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Studies on Structure-Activity Relationship of Analgetics. XVII.[1] Syntheses of Homobenzomorphans and Related Compounds. (2)

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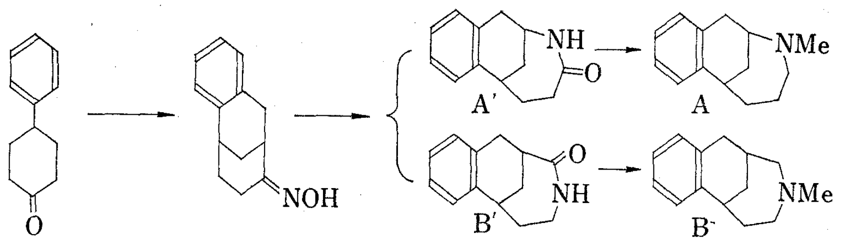
New synthetic routes of 3-methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (A) and 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (B) were described.

A Schmidt reaction of ethyl 2-oxo-5-phenylcyclohexanecarboxylate (I) gave the corresponding lactam (II), which in turn was reduced with lithium aluminum hydride to afford 2-hydroxymethyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine (III). The N-benzoyl derivative (IV) of III was oxidized with dimethylsulfoxide and dicyclohexylcarbodiimide to give the corresponding aldehyde (V), which was submitted to oxidation with silver hydroxide to give N-benzoyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine-2-carboxylic acid (VI). Cyclization of VI by heating with polyphosphoric acid yielded 2,3,-4,5-tetrahydro-2,7-methano-1*H*-3-benzazonin-7(6*H*)-one (VII). A Wolff-Kishner reduction and the successive N-methylation gave the final compound A. While, Wolff-Kishner reduction of the N-methyl derivative (IX) of VII gave an elimination product, 1-(N-methylaminopropyl)-1,2-dihydronaphthalene (XI).

Treatment of 4-(N,N-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XII) with ethyl chlorocarbonate afforded a carbamate, 4-(N-methyl-N-ethoxycarbonylaminoethyl)-3,4-dihydro-naphthalen-1(2*H*)-one (XIII), which was hydrolized, followed by a Mannich reaction with formaldehyde to yield 4-methyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one (XV). Reduction of the ketone XV with lithium aluminum hydride or by catalytic hydrogenation over Adams' catalyst gave the corresponding hydroxyl derivative (XVI), which was reduced with hydriodic acid and red phosphorus to give the final compound B.

In the previous paper[3] we reported the syntheses of 3-methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (A) and 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (B) through a Beckmann rearrangement of 5,9-methanobenzocycloocten-8-one oxime. This method, however, was thought to be unsuitable for the independent synthesis of A and B, because the Beckmann rearrangement afforded two isomeric lactam A′ and B′, simultaneously.



Now, in this paper we wish to describe the new methods for the synthesis of A and of B, respectively. The synthetic schemes are shown in Chart 1 and Chart 2.

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1) Part XVI: K. Nomura, J. Adachi, M. Hanai, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 439 (1973). A part of this paper was presented at the 34th Annual Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, June 1972.

2) Location: *Hongo, Toyama.*

3) S. Shiotani, T. Kometani, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 277 (1972).

A Schmidt reaction of ethyl 2-oxo-5-phenylcyclohexanecarboxylate (I)[3] in polyphosphoric acid (PPA) afforded 7-ethoxycarbonyl-5-phenyl-4, 5, 6, 7-tetrahydro-1*H*-azepin-2(3*H*)-one (II), mp 94—96°, in a satisfactory yield. In the infrared (IR) spectrum II showed the characteristic bands of lactam at 1650 cm^{-1} ($\nu_{C=O}$) and 3250 cm^{-1} (ν_{N-H}) and of ester at 1760 cm^{-1} ($\nu_{C=O}$) and 1230 cm^{-1} (ν_{C-O}). The nuclear magnetic resonance (NMR) spectrum of II exhibited signals of an amide-proton at 3.45 τ (broad one peak) and of an ethoxyl at 5.77 τ (quartet, J=7.5 Hz) and 8.72 τ (triplet, J=7.5 Hz). The elemental analysis confirmed the lactam-ester to have the formula $C_{15}H_{19}O_3N$. The same reaction in concentrated sulfuric acid gave II in a lower yield accompanying formation of a considerable amount of the corresponding lactam-carboxylic acid (II'), mp 237—240°, which was convertiable to the lactam-ester II. Several attempts to form the B-ring of the homobenzomorphan by intramolecular cyclization of II or II' with PPA or concentrated sulfuric acid were unsuccessful. Thus, the lactam-ester II was reduced with lithium aluminum hydride to give 2-hydroxymethyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine (III), bp 120—140° (0.05 mmHg), which showed bands of a primary alcohol at 3100—3400 cm^{-1} (ν_{O-H}) and 1030 cm^{-1} (ν_{C-O}). Benzoylation of the amino-alcohol III by a Schotten–Baumann method afforded 1-benzoyl-2-hydroxymethyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine (IV), mp 170—172.5°. The structural assignment of IV was supported by the IR spectrum showing $\nu_{C=O}$ band at 1620 cm^{-1} and ν_{O-H} band at 3420 cm^{-1} and by the elemental analysis.

