Chem. Pharm. Bull. 20(2) 277—283 (1972)

UDC 547.94.057 : 615.212.011.5

Studies on Structure-Activity Relationship of Analgetics. XIII.[1] Syntheses of Homobenzomorphans and Related Compounds. (1)

Shunsaku Shiotani, Tadashi Kometani[2a] and Kemmotsu Mitsuhashi[2b]

Toyama Technical College[2a] and Faculty of Pharmaceutical Sciences, University of Toyama[2b]

(Received July 22, 1971)

Synthetic routes of 3-methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (X-A), 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (X-B) and 2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (XX) having a new ring system were described.

4-Phenylcyclohexanone (I) was condensed with diethyl oxalate followed by decarbonylation to give ethyl 2-oxo-5-phenylcyclohexanecarboxylate (II), which was hydrolyzed to afford 4-phenylpimelic acid (III). 5,9-Methanobenzocycloocten-8,10-dione (IV) obtained by cyclization of III with PPA was reduced to 10-hydroxy-5,9-methanobenzocycloocten-8-one (V), which in turn was derived to 8-acetoxy-5,9-methanobenzocyclooctene (VI) by catalytic reduction over Adams catalyst in acetic acid containing a small amount of perchloric acid. VI was hydrolyzed, followed by a Jones oxidation to give 5,9-methanobenzocycloocten-8-one (VII). The oxime (VIII) of VII was submitted to a Beckmann rearrangement with PPA to afford a mixture of 2,3,6,7-tetrahydro-2,7-methano-1*H*-3-benzazonin-4(5*H*)-one (IX-A) and 2,3,6,7-tetrahydro-1,6-methano-1*H*-4-benzazonin-5(4*H*)-one (IX-B) (ratio: *ca.* 10 : 1), which were separated by fractional recrystallization. Both IX-A and IX-B were reduced with lithium aluminum hydride, followed by Clarke–Eschweiler methylation to give X-A and X-B, respectively.

4-Benzylcyclohexanone (XIV) obtained by catalytic reduction of *p*-benzylphenol (XIII) and the subsequent oxidation with chromic acid was derived to 3-benzyladipic acid (XV) by nitric acid oxidation, which was then cyclized to 4-oxo-1,2,3,4-tetrahydronaphthalene-2-propionic acid (XVI). The ethyl ester (XVII) of XVI was derived to the oxime (XVIII), which was reduced to an amino-ester followed by cyclization to give 4,5,6,7-tetrahydro-1,6-methano-1*H*-2-benzazonin-3(2*H*)-one (XIX). Reduction of XIX with lithium aluminum hydride and the subsequent methylation afforded XX.

For the systematic studies on the relationship between chemical structure and pharmacological activity of analgetics, we had already reported the syntheses and pharmacological tests of some diazabenzobicyclo[3.3.1]nonane, azabenzobicycloalkane and tetrahydronaphthylamine systems.[3] Now, the present investigation has aimed at extending the chemical modifications of benzomorphan, a parent structure of morphine-like analgetics, with enlargement of B- and C-ring in the parent structure. This paper deals with the syntheses of 3-methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (X-A), 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (X-B) and 2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (XX).

In order to prepare ethyl 2-oxo-5-phenylcyclohexanecarboxylate (II), 4-phenylcyclohexanone (I)[4] was condensed with ethyl oxalate, followed by decarbonylation under heating with soft-glass and iron powder. The *β*-keto ester II was hydrolyzed with aqueous sodium hydroxide solution to give 4-phenylpimelic acid (III),[5] which in turn was heated with poly-

1) Part XII: S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **92**, 92 (1972).
2) Location: *a) Hongo, Toyama; b) Gofuku, Toyama.*
3) *a)* K. Mitsuhashi, S. Shiotani, R. Oh-uchi and K. Shiraki, *Chem. Pharm. Bull.* (Tokyo), **17**, 434 (1969) and references therein cited; *b)* M. Kimura, R. Mukai, K. Mitsuhashi and S. Shiotani, Abstracts of Papers of 31st Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, October 1970.
4) H.E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).
5) K. Suzuki, *Nippon Kagaku Zasshi*, **82**, 730 (1961).

phosphoric acid (PPA)[6] to obtain 5,9-methanobenzocycloocten-8,10-dione (IV). From the reaction mixture, however, two crystalline compounds of mp 111—113° and of mp 109—112° (ratio: *ca.* 10:2) were isolated by silica gel column chromatography. Both of them were determined to have the formula $C_{13}H_{12}O_2$ by elemental analyses. The former exhibited infrared (IR) absorption bands at 1730 (R-C-R) and 1680 cm^{-1} (Ar-CO-) and nuclear magnetic

resonance (NMR) spectral signals of aromatic protons at 2.03 τ (1H, a pair of doublet, J=8.0 Hz, J'=2.5 Hz, proton at *ortho*-position to a carbonyl group) and 2.15—2.80 τ (3H, multiplet) and of aliphatic protons at 6.30 τ (1H, broad singlet, -CO-CH-CO-), 6.57 τ (1H, broad singlet, Ar-CH<) and 6.80—8.10 τ (6H, complex multiplet), while the latter IR band at 1710 cm^{-1} (Ar-CO-) and NMR signals of aromatic protons (AB_2-type) at 1.74 τ (2H, doublet, J=7.5 Hz, proton at *ortho*-position to a carbonyl group) and 2.54 τ (1H, triplet, J=7.5 Hz) and of aliphatic protons at 6.40—8.55 τ (9H, complex multiplet). Thus, the former was confirmed to be IV and the latter 2,3,3a,4,5,6-hexahydrophenalen-1,6-dione (IV').

