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12. Shunsaku Shiotani, Takako Hori and Kemmotsu Mitsuhashi : Studies on Diazabenzobicyclo[3.3.1]nonane System. Ⅵ.*1 Syntheses of 1,2,3,4-Tetrahydro-6*H*-1,5-methanobenzo[*d*][1,2] diazocine Derivatives.

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Synthetic procedures of 1,2-dihydro-6*H*-1,5-methanobenzo[*d*][1, 2]diazocin-3(4*H*)-one (XV) and 9-methoxy-4,11-dimethyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*d*][1, 2]diazocine (XXII) by using ethyl isoquinoline-4-carboxylate (II) and *m*-methoxyphenylacetone (XVI) as a starting material, respectively, were investigated.

Methyl 1,2,3,4-tetrahydroisoquinoline-4-acetate (XIII) was prepared by catalytic reduction of II, lithium aluminum hydride reduction of the carbethoxy group to the hydroxymethyl, conversion to the N-benzyl derivative, cyanization of the corresponding bromide, methanolysis of the nitrile, and debenzylation. The amino ester was nitrosated to the N-nitroso derivative which on reduction with zinc and acetic acid yielded XV.

5-(*m*-Methoxyphenyl)-2,6-dimethyl-4,5-dihydropyridazin-3(2*H*)-one (XIX) was prepared by condensation of *m*-methoxyphenylacetone with ethyl bromoacetate, hydrolysis of the ester and condensation of the resulting keto acid with methylhydrazine. XIX was reduced to the 1,4,5,6-tetrahydro derivative which was converted to 9-methoxy-4,11-dimethyl-1,2-dihydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocin-3(4*H*)-one (XXI) by the Pictet-Spengler reaction. XXI was reduced to XXII with lithium aluminum hydride.

Configurations of XX, XXI and XXII were examined by NMR spectra, and these are assumed to exist in conformations XX′ and XXI′.

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In continuation of our work on the studies of diazabenzobicyclo[3.3.1]nonane system which would be expected to possess an analgesic and/or other pharmacological activities, we report herein the syntheses of some derivatives of 1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocine (I). For the synthesis of the skeleton (I) which has not been known yet, we investigated two routes, A (Chart 1) and B (Chart 2).

Route A Ethyl isoquinoline-4-carboxylate (II)[1] was hydrogenated over Adams catalyst to give ethyl 1,2,3,4-tetrahydroisoquionoline-4-carboxylate (III). Reduction of III with lithium aluminum hydride in the usual procedure yielded 4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (IV). The hydroxyl compound was converted to the bromo compound (V) by heating with concentrated hydromic acid at 100° (Chart 1).

Though attempts to obtain the corresponding cyano compound (VII or VIII) from V or its N-acetyl derivative (VI) by treating with potassium cyanide in ethanol or with sodium cyanide in liquid hydrogen cyanide[2] were unsuccessful, the conversion of the bromomethyl group to the cyanomethyl was achieved with N-benzyl derivative (X). Bromination of the N-benzyl derivative (IX) of IV with concentrated hydrobromic acid followed by cyanization wtih potassium cyanide in aqueous ethanol afforded 2-benzyl-4-cyanomethyl-1,2,3,4-tetrahydroisoquinoline (XI). The structure of XI was confirmed by the elemental analysis and the infrared spectrum of the compound, in which -C≡N band appeared at 2240 cm^{-1}.

The cyano group of XI was converted to carbomethoxyl by heating with an excess methanol, concentrated sulfuric acid and a calculated amount of water in a sealed

*1 Part V. S. Shiotani, K. Mitsuhashi : This Bulletin, **14**, 608 (1966).
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1) F. W. Bergstrom, J. H. Rodda : J. Am. Chem. Soc., **62**, 3030 (1940).
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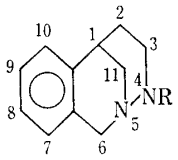

