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90. Shunsaku Shiotani and Kemmotsu Mitsuhashi : Studies on Diazabenzobicyclo[3.3.1]nonane System. I.[*1] Syntheses of 3,4,5,6-Tetrahydro-2*H*-1,5-methanobenzo[*g*]-[1,4]diazocine and its Derivatives.[*2]

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No report concerning the compounds of the diazabenzobicyclo[3.3.1]nonane system has appeared so far in the literature. This system as shown by formula (I) is of interest since it has a frame-work comparable to 6,7-benzomorphan, some derivatives of which retain morphine-like analgesic activity,[1] and it is expected that any physiologically active compounds may be found in this system. Therefore, the authors have attempted to synthesize a number of compounds belonging to this system in order to examine their physiological activity. This paper deals with the syntheses of 4-methyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine (IIa) and its 9-methoxyl derivative (IIb).

Although Ueda[2] had prepared 3-benzamido-3,4-dihydrocarbostyril (Va) by reduction of the azlactone (IVa) with hydriodic acid and red phosphor, followed by benzoylation, this method did not seem to be suitable for the preparation of 3-benzamido-7-methoxy-3,4-dihydrocarbostyril (Vb) because hydrolysis of the methoxyl group might occur under such vigorous condition.

The preparation of 3-benzamido-3,4-dihydrocarbostyrils (Va and Vb) was achieved readily by catalytic reduction of the azlactones (IVa and IVb) over Adams catalyst or Raney nickel under pressure. The products (Va and Vb) showed two amide absorption bands at 1675 cm^{-1} and 1635 cm^{-1} and at 1670 cm^{-1} and 1630 cm^{-1}, respectively, in the infrared spectra. They were then converted to the corresponding 3-benzamido-1,2,3,4-tetrahydroquinolines (VIa and VIb) by reduction with lithium aluminum hydride in boiling tetrahydrofuran (THF). Structures of VIa and VIb were confirmed by the facts that in the infrared spectra both of them had a carbonyl absorption band due to a benzamide group (1620 cm^{-1} for VIa and 1640 cm^{-1} for VIb) and that hydrolysis of VIa with sulfuric acid gave benzoic acid.

Reduction of both Va and VIa with lithium aluminum hydride in boiling dioxane afforded 3-benzylamino-1,2,3,4-tetrahydroquinoline (XIII). Since an attempt to obtain

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[*1] For preliminary studies see the following papers. *a)* K. Mitsuhashi, S. Shiotani : Yakugaku Zasshi, **80**, 1348 (1960). *b)* *Idem* : *Ibid.*, **82**, 773 (1962).

[*2] Reported at the 82nd Annual Meeting of the Pharmaceutical Society of Japan, Shizuoka, Nov., 1962.

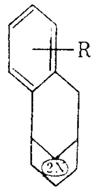
[*3] Gofuku, Toyama (塩谷俊作, 三橋監物).

1) E.L. May, J.C. Murphy : J. Org. Chem., **20**, 257 (1955); E.L. May, N.B. Eddy : *Ibid.*, **24**, 294, 1435 (1959).

2) H. Ueda : Ber., **61**, 146 (1928).

4-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine from XIII by condensation with 1,2-dibromoethane[3] failed, the authors followed the following route.

Treatment of the tetrahydroquinolines (VIa and VIb) with methanol solution of ethylene oxide in a sealed tube at 100° afforded 1-(2-hydroxyethyl)-3-benzamido-1,2,3,4-tetrahydroquinolines (VIIa and VIIb), which were reduced respectively to 3-benzylamino-1,2,3,4-tetrahydroquinoline derivatives (VIIIa and VIIIb) with lithium aluminum hydride in boiling dioxane.



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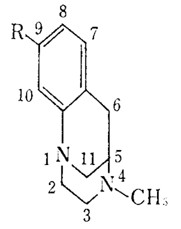

