[Chem. Pharm. Bull. 24(3) 541—544 (1976)]

UDC 547.898.04 : 547.824.04

Synthesis of Homobenzomorphans and the Related Compounds. III.[1] 3-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine

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(Received June 18, 1975)

3-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine (VIIb) has been synthesized. A four-step sequence [from 5-phenylpiperidone-2 (I)] gave N-methyl-N-carbethoxyaminomethyl-α-tetralone (III). Compound (III) was condensed with glyoxylic acid to give 2-carboxymethylene derivative (IVa) of III, which was converted to seven-membered lactam (VI) by hydrogenation, hydrolysis, esterification and cyclization. Reduction of the carbonyl groups in VI afforded VIIb.

Cyclization of N-carboxymethyl compound (IXb) prepared from III did not afford the 1*H*-3-benzazonine derivative, but 3-benzazocine derivative (X).

For the systematic studies on the correlations between analgetic activity and chemical structure, we have synthesized derivatives of 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine, 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine and 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine where ring-C of benzomorphan has been modified by enlargement to seven-membered ring.[1,3] This paper deals with synthesis of 3-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine (VIIb), a new member of homobenzomorphans.

The strating material, 5-phenyl-2-piperidone (I), was prepared by known procedure.[4] Lactam (I) was hydrolyzed with barium hydroxide, N-methylated with formic acid–formalin and cyclized with polyphosphoric acid (PPA) to give 4-(N,N-dimethylaminomethyl)-3,4-dihydronaphthalen-1(2*H*)-one (II). Several attempts to introduce a carbethoxymethyl group at 2-position of the tetralone (II) by alkylation with ethyl bromoacetate in the presence of sodium hydride in benzene and dimethylformamide or on an enamine of II were unsuccessful.

Thus, compound (II) was converted to carbamate (III) by refluxing with ethyl chloroformate in benzene, which was condensed with glyoxylic acid[5] to give compound (IVa). The ethyl ester (IVb) of IVa was hydrogenated over palladium-charcoal, hydrolyzed, and esterified to give the amino ester (Vb), which was cyclized by heating at 200° (40 mmHg) to afford 3-methyl-2,3-dihydro-1,6-methano-1*H*-3-benzazonin-4(5*H*),7(6*H*)-dione (VI). The structure of VI was confirmed by its infrared (IR), nuclear magnetic resonance (NMR) and mass spectra and the elemental analysis (Experimental).

The lactam VI was reduced with lithium aluminum hydride to give the corresponding amino alcohol (VIIa), from which the final compound (VIIb) was obtained by reduction with hydriodic acid and red phosphorus.

For the preparation of the final framework compound, we tried an alternative route, cyclization of the N-carboxymethyl derivative (IXb) with PPA, which was prepared from compound (III) by hydrolysis and N-alkylation with ethyl bromoacetate. Treatment of IXb with

1) Part II: S. Shiotani and T. Kometani, *Chem. Pharm. Bull.* (Tokyo), **21**, 1053 (1973). This work was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, April, 1975, Nishinomiya.
2) Location: *a) Hongo 13, Toyama; b) Tawame 1076, Sakado-machi, Saitama.*
3) S. Shiotani, T. Kometani, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 277 (1972).
4) A.V. El'tsov, A.G. Chigarev, and N.T. Starykh, *Akad. Nauk SSSR*, **1965**, 109 [*C. A.*, **63**, 16299 (1965)].
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PPA, however, did not give the desired product, but 3-methyl-1,2,3,4-tetrahydro-1,5-methano-3-benzazocin-6(5*H*)-one (X). The structure of compound (X) was confirmed by the following facts: Elemental analysis and mass spectrum suggested the formula, $C_{13}H_{15}ON$. Its IR spectrum showed only one carbonyl band at 1685 cm^{-1}. This result may be caused by dehydration and decarbonylation of compound (IXb), and resemble formation of Py-tetrahydroisoquinoline derivative from N-tosyl-N-phenethylglycine derivative.[6] The carbonyl group in X was converted to methylene by hydrogenation over palladium-charcoal and the subsequent reduction with hydriodic acid and red phosphorus to give compound (XIb).