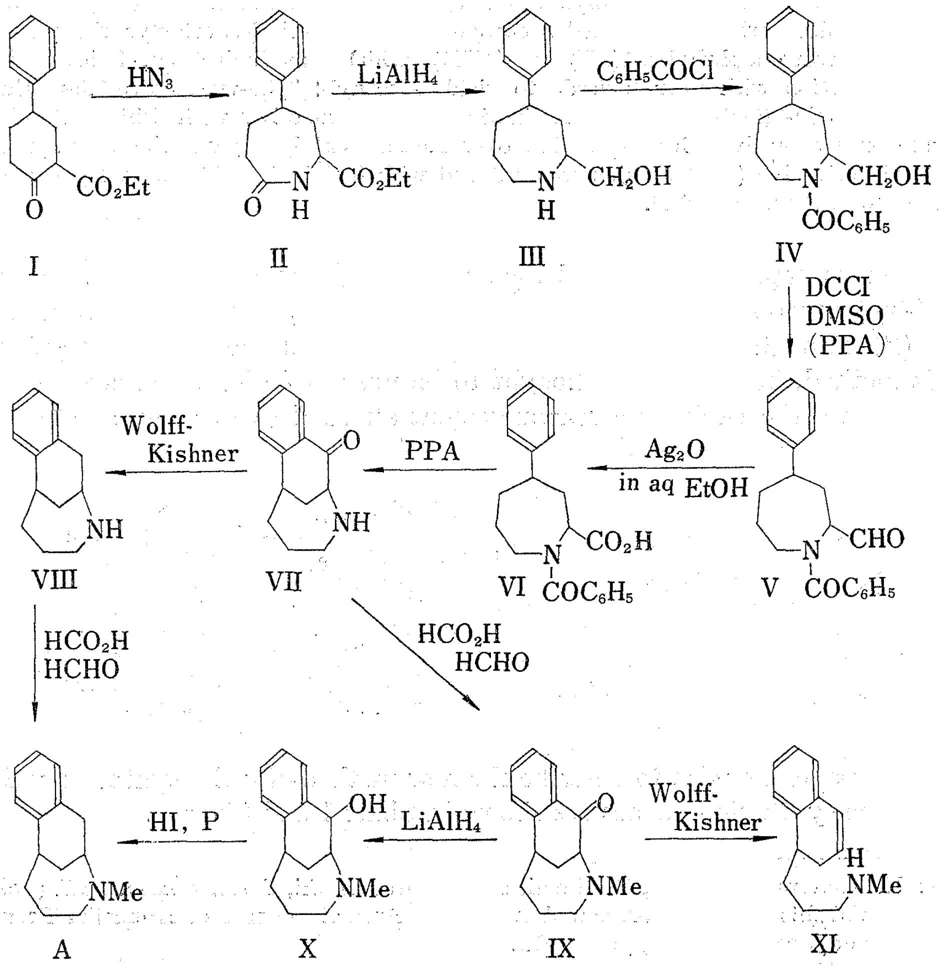

Chart 1

Oxidation of the hydroxylmethyl group with potassium permanganate under several conditions gave no satisfactory result, but the desired product 1-benzoyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine-2-carboxylic acid (VI) was obtained by the two-step oxidation as follows. Treatment of IV with dicyclohexylcarbodiimide (DCCI) in dimethylsulfoxide in the presence of PPA[4] gave an aldehyde compound (V), which showed the characteristic IR bands of aldehyde group at 2730 cm^{-1} and 1750 cm^{-1} and of benzoyl group at 1630 cm^{-1}. Oxidation of V with silver hydroxide yielded the carboxylic acid VI in a good yield.

Intramolecular cyclization for the formation of the B-ring was performed by heating the carboxylic acid VI with PPA to give 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonin-1-one (VII). The structure of VII was supported by the IR spectrum showing $\nu_{\text{C=O}}$ band at 1705 cm^{-1} and $\nu_{\text{N-H}}$ band at 3400 cm^{-1}, and by the NMR spectrum showing a singlet of N$\underline{\text{H}}$ at 7.57 τ, a triplet due to a proton at C-2 at 6.79 τ and signals of aromatic protons at 1.95 τ and 2.25—2.80 τ (1H: 3H). Reduction of the carbonyl group in VII by a Wolff–Kishner reduction afforded 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (VIII), which in turn was methylated by an Eschweiler–Clarke method to give the final compound, A. The IR spectrum of A was identical with that of the sample prepared by the previous method.[3]

Reduction of the N-methyl derivative (IX) of the amino-ketone VII with lithium aluminum hydride afforded the corresponding amino-alcohol (X), from which also the compound A was obtained by reduction with hydriodic acid and red phosphorus. While, Wolff–Kishner reduction of the amino-ketone IX did not give the normal reduction product A, but an olefinic amine (XI), 1-(N-methylaminopropyl)-1,2-dihydronaphthalene,[5] the structure of which was confirmed by the following spectral data. The high resolution mass spectrum of XI proved the formula to be $C_{14}H_{19}N$. The NMR spectrum exhibited signals of olefinic protons at 4.18 τ (multiplet, 1H) and at 1.90—3.00 τ (lapping over the signals of aromatic protons), of NH proton at 8.32 τ (singlet, 1H, disappeared by treatment with D_2O) and of N-methyl protons at 7.60 τ (singlet, 3H). This result is much different from that of Wolff–Kishner reduction of 3-methyl-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2*H*)-one[6] giving the normal reduction product, and would be caused by the instability of aliphatic seven-membered ring.

