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Studies on Diazabenzobicyclo[3.3.1]nonane System. VIII.[1] Synthesis of 8,9-Dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-2,6-imino-3-benzazocin-4(3*H*)-one

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A synthetic route of 8,9-dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-2,6-imino-3-benzazocin-4(3*H*)-one (IX-B) having a new ring system was described.

3-(3,4-Dimethoxyphenyl)alanine ethyl ester (I) was condensed with diethyl malonate followed by cyclization with phosphoryl chloride to give ethyl 1-carbethoxymethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (III), which was reduced to ethyl 3-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (IV). N-benzoyl derivative (V) of IV was cyclized by a Dieckmann condensation to a tricyclic β-ketoester (VI), which was derived to 7,8-dimethoxy-10-benzoyl-4,5-dihydro-1*H*-1,4-iminobenzocyclohepten-3(2*H*)-one (VII) by treating with dil. HCl. A Beckmann rearrangement of the oxime (VIII) of VII gave 8,9-dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-1,5-imino-3-benzazocin-4(3*H*)-one (IX-A) and IX-B.

In connection with our studies on diazabenzobicyclo[3.3.1]nonane system, now we wish to report the synthesis of 8,9-dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-2,6-imino-3-benzazocin-4(3*H*)-one (IX-B) by a Beckmann rearrangement of 7,8-dimethoxy-10-benzoyl-4,5-dihydro-1*H*-1,4-iminobenzocyclohepten-3(2*H*)-one oxime (VIII).

The scheme of the synthesis from 3-(3,4-dimethoxyphenyl)alanine ethyl ester (I)[3] is shown in Chart 1.

Thus I was condensed with diethyl malonate to form N-(carbethoxyacetyl)-3-(3,4-dimethoxyphenyl)alanine ethyl ester (II).

The Bischler-Napieralski cyclization of II to form the B-ring by the conventional procedure heating with phosphoryl chloride or phosphorus pentoxide in toluene gave only a resinous product, but the desired product ethyl 1-carbethoxymethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (III) was most conveniently obtained by treating the amide with phosphoryl chloride at 10—15° for 2—3 days. The structure of III in which the newly created double bond is exocyclic[4] was confirmed by the fact that in the nuclear magnetic resonance spectrum III showed an NH-proton singal at 0.6τ (singlet 1H) and an olefin-proton signal at 4.85τ (singlet 1H).

III was catalytically reduced over Adams catalyst to give ethyl 3-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (IV). The configuration of IV was not examined, since not only the *cis*- but also *trans*-isomer, through epimerization at position 3, would give the same β-ketoester by Dieckmann reaction.[5]

The N-benzoyl derivative (V) of IV was treated with sodium hydride in boiling tetrahydrofuran to give a cyclic β-ketoester (VI). The ketoester gave bluish purple color with

1) Part VII: S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 761 (1967).
2) Location: *Gofuku, Toyama.*
3) I. Murakoshi, *Yakugaku Zasshi*, **76**, 1139 (1956).
4) N.A. Nelson, K.O. Gelotte, Y. Tamura, H.B. Sinclair, J.M. Schuck, V.J. Bauer, and R.W. White, *J. Org. Chem.*, **26**, 2599 (1961); W. Schneider and K. Schilken, *Arch. Pharm.*, **286**, 389 (1963).
5) N. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **12**, 1478 (1964).

