : 2200-2700 betaine $\ddot{\text{N}}\text{H}$; nmr δ (trifluoroacetic acid): 2.69-4.25 (6H, multiplet, $\text{C}_4\text{-H}_2$, $\text{C}_5\text{-H}_2$ and $\text{C}_{11}\text{-H}_2$), 3.30 (3H, singlet, NCH_3), 4.87 (2H, singlet, $\text{C}_1\text{-H}_2$), 6.45 (1H, doublet, $J = 3$ Hz, $\text{C}_7\text{-H}$), 7.05 (1H, doublet, doublet, $J = 8.2, 3$ Hz, $\text{C}_9\text{-H}$), 7.35 (1H, doublet, $J = 8.2$ Hz, $\text{C}_{10}\text{-H}$), 7.55 (5H, singlet, C_6H_5); this was recrystallized from methanol to give colorless prisms, m.p. 254-255° dec.

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.12; H, 7.04; N, 9.97.

3-(3-Methoxyphenyl)-1-methyl-3-phenylpyrrolidin-2-one (XII).

(a) To a stirred mixture of 50 ml. of dry dimethylformamide and 1.7 g. of sodium hydride (50% suspension in mineral oil) was added 9.2 g. of IV at 40°. The stirring was continued for 1 hour and then

2.3 g. of *N*-methylaminoethyl chloride was added to the above mixture at 30°. After the stirring had been continued for 3 hours, the mixture was poured into 400 ml. of ice-water and extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated. After removal of the starting material (IV) by distillation *in vacuo*, the remaining residue was chromatographed on silica gel using chloroform as an eluant. Removal of the solvent afforded 1.5 g. (15.6%) of XII as colorless needles, m.p. 68.5-69.5° (from benzene-petroleum ether); ν max (potassium bromide) cm^{-1} : 1680 (C=O); nmr δ (carbon tetrachloride): 2.65 (2H, triplet, $\text{C}_4\text{-H}_2$), 2.87 (3H, singlet, NCH_3), 3.30 (2H, triplet, $\text{C}_5\text{-H}_2$), 3.75 (3H, singlet, OCH_3), 6.50-7.54 (9H, multiplet, aromatic H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.47; H, 6.62; N, 5.10.

(b) The ester-amine (VI) (100 mg.) was heated on a water-bath for 1 hour. The mixture was extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated. The resulting residue was recrystallized from benzene-petroleum ether to give 62 mg. (72.2%) of XII as colorless needles, which were identical with the product obtained from IV in all respects.

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