Studies on the Syntheses of Analgesics. Part XXXVI (1). Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methano-6-phenyl-2-benzazocine [Studies on the Syntheses of Heterocyclic Compounds. Part DXI (2)]

Tetsuji Kametani (3) and Toyohiko Aoyama

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan and
Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabedori 3-Chome, Mizuho-ku, Nagoya, Japan

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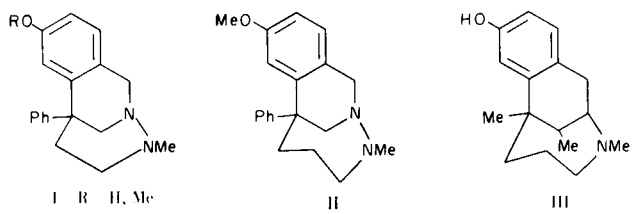
An attempt to obtain 2,3,4,5,6,7-hexahydro-1*H*-2,7-methano-9-methoxy-3-methyl-7-phenyl-2,3-benzodiazonine (II) by the Pictet-Spengler reaction of 2,3,4,5,6,7-hexahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepine (XI) prepared through several steps from 1-(3-methoxyphenyl)phenylacetonitrile (IV) resulted instead, in the formation of 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-6-phenyl-2-benzazocine (XIV).

In the previous paper (4), we reported the synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-3-methyl-6-phenyl-2,3-benzodiazocines (I), in which one nitrogen atom was introduced instead of the C_2-carbon of the benzomorphan ring, for the purpose of obtaining drugs effective on the central nervous system, particularly those having analgesic activity.

Recently, a number of 2,6-methano-3-benzazonines (5) were synthesized, one of which, 2,3,4,5,6,7-hexahydro-1*H*-2,7-methano-3,7,12-trimethyl-3-benzazonine (III) was shown to be comparable to morphine as an analgesic.

Therefore, we have investigated the synthesis of 2,3,4,5,6,7-hexahydro-1*H*-2,7-methano-9-methoxy-3-methyl-7-phenyl-2,3-benzodiazonine (II), in which one nitrogen atom was introduced instead of the C_2-carbon atom of 2,7-methano-3-benzazonine ring, using 1-(3-methoxyphenyl)phenylacetonitrile (IV) (6) as a starting material. Herein we wish to report these results.

