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45. Shunsaku Shiotani and Kemmotsu Mitsuhashi: Studies on Diazabenzobicyclo[3.3.1]nonane System. IV.*1 Synthesis of 1,2,3,4,5,6,-Hexahydro-1,5-methanobenzo[*e*][1,3]diazocine Derivatives.

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The present work is a part of our synthetic research of diazabenzobicyclo [3.3.1] nonane system which would be expected to possess an analgesic and/or other pharmacological activities. In the previous papers, we reported the syntheses of 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*e*][1,4]diazocine (A),[1] 3,4-dihydro-2*H*,6*H*-1,5-methanobenzo[*b*][1,5]diazocine (B),[2] 1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (C),*1 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*f*][1,4]diazocine (D)[3] and some derivatives of them.

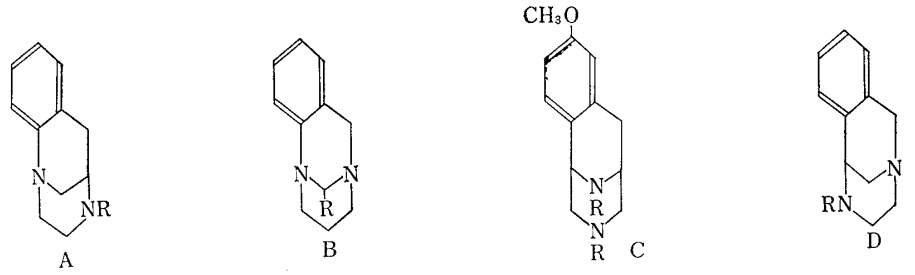

Chart 1.

This paper deals with the synthesis of some derivatives of 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine. As a key intermediate for this synthetic purpose, *cis*-1,2,3,4-tetrahydro-1,3-naphthalenediamine (V) was chosen because most of the hexahydropyrimidines[4] are obtained by condensation of 1,3-propanediamine derivatives and a carbonyl compound, and this method could be applied to the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine skeleton. However, there was no evidence as to how the *cis*-1,3-diamine (V) and its N,N′-dialkyl derivatives behave when allowed to react with aldehydes.[5] Molecular models of the *cis*-1,3-diamines reveal that some conformations may exist in which the nitrogen atoms are close together while in others they are far apart. Then, one might expect the condensation reactions with the *cis*-1,3-diamines to yield cyclic products, polymers, or a mixture of both.

For the preparation of the *cis*-1,3-diamine (V) we found that it would be advantageous to perform the following routs as outlined in Chart 2.

Catalytic reduction of methyl 4-hydroximino-1,2,3,4-tetrahydro-2-naphthoate (I)[6] over Adams catalyst in methanol-acetic acid afforded an oily basic product. As it would be expected that the reduction product would consist of methyl *cis*-4-amino-1,2,3,4-tetrahydro-2-naphthoate (II) and the *trans*-isomer (II′), and that the *cis*-isomer