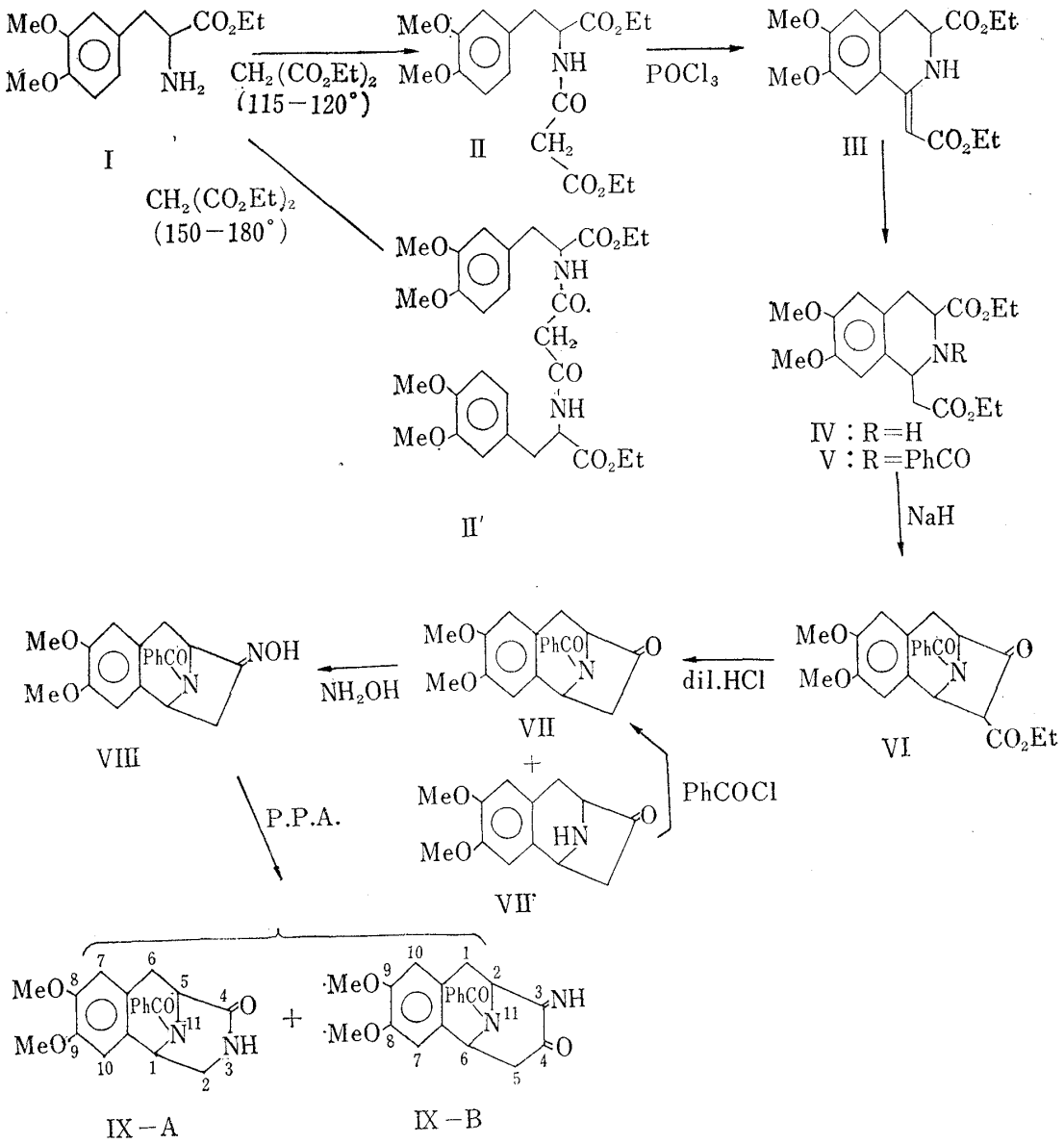


Chart 1

ferric chloride, and showed three $\nu_{C=O}$ bands at 1730 cm^{-1} (five-membered cyclic ketone), 1690 cm^{-1} (ester carbonyl) and 1620 cm^{-1} (amide carbonyl) in the infrared spectrum.

The β-ketoester was treated with diluted hydrochloric acid to afford 7,8-dimethoxy-10-benzoyl-4,5-dihydro-1*H*-1,4-iminobenzocyclohepten-3(2*H*)-one (VII).