I

Route A

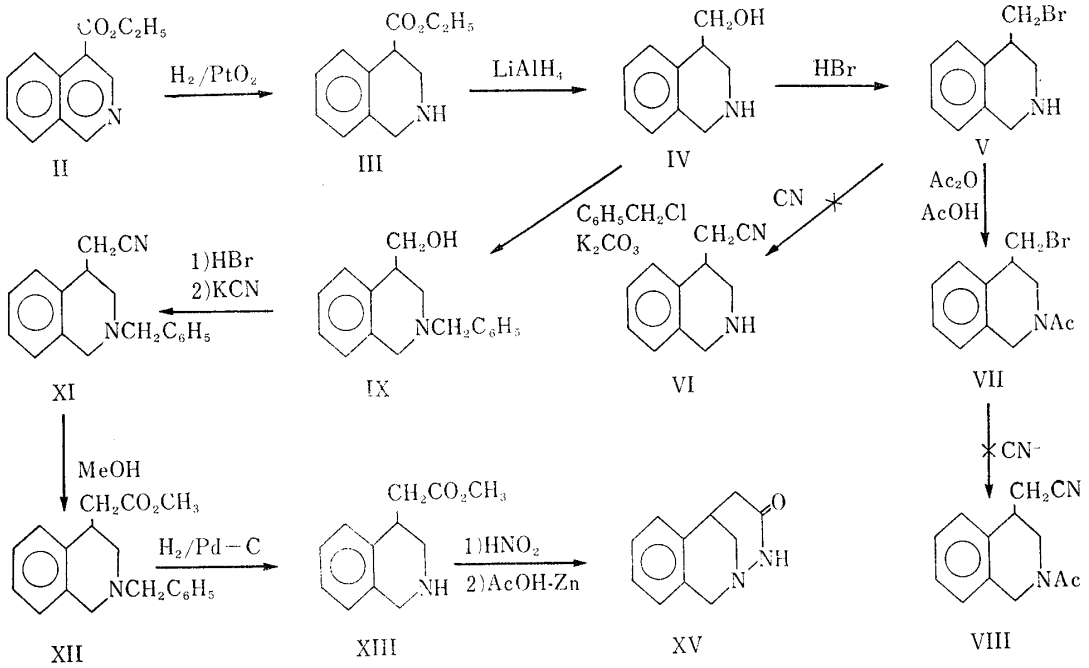

Chart 1.

tube at 100° for 50~70 hours. Hydrogenolysis of methyl 2-benzyl-1,2,3,4-tetrahyroisoquinoline-4-acetate (XII) over palladium-carbon in methanol-hydrochloric acid afforded methyl 1,2,3,4-tetrahydroisoquinoline-4-acetate (XIII). Nitrosation of XIII with nitrous acid in the usual procedure gave methyl 2-nitroso-1,2,3,4-tetrahydroisoquinoline-4-acetate (XIV), which was used in the following reaction without purification.

When XIV was reduced with zinc and acetic acid, a crystalline product (XV) melting at 247~249° was obtained. The elemental analysis of XV suggested that the intramolecular cyclization occurred in the course of the above reduction. The compound showed $\nu_{C=O}$ band ascribable to six-membered lactam at 1640 cm^{-1} and ν_{NH} band at 3160 cm^{-1} in its infrared spectrum. Based on the above evidences and the nuclear magnetic resonance spectrum (Fig. 1), the compound was characterized as 1,2-dihydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocin-3(4*H*)-one.

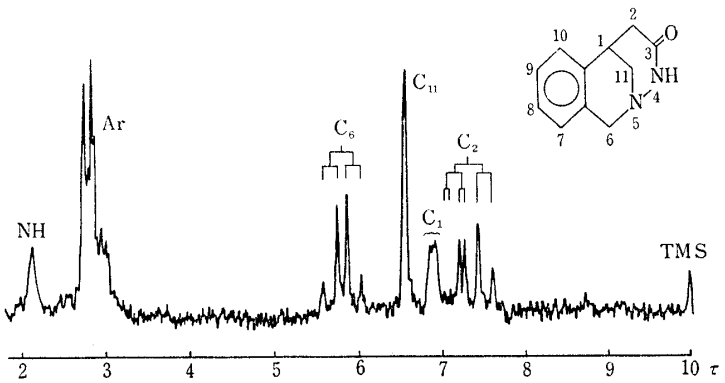

Fig. 1. Nuclear Magnetic Resonance Spectrum of XV. ($CDCl_3$) (100-Mc., JNM-4H-100)