Scheme 1



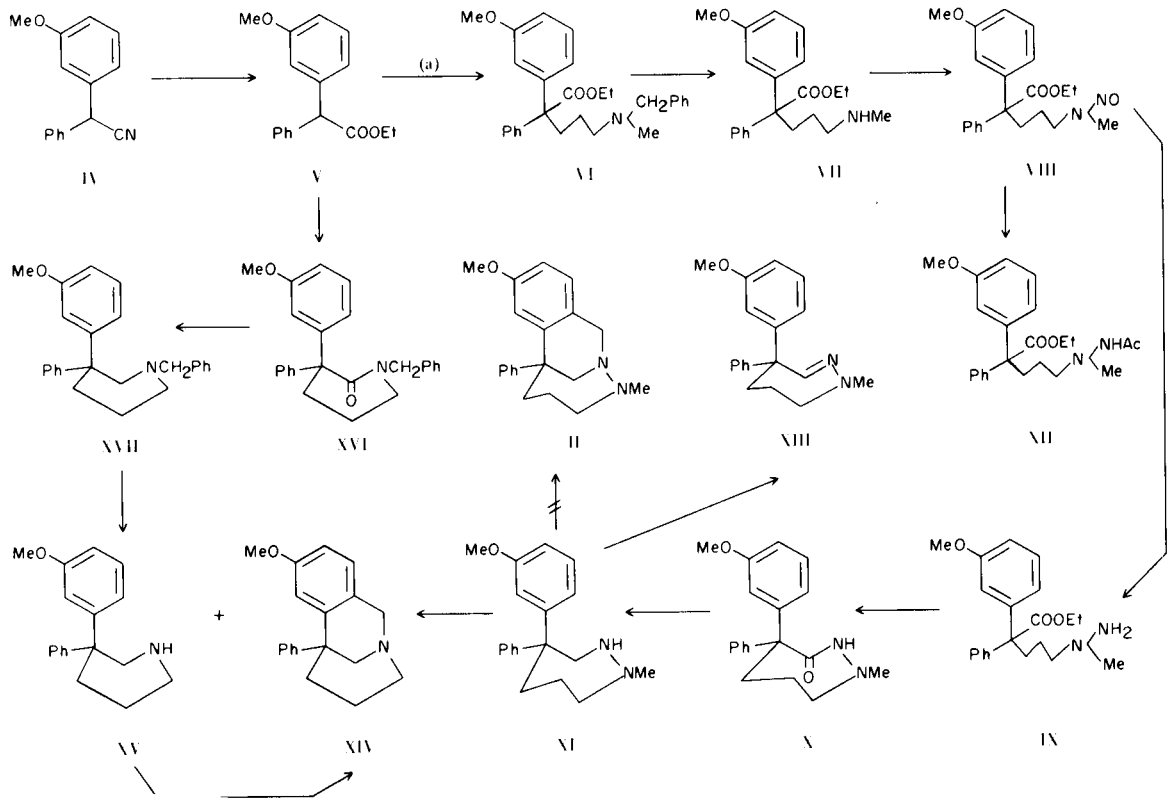
The key intermediate X was synthesized as shown in Scheme 2 (route a). Hydrolysis of 1-(3-methoxyphenyl)-phenylacetonitrile (IV) (6), which was prepared by the benzyne reaction of *o*-chloroanisole with phenylacetonitrile, followed by esterification of the corresponding carboxylic acid, afforded ethyl 2-(3-methoxyphenyl)-phenylacetate (V) (7). The ester V was condensed with 3-(*N*-benzyl-*N*-methylamino)-1-chloropropane to give ethyl 2-[3-(*N*-benzyl-*N*-methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (VI), the structure of which was confirmed on the basis of microanalysis of its oxalate, m.p. 113-114° and spectroscopic data. Its infrared (ir) spectrum (liquid) showed an absorption band due to a carbonyl group at 1725 cm^{-1}. Reductive debenzylation of VI using 15% palladium-charcoal as a catalyst afforded ethyl 2-[3-(*N*-methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (VII). Nitrosation of VII, followed by reduction of the nitroso derivative using zinc powder and acetic acid, afforded ethyl 2-[3-(*N*-amino-*N*-methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (IX). The hydrazine IX was fused to give 2,3,4,5,6,7-hexahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepine-3-one (X). Its ir spectrum showed an absorption band due to a carbonyl group at 1625 cm^{-1} and a secondary amine at 3240 cm^{-1}. In this case, the direct synthesis of X from the nitroso compound VIII by Mitsuhashi's method (8) was investigated. However, the formation of X was unsuccessful and only acetylhydrazine XII was obtained.

aluminum hydride to give 2,3,4,5,6,7-hexahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepine (XI). The structure of XI was confirmed on the basis of microanalysis of its hydrochloride, m.p. 225-229° dec. and spectroscopic data as described in the experimental section. When the free base of XI was allowed to stand in the air, the dehydro-base XIII was formed. The structure of XIII was confirmed on the basis of microanalysis and spectroscopic data. The nuclear magnetic resonance (nmr) spectrum of XIII showed the protons of *N*-methyl group at 3.34 ppm as singlet and *O*-methyl group at 3.66 ppm as singlet, but the signal of the methylene at C_3-position could not be observed.

Pictet-Spengler reaction of XI with formalin under acidic conditions gave 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-6-phenyl-2-benzazocine (XIV) and 3-(3-methoxyphenyl)-3-phenylpiperidine (XV) as unexpected products. The microanalysis of the hydrochloride of XIV agreed with the formula of $C_{19}H_{21}NO \cdot HCl$ and the nmr spectrum showed a pair of doublets (J = 16.5 Hz) attributable to the C_1-protons at 3.73, 4.46, a doublet (J = 3 Hz) at 6.03 due to the C_7-proton, a pair of doublets (J = 8.3, 3 Hz) centered at 6.57 due to the C_9-proton, and a doublet (J = 8.3 Hz) at 6.90 ppm assigned to the C_{10}-proton. These facts indicate that the cyclization occurred at the *para* position to the methoxy group with demethylamination on Pictet-Spengler reaction of XI. The structure of XV was confirmed on the basis of microanalysis of its hydrochloride, m.p. 92-94°, and spectroscopic data. Pictet-Spengler reaction of XI with formalin to obtain the 2,7-methano-2,3-benzodiazonine (II) was unsuccessful.