Beckmann rearrangement of the oxime (VIII) of VII to form tricyclic lactam also presented some difficulty. Treatment with 75%-, 85%- and 98%-sulfuric acid, tosyl chloride in pyridine or phosphorus pentachloride in chloroform gave the starting oxime and/or a resinous product. However, treatment of the oxime with polyphosphoric acid at 90—100° for 15 minutes gave two reaction products: (IXa) colorless plates mp 143—146° (from benzene) and (IXb) colorless needles mp 216—218° (from benzene).

The molecular formulas of IXa and IXb were confirmed by the elemental and the mass spectral analyses to be $C_{20}H_{20}O_4N_2 \cdot C_6H_6$[6] for IXa and $C_{20}H_{20}O_4N_2$ for IXb. In the mass spectra both IXa and IXb showed fragments at *m/e* 294, 247, 189, 105 and 77 understandable

6) After heating at 120—130°/0.1 mmHg for 24 hr, IXa showed mp 259—260° and its elemental analysis supported the molecular formula $C_{20}H_{20}O_4N_2$.

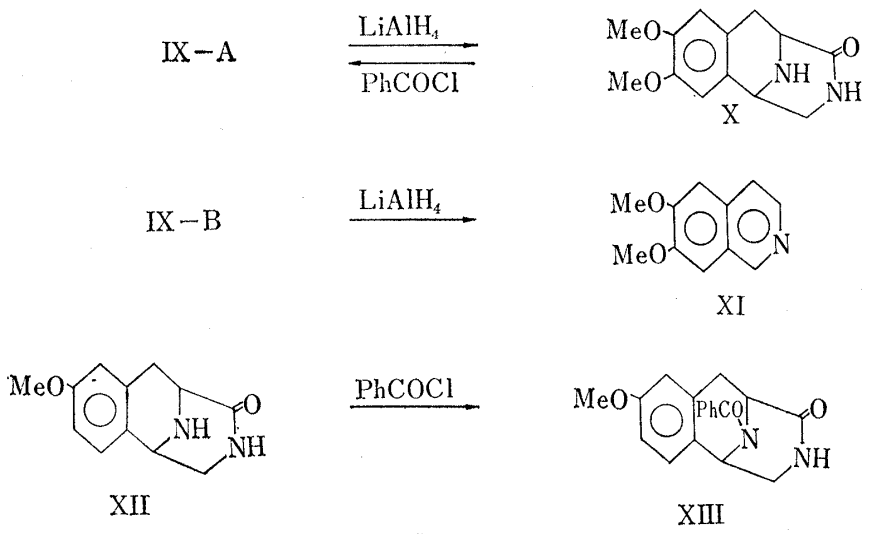
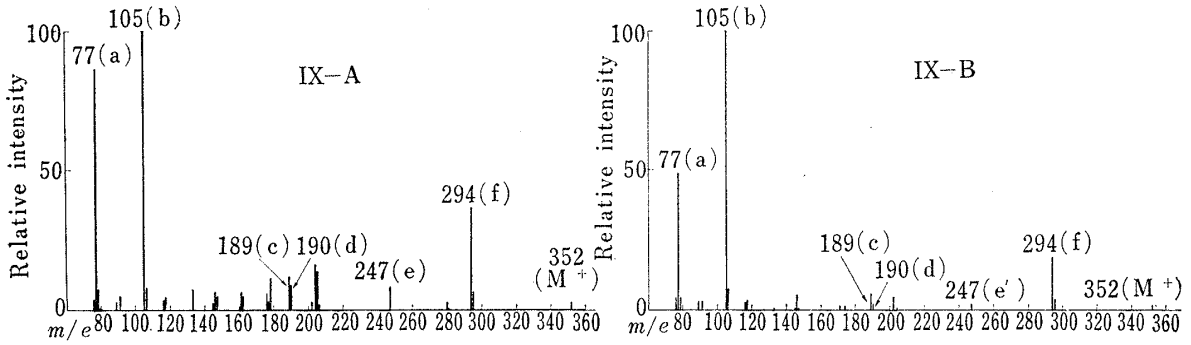


Chart 2

as ions shown in Fig. 1, which supported that both compounds possess N-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline skeleton. In the infrared spectra, both showed two $\nu_{C=O}$ bands (1645 cm^{-1} and 1625 cm^{-1} for IXa and 1640 cm^{-1} and 1620 cm^{-1} for IXb), respectively, which were assignable to six-membered lactam and benzamide carbonyl groups.

