[Chem. Pharm. Bull. 15(6) 761~767 (1967)]

UDC 547.836.07

92. Shunsaku Shiotani and Kemmotsu Mitsuhashi: Studies on Diazabenzobicyclo[3.3.1]nonane System. Ⅶ.*1 Synthesis of 1,2,3,4,5,6-Hexahydro-1,5-methanobenzo[*e*][1,2]diazocine Derivatives and an Example of Abnormal Cleavage of Hydrazide by Lithium Aluminum Hydride.

(*Faculty of Pharmaceutical Sciences, University of Toyama**2)

3-Oxo-1,2,3,4-tetrahydro-1-naphthoic acid obtained by reduction of 3-methoxy-1-naphthoic acid with sodium amalgam was condensed with N-methyl-N-acetylhydrazine to give the corresponding hydrazone (Ⅷ). Ⅷ was submitted to catalytic reduction over Adams catalyst, methylation with formic acid-formalin, hydrolysis with hydrochloric acid, esterification with methanol and intramolecular cyclization to afford 3,4-dimethyl-3,4,5,6-tetrahydro-1,5-methanobenzo[*e*][1,2]diazocin-2(1*H*)-one (Ⅻ).

Treatment of Ⅻ with lithium aluminum hydride gave an abnormally cleft product, 4-methyl-5,6-dihydro-1*H*,4*H*-1.5-methanobenzo[*e*][1,2]diazocine (XVⅡ). XVⅡ was reduced with lithium aluminum hydride to give 4-methyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo-[*e*][1,2]diazocine (XVⅢ).

Structures of Ⅻ, XVⅡ and XVⅢ were confirmed by chemical as well as spectral methods.

(Received July 25, 1966)

In continuation of our previous papers, in which we reported the syntheses of six kinds of skeletons, A, B, C, D, E and F, of diazabenzobicyclo[3.3.1]nonane system, we

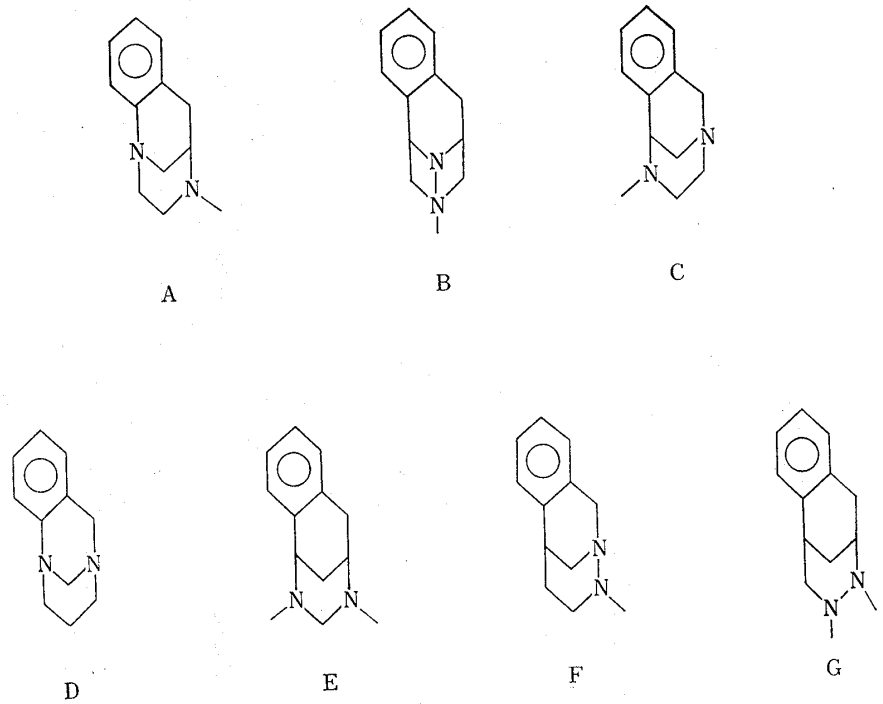


Chart 1.