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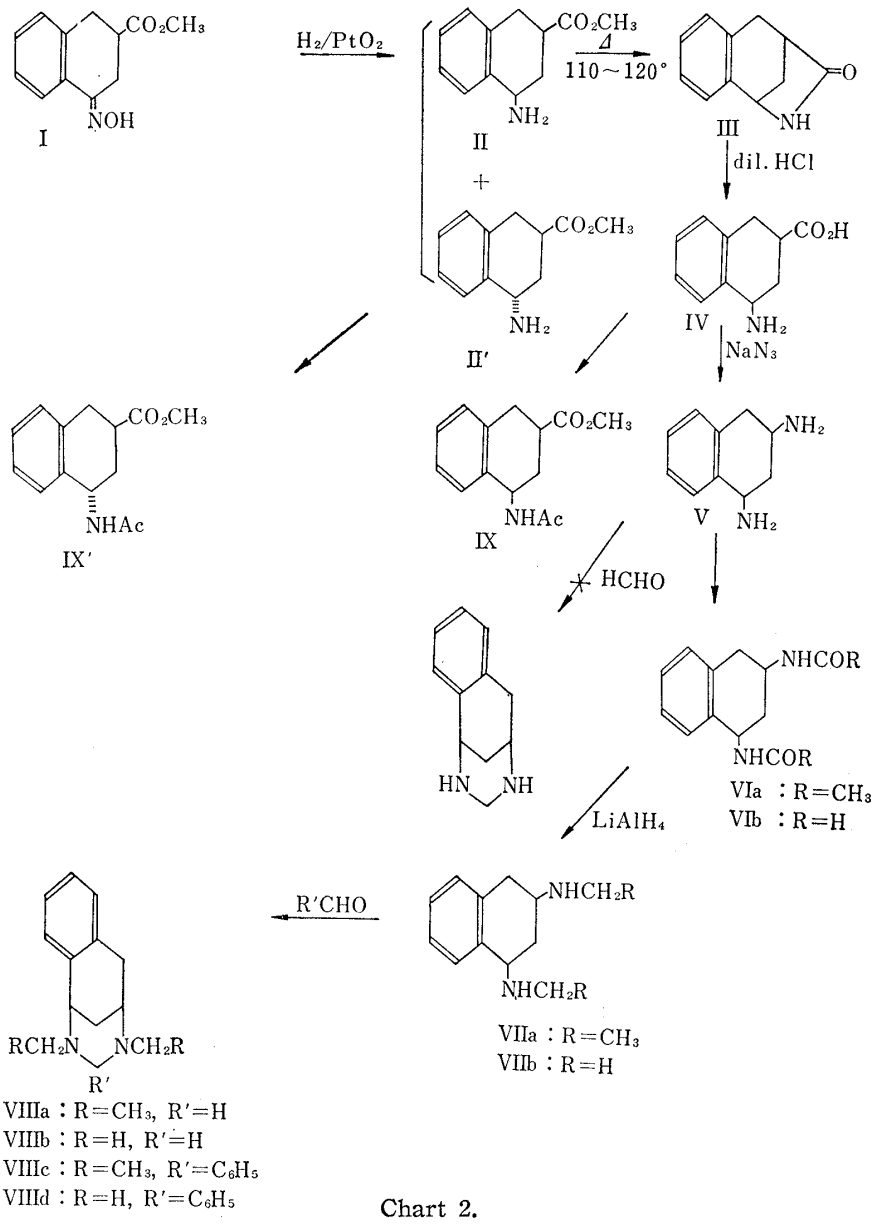

Chart 2.

would cyclize to a lactam (Ⅲ) by heating while the *trans*-isomer unchange, the product was heated at 110～120°. The resulting mixture was separated to a neutral and a basic fractions, whose ratio varied with temperature of the reduction (ca. 6:1 at room temperature; ca. 30:1 at 40～50°).

The neutral substance (Ⅲ), m.p. 145～146.5°, $C_{11}H_{11}ON$, showed a carbonyl band in the infrared spectrum at 1685 cm^{-1}(five-membered lactam); the basic substance (Ⅱ′), b.p_2 130～133°, at 1710 cm^{-1}(-COOMe); and N-acetyl derivative (Ⅸ′) of Ⅱ′, m.p. 136～138°, $C_{14}H_{17}O_3N$, two carbonyl bands at 1730 cm^{-1}(-COOMe) and 1630 cm^{-1}(-NHCOMe). From these data, structures of the neutral (Ⅲ) and the basic substance (Ⅱ′) were confirmed as 4, 5-dihydro-1, 4-methano-1*H*-2-benzazepin-3(2*H*)-one and methyl *trans*-4-amino-1,2,3,4-tetrahydro-2-naphthoate, respectively.

The lactam (Ⅲ) was hydrolyzed by refluxing with diluted hydrochloric acid to give *cis*-4-amino-1,2,3,4-tetrahydro-2-naphthoic acid hydrochloride (Ⅳ) which was esterified, followed by acetylation to afford methyl *cis*-4-acetamido-1,2,3,4-tetrahydro-2-naphthoate (Ⅸ).

Conformations of IX and IX′ were examined by comparing the nuclear magnetic resonance spectra of them. The signal ascribable to C_4-proton appeared as a multiplet, whose coupling constants ($J_{3,4}=6$ c.p.s., $J_{3',4}=10$ c.p.s., $J_{4,NH}=9$ c.p.s.*3 for IX and $J_{3,4}=3$ c.p.s., $J_{3',4}=4\sim5$ c.p.s., $J_{4,NH}=7.5$ c.p.s.*3 for IX′) provided a valuable information concerning the conformational features of them. The difference of the coupling constants would be related to the dihedral angle between C_3-H and C_4-H. Thus, the *cis*-isomer (IX) is assumed to exist in conformation (X) in which proton at C_4 and one of the protons at C_3 are quasi-diaxial, and the *trans*-isomer (IX′) in conformation (X′), as illustrated in Fig. 1.