For the synthesis of 4-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (B), 4-(N,N-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XII) was chosen as the starting material, which was prepared from 4-phenylcyclohexanone by our method.[6] Treatment of XII with ethyl chlorcarbonate afforded 4-(N-methyl-N-ethoxycarbonylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XIII) as a colorless oil of bp 101—102° (0.17 mmHg).[7] In the IR spectrum XIII showed a carbonyl band at 1715 cm^{-1}. The NMR spectrum exhibited signals due to the protons of O-Et at 6.54 τ (quartet, $J=8$ Hz), and 8.75 τ (triplet, $J=8$ Hz), of N-Me at 7.11 τ (singlet) and of aromatic at 1.98 τ (a pair of ill-splitted doublet, 1H) and 2.30—2.85 τ (complex multiplet, 3H). The urethan derivative XIII was hydrolyzed by refluxing with concentrated hydrochloric acid to give 4-(N-methylaminoethyl-3,4-dihydronaphthalen-1(2*H*)-one (XIV) hydrochloride, mp 164—167°, the structure of which was supported by the elemental analysis.

A Mannich reaction of XIV hydrochloride with formaldehyde afforded an oily basic product (XV), whose chemical formula was found to be compatible with $C_{14}H_{17}ON$ by the elemental analysis of the picrate. This product showed a carbonyl band at 1690 cm^{-1} and a characteristic band of N-methyl at 2780 cm^{-1} but not bands of NH in the IR spectrum. The

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4) K.E. Pfitaner and J.G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

5) N.J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3269 (1955).

6) K. Mitsuhashi, S. Shiotani, R. Oh-uchi, and K. Shiraki, *Chem. Pharm. Bull.* (Tokyo), **17**, 434 (1969).

7) W.B. Wright, Jr. and H.J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961); E.H. Flynn, M.V. Sigal, Jr., P.F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).

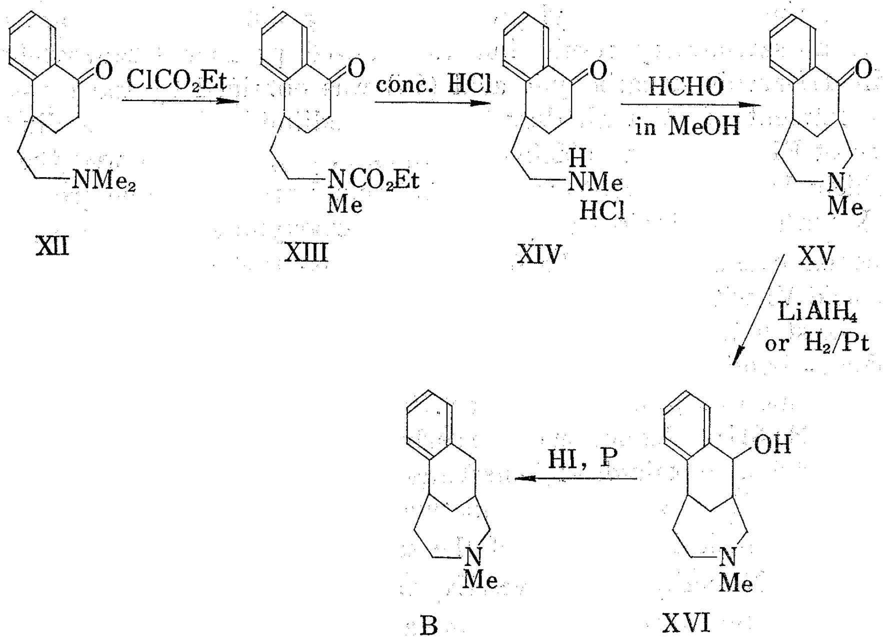

Chart 2

NMR spectrum showed a signal of N-methyl at 7.70 (singlet, 3H), but not the signal of NH. Thus, the structure of XV was suggested to be 4-methyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one. Reduction of XV with lithium aluminum hydride gave the corresponding hydroxyl derivative (XVI). Catalytic reduction of XV with Adams' plutinum catalyst in acetic acid also afforded the same product. Reductive elimination of the hydroxyl group in XVI was performed by refluxing with hydriodic acid and red phosphorus to afford the final compound B. The IR spectrum of this product was superimposable with that of the sample prepared by the previous method.[3]