*1 Part Ⅵ. S. Shiotani, T. Hori, K. Mitsuhashi: This Bulletin, **15**, 88 (1967).
*2 Gofuku, Toyama (塩谷俊作, 三橋監物).

1) H. Cassebaum: Ber., **90**, 2886 (1957).
2) G. J. Leick, R. P. Perkins: J. Am. Chem. Soc., **51**, 1831 (1929).
3) M. J. S. Dewar, P. J. Grisdale: *Ibid.*, **84**, 3541 (1962).

now wish to report the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1.2]diazocine (G) derivatives and an example of abnormal cleavage of hydrazide with lithium aluminum hydride.

Reduction of 3-methoxy-1-naphthoic acid (Ⅵ)[4] with one molar equivalent of 3% sodium amalgam, which was prepared by the route shown in Chart 2, gave

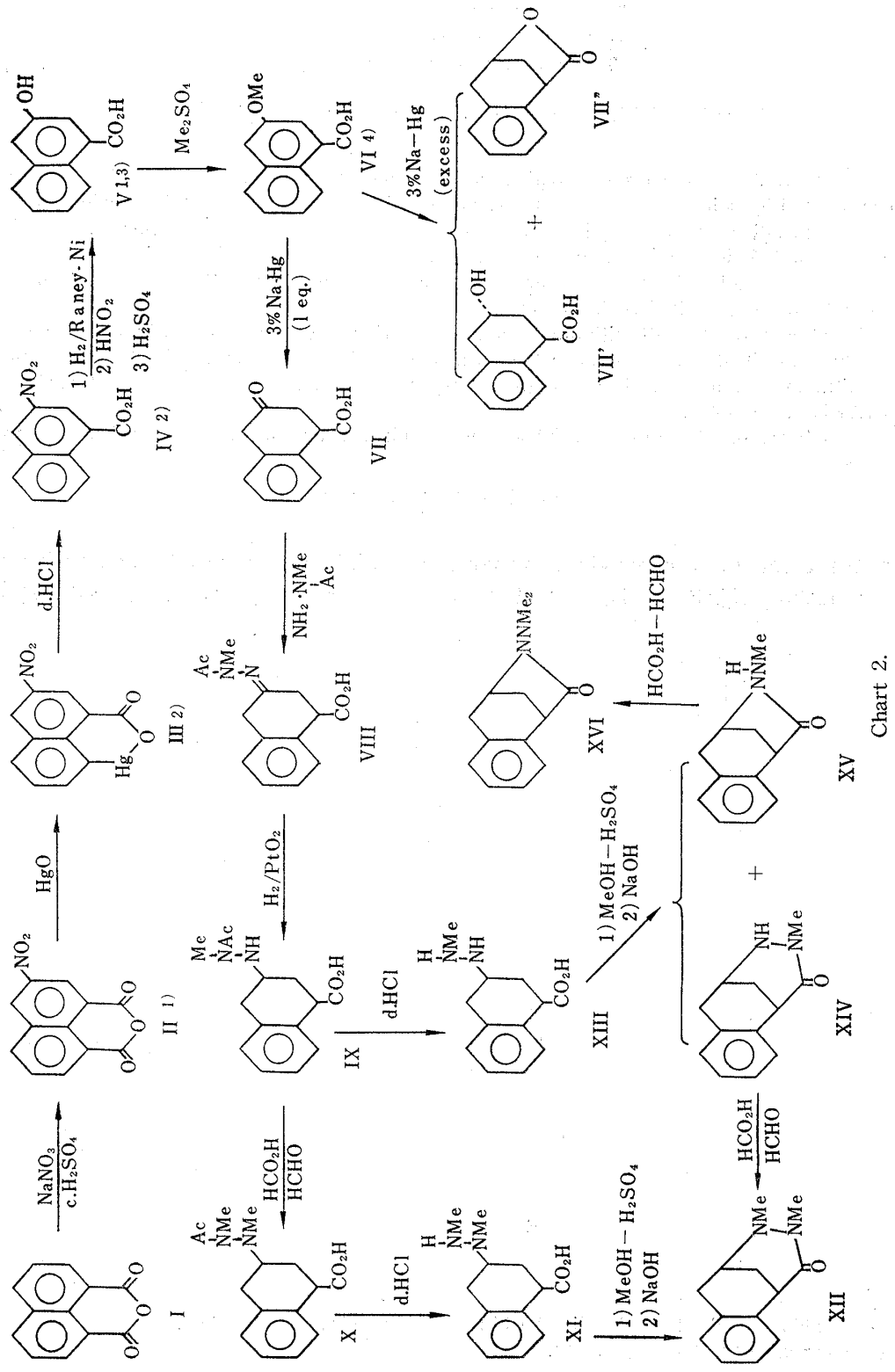


Chart 2.

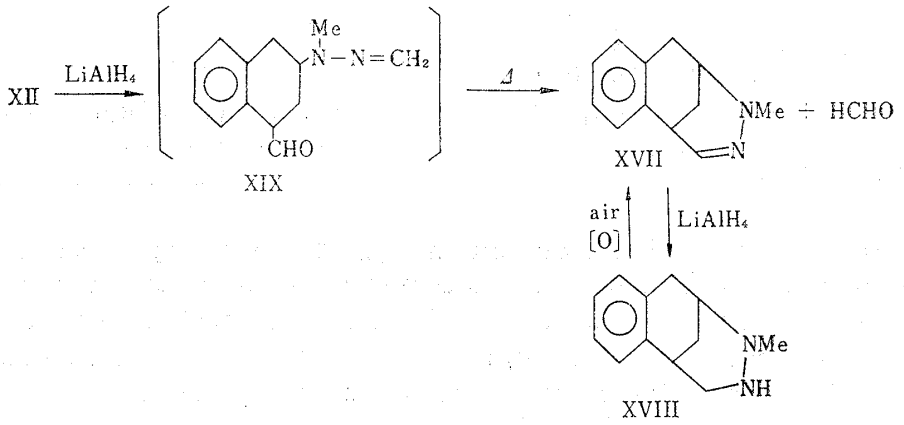
4) R. Lesser, G. Gad: Ber., **58**, 2553 (1925).

3-oxo-1,2,3,4,-tetrahydro-1-naphthoic acid (Ⅶ); whereas, use of an excess of the amalgam gave overreduced products, *trans*-3-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid (Ⅶ′) and the lactone of the *cis*-isomer (Ⅶ″).

Condensation of Ⅶ with N-methyl-N-acetylhydrazine[5] afforded the corresponding hydrazone (Ⅷ), $C_{14}H_{16}O_3N_2$, m.p. 189~192°. The hydrazone was derived to 3,4-dimethyl-3,4,5,6-tetrahydro-1,5-methanobenzo[*e*][1,2]diazocin-2(1*H*)-one (Ⅻ) by the following procedures.

Catalytic reduction of Ⅷ over Adams catalyst in acetic acid gave 3-(N-methyl-N-acetylhydrazino)-1,2,3,4-tetrahydro-1-naphthoic acid (Ⅸ), whose N′-methyl derivative (Ⅹ) was obtained by Clarke-Eschweiler method. Without any purification, Ⅹ was refluxed with 20% hydrochloric acid to give 3-(N,N′-dimethylhydrazino)-1,2,3,4-tetrahydro-1-naphthoic acid (Ⅺ). Ⅺ was esterified with methanol-sulfuric acid, followed by intramolecular cyclization to give Ⅻ, m.p. 114~117°. An alternative route for this preparation was carried out to confirm the structure of Ⅻ.