The absorption at 3μ region of IXa was much similar to that of 8-methoxy-11-benzoyl-1,2,5,6-tetrahydro-1,5-imino-3-benzazocin-4(3*H*)-one (XIII), and suggested the presence of hydrogen bonded amide grouping. Moreover, multiplet signals at 6.3—7.7τ in the nuclear magnetic resonance spectrum of IXa suggested the presence of -$\underline{CH_2}$-NH-CO- and Ar-$\underline{CH_2}$-, while the signals at 7.0—7.5τ and at ~4.0τ of IXb the presence of -$\underline{CH_2}$-CO-, Ar-$\underline{CH_2}$- and -CO$\underline{N}$-$\underline{C}$$\underline{H}$-$\underline{N}$CO-.

Thus, the structures of IXa and IXb were ascribed to 8,9-dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-1,5-imino-3-benzazocin-4(3*H*)-one (IX-A) and 8,9-dimethoxy-11-benzoyl-1,2,5,6-tetrahydro-2,6-imino-3-benzazocin-4(3*H*)-one (IX-B), respectively.



a : Ph^+ , b : $[Ph{\cdot}C{=}O]^+$, c : , d : , e : , e' : , f :

Fig. 1. Mass Spectra of IX-A and IX-B

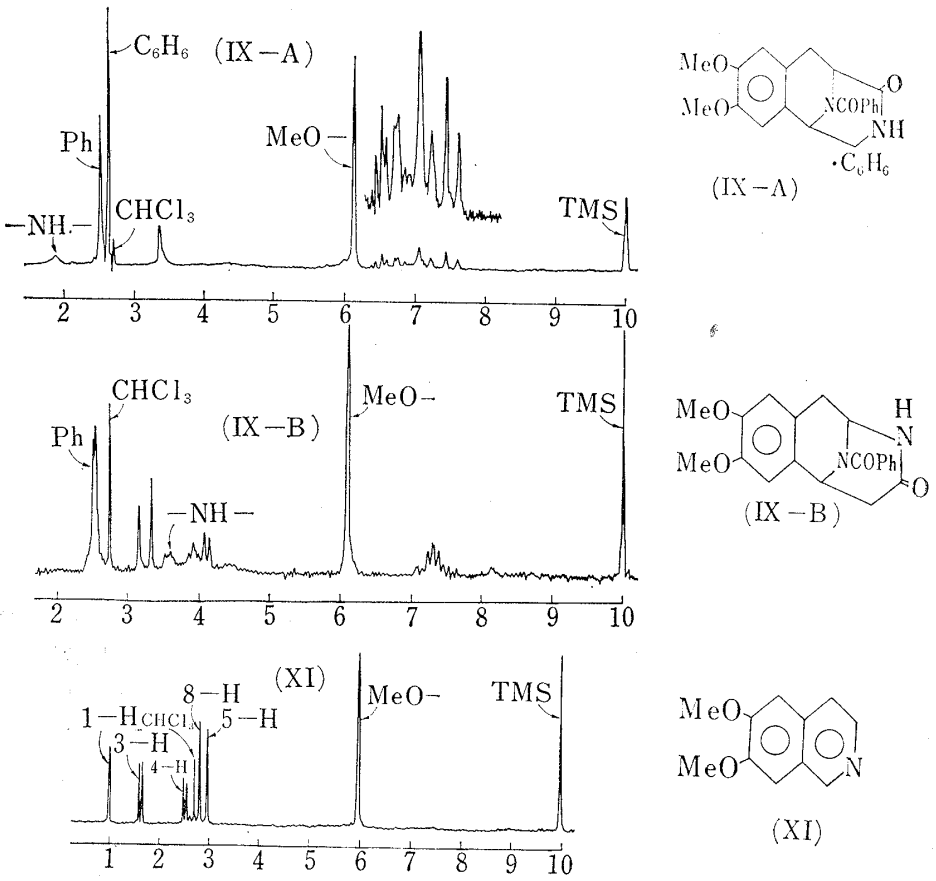


Fig. 2. NMR Spectra of IX–A, IX–B and XI (in $CDCl_3$, 100 Mc)