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Any trials to reduce the carbonyl group of XV to methylene with lithium aluminum hydride were unsuccessful, that is, only the starting material was recovered under the mild conditions, and a mixture of complicated products was afforded under the more drastic conditions.*3

Route B

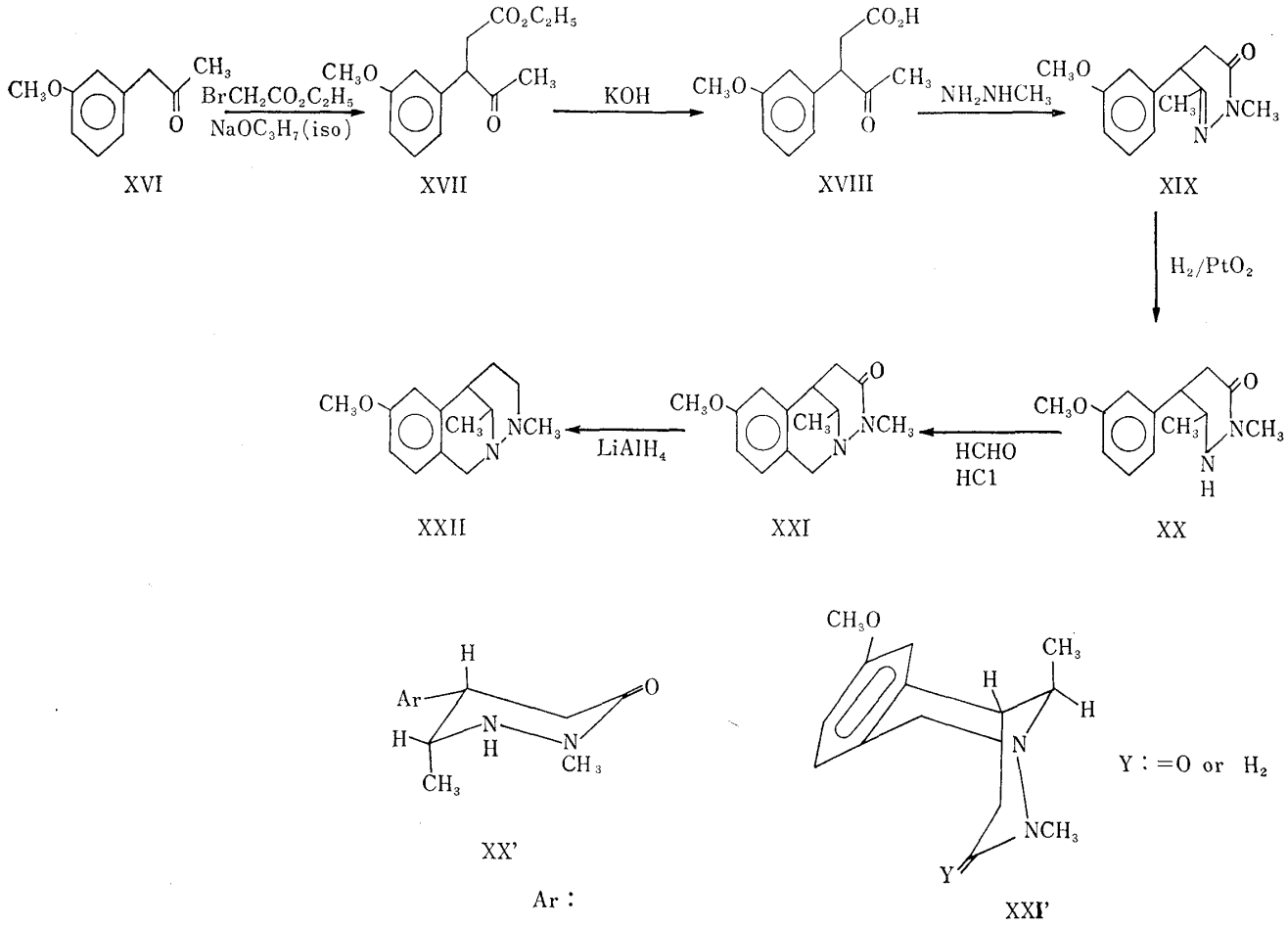

Chart 2.