The carboxyl group of IV was replaced by an amino group affording *cis*-1,3-diamino-1,2,3,4-tetrahydronaphthalene (V) by Schmidt reaction in about 65% yield.

Since condensation of V with formaldehyde to obtain 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine failed, giving only a resinous product, we followed the following route.

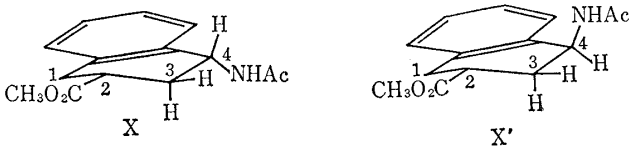

Fig. 1.

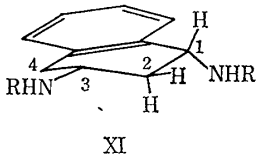

Fig. 2.

Acetylation of V with acetic anhydride in acetic acid afforded *cis*-1,3-diacetamido-1,2,3,4-tetrahydronaphthalene (VIa) which, in turn, was reduced with lithium aluminum hydride to afford *cis*-1,3-diethylamino-1,2,3,4-tetrahydronaphthalene (VIIa). Condensation of VIIa with formaldehyde and benzaldehyde yielded 2,4-diethyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine (VIIIa) and the 3-phenyl derivative (VIIIc), respectively. Analogously, 2,4-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine (VIIIb) and the 3-phenyl derivative (VIIId) were prepared from the N,N′-diformyl derivative (VIb) of V.

In the nuclear magnetic resonance spectra, the C_1-proton signal of VIIa and VIIb appeared as a quartet,*4 and the C_1-proton signal of VIIIa, VIIIb, VIIIc, and VIIId as a triplet. From these coupling patterns, it is assumed that VIIa and VIIb exist in conformation (XI) in which both amino groups at C_1 and at C_3 are equatorial.

Table I. Chemical Shifts of Protons (τ)[a]

	C_4-H	$J_{3,4}$ (c/s)	$J_{3',4}$ (c/s)	$J_{4,NH}$ (c/s)		C_1-H	$J_{1,2}$ (c/s)	$J_{1,2'}$ (c/s)
IX	4.77[b] (m)	6	10	9	VIIa	6.09[b] (q)	6	9
IX′	4.81[b] (〃)	3	4~5	7.5	VIIb	6.12[b] (〃)	6	9
					VIIIa	6.15[b] (t)	3	—
					VIIIb	6.30[b] (〃)	3	—
					VIIIc	5.92[c] (〃)	4	—
					VIIId	6.12[c] (〃)	3	—

a) Spectra were determined on about 10% (w/v) solutions in $CDCl_3$ or in CCl_4, using TMS as internal reference by J.N.M. C-60 and J.N.M. 3H-60 spectrometers operated at 60 Mc.
b) $CDCl_3$ c) CCl_4 (m): multiplet (q): quartet (t): triplet

*3 -NH-proton signal appeared as a doublet at 3.48 τ for IX and at 3.49 τ for IX′.
*4 The signal did not couple with -NH-proton, -NH-proton signal appeared as a singlet at 8.10 τ for VIIa and at 7.85 τ for VIIb.

VIIIa was hydrolyzed to VIIa and formaldehyde by refluxing with hydrochloric acid, but not hydrolyzed by treating with the same reagent at room temperature.

The pharmacological testings of VIIIb are now in progress.

Experimental*5

4,5-Dihydro-1,4-methano-1*H*-2-benzazepin-3 (2*H*)-one (III) and Methyl *trans*-4-Amino-1,2,3,4-tetrahydro-2-naphthoate (II')——a) Methyl 4-hydroximino-1,2,3,4-tetrahydro-2-naphthoate (I) (11.0 g.) in AcOH (80 ml.)-MeOH (80 ml.) was shaken with PtO_2 (800 mg.) in H_2 atmosphere at room temperature. After removal of the catalyst and the solvents, the residue was dissolved in water and extracted with benzene. The aqueous layer was made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over K_2CO_3. From the benzene solution 0.42 g. of I was recovered. The residue left after evaporation of the above $CHCl_3$ solution was heated at 110~120°/2 mm. Hg for 2 hr., then distilled *in vacuo*. The distilate (b.p_2 130~165°) was dissolved in $CHCl_3$ and extracted with 5% HCl. The $CHCl_3$ layer was washed with water and dried over Na_2SO_4. After evaporation of $CHCl_3$, crude III (5.134 g.) was recrystallized from ether, m.p. 145~146.5° (colorless needles). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.44; H, 6.30; N, 8.00. IR ν_{max}^{KBr} cm^{-1}: 3200, 3070 (NH), 1685 (-CONH-).

