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Studies on the Syntheses of 7,8-Disubstituted 1-Benzylisoquinoline and Related Compounds. (4).[1] Synthesis of *dl*-Cularidine

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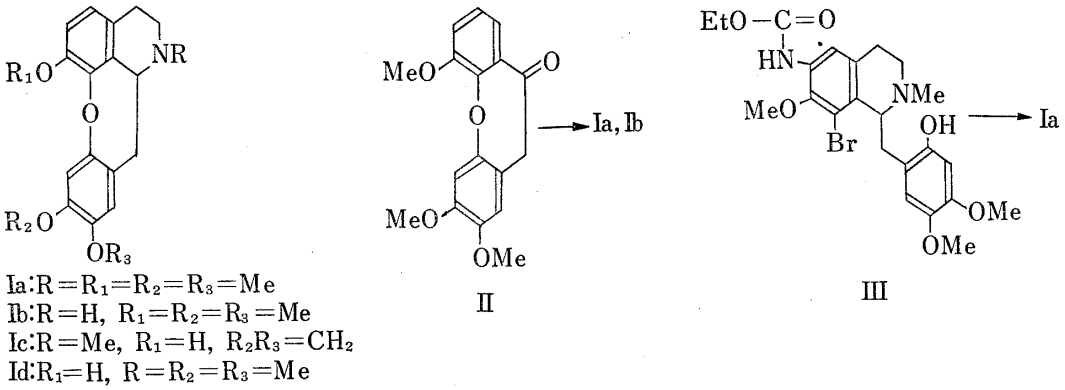
Bischler–Napieralski reaction of phenolic bromo amide (VIII), which was obtained from the Schotten–Baumann reaction of 4-benzyloxy-2-bromo-5-hydroxyphenethylamine (VI) with 2-bromo-4,5-dimethoxyphenylacetyl chloride (VII) and then reduction with $NaBH_4$ of the resultant dihydroisoquinoline (IX) gave 7-benzyloxy-5-bromo-1-(2-bromo-4,5-dimethoxybenzyl)-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (X).

N-Methylation of X afforded XI. The Ullmann reaction of XI in the presence of potassium carbonate and cupric oxide in pyridine gave 6-benzyloxy-4-bromo-1-methyl-9,10-dimethoxy-1,2,3,12,12a-pentahydrobenzoxepino[2,3,4-*i*,*j*]isoquinoline (XII).

Subsequent debenzylation and debromination of XII with hydrogen over 10% palladium-charcol gave *dl*-cularidine (Id) which was identified with natural cularidine by infrared and nuclear magnetic resonance spectral comparisons.

Four culaline type alkaloids, culaline (Ia), culamine (Ib), culaicine (Ic) and culaidine (Id) were isolated from the genera *Corydalis* and *Dicentra* by R.H.F. Manske.[3]



Ia: $R=R_1=R_2=R_3=Me$
Ib: $R=H$, $R_1=R_2=R_3=Me$
Ic: $R=Me$, $R_1=H$, $R_2R_3=CH_2$
Id: $R_1=H$, $R=R_2=R_3=Me$

II III

Chart 1

Compounds (Ia) and (Ib) were synthesized by Kametani and his co-workers[4] *via* the keto-oxepine (II) as an intermediate. Culaline (Ia) was also synthesized by Ishiwata and his co-workers[5] *via* the ethoxycarbamido compound (III). Recently, in the previous papers[1,6] we described that Ia, Ib, and Ic could be obtained by the intramolecular Ullmann reaction of 7,8-disubstituted isoquinoline (Va), (Vb) and (Vc), which were synthesized by the usual Bischler–Napieralski reaction from phenolic bromo amide (IVa) and (IVb).

1) Part 3: H. Iida, H.C. Hsu, T. Kikuchi, and K. Kawano, *Yakugaku Zasshi*, **92**, 1242 (1972).
2) Location: *No. 20–1, 3-chome, Kitashinjuku, Shinjuku-ku, Tokyo.*
3) *a*) R.H.F. Manske, *Can. J. Res.*, **16B**, 81 (1938); *b*) *Idem, ibid.*, **18B**, 97 (1947); *c*) *Idem, Can. J. Chem.*, **43**, 989 (1965); *d*) *Idem, ibid.*, **44**, 561 (1966); *e*) *Idem, J. Am. Chem. Soc.*, **72**, 55 (1950).
4) *a*) T. Kametani and K. Fukumoto, *J. Chem. Soc.*, **1963**, 4289; *b*) T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *J. Chem. Soc.*, **1964**, 4146.
5) S. Ishiwata, T. Fujii, N. Miyaji, Y. Sato, and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1850 (1970).
6) H.C. Hsu, T. Kikuchi, S. Aoyagi, and H. Iida, *Yakugaku Zasshi*, **92**, 1030 (1972).