Ⅸ was hydrolized by refluxing with 20% hydrochloric acid to give 3-(N-methylhydrazino)-1,2,3,4-tetrahydro-1-naphthoic acid (ⅩⅢ) which was esterified, followed by cyclization to give a mixture of 3-methyl-3,4,5,6-tetrahydro-1,5-methanobenzo[*e*][1,2]-diazocin-2(1*H*)-one (XIV) and 3-methylamino-3,4-dihydro-5*H*-1,4-methano-3-benzazepin-2(1*H*)-one (XV), which were separated by column chromatography on alumina. Both



cf.

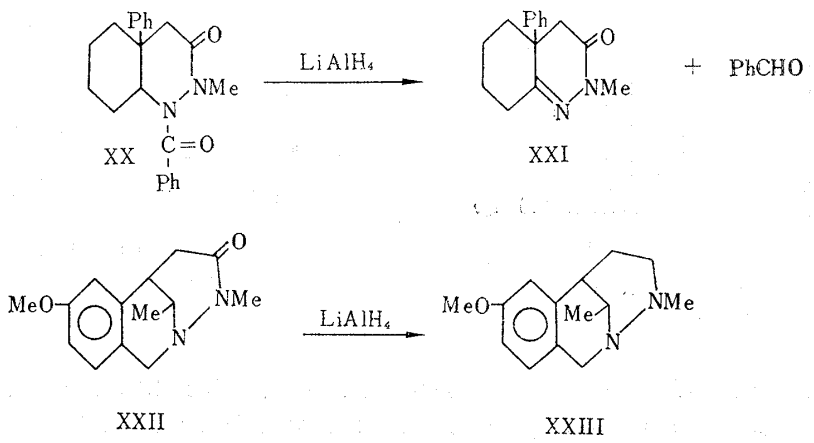


Chart 3.

5) K. Ronco, B. Prijs, H. Erlenmeyer : Helv. Chim. Acta, **39**, 1253 (1956).

compounds were methylated by Clarke-Eschweiler method to give XII and 3-dimethylamino-3,4-bihydro-5*H*-1,4-methano-3-benzazepin-2(1*H*)-one (XVI), respectively.

Treatment of the cyclic hydrazide, XII, with lithium aluminum hydride in ether for about 3~5 minutes gave a mixture of several compounds, from which only one compound (XVII), a colorless oil boiling at 85~90°/0.03 mm., was isolated by column chromatography on alumina in about 20% yield. Infrared spectrum of XVII showed no $\nu_{C=O}$ bands. The elemental analysis suggested a molecular formula, $C_{12}H_{14}N_2$ (molecular weight : 186.25). The mass spectrum analysis, giving parent peak at m/e 186 and isotope abundance data : p : p+1 : p+2=100 : 12.7 : 0.95, also supported this molecular formula. Moreover, fragment at m/e 95 was understandable as N-methylpyridazinium ion, which supports XVII as a pyridazine derivative. In nuclear magnetic resonance spectrum XVII showed a N-CH_3 signal (6.90τ, 3H, singlet) and an olefinic proton signal (3.33τ, 1H, doublet, J=3.0 c/s). Based on the above said evidences, structure of XVII was confirmed as 4-methyl-5,6-dihydro-1*H*,4*H*-1,5-methanobenzo[*e*][1,2]diazocine.

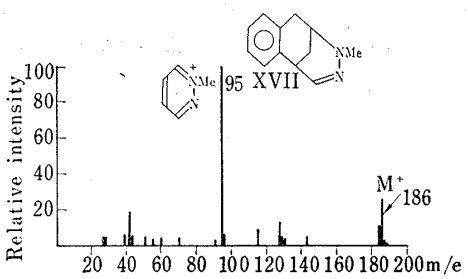


Fig. 1. Mass Spectrum of XVII

Hitachi Mass Spectrometer
Model RMU 6C.