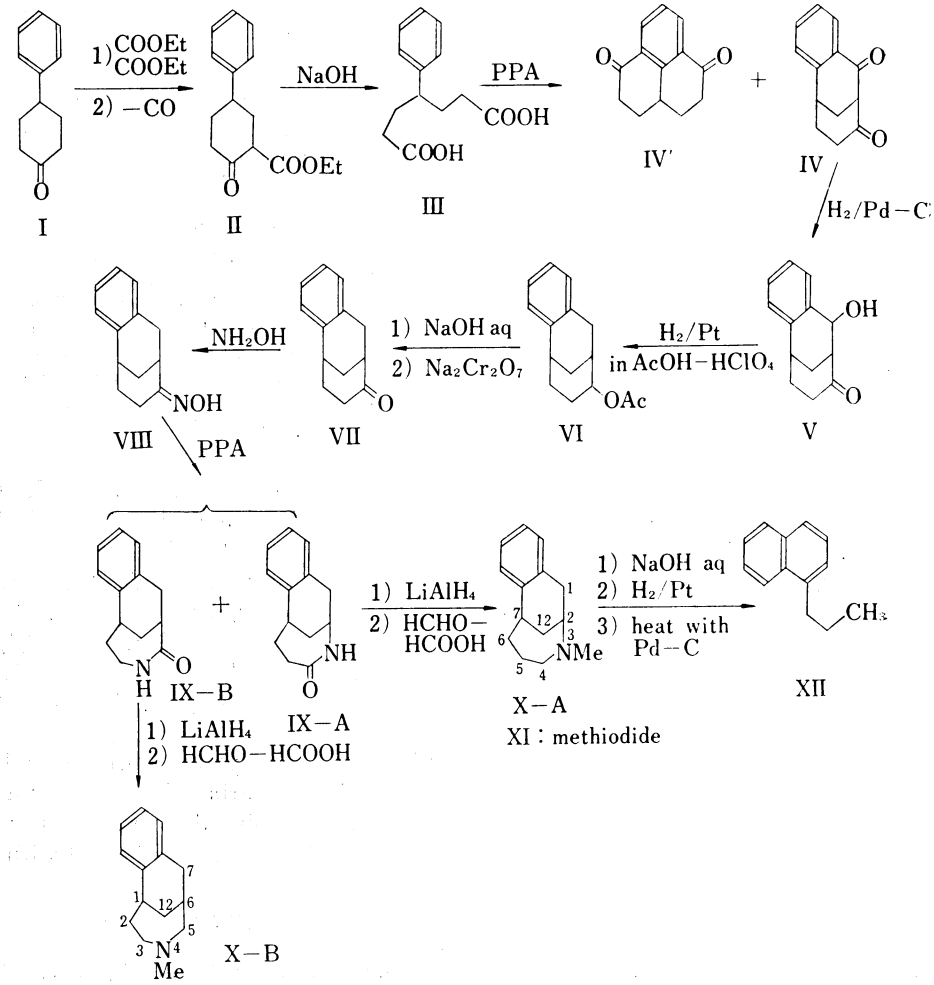

Chart 1

6) W.H.G. Caple, *J. Am. Chem. Soc.*, **84**, 3517 (1962).

Catalytic reduction of IV over palladium-charcoal yielded 10-hydroxy-5,9-methanobenzocycloocten-8-one (V) as cubes of mp 108—113°. The structural assingment of V was supported by the NMR spectrum in which a poorly splitted doublet due to a proton attached to benzylic carbon bearing a hydroxyl group appeared at 4.87 τ (J=7.0 Hz), and by the IR spectrum showing $\nu_{C=O}$ band at 1705 cm^{-1}. Some trials to remove the hydroxyl group in V, remaining the carbonyl group unchanged, were unsuccessful. Therefore, the hydroxyketone was catalytically reduced over Adams platinum catalyst in acetic acid containing a small amount of perchloric acid to give 8-acetoxy-5,9-methanobenzocyclooctene (VI), whose structure was supported by the presence of NMR signals assignable to a proton attached to carbon bearing an acetoxyl group at 5.09 τ (a pair of triplet, J=5.0 Hz, J'=9.0 Hz) and protons of acetyl methyl at 7.94 τ (singlet). The ester VI was hydrolyzed with aqueous sodium hydroxide solution, and then oxidized with Jones reagent to give 5,9-methanobenzocycloocten-8-one (VII) as an oil of bp 115—125° (1 mmHg).