IIa, IIb

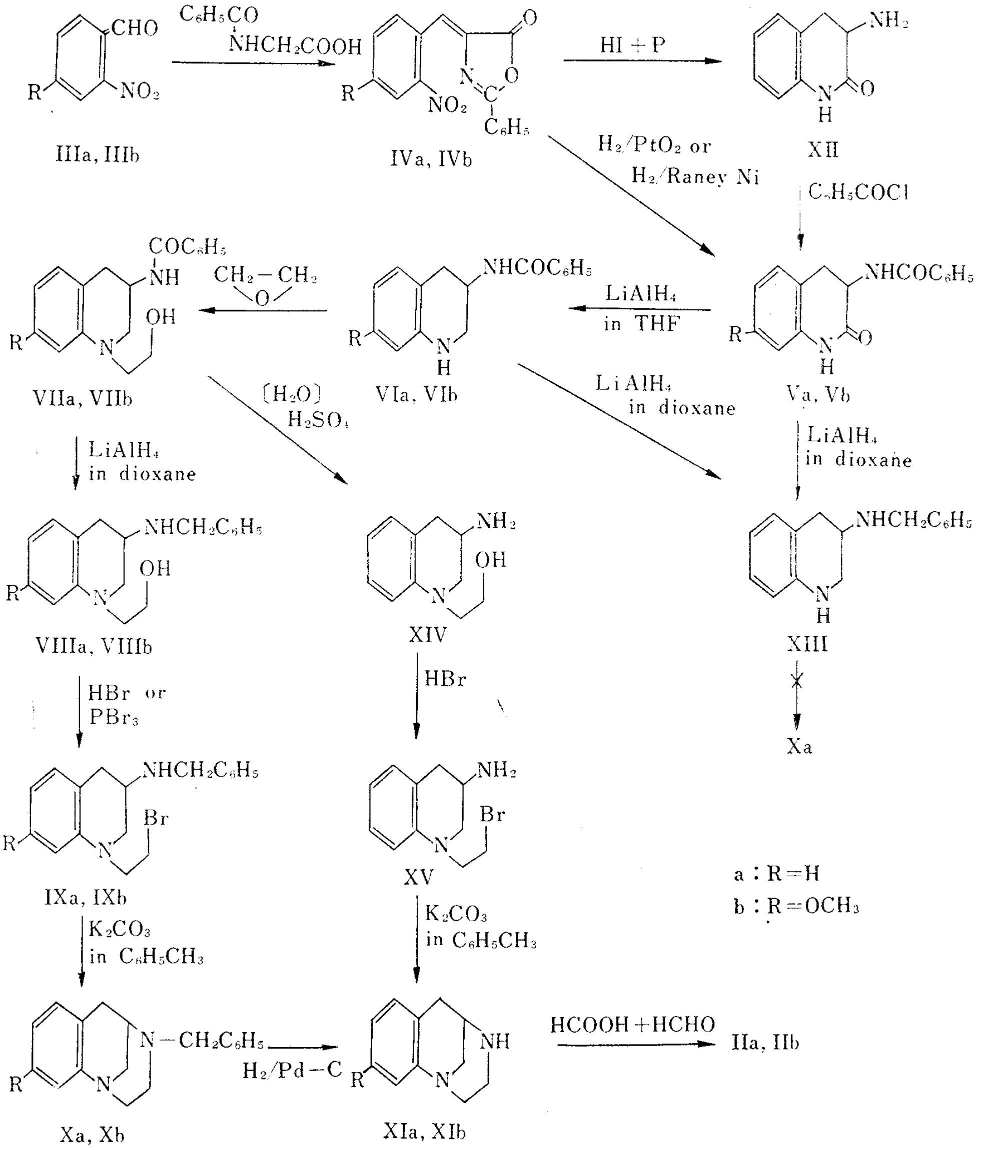

Chart 1. Syntheses of 3,4,5,6-Tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocines

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[3] T. Yamazaki: Yakugaku Zasshi, **79**, 1003 (1959).

Replacement of the hydroxyl group of VIIIa by bromine was effected by heating at 100° with hydrobromic acid (saturated at 0°) in a sealed tube, whereas in the case of VIIIb phosphorus tribromide was used in carbon tetrachloride. Both bromo-compounds (IXa and IXb) afforded halogen free products (Xa : melting at 67~68.5°) and (Xb : boiling at 172~182°/0.03~0.05) by treating with potassium carbonate in toluene under reflux. The molecular weight measurement (Rast) and the elemental analysis of Xa suggested that the intramolecular dehydrobromination occurred. The compounds (Xa and Xb) were negative to Liebermann's nitrosamine test, and showed no bands characteristic of >NH, -OH and vinyl groups in the infrared spectra. They were further characterized as 4-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine and its 9-methoxyl derivative, respectively.

Hydrogenolysis of Xa and Xb led to 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]-diazocine (XIa) and its 9-methoxyl derivative (XIb). XIa was also prepared by an alternative route. Hydrolysis of 1-(2-hydroxyethyl)-3-benzamido-1,2,3,4-tetrahydroquinoline (VIIa) with sulfuric acid gave 3-amino derivative (XIV). The hydroxyl group of XIV was replaced by bromine by the action of hydrobromic acid (saturated at 0°), and the resulting product was dehydrobrominated with potassium carbonate in boiling toluene to afford XIa.