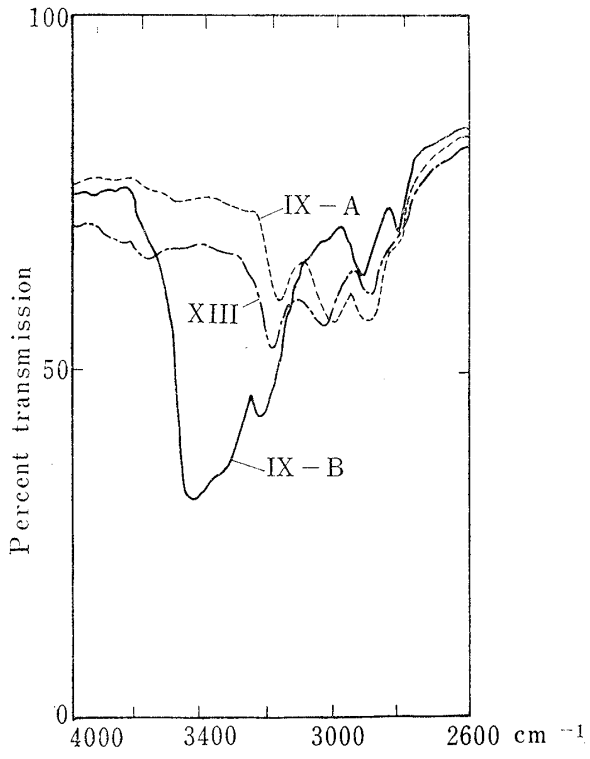


Fig. 3. IR Spectra of IX–A, XI–B and XIII (KBr)

While treatment of IX–A with lithium aluminum hydride gave 8,9–dimethoxy–1,2,5,6–tetrahydro-1,5-imino-3-benzazocin–4(3*H*)–one (X), the reaction of IX–B with the same reagent gave 6,7–dimethoxyisoquinoline (XI) which was identified by nuclear magnetic resonance spectrum of the base and elemental analysis of the picrate.

A reaction course for this result may be depicted as follows: At the first stage of the reaction, lithium aluminum hydride attacks the benzoyl group at 11–position of IX–B to give an amide anion (a), and this is reasonable from the fact that the reaction of IX–A with lithium aluminum hydride gave X. At the successive stages, the anion center of the intermediate (a) would transfer to the methylene carbon at 5–position giving an anion (b) under cleavage of C_5–C_6 bond. Hydrogen at 1–position would be removed to the C_5–methylene giving an anion (c), from which acetamide anion (d) would be eliminated affording 6,7–dimethoxyisoquinoline (XI).

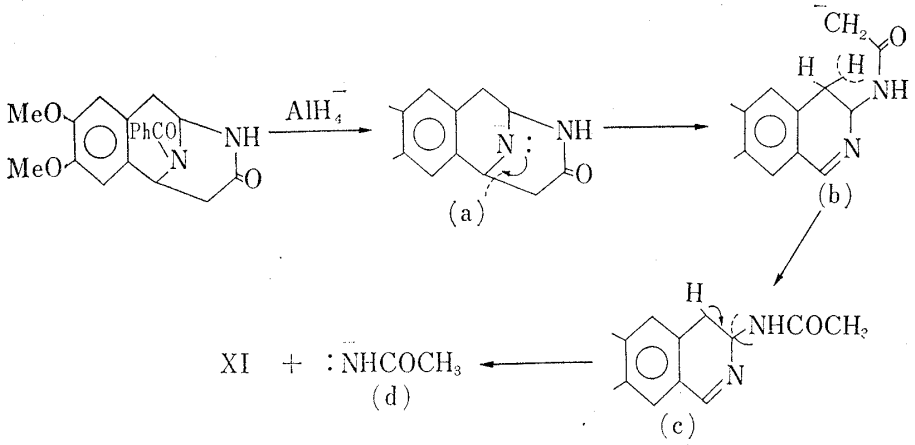


Chart 3

Experimental[7]