Table I. Mass Spectral Data of A and B

m/e	A		B	
	Relative intensity	% Compn.[a]	Relative intensity	% Compn.[a]
201	100	$C_{14}H_{19}N(M^+)$	85.5	$C_{14}H_{19}N(M^+)$
200	28	$C_{14}H_{18}N(M^+-1)$	12	$C_{14}H_{18}N(M^+-1)$
186	34.5	$C_{13}H_{16}N(M^+-Me)$	7	$C_{13}H_{16}N(M^+-Me)$
173	10.5	$C_{12}H_{15}N$	—	
172	18.5	$C_{12}H_{14}N$	—	
158	11.0	$C_{11}H_{12}N$	—	
130	10.0	$C_{10}H_{10}$	15.5	$C_{10}H_{10}$
129	20.5	$C_{10}H_9$	16.5	$C_{10}H_9$
128	19.5	$C_{10}H_8$	28	$C_{10}H_8$
115	12	C_9H_7	11	C_9H_7
110	30	$C_7H_{12}N$	—	
97	14	$C_6H_{11}N$	—	
96	25.5	$C_6H_{10}N$	—	
83	11	C_5H_9N	—	
82	15.5	C_5H_8N	—	
70	23	C_4H_8N	100	C_4H_8N
58	—		31	C_3H_8N
57	—		18	C_3H_7N
45	—		32	C_2H_7N

[a] Composition of each fragment was determined by high resolution mass spectrometer (JEOL Model JMS-OlSG).

The mass spectra of compound A and B reflected the structural features of the both compounds. In the case of A, the molecular ion undergoes two major fragmentation processes involving fission of the B-ring and cleavage of the C-ring. Thus, the moderately intense ions at *m/e* 110, 97, 96, 83, 82 and 70 would be formed from the intermediate ion M'+ which was initiated by fission of the benzylic carbon-carbon bond at 1—2; while, ions at *m/e* 173, 172, 130, 129 and 128 would be formed from the molecular ion by cleavage of the C-ring.