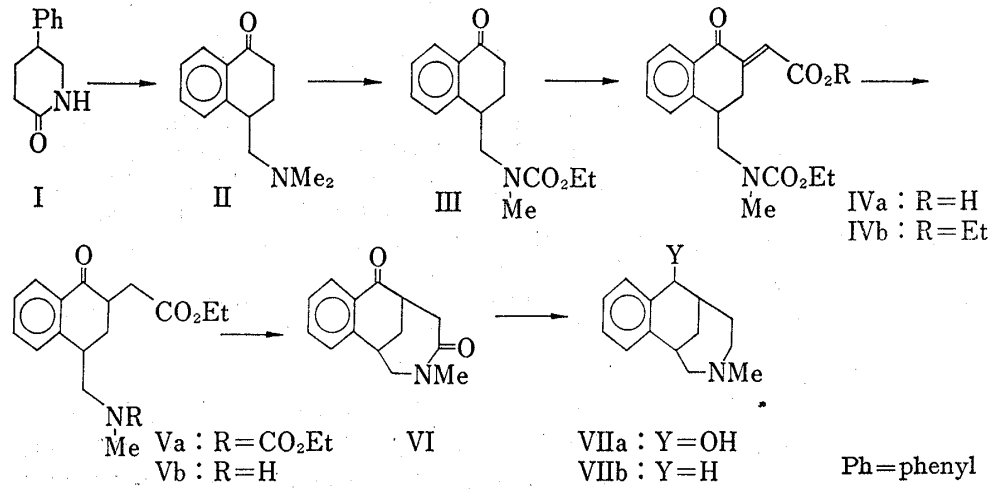

Chart 1

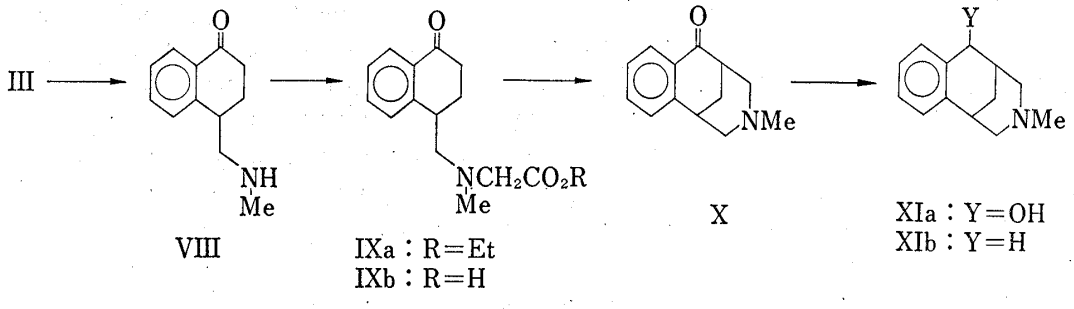

Chart 2

Experimental

Melting points were taken with a Yanagimoto micro melting point apparatus and uncorrected. NMR spectra were obtained on a JNM C-60H spectrometer using TMS as an internal standard. Mass spectra were determined on a JMS-OlSG spectrometer at 75 eV.

4-(N,N-Dimethylaminomethyl)-3,4-dihydronaphthalen-1(2*H*)-one (II)——5-Phenyl-2-piperidone (I) (1.0 g), $Ba(OH)_2 \cdot 8H_2O$ (10 g) and H_2O (100 ml) were refluxed for 8 hr, cooled, neutralized with 20% H_2SO_4 and filtered (Celite). The filtrate was evaporated to dryness. The solid residue (1.2 g) was mixed with HCO_2H (10 ml) and HCHO (37%, 5 ml), and heated on a water bath for 1.5 hr. After evaporation to dryness, the residue (1.2 g) and PPA (20 g) were heated on a water bath for 5 hr, cooled, diluted with ice-water, basified with KOH and extracted with ether. Drying (K_2CO_3) and evaporation of the solvent gave 0.7 g of an oil, which was distilled to give 0.59 g of pure II, bp 128—135° (3 mmHg). IR ν_{max}^{film} cm^{-1}: 2770, 2805 (NMe_2), 1700 (C=O). NMR ($CDCl_3$) τ: 7.69 (s, 6, NMe_2), 2.85—2.50 (complex m, 3, C-5, C-6, C-7H), 1.98 (a pair of d, $J_{7,8}$= 8.0 Hz, $J_{6,8}$=2.0 Hz, 1, C-8 H). Picrate: mp 172—175° (from MeOH). *Anal.* Calcd. for $C_{19}H_{20}O_8N_4$: C, 52.78; H, 4.66; N, 12.96. Found: C, 52.84; H, 4.45; N, 12.70.