N-Carbethoxyacetyl-3-(3,4-dimethoxyphenyl)alanine Ethyl Ester (II)——A solution of 3,4-dimethoxyphenylalanine ethyl ester (I)[3] (2.1 g) in diethyl malonate (40 ml) was heated at 115—120° for *ca.* 1 hr under stirring. After removal of the excess diethyl malonate, the crystalline residue was purified by recrystallization from ether to show mp 73—74° (colorless needles), yield 2.6 g. IR cm^{-1}: ν_{NH} 3320; $\nu_{C=O}$ 1620, 1710 (KBr). *Anal.* Calcd. for $C_{18}H_{25}O_7N$: C, 58.84; H, 6.86; N, 3.81. Found: C, 59.08; H, 7.03; N, 3.34.

When this condensation was carried out at 150—180°, bis-amide derivative (II′) was afforded. mp 141—142° (colorless needles, from ethanol). IR cm^{-1}: ν_{NH} 3250; $\nu_{C=O}$ 1630, 1720 (KBr). *Anal.* Calcd. for $C_{29}H_{38}O_{10}N_2$: C, 60.61; H, 6.67; N, 4.88. Found: C, 60.39; H, 6.59; N, 5.12.

Ethyl 1-Carbethoxymethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (III)——A mixture of II (100 mg) and $POCl_3$ (0.5 ml) was kept at 10—13° for 112 hr. After evaporation of the excess $POCl_3$, the pale yellow residue was treated with few drops of EtOH and then with chilled 10% HCl. The aqueous solution was washed with benzene, made alkaline with $NaHCO_3$, extracted with chloroform and dried over Na_2SO_4. After evaporation of the solvent, the crystalline residue was recrystallized from ether; mp 131—131.5° (pale yellow needles), yield 50 mg. IR cm^{-1}: ν_{NH} 3230; $\nu_{C=O}$ 1710 (KBr). *Anal.* Calcd. for $C_{18}H_{23}O_6N$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.71; H, 6.33; N, 4.01.

Ethyl 3-Carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (IV)——III (3.85 g) in AcOH (100 ml)–EtOH (100 ml) was shaken with H_2 over Pt-catalyst prepared from $PtO_2 \cdot 2H_2O$ (350 mg) and 250 ml of H_2 was absorbed at room temperature. The catalyst was removed by filtration, filtrate was evaporated *in vacuo*. The yellow oily residue was dissolved in water, made alkaline with $NaHCO_3$, extracted with ether, washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residual syrup was distilled *in vacuo*. A fraction of bp 183—186° (0.0003—0.0006 mmHg) solidified on standing was recrystallized from ether; mp 77—78° (colorless cubes), yield 3.4 g. IR cm^{-1}: ν_{NH} 3400; $\nu_{C=O}$ 1700 (KBr). *Anal.* Calcd. for $C_{18}H_{25}O_6N$: C, 61.51; H, 7.17. Found: C, 60.96; H, 7.07.

Ethyl 2-Benzoyl-3-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (V)——A mixture of IV (3.4 g) and PhCOCl (1.25 g) in C_5H_5N (150 ml) was stood in a refrigerator overnight. After evaporation of the solvent, the residue was dissolved in chloroform, washed with 5%–HCl, aqueous $NaHCO_3$ and water. After drying over Na_2SO_4, chloroform was evaporated and the residue was recrystallized from ether to give colorless needles melting at 110—111.5°. Yield 3.26 g. IR cm^{-1}: $\nu_{C=O}$ 1620, 1720 (KBr). *Anal.* Calcd. for $C_{25}H_{29}O_7N$: C, 65.92; H, 6.42: N, 3.08. Found: C, 65.97; H, 6.70; N, 2.76.