Route B Condensation of *m*-methoxyphenylacetone (XVI)[3] with ethyl bromoacetate gave ethyl 3-(*m*-methoxyphenyl)levulinate (XVII), which was saponified with potassium hydroxide in ethanol to afford 3-(*m*-methoxyphenyl)levulinic acid (XVIII).

Condensation of XVIII with methylhydrazine according to the procedure described earlier[4] afforded 5-(*m*-methoxyphenyl)-2,6-dimethyl-4,5-dihydropyridazin-3(2*H*)-one (XIX). Hydrogenation of XIX over Adams catalyst in ethanol-acetic acid gave a colorless vircous oil (XX), which was purified as the hydrochloride. The product (XX) was positive to Liebermann's nitrosamine test and reduced Fehling solution. In the infrared spectrum, XX showed $\nu_{C=O}$ band at 1620 cm^{-1} and ν_{NH} band at 3280 cm^{-1}. Thus, XX was characterized as 5-(*m*-methoxyphenyl)-2,6-dimethyl-1,4,5,6-tetrahydropyridazin-3(2*H*)-one.

The Pictet-Spengler reaction of XX gave 9-methoxy-4,11-dimethyl-1,2-dihydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocin-3(4*H*)-one (XXI), which was reduced with lithium

*3 This result is similar to that of R.L. Hinman for some acylhydrazines.[5]

3) Z. Horii, *et al.*: J. Chem. Soc., **1963**, 3940.
4) K. Mitsuhashi, S. Shiotani: Yakugaku Zasshi, **80**, 1348 (1960).
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aluminum hydride to afford 9-methoxy-4,11-dimethyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*d*][1,2]diazocine (XXII).

Structures of XXI and XXII were confirmed by the fact that in the nuclear magnetic resonance spectra (Fig. 2) both of them showed an ABX type multiplet pattern of aromatic protons (at 2.98~3.367τ (J_{AB}=8.5 c.p.s.; J_{AX}≒0 c.p.s.; J_{BX}=3.0 c.p.s.) for XXI and at 2.90~3.41τ (J_{AB}=8.5 c.p.s.; J_{AX}=0 c.p.s.; J_{BX}=3.0 c/p.s.) for XXII) and an AB type quartet assignable to C_6-methylene protons (at 5.83τ and 6.02τ (J_{AB}=18 c.p.s.) for XXI and at 5.87τ and 6.17τ (J_{AB}=19 c.p.s.) for XXII.

Relative configurations at C_5 and C_6 of XX, and at C_1 and C_{11} of XXI and XXII were examined by the nuclear magnetic resonance spectra (Fig. 2). XX showed a multiplet ascribable to C_6-methyne proton at 6.51τ ($J_{5,6}$=3.5 c.p.s.; $J_{6,6Me}$=6.5 c.p.s.). The coupling constant ($J_{5,6}$) would be related to the dihedral angle between C_5-H and C_6-H. On the other hand, the aryl group would be assumed to exist preferentially in quasi equatorial. Thus, XX is assumed to exist in conformation XX′ in which both substituents at C_5 and C_6 are *cis*. As the relative configuration at C_5 and C_6 of XX may be retained in the course of the Pictet-Spengler reaction, it may be assumed that XXI and XXII exist in conformation XXI′.