The mechanism to explain the formation of these products remained unclear, but heating of XI with hydrochloric acid gave the starting material. On the other hand, when an aqueous mixture of the hydrochloride of XI and formalin was stirred at room temperature, XV was observed as one spot in addition to the starting material, whereas on heating on a water-bath, XIV and XV were recognized as two spots on the tlc plate. According to the above results demethylamination occurred in the

Scheme 2



presence of formalin in the case of Pictet-Spengler reaction.

Furthermore, compounds XIV and XV were shown to be identical with samples synthesized as shown in Scheme 2 (route b). Condensation of V with 3-(*N*-benzylamino)-1-chloropropane gave 1-benzyl-3-(3-methoxyphenyl)-3-phenylpiperidine-2-one (XVI). The structure of XVI was confirmed by microanalysis and spectroscopic data. The ir spectrum (liquid) showed an absorption band due to a carbonyl group at 1640 cm^{-1}. Reduction of XVI with lithium aluminum hydride, followed by reductive debenzylation of XVII using 15% palladium-charcoal as the catalyst, afforded 3-(3-methoxyphenyl)-3-phenylpiperidine (XV).

The Pictet-Spengler reaction of XV with formalin under acidic conditions gave the 2,6-methano-2-benzazocine (XIV) as the expected product.

Compounds XIV and XV were shown to be identical with samples, prepared by the Pictet-Spengler reaction of XI and formalin by comparing spectroscopic data and melting point. Their pharmacological activity is under examination.

EXPERIMENTAL (9)

Ethyl 2-(3-Methoxyphenyl)phenylacetate (V).

A mixture of 95 g. of IV (6), 225 g. of potassium hydroxide and 150 ml. of water was refluxed for 6 hours. After cooling, the mixture was diluted with 1000 ml. of water and washed with benzene. The aqueous layer was made acidic with hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated. A mixture of the resulting residue, 700 ml. of ethanol and 10 ml. of concentrated sulfuric acid was refluxed for 6 hours. The solvent was evaporated and the residue was diluted with water and extracted with ether. The extract was washed with 5% potassium carbonate solution and water, and dried over magnesium sulfate. The solvent was evaporated and the residue was distilled *in vacuo* to give 84 g. (73.0%) of V as a pale yellow oil, b.p. 139-142° (0.15 mm) [lit. (7), b.p. 162-164° (1.0 mm)].

Ethyl 2-[3-(*N*-Benzyl-*N*-methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (VI).

To a suspension of 4.2 g. of sodium hydride (66% suspension in mineral oil) in 80 ml. of dimethylformamide (DMF) was added dropwise a solution of 28 g. of V in 30 ml. of DMF at 40°. The mixture was stirred for 1 hour and then 22.5 g. of 3-(*N*-benzyl-*N*-methylamino)-1-chloropropane was added to the above solution at 60° with stirring. After the stirring had been continued for 4 hours, the solution was poured into 500 ml. of water and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated to give a residue, the oxalate of which was recrystallized from 2-propanol-ether to give 42.7 g. (79.1%) of VI as a colorless powder, m.p. 113-114°; ir ν (liquid) cm^{-1} (free base): 1725 (C=O); nmr δ (in carbon tetrachloride): 1.15 (3H, t, CH_2CH_3), 1.10-1.45 (2H, m, $CH_2CH_2CH_2$), 2.08 (3H, s, N-CH_3), 2.00-2.62 (4H, m, $CH_2CH_2CH_2N$), 3.45 (2H, s, CH_2Ph), 3.78 (3H, s, OCH_3), 4.19 (2H, q, CH_2CH_3), 6.58-7.38 (14H, m, Ar-H).

Anal. Calcd. for $C_{28}H_{33}NO_3 \cdot C_2H_2O_4 \cdot H_2O$: C, 66.77; H, 6.91; N, 2.60. Found: C, 66.69; H, 6.62; N, 2.71.

Ethyl 2-[3-(*N*-Methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (VII).