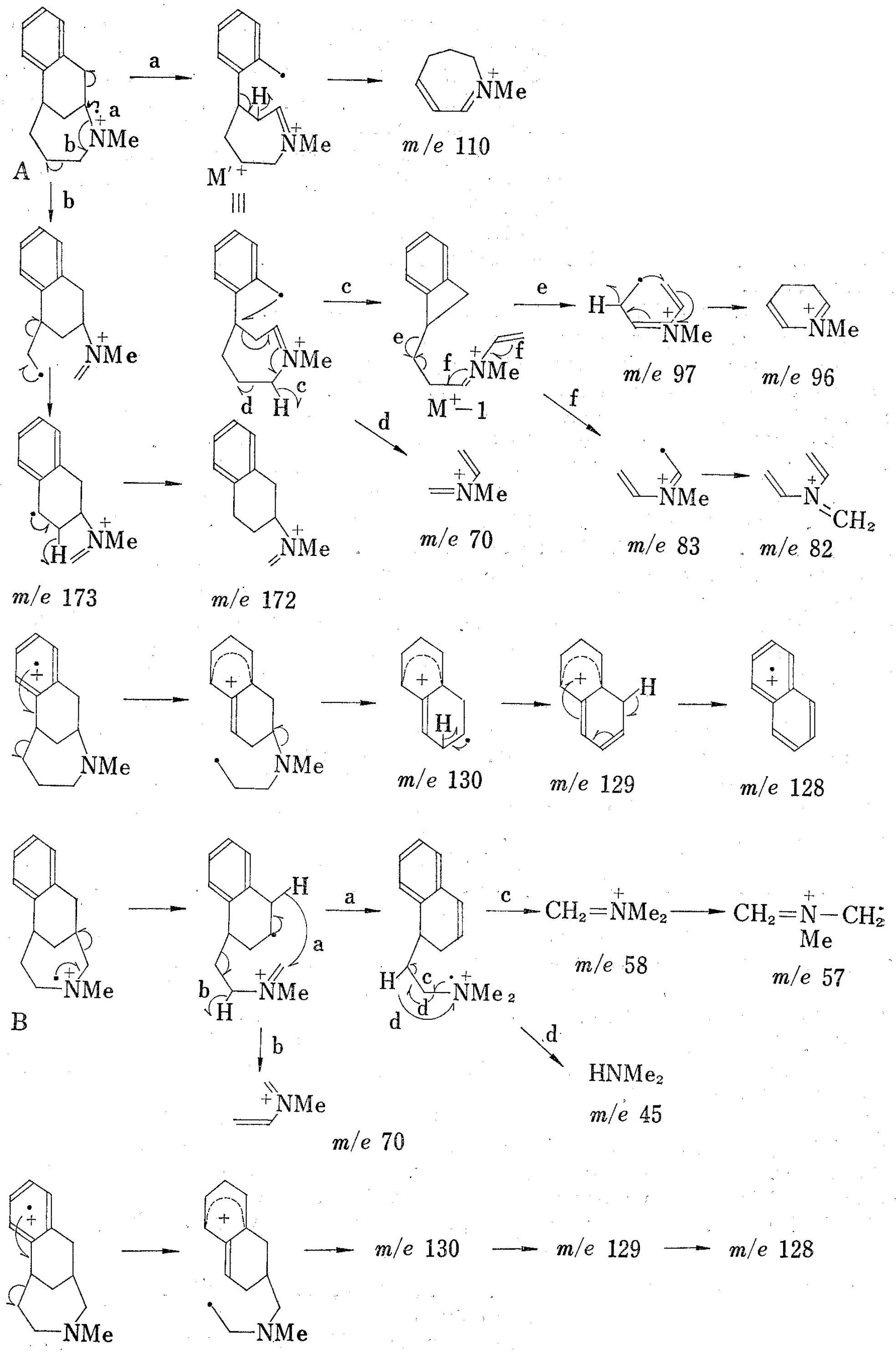

Chart 3

These behaviors resemble to those of N-methyl-benzomorphans.[8] On the other hand, the spectrum of B suggested that the molecular ion is decomposed to form naphthalene and small nitrogen-containing fragment ions with cleavage of the C-ring; this is supported by the presence of intense peaks at *m/e* 130, 129, 128, 70, 58, 57 and 45. The plausible fragmentation processes and structures for these ions are depicted in Chart 3.

Experimental[9]

7-Ethoxycarbonyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-azepin-2(3*H*)-one (II)——a) To a stirred mixture of 7.4 g of ethyl 2-oxo-5-phenylcyclohexanecarboxylate (I)[1] and PPA prepared from 97.5 g of P_2O_5 and 93.5 ml of 85% H_3PO_4 was added 3.0 g of NaN_3 at 15—20° during 1 hr in N_2 atmosphere. The reaction mixture was stirred at room temperature for 3 hr and at 45° for 0.5 hr. Then, the mixture was poured onto ice and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water, and dried over Na_2SO_4. The residue of the chloroform solution was recrystallized from ether to give 5.8 g of II, mp 94—96°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280 (NH), 1770 (C=O of ester), 1660 (C=O of lactam). NMR ($CDCl_3$) τ: 2.77 (one peak, 5H, arom. H), 3.45 (broad one peak, 1H, $-CO-N\underline{H}-$, disappeared by treatment with D_2O), 5.77 (quartet, $J=7.5$ Hz, 2H, $-O-C\underline{H}_2-Me$), 5.80 (multiplet, 1H, $-NH-C\underline{H}-CO_2Et$), 6.80—9.00 (complex multiplet, 7H, aliph. H), 8.72 (triplet, $J=7.5$ Hz, 3H, $-CH_2-C\underline{H}_3$). *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 6.77; N, 5.32.

b) To a mixture of 7.2 g of I in 60 ml of $CHCl_3$ and 12 ml of conc. H_2SO_4 was added 3.5 g of NaN_3 in portions during 3.5 hr with stirring at room temperature, and then stirred for 2 days at the same temperature. The reaction mixture was diluted with water, and the chloroform layer was separated. The chloroform solution was washed with water and extracted with $NaHCO_3$ solution.

From the chloroform solution 5.4 g of a light brown viscous oil was obtained, which solidified on scratching the flask. The solid mass was recrystallized from ether to give 2.0 g of II.

The above $NaHCO_3$ extract was acidified, extracted with $CHCl_3$, and dried over $MgSO_4$. The solvent was evaporated to leave 2.3 g of a pale yellow viscous oil, from which 0.9 g of colorless crystalline powder (II′), mp 237—240°, was obtained by recrystallization from acetone–ethanol. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.67; H, 6.77; N, 5.91.

This acidic product, II′, was convertible into the ester II by esterification in the usual manner.

2-Hydroxymethyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine (III) and Its N-Benzoyl Derivative (IV)—— A solution of 5.8 g of II in 115 ml of tetrahydrofuran was dropped into a stirred suspension of 1.5 g of $LiAlH_4$ in 100 ml of the same solvent at room temperature during 0.5 hr. The mixture was refluxed for 6 hr with stirring. When cooled, 300 ml of saturated Rochelle salt solution was added to the mixture, then the mixture was extracted with $CHCl_3$. After evaporation of the dried chloroform solution, the yellow oily residue was distilled *in vacuo* to give 3.8 g of a colorless viscous syrup, bp 120—133° (0.08 mmHg), which was used for the next step without purification. IR $\nu_{\max}^{\text{liq}}$ cm^{-1}: 3400—3100 (broad, OH and NH).

To a mixture of 3.8 g of III in 30 ml of ether and 15 ml of 10% NaOH was added 3.9 g of PhCOCl in portionwise at room temperature with vigorous stirring. After stirring for 0.5 hr, the ethereal layer was washed with 10% NaOH, 10% HCl and water. The residue of the ethereal solution was recrystallized from dilute acetone to give colorless needles (IV) of mp 170—172.5°. Yield, 4.8 g. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3420 (OH), 1620 (C=O). *Anal.* Calcd. for $C_{20}H_{23}O_2N$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.80; H, 7.54; N, 4.80.

