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Syntheses of Azabenzobicycloalkanes[1]

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In order to examine the pharmacological activity, some derivatives of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine, 1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine, 3,4,5,6-tetrahydro-2*H*-1,5-methano-1-benzazocine, 1,2,3,4,5,6-hexahydro-1,5-iminobenzocycloöctene, 3,4,5,6-tetrahydro-1*H*-2,6-methano-2-benzazocine, 2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine, 2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine, 2,3,4,5-tetrahydro-1,4-methano-1*H*-1-benzazepine, 2,3,4,5,-tetrahydro-1,4-imino-1*H*-benzocycloheptene and 4,5-dihydro-3*H*-2,5-methano-1*H*-2-benzazepine were synthesized.

For the investigations of the structure–activity relationship of analgetics, we attempted to synthesize compounds possessing skeletons comparable to 6,7-benzomorphan (A),[3] and previously reported the syntheses of diazabenzobicyclo[3.3.1]nonanes[4] which are regarded as aza-analogues of 6,7-benzomorphan.

In this paper we wish to report the syntheses of some derivatives of eleven members of azabenzobicycloalkanes, the homologues and isomers of 6,7-benzomorphan: 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (6,7-benzomorphan)(A), 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (B), 1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (C), 3,4,5,6-tetrahydro-2*H*-1,5-methano-1-benzazocine (D), 1,2,3,4,5,6-hexahydro-1,5-iminobenzocycloöctene (E), 3,4,5,6-tetrahydro-1*H*-2,6-methano-2-benzazocine (F), 2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (G), 2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (H), 2,3,4,5-tetrahydro-1,4-methano-1*H*-1-benzazepine (I), 2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocycloheptene (J) and 4,5-dihydro-3*H*-2,5-methano-1*H*-2-benzazepine (K).

1) 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocine (A) Derivatives

May and his co-workers[3] reported the syntheses of a number of derivatives of 6-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine which possess analgetic activity to some extent, however, 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine had not been synthesized.[5]

We synthesized N-methyl-6,7-benzomorphan not only as a member of azabenzobicycloalkanes, but as the parent structure to evaluate the role and importance of the quaternary carbon in the morphine-like analgetics.

1) Studies on Structure–Activity Relationship of Analgetics. IX (Previous papers titled "Studies on Diazabenzobicyclo[3.3.1]nonane System" are included in this series. For the preceding paper see literature 4*f*).

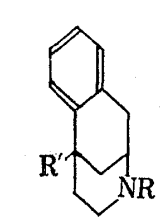
2) Location: *Gofuku, Toyama*; *a*) Present address: *Toyama Technical College, Hongo, Toyama.*

3) E.L. May, L.J. Sargent, "Analgetics," Chapter IV, ed. by deStevens, Academic Press Inc., New York, N.Y., 1966.

4) *a*) S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **12**, 647 (1964); *b*) *Idem, ibid.*, **14**, 324 (1966); *c*) *Idem, ibid.*, **14**, 608 (1966); *d*) *Idem, ibid.*, **15**, 761 (1967); *e*) S. Shiotani, T. Hori, and K. Mitsuhashi, *ibid.*, **15**, 88 (1967); *f*) *Idem, ibid.*, **16**, 239 (1968); *g*) S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **84**, 656 (1964); *h*) *Idem, ibid.*, **84**, 1032 (1964); *i*) *Idem, ibid.*, **86**, 169 (1966).

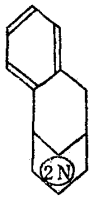
5) During the preparation of this paper, there appeared a short communication reporting on the synthesis of 6,7-benzomorphan from 4-phenylpyridine.[6]

6) K. Kanematsu, R.T. Parfitt, A.E. Jacobson, J.H. Ager, and E.L. May, *J. Am. Chem. Soc.*, **90**, 1064 (1968).

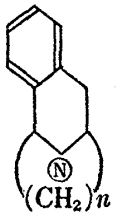


6,7-benzomorphan

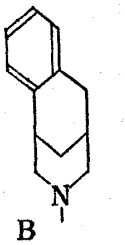
A



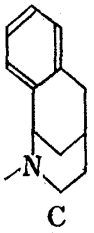
diazabenzobicyclo [3.3. 1] nonane



azabenzobicycloalkane



B



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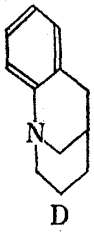

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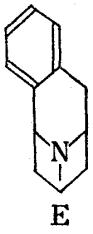

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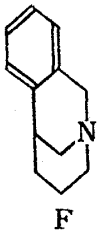
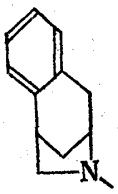
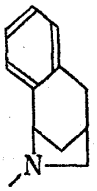


F



G



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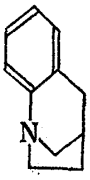
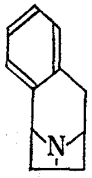
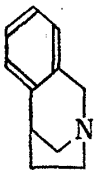


I

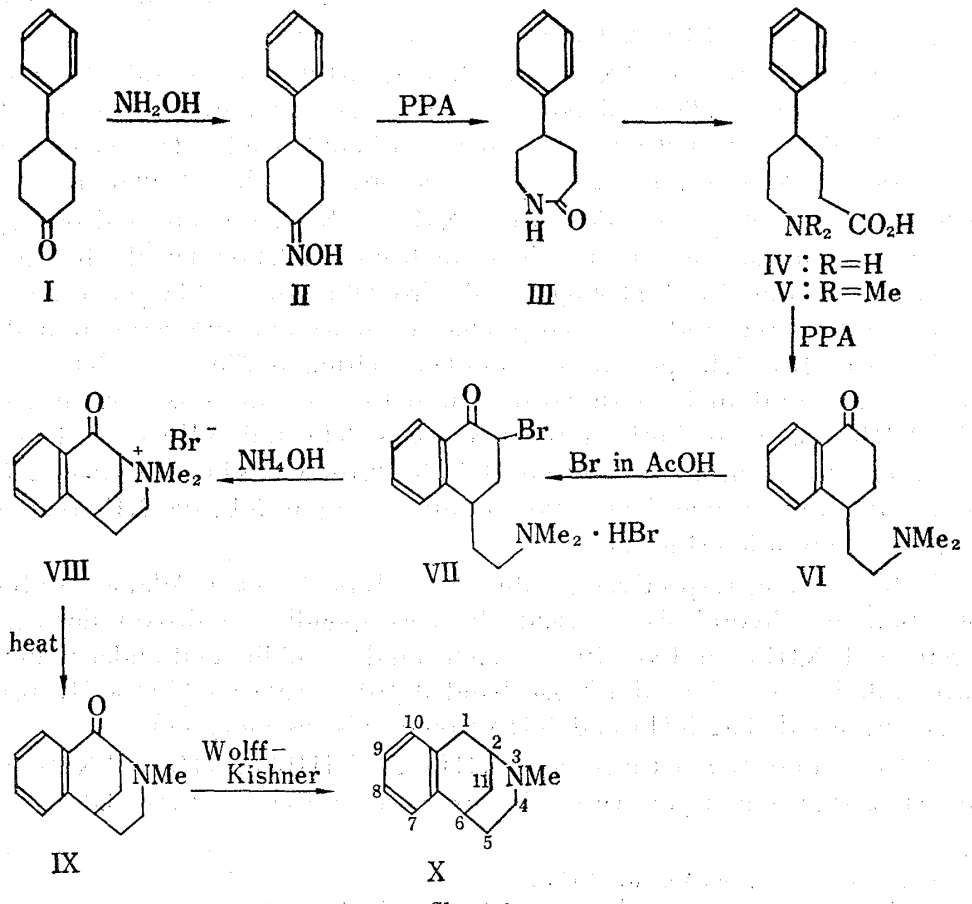


J



K

Chart 1



I II III VIII VII VI IX X

Chart 2

Thus, 4-phenylcyclohexanone oxime (II)[7] was submitted to a Beckmann rearrangement with polyphosphoric acid to give 5-phenylcaprolactam (III) as colorless prisms melting at 199—200°, which showed a carbonyl band at 1650 cm^{-1} in the infrared (IR) spectrum. After hydrolysis of the lactam with barium hydroxide, the resulted amino acid (IV) was methylated by a Clarke–Eschweiler method to afford 4-phenyl-6-(N,N-dimethylamino)hexanoic acid (V), which was in turn cyclized by heating with polyphosphoric acid to give 4-(N,N-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI) as a colorless oil, bp 125—143° (0.35 mmHg). The tetralon derivative (VI) showed a carbonyl band at 1665 cm^{-1} and a band characteristic of N–Me at 2750 cm^{-1}. From the above spectral data and the elemental analysis of the picrate the structure of VI was confirmed. Hydrobromide of VI was converted to 2-bromo-4-(N,N-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one hydrobromide (VII) by treating with bromine in acetic acid.

Treatment of VII with aqueous ammonia produced 3-methyl-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2*H*)-one methobromide (VIII) as colorless prisms, mp >300°, whose IR spectrum showed a carbonyl band at 1660 cm^{-1}. The methobromide (VIII) was dry distilled under diminished pressure to yield 3-methyl-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2*H*)-one (IX) as a yellow oil, bp 105—115° (0.5 mm Hg). The nuclear magnetic resonance NMR spectrum of IX showed the signal of N–Me at 7.72 τ as singlet, the signal of C_2-proton at 6.93τ as triplet, the signal of C_{10}-proton at 1.95—2.17 τ (deshielded by the carbonyl group) as multiplet and the signals of the other three aromatic protons at 2.40—2.93τ as complex multiplet.

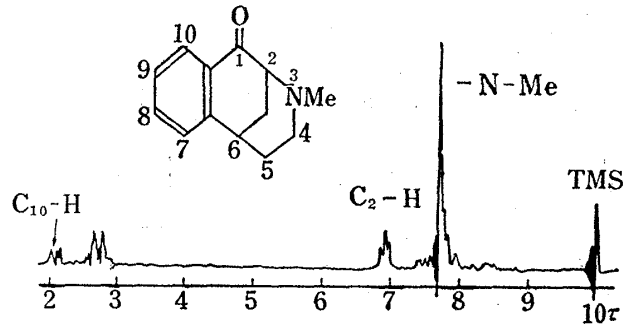


Fig. 1. NMR Spectrum of IX (in CCl_4, 60Mc)

Wolff–Kishner reduction of IX yielded 3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (X) as a pale yellow oil boiling at 108—114° (2 mmHg). In the IR spectrum X showed the N–Me band at 2760 cm^{-1} and no carbonyl band. The elemental analysis of the hydrochloride of X, mp 227—229°, was in accord with the calculated values.

In order to prepare 8-hydroxy derivative (XIIa) of X, X was nitrated by the method of May[8] for the synthesis of 3,6-dimethyl-8-hydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine from 3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine. Recrystallization of the picrate of the crude nitrated product from acetone afforded two kinds of picrate, one melting at 210—213° (XIa–picrate) and another melting at 239—244° (XIb–picrate) (ratio: *ca.* 2:1), whose elemental analyses supported the both compounds as mono-nitro derivatives of X. The NMR spectra of both of the free bases (XIa and XIb) showed an ABX–type signal pattern due to the aromatic protons at 1.83—2.70τ for XIa, and 1.83—2.75τ for XIb. These data could not determine the positions of nitro group in XIa and XIb, though confirmed to be either 8- or 9-position (Fig. 2).

The free bases were, respectively, reduced catalytically over Adams catalyst, followed by diazotization and hydrolysis to yield the corresponding hydroxyl derivatives (XIIa), mp 205—209°, and (XIIb), mp 193—197°, which could be sublimated under reduced pressure. Both hydroxyl derivatives showed a broad band at 3100—2200 cm^{-1} in the IR spectra, respectively, which suggested that XIIa and XIIb would exist as inner salt.

The NMR spectra of the methyl ethers (XIIIa and XIIIb) of XIIa and XIIb, respectively, showed an ABX–type signal pattern of the aromatic protons at 2.78—3.33τ for XIIIa and

7) H.E. Ungnade, *J. Org. Chem.*, **13**, 361 (1948).
8) N.B. Eddy, J.G. Murphy, and E.L. May, *J. Org. Chem.*, **22**, 1370 (1957).

2.87—3.35τ for XIIIb, and these data also could not determine the positions of the substituent in XIIIa and XIIIb (Fig. 2).