The above aqueous layer was made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over Na_2SO_4. Evaporation of the solvent gave a slightly colored oil (II') which was purified by distillation *in vacuo*, b.p_2 130~133°, yield 0.9 g. IR ν_{max}^{Film} cm^{-1}: 3450, 3350 (NH), 1710 (-COOMe).

b) A solution of I (16.5 g.) in AcOH (90 ml.)-MeOH (90 ml.) was shaken with PtO_2 (1.0 g.) in H_2 atmosphere at 40~50°. The reaction mixture was treated as described in a). Nine grams of III and 0.3 g. of II' were obtained.

Methyl *trans*-4-Acetamido-1,2,3,4-tetrahydro-2-naphthoate (IX')——A solution of II' (126 mg.) in AcOH (2.0 ml.) and Ac_2O (1.5 ml.) was heated on a water bath for 2 hr. After evaporation of AcOH and excess Ac_2O, the residue was dissolved in ether, washed with dil. HCl, $NaHCO_3$ solution and water, and dried over Na_2SO_4. The residue left after removal of the solvent solidified on standing. Recrystallized from ether, m.p. 136~138° (colorless needles), yield 100 mg. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.97; H, 7.04; N, 5.46. IR ν_{max}^{KBr} cm^{-1}: 3320, 3080 (NH), 1730 (-$COOCH_3$), 1630 (-$NHCOCH_3$).

***cis*-4-Amino-1,2,3,4-tetrahydro-2-naphthoic Acid Hydrochloride (IV) and Methyl *cis*-4-Acetamido-1,2,3,4-tetrahydro-2-naphthoate (IX)**——A solution of III (1.0 g.) in 20% HCl (12 ml.) was refluxed for 6 hr. Evaporation of HCl under reduced pressure gave a colorless crystalline mass (IV) (1.3 g.), which was used for the next reactions without further purification.

A solution of IV (300 mg.) in MeOH (40 ml.) was saturated with hydrogen chloride cooling with an ice bath, and was stood over night at room temperature. After evaporation of the solvent, the residue was dissolved in water, made alkaline with $NaHCO_3$, extracted with ether and dried over Na_2SO_4. Ether was evaporated under reduced pressure at room temperature to give a light yellow oil (260 mg.). The oily product (260 mg.) was dissolved in AcOH (0.5 ml.) and Ac_2O (0.5 ml.), and heated on a water bath for 2 hr. After cooling, the reaction mixture was diluted with water and made alkaline with $NaHCO_3$. A colorless crystalline precipitate (IX) formed was filtered. Recrystallization from benzene afforded colorless needles, m.p. 163~165°, yield 246 mg. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.52; H, 6.95; N, 5.53. IR ν_{max}^{KBr} cm^{-1}: 3410, 3100 (NH), 1730 (-$COOCH_3$), 1640 (-$NHCOCH_3$).

***cis*-1,2,3,4-Tetrahydro-1,3-naphthalenediamine (V)**——To a mixture of IV (1.3 g.) in conc. H_2SO_4 (4 ml.) and $CHCl_3$ (20 ml.) was added powdered NaN_3 during a period of 5 hr. with stirring at 45°. After the azide had been added, stirring was continued for about 15 hr. The reaction mixture was poured onto ice and separated the two layers. The aqueous layer was made alkaline with NaOH solution, salted out with K_2CO_3, extracted several times with $CHCl_3$ and dried over K_2CO_3. After removal of $CHCl_3$, the residual oil (V) was distilled *in vacuo*, b.p_2 120~130° (bath temp.) (colorless oil), yield 594 mg. N,N'-Ditosyl derivative: m.p. 276~277.5° (from EtOH) (slightly yellow needles). *Anal.* Calcd. for $C_{24}H_{26}O_4N_2S_2 \cdot H_2O$: C, 58.99; H, 5.78; N, 5.73. Found: C, 58.93; H, 5.69; N, 5.55.

An Attempt to obtain 1,2,3,4,5,6-Hexahydro-1,5-methanobenzo[*e*][1,3]diazocine from V——A mixture of V (100 mg.) and 35% formalin (0.06 ml.) in MeOH (6 ml.) was warmed on a water bath at 45~50° for 2 hr. Removel of the solvent afforded only a insoluble resinous product.