The ketone VII was converted to the oxime (VIII) of mp 158—162°, which was then submitted to a Beckmann rearrangement with PPA. From the crude crystalline product, two kinds of lactams were isolated by fractional recrystallization from ethyl acetate: one (IX-A) is of mp 194—197° and the other (IX-B) of mp 188—190.5° (ratio: *ca.* 10:1). The elemental analyses confirmed both the lactam to have the formula $C_{13}H_{15}ON$. In the IR spectra, the former showed ν_{NH} bands at 3170 and 3020 cm^{-1} and $\nu_{C=O}$ band at 1658 cm^{-1}, and the latter ν_{NH} bands at 3180 and 3030 cm^{-1} and $\nu_{C=O}$ band at 1660 cm^{-1}. The NMR spectrum of the former exhibited multiplet singal at 6.32 τ ascribable to a proton of >C<u>H</u>-NHCO- and signals at 6.45—7.25 τ ascribable to three protons of Ar-C<u>H</u><, Ar-C<u>H</u>$_2$-; while the latter at 6.50—7.50 τ ascribable to six protons of -C<u>H</u>$_2$-NHCO-, >C<u>H</u>-CO-, Ar-C<u>H</u>< and Ar-C<u>H</u>$_2$-. From these facts, the structures of IX-A and IX-B were suggested to be 2,3,6,7-tetrahydro-2,7-methano-1*H*-3-benzazonin-4(5*H*)-one and 2,3,6,7-tetrahydro-1,6-methano-1*H*-4-benzazonin-5(4*H*)-one, respectively.

The lactams IX-A and IX-B were reduced with lithium aluminum hydride, followed by methylation with formic acid and formalin to afford the final compounds, 3-methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (X-A) and 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (X-B), respectively. Compound X-A showed an IR band of N-methyl at 2780 cm^{-1} and an NMR signal of N-methyl at 7.56 τ, while X-B at 2775 cm^{-1} and at 7.70 τ. The 0.14 ppm difference in the N-methyl chemical shift between X-A and X-B would be the result of a change in environment of the N-methyl protons from a position above the A-ring to one away from the A-ring. In the compound X-B, the conformation of the C-ring would be chair-form like and ring current effect of the A-ring would produce a upfield shift. The more definitive evidence for the structural assignment of X-A and X-B was presented by the following fact.

The methiodide (XI) of X-A was heated with aqeous sodium hydroxide solution, followed by reduction over Adams catalyst and dehydrogenation to give 1-propylnaphthalene (XII), whose NMR spectrum showed a triplet of C-methyl at 8.98 τ, a sextet of CH_2-C<u>H</u>$_2$-CH_3 at 8.27 τ, triplet of Ar-C<u>H</u>$_2$-CH_2- at 6.98 τ and a multiplet of aromatic protons at 1.95—2.85 τ.

For the synthesis of 2-methyl-2,3,4,5,6,7-hexahydro-1H-2-benzazonine (XX), *p*-benzylphenol (XIII) was chosen as the starting material. Catalytic reduction of XI over Raney nickel afforded 4-benzylcyclohexanol,[7] which in turn was oxidized with chromic acid to give 4-benzylcyclohexanone (XIV) as a colorless oil of bp 120—130° (3 mmHg). Though permanganate oxidations[7] of 4-benzylcyclohexanol or the ketone XIV to prepare 3-benzyladipic acid (XV) did not give sufficient results, nitric acid oxidation of the ketone afforded the acid in satisfactory yield. Treatment of the dicarboxylic acid with concentrated sulfuric acid at room temperature gave 4-oxo-1,2,3,4-tetrahydronaphthalene-2-propionic acid (XVI).

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

This compound possessed the formula compatible with $C_{13}H_{14}O_3$, and showed ν_{OH} of carboxylic group at 3300—2400 cm^{-1} and $\nu_{C=O}$ at 1725 (-COOH) and 1700 cm^{-1} (Ar-CO-).