However, it was notable that the half height width of the signals due to the proton at meta-position to the substituent in the aromatic ring of a-series is larger than that of the signals of b-series (Fig. 2 and Table I). It may be assumed that the signals of C_7- and C_{10}-

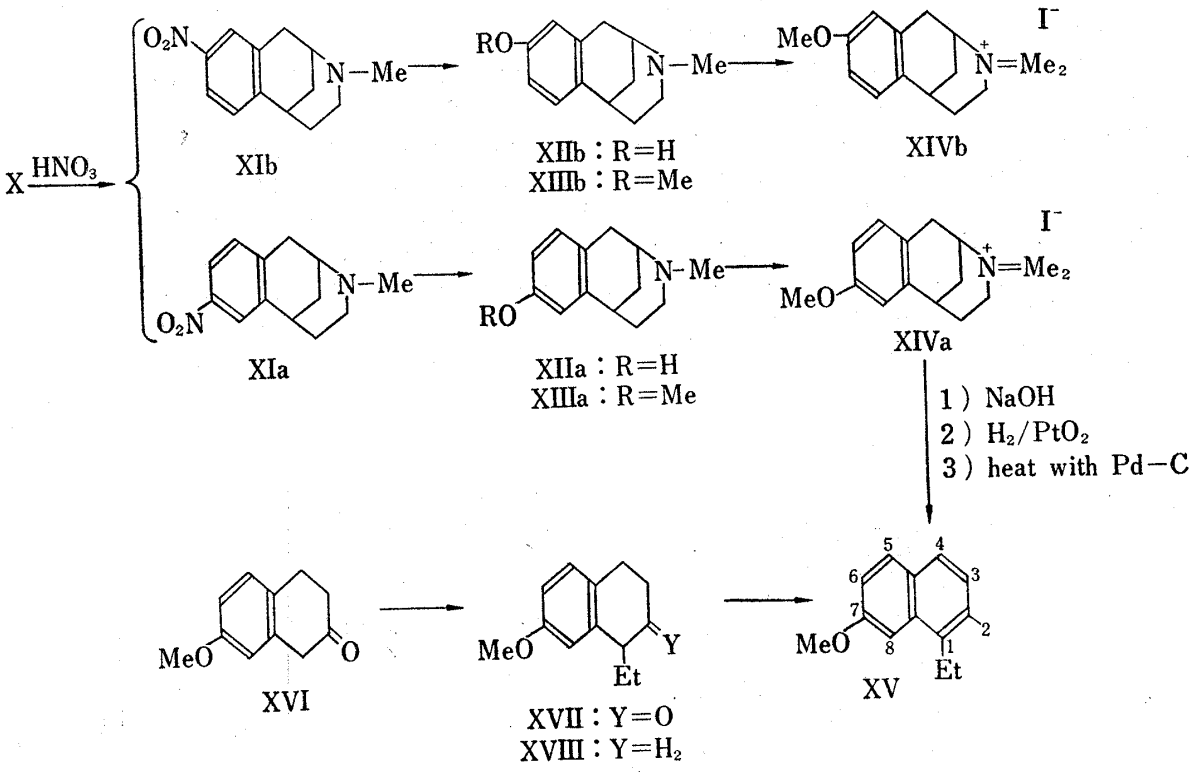


Chart 3

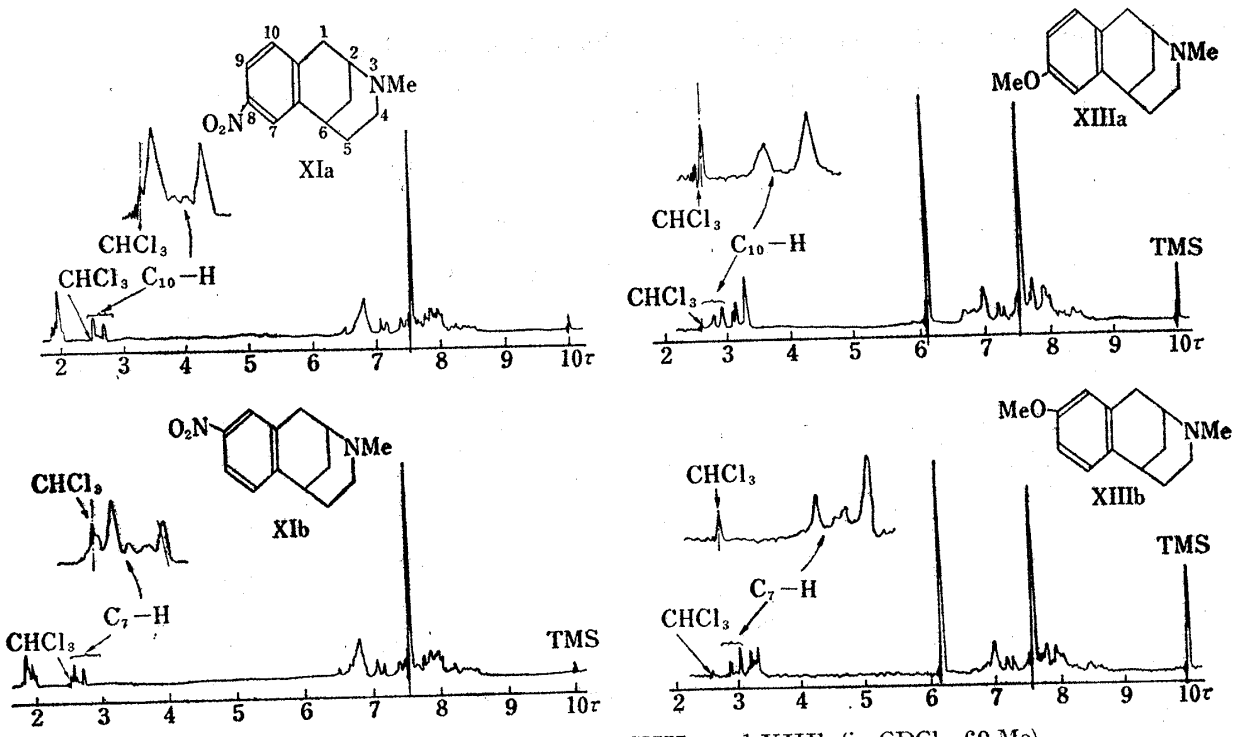


Fig. 2. NMR Spectra of XIa, XIb, XIIIa and XIIIb (in $CDCl_3$, 60 Mc)

proton would be splitted by long-range coupling[9] with the proton at *peri*-position to C_7- or C_{10}-position, consequently, the difference in half height width would be related to the number of protons at *peri*-position, that is, the larger the number, the larger the half height width is. Accordingly, it may be suggested that the substituent in a-series would be at 8-position and that in b-series would be at 9-position. This suggestion was confirmed as follows.

The methiodide (XIVa) of XIIIa was heated with aqueous sodium hydroide solution, followed by reduction over Adams catalyst and dehydrogenation to give a 1-ethylnaphthalene substituted with a methoxyl group (XV).

On the other hand, the authentic sample of 1-ethyl-7-methoxynaphthalene was synthesized by the following procedure.

Pyrrolidine enamine of 7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one[10] (XVI) was refluxed with ethyl iodide to give 1-ethyl-7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one (XVII). After reduction of XVII by a Huang-Minlon method, the resulting tetralin derivative (XVIII) was submitted to dehydrogenation with palladium-charcoal to give 1-ethyl-7-methoxynaphthalene. As shown in Fig. 3 and 4, the IR and NMR spectra of this authentic sample of 1-ethyl-7-methoxynaphthalene and those of XV were superimposable. Accordingly, the position of the substituent in a-series was confirmed to be 8- and that in b-series 9-position.

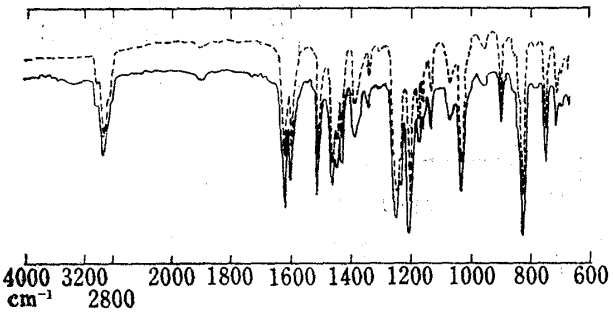


Fig. 3. IR Spectra of XV (liq.)
—— from XVI, ------ from XIVa

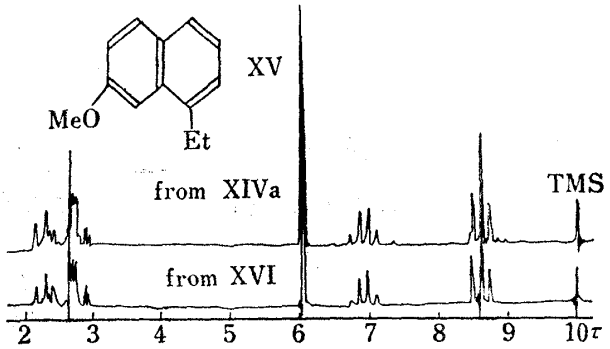


Fig. 4. NMR Spectra of XV (in $CDCl_4$, 60 Mc)

2) 1,3-Diemthyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (B)

For the one-step synthesis of this skeleton, at first we tried a Mannich condensation of 3,4-dihydronaphthalen-2(1*H*)-one (XIX) with methylamine and formalin under the reported

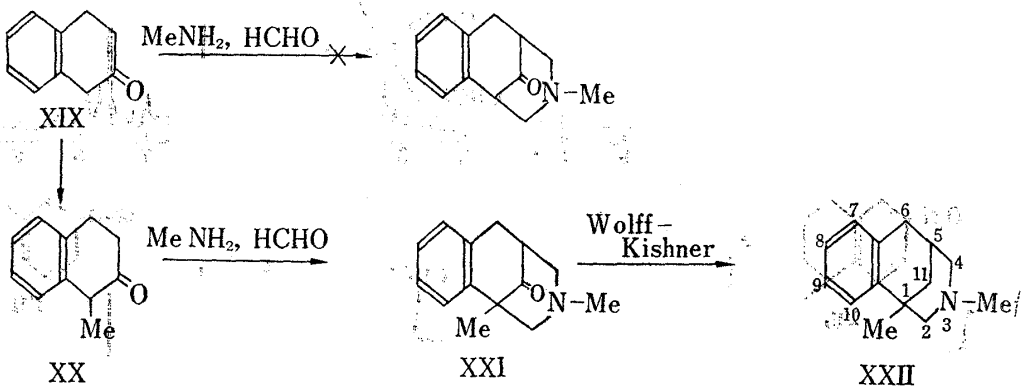


Chart 4

9) T. Gotō and K. Tori, "Jikken Kagaku Kōza, Zoku," Vol. XII, ed. by Chemical Society of Japan, Maruzen, Tokyo, 1967, pp. 319—454.
10) H. Cassebaum, *Chem. Ber.*, **90**, 2876 (1957).

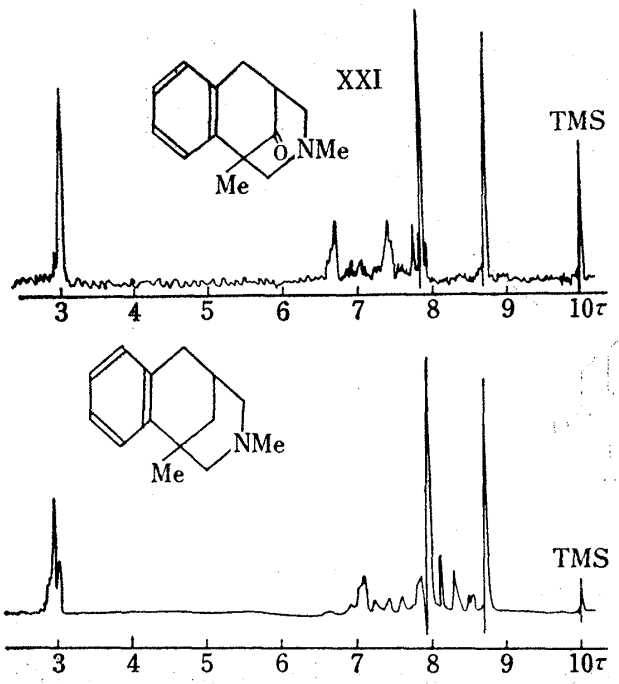


Fig. 5. NMR Spectra of XXI and XXII (in CCl_4, 60 Mc)

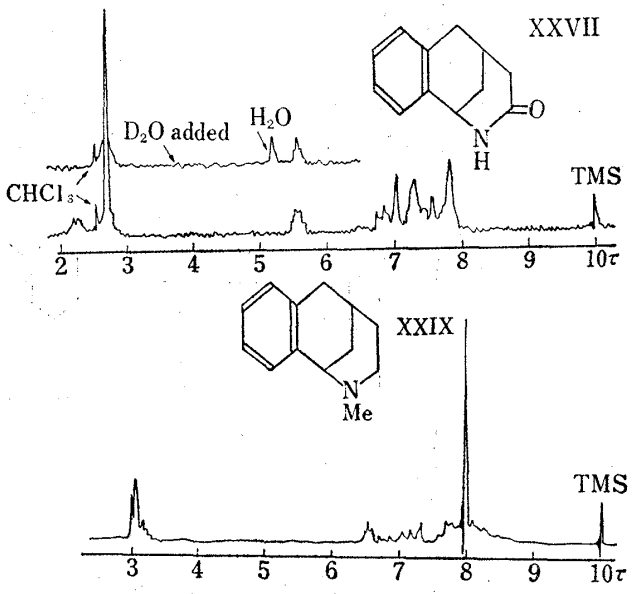


Fig. 6. NMR Spectra of XXVII and XXIX (in $CDCl_3$ and CCl_4, 60 Mc)

condition for the synthesis of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one from cyclohexanone,[11] but only a resinous product was afforded.