1-Benzoyl-2-formyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine (V)——A mixture of 4.8 g of IV, 8 ml of PPA and 9.6 g of DCCI in 40 ml of dimethylsulfoxide was stood for 5.5 hr at room temperature. The reaction mixture was poured into a large volume of ice-water, extracted with ether and dried over Na_2SO_4. The ethereal solution was condensed to about one-third of the volume, then filtered off the precipitate of the urea derivative. The filtrate was evaporated to dryness *in vacuo*, leaving a pale brown syrup (3.8 g). The crude product was used for the next step without any purification. IR $\nu_{\max}^{\text{liq}}$ cm^{-1}: 2720 (–CHO), 1750 (C=O of –CHO), 1630 (C=O of amide).

1-Benzoyl-4-phenyl-2,3,4,5,6,7-hexahydro-1*H*-azepine-2-carboxylic Acid (VI)——To a stirred solution of 3.8 g of V and 4.64 g of $AgNO_3$ in 300 ml of 90% EtOH was added 125 ml of 0.5N NaOH at room temperature during 0.5 hr. Stirring was continued for 6 hr. After removal of Ag and the excess Ag_2O, the filtrate was evaporated *in vacuo* to about one-fifth of the volume. The aqueous solution was filtered with charcoal, acidified with conc. HCl under ice-cooling, and extracted with ether. The syrupy residue (2.3 g)

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[8] S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), 20, 1980 (1972).

[9] Melting points were taken with a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H spectrometer using TMS as an internal standard. Mass spectra were determined on a JMS-O1SG double focus high resolution spectrometer.

of the dried ethereal solution was used for the next step without any purification. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400—2400 (OH of $-CO_2H$), 1750 (C=O of $-CO_2H$), 1620 (C=O of amide).

2,3,4,5,6,7-Hexahydro-2,7-methano-3(1*H*)-benzazonin-1-one (VII) and Its N-Methyl Derivative (IX)——A mixture of 2.3 g of VI and 60 g of PPA prepared from 30 g of P_2O_5 and 30 g of 85% H_3PO_4 was heated at 145—155° for 15 hr. When cooled, the mixture was poured onto ice. After washing with $CHCl_3$, the aqueous layer was made alkaline with KOH, extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the brown oily residue was distilled *in vacuo* to give a pale yellow oil of bp 145—160° (2 mmHg) (bath temp.). Yield, 250 mg. IR ν_{max}^{liq} cm^{-1}: 3400 (NH), 1705 (C=O). NMR ($CDCl_3$) τ: 1.95 (a pair of doublet, J=8.0 Hz, J'=2.0 Hz, 1H, C-11 H), 2.25—2.80 (multiplet, 3H, C-8, C-9, and C-10H), 6.79 (triplet, J=4.5 Hz, 1H, C-2 H), 6.62 (ill-splitted quintet, J=4.0 Hz, 1H, C-7 H), 6.99 (four peaks, 2H, C-4 H), 7.55 (four peaks, 2H, C-6 H), 7.80—9.10 (multiplet, 4H, C-5 and C-12 H), 7.57 (singlet, 1H, N$\underline{H}$, disappeared by treatment with D_2O).

A mixture of 250 mg of VII, 3.8 ml of HCO_2H and 2.2 ml of 37% formalin was heated on a water bath for 1 hr. After evaporation of the excess HCO_2H and formalin *in vacuo*, the pale yellow residue was dissolved in dil. HCl, washed with benzene, made alkaline with 10% NaOH, and extracted with ether. The residue of the dried ethereal extract was distilled under reduced pressure to give 230 mg of pale yellow oil of bp 155—160° (1.8 mmHg) (bath temp.). IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 (N–Me), 1705 (C=O). NMR ($CDCl_3$) τ: 2.02 (a pair of doublet, J=8.0 Hz, J'=2.0 Hz, 1H, C-11 H), 2.40—2.90 (multiplet, 3H, C-8, C-9 and C-10 H), 7.53 (singlet, 3H, N–Me), 6.60—8.92 (complex multiplet, 10H, aliph. H). Picrate: mp 202—203° (decomp.) (yellow sandy crystals from MeOH). *Anal.* Calcd. for $C_{14}H_{17}ON \cdot C_6H_3O_7N_3$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.24; H, 4.32; N, 12.54.