On treatment of XIa and XIb with formic acid and formaldehyde, 4-methyl derivatives (IIa) and (IIb) were obtained respectively.

The physiological testings of these compounds are now in progress.

Experimental[*4]

3-Benzamido-3,4-dihydrocarbostyril (Va) and its 7-Methoxyl Derivative (Vb)——Va : Azlactone (IVa) (1 g.) in AcOH (20 ml.) was stirred with PtO_2 under 4 kg./cm^2 pressure of H_2 at room temperature for 5 hr. The reaction mixture was treated in the usual manner to give a crude crystalline product. Recrystallization from EtOH gave colorless needles, m.p. 205°; yield, 52%. The melting point of this product was not depressed by admixture with that prepared by Ueda's method. IR cm^{-1} : $\nu_{C=O}$ 1675 (Ar-NH-CO-), 1635 (-NH-CO-Ph) (KBr).

Vb : Condensation of 2-nitro-4-methoxybenzaldehyde (III)[4] with hippuric acid afforded azlactone (IVb), m.p. 163~165° (yellow needles (from Me_2CO)); yield, 70%. The azlactone (2 g.) in EtOH (60 ml.) was stirred with Raney Ni (ca. 0.5 g.) under 5 kg./cm^2 of H_2 at 40~60° for 6 hr. The crude crystalline product was recrystallized from MeOH, m.p. 205~207° (colorless needles); yield, 76%. *Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.90; H, 5.44; N, 9.45. Found : C, 69.21; H, 5.46; N, 9.75. IR cm^{-1} : $\nu_{C=O}$ 1670 (Ar-NH-CO-), 1630 (-NH-CO-Ph) (KBr).

3-Benzamido-1,2,3,4-tetrahydroquinoline (VIa) and its 7-Methoxyl Derivative (VIb)——VIa : A solution of carbostyril (Va) (6 g.) in THF (100 ml.) was added dropwise to a suspension of $LiAlH_4$ (1.9 g.) in THF (50 ml.) over a period of 10 min. under stirring at room temperature. The mixture was stirred and refluxed for 5 hr. After cooling, a small quantity of H_2O and then 200 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 Na_2SO_4. The solvents were removed under reduced pressure to afford a crude crystalline residue. Recrystallization from EtOH gave colorless cubes, m.p. 150~152°; yield, 60%. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.20; H, 6.30. Found : C, 76.18; H, 6.47. IR : $\nu_{C=O}$ 1620 cm^{-1} (KBr).

VIb : The procedure used for the preparation of this compound was identical with that described for VIa. M.p. 166~168° (colorless plates (from MeOH)); yield, 61.7%. *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$: C, 72.31; H, 6.43; N, 9.92. Found : C, 72.47; H, 6.44; N, 9.97. IR : $\nu_{C=O}$ 1640 cm^{-1} (KBr).

Hydrolysis of VIa——A mixture of VIa (0.1 g.) and H_2SO_4 (70%, 2 ml.) was refluxed for 35 min., diluted with H_2O, and extracted with $CHCl_3$. Removal of the solvent gave a crystalline residue, melting at 117~120°, undepressed by admixture with an authentic sample of BzOH.

3-Benzylamino-1,2,3,4-tetrahydroquinoline (XIII)——A solution of Va (1.9 g.) in dioxane (50 ml.) was added under stirring to a suspension of $LiAlH_4$ (1.5 g.) in dioxane (50 ml.). The mixture was stirred and

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[*4] All melting points are uncorrected.

4) U. S. Pat. 2,813,128 (Upjohn Co.); (C. A., **52**, 5477 (1958)).

refluxed for 17 hr., and treated as described for the preparation of VIa. The oily crude product was distilled *in vacuo*. The distillate (b.p$_{0.05\sim0.06}$ 165~174°) solidified on standing. Recrystallization from Et_2O gave colorless needles, m.p. 84~85.5°; yield, 90%. A mixed melting point with the product obtained by reduction of VIa with $LiAlH_4$ in boiling dioxane was 84~85.5°. This compound showed no $\nu_{C=O}$ peak in IR spectrum. *Anal.* Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.60. Found: C, 80.44; H, 7.60.

An Attempt to obtain 4-Benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine from XIII——To a solution of XIII (1 g.) in toluene, 1,2-dibromoethane (0.76 g.) and K_2CO_3 (1.3 g.) were added. The mixture was stirred and refluxed for 3 hr., cooled, and filtered. The filtrate (negative to Beilstein test) was evaporated to dryness under reduced pressure. The residue which solidified on standing was recrystallized from Et_2O to show m.p. 85°. No depression in melting point was observed in admixture of this product with XIII.