As it was assumed that the failure would be caused by the too much difference in activity of the two methylenes at C_1 and C_3, *i.e.* two molecules of formaldehyde would attack at C_1, the same reaction with 1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (XX) was carried out. Thus, the objective product, 1,3-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocin-11-one (XXI) was obtained as colorless needles melting at 113°, in about 23% yield. The IR spectrum of XXI showed a carbonyl band at 1680 cm^{-1}, and the NMR spectrum showed the signals of N–Me at 7.94τ and of C_1–Me at 8.70τ as singlets (Fig. 5). These spectral data and the elemental analysis supported the structure XXI.

Reduction of the carbonyl group in XXI by a Huang–Milnon method afforded 1,3-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (XXII), in the IR spectrum of which the carbonyl band shown in case of XXI disappeared.

3) 2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (C)

Ethyl ester (XXIV) of 4-oxo-1,2,3,4-tetrahydronaphthalen-2-acetic acid[12] (XXIII) was treated with hydroxylamine in the usual manner to give ethyl 4-hydroximino-1,2,3,4-tetrahydro-2-acetate (XXV). Catalytic reduction of XXV over Adams catalyst gave an oily baisc product which would be mainly composed of ethyl *cis*-4-amino-1,2,3,4-tetrahydronaphthalen-2-acetate (XXVI).[4b] The crude basic product was heated at 160—170° to cyclize the *cis*-amino ester to a lactam, 1,2,5,6-tetrahydro-1,5-methano-2-benzazocin-3(4*H*)-one (XXVII). The structure of XXVII was confirmed by the facts that in the IR spectrum XXVII showed a carbonyl band due to a six-membered lactam at 1650 cm^{-1} and that in the NMR spectrum showed the signal of NH at 2.27τ as a broad one peak and the signal of C_1–H at 5.60τ as a broad one peak.

11) H.O. House, P.P. Wickham, and H.P. Muller, *J. Am. Chem. Soc.*, **84**, 3139 (1962); B. Shimizu, A. Ogiso, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **11**, 333, 770 (1963).
12) A. Stevenson and J.F. Thorpe, *J. Chem. Soc.*, **121**, 1717 (1922).

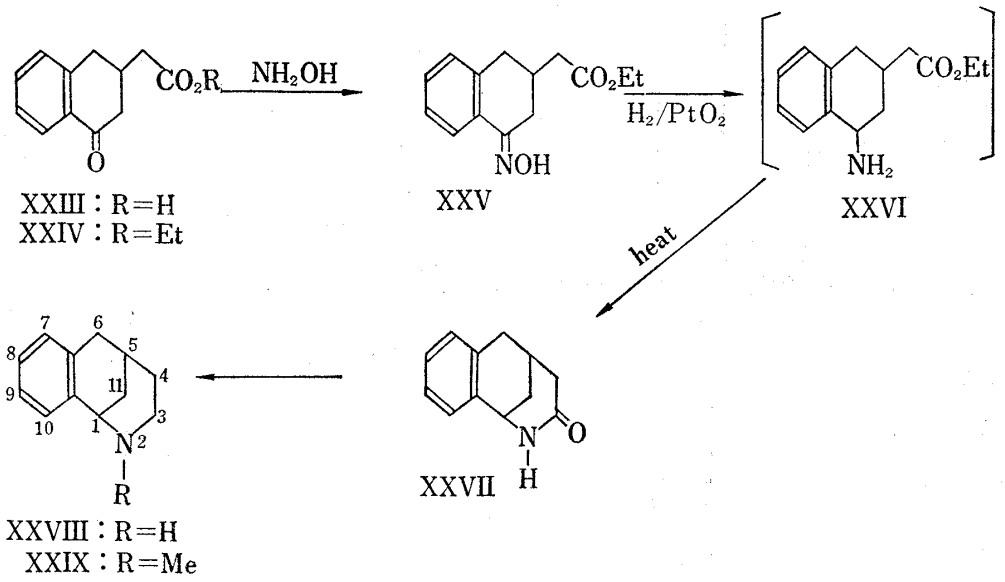


Chart 5

The lactam (XXVII) was reduced with lithium aluminum hydride to give 1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (XXVIII), and then XXVIII was methylated by a Clarke–Eschweiler method to give the N-methyl derivative (XXIX).

4) 3,4,5,6-Tetrahydro-2*H*-1,5-methano-1-benzazocine (D), 2,3,4,5-Tetrahydro-1,4-methano-1*H*-1-benzazepine (I) and 2,3,4,5-Tetrahydro-1,4-methano-1*H*-2-benzazepine (H) Derivatives

Beckmann rearrangement of methyl 4-hydroximino-1,2,3,4-tetrahydronaphthalene-2-carboxylate (XXX) was carired out according to the procedure of Lloyd, *et al.*[13] to give methyl 3,4-dihydrocarbostyril-3-acetate (XXXI). Reduction of XXXI with lithium aluminum hydride gave 3-(β-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (XXXII) as colorless needles melting at 91—92°, whose IR spectrum showed a broad band due to ν_{NH} and ν_{OH} at 3400—3100 cm^{-1} and a band of ν_{C-OH} at 1050 cm^{-1}.

The hydroxyl derivative (XXXII) was converted to the corresponding bromo derivative (XXXIII) by heating with concentrated hydrobromic acid. By treating with potassium carbonate in benzene under reflux, the bromo compound afforded a halogen free product (XXXIV: a colorless oil, bp 119—121° (0.3 mmHg)) which showed no bands characteristic of –NH, –OH and vinyl groups in the IR spectrum. From these spectral data and the elemental analysis of the picrate of XXXIV, the structure was characterized as 2,3,4,5-tetrahydro-1,4-methano-1*H*-1-benzazepine.

Treatments of the bromo compound (XXXIII) with potassium (or sodium) cyanide under several coditions afforded the cyclized product (XXXIV), not 3-(β-cyanoethyl)-1,2,3,4-tetrahydroquinoline, hence we followed by following route.

3-(β-Hydroxyethyl)-1,2,3,4-tetrahydroquinoline (XXXII) was benzoylated to protect the basic nitrogen at 1–position, and the resulted benzoyl derivative, 1-benzoyl-3-(β-benzoxyethyl)-1,2,3,4-tetrahydroquinoline (XXXV), was saponified with a calculated amount of potassium hydroxide in ethanol to yield 1-benzoyl-3-(β-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (XXXVI) as colorless needles, mp 117.5—119°. By treating XXXVI with phosphorus tribromide, the hydroxyl derivative (XXXVI) was converted to the bromo compound (XXXVII), which was treated with potassium cyanide to give 1-benzoyl-3-(β-cyanoethyl)-1,2,3,4-tertahydroquinoline (XXXVIII). The nitrile (XXXVIII) was hydrolyzed by heating

13) H.A. Lloyd, L.U. Matternas, and E.C. Horning, *J. Am. Chem. Soc.*, **77**, 5932 (1955).

with concentrated hydrochloric acid in acetic acid in a selaed tube, followed by esterification to yield methyl 1,2,3,4-tetrahydroquinoline-3-propionate (XXXIX). After reduction of the carboxyl group in XXXIX with lithium aluminum hydride, the resulted hydroxyl compound (XL) was treated with concentrated hydrobromic acid to give 3-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoline (XLI) hydrobromide. Cyclization of XLI to 3,4,5,6-tettahydro-2*H*-1,5-methano-1-benzazocine (XLII) was effected by heating with potassium hy droxide in ethanol.

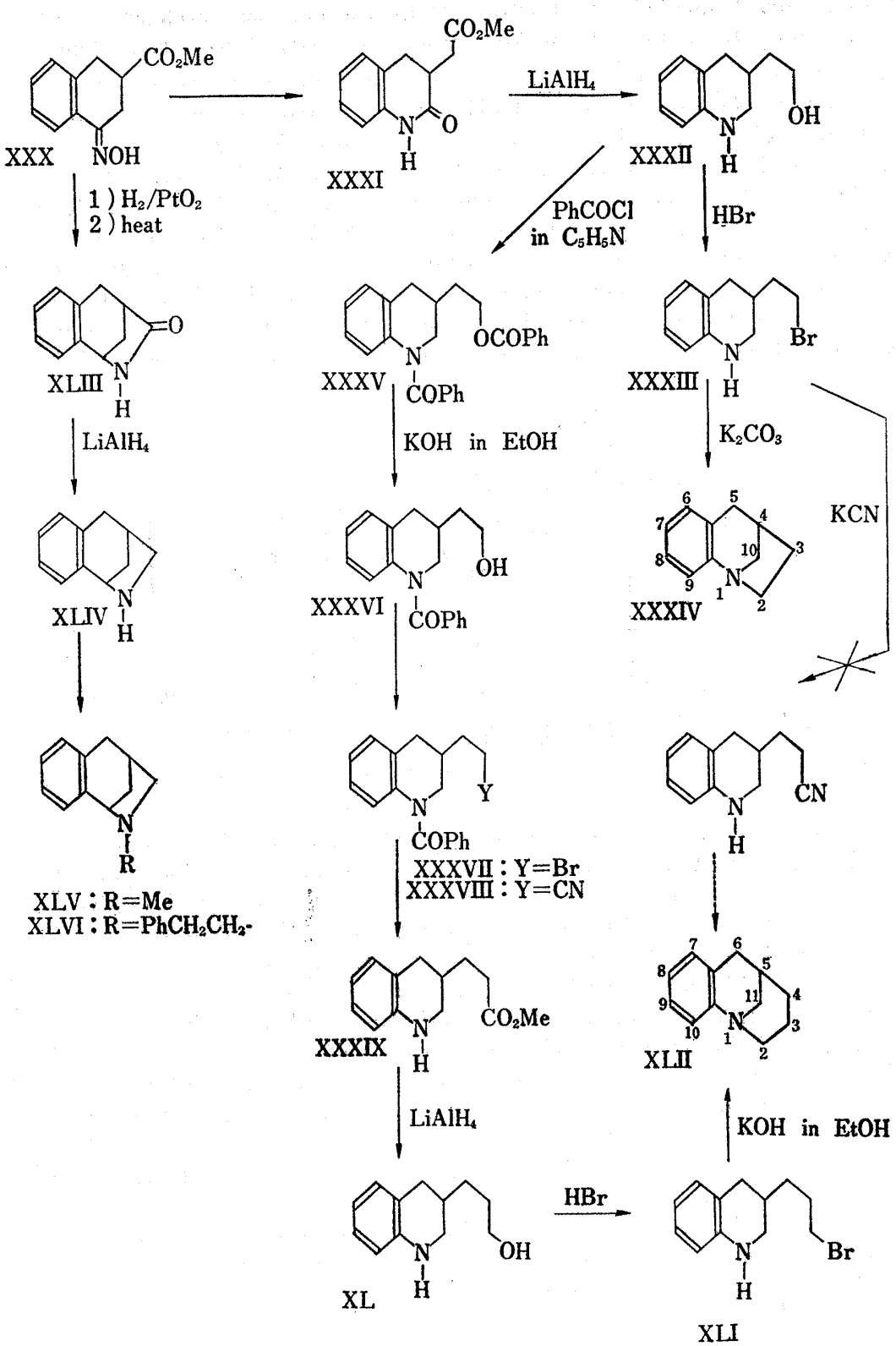


Chart 6

Reduction of 4,5-dihydro-4,5-methano-1*H*-2-benzazepin-3(2*H*)-one (XLIII) with lithium aluminum hydride which was prepared from XXX by the procedure reported in our previous paper[4b] afforded 2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (XLIV). Methylation of XLIV by a Clarke–Eschweiler method gave the N-methyl derivative (XLV) and phenethylation with phenethyl bromide gave the N-phenethyl derivative (XLVI). Both compounds were characterized as picrate, respectively.

5) 8,9-Dimethoxy-11-methyl-1,2,3,4,5,6-hexahydro-1,5-iminobenzocyclooctene (LI) (E) and 7,8-Dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocycloheptene (LVII) (J)

An intermediate for the synthesis of LI, 11-benzyl-8,9-dimethoxy-1,2,5,6-tetrahydro-1,5-iminobenzocycloöcten-3(4*H*)-one (XLVIII), was prepared starting from 3-(3,4-dimethoxyphenyl)alanine (XLVII) according to the route reported by Yoneda.[14]

The tricyclic ketone (XLVIII) was reduced by a Huang–Minlon method to give 11-benzyl-8,9-dimethoxy-1,2,3,4,5,6-hexahydro-1,5-iminobenzocycloöctene (IL), in the IR spectrum of which the carbonyl band shown at 1700 cm^{-1} in case of XLVIII disappeared. The benzyl group of IL was removed by hydrogenolysis over palladium–charcoal to afford 8,9-dimethoxy-1,2,3,4,5,6-hexahydro-1,5-iminobenzocyclooctene (L). The N-methyl derivative (LI) of L was obtained by a Clarke–Eschweiler method as a colorless oil boiling at 152—160° (0.07 mmHg). The IR and NMR spectral data and the elemental analysis were in accord with the structure LI.