2,3,4,5,6,7-Hexahydro-2,7-methano-1*H*-3-benzazonine (VIII)——A mixture of 43 mg of VII, 0.09 g of KOH and 0.09 ml of $H_2NNH_2 \cdot H_2O$ in 0.57 ml of triethyleneglycol was heated at 170—180° for 2 hr and at 180—190° for 3 hr. After cooling, the reaction mixture was diluted with 10 ml of water and extracted with ether. The ethereal extract was dried over K_2CO_3, and then evaporated under reduced pressure to leave 30 mg of yellow oil, which was distilled *in vacuo* to give 23 mg of almost colorless oil of bp 110—120° (1 mmHg) (bath temp.). The IR spectrum of this product was identical with that of the sample synthesized by our previous method.[3)]

3-Methyl-2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonin-1-ol (X)——A mixture of 29 mg of IX and 100 mg of $LiAlH_4$ in 5 ml of dioxane was refluxed for 7 hr. After cooling, 50 ml of saturated Rochelle salt solution was added to the mixture with ice-cooling, then the mixture was extracted with $CHCl_3$. After drying with K_2CO_3, the extract was evaporated under reduced pressure to leave a red-brown syrup, which was distilled *in vacuo* to give a pale yellow viscous oil of bp 125—135° (0.15 mmHg) (bath temp.). Yield, 27.5 mg. IR ν_{max}^{liq} cm^{-1}: 3420 (OH), 2800 (N–Me).

3-Methyl-2,3,4,5,6,7-hexahydro-2,7-1*H*-3-benzazonine (A)——a) A mixture of 23 mg of VIII, 0.35 ml of HCO_2H and 0.2 ml of 37% formalin was heated on a water bath for 1 hr. After evaporation of the excess HCO_2H and formalin, the residual syrup was dissolved in 10% HCl, washed with benzene, made alkaline with NaOH, and extracted with ether. The residue of the dried ethereal extract was distilled *in vacuo* to give a colorless oil of bp 100—110° (1 mmHg) (bath temp.). Yield, 19 mg. The IR spectrum of this product was superimposable with that of the sample prepared by our previous method.[3)] Picrate: mp 170—173° (decomp.) (yellow needles 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, 55.76; H, 5.20; N, 12.88.

b) A mixture of 27 mg of X, 1.0 ml of 57% HI, 10.0 mg of P (red) and 0.5 ml of water in 2.0 ml of AcOH was refluxed for 4.5 hr. When cooled, the reaction mixture was diluted with water and the excess of red phosphorus was filtered off. The filtrate was evaporated under reduced pressure, diluted with water, made alkaline with NaOH, and extracted with ether. The residual oil of the dried ethereal extract was distilled *in vacuo* to give 11.6 mg of pale yellow oil, bp 120—130° (1 mmHg) (bath temp.). The IR spectrum of this product was identical with that of the sample synthesized by the method a).

Wolff–Kishner Reduction of IX——A mixture of 200 mg of IX, 1.5 g of KOH and 1.5 ml of $H_2NNH_2 \cdot H_2O$ in 25 ml of triethylene glycol was heated at 180—190° for 5 hr. After cooling, the mixture was diluted with 150 ml of water and extracted with ether. The oily residue of the dried ethereal extract was distilled *in vacuo* to give 100 mg of pale yellow oil of bp 120—130° (1 mmHg) (bath temp.). IR ν_{max}^{liq} cm^{-1}: 3380 (broad, NH), 2800 (N–Me). NMR ($CDCl_3$) τ: 1.90—3.00 (multiplet, 5H, arom. and olefinic H), 4.18 (multiplet, 1H, olefinic H), 6.75—8.85 (complex multiplet, 9H, aliph. H), 7.55 (singlet, 3H, N–Me), 8.32 (singlet, 1H, N$\underline{H}$, disappeared by treatment with D_2O). Mass Spectrum: M$^+$, *m/e* 201.148 (Calcd. for $C_{14}H_{19}N$: 201.152); fragment ions, *m/e* (relative intensity, %): 201 (32) (M$^+$), 200 (14) (M$^+$−1), 199 (28) ($C_{14}H_{17}N$), 141 (16) ($C_{11}H_9$), 128 (16) ($C_{10}H_8$), 71 (16) (C_4H_9N), 70 (14) (C_4H_8N), 57 (52) (C_3H_7N), 44 (100) (C_2H_6N). From these data, the structure of this product was confirmed to be 1-(N-methylaminopropyl)-1,2-dihydronahthalene (XI).

4-(N-Ethoxycarbonyl-N-methylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XIII)——To a stirred mixture of 20 g of 4-(N,N-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XII)[6)] in 400 ml of benzene was added 15 g of $ClCO_2Et$ during 30 min under refluxing. Stirring and refluxing were continued for an-other hr. After cooling, the benzene solution was washed with 5% HCl, and dried over $MgSO_4$. The yellow residual oil of the benzene solution was distilled *in vacuo* to give 22 g of colorless viscous oil of bp 101—102° (0.17 mmHg). IR $\nu_{\max}^{\text{liq}}$ cm^{-1}: 1715 (C=O). NMR ($CDCl_3$) τ: 1.98 (a pair of ill-splitted doublet, J=8.0 Hz, J'=2.0 Hz, 1H, C-8 H), 2.30—2.85 (complex multiplet, 3H, C-5, C-6, C-7 H), 5.86 (quartet, J=8.0 Hz, 2H, O–CH_2–Me), 6.54 (triplet, J=8.0 Hz, 2H, –CH_2–$C\underline{H}_2$–N–CO), 7.11 (singlet, 3H, N–Me), 6.80—8.30 (complex multiplet, 7H, aliph. H), 8.75 (triplet, J=8.0 Hz, 3H, O–CH_2–$C\underline{H}_3$).