1-(2-Hydroxyethyl)-3-benzamido-1, 2, 3, 4-tetrahydroquinoline (VIIa) and its 7-Methoxyl Derivative (VIIb)——VIIa: A mixture of VIa (7.5 g.) and ethylene oxide (2.5 g.) in MeOH (80 ml.) in a sealed tube was heated at 100° for 10 hr. The solvent was evaporated, and the crystalline residue was recrystallized from MeOH to show m.p. 167~168° (colorless cubes); yield, 78.4%. *Anal.* Calcd. for $C_{18}H_{20}O_2N_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.23; H, 6.84; N, 9.51.

VIIb: This compound was prepared by the same method as described for VIIa. M.p. 174~175.5° (colorless needles (from MeOH)); yield, 69.2%. *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$: C, 69.92; H, 6.79; N, 8.59. Found: C, 69.73; H, 6.75; N, 8.49.

1-(2-Hydroxyethyl)-3-benzylamino-1,2,3,4-tetrahydroquinoline (VIIIa) and its 7-Methoxyl Derivative (VIIIb)——VIIIa: A solution of VIIa (4.0 g.) in dioxane (100 ml.) was added to a suspension of $LiAlH_4$ (1.6 g.) in dioxane (100 ml.) under stirring over a period of 15 min. The mixture was stirred and refluxed for 8 hr., and treated as described for the preparation of VIa. The resulting crude product was distilled *in vacuo*. The distillate (b.p$_{0.07\sim0.08}$ 195~200°) solidified on standing. Recrystallization from Et_2O gave colorless needles, m.p. 70~72°; yield, 85%. *Anal.* Calcd. for $C_{18}H_{22}ON_2$: N, 9.9. Found: N, 9.77. Picrate: m.p. 156~160° (decomp.) (red needles (from EtOH)). *Anal.* Calcd. for $C_{18}H_{22}ON_2 \cdot C_6H_3O_7N_3$: C, 56.35; H, 4.93; N, 13.69. Found: C, 56.37; H, 5.19; N, 13.63.

VIIIb: This compound was prepared by the method similar to that described for VIIIa. B.p$_{0.08}$ 212~220°, m.p. 72~75° (from Et_2O); yield, 85%. *Anal.* Calcd. for $C_{19}H_{24}O_2N_2$: N, 9.0. Found: N, 8.94.

1-(2-Bromoethyl)-3-benzylamino-1, 2, 3, 4-tetrahydroquinoline (IXa) and its 7-Methoxyl Derivative (IXb)——IXa: A mixture of VIIIa (0.7 g.) and HBr (saturated at 0°) (2 ml.) in a sealed tube was heated at 100° for 3 hr. The mixture was diluted with H_2O, whereby a pale blue solid precipitated. After filtration, the solution was made alkaline with dil. NaOH solution, extracted several times with Et_2O, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a light brown oil, which was used for the next reaction without purification.

The pale blue solid described above was recrystallized from EtOH to give colorless needles, m.p. 199~200° (decomp.). *Anal.* Calcd. for $C_{18}H_{21}N_2Br \cdot HBr$: C, 50.72; H, 5.20; N, 6.57. Found: C, 51.04; H, 5.32; N, 6.55.

When constant-boiling HBr was used for this reaction, the bromination did not occur.

IXb: VIIIb (1.5 g.) was treated with PBr_3 (0.8 g.) in CCl_4 (50 ml.) at room temperature for 3 hr. After refluxing for 35 min., the reaction mixture was cooled, poured onto ice, made alkaline with dil. NaOH solution, extracted several times with $CHCl_3$, and dried over K_2CO_3. Removal of the solvent under reduced pressure afforded a light brown oil, which was used for the next reaction without purification.

4-Benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine (Xa) and its 9-Methoxyl Derivative (Xb)——Xa: IXa, derived from VIIIa (3.75 g.) as described above, was refluxed with K_2CO_3 (6 g.) in toluene (30 ml.) for 8 hr. The reaction mixture (negative to Beilstein test) was cooled, washed with H_2O, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was distilled *in vacuo*. The distillate (b.p$_{0.06}$ 156~175°) solidified on standing. Recrystallization from petr. ether gave colorless needles, m.p. 67~68.5°; yield, 85%. *Anal.* Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63. Found: C, 81.90; H, 7.61. The molecular weight by the Rast method was 246. This compound was negative to Liebermann's nitrosamine test, and showed no peak characteristic of $>$NH, -OH and $-CH=CH_2$ groups in IR spectrum.