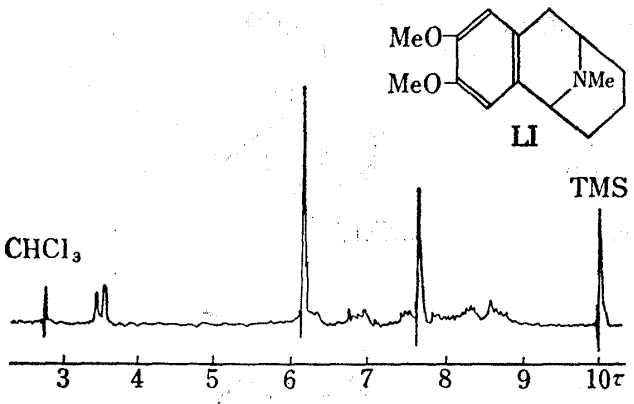


Fig. 7. NMR Spectrum of LI (in $CDCl_3$, 60 Mc)

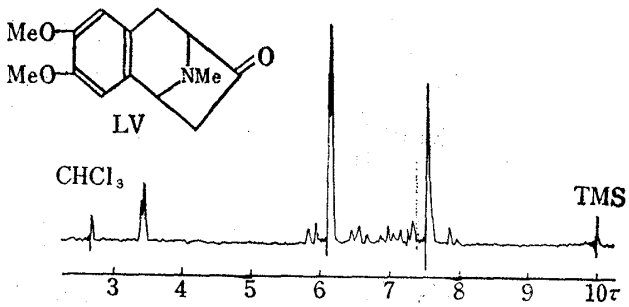


Fig. 8. NMR Spectrum of LV (in $CDCl_3$, 60 Mc)

Next, ethyl 3-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (LII) was prepared from XLVII by the procedure described in our previous paper,[4f] and then methylated by a Clarke–Eschweiler method to give the N-methyl derivative (LIII). The N-methyl derivative was submitted to a Dieckmann cyclization with sodium hydride to afford ethyl 3-oxo-7,8-dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocycloheptene-2-carboxylate (LIV) which gave purple color with ferric chloride.

Hydrolysis of LIV with diluted hydrochloric acid yielded 7,8-dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocyclohepten-3-one (LV) as colorless needles melting at 121—122°, whose IR spectrum showed a carbonyl band at 1740 cm^{-1} (five-membered cyclic ketone). The NMR spectrum showed signals at 3.40 and 3.43τ (2H, two lines, arom. protons), 5.87τ (1H, doublet, J=6 cps, C_1–H), 6.10 and 6.12τ (6H, two lines, 2×O–Me), 7.54τ (3H, singlet, N–Me) (Fig. 8). From these spectral data and the elemental analysis, the structure of LV was confirmed.

Reduction of LV with sodium borohydride gave the corresponding hydroxyl derivative (LVI), and the Huang–Minlon reduction afforded 7,8-dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocycloheptene (LVII).

14) N. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **12**, 1478 (1964).

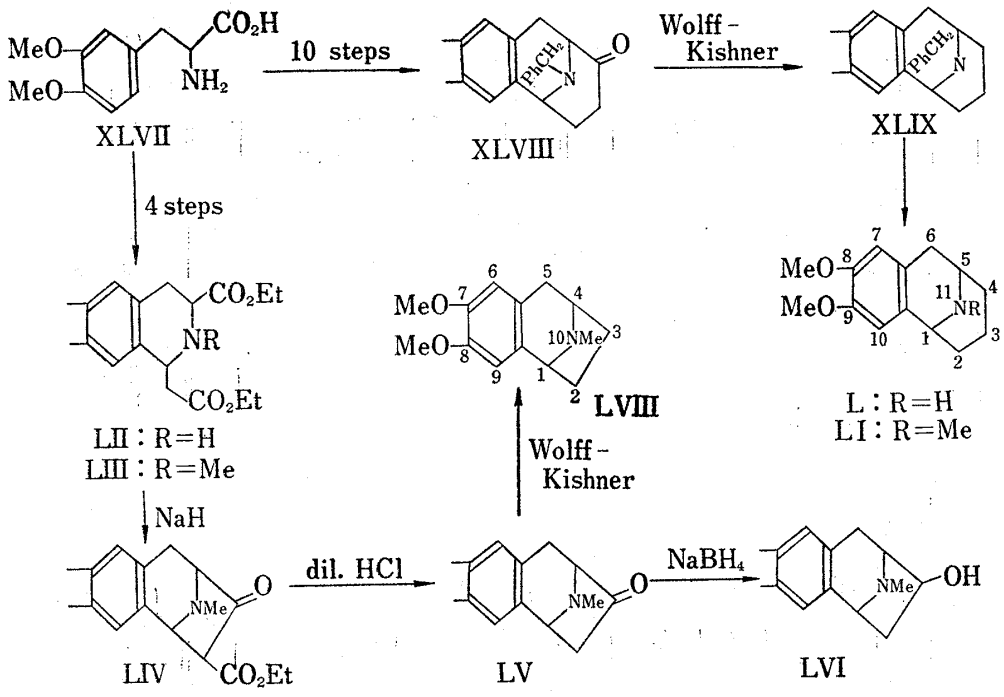


Chart 7

6) 3,4,5,6-Tetrahydro-1*H*-2,6-methano-2-benzazocine (F) and 4,5-Dihydro-3*H*-2,5-methano-1*H*-2-benzazepine (K)

As shown in Chart 8, ethyl 1,2,3,4-tetrahydroisoquinoline-4-carboxylate (LVIII)[4e] was condensed with ethyl acrylate to give ethyl 4-carbethoxy-1,2,3,4-tetrahydroisoquinoline-2-propionate (LIX), which was purified and characterized as its oxalate, mp 130.5—131.5°. The diester (LIX) was submitted to a Dieckmann cyclization, and the resulted ketoester was in turn hydrolyzed by heating with diluted hydrochloric acid to yield 3,4-dihydro-1*H*-2,6-methano-2-benzazocin-5(6*H*)-one (LX). In the IR spectrum LX showed a carbonyl band at 1685 cm^{-1}. The NMR spectrum of LX showed signals of C_1-protons as an AB-type quartet at 5.50 and 6.16τ (J_{AB}=17.5 cps) and signals of C_4-methylene protons as AB part of an ABXY-pattern (N-CH_2-CH_2-CO) at 7.52 and 8.02τ (J_{AB}=14.5 cps, J_{AX}=9 cps, $J_{BX}=J_{BY}$=3 cps, J_{AY}=0 cps) (Fig. 9). These spectral and the elemental analysis of the picrate confirmed the structure LX. Reduction of LX by a Huang-Minlon method afforded 3,4,5,6-tetrahydro-1*H*-2,6-methano-2-benzazocine (LXI) as a colorless oil, bp 125—135° (0.2 mmHg) (bath temp.). This compound was characterized as its picrate, mp 150—152° (decomp.).

Preparation of methyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-acetate (LXII) from LVIII was effected by the procedure reported in our previous paper,[4e] and the resulted ester was reduced by lithium aluminum hydride to give 2-benzyl-4-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (LXIII). LXIII was debenzylated by hydrogenolysis over palladium-charcoal, followed by bromination with hydrobromic acid and cyclization of the resulting bromo compound to produce 4,5-dihydro-3*H*-2,5-methano-1*H*-2-benzazepine (LXVI), which was characterized as its picrate, mp 162—163°.

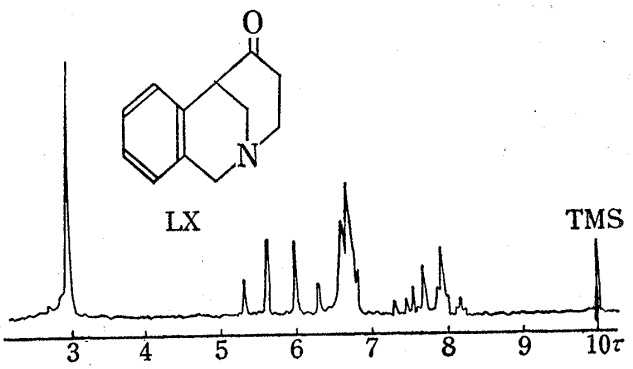


Fig. 9. NMR Spectrum of LX (in CCl_4, 60 Mc)

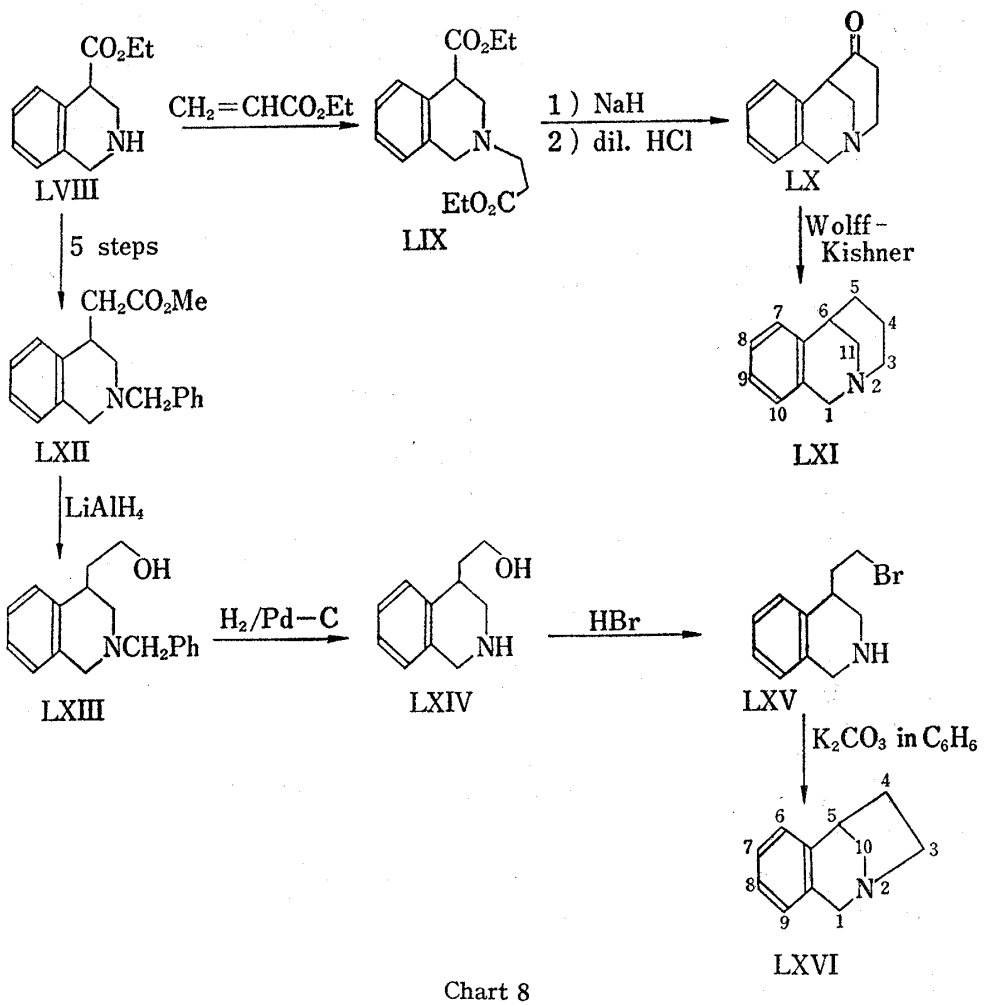


Chart 8

7) 2,3,4,5-Tetrahydro-1,4-methano-1*H*-3-benzazepine (G) Derivatives

3-Oxo-1,2,3,4-tetrahydro-1-naphthoic acid (LXVII) synthesized by the route reported in our previous paper[4d] was esterified in the usual manner, followed by oximation to give methyl 3-hydroximino-1,2,3,4-tetrahydro-1-naphthoate (LXIX) as colorless fine needles, mp 94.5—96.5°. In the IR spectrum LXIX showed a band of ν_{OH} at 3400—3000 cm^{-1} and a carbonyl band at 1705 cm^{-1}. The oxime was catalytically reduced over Adams catalyst to give an aminoester which would be mainly composed of methyl *cis*-3-amino-1,2,3,4-tetrahydronaphthalene-1-carboxylate,[4b] and the resulted basic product was heated at 150° to yield 4,5-dihydro-1,4-methano-1*H*-3-benzazepin-2(3*H*)-one (LXX). The lactam (LXX), mp 124—127°, showed a carbonyl band at 1665 cm^{-1} and a band of ν_{NH} at 3250—3050 cm^{-1} in the IR spectrum. Reduction of LXX with lithium aluminum hydride afforded 2,3,4,5-tetrahydro-1,4-methano-1*H*-benzazepine (LXXI) as a slightly yellow oil boiling at 132—138° (10 mmHg) (bath temp.), whose IR spectrum showed an NH-band at 3300 cm^{-1} and no carbonyl band.

Methylation of LXXI by a Clarke–Eschweiler method gave a colorless basic oil (LXXII), bp 120—125° (10 mmHg) (bath temp.). In the IR spectrum LXXII showed a band due to N-Me at 2770 cm^{-1} and the NH-band showh at 3300 cm^{-1} in case of LXXI disappeared. From the above spectral data and the elemental analysis of the picrate, LXXII was characterized as 3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine.