4-(N-Carbethoxyl-N-methylaminomethyl)-2-carbethoxymethylene-3,4-dihydronaphthalen-1(2*H*)-one (IVb)——Ethyl chloroformate (2.8 g) was rapidly added to a refluxing solution of II (2.0 g) in benzene (80 ml).

6) J.v. Braun, O. Bayer, and L. Cassel, *Chem. Ber.*, **60**, 2602 (1927).

The mixture was refluxed for 2.5 hr, cooled, washed with 5% HCl and H_2O, and dried ($MgSO_4$). After evaporation of the solvent, the colorless oily residue was distilled *in vacuo* to give 2.0 g of III, bp 160—165° (2 mmHg). IR ν_{max}^{film} cm^{-1}: 1715 (C=O). NMR ($CDCl_3$) τ: 8.80 (t, J=7.0 Hz, 3, O-$CH_2\underline{CH_3}$), 7.05 (s, 3, NMe), 5.90 (q, J=7.0 Hz, 2, O-$\underline{CH_2}CH_3$), 2.90—2.40 (complex m, 3, C-5, C-6, C-7 H), 1.95 (a pair of d, $J_{7,8}$=8.0 Hz, $J_{6,8}$=2.0 Hz, 1, C-8 H).

To an ice-cooled mixture of $HIO_4 \cdot 2H_2O$ (2.05 g), NaOH (0.36 g) and H_2SO_4 (0.18 ml) in H_2O (6.5 ml) was added a solution of tartaric acid (1.35 g) in H_2O (2.7 ml). After 5 min-stirring, the ice bath was removed and the mixture was stirred at room temperature for 25 min. Then, to this solution compound (III) (2.0 g) in EtOH (5 ml), NaOH (1.35 g) in H_2O (25 ml) and EtOH (23 ml) were added. After stirring for 15 hr, the mixture was heated at 60° for 10 min, cooled, diluted with water and washed with ether. The alkaline layer was acidified with 10% HCl and extracted with $CHCl_3$. Drying ($MgSO_4$) and evaporation of the solvent gave 3.0 g of crude IVa as a dark syrup. IR ν_{max}^{film} cm^{-1}: 3600—2400 (COOH).

A mixture of IVa (3.0 g), EtOH (26 ml), benzene (17 ml) and H_2SO_4 (0.9 ml) was refluxed for 8 hr. After evaporation of EtOH and benzene, the residual oil was dissolved in ether, washed with 5% $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent gave 2.1 g of IVb as a yellow oil, distilled at 190—200° (bath temp., 0.17 mmHg). IR ν_{max}^{film} cm^{-1}: 1700—1750 (C=O), 1635 (C=C). Mass Spectrum *m/e*: 345 (M^+).

3-Methyl-2,3-dihydro-1,6-methano-1*H*-3-benzazonin-4(5*H*),7(6*H*)-dione(VI)——Hydrogenation of IVb (2.1 g) over 5% Pd-C (150 mg) in EtOH (25 ml) gave 1.64 g of Va, distilled at 190—220° (bath temp., 0.11 mmHg). IR ν_{max}^{film} cm^{-1}: 1680—1760 (C=O). NMR ($CDCl_3$) τ: 8.71 (t, J=7.0 Hz, 6, 2×O-$CH_2\underline{CH_3}$), 7.01 (s, 3, NMe), 5.85 (q, J=7.0 Hz, 4, 2×O$\underline{CH_2}CH_3$), 3.00—2.30 (complex m, 3, C-5, C-6, C-7 H), 1.98 (a pair of d, $J_{7,8}$=7.0 Hz, $J_{6,8}$=2.0 Hz, 1, C-8 H).

Carbamate (Va) (1.64 g) and conc. HCl (75 ml) were refluxed for 10 hr. The reaction mixture was diluted with water, washed with benzene and evaporated to dryness. The residual syrup (1.2 g), EtOH (30 ml), H_2SO_4 (1 ml) and benzene (20 ml) were refluxed for 10 hr. After evaporation of EtOH and benzene, the residual syrup was dissolved in water, washed with benzene, basified with 10% NaOH, extracted with ether and dried (K_2CO_3). Evaporation of the solvent gave 0.21 g of crude amino ester (Vb). IR ν_{max}^{film} cm^{-1}: 3100 (NH), 2800 (NMe), 1750 (C=O of ester), 1700 (C=O of ketone).