***cis*-1,3-Diacetamido- (VIa) and *cis*-1,3-Diformamido-1,2,3,4-tetrahydronaphthalene (VIb)**——VIa: V (560 mg.) was dissolved in AcOH (1 ml.)-Ac_2O (1 ml.) and heated on a water bath for 2 hr. After cooling, the reaction mixture was diluted with water and neutralized with $NaHCO_3$. The precipitated crystals were collected by filtration and washed with water to give crude VIa (700 mg.). Recrystallization from

*5 Melting points and boiling points are uncorrected.

MeOH gave colorless needles, m.p. 272.5~274°. *Anal.* Calcd. for $C_{14}H_{18}O_2N_2$: C, 68.27; H, 7.37; N, 11.37. Found : C, 68.10; H, 7.20; N, 11.63. IR ν_{max}^{KBr} cm^{-1} : 3300 (NH), 1620 (-NHCOCH$_3$).

Ⅵb : A mixture of HCOOH (3.4 ml.) and Ac_2O (8.2 ml.) was warmed on a water bath at 50° for 2 hr. Ⅴ (500 mg.) was dissolved in the mixture. After standing at room temperature for a day, excess anhydride was evaporated under reduced pressure. The resulting crystalline mass (Ⅵb) was recrystallized from benzene to give colorless plates, m.p. 201~203°, yield 507 mg. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found : C, 66.06; H, 6.49; N, 12.66. IR ν_{max}^{KBr} cm^{-1} : 3400 (NH), 1655 (-NHCHO).

***cis*-1,3-Diethyl- (VIIa) and *cis*-1,3-Dimethyl-1,2,3,4-tetrahydronaphthalene (VIIb)**——Ⅶa : A suspension of Ⅵa (1.514 g.) and $LiAlH_4$ (1.077 g.) in dioxane (200 ml.) was refluxed for 7 hr. under stirring. After cooling, a small amount of water and then 50 ml. of Rochelle salt solution (saturated) were added. The aqueous layer separated from the organic layer was extracted with $CHCl_3$. The organic layer and the extracts were combined and dried over K_2CO_3. The solvents were removed under reduced pressure to afford a crude oily residue. Distillation of the residue *in vacuo* afforded a slightly yellow oil. For the purification, the crude base was converted to dihydrochloride and recrystallized from EtOH, m.p. 257~260° (decomp.) (colorless needles). *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot 2HCl \cdot H_2O$: C, 54.19; H, 8.71; N, 9.03. Found : C, 54.67; H, 8.56; N, 9.10. The free base was obtained from the salt in almost quantitative yield, b.p_1 130~135° (bath temp.) (colorless oil). Ⅶb : A suspension of Ⅵb (400 mg.) and $LiAlH_4$ (315 mg.) in tetrahydrofuran was refluxed for 8 hr. under stirring. The reaction mixture was treated as described for Ⅶa to afford Ⅶb, b.$p_{0.5}$ 105~110° (bath temp.) (slightly yellow oil). Dihydrochloride : m.p. 245~248.5° (decomp.) (from MeOH, colorless needles). *Anal.* Calcd. for $C_{12}H_{18}N_2 \cdot 2HCl \cdot H_2O$: C, 51.25; H, 7.83; N, 9.96. Found : C, 51.28; H, 7.96; N, 9.86.

2,4-Diethyl-(VIIIa) and 2,4-Diethyl-3-phenyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine (VIIIc)——Ⅷa : A solution of Ⅶa (470 mg.) and 35% formalin (0.2 ml.) in MeOH (50 ml.) was warmed on a water bath at 45~50° for 2 hr. After removal of the solvent, the residue was extracted with ether and dried over K_2CO_3. Evaporation of the solvent gave a slightly yellow oil. The oil was distilled *in vacuo*, b.$p_{0.5}$ 110~120° (bath temp.), yield 493 mg. *Anal.* Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found : C, 47.31; H, 4.30; N, 11.97. Dipicrate : m.p. 141~150° (from MeOH, yellow needles). *Anal.* Calcd. for $C_{15}H_{22}N_2 \cdot 2C_6H_3O_7N_3$: C, 47.13; H, 4.10; N, 16.31. Found : C, 47.31; H, 4.30; N, 16.60.