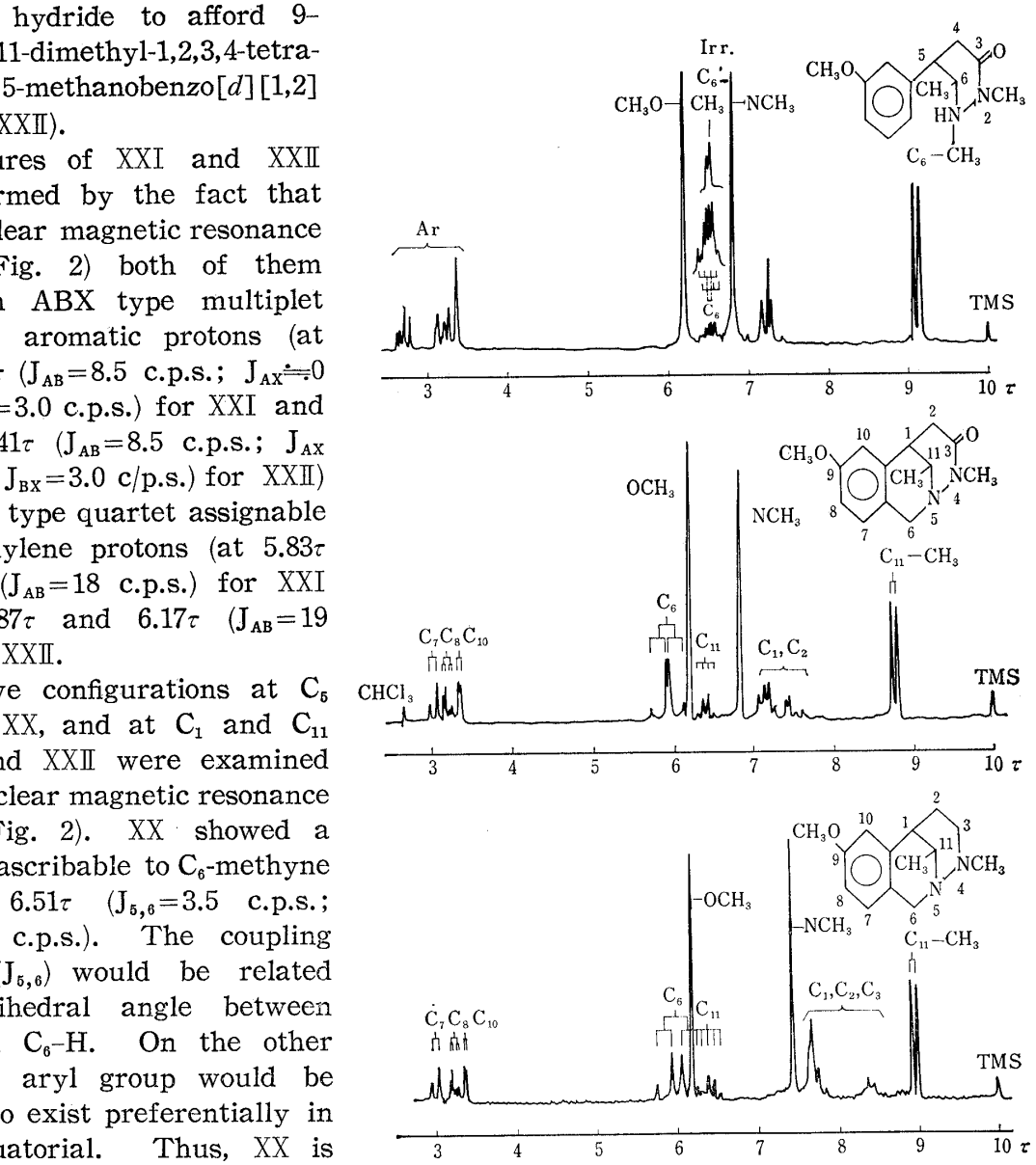

Fig. 2. Nuclear Magnetic Resonance Spectra of XX, XXI and XXII ($CDCl_3$) (100-Mc., JNM-4H-100)

The pharmacological testings of XV and XXII are now in progress.

Experimental

Ethyl 1,2,3,4-Tetrahydroisoquinoline-4-carboxylate (III)——Ethyl isoquinoline-4-carboxylate (II) hydrochloride[1] (5.0 g.) in AcOH (20 ml.)-EtOH (20 ml.) was shaken with PtO_2 (0.5 g.) in H_2 atmosphere at room temperature for about 3.5 hr. After removal of the catalyst and the solvents, the residue was dissolved in water, made alkaline with 10% NaOH, extracted with ether and dried over K_2CO_3. The yellow residue (3.9 g.) left after evaporation of ether was used in the next reaction without purification because the product decomposed on distillation even under reduced pressure. Picrate: m.p. 175~176° (from EtOH) (yellow needles). *Anal.* Calcd. for $C_{12}H_{15}O_2N \cdot C_6H_3O_7N_3$: C, 49.77; H, 4.18; N, 12.90. Found: C, 49.78; H, 4.37; N, 12.75.