The crude amino ester (Vb) (0.21 g) was heated at 200° (40 mmHg) for 1 hr, and then distilled at 200° (bath temp., 0.17 mmHg). The distillate solidified on standing was recrystallized from AcOEt to give 76 mg of VI as colorless plates of mp 177—178°. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O of ketone), 1635 (C=O of lactam). NMR ($CDCl_3$) τ: 7.60 (s, 3, NMe), 2.80—2.50 (m, 3, C-9, C-10, C-11 H), 1.95 (a pair of d, $J_{8,9}$=7.0 Hz, $J_{8,10}$=2.0 Hz, 1, C-8 H). Mass Spectrum *m/e*: 229 (M^+). *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.43; H, 6.60; N, 6.08.

3-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine (VIIb)——A mixture of VI (76 mg) and $LiAlH_4$ (100 mg) in dioxane (8 ml) was refluxed for 10 hr. After cooling, the mixture was treated with aq. Rochelle salt solution, extracted with $CHCl_3$ and dried (K_2CO_3). Evaporation of the solvent gave 70 mg of crude VIIa, distilled at 150—170° (bath temp., 0.17 mmHg) to give 62 mg of pure VIIa. IR ν_{max}^{film} cm^{-1}: 3400 (OH). NMR ($CDCl_3$) τ: 7.72 (s, 3, NMe), 5.22 (d, J=6.0 Hz, 1, C-7 H), 2.90—2.70 (m, 3, C-9, C-10, C-11 H), 2.70—2.30 (m, 1, C-8 H). Mass Spectrum *m/e*: 217 (M^+).

A mixture of VIIa (42.8 mg), P (red, 10 mg), AcOH (1.5 ml), H_2O (0.5 ml) and 57% HI (1.0 ml) was refluxed for 4 hr. The cooled mixture was filtered and evaporated. The brown oily residue was dissolved in water, made alkaline with 10% NaOH, extracted with ether and dried (K_2CO_3). The residue of the ethereal solution was distilled *in vacuo* to give 25 mg of VIIb, bp 110—120° (bath temp., 1 mmHg). IR ν_{max}^{Film} cm^{-1}: 2790 (NMe). NMR ($CDCl_3$) τ: 7.77 (s, 3, NMe), 2.90—2.70 (m, 4, arom. H). Mass Spectrum *m/e*: 201 (M^+). Picrate: mp 157—159° (from MeOH). *Anal.* Calcd. for $C_{20}H_{22}O_7N_4$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.57; H, 5.20; N, 12.68.

4-(N-Carbethoxymethyl-N-methylaminomethyl)-3,4-dihydronaphthalen-1(2*H*)-one (IXa)——A mixture of compound (III) (0.7 g) and conc. HCl (20 ml) was refluxed for 24 hr, cooled, washed with ether and evaporated to dryness. The resultant solid mass (0.85 g) was recrystallized from MeOH–$(CH_3)_2CO$ to give 0.45 g of VIII·HCl, mp 220—223°. IR ν_{max}^{KBr} cm^{-1}: 2790, 2480 ($^+NH_2$), 1710 (C=O). *Anal.* Calcd. for $C_{12}H_{15}ON$·HCl: C, 63.86; H, 7.14; N, 6.21. Found: C, 64.06; H, 7.25; N, 6.44.

The free base (VIII) (prepared from 0.3 g of VIII·HCl) in benzene (45 ml) was refluxed with $BrCH_2CO_2$-Et (0.45 g) in the presence of K_2CO_3 (2 g) for 8 hr. The cooled mixture was filtered and extracted with 5% HCl. The aqueous layer was neutralized with 10% NaOH, extracted with ether and dried (K_2CO_3). After evaporation of solvent, the resultant oil was distilled *in vacuo* to give 0.22 g of IXa as a pale yellow oil, bp 150—170° (bath temp., 1 mmHg). IR ν_{max}^{film} cm^{-1}: 1705 (Ar-C=O), 1760 (CO_2Et), 2800 (NMe). NMR ($CDCl_3$) τ: 8.74 (t, J=7.0 Hz, 3, O-$CH_2\underline{CH_3}$), 7.50 (s, 3, NMe), 6.68 (s, 2, N-$\underline{CH_2}CO_2Et$), 5.84 (q, J=7.0 Hz, 2, O-$\underline{CH_2}CH_3$), 2.90—2.50 (m, 3, C-5, C-6, C-7 H), 2.01 (a pair of d, $J_{7,8}$=8.0 Hz, $J_{6,8}$=2.0 Hz, 1, C-8 H).