Nitration of LXXII gave two nitro derivatives (LXXIIIa and LXXIIIb), as the case of N-methyl-6,7-benzomorphan (X). The separation of the two nitro derivative was effected by fractional recrystallization of the picrates from acetone. Both of the nitro compounds

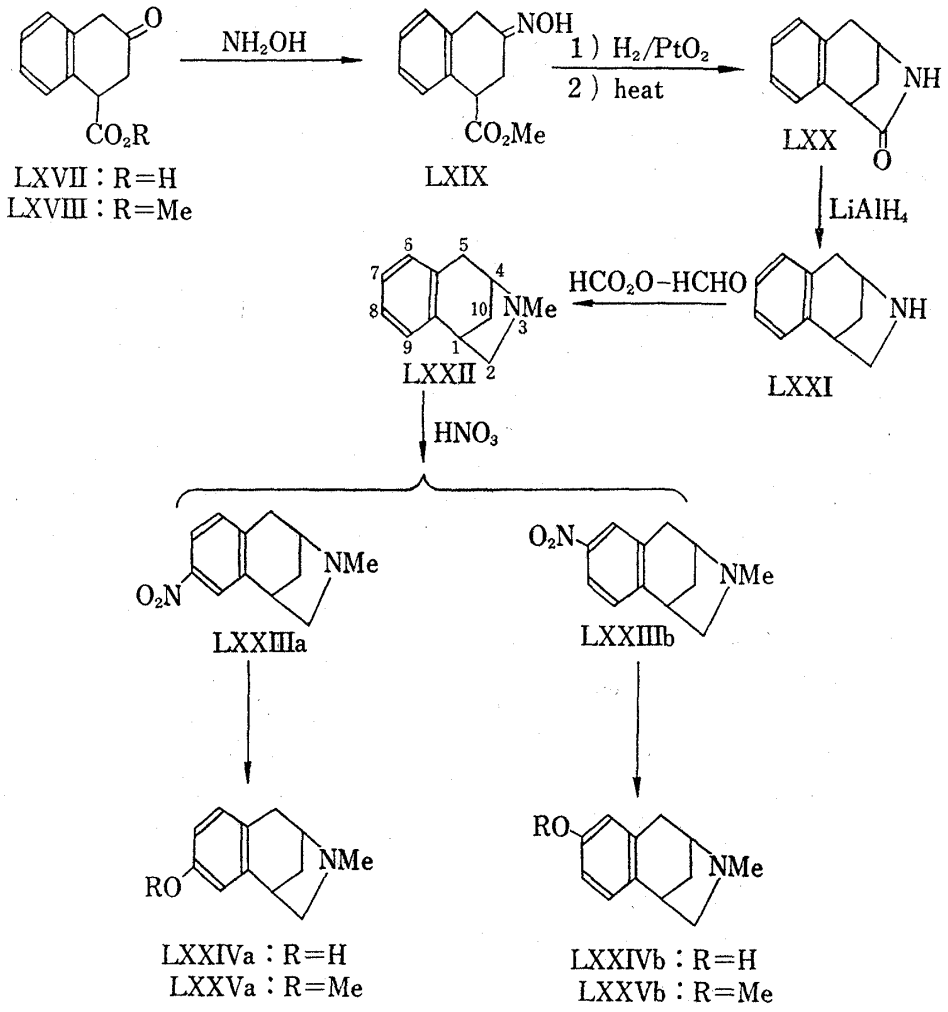


Chart 9

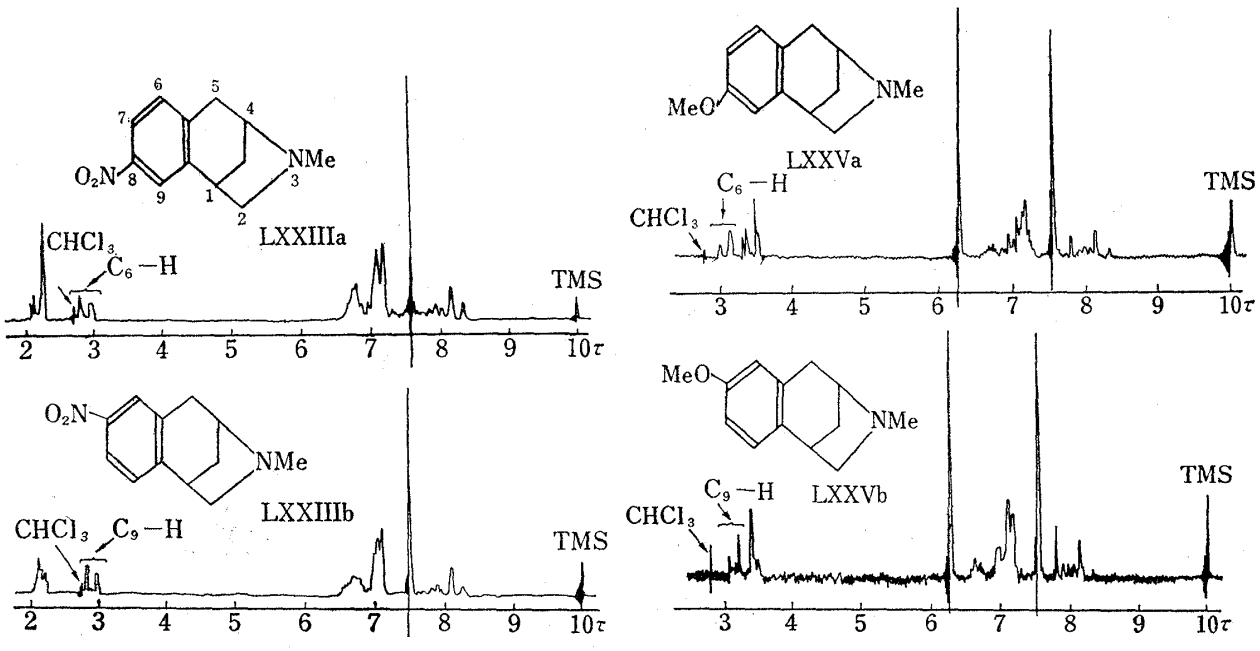


Fig. 10. NMR Spectra of LXXIIIa, LXXIIIb, LXXVa and LXXVb (in $CDCl_3$, 60 Mc)

Table I. Half Height Width of Protons at *meta*-Position to the Substituent

Nitro derivatives		Methoxyl derivatives	
XIa	2.4 cps	XIIIa	2.2 cps
XIb	1.7	XIIIb	1.5
LXXIIIa	3.6	LXXVa	3.0
LXXIIIb	2.0	LXXVb	1.5

were converted to the corresponding methoxyl derivatives (LXXVa and LXXVb), respectively, by the same procedure as described for N-methyl-6,7-benzomorphan derivatives.

In the NMR spectra, every one of the nitro and methoxyl derivatives showed an ABX-type signal pattern of the aromatic protons (Fig. 10), and it was found that the signal pattern of the aromatic protons of LXXIIIa is similar to that of XIa, LXXIIIb to XIb, LXXVa to XIIIa and LXXVb to XIIIb and that the half height width of the signals due to the proton at *meta*-position to the substituent of the aromatic ring in a-series is larger than that of the signals in b-series (Table I.).

Thus, the structures of LXXIIIa, LXXIIIb, LXXVa and LXXVb were confirmed as 3-methyl-8-nitro-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine, 3-methyl-7-nitro-2,3,4,5,-tetrahydro-1,4-methano-1*H*-3-benzazepine, 3-methyl-8-methoxy-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine and 3-methyl-7-methoxy-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine, respectively.

The testings for analgetic activity of X, XIIa, XXII, XXIX, XXXIV, XLII, XLV, XLVI, LI, LVI, LVII, LXI, LXVI, LXXII and LXXIVa are now in progress. Interesting results were found in some of the above compounds, the details will be presented later.

Experimental[15]

5-Phenylcaprolactam (III)——A mixture of 4-phenylcyclohexanone[7] (II) (4.0 g) and polyphosphoric acid (prepared from 30 g of P_2O_5 and 30 g of 85% H_3PO_4) was heated at 100° for 10 min and then at 160—170° for 5 min. After cooling, the reaction mixture was diluted with ice-water, extracted with $CHCl_3$ and dried over Na_2SO_4. On evaporating the solvent, the residue solidified, which was recrystallized from MeOH to yield colorless prisms, mp 199—200°, yield, 3.8 g. IR cm^{-1}: ν_{NH} 3200; $\nu_{C=O}$ 1650 (KBr). *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.19; H, 7.98; N, 7.69.

4-(N,N-Dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI)——A mixture of III (3.5 g) and Ba $(OH)_2 \cdot 8H_2O$ (30 g) in water (300 ml) was refluxed for 6 hr. The reaction mixture was neutralized with dil. H_2SO_4, filtered with celite, and the clear filtrate was evaporated to dryness *in vacuo*. The solid residue (IV) (4.0 g) was mixed with formic acid (99%, 20 ml) and formalin (37%, 7 ml), and heated on a water bath for 1 hr. From the pale yellow reaction mixture, the excess formic acid and formalin were removed *in vacuo*. To the syrupy residue (V) (4.5 g) polyphosphoric acid(prepared from 20 g of P_2O_5 and 20 g of 85% H_3PO_4) was added, and heated on a water bath for 3 hr. The dark reaction mixture was diluted with chilled water, made alkaline with 40% KOH solution, extracted with ether and dried over K_2CO_3. After evaporation of the solvent, the residual dark oil was distilled *in vacuo* to give VI as a pale yellow oil, bp 125—143 (0.35 mmHg). Yield, 2.9 g. IR cm^{-1}: $\nu_{C=O}$ 1665; 2750 (N-Me) (liq.). Picrate: yellow prisms, mp 142—143° (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, 53.75; H, 5.23; N, 12.45.

3-Methyl-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2*H*)-one Methobromide (VIII)——VI (19.3 g) was converted to the hydrobromide. To a solution of the hydrobromide in AcOH (75 ml) was added Br_2 (17.3 g) in AcOH (35 ml) dropwise under gentle refluxing during 20 min. After cooling, the reaction mixture was diluted with ether to deposit the hydrobromide of the bromo derivative (VII) as a semi-solid mass. The crude hydrobromide (VII) was dissolved in water (20 ml), neutralized with aqueous ammonia under cooling and filtered with charcoal. The clear filtrate was evaporated to dryness *in vacuo*. The crystalline

15) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H recording spectrometer in $CDCl_3$ (or CCl_4) with TMS as an internal standard.

residue was recrystallized from MeOH to give VIII as colorless needles, mp>300°. Yield, 18.1 g. IR cm^{-1}: $\nu_{C=O}$ 1660 (KBr). *Anal.* Calcd. for $C_{14}H_{18}ONBr$: C, 56.76; H, 6.13; N, 4.73. Found: C, 56.47; H, 6.10; N, 4.47.

3-Methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (X)——The methobromide (VIII) (18.1 g) was dry distilled at a bath temperature of 240—260° (0.2—0.3 mmHg) in five portions to give the base IX which was redistilled *in vacuo*, bp 105—115° (0.5 mmHg).

To the distillate (IX) (7.6 g) in triethylene glycol (95 ml) was added $NH_2NH_2 \cdot H_2O$ (80%, 14.3 ml) and KOH (14.3 g), and the mixture was heated 170—180° for 2 hr and at 180—190° for 3 hr. After cooling, the mixture was diluted with water (*ca.* 100 ml), extracted with ether and dried over K_2CO_3. The residue (6.6 g) of the ethereal solution was distilled *in vacuo* to give X as a pale yellow oil, bp 108—114° (2 mmHg). Yield, 5.0 g. IR cm^{-1}: 2760 (N–Me), no carbonyl band (liq.). Hydrochloride: colorless cubes, mp 227—229° (from acetone). *Anal.* Calcd. for $C_{13}H_{17}N \cdot HCl$: C, 69.78; H, 8.11; N, 6.26. Found: C, 69.52; H, 8.16; N, 6.17.

8-Nitro-(XIa) and 9-Nitro-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (XIb)——To a mixture of HNO_3 (d: 1.50, 7.5 ml) and AcOH (4.5 ml) a solution of X (1.5 g) in AcOH (3.0 ml) was added during 2 hr under cooling at 2—5° with stirring. The reaction mixture was stood overnight at room temperature, and evaporated *in vacuo* at a bath temperature below 60°. The residue was diluted with ice-water, basified with aqueous ammonia, extracted with ether and dried over K_2CO_3 for 30 min. After evaporation of ether, The pale brown oil (1.8 g) in acetone (6 ml) was added to picric acid (1.7 g) in acetone (17 ml), and stood overnight at room temperature to deposit the picrate (3.0 g).

The crude picrate was fractionally recrystallized from acetone to give a picrate of mp 210—213.5° (yellow needles (XIa-picrate)) (0.9 g) and a picrate of mp 239—244° (yellow prisms (XIb-picrate)) (0.5 g). From the mother liqour 0.6 g of the mixed picrate were obtained.

XIa-picrate: *Anal.* Calcd. for $C_{13}H_{16}O_2N_2 \cdot C_6H_3O_7N_3$: C, 49.46; H, 4.15; N, 15.18. Found: C, 49.44; H, 4.13; N, 15.30.

XIb-picrate: *Anal.* Calcd. for $C_{13}H_{16}O_2N_2 \cdot C_6H_3O_7N_3$: C, 49.46; H, 4.15; N, 15.18. Found: C, 49.72; H, 3.97; N, 14.94.

Free Base XIa: yellow syrup (solidified gradually on standing), bp 120—140° (0.1 mmHg) (bath temp.). IR cm^{-1}: 1345, 1510 ($-NO_2$) (KBr).