The ethyl ester (XVII) of XVI was derived to the oxime (XVIII) of mp 96—97°, whose IR spectrum showed ν_{OH} at 3250 cm^{-1} and $\nu_{C=O}$ at 1743 cm^{-1}. Catalytic reduction of the oxime XVIII over Adams catalyst in methanol–acetic acid afforded an oily basic product. As it was expected that the reduction product would consist of ethyl *cis*-4-amino-1,2,3,4-tetrahydro naphthalene-2-propionate and the *trans*-isomer and that the *cis*-isomer would cyclize to lactam (XIX) by heating,[8] the reduction product was heated at 200° (40 mmHg). From the resulting mixture a neutral compound was isolated and recrystallized from ether to give colorless prisms of mp 115—117.5°, whose chemical formula was compatible with $C_{13}H_{15}ON$. This compound showed ν_{NH} bands at 3240 and 3050 cm^{-1} and $\nu_{C=O}$ band at 1655 cm^{-1} (lactam C=O) in the IR spectrum and exhibited a signal of NH at 2.40 τ and a signal ascribable to a proton of Ar-CH-NH-CO- at 5.70 τ in the NMR spectrum. Thus, the neutral compound was confirmed to be 4,5,6,7-tetrahydro-1,6-methano-1*H*-2-benzazonin-3(2*H*)-one (XIX). The lactam XIX was reduced with lithium aluminum hydride, followed by Clarke–Eschweiler methylation to give 2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (XX), which showed an N-methyl band at 2790 cm^{-1} in the IR spectrum and a signal of N-methyl at 7.42 τ and a signal of C-1 proton at 6.26 τ as a pair of doublet (J=6.0 Hz, J'=1.5 Hz) in the NMR spectrum.

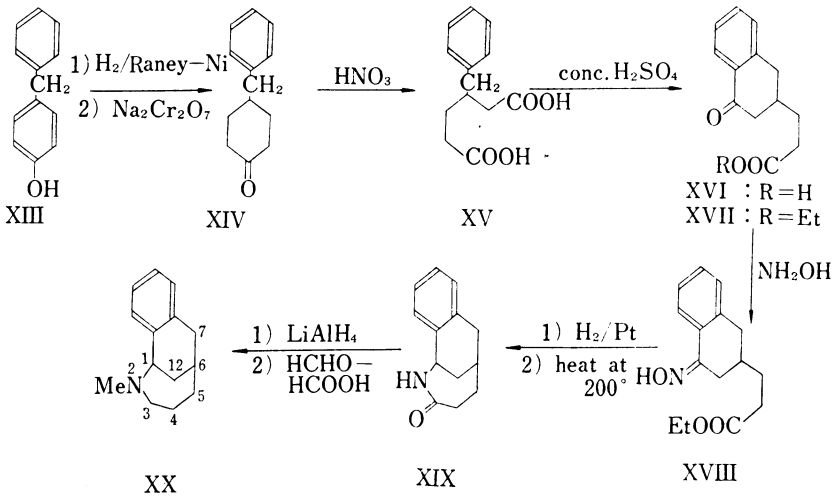

Chart 2

Experimental[9]

5,9-Methanobenzocycloocten-8,10-dione (IV)——To a solution of NaOEt (prepared by dissolving 1.3 g of Na in 30 ml of EtOH) was added a mixture of 8 g of diethyl oxalate and 9.5 g of 4-phenylcyclohexanone (I)[4] under ice-cooling with mechanical stirring during 15 min. The reaction mixture was stirred for 1 hr under ice-cooling and then at room temperature for 6 hr. The mixture was acidified with 30 ml of 10% H_2SO_4, and the precipitate was extracted with C_6H_6, washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled *in vacuo* to collect a fraction boiling at 120—170° (1.0 mmHg). Yield, 9.9 g. The distillate was heated at 170—200° (at 20 mmHg) with small amounts of soft glass powder and iron powder, when evolution of CO had ceased the residual oil was distilled *in vacuo* to give ethyl 2-oxo-5-phenylcyclohexanecarboxylate (II) as a slightly yellow viscous oil of bp 125—135°

8) S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **14**, 324 (1966).
9) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H recording spectrometer with TMS as an internal standard.

(1 mmHg), which gave purple color with $FeCl_3$ in EtOH. Yield, 7.2 g. IR ν_{max}^{liq} cm^{-1}: 1740 (keto-ester), 1665 (enol ester).

A mixture of 6.0 g of II, 6.0 g of NaOH in 20 ml of MeOH was heated at 120° for 2.5 hr. After cooling, the reaction mixture was diluted with 100 ml of water and extracted with C_6H_6. The aqueous layer was acidified with conc. HCl, extracted with ether and washed with water. The ethereal layer was extracted with aqueous $NaHCO_3$ solution. After washing with C_6H_6, the alkaline aqueous layer was made acidic, extracted with ether, washed with water and dried over $MgSO_4$. Evaporation of the solvent gave crude 4-phenylpimelic acid (III), yield 6.0 g, as a colorless viscous syrup which solidified on standing. Recrystallization from C_6H_6 gave colorless needles melting at 78—81° (lit. mp 80—82°).[5] IR ν_{max}^{KBr} cm^{-1}: 3300—2400, 1740 (-COOH).