3-Methyl-1,2,3,4-tetrahydro-1,5-methano-3-benzazocin-6(5*H*)-one (X)——The amino ester (IXa) (220 mg), $Ba(OH)_2 \cdot 8H_2O$ (2 g), EtOH (10 ml) and H_2O (10 ml) were refluxed for 2 hr. The cooled mixture was neutralized with dil. H_2SO_4 and filtered (Celite). The filtrate was evaporated to dryness. The residue (IXb, 170 mg) was heated with PPA (5 g) at 150—160° for 4 hr, cooled, treated with ice-water, basified with KOH and extracted with $CHCl_3$. Drying (K_2CO_3) and evaporation of the solvent gave 132 mg of a yellow oil, which

was distilled *in vacuo* to give 120 mg of X as colorless oil (solidified on standing), bp 120—130° (bath temp., 1 mmHg). IR ν_{max}^{film} cm^{-1}: 2780 (NMe), 1685 (Ar–C=O). NMR ($CDCl_3$) τ: 7.40 (s, 3, NMe), 2.83—2.45 (m, 3, C-8, C-9, C-10 H), 2.01 (a pair of d, $J_{7,8}$=7.5 Hz, $J_{7,9}$=2.0 Hz, 1, C-7 H). Mass Spectrum *m/e*: 201 (M^+). Picrate: mp 245—247° (from MeOH). *Anal.* Calcd. for $C_{19}H_{18}O_8N_4$: C, 53.02; H, 4.22; N, 13.02. Found: C, 53.09; H, 4.23; N, 12.75.

3-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (XIb)——Amino ketone (X) (126 mg) was hydrogenated over Pd-C (40%, 70 mg) in EtOH (6 ml) and AcOH (2 ml) for 2 hr. After removal of the catalyst and solvent, the residual syrup was dissolved in water, basified with 10% NaOH, extracted with ether, and dried (K_2CO_3). The residue of the ethereal solution was distilled *in vacuo* to give 98 mg of XIa as a colorless oil, bp 135—140° (bath temp., 1 mmHg). IR ν_{max}^{film} cm^{-1}: 3440 (OH), 2790 (NMe). NMR ($CDCl_3$) τ: 7.92 (s, 3, NMe), 5.12 (d, J=7.5 Hz, 1, C-6 H). Picrate: mp 222—224° (from MeOH). *Anal.* Calcd. for $C_{19}H_{20}O_8N_4$: C, 52.78; H, 4.66; N, 12.96. Found: C, 52.91; H, 4.67; N, 12.65.

Compound (XIa) (56 mg), 57% HI (2 ml), P (red, 20 mg), AcOH (4 ml) and H_2O (1 ml) were refluxed for 4 hr. The cooled mixture was filtered and evaporated. The brown residue was dissolved in water, basified with 10% NaOH, extracted with ether and dried (K_2CO_3). Evaporation of the solvent gave 48 mg of XIb as a colorless oil, distilled at 95—100° (bath temp., 1 mmHg). IR ν_{max}^{film} cm^{-1}: 2780 (NMe). NMR ($CDCl_3$) τ: 7.92 (s, 3, NMe), 2.95 (s, 4, arom. H). Picrate: mp 246—248° (from MeOH). *Anal.* Calcd. for $C_{19}H_{20}O_7N_4$: C, 54.80; H, 4.84; N, 13.46. Found: C, 54.88; H, 4.82; N, 13.23.

[Chem. Pharm. Bull. 24(3) 544—546 (1976)]

UDC 547.466.1.04 : 542.953

Studies on Peptides. LVIII.[1,2] Synthesis of Tyr^1-Substance P

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(Received July 7, 1975)

In order to obtain a useful compound for the radioimmunoassay of substance P, Tyr^1-substance P was synthesized by the conventional method.

Since the complete amino acid sequence of substance P from bovine hypothalami and horse intestine was determined by Leeman, *et al.*[4] and Studer, *et al.*[5] respectively, this important physiological principle was synthesized by the conventional method[6,7] as well as by the solid phase method.[8–10] As far as the conventional method is concerned, we recorded the first synthesis of the undecapeptide amide corresponding to the entire amino acid sequence of substance P. We wish to record further the synthesis of a useful derivative for its radio-

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2) Amino acids, peptides and their derivatives are of the L-configuration. Following abbreviations were used: Z=benzyloxycarbonyl, Z(OMe)=*p*-methoxybenzyloxycarbonyl, DCC=dicyclohexylcarbodiimide, DMF=dimethylformamide, TFA=trifluoroacetic acid.
3) Location: *a) Sakyo-ku, Kyoto, 606, Japan; b) Kasumi-cho, Hiroshima, 734, Japan.*
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