4-(N-Methylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (XIV) Hydrochloride——A mixture of 20.5 g of XIII and 300 ml of conc. HCl was refluxed for 16 hr. The reaction mixture was diluted with water, washed with benzene, and evaporated to dryness under reduced pressure. The crystalline residue was recrystallized from MeOH to give 11 g of colorless plates, mp 164—167°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2760, 2450 (NH_2^+), 1700 (C=O). NMR (D_2O, internal standard: DSS) τ: 2.00 (a pair of ill-splitted doublet, J=8.0 Hz, J'=2.0 Hz, 1H, C-8 H), 2.20—2.65 (complex multiplet, 3H, C-5, C-6, C-7 H), 6.50—8.50 (complex multiplet, 9H, aliph. H), 7.20 (singlet, 3H, N–Me). *Anal.* Calcd. for $C_{13}H_{17}ON \cdot HCl$: C, 65.12; H, 7.56; N, 5.84. Found: C, 65.07; H, 7.62; N, 5.95.

The free base (XIV) was much instable and easyly polymerized at room temperature.

4-Methyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one (XV)——A solution of 10 g of XIV and 7.2 ml of 37% formalin in 150 ml of MeOH was warmed at 40° for 2 days. After evaporation of the solvent, the residue was dissolved in 5% HCl, washed with benzene, basified with NaOH and extracted with ether. The pale brown syrupy residue of the dried ethereal extract was distilled *in vacuo* to give 6 g of pale yellow viscous oil, bp 149—156° (3 mmHg). IR $\nu_{\max}^{\text{liq}}$ cm^{-1}: 2780 (N–Me), 1690 (C=O). NMR ($CDCl_3$) τ: 2.03 (a pair of ill-splitted doublet, J=8.0 Hz, J'=2.0 Hz, 1H, C-8 H), 2.30—2.90 (complex multiplet, 3H, C-9, C-10, C-11 H), 6.50—8.30 (complex multiplet, 10H, aliph. H), 7.70 (singlet, 3H, N–Me). Picrate: mp 174—176° (decomp.) (yellow needles from MeOH). *Anal.* Calcd. for $C_{14}H_{17}ON \cdot C_6H_3O_7N_3$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.91; H, 4.64; N, 12.34.

4-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonin-7-ol (XVI)——a) A solution of 307 mg of XV in 15 ml of AcOH, added with 120 mg of Adams' Pt catalyst, was submitted to catalytic hydrogenation at ordinary temperature and pressure. After uptake of H_2 (44 ml) had ceased, the catalyst and the solvent were removed. The residue was dissolved in water, basified with $NaHCO_3$ and extracted with $CHCl_3$. The pale brown residue of the dried extract was distilled *in vacuo* to give 244 mg of pale yellow syrup, bp 160—195° (0.15 mmHg) (bath temp.). IR $\nu_{\max}^{\text{liq}}$ cm^{-1}: 3400—3200 (broad, OH), 2800 (N–Me). NMR ($CDCl_3$) τ: 2.25—2.60 (multiplet, 1H, C-8 H), 2.60—3.00 (multiplet, 3H, C-9, C-10, C-11 H), 5.12 (doublet, J=4.0 Hz, 1H, C-7 H), 7.00 (singlet, 1H, –O$\underline{H}$, disappeared by treatment with D_2O), 7.70 (singlet, 3H, N–Me), 6.70—8.30 (complex multiplet, 10H, aliph. H).

Picrate: mp 214—217° (decomp.) (yellow needles from MeOH). *Anal.* Calcd. for $C_{14}H_{19}ON \cdot C_6H_3O_7N_3$: C, 53.81; H, 4.97; N, 12.55. Found: C, 53.83; H, 4.89; N, 12.33.

b) A mixture of 740 mg of XV and 100 mg of $LiAlH_4$ in 30 ml of dioxane was refluxed for 8 hr. When cooled, to the mixture was added *ca.* 50 ml of saturated Rochelle salt solution, and extracted the mixture with $CHCl_3$. The red brown viscous residue of the dried extract was distilled *in vacuo* to give 600 mg of pale yellow syrup, bp 150—160° (0.15 mmHg) (bath temp.). The IR and NMR spectra were identical with those of the sample prepared in the above.

4-Methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (B)——A mixture of 2.0 g of XVI, 0.44 g of P (red), 44 ml of AcOH, 16.7 ml of water and 33.4 ml of 57% HI was refluxed for 4 hr. When cooled, the mixture was filtered and evaporated under reduced pressure. The orange colored residue was dissolved in water, made alkaline with NaOH, and extracted with ether. The pale yellow oily residue of the dried extract was distilled *in vacuo* to give 1.52 g of colorless oil, bp 120—130° (2 mmHg). The IR and NMR spectra of this product was superimposable with those of the sample synthesized by the previous method.[3] Picrate: mp 199—205° (decomp.) (yellow needles 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, 55.75; H, 5.23; N, 12.79.

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