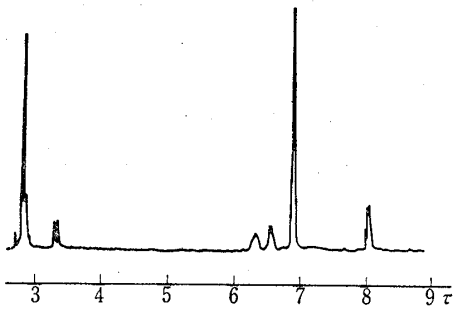


Fig. 2. Nuclear Magnetic Resonance Spectrum of XVII

JNM 4H-100 at 100 Mc.

XVII was reduced with lithium aluminum hydride to afford a colorless oil (XVIII), b.p. 75~85°/0.05 mm., whose structure was confirmed by the following spectral data. In nuclear magnetic resonance spectrum, XVIII showed no olefinic proton signal. The mass spectrum gave parent peak at m/e 188 and isotope abundance data : p : p+1 : p+2=100 : 14.4 : 1.2. The infrared spectrum showed a ν_{NH} band at 3190 cm^{-1}. XVIII was air-sensitive and dehydrogenated by air oxidation to reproduce XVII.

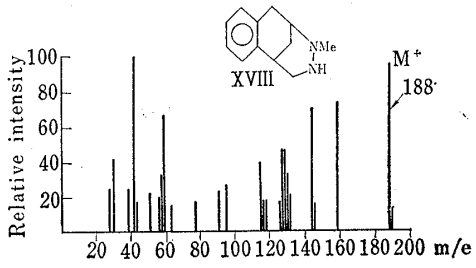


Fig. 3. Mass Spectrum of XVIII

Hitachi Mass Spectrometer
Model RMU 6C.

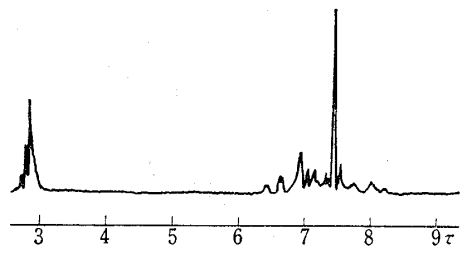


Fig. 4. Nuclear Magnetic Resonance Spectrum of XVIII

JNM 3H-60 at 60 Mc.

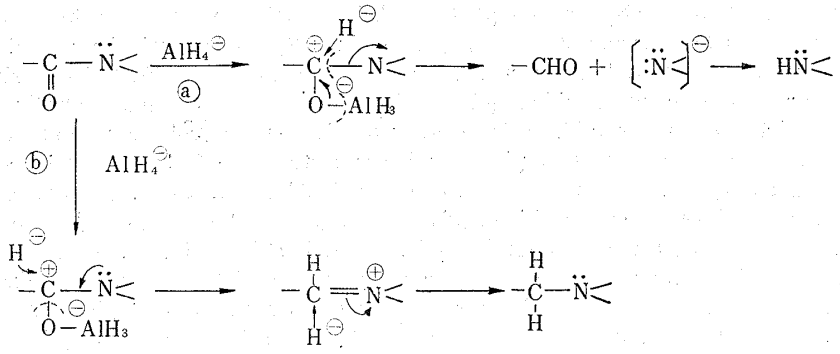
It would be reasonable that in the reaction of XII with lithium aluminum hydride XVII was formed through an intermediated, XIX, and the possibility of the formation of XIX was supported by the following observations. As shown in Fig. 5., the thin-layer chromatogram of XVII on alumina was different from that of the crude product treated without heating. The crude product showed a $\nu_{C=O}$ band at 1705 cm^{-1} in the

infrared spectrum. When the crude product was heated on a water bath, formaldehyde was evolved.

Fig. 5. Thin-layer Chromatograms on Alumina

Solvent: $CHCl_3$
1: Crude reaction product of XII with $LiAlH_4$ treated without heating.
2: XVII.