A mixture of 3.5 g of III and 30 g of PPA (prepared from 15 g of 85% H_3PO_4 and 15 g of P_2O_5) was heated on a water bath for 1.5 hr. The mixture was poured onto ice and diluted with water, extracted with $CHCl_3$ and dried over Na_2SO_4. The brown syrupy residue (3.0 g) of the chloroform solution was chromatographed on a silica gel (100 g) column. A first eluate fraction with C_6H_6 gave crystals (1.0 g) which were recrystallized from ether to give IV as colorless prisms, mp 111—113°. *Anal.* Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.14; H, 6.09. IR ν_{max}^{KBr} cm^{-1}: 1730, 1680. NMR ($CDCl_3$) τ: 2.03 (1H, a pair of doublet, $J=8.0$ Hz, $J'=2.5$ Hz, C_1-H), 2.15—2.80 (3H, complex multiplet, C_2-, C_3- and C_4-H), 6.30 (1H, one peak, C_9-H), 6.57 (1H, one peak, C_5-H), 6.80—8.10 (6H, complex multiplet, C_6-, C_7- and C_{11}-methylene H). A second eluate fraction with C_6H_6–$CHCl_3$ (1:1) gave crystals (0.2 g) which were recrystallized from ether to give IV′ as colorless cubes of mp 109—112°. *Anal.* Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.83; H, 6.14. IR ν_{max}^{KBr} cm^{-1}: 1710. NMR ($CDCl_3$) τ: 1.74 (2H, doublet, $J=7.5$ Hz, C_7- and C_9-H), 2.54 (1H, triplet, $J=7.5$ Hz, C_8-H), 6.40—7.45 (5H, complex multiplet, C_2- and C_6-methylene and C_4-methine H), 7.50—8.55 (4H, complex multiplet, C_3- and C_5-methylene H).

10-Hydroxy-5,9-methanobenzocycloocten-8-one (V)——A solution of 1.1 g of IV in MeOH–AcOH (20 ml+5 ml) was shaken with 10% Pd-C in H_2. After absorption of H_2 had ceased (about 2 hr), the catalyst and the solvent were removed, and the resultant crystalline mass was recrystallized from ether to give colorless cubes melting at 108—113°. Yield, 0.6 g. *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.02; H, 6.98. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1705 (C=O). NMR ($CDCl_3$) τ: 2.30—3.00 (4H, multiplet, arom. H), 4.87 (1H, poorly splitted doublet, C_{10}-H, changed to a sharp doublet ($J=7.0$ Hz) by treatment with D_2O), 6.34 (1H, broad one peak, -OH, disappeared by treatment with D_2O), 6.75—7.09 (2H, one peak, C_5- and C_9-methine H), 7.45—8.15 (6H, multiplet, C_6-, C_7- and C_{11}-methylene H).

8-Acetoxy-5,9-methanobenzocyclooctene (VI)——A solution of 0.6 g of V in 12 ml of glacial acetic acid containing 5 drops of 60% $HClO_4$ was shaken with PtO_2 in H_2. After hydrogen uptake was completed, the catalyst and the solvent were removed. The oily residue was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$, and dried over $MgSO_4$. The yellow residue of the chloroform solution was distilled *in vacuo* to give VI as a slightly yellow viscous oil of bp 125—140° (1 mmHg) (bath temp.). Yield, 0.44 g. IR ν_{max}^{liq} cm^{-1}: 1750 ($\nu_{C=O}$), 1240 (ν_{C-O}). NMR ($CDCl_3$) τ: 2.98 (4H, one peak, arom. H), 5.09 (1H, a pair of triplet, $J=5.0$ Hz, $J'=9.0$ Hz, C_8-H), 6.95—7.25 (3H, poorly splitted two peaks, C_5-methine and C_{10}-methylene H), 7.94 (3H, singlet, -$COCH_3$), 7.40—9.15 (7H, complex multiplet, C_6-, C_7- and C_{11}-methylene and C_9-methine H).

5,9-Methanobenzocycloocten-8-one (VII) and Its Oxime (VIII)——A mixture of 443 mg of VI and 1.0 g of NaOH in 20 ml of 80% EtOH was refluxed for 1 hr on a water bath. After evaporation of the solvent, the residue was dissolved in ether, washed with water and dried over $MgSO_4$. The yellow viscous oil (300 mg) was used for the next procedure without any purification. IR ν_{max}^{liq} cm^{-1}: 3440 (ν_{OH}), no carbonyl band.

A solution of 300 mg of the hydroxyl derivative in 3 ml of ether was added dropwise to a solution of 0.23 g of $Na_2Cr_2O_7 \cdot 2H_2O$ and 0.18 ml of conc. H_2SO_4 in 1.1 ml of water under stirring during 30 min at 24—28°. After stirring at room temperature for 3 hr, the reaction mixture was diluted with water and extracted with large volume of ether. The residue of the dried ether solution was distilled *in vacuo* to give VII, bp 115—125° (1 mmHg) (bath temp.). Yield, 155 mg. IR ν_{max}^{liq} cm^{-1}: 1730 ($\nu_{C=O}$). NMR (CCl_4)τ: 2.96 (4H, singlet, arom. H), 6.60—7.50 (3H, multiplet, C_5-methine and C_{10}-methylene H), 7.50—9.20 (7H, complex multiplet, C_6-, C_7- and C_{11}-methylene and C_9-methine H). Mass Spectrum Calcd. for $C_{13}H_{14}O$: MW, 186.104. Found: M^+, 186.106.