Free Base XIb: pale yellow syrup, bp 120—140° (0.1 mmHg) (bath temp.). IR cm^{-1}: 1345, 1515 ($-NO_2$) (liq).

8-Hydroxy-(XIIa) and 9-Hydroxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (XIIb)——XIIa: A solution of XIa (0.5 g) in MeOH (20 ml) was shaken with Pd–C (40%, 150 mg) in H_2 atmosphere. After absorption of three molecular equivalents of H_2 (*ca.* 4 hr), the catalyst and the solvent were removed. The orange colored residue was dissolved in 3N H_2SO_4 (4 ml), cooled in an ice-bath, and a solution of $NaNO_2$ (150 mg) in water (*ca.* 2 ml) was added to this solution during 10 min under stirring. After stirring for an additional 10 min, the solution of the diazonium salt was added to a dil. H_2SO_4 (1:1, 30 ml) and heated on a water bath for 25 min. The cooled mixture was basified with aqueous ammonia, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. The crystalline residue was recrystallized from acetone to give XIIa as colorless sandy crystals, mp 205—209°, a small portion of which was sublimated *in vacuo*, 140—150° (0.2 mmHg) (bath temp.). Yield, 0.25 g. IR cm^{-1}: 3100—2200 (broad) ($\overset{+}{>}NH$), 1270 (C–OH) (KBr). *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.59; H, 8.66; N, 6.70.

XIIb: This compound was prepared from XIb (0.2 g) by the same method as described for XIIa, mp 193—197°, sublimed at 140—150° (0.2 mmHg) (bath temp.). Yield, 0.1 g. IR cm^{-1}: 3100—2200 (broad) ($\overset{+}{>}NH$), 1265 (C–OH) (KBr).

8-Methoxy-(XIIIa) and 9-Methoxy-3-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (XIIIb)——XIIIa: To a solution of XIIa (250 mg) in MeOH a solution of CH_2N_2 in ether was added at room temperature and stood overnight. After evaporation of the excess CH_2N_2 and the solvents the resultant oil was distilled *in vacuo*, bp 110—130° (0.2 mmHg) (bath temp.). Yield, 244 mg. IR cm^{-1}: 1035, 1255 (C–OMe); 1225 (unassignable) (liq.). Methiodide: colorless plates, mp 229—233° (from MeOH–AcOEt). *Anal.* Calcd. for $C_{15}H_{22}ONI$: C, 50.15; H, 6.17; N, 3.90. Found: C, 50.28; H, 6.38; N, 3.76.

XIIIb: This compound was prepared from XIIb (0.1 g) by the same procedure as described for XIIIa, bp 110—130° (0.2 mmHg) (bath temp.). Yield, 73 mg. IR cm^{-1}: 1035, 1255 (C–OMe) (liq.). Methiodide: colorless crystalline powder, mp 222—225° (from MeOH–AcOEt). *Anal.* Calcd. for $C_{15}H_{22}ONI$: C, 50.15; H, 6.17; N, 3.90. Found: C, 50.04; H, 6.24; N, 3.74.

1-Ethyl-7-methoxynaphthalene (XV)——a) From XIVa: A solution of the methiodide (XIVa) (265 mg) in 10% NaOH (10 ml) was refluxed for 3 hr. The resultant oil was dried in $CHCl_3$ and distilled *in vacuo* to give a colorless oil (156 mg), bp 120—130° (0.2 mmHg) (bath temp.). The distillate (156 mg) in MeOH was hydrogenated over PtO_2 in the usual manner, and absorbed 35 ml of H_2 in 6 hr. The filtered solution was evaporated *in vacuo*, and the residue was distilled *in vacuo* to give a colorless oil, bp 100—120° (0.2 mmHg) (bath temp.). Yield, 150 mg. The distillate (90 mg) was mixed with Pd–C (10%, 50 mg) in a long test tube and heated at 280—310° for 20 min. The cooled mixture was extracted with ether. The ether 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 110—120° (3 mmHg) (bath temp.).

b) From 7-Methoxy-3,4-dihydronaphthalen-2(1*H*)-one (XVI): A mixture of XVI[10] (0.6 g), pyrrolidine (4 ml) and C_6H_6 (25 ml) was refluxed for 20 hr, the water formed being collected in a Dean–Stark trap. After evaporation of the solvent and the excess of pyrrolidine, the resulted enamine (dark brown syrup) was mixed with EtI (7 ml) in dioxane (20 ml) and refluxed for 14 hr. AcOH (0.5 ml) in water (5 ml) was added, heated for 5 hr and the solvents were evaporated *in vacuo*. The residue was dissolved in ether, washed with dil. HCl and dried over Na_2SO_4. The residue of the ethereal solution was distilled *in vacuo* to give a pale yellow oil, bp 90—140° (0.2 mmHg) (bath temp.), yield, 430 mg.

Although the product (XVII) was found to be not a single compound by gas chromatography, the distillate was used for the next procedure without separation.

A mixture of XVII (0.43 g), $NH_2NH_2 \cdot H_2O$ (80%. 0.5 ml), KOH (1.0 g) and triethylene glycol was heated at 170—180° for 2 hr and at 200—210° for 3 hr. The cooled mixture was diluted with water (*ca.* 80 ml), extracted with ether, dried over Na_2SO_4 and evaporated the solvent. The oily residue was distilled *in vacuo* to give a colorless oil (180 mg), bp 90—130° (1 mmHg) (bath temp.). As it was found that the product was mainly composed of three components by gas chromatography, the distillate was separated by gas chromatography, and the major fraction, which would be the objective compound (XVIII), was collected. Yield, 50 mg. NMR (in $CDCl_3$) τ: 2.83—3.32 (3H, ABX-type pattern, $J_{AB}=9$ cps, $J_{AX}=3$ cps, $J_{BX}=0$ cps, arom. protons), 6.15 (3H, singlet, O–Me), 7.10—7.45 (3H, multiplet, C_1–H and C_4–methylene), 8.00—8.50 (6H, multiplet, C_2- and C_3-methylene and $-CH_2-CH_3$), 9.03 (3H, triplet, $J=7.0$ cps, $-CH_2-CH_3$).

A mixture of XVIII (37 mg) and Pd–C (10%, 50 mg) in a long test tube was heated at 280—310° for 20 min. The cooled mixture was extracted with ether. The residue of the ether extract was distilled *in vacuo* to give a colorless oil, bp 110—120° (1 mmHg) (bath temp.). The IR and NMR spectra of this distillate were superimposable with those of XV prepared from XIVa. An analytical sample was purified by gas chromatography. *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.74; H, 7.65.

1,3-Dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocin-11-one (XXI)——A mixture of 1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (XX) (11.6 g), $MeNH_2 \cdot HCl$ (4.89 g) and formalin (37%, 17.6 g) in AcOH (100 ml) was refluxed for 3.5 hr. After evaporation of the solvent *in vacuo*, the residue was mixed with dil. HCl, washed with $CHCl_3$, made alkaline with NaOH and extracted with $CHCl_3$. The chloroform extract was washed with water, dried over Na_2SO_4 and evaporated the solvent *in vacuo*. On adding *p*-toluenesulfonic acid in iso-PrOH to the residue, the crystalline tosylate precipitated as pale yellow leaves, mp 218—219°. The second crop was obtained by concentrating the mother liquor. The crystals were dissolved in water, made alkaline with K_2CO_3 and extracted with $CHCl_3$. After drying, the solvent was evaporated *in vacuo* to leave a crystalline mass. Recrystallization from EtOH gave colorless needles, mp 113°. Yield, 3.52 g. IR cm^{-1}: 2755 (N–Me) (KBr). *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.06; H, 7.91; N, 6.44.

1,3-Dimethyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (XXII)——A mixture of XXI (1.5 g), $NH_2NH_2 \cdot H_2O$ (80%, 2.02 g), KOH (2.0 g) in diethylene glycol was heated at 190—200° for 4 hr. After cooling, the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried over K_2CO_3 and evaporated the solvent to leave a pale brown oily residue. The crude product was purified as its picrate. Recrystallization of the picrate from MeOH gave yellow needles (1.35 g) melting at 224°. *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, 55.87; H, 5.26; N, 13.07.

From the picrate, free base (XXII) (0.44 g) was obtained as a colorless oil, bp 120—125° (3 mmHg) (bath temp.). IR cm^{-1}: 2750 (N–Me), no carbonyl band (liq.). *Anal.* Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.68; H, 9.52; N, 7.06.

1,2,5,6-Tetrahydro-1,5-methano-2-benzazocin-3(4*H*)-one (XXVII)——4-Oxo-1,2,3,4-tetrahydronaphthalen-2-acetic acid (XXIII) was prepared by the method of Stevenson, *et al.*[12] mp 104—109° (from ether–cyclohexane) (lit.[12] mp 110—111°). *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.60; H, 6.00.

XXIII (2.3 g) in EtOH (100 ml) was saturated with HCl gas under cooling with ice-bath and stood overnight. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, washed with $NaHCO_3$ solution and water, and dried over Na_2SO_4. The residue of the chloroform solution was distilled *in vacuo* to give a pale yellow oil (XXIV), bp 160—170° (1 mmHg) (bath temp.).

The distillate (1.2 g) in C_5H_5N (6 ml) was mixed with $NH_2OH \cdot HCl$ (0.5 g) in EtOH (6.0 ml), and then refluxed for 8 hr. After evaporation of the solvents, the residual syrup was dissolved in $CHCl_3$, and washed with 10% HCl, water and $NaHCO_3$ solution. Evaporation of the solvent left XXV (1.5 g) as a pale yellow syrup. The crude XXV (1.5 g) in AcOH (20 ml)–EtOH (20 ml) was shaken with PtO_2 (0.2 g) in H_2 atmosphere at room temperature. After removal of the catalyst and the solvents, the residue was dissolved in water, made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over Na_2SO_4. The residue left after evaporation of the solvent was heated at 160—170°/25 mmHg for 2 hr, then distilled *in vacuo*. The distillate, bp 180—230° (1 mmHg), was dissolved in $CHCl_3$ and extracted with 10% HCl. The chloroform layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent, crude XXVII (0.7 g) was

recrystallized from ether to give colorless cubes, mp 148—151°. IR cm^{-1}: ν_{NH} 3260; $\nu_{C=O}$1650 (KBr). *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.24; H, 6.84; N, 7.75.

1,2,3,4,5,6-Hexahydro-1,5-methano-2-benzazocine (XXVIII) and Its 2-Methyl Derivative (XXIX)——A mixture of XXVII (0.5 g) and $LiAlH_4$ (0.7 g) in dioxane (30 ml) was refluxed for 8.5 hr. After cooling, a small quantity of water and then Rochelle salt solution were added with chilling. The aqueous layer separated from the organic one was repeatedly extracted with $CHCl_3$ and the extracts were combined with the above organic layer. After drying over K_2CO_3, the solvents were evaporated *in vacuo*. The oily residue was distilled *in vacuo* to give XXVIII as colorless oil, bp 120—160° (1 mmHg) (bath temp.). Yield, 280 mg. IR cm^{-1}: ν_{NH} 3250 (broad), no carbonyl band (liq.).

A mixture of XXVIII (280 mg), formic acid (99%, 2.0 ml) and formalin (37%, 1.3 ml) was heated on a water bath for 1.5 hr. The mixture was diluted with 10% HCl (10 ml), washed with $CHCl_3$ and filtered. The filtrate was made alkaline with NaOH and extracted with ether. The residue left after drying and evaporation of the ethereal solution was distilled *in vacuo*, bp 80—100° (1 mmHg) (bath temp.). The distillate (240 mg) was chromatographed on alumina (10 g) column. An eluate fraction with benzene gave XXIX as a colorless oil, bp 90—105° (1 mmHg) (bath temp.). Yield, 150 mg. IR cm^{-1}: 2765 (N–Me) (liq.). NMR (in CCl_4) τ: 2.95—3.30 (4H, 6 peaks, arom. protons), 6.54(1H, triplet, $J=4$ cps, C_1–H), 6.70—9.00 (9H, complex multiplet, methylenes and methyne), 7.96 (3H, singlet, N–Me). Picrate: yellow fine needles, mp 181—184° (decomp.) (from MeOH). *Anal.* Calcd. for $C_{13}H_{17}N \cdot C_6H_3O_7N_3$: C, 54.80; H, 4.84; N, 13.46. Found: C, 54.95; H, 4.68; N, 13.45.

3-(β-Hydroxyethyl)-1,2,3,4-tetrahydroquinoline (XXXII)——To a suspension of $LiAlH_4$ (3.7 g) in tetrahydrofuran (40 ml) was added a solution of methyl 3,4-dihydrocarbostyril-3-acetate[13] (XXXI) (5.8 g) in the same solvent (60 ml) with stirring at room temperature, and refluxed for 1.5 hr. Rochelle salt solution (30 ml) was added to the cooled mixture, and the aqueous layer separated from the organic one was extracted with $CHCl_3$. The extract and the above organic layer were combined, dried over Na_2SO_4 and evaporated the solvents to give a solid mass. Recrystallization from ether afforded 3.8 g of XXXII as colorless needles, mp 91—92°. IR cm^{-1}: 3400—3100 (ν_{NH} and ν_{OH}), 1050 (C–OH) (KBr). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.81; H, 8.35; N, 7.75.