4-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (IV)——A solution of III (3.9 g.) in tetrahydrofuran (30 ml.) was added to a suspension of $LiAlH_4$ (2.5 g.) in the same solvent (40 ml.) with stirring at room temperature and stirring was continued for 1.5 hr. at room temperature. A small quantity of water and then 100

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ml. of Rochelle salt solution (saturated) were added. The aqueous layer separated from the organic one 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 an oily residue (3.0 g.). For the purification, the crude base was converted to oxalate and recrystallized from EtOH, m.p. 212~213.5° (decomp.) (colorless cubes). *Anal.* Calcd. for $C_{10}H_{13}ON \cdot \frac{1}{2}C_2H_2O_4$: C, 63.51; H, 6.78; N, 6.73. Found : C, 63.31; H, 6.67; N, 6.76.

2-Acetyl-4-bromomethyl-1,2,3,4-tetrahydroisoquinoline (VII)——A mixture of Ⅳ (104 mg.) and hydrobromic acid (saturated at 0°) (1 ml.) in a sealed tube was heated at 100° for 5 hr. After cooling, the mixture was diluted with water, made alkaline with NaOH solution, extracted with ether and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave a light brown oil (Ⅴ) (111 mg.).

When Ⅴ was refluxed with KCN in aqueous EtOH, a brown oil was obtained. The oil revealed five spots on thin-layer chromatography, and all attempts to isolate the cyano compound (Ⅵ) from the oil was failed.

Crude Ⅴ (784 mg.) was dissolved in AcOH (6 ml.)-Ac_2O (6 ml.) and heated on a water-bath for 2 hr. After evaporation of the excess Ac_2O and AcOH, the residue was dissolved in ether, washed with dil. HCl, dil. NaOH and water, and dried over Na_2SO_4. The crystalline residue (708 mg.) of the ethereal solution was recrystallized from MeOH-ether to show m.p. 103~104.5° (colorless needles). *Anal.* Calcd. for $C_{12}H_{14}ONBr$: C, 53.78; H, 5.27; N, 5.23. Found : C, 53.69; H, 5.16; N, 5.12.

When Ⅶ (100 mg.) was refluxed with KCN (50 mg.) in aqueous EtOH, an oily product was obtained which did not show -C≡N band in IR spectrum.

When Ⅶ (100 mg.) was treated with NaCN (1.0 g.) in liq. HCN (15 ml.), only the starting material was recovered.

2-Benzyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (IX)——A mixture of Ⅳ (2.25 g.), $C_6H_5CH_2Cl$ (1.8 g.) and K_2CO_3 (3.0 g.) was refluxed for 2.5 hr. with stirring. The mixture was cooled, washed with water and extracted with 10% HCl. The aqueous layer was washed with C_6H_6, filtered, made alkaline with 10% NaOH, extracted with $CHCl_3$ and dried over K_2CO_3. The residue of the $CHCl_3$ solution was distilled *in vacuo*, $b.p_{0.02}$ 167~170° (bath temp.). Yield, 3.1 g. For the elemental analysis, the procuct was purified by chromatography over alumina column using C_6H_6 as eluent. *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found : C, 80.75; H, 7.78; N, 5.50.

2-Benzyl-4-bromomethyl-1,2,3,4-tetrahydroisoquinoline (X)——A mixture of Ⅸ (1.7 g.) and hydrobromic acid (saturated at 0°) (15 ml.) was heated at 100° for 5 hr. After cooling, the mixture was diluted with water (50 ml.) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% NaOH and then with water, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a light brown oil (2.0 g.), which was used for the next reaction without purification.

2-Benzyl-4-cyanomethyl-1,2,3,4-tetrahydroisoquinoline(XI)——X (2.0 g.) was refluxed with KCN (1.0 g.) in aqueous EtOH (90%, 40 ml.) for 3 hr. After evaporation of the solvent, the brown residue was dissolved in ether, washed with water and dried over K_2CO_3. The solvent was evaporated to give a brown oil (1.45 g.) which was chromatographed over silicagel column using C_6H_6-$CHCl_3$ (1:1) as eluent, and elution with the same solvent gave pure X (0.9 g.). $B.p_{0.002}$ 185~190° (bath temp.) (colorless oil). IR $\nu_{max}^{liq.}$ cm^{-1} : 2250 (-C≡N). *Anal.* Calcd. for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68. Found : C, 82.03; H, 7.01; N, 10.76.