The formation of XIX would be similar to that of 2-methyl-4a-phenyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (XXI) in the reaction of 1-benzoyl-2-methyl-4a-phenyldecahydro-3-cinnolinone-(XX) with lithium aluminum hydride.[6] On the other hand, it is well known that some amides are cloven with lithium aluminum hydride to yield the carbonyl derivative and the starting amine; and for this cleavage a mechanism illustrated in Chart 4 is admitted.[7]



ⓐ : abnormal cleavage.
ⓑ : normal reduction.

Chart 4.

Thus, a mechanism for the reactions of XII and XX with lithium aluminum hydride may be postulated (Chart 5). The carbonyl group is attacked by aluminum hydride ion to form an intermediate (a), followed by cleavage of the C-N bond to afford the aldehyde and the hydrazide anion (b). The hydrogen on the carbon adjacent to N_1 in the anion is removed as a hydride anion by AlH_3 or its equivalents giving the corresponding hydrazone derivative.

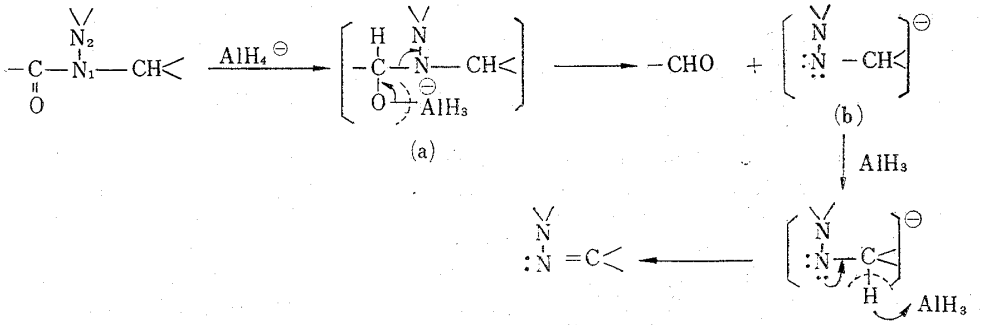


Chart 5.

In the preceeding paper,*1 we reported that 4,11-dimethyl-9-methoxy-1,2-dihydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocin-3(2*H*)-one (XXII), a cyclic hydrazide, was normally

6) K. Mitsuhashi, S. Shiotani: Yakugaku Zasshi, **80**, 1348 (1960).
7) N.G. Gaylord: Experientia, **10**, 166 (1954), *Idem*: "Reduction with complex metal hydride," Interscience Publishers, Inc., New York, p. 546 (1956).

reduced with lithium aluminum hydride to yield 4,11-dimethyl-9-methoxy-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocine (XXIII). As it is difficult to suggest a suitable reason for this discrepancy at present, we hope to report with further investigation.

Experimental*3

3-Oxo-1,2,3,4-tetrahydro-1-naphthoic Acid (VII)——A mixture of 3-methoxy-1-naphthoic acid[4] (7.2 g.) and 3% Na-Hg (60 g.) in 10% NaOH solution (150 ml.) was refluxed for 8 hr. The aqueous layer was acidified with conc. HCl and refluxed for 1 hr. After cooling, the reaction mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. The residue (6.8 g.) of the $CHCl_3$ solution was recrystallized from Me_2CO-ether to give VII, m.p. 150~152°(colorless needles). Yield, 4.5 g. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.25; H, 5.36.