A mixture of 120 mg of VII, 140 mg of $NH_2OH \cdot HCl$ and 142 mg of $AcONa \cdot 3H_2O$ in 20 ml of 50% EtOH was refluxed on a water bath for 1.5 hr. After evaporation of EtOH, the colorless residue was extracted with $CHCl_3$, washed with 5% $NaHCO_3$, and dried over $MgSO_4$. The crystalline residue of the chloroform solution was recrystallized from ether to give pure VIII, melting at 158—162°. Yield, 200 mg. *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.36; H, 7.69; N, 6.83. IR ν_{max}^{KBr} cm^{-1}: 3250, 3080 (ν_{OH}), 1665 ($\nu_{C=N}$).

2,3,6,7-Tetrahydro-2,7-methano-1*H*-3-benzazonin-4(5*H*)-one (IX-A) and 2,3,6,7-Tetrahydro-1,6-methano-1*H*-4-benzazonin-5(4*H*)-one (IX-B)——A mixture of 1.0 g of the oxime VIII and 18 g of PPA (prepared from 10 g of P_2O_5 and 8.0 g of 85% H_3PO_4) was heated on a water bath for 15 min, and then poured onto ice. The mixture was extracted with $CHCl_3$, washed with water, with 5% $NaHCO_3$ and with water. The pale yellow residue of the dried chloroform solution was fractionally recrystallized from AcOEt to give 300 mg of IX-A, mp 194—197° (colorless prisms) and 30 mg of IX-B, mp 188—190.5° (colorless plates). IX-A:

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.31; H, 7.27; N, 6.68. IR ν_{max}^{KBr} cm^{-1}: 3170, 3020 (ν_{NH}), 1658 (lactam C=O). NMR ($CDCl_3$)τ: 2.97 (4H, singlet, arom. H), 3.22 (1H, broad one peak, NH, disappeared by treatment with D_2O), 6.32 (1H, broad one peak, C_2-H, the half-height width became smaller by treatment with D_2O), 6.45—7.25 (3H, multiplet, C_1-methylene and C_7-methine H), 7.65—8.30 (6H, multiplet, C_5-, C_6- and C_{12}-methylene H). IX-B: *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.75; H, 7.28; N, 6.87. IR ν_{max}^{KBr} cm^{-1}: 3180, 3030 (ν_{NH}), 1660 (lactam C=O). NMR ($CDCl_3$) τ: 2.97 (4H, singlet, arom. H), 3.30 (1H, broad one peak, NH, disappeared by treatment with D_2O), 6.50—7.50 (6H, complex multiplet, C_8- and C_7-methylene H and C_1- and C_6-methine H), 7.60—8.25 (4H, multiplet, C_2- and C_{12}-methylene H).

3-Methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (X-A) and 4-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (X-B)——a) X-A: a mixture of 93.2 mg of IX-A and 0.3 g of $LiAlH_4$ in 30 ml of dioxane was refluxed for 8 hr. To the cooled mixture was added Rochelle salt solution (100 ml), and the mixture was extracted with $CHCl_3$. The residue (88 mg) of the dried chloroform solution was distilled *in vacuo* to give a slightly yellow oil, bp 130—140° (1 mmHg)(bath temp.) which showed ν_{NH} at 3330 cm^{-1} and no carbonyl band in the IR spectrum.

A mixture of 82.5 mg of the above distillate, 0.7 ml of HCOOH and 0.4 ml of 35% formalin was heated on a water bath for 1.5 hr. After evaporation of the excess HCOOH and formalin, the residual oil was dissolved in 10% HCl and washed with C_6H_6. The aqueous layer was made alkaline and extracted with ether. The yellow oily residue of the dried ether extract was distilled *in vacuo* to give 80 mg of pure X-A as a colorless oil, bp 100—120° (1 mmHg) (bath temp.). The gas chromatogram of the distillate showed a peak. IR ν_{max}^{liq} cm^{-1}: 2780 (N-Me). NMR ($CDCl_3$)τ: 2.94 (4H, singlet, arom. H), 7.56 (3H, singlet, N-Me), 6.70—8.75 (12H, complex multiplet, aliph. H). Mass Spectrum Calcd. for $C_{14}H_{19}N$: MW, 201.152. Found: M^+, 201.153.

b) X-B: this compound was synthesized from 25 mg of IX-B by the Same method as described for X-A from IX-A. Yield, 15 mg. Bp 100—120° (1 mmHg)(bath temp.), colorless oil. This product showed a peak in the gas chromatogram. IR ν_{max}^{liq} cm^{-1}: 2775 (N-Me). NMR ($CDCl_3$)τ: 2.85 (4H, singlet, arom. H), 7.70 (3H, singlet, N-Me), 6.65—8.30 (12H, complex multiplet, aliph. H). Mass spectrum Calcd. for $C_{14}H_{19}N$: MW, 201.152. Found: M^+, 201.149.