Ⅷc : A solution of Ⅶa (100 mg.), benzaldehyde (53 mg.) and 50% AcOH (1 drop) in MeOH (5 ml.) was warmed on a water bath at 60° for 2 hr. After evaporation of the solvent, the oily residue was extracted with ether, washed with a small amount of water and dried over K_2CO_3. After removal of the solvent, the residue was distilled *in vacuo*. The distillate (b.$p_{0.33}$ 120~145°) solidified on standing. Recrystallization from petr. ether gave colorless needles, m.p. 81~84°, yield 101 mg. *Anal.* Calcd. for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found : C, 82.12; H, 8.45; N, 9.25.

2,4-Dimethyl- (VIIIb) and 2,4-Dimethyl-3-phenyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]-diazocine (VIIId)——Ⅷb : This compound was prepared from Ⅶb (645 mg.) and 35% formalin (0.32 ml.) as described for the preparation of Ⅷa. B.$p_{0.5}$ 100~103° (bath temp.) (colorless oil), yield 620 mg. Dipicrate : m.p. 176~178° (from MeOH, yellow needles). *Anal.* Calcd. for $C_{13}H_{18}N_2 \cdot 2C_6H_3O_7N_3$: C, 45.49; H, 3.67; N, 16.98. Found : C, 45.25; H, 3.61; N, 16.72.

Ⅷd : This compound was prepared from Ⅶb (100 mg.) and benzaldehyde (53 mg.) by the same method as described for Ⅷc, yield 100 mg. B.$p_{0.06}$ 120~135° (bath temp.), m.p. 128~129°. *Anal.* Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found : C, 81.71; H, 7.91; N, 10.06.

Hydrolysis of VIIIa with Hydrochloric Acid——a) Ⅷa (10 mg.) in 20% HCl was refluxed for 2 hr. After removal of HCl under reduced pressure, the residue was diluted with water, made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over K_2CO_3. Evaporation of the solvent gave a slightly yellow oil. The IR spectrum and the thin-layer chromatogram on Al_2O_3 of the product were identical with those of Ⅶa.

b) Ⅷa (20 mg.) in 20% HCl (2 ml.) was stood at room temperature for 5 hr., and then evaporated HCl at 50° under reduced pressure. The residue was diluted with water, made alkaline with $NaHCO_3$, extracted with $CHCl_3$ and dried over K_2CO_3. Evaporation of the solvent gave a slightly yellow oil. The IR spectrum and the thin-layer chromatogram on Al_2O_3 of the product were identical with those of Ⅷa.

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Summary

In order to test the pharmacological activities, some derivatives of 1,2,3,4,5,6-hexahydro-1,5-methanobenzo[*e*][1,3]diazocine were synthesized.

cis-1,2,3,4-tetrahydro-1,3-naphthalenediamine (V) was prepared by Schmidt reaction of *cis*-4-amino-1,2,3,4-tetrahydro-2-naphthoic acid (IV) which was obtained by catalytic reduction of methyl 4-hydroximino-1,2,3,4-tetrahydro-2-naphthoate (I), followed by cyclization and hydrolysis.

Reduction of N,N′-diacetyl- (VIa) and N,N′-diformyl- (VIb) derivatives of V with lithium aluminum hydride afforded N,N′-diethyl- (VIIa) and N,N′-dimethyl- (VIIb) derivatives, respectively. Condensation of VIIa with formaldehyde and benzaldehyde gave 2,4-diethyl- (VIIIa) and 2,4-dimethyl-3-phenyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo [*e*] [1,3]-diazocine (VIIIc). Similarly, 2,4-dimethyl derivatives (VIIIb) and (VIIId) were prepared.

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46. Hisashi Nogami, Tsuneji Nagai, and Akira Suzuki*1 : Studies on Powdered Preparations. XVII.*2 Dissolution Rate of Sulfonamides by Rotating Disk Method.*3,*4

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When solid preparations are administered orally, the rate-determining step of an appearance of the medicinal effect has been often observed in the dissolution process in digestive tract.[1~3] Even in the manufacturing of various kinds of liquid preparations, the dissolution is a very important process. Therefore, it is considered to be significant to investigate pharmaceutically what kinds of factors give an influence on the dissolution rate of drugs.

Two types of dissolution, transport controlled dissolution and chemically controlled one,[4~6] have been taken into consideration. Dissolution of medicinal preparations is usually a transport controlled reaction, except a few cases[7,8] and its rate is generally represented by the Noyes-Nernst equation (1).

$$\frac{dC}{dt}=k(C_0-C)=\frac{S}{V}K_T(C_0-C)=\frac{S}{V}\frac{D}{\delta}(C_0-C) \qquad (1)$$

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