Dihydrobromide: m.p. 246~247° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{18}H_{20}N_2 \cdot 2HBr$: C, 50.72; H, 5.20; N, 6.57. Found: C, 50.77; H, 5.48; N, 6.57.

Xb: IXb, derived from VIIIb (1.5 g.), was treated as described for the preparation of Xa. B.p$_{0.03\sim0.05}$ 172~182° (pale yellow oil); yield, 85%. This compound was negative to Liebermann's nitrosamine test, and showed no peak characteristic of $>$NH, -OH and $-CH=CH_2$ groups in IR spectrum. Dihydrobromide: m.p. 220~222° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot 2HBr$: C, 50.02; H, 5.30; N, 6.14. Found: C, 51.91; H, 5.65; N, 6.46.

3,4,5,6-Tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine (XIa) and its 9-Methyoxyl Derivative (XIb)——XIa: A) To a solution of Xa (1.79 g.) in MeOH (15 ml.) containing 2 ml. of conc. HCl, was added 1.0 g. of Pd-C (5%). The mixture was shaken in H_2 atmospher for 12 hr. After removal of the catalyst and the solvent, the residue was dissolved in a small amount of H_2O and extracted with Et_2O. The aqueous layer was made alkaline with dil. NaOH solution, extracted with $CHCl_3$, and dried over K_2CO_3. From the ethereal solution toluene was isolated (identified by IR spectrum).

The residue left after evaporation of the above $CHCl_3$ solution was distilled *in vacuo*, b.p$_{0.3}$ 87～92° (colorless liquid): yield, 72%.
Dihydrobromide: m.p. 265～266° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{11}H_{14}N_2 \cdot 2HBr \cdot H_2O$: C, 37.31; H, 5.12; N, 7.91; Br, 45.13. Found: C, 37.96; H, 5.06; N, 7.97; Br, 44.60.

B) A mixture of Ⅶa (7 g.) and H_2SO_4 (70%, 70 ml.) was refluxed for 2 hr. The mixture was diluted with H_2O and extracted with benzene to remove BzOH. The aqueous layer was made alkaline with dil. NaOH solution, extracted several times with $CHCl_3$, and dried over K_2CO_3. After removal of the solvent, the residue was distilled *in vacuo*; b.p$_{0.3}$ 150～165°; yield, 79.3%.

The distillate (XIV) (3.6 g.) was heated with HBr (saturated at 0°) in a sealed tube for 6 hr. at 100°. The mixture was diluted with H_2O, made alkaline, extracted with $CHCl_3$, and dried over K_2CO_3 for 1.5 hr. After removal of the solvent, the residue (XV) was refluxed with K_2CO_3 (5 g.) in toluene (50 ml.) for 18 hr. under stirring. After cooling, inorganic materials and the solvent were removed, and the residue was distilled *in vacuo*; b.p$_{0.2}$ 97～110° (pale yellow liquid); yield, 42% (from XIV). The IR spectrum of the distillate was identical with that of the product obtained by the method A).
Ⅺb: This compound was prepared by the method A). B.p$_{0.2}$ 126～127° (colorless liquid); yield, 30%.

4-Methyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine (IIa) and its 9-Methoxyl Derivative (IIb)——Ⅱa: A mixture of Ⅺa (1.4 g.), HCOOH (2.5 ml.) and formalin (ca. 35%, 3.0 ml.) was heated on a water bath for 6 hr., diluted with H_2O, made alkaline with dil. NaOH solution, extracted with $CHCl_3$, and dried over K_2CO_3. After removal of the solvent, the residue was distilled *in vacuo*. B.p$_{0.27}$ 90～95° (colorless oil); yield, 92%. Dihydrobromide: m.p. 252～256° (decomp.) (from EtOH). Dihydrochloride: m.p. 244～246° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{12}H_{16}N_2 \cdot 2HCl$: C, 55.19; H, 6.94; N, 10.73. Found: C, 55.50; H, 6.91; N, 10.76.
Ⅱb: This compound was prepared by the same method as described for Ⅱa. B.p$_{0.06}$ 125° (bath temp.) (colorless oil); yield, 50%. Dihydrochloride: m.p. 249～251° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{13}H_{18}ON_2 \cdot 2HCl$: C, 53.61; H, 6.92; N, 9.62. Found: C, 53.51; H, 7.58; N, 9.13.

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Summary

The authors have attempted to synthesize a number of compounds belonging to the diazabenzobicyclo[3.3.1]nonane system shown by formula (I).

Some derivatives of 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine, *e.g.*, 4-methyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*g*][1,4]diazocine (Ⅱa) and its 9-methoxyl derivative (Ⅱb), were synthesized, and their structures were confirmed by chemical as well as spectral methods.

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