Methyl 2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4-acetate (XII)——A mixture of Ⅺ (3.3 g.), MeOH (40 ml.), H_2O (2.5 ml.) and conc. H_2SO_4 (6 ml.) in a sealed tube was heated at 100° for 50 hr. The solvent was evaporated and the residue was dissolved in water, made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and the solvent was evaporated to give a dark oil (3.5 g.), which was chromatographed over silicagel column. From the eluates with C_6H_6-$CHCl_3$ (5:1-1:1), pure Ⅻ was obtained as a colorless oil (1.76 g.), $b.p_{0.002}$ 155~160° (bath temp.). IR $\nu_{max}^{liq.}$ cm^{-1} : 1740 (-CO_2Me). *Anal.* Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found : C, 77.51; H, 7.32; N, 4.83.

Methyl 1,2,3,4-Tetrahydroisoquinoline-4-acetate (XIII)——Ⅻ (5.5 g.) in MeOH (100 ml.)-conc. HCl (10 ml.) was shaken with Pd-C (40%, 2.1 g.) in H_2 atmosphere at room temperature for 6 hr. After removal of the catalyst and the solvents, the residue was recrystallized from MeOH to give hydrochloride of XIII (2.07 g.), m.p. 170~173° (colorless needles). *Anal.* Calcd. for $C_{12}H_{15}O_2N \cdot HCl$: C, 59.63; H, 6.67; N, 5.79. Found : C, 59.41; H, 6.44; N, 5.74.

Methyl 2-Nitroso-1,2,3,4-tetrahydroisoquinoline-4-acetate (XIV)——The above mentioned hydrochloride (2.07 g.) was nitrosated in the usual procedure. The product (1.4 g.) was used in the next reaction without purification.

1,2-Dihydro-6*H*-1,5-methanobenzo[*d*][1, 2] diazocin-3(4*H*)-one (XV)——A solution of XIV (1.4 g.) in AcOH (20 ml.) was added gradually to a suspension of powdered Zn (3 g.) in H_2O (10 ml.) at 5~10° with stirring. The mixture was stirred at room temperature for 1 hr. and refluxed for 6 hr. After removal of the excess Zn, the solvents were evaporated under reduced pressure. The residue was dissolved in water, extracted with $CHCl_3$ and dried over Na_2SO_4. Removal of the solvent afforded a crystalline residue (0.63 g.), which was recrystallized from MeOH to show m.p. 247~248°. IR ν_{max}^{KBr} cm^{-1} : 1640 (-CONH-), 3160 (NH). *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found : C, 69.72; H, 6.57; N, 15.03.

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Ethyl 3-(*m*-Methoxyphenyl)levulinate (XVII)——*m*-Methoxyphenylacetone (XVI)[3] (10 g.) was added to a solution of Na (1.45 g.) in iso-PrOH (60 ml.) over a period of 1/2 hr. with stirring. Ethyl bromoacetate (10.5 g.) was added to the resulting light brown mixture with ice-cooling and stirring. Stirring was continued for 2 hr. with ice-cooling. The solvent was then evaporated under reduced pressure. The residue was mixed with water and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated to leave a brown viscous oil, which was distilled *in vacuo*. B.p_3 163～163.5°(faintly yellow viscous oil). Yield, 5.5 g. IR $\nu_{max}^{liq.}$ cm^{-1} : 1710 (-CO_2Et).