A mixture of 9 g. of VI, 100 ml. of ethanol, 2.8 ml. of concentrated hydrochloric acid solution and 3.5 g. of 15% palladium-charcoal was shaken in a current of hydrogen until uptake of hydrogen ceased. After the catalyst had been filtered off, the solvent was evaporated to give 7.5 g. of the hydrochloride of VII as a pale yellow syrup, the crystallization of which was unsuccessful; ir ν (liquid) cm^{-1} (free base): 1725 (C=O), nmr δ (in carbon tetrachloride): 1.15 (3H, t, CH_2CH_3), 1.10-1.48 (2H, m, $CH_2CH_2CH_2$), 2.05-2.75 (7H, m, NCH_3, $CH_2CH_2CH_2$), 3.74 (3H, s, OCH_3), 4.15 (2H, q, CH_2CH_3), 6.50-7.32 (9H, m, Ar-H).

Ethyl 2-[3-(*N*-Methyl-*N*-nitrosoamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (VIII).

To a stirred solution of 10.7 g. of hydrochloride of VII in 70 ml. of water was added dropwise a solution of 2.1 g. of sodium nitrite in 15 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 give an oil, which was chromatographed on silicic acid using chloroform as an eluant to afford 7.2 g. (68.5%) of VIII as a pale yellow oil; ir ν (liquid) cm^{-1}: 1725 (C=O); nmr δ (carbon tetrachloride): 1.15 (3H, t, CH_2CH_3), 1.25-1.72 (2H, m, $CH_2CH_2CH_2$), 2.28 (2H, t, $CH_2CH_2CH_2$), 2.78 (3H, s, N-CH_3), 3.72 (3H, s, OCH_3), 4.02 (2H, t, $CH_2CH_2CH_2N$), 4.10 (2H, q, CH_2CH_3), 6.55-7.22 (9H, m, Ar-H).

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.21; H, 7.24; N, 7.32.

Ethyl 2-[3-(*N*-Amino-*N*-methylamino)-1-propyl]-2-(3-methoxyphenyl)phenylacetate (IX).

A mixture of 19 g. of VIII, 28 g. of zinc powder, 120 ml. of glacial acetic acid and 70 ml. of water was stirred for 5 hours at 25-30°. After removal of the excess of zinc powder by filtration, the filtrate was made basic with concentrated ammonia and extracted with ether. The ethereal layer was extracted with 10% hydrochloric acid; the aqueous layer was made basic with concentrated ammonia and extracted with ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated to give 16.4 g. of IX as a pale yellow oil, which was used for the following reaction without purification.

2,3,4,5,6,7-Hexahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepin-3-one (X).

Heating of 0.8 g. of IX at 210-215° for 45 minutes, followed by chromatography on silicic acid using chloroform as an eluant, afforded 120 mg. (17.2%) of X as a colorless oil; ir ν (liquid) cm^{-1}: 3240 (NH), 1625 (C=O); nmr δ (carbon tetrachloride): 1.80 (2H, m, $CH_2CH_2CH_2$), 2.52 (2H, t, $CH_2CH_2CH_2N$), 2.58 (3H, s, NCH_3), 3.52 (2H, t, CH_2N), 3.70 (3H, s, OCH_3), 6.55-7.25 (9H, m, Ar-H). The hydrochloride prepared as usual was recrystallized from 2-propanol-ether to give colorless needles, m.p. 155-157°.

Anal. Calcd. for $C_{19}H_{22}N_2O_2 \cdot HCl \cdot 0.5H_2O$: C, 64.13; H, 6.80; N, 7.87. Found: C, 64.14; H, 6.60; N, 7.76.

Ethyl 2-[3-(*N*-Acetylhydrazino-*N*-methyl-1-propyl]-2-(3-methoxyphenyl)phenylacetate (XII).

A mixture of 7 g. of VIII, 13 g. of zinc powder, 90 ml. of glacial acetic acid and 45 ml. of water was refluxed for 8 hours with stirring. After filtration of the excess of zinc powder, the filtrate was made basic with concentrated ammonia and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated to give a yellow oil, which was chromatographed on silicic acid using chloroform as an eluant to afford 1.6 g. (21.3%) of XII as a pale yellow oil; ir ν (liquid) cm^{-1}: 1730, 1655 (C=O); nmr δ (carbon tetrachloride): 1.15 (3H, s, NCH_3), 2.15-2.80 (4H, m, $CH_2CH_2CH_2N$), 3.72 (3H, s, OCH_3), 4.10 (2H, q, CH_2CH_3), 6.45-7.20 (9H, m, Ar-H).

Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.54; H, 7.67; N, 7.00.

2,3,4,5,6,7-Hexahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepine (XI).

A mixture of 1 g. of X, 100 ml. of dry ether and 140 mg. of lithium aluminum hydride was refluxed for 15 hours. The excess of reagent was decomposed with 30% sodium hydroxide solution under a current of nitrogen and the inorganic precipitate was filtered off. The organic layer was dried over magnesium sulfate and evaporated to give a yellow oil, the hydrochloride of which was recrystallized from 2-propanol-ether to afford 480 mg. (44.8%) of XI as pale yellow needles, m.p. 225-229° dec.; nmr δ (trifluoroacetic acid): 1.93-2.40 (2H, m, $CH_2CH_2CH_2$), 2.40-2.80 (2H, m, $CH_2CH_2CH_2N$), 3.13 (3H, s, NCH_3), 3.33-3.73 (2H, m, CH_2CH_2N), 4.03 (3H, s, OCH_3), 4.17 (2H, s, CH_2N), 6.77-7.50 (9H, m, Ar-H).

Anal. Calcd. for $C_{19}H_{24}N_2O\cdot HCl$: C, 68.55; H, 7.57; N, 8.41. Found: C, 68.38; H, 7.65; N, 8.18.

Exposure of the free base of XI in the air gave 4,5,6,7-tetrahydro-1*H*-4-(3-methoxyphenyl)-1-methyl-4-phenyl-1,2-diazepine (XIII), which was recrystallized from ether-petroleum ether to afford colorless prisms, m.p. 93-95°; nmr δ (carbon tetrachloride): 1.57 (2H, q, $CH_2CH_2CH_2$), 2.30 (2H, t, $CH_2CH_2CH_2N$), 2.93 (2H, t, $CH_2CH_2CH_2N$), 3.43 (3H, s, NCH_3), 3.66 (3H, s, OCH_3), 6.20-7.26 (10H, m, CH=N, Ar-H).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.60; H, 7.59; N, 9.39.

1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-6-phenyl-2-benzazocine (XIV) and 3-(3-Methoxyphenyl)-3-phenylpiperidine (XV).

A mixture of 400 mg. of the hydrochloride of XI, 4 g. of 37% formalin, 4 g. of water and two drops of concentrated hydrochloric acid was heated on a water-bath for 3 hours. The reaction mixture was made basic with concentrated ammonia and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated. The resulting residue was chromatographed on silicic acid using chloroform as an eluant. Removal of the solvent afforded 130 mg. of the mixture of XIV and XV, which was chromatographed on alumina using benzene as an eluant.

The first fraction was evaporated to give 42 mg. (12.5%) of XIV as a pale yellow oil; nmr δ (carbon tetrachloride): 1.17-1.73 (2H, m, C_4-H_2), 1.90-2.48 (2H, m, C_5-H_2), 2.97 (2H, s, C_{11}-H_2), 2.77-3.34 (2H, m, C_3-H_2), 3.57 (3H, s, OCH_3), 3.73, 4.46 (2H, d, d, J = 16.5 Hz, C_1-H_2), 6.03 (1H, d, J = 3 Hz, C_7-H), 6.57 (1H, d, d, J = 8.3 and 3 Hz, C_9-H), 6.90 (1H, d, J = 8.3 Hz, C_{10}-H), 7.23 (5H, s, Ar-H). The hydrochloride prepared as usual was recrystallized from 2-propanol-ether to give colorless prisms, m.p. 193-195°.

Anal. Calcd. for $C_{19}H_{21}NO\cdot HCl\cdot 0.5H_2O$: C, 70.24; H, 7.13; N, 4.31. Found: C, 69.98; H, 7.08; N, 4.40.

The second fraction was evaporated to give 23 mg. (7.2%) of XV as a pale yellow oil; nmr δ (carbon tetrachloride): 1.28-1.83 (2H, m, $CH_2CH_2CH_2$), 2.43 (2H, t, $CH_2CH_2CH_2N$), 2.83 (2H, t, CH_2CH_2N), 3.40 (2H, s, CH_2N), 3.77 (3H, s, OCH_3), 6.60-7.37 (9H, m, Ar-H). The hydrochloride was recrystallized from methanol-ether to give colorless needles, m.p. 92-94°.