1-*n*-Propylnaphthalene (XII)——By the usual method 40 mg of X-A was converted to the methiodide (XI), mp 214—216° (colorless needles, from MeOH–AcOEt). *Anal.* Calcd. for $C_{15}H_{22}NI$: C, 52.48; H, 6.46; N, 4.08. Found: C, 52.27; H, 6.34; N, 3.98. A mixture of 57 mg of XI and 8 ml of 3% NaOH was refluxed for 1.5 hr. The resultant oil was dried in $CHCl_3$ and distilled *in vacuo* to give a colorless oil (35 mg), bp 110—120° (1 mmHg)(bath temp.), which showed IR band of $N\text{-}Me_2$ at 2800 and 2760 cm^{-1}. The distillate (35 mg) in MeOH was hydrogenated over Pt in the usual manner, and absorbed 3.5 ml of H_2 in 2.5 hr. The filtrate was evaporated *in vacuo*, and the residue was distilled *in vacuo* to give a colorless oil of bp 80—110° (1 mmHg) (bath temp.). Yield, 35 mg. The distillate (35 mg) was mixed with Pd-C (40%, 50 mg) in a long test tube and heated at 260—280° for 20 min. The cooled mixture was extracted with ether. The extract was washed with dil. HCl and then with water. The residue of the ethereal solution was distilled *in vacuo* to give a colorless oil, bp 80—90° (1 mmHg)(bath temp.)(lit. bp 133.5° (12 mmHg)).[10] The distillate showed a peak in the gas chromatogram. *Anal.* Calcd. for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.92; H, 8.07. NMR (CCl_4)τ: 1.95—2.85 (7H, complex multiplet, arom. H), 6.98 (2H, triplet, J=8.0 Hz, Ar-CH_2-CH_2-), 8.27 (2H, sextet, J=8.0 Hz, -CH_2-CH_2-CH_3), 8.98 (3H, triplet, J=8.0 Hz, -CH_2-CH_3).

4-Oxo-1,2,3,4-tetrahydronaphthalene-2-propionic Acid (XVI) and Its Ethyl Ester (XVII)——A mixture of 10 g of *p*-benzylphenol (XIII) and 0.5 g of NaOEt in 50 ml of EtOH was shaken with Raney Ni in an autoclave at 110 kg/cm^2 of H_2 and 140—160°. After removal of the catalyst and the solvent, the residual syrup was dissolved in ether, washed with 10% NaOH and then with water, and dried over Na_2SO_4. The residue of the ethereal solution was distilled *in vacuo* to give a colorless viscous oil, bp 155—165° (10 mmHg). Yield, 9.2 g. IR ν_{max}^{liq} cm^{-1}: 3370 (ν_{OH}), 747, 700. To a mixture of 10 g of the above distillate, 10 ml of AcOH and 15 ml of water was added a solution of 6.3 g of $Na_2Cr_2O_7 \cdot 2H_2O$ and 3 ml of conc. H_2SO_4 in 15 ml of water over a period of 1 hr under ice-cooling and stirring, and then the mixture was stirred at 60° for 3 hr. The reaction mixture was diluted with water and extracted with C_6H_6. The benzene solution was washed with 5% $NaHCO_3$ and with water. The residue of the dried benzene solution was distilled *in vacuo* to give a colorless oil (XIV) of bp 120—130° (3 mmHg). Yield, 7.4 g. IR ν_{max}^{liq} cm^{-1}: 1738 ($\nu_{C=O}$), 765, 750, 709.

7.4 g of XIV was added portion-wise into 20 ml of HNO_3 (d=1.32) at 85—90° with stirring during 15 min, then the mixture was stirred at the temperature for 1 hr. The cooled reaction mixture was diluted with water and extracted with ether. The etereal solution was washed with water, and extracted with 5% $NaHCO_3$. The aqueous layer was washed with C_6H_6, acidified with conc. HCl and extracted with ether. The residue of the dried ethereal solution was recrystallized from water to give 3-benzyladipic acid (XV), mp 108—110° (lit. mp 110—111°[7]). Yield, 6.0 g. A mixture of XV in 65 g of conc. H_2SO_4 was stood at room temperature for 24 hr. The mixture was poured onto ice and diluted with water. The solid deposted was extracted with

10) H. Luther and G. Wächter, *Chem. Ber.*, **82**, 170 (1949).

$CHCl_3$ and dried over Na_2SO_4. The crystalline residue of the chloroform solution was recrystallized from dil. EtOH to give XVI as colorless sandy crystals of mp 136.5—137°. Yield, 2.9 g. *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.53; H, 6.21. IR ν_{max}^{KBr} cm^{-1}: 3300—2400 (ν_{OH} of -COOH), 1725 ($\nu_{C=O}$ of -COOH), 1700 ($\nu_{C=O}$ of Ar-CO-).