Ethyl 3-Oxo-7,8-dimethoxy-10-benzoyl-2,3,4,5-tetrahydro-1*H*-1,4-iminobenzocycloheptene-2-carboxylate (VI)——To a suspension of NaH (50% oil dispersion, 440 mg) in tetrahydrofuran (30 ml) was added dropwise a solution of V (1.392 g) in the same solvent (30 ml) at room temperature under N_2 atmosphere during 15 min with stirring, and then stirred at 60—70° for 7.5 hr. After cooling, AcOH (5 ml) in benzene (40 ml) was added and the solvents were evaporated *in vacuo*. The residue was mixed with water and extracted with ether. The ethereal solution was washed with water, dried over Na_2SO_4 and evaporated the solvent to give a crystalline mass. The crude product was recrystallized from ether to give colorless cubes melting at 145—146°, which gave bluish purple color with 5% $FeCl_3$–EtOH solution. Yield 526 mg. IR cm^{-1}: $\nu_{C=O}$ 1620, 1690, 1730 (KBr). *Anal.* Calcd. for $C_{23}H_{23}O_6N$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.33; H, 5.71; N, 2.64.

7) All melting points are uncorrected.

7,8-Dimethoxy-10-benzoyl-4,5-dihydro-1*H*-1,4-iminobenzocyclohepten-3(2*H*)-one (VII)——VI (1.15 g) was dissolved in EtOH (40 ml)–dil. HCl (3.5%, 40 ml) and refluxed for 7 hr. After removal of the solvents, the residue was dissolved in 10% HCl (10 ml) and extracted with ether. The aqueous layer was made alkaline with $NaHCO_3$, extracted with chloroform and dried (Na_2SO_4). The above ethereal layer was washed with aqueous $NaHCO_3$ solution and dried (Na_2SO_4). The alkaline aqueous layer was acidified with HCl and extracted with chloroform.

From the first chloroform solution, a crystalline product (VII′) melting at 146—147°(from ether) was obtained, yield 163 mg. IR cm^{-1}: $\nu_{C=O}$ 1710; ν_{NH} 3300 (KBr). *Anal.* Calcd. for $C_{18}H_{15}O_3N$: (7,8–Dimethoxy–4,5–dihydro–1*H*–1,4–iminobenzocyclohepten–3(2*H*)–one): C, 66.93; H, 6.48; N, 6.01. Found: C, 67.19; H, 6.62; N, 6.27.

From the second chloroform solution, benzoic acid was obtained (identified with authentic sample by IR spectrum), yield 51 mg.

From the ethereal solution a colorless glassy residue of VII was obtained, which was used for the next procedure without purification. Yield 730 mg.

Benzoylation of VII′ with PhCOCl as described for the preparation of V gave VII (identified by IR spectrum).

7,8-Dimethoxy-10-benzoyl-4,5-dihydro-1*H*-1,4-iminobenzocyclohepten-3(2*H*)-one Oxime (VIII)——A mixture of VII (682 mg), $NH_2OH \cdot HCl$ (200 mg) and AcONa (236 mg) in 50% EtOH (60 ml) was refluxed for 3.5 hr on a water bath. After evaporation of the solvents, the solid residue was dissolved in chloroform and washed with dil. $NaHCO_3$, 5% HCl and water. The residue of the dired chloroform solution was recrystallized from ether–*n*–hexane to give colorless powdered crystals (VIIIa), mp 115—120°, yield 488 mg. Recrystallization of VIIIa from benzene gave colorless cubes (VIIIb) melting at 195—198°. VIIIa and VIIIb were interconvertable in crystallization. Though the infrared spectra of VIIIa and VIIIb in KBr tablet were not identical, those in chloroform and the nuclear magnetic resonance spectra in deuteriochloroform were found to be completely superimposable, respectively.[8] *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.67; H, 5.91; N, 7.61.