***trans*-3-Hydroxy-1,2,3,4-tetrahydro-1-naphthoic Acid (VII′) and the Lactone of the *cis*-Isomer (VII″)**——A mixture of VI (1.4 g.) and 3% Na-Hg (25 g.) in 10% NaOH solution (30 ml.) was refluxed for 3 hr. The aqueous layer was treated as described for the preparation of VII. The residue (0.67 g.) of the $CHCl_3$ extract was chromatographed on silica gel (50 g.) column. A first eluate fraction with C_6H_6–$CHCl_3$ (3:2) gave crystals which were recrystallized from ether to give VII″ as colorless sandy crystals, m.p. 97~101°. Yield, 240 mg. IR ν_{max}^{KBr} cm^{-1}: 1755 (five-membered lactone). NMR_{CDCl_3}: 2.8 τ singlet (4H, arom.), 4.95 τ quintet (1H, C_3-H, $J_{2,3}$=6.0 c/s, $J_{3,4}$=2.9 c/s), 6.15 τ doublet (1H, C_1-H, $J_{1,2}$=6.0 c/s), 6.87 τ doublet (2H, C_4-H, $J_{3,4}$=2.9 c/s), 7.19~8.09 τ multiplet (2H, C_2-H, $J_{A,B}$=12.0 c/s, $J_{1,2}$=$J_{2,3}$=6.0 c/s, $J_{1,2'}$=$J_{2',3}$=0 c/s). *Anal.* Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.69; H, 5.56.

A second eluate fraction with the same solvent gave crystals which were recrystallized from AcOEt to give VII′ as colorless needles, m.p. 142~144°. Yield, 182 mg. After heating at 170~180° for 10~15 minutes, the melting point of VII′ did not change. IR ν_{max}^{KBr} cm^{-1}: 3300~2500 (broad, carboxylic OH), 1680 (-CO_2H). *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.77; H, 6.07.

N-Methyl-N-acetylhydrazone (VIII) of VII——A mixture of VII (1.3 g.) and N-methyl-N-acetylhydrazine[5] (0.8 g.) in EtOH (30 ml.) was allowed to stand at room temperature for 3 days. The solvent was removed under reduced pressure and the residue was recrystallized from AcOEt to give VIII as colorless sandy crystals, m.p. 189~192°. Yield, 1.1 g. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.34; H, 6.32; N, 10.60.

3,4-Dimethyl-3,4,5,6-tetrahydro-1,5-methanobenzo[*e*][1,2]diazocin-2(1*H*)-one (XII) and 3-Methylamino-3,4-dihydro-5*H*-1,4-methano-3-benzazepin-2(1*H*)-one (XV)——a) VIII (8.5 g.) in AcOH (100 ml.) was shaken with Adams catalyst (0.5 g.) in a H_2 atmosphere. Hydrogenation was completed in 3 hr. with absorption of 750 ml. of H_2. The catalyst was removed by filtration and the solvent was evaporated to leave a viscous material (IX). IX was heated with formic acid (47 ml.) and formalin (35%, 37 ml.) on a water bath for 1 hr. After evaporation of the excess formic acid and formalin under reduced pressure, the residue was refluxed with 20% hydrochloric acid (300 ml.) for 6.5 hr. The solvent was removed under reduced pressure to the dryness and the residual syrupy material was refluxed with MeOH (800 ml.) and conc. H_2SO_4 (35 ml.) for 5 hr., and the solvent was removed *in vacuo*. To the residue water (*ca.* 300 ml.) was added and the solution was filtered with charcoal. The filtrate was made alkaline with NaOH under chilling, extracted with $CHCl_3$ several times, dried over K_2CO_3 and the solvent was evaporated. The residue was recrystallized from ether to give XII, m.p. 114~117° as colorless needles. Yield, 1.5 g. IR ν_{max}^{KBr} cm^{-1}: 1660. NMR_{CCl_4}: 7.13 τ singlet (3H, N_3-Me), 7.41 τ singlet (3H, N_4-Me). *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.31; H, 7.41; N, 12.61.

b) Crude IX prepared from 100 mg. of VIII was refluxed with 20% hydrochloric acid (15 ml.) for 5 hr. After removal of the solvent, the residue was refluxed with MeOH (10 ml.) and conc. H_2SO_4 (0.5 ml.) for 3 hr., evaporated the solvent, dissolved in water, made alkaline with NaOH and extracted with $CHCl_3$. The crude viscous residue (58 mg.) of the extract was chromatographed on alumina (12 g.) column.