A mixture of 2.9 g of XVI, 17 ml of EtOH, 11 ml of C_6H_6 and 0.6 ml of conc. H_2SO_4 was refluxed for 10 hr with a water-separatory. After evaporation of the solveut, the residual oil was dissolved in ether, washed with water and with 5% $NaHCO_3$, and dried over Na_2SO_4. The residue of the ethereal solution was distilled *in vacuo* to give a colorless oil (XVII) of bp 182—190° (4 mmHg). Yield, 2.7 g. This product showed a peak in the gas chromatogram. IR ν_{max}^{liq} cm^{-1}: 1750 ($\nu_{C=O}$ of COOEt), 1700 ($\nu_{C=O}$ of Ar-CO-). NMR ($CDCl_3$)τ: 1.80—2.05 (1H, multiplet, C_5-H), 2.30—2.83 (3H, multiplet, C_6-, C_7- and C_8-H), 5.82 (2H, quartet, J=7.0 Hz, -O-C$\underline{H}_2$-CH_3), 8.75 (3H, triplet, J=7.0 Hz, -CH_2-C$\underline{H}_3$), 6.60—8.45 (9H, complex multiplet, aliph. H).

Ethyl 4-Hydroximino-1,2,3,4-tetrahydronaphthalene-2-propionate (XVIII)——A mixture of 4.9 g of XVII, 7.8 g of $NH_2OH \cdot HCl$ and 39.2 ml of C_5H_5N in 56.5 ml of EtOH was heated on a water bath for 2 hr. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, washed with 10% HCl and dried over Na_2SO_4. The solvent was evaporated and the resulting solid mass was recrystallized from dil. EtOH to give XVIII as colorless needles melting at 96—97°. Yield, 4.6 g. *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.47; N, 5.30. IR ν_{max}^{KBr} cm^{-1}: 3280 (ν_{OH}), 1743 ($\nu_{C=O}$).

4,5,6,7-Tetrahydro-1,6-methano-1*H*-2-benzazonin-3(2*H*)-one (XIX)——A solution of 2.0 g of XVIII in 60 ml of MeOH–AcOH (1: 1) was shaken with PtO_2 in H_2. After uptake of H_2 had ceased (3.5 hr), the catalyst and the solvent were removed. The pale brown oily residue was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave 2.0 g of light brown oil, which was submitted to cyclization without any purification. The crude amino-ester (2.0 g) was heated at 200° (40 mmHg) for 1 hr, and then distilled at 200—215° (0.13 mmHg). The distillate solidified on standing was recrystallized from ether to afford 0.3 g of XIX as colorless prisms of mp 115—117.5°. *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.43; H, 7.58; N, 7.08. IR ν_{max}^{KBr} cm^{-1}: 3240, 3050 (ν_{NH}), 1660 ($\nu_{C=O}$). NMR ($CDCl_3$)τ: 2.40 (1H, broad one peak, N$\underline{H}$, disappeared by treatment with D_2O), 5.69 (1H, broad one peak, C_1-H, changed to a poorly splitted triplet by treatment with D_2O), 6.55—8.30 (9H, complex multiplet, aliph.H).

2-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (XX)——A mixture of 276 mg of XIX and 0.5 g of $LiAlH_4$ in 20 ml of dioxane was refluxed for 8 hr. To the cooled mixture 200 ml of aq. Rochelle salt solution was added, and then extracted with $CHCl_3$. After drying over K_2CO_3, the solvent was removed to leave a pale brown oil which was distilled *in vacuo* to give a colorless viscous oil of bp 130—136° (1 mmHg)(bath temp.). Yield, 228.5 mg. The distillate 228 mg was dissolved in a mixture of 1.3 ml of 35% formalin and 2.0 ml of HCOOH, and then heated on a water bath for 1.5 hr. After evaporation of the excess of formalin and HCOOH, the residue was dissolved in 10% HCl and washed with C_6H_6. The aqueous layer was basified with 10% NaOH solution, extracted with ether, and the extract was dried over K_2CO_3. The residual oil of the ethereal solution was distilled *in vacuo* to give XX as a colorless oil, bp 130—135° (1 mmHg) (bath temp.). Yield, 225 mg. IR ν_{max}^{liq} cm^{-1}: 2780 (N-Me). NMR($CDCl_3$)τ: 2.45—2.93 (4H, multiplet, arom. H), 6.26 (1H, a pair of doublet, J=6.0 Hz, J'=1.5 Hz, C_1-H), 7.42 (3H, singlet, N-Me), 6.78—9.00 (11H, complex multiplet, aliph. H). Mass Spectrum Calcd. for $C_{14}H_{19}N$: MW, 201.152. Found: M^+, 201.149. Picrate of XX: mp 146.5—147.5°, yellow cubes (from EtOH). *Anal.* Calcd. for $C_{14}H_{19}N \cdot C_6H_3O_7N_3$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.97; H, 4.91; N, 12.76.

Acknowledgement The authors wish to express their deep appreciation to Mr. H.Takami for elemental microanalyses, to Mr. M. Morikoshi for measurements of NMR spectra.