Beckmann Rearrangement of VIII——A mixture of VIIIb (1.0 g) and polyphosphoric acid (prepared from 15.0 g of P_2O_5 and 15.0 g of 80% H_3PO_4) was heated on a water bath under manual stirring with a glass–rod for 15 min. The light brown reaction mixture was poured onto ice, diluted with water and extracted with chloroform. The chloroform solution was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to afford a solid residue. The residue was fractionally recrystallized from benzene to give colorless plates (IX–A), mp 143—146° (335 mg) and colorless needles (IX–B), mp 216—218° (208 mg).

IX–A: *Anal.* Calcd. for $C_{20}H_{20}O_4N_2 \cdot C_6H_6$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.16; H, 5.88; N, 6.55. The crystal benzene of IX–A was removed by heating at 120—130°/0.1 mmHg for 24 hr, and mp changed to 259—260°. *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.15; H, 5.60; N, 7.73.

IX–B: *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.40; H, 5.61; N, 8.05.

Reduction of IX-A with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (180 mg) in tetrahydrofuran (30 ml) was added a solution of IX–A (178 mg) in the same solvent (30 ml) and refluxed for 30 min on a water bath. 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 chloroform and the extracts were combined with the above organic layer . After drying over K_2CO_3, the solvents were evaporated *in vacuo*. The solid residue was recrystallized from methanol to give colorless needles, mp 189—190°, yield 33 mg. IR cm^{-1}: ν_{NH} 3340, 3260; $\nu_{C=O}$ 1620 (KBr). *Anal.* Calcd. for $C_{13}H_{16}O_3N_2$ (8,9–Dimethoxy–1,2,5,6–tetrahydro–1,5–imino–3–benzazocin–4(3*H*)–one (X)): C, 62.89; H, 6.50; N, 11.28. Found: C, 62.43; H, 6.57; N, 11.24.

Benzoylation of X with PhCOCl as described for the preparation of V gave IX–A (identified by IR spectrum and mixed melting point measurement).

Treatment of IX-B with Lithium Aluminum Hydride——A solution of IX–B (180 mg) in tetrahydrofuran (30 ml) was added to a suspension of $LiAlH_4$ (180 mg) in the same solvent (30 ml) and warmed at 38—39° for 15 min on a water bath. After cooling, the reaction mixture was treated as described for the reaction of IX–A with $LiAlH_4$. Ether soluble material (95 mg) of the crude product was chromatographed on Al_2O_3 (4.7 g) column. An eluate fraction with benzene gave XI as a colorless oil, bp 80—100° (0.01 mmHg) (bath temp.), yield 23 mg. Picrate: mp 230—232° (decomp., yellow needles). *Anal.* Calcd. for $C_{11}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 48.81; H, 3.37; N, 13.39. Found: C, 48.94; H, 3.41; N, 13.11.

8-Methoxy-11-benzoyl-1,2,5,6-tetrahydro-1,5-imino-3-benzazocin-4(3*H*)-one (XIII)——A mixture of 8–methoxy–1,2,5,6–tetrahydro–1,5–imino–3–benzazocin–4(3*H*)–one (XII)[9] (708 mg) and PhCOCl (827 mg) in C_5H_5N was refluxed for 8 hr. After removal of C_6H_5N, the residual syrup was dissolved in chloroform and washed with 5% HCl, 5% NaOH and water. The residue of the dried (Na_2SO_4) chloroform solution was

8) From these facts, it is most probable that VIIIa and VIIIb would be dimorphous.
9) S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **86**, 169 (1966).

recrystallized from benzene to give colorless fine needles, mp 184—185°, yield 430 mg. *Anal.* Calcd. for $C_{19}H_{18}O_3N$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.73; H, 5.03; N, 8,80.

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