Anal. Calcd. for $C_{18}H_{21}NO\cdot HCl$: C, 71.15; H, 7.29; N, 4.61. Found: C, 71.41; H, 7.40; N, 4.78.

3-(3-Methoxyphenyl)-3-phenyl-1-benzylpiperidin-2-one (XVI).

To a mixture of 1.45 g. of sodium hydride (66% suspension in mineral oil) in 30 ml. of dimethylformamide (DMF) was added dropwise a solution of 10 g. of V in 10 ml. of DMF at 40°. To a stirred mixture for 20 minutes 7.5 g. of 3-(*N*-benzylamino)-1-chloropropane was added at 80° with stirring. After the stirring had been continued for 3 hours, the mixture was poured into 300 ml. of water and extracted with ether. The extract was washed with water, dried over magnesium sulfate and evaporated. After the resulting oil had been heated at 200-210° *in vacuo* (15 mm Hg) for 5 hours, the reaction mixture was distilled *in vacuo* to give 4.5 g. (32.7%) of XVI as a pale yellow oil, b.p. 210-214° (0.3 mm); ir ν (liquid) cm^{-1}: 1640 (C=O); nmr δ (carbon tetrachloride): 1.70 (2H, m, $CH_2CH_2CH_2$), 2.53 (2H, t, $CH_2CH_2CH_2N$), 3.27 (2H, t, CH_2N), 3.67 (3H, s, OCH_3), 4.47, 4.77 (2H, d, d, J = 14.2 Hz, CH_2Ph), 6.57-7.40 (14H, m, Ar-H).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.84; H, 7.02; N, 3.84.

3-(3-Methoxyphenyl)-3-phenyl-1-benzylpiperidine (XVII).

A mixture of 3 g. of XVI, 600 mg. of lithium aluminum hydride in 100 ml. of dry ether was refluxed for 8 hours with stirring. The excess of lithium aluminum hydride was decomposed with 30% sodium hydroxide solution and the inorganic precipitate was then filtered off. The organic layer was dried over magnesium sulfate and evaporated to afford a colorless oil, the hydrochloride of which was recrystallized from ethanol-ether to give 1.71 g. (53.8%) of XVII as colorless prisms, m.p. 228° dec. (darkens at 218°); nmr δ (carbon tetrachloride) (free base): 1.30-178 (2H, m, $CH_2CH_2CH_2$), 2.28 (2H, t, $CH_2CH_2CH_2N$), 2.48 (2H, t, CH_2CH_2N), 2.90 (2H, s, CH_2N), 3.52 (2H, s, CH_2Ph), 3.70 (3H, s, OCH_3), 6.50-7.40 (14H, m, Ar-H).

Anal. Calcd. for $C_{25}H_{27}NO\cdot HCl$: C, 76.23; H, 7.16; N, 3.56. Found: C, 76.24; H, 6.89; N, 3.50.

3-(3-Methoxyphenyl)-3-phenylpiperidine (XV).

A mixture of 1.5 g. of the hydrochloride of XVII, 100 ml. of ethanol and 1 g. of 15% palladium-charcoal was shaken in a current of hydrogen until the cease of uptake of hydrogen. After the catalyst had been filtered off, the solvent was evaporated to give the residue, which was recrystallized from methanol-ether to give 0.8 g. (69.0%) of the hydrochloride of XV. This was identical with an authentic sample prepared by route a.

1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-6-phenyl-2-benzazocine (XIV).

A mixture of 600 mg. of the hydrochloride of XV, 5 g. of 37% formalin, 5 g. of water and two drops of concentrated hydrochloric acid was heated on a water-bath for 3 hours. The reaction mixture was made basic with concentrated ammonia and extracted with ether. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated to give an oil, which was chromatographed on silicic acid using chloroform as an eluant. Removal of the solvent afforded 240 mg. (43.5%) of XIV as a colorless oil, the hydrochloride of which was recrystallized from 2-propanol-ether to give colorless prisms, identical with the authentic sample prepared by route a.

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