A first eluate fraction with C_6H_6 gave crystals which were recrystallized from petr. ether to give XV as colorless needles, m.p. 120~123.5°. Yield, 28 mg. *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.67; H, 6.88; N, 13.92. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1680 (five-membered lactam). XV (75 mg.) was heated with formic acid (0.5 ml.) and formalin (35%, 0.3 ml.) on a water bath for 1 hr. The reaction mixture was diluted with water and made alkaline with NaOH, extracted with $CHCl_3$ and dried over K_2CO_3. After removal of the solvent, the residue was distilled *in vacuo* to give XVI, $b.p._{0.06\sim0.08}$ 120°(bath temp.). The distillate solidified on standing, m.p. 69~71.5°. Yield, 70 mg. IR ν_{max}^{KBr} cm^{-1}: 1705. NMR_{CCl_4}: 7.33 τ singlet (6H, 2×N-Me).

A second eluate fraction with C_6H_6 gave crystals which were recrystallized from petr. ether to give XIV as colorless needles, m.p. 128~129°. Yield, 27 mg. IR ν_{max}^{KBr} cm^{-1}: 3270 (NH), 1625 (six-membered

*3 All melting points and boiling points are uncorrected.

lactam). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.56; H, 7.10; N, 13.58. XIV (22 mg.) was methylated as described for the preparation of XVI from XV to afford a crystalline product melting at 114~117°. Yield, 22 mg. The melting points of the product and XII were not depressed by admixture and their IR spectra were shown to be superimposable.

4-Methyl-5,6-dihydro-1*H*,4*H*-1,5-methanobenzo[*e*][1,2]diazocine (XVII)——A mixture of XII (182 mg.) and $LiAlH_4$ (30 mg.) in ether (30 ml.) was swirled for 5 min. at room temperature. The excess $LiAlH_4$ was decomposed with Rochelle salt solution and the aqueous layer was extracted with ether several times. The organic layer and the extracts were combined, dried over K_2CO_3 and the solvent was evaporated *in vacuo* at 0~10°. The residue (174 mg.) was distilled *in vacuo* and the distillate boiling at 90~100°/0.04 mm. was chromatographed on alumina (5 g.) column. An eluate fraction with C_6H_6 gave XVII as a colorless oil, $b.p_{0.03}$ 80~85°. Yield, 40 mg. *Anal.* Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.48; H, 7.75; N, 14.83.

4-Methyl-1,2,3,4,5,6,-hexahydro-1,5-methanobenzo[*e*][1,2]diazocine (XVIII)——A mixture of XVII (95 mg.) and $LiAlH_4$ (100 mg.) in ether was swirled for 5 min. at room temperature. The excess $LiAlH_4$ was decomposed with Rochelle salt solution and the aqueous layer was extracted with ether. The organic layer and the extracts were combined, dried over K_2CO_3 and the solvent was evaporated *in vacuo*. The residue was distilled *in vacuo* to give XVIII as a colorless oil, $b.p_{0.05}$ 75~85°. These treatments were carried out in a N_2 atmosphere.

Air Oxidation of XVIII——Air was bubbled into a solution of XVIII (83 mg.) in C_6H_6 under refluxing for 4 hr. After evaporation of the solvent, the residue was chromatographed on alumina (10 g.) column. An eluate fraction with C_6H_6 gave a colorless oil, $b.p_{0.04}$ 80~85°, which was identified with XVII by IR spectrum and thin-layer chromatography. Yield, 65 mg.

The authors expess their gratitude to Prof. Toshihiko Okamoto of University of Tokyo for his kind and helpful advice. They are grateful to the members of the Central Analysis Room of Faculty of Pharmaceutical Sciences, University of Tokyo, the members of the Elemental Analysis Center of Kyoto University and Mr. M. Morikishi of this Faculty for the elemental analyses. Thanks are also due to Dr. T. Ibuka of Kyoto University for mass spectral measurements, and Mr. T. Matsuoka for his technical help.