2,3,4,5-Tetrahydro-1,4-methano-1*H*-1-benzazepine (XXXIV)——A mixture of XXXII (2.0 g) and conc. HBr (saturated at 0°, 10 g) in a sealed tube was heated at 100° for 8 hr. After dilution with water, the reaction mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The chloroform extract was dried over Na_2SO_4 and evaporated *in vacuo* to leave a yellow oil (XXXIII) (2.5 g), which was used for the next procedure without purification.

A solution of XXXIII (2.5 g) in benzene was refluxed with K_2CO_3 (25 g) for 2 hr. After removal of inorganic materials by filtration, the filtrate was evaporated to give a pale brown oily residue, which was distilled *in vacuo*, bp 119—121° (0.3 mmHg). Yield, 1.25 g. The distillate showed no NH–, –OH and CH_2=CH–bands in the IR spectrum.

Picrate: yellow fine plates, mp 160.5—161.5° (from MeOH). *Anal.* Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.50; H, 4.27; N, 14.54.

1-Benzoyl-3-(β-benzoxyethyl)-1,2,3,4-tetrahydroquinoline (XXXV)——PhCOCl (9.6 g) was added to a solution of XXXII (5.5 g) in C_5H_5N (80 ml) with cooling and stood overnight. The reaction mixture was evaporate under reduced pressure at a temperature of below 60°. The residue was dissolved in $CHCl_3$, washed with 5% HCl and 5% NaOH, and evaporated the solvent to leave a crystalline mass. Recrystallization of the crude product from ether afforded colorless needles, mp 91—93°. Yield, 12.8 g. IR cm^{-1}: 1705, 1275, 1115 (PhCOO–), 1625 (PhCON=) (KBr).

1-Benzoyl-3-(β-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (XXXVI)——A mixture of XXXV (12.84 g), KOH (1.87 g) in EtOH (200 ml) was refluxed on a water bath for 1 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$, washed with 5% NaOH and water, and over Na_2SO_4. The residue of the chloroform solution was recrystallized from ether to give colorless needles, mp 117.5—119°. Yield, 7.4 g. IR cm^{-1}: ν_{OH} 3450, $\nu_{C=O}$1625, 1060 (C–OH) (KBr). *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.78; H, 6.76; N, 4.98. Found: C, 76.79; H, 7.03; N, 4.77.

1-Benzoyl-3-(β-cyanoethyl)-1,2,3,4-tetrahydroquinoline (XXXVIII)——To a solution of XXXVI (7.38 g) in CCl_4 (250 ml) was added PBr_3 (2.85 g) at room temperature, and the mixture was refluxed on a water bath for 2 hr. After cooling, water (50 ml) was added with stirring and the aqueous layer was extracted with ether. The organic layers were combined and washed with 10% $NaHCO_3$ solution and water. The residue (XXXVII) (7.02 g) of the dried solution was used for the next procedure.

A mixture of XXXVII (7.02 g) and KCN (1.33 g) in EtOH (250 ml) was refluxed for 7 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$ and washed with water. Evaporation of the solvent left a crystalline residue, which was recrystallized from ether–acetone to afford XXXVIII as colorless needles, mp 119—121°. Yield, 6.39 g. IR cm^{-1}: 2250 (–C≡N), 1625 (C=O) (KBr). *Anal.* Calcd. for $C_{19}H_{18}ON_2 \cdot 1/2H_2O$: C, 76.23; H, 6.40; N, 9.36. Found: C, 77.02; H, 6.22; N, 9.06.

Methyl 1,2,3,4-Tetrahydroquinoline-3-propionate (XXXIX)——A mixture of XXXVIII (3.04 g) in conc. HCl (12.5 ml)–AcOH (12.5 ml) in a sealed tube was heated at 150° for 15 hr. After evaporation of HCl

and AcOH, the residue was dissolved in water (80 ml), washed with benzene and evaporated to dryness *in vacuo*. The glassy residue was dissolved in MeOH (150 ml) and saturated with HCl gas, and stood overnight. After removal of the solvent, the residual syrup was dissolved in water (10 ml), basified with 5% NaOH and extracted with $CHCl_3$. The dried chloroform solution was evaporated and the residue was distilled *in vacuo*, bp 120—140° (1 mmHg) (bath temp.). Yield, 1.54 g. IR cm^{-1}: ν_{NH} 3450, $\nu_{C=O}$1710 (liq.).

3-(γ-Hydroxypropyl)-1,2,3,4-tetrahydroquinoline (XL)——To a suspension of $LiAlH_4$ (1.33 g) in dioxane (100 ml) was added a solution of XXXIX (1.54 g) in dioxane (50 ml) with stirring at room temperature, and the mixture was refluxed for 0.5 hr. To the cooled reaction mixture was added 20% Rochelle salt solution (50 ml) under chilling, and the mixture was extracted with $CHCl_3$. The residue of the dried chloroform solution was distilled *in vacuo*, bp 146—180° (2.5 mmHg) (bath temp.). Yield, 0.996 g. IR cm^{-1} ν_{NH} 3450—3350, 1055 (C–OH) (liq.).

3-(γ-Bromopropyl)-1,2,3,4-tetrahydroquinoline (XLI) Hydrobromide——A mixture of XL (0.996 g) and conc. HBr (saturated at 0°) (4.0 ml) in a sealed tube was heated at 100° for 11 hr. On evaporating the mixture to dryness, the residue solidified, which was recrystallized from MeOH to give colorless needles (1.4 g), mp 162—167° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}NBr \cdot HBr$: C, 43.01; H, 5.11; N, 4.18. Found: C, 42.80; H, 5.30; N, 4.22.

3,4,5,6-Tetrahydro-2*H*-1,5-methano-1-benzazocine (XLII)——A mixture of XLI form the hydrobomide (1.4 g) and KOH (2.7 g) in EtOH (150 ml) was refluxed on a water bath for 2 hr. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, washed with water and dried over K_2CO_3. The residue of the solution was distilled *in vacuo*, bp 80—100° (2 mmHg) (bath temp.). Yield, 0.485 g. The distillate showed no NH-, –OH and $CH_2=CH$– bands in the IR spectrum. This product showed a peak in the gas chromatogram and a spot in the thin-layer chromatogram (system: alumina, benzene–chloroform (20:5)). *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.22; H, 8.81; N, 8.31.

2,3,4,5-Tetrahydro-1,4-methano-1*H*-benzazepine (XLIV)——To a suspension of $LiAlH_4$ (362 mg) in tetrahydrofuran (5 ml) was added a solution of 4,5-dihydro-1,4-methano-1*H*-2-benzazepin-3(2*H*)-one[4b] (XLIII) (730 mg) in the same solvent at room temperature and refluxed for 3 hr. After cooling, 20% Rochelle salt solution (5 ml) was added, and extracted with $CHCl_3$. The oily residue of the dried chloroform solution was distilled *in vacuo* to give a colorless oil, bp 145—155° (10 mmHg) (bath temp.). Yield, 490 mg. IR cm^{-1}: 3300 (broad) (ν_{NH}), no carbonyl band (liq.).

2-Methyl-(XLV) and 2-Phenethyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (XLVI)——XLV: A mixture of XLIV (126 mg), HCO_2H (99%, 1 ml) and HCHO (37%, 1 ml) was heated on a water bath for 1.5 hr. Evaporation of the excess HCO_2H and HCHO left a yellow syrup, which was dissolved in 5% HCl and filtered. The clear filtrate was bsaified with NaOH, extracted with $CHCl_3$ and dried over K_2CO_3. The solvent was evaporated and the resulted yellow oil was distilled *in vacuo* to give a colorless oil, bp 110—125° (10 mmHg) (bath temp.). Yield, 50 mg. IR cm^{-1}: 2760 (N–Me) (liq.). Picrate: yellow needles, mp 174—177° (from MeOH). *Anal.* Calcd. for $C_{12}H_{15}N \cdot C_6H_3O_7N_3$: C, 53.73; H, 4.51; N, 13.93. Found: C, 54.05; H, 4.30; N, 13.49.

XLVI: A mixture of XLIV (214 mg), $PhCH_2CH_2Br$ (328 mg) and K_2CO_3 (900 mg) in benzene was refluxed under stirring. After cooling, the benzene solution was extracted with 10% HCl. The aqueous solution was basified with NaOH, extracted with $CHCl_3$ and dried over Na_2SO_4. The residue of the chloroform solution was distilled *in vacuo* to give a colorless oil, bp 160—190° (5 mmHg) (bath temp.). Yield, 237 mg. Picrate: yellow crystalline powder, mp 164.5—166° (from MeOH). *Anal.* Calcd. for $C_{19}H_{21}N \cdot C_6H_3O_7N_3$: C, 60.97; H, 4.91; N, 11.38. Found: C, 60.88; H, 4.64; N, 11.17.

11-Benzyl-8,9-dimethoxy-1,2,3,4,5,6-hexahydro-1,5-iminobenzocycloöctene (XLIX)——A mixture of 11-benzyl-8,9-dimethoxy-1,2,5,6-tetrahydro-1,5-iminobenzocycloöcten-3(4*H*)-one[14] (XLVIII) (1.2 g), $NH_2NH_2 \cdot H_2O$ (80%, 4,5 ml) and KOH (4.5 g) in triethylene glycol (30 ml) was heated at 180—200° for 4.5 hr. After cooling, the reaction mixture was diluted with water (*ca.* 200 ml) and extracted with $CHCl_3$. The chloroform extract was washed with water, dried over Na_2SO_4 and evaporated the solvent. The oily basic product was purified as its picrate. Recrystallization from AcOEt gave yellow prisms, mp 216—221°. *Anal.* Calcd. for $C_{21}H_{25}O_2N \cdot C_6H_3O_7N_3$: C, 58.69; H, 5.11; N, 10.14. Found: C, 58.92; H, 4.98; N, 10.13.

8,9-Dimethoxy-1,2,3,4,5,6-hexahydro-1,5-iminobenzcycloöctene (L)——A solution of XLIX (1.2 g) freed from the picrate and conc. HCl (1.0 ml) in EtOH (25 ml) was shaken with 40% Pd–C catalyst (200 mg) in H_2 atmosphere under heating with IR lamp, absorbing 90 ml of H_2 in about 6 hr. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in water, washed with benzene, made alkaline with Na_2CO_3 and extracted with $CHCl_3$. After drying over Na_2SO_4, the solvent was evaporated and the yellow oily residue (0.7 g) was purified as its hydrochloride. By recrystallization from MeOH–acetone the hydrochloride was obtained as colorless fine needles, mp 234—237°. *Anal.* Calcd. for $C_{14}H_{19}O_2N \cdot HCl$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.49; H, 7.22; N, 5.39.

8,9-Dimethoxy-11-methyl-1,2,3,4,5,6-hexahydro-1,5-iminobenzocycloöctene (LI)——A mixture of L (407 mg), formalin (37%, 2 ml) and formic acid (99%, 4 ml) was heated on a water bath for 1.5 hr. After evaporation of the excess fromalin and formic acid, the residue was dissolved in water and filtered. The filtrate was made alkaline with $NaHCO_3$, extracted with ether, dried over Na_2SO_4 and evaporated the solvent. The yellow oily residue was distilled *in vacuo* to give a colorless oil, bp 152—160° (0.07 mmHg) (bath

temp.). Yield, 366 mg. NMR (in $CDCl_3$)τ: 3.45 (1H, singlet), 3.55 (1H, singlet) (C_7–H and C_{10}–H), 6.15 (6H, singlet, 2×O–Me), 6.15—8.85 (10H, complex multiplet, methylenes and methynes), 7.65 (3H, singlet, N–Me). Picrate: yellow prisms, mp 203—204° (from AcOEt). *Anal.* Calcd. for $C_{15}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.01; H, 5.23; N, 11.63.

Ethyl 3-Carbethoxy-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-acetate (LIII)——A mixture ethyl of 3-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate[4f] (LII)(4.4 g), formic acid (99%, 1.3 ml) and formalin (37%, 1.2 ml) was heated on a water bath for 0.5 hr. After evaporation of the excess formic acid and formalin under diminished pressure, the residual syrup was dissolved in water, made alkaline with $NaHCO_3$, extracted with ether and dried over Na_2SO_4. The solvent was removed and the residue was distilled *in vacuo* to afford LIII as a colorless viscous oil, bp 185—195° (0.05—0.08 mmHg). Yield, 3.9 g.

7,8-Dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocyclohepten-3-one (LV)——To a suspension of NaH (50% oil dispersion, 1.297 g) in tetrahydrofuran (60 ml) was added dropwise a solution of LIII (3.945 g) in the same solvent (60 ml) at room temperature under N_2 atmosphere during 15 min with stirring, and then stirred at 65—70° for 7.5 hr. After cooling, AcOH (5 ml) in benzene (40 ml) was added and the solvents were evaporated under diminished pressure. The residue was mixed with water, made alkaline with $NaHCO_3$ and extracted with ether. The ethereal solution was extracted several times with 5% HCl. The aqueous layer was made alkaline with $NaHCO_3$, extracted with ether, dried over Na_2SO_4 and evaporated the solvent to give a crystalline mass (1.67 g). The crude product (LIV) was used for the next procedure without purification.