3-(*m*-Methoxyphenyl)levulinic Acid (XVIII)——A mixture of XVII (19.5 g.) and KOH solution (KOH 13.1 g. in EtOH (200 ml.) and H_2O (10 ml.)) was refluxed for 2 hr. The solvent was evaporated under reduced pressure to leave a semi-solid, which was dissolved in water and washed with $CHCl_3$. The aqueous layer was acidified with HCl, extracted with ether and washed with water. The ether solution was extracted with dil. $NaHCO_3$ solution. The aqueous layer was washed with benzene and filtered with charcoal. The almost colorless filtrate was acidified with HCl, extracted with ether, washed with water and dried over Na_2SO_4. The solvent was evaporated to give a slightly yellow viscous oil, which was solidified by treating with a small quantity of petr. ether. M.p.78～79°(from ether-petr. ether) (colorless plates). Yield, 14.1 g. IR ν_{max}^{KBr} cm^{-1} : 1685 (CO_2H). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.66; H, 6.51.

5-(*m*-Methoxyphenyl)-2,6-dimethyl-4,5-dihydropyridazin-3(2*H*)-one (XIX)——Methylhydrazine sulfate (8.76 g.) was added to a solution of XVIII (13.5 g.) in Na_2CO_3 solution (Na_2CO_3 6.45 g. in 28 ml. of H_2O) and heated on a water-bath for 3 hr. The reaction mixture was cooled, extracted with ether and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled *in vacuo*, b.$p_{0.03}$ 137～140°(slightly yellow viscous oil). Yield, 10 g. IR $\nu_{max}^{liq.}$ cm^{-1} : 1650 (-CONMe-).

5-(*m*-Methoxyphenyl)-2,6-dimethyl-1,4,5,6-tetrahydropyridazin-3(2*H*)-one (XX)——XIX (1.6 g.) in AcOH (25 ml.)-EtOH (25 ml.) was shaken with PtO_2 (0.2 g.) in H_2 atmosphere at room temperature for 4 hr. After removal of the catalyst and the solvents, the residue was mixed with water, made alkaline with $NaHCO_3$ and extracted with ether. The ether layer was then extracted with 5% HCl, and the aqueous layer was washed with C_6H_6, filtered, made alkaline with $NaHCO_3$, extracted with ether and dried over K_2CO_3. The solvent was evaporated to give a yellow viscous oil (729 mg.), which was distilled *in vacuo*, b.$p_{0.1}$ 150～155° (bath temp.) (colorless viscous oil). Yield, 708 mg. Hydrochloride : M.p. 164～165°(from MeOH-AcOEt) (colorless plates). *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$•HCl : C, 57.61; H, 7.07; N, 10.34. Found : C, 57.98; H, 7.34; N, 10.34.

From the foregoing ethereal mother solution, the staring material (XIX) (441 mg.) was recovered.

9-Methoxy-4,11-dimethyl-1,2-dihydro-6*H*-1,5-methanobenzo [*d*] [1,2] diazocin-3(4*H*)-one (XXI)——A mixture of XX (281 mg.) and formalin (37%, 0.14 ml.) in 20% HCl (15 ml.) was heated on a water-bath for 1.5 hr. After removal of the solvent, the residue was mixed with water, made alkaline with $NaHCO_3$, extracted with ether, dried (K_2CO_3) and evaporated to give a yellow viscous oil. Vacuum distillation of the oil afforded pure XXI, b.$p_{0.04}$ 145～160°. Yield, 132 mg. IR $\nu_{max}^{liq.}$ cm^{-1} : 1620 (-CONMe-).

9-Methoxy-4,11-dimethyl-1,2,3,4-tetrahydro-6*H*-1,5-methanobenzo[*d*] [1,2] diazocine (XXII)——A solution of XXI (132 mg.) in ether (15 ml.) was added to a suspension of $LiAlH_4$ (110 mg.) in ether (35 ml.) and the mixture was swirled for 4 min. A small quantity of water and then Rochelle salt solution were added with chilling. The aqueous layer separated from the ethereal one was repeatedly extracted with ether. The ether solution and the extracts were combined, dried (K_2CO_3) and evaporated to give a slightly yellow oil, which was fractionated by vacuum distillation. A fraction of b.$p_{0.025}$ 100～115° solidified on standing was sublimated *in vacuo* (63～73°/0.025 mm. Hg). M.p. 90～91°(colorless needles). Yield, 20 mg. *Anal.* Calcd. for $C_{14}H_{20}ON_2$: C, 72.38; H, 8.68; N, 12.06. Found : C, 72.02; H, 8.99; N, 11.71.

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