To a solution of LIV (1.67 g) in EtOH (55 ml) was added 3% HCl (65 ml) and refluxed for 5 hr. The solvents were evaporated *in vacuo*, and the residue was mixed with water. The aqueous solution was washed with $CHCl_3$, made alkaline with $NaHCO_3$, extracted with ether and dried over Na_2SO_4. After evaporation of the solvent, the residual crystalline mass was recrystallized from ether to give colorless needles melting at 121—122°. Yield, 620 mg. IR cm^{-1}: $\nu_{C=O}$ 1740 (KBr). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.83; H, 6.92; N, 5.68.

7,8-Dimethoxy-10-methyl-2,3,4,5-tetrahydro-1,4-imino-1*H*-benzocyclohepten-3-ol (LVI)——To a solution of LV (445 mg) in MeOH (8 ml) was added $NaBH_4$ (135 mg) in portions at room temperature with stirring during 1 hr, and then warmed at 45° for 1.5 hr. After cooling, AcOH (1 ml) in MeOH (4 ml) was added and the solvent was evaporated *in vacuo*. The residue was mixed with water, made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over Na_2SO_4. After evaporation of the solvent, the residual syrup was treated with a small amount of ether to give colorless crystals. Recrystallization from ether gave colorless plates, mp 147—149°. Yield, 335 mg. IR cm^{-1}: 3150 (ν_{OH}) (KBr). *Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.24; H, 7.67; N, 5.54.

Ethyl 4-Carbethoxy-1,2,3,4-tetrahydroisoquinoline-2-propionate (LIX)——A mixture of ethyl 1,2,3,4-tetrahydroisoquinoline-4-carboxylate[4e] (LVIII) (2.1 g) and ethyl acrylate (1.2 g) was stood overnight at room temperature, and diluted with ether. To the mixture was added a solution of oxalic acid in ethanol to deposit the oxalate. Recrystallization of the oxalate from acetone afforded colorless plates, mp 130.5—131.5°. Yield, 2.2 g. *Anal.* Calcd. for $C_{17}H_{23}O_4N \cdot C_2H_2O_4$: C, 57.71; H, 6.37; N, 3.54. Found: C, 57.68; H, 6.46; N, 3.29.

3,4-Dihydro-1*H*-2,6-methano-2-benzazocin-5(6*H*)-one (LX)——A solution of LIX from the oxalate (2.1 g) in toluene (15 ml) was added to a suspension of NaH (0.3 g) in toluene (15 ml) at 90° with stirring during 15 min. After stirring for an additional 1.5 hr at 110—120°, a solution of AcOH (1 ml) in benzene (10 ml) and then dil. $NaHCO_3$ solution was added. The organic layer was washed with water, dried over K_2CO_3 and evaporated to leave an oily residue (1.2 g), which gave violet color with ferric chloride.

The oily product (1.2 g) was dissolved in 10% HCl and heated on a water bath for 11.5 hr. After filtration with charcoal, the filtrate was basified with K_2CO_3 and extracted with $CHCl_3$. The pale brown residue of the dried chloroform solution was distilled *in vacuo* to give a colorless viscous oil, bp 125—135° (0.2 mmHg) (bath temp.). Yield, 611 mg. Picrate: yellow prisms, mp 229—232° (from acetone). *Anal.* Calcd. for $C_{12}H_{13}ON \cdot C_6H_3O_7N_3$: C, 51.92; H, 3.87; N, 13.46. Found: C, 52.21; H, 3.86; N, 13.23.

3,4,5,6-Tetrahydro-1*H*-2,6-methano-2-benzazocine (LXI)——A mixture of LX (0.5 g), $NH_2NH_2 \cdot H_2O$ (80%, 1.5 ml) and KOH (1.5 g) in triethylene glycol (10 ml) was heated at 160—180° for 2 hr and at 180—200° for 3 hr. After cooling, the mixture was diluted with water (100 ml) and extracted with $CHCl_3$. The yellow oily residue of the chloroform solution was distilled *in vacuo* to give LXI as a colorless oil, bp 90—100° (0.4 mmHg) (bath temp.). The distillate showed a peak in the gas chromatogram and a spot in the thin-layer chromatogram (system: alumina, chloroform). In the IR spectrum this product showed no carbonyl band. Picrate: yellow prisms, mp 150—152° (from acetone). *Anal.* Calcd. for $C_{12}H_{15}N \cdot C_6H_3O_7N_3$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.46; H, 4.39; N, 13.77.

2-Benzyl-4-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (LXIII)——To a suspension of $LiAlH_4$ (1.0 g) in tetrahydrofuran (20 ml) was added a solution of LXII[4e] (2.1 g) in tetrahydrofuran (5 ml) and stirred for 1.5 hr at room temperature. A solution of Rochelle salt in water was added, extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. The residue of the chloroform solution was purified as its picrate. Recrystallization from MeOH–AcOEt gave yellow needles melting at 131—133°. *Anal.* Calcd. for $C_{19}H_{21}ON \cdot$

$C_6H_3O_7N_3$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.22; H, 4.80; N, 10.72. The free base (LXIII) (0.9 g) was obtained from the picrate (2.0 g) as a colorless oil, bp 169—172° (0.08 mmHg) (bath temp.).

4,5-Dihydro-3*H*-2,5-methano-1*H*-2-benzazepine (LXVI)——A solution of LXIII (2.353 g) in MeOH (125 ml)–conc. HCl (5 ml) was shaken with 40% Pd–C in H_2 atmosphere and 410 ml of H_2 was absorbed at room temperature. After removal of the catalyst and solvent, the residual syrup was mixed with water, washed with benzene and filtered. The clear filtrate was basified with 10% NaOH, extracted with $CHCl_3$ and dried over K_2CO_3. The residue of the chloroform solution was distilled *in vacuo*, bp 130—155° (0.3 mmHg) (bath temp.).

The distillate (LXIV) (1.0 g) was mixed with conc. HBr (saturated at 0°) (1.5 ml) in a sealed tube and heated on a water bath for 7.5 hr. After cooling, the reaction mixture was diluted with water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The yellow oily residue (900 mg) of the dried chloroform solution was used for the next reaction without purification.

The above mentioned bromo–derivative (900 mg) in benzene (80 ml) was refluxed with K_2CO_3 (10 g) for 6 hr. After removal of the inorganic materials, the benzene solution was evaporated under reduced pressure and the residual oil was distilled *in vacuo*, bp 104—112° (5 mmHg) (bath temp.). Yield, 626 mg. This product showed no –NH, –OH and CH_2=CH– bands in the IR spectrum. Picrate: yellow needles, mp 164—167.5° (from MeOH). *Anal.* Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.29; H, 3.99; N, 14.09.

Methyl 3-Hydroximino-1,2,3,4-tetrahydro-1-naphthoate (LXIX)——A solution of 3-oxo-1,2,3,4-tetrahydro-1-naphthoic acid[4d] (LXVII) (4.2 g) and conc. HCl (20 ml) in MeOH (300 ml) was refluxed for 3.5 hr. After evaporation of the excess methanol, the residual yellow oil was dissolved in ether, washed with dil. $NaHCO_3$ solution and dried over Na_2SO_4. The residue of the ethereal solution was distilled *in vacuo* to give LXVIII as a pale yellow oil, bp 142—146° (0.8 mmHg). Yield, 3.14 g. IR cm^{-1}: $\nu_{C=O}$ 1710 (liq.).

A mixture of LXVIII (3,1 g), $NH_2OH \cdot HCl$ (2.38 g), C_5H_5N (10 ml) and MeOH (55 ml) was refluxed on a water bath for 3 hr. After evaporation of the solvents under reduced pressure, the residual pale green syrup was dissolved in ether. The ether solution was washed with dil. HCl, dil. $NaHCO_3$ and water. The residue of the dried ethereal solution solidified on standing. Recrystallization from ether gave colorless fine needles, mp 94.5—96.5°. Yield, 1.5 g. IR cm^{-1}: ν_{OH} 3400—3000, $\nu_{C=O}$ 1705 (KBr). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74: H, 5.98; N, 6.39. Found: C, 65.48; H, 6.13; N, 6.20.

4,5-Dihydro-1,4-methano-1*H*-3-benzoazepin-2(3*H*)-one (LXX)——LXIX (1.2 g) in AcOH (20 ml)– MeOH (20 ml) was shaken with H_2 over Pt–catalyst prepared from $PtO_2 \cdot 2H_2O$ (200 mg) and 275 ml of H_2 was absorbed. After removal of the catalyst and solvent, the yellow oily residue was mixed with water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The chloroform extract was washed with water, dried over Na_2SO_4 and evaporated. The brown residue (0.91 g) was heated at 150°/20 mmHg for 1.5 hr and then distilled *in vacuo* to give a pale yellow viscous oil, bp 180—220° (2—3 mmHg). The distillate (0.62 g) solidified on standing was recrystallized from ether to afford colorless needles, mp 124—127°. IR cm^{-1}: ν_{NH} 3250–3050, $\nu_{C=O}$ 1665 (KBr). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.55; H, 6.02; N, 7.77.

2,3,4,5-Tetrahydro-1,4-methano-1*H*-3-benzazepine (LXXI)——To a suspension of $LiAlH_4$ (1.2 g) in tetrahydrofuran (50 ml) was added a solution of LXX (1.5 g) in the same solvent and refluxed for 2 hr. To the cooled reaction mixture was added a solution of Rochelle salt, and the aqueous layer separated from the organic one was extracted with $CHCl_3$. The organic layer and the extract were combined, dried over K_2CO_3 and evaporated the solvents. The light–brown oily residue was distilled *in vacuo* to give a pale yellow oil, bp 132—143° (10 mmHg) (bath temp.). Yield, 1.3 g. IR cm^{-1}: ν_{NH} 3300, no carbonyl band. Picrate: yellow plates, mp 175—178.5° (from AcOEt). *Anal.* Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.49; H, 4.52; N, 14.70.

3-Methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (LXXII)——A mixture of LXXI (0.361 g), formalin (37%, 2 ml) and formic acid (99%, 3 ml) was heated on a water bath for 1 hr. After evaporation of the excess formalin and formic acid under diminished pressure, the residue was dissolved in dil. HCl and filtered. The filtrate was basified with K_2CO_3, extracted with $CHCl_3$. The residue of the dried chloroform solution was distilled *in vacuo* to give colorless oil, bp 120—125° (10 mmHg) (bath temp.). Yield, 0.29 g. IR cm^{-1}: 2760 (N–Me) (liq.). Picrate: yellow cubes, mp 123—126° (from MeOH). *Anal.* Calcd. for $C_{12}H_{15}N \cdot C_6H_3O_7N_3$: C, 53.73; H, 4.51; N, 13.93. Found: C, 53.55; H, 4.52; N, 13.63.

8-Nitro-(LXXIIIa) and 7-Nitro-3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (LXXIIIb)——A solution of LXXII (0.8 g) in AcOH (2.5 ml) was added to a mixture of HNO_3 (d: 1.50, 5 ml) and AcOH (3 ml) with stirring at 2—5° during 2 hr, and stood overnight. The acids were evaporated *in vacuo* at a bath temperature below 60°, and the residue was basified with aqueous ammonia and extracted with ether. The residue (0.97 g) of the dried ether solution was dissolved in acetone (10 ml) and added to a solution of picric acid (1.4 g) in acetone (15 ml). The yellow crystals deposited were recrystallized from acetone to give picrate of LXXIIIa as yellow prisms, mp 205—208°. Yield, 1.0 g. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2 \cdot C_6H_3O_7N_3$: C, 48.32; H, 3.83; N, 15.66. Found: C, 48.62; H, 3.89; N, 15.59.

On concentrating the first mother liquor, crude crystals of picrate of LXXIIIb were obtained. Recrystallization from acetone gave the pure picrate as yellow prisms, mp 172—174°. Yield, 274 mg. *Anal.*

Calcd. for $C_{12}H_{14}O_2N_2 \cdot C_6H_3O_7N_3$: C, 48.32; H, 3.83; N, 15.66. Found: C, 48.56; H, 3.94; N, 15.61. Free base LXXIIIa: pale yellow oil. IR cm^{-1}: 1520, 1345 ($-NO_2$). Free base LXXIIIb: pale yellow oil. IR cm^{-1}: 1515, 1345 ($-NO_2$).

8-Methoxy-(LXXVa) and 7-Methoxy-3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (LXXVb)——LXXVa: LXXIIIa (475 mg) was derived to the corresponding hydroxyl derivative (LXXIVa) by the same method as described for XIIa from XIa. mp 204—206°, colorless crystalline powder from acetone. Yield, 250 mg. *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.93; H, 8.21; N, 7.38.

LXXIVa was converted to its methyl ether (LXXVa) with CH_2N_2 in the usual manner. bp 65—80° (0.03 mmHg) (bath temp.), colorless oil. IR cm^{-1}: 1045, 1265 (C–OMe), 1230 (unassignable) (liq.).

LXXVb: From LXXIIIb (120 mg) the hydroxyl derivative (LXXIVb) was afforded by the same method as described for XIIb and the crude hydroxyl derivative was converted to its methyl ether (LXXVb) with CH_2N_2 in the usual manner. bp 80—90° (0.04 mmHg) (bath temp.), pale yellow oil. IR cm^{-1}: 1040, 1260 (C–OMe) (liq.). This product showed a peak in the gas chromatogram.

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