Cularidine (Id), $C_{19}H_{21}O_4N$, has been assigned the structure by chemical[3d] and spectroscopic methods.[7] However, a total synthesis of Id have not been achieved yet. In the present paper, the authors wish to report the synthesis of Id by the method described previously,[1,6] confirming the structure of Id proposed by Manske[3d] and Kametani.[7]

The Schotten–Baumann reaction of 4-benzyloxy-2-bromo-5-hydroxyphenethylamine (VI)[1] with the acid chloride (VII) prepared from 2-bromo-4,5-dimethoxyphenylacetic acid[8] and thionyl chloride, gave the phenolic amide (VIII). Compound (VIII) was subjected to the Bischler–Napieralski reaction carried out with phosphoryl chloride in acetonitrile to give 7,8-dioxygenated 3,4-dihydroisoquinoline hydrochloride (IX) which was converted into 1,2,3,4-tetrahydroisoquinoline (X) by reducing with sodium borohydride in methanol. Structure (X) was verified by micro elemental analysis and spectral data: the infrared (IR) spectrum (in chloroform) showed the presence of hydroxy group (3590 cm^{-1}) and disappearance of carbonyl group absorption, which was present in phenolic bromo amide (VIII); the nuclear magnetic resonance (NMR) spectrum (in deuterochloroform) showed a methine proton at C-1 (5.50 τ, quartet).

N-Methylation of compound (X) with formalin and sodium borohydride afforded the 1,2,3,4-tetrahydro-2-methylisoquinoline (XI), which was characterised as its hydrochloride.

Compound (XI) was submitted to the Ullmann reaction using cupric oxide in the presence of anhydrous pyridine and anhydrous potassium carbonate at 160—170° for 3 hours to give reaction product (XII). Structure (XII) was verified by micro elemental analysis and spectral data: the IR spectrum (in chloroform) showed disappearance of hydroxy group absorption;

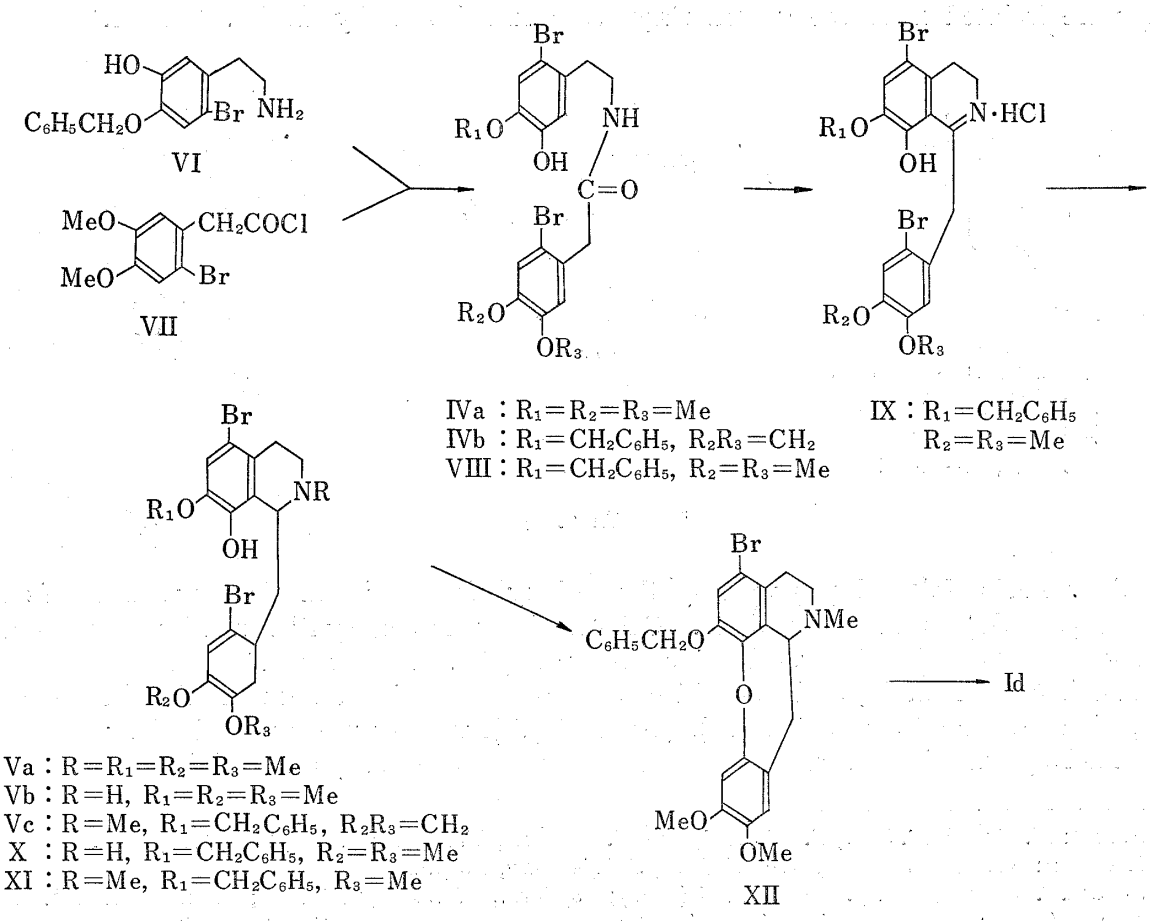


Chart 2

7) T. Kanetani, S. Shibuya, C. Kibayashi, and S. Sasaki, *Tetrahedron Letters*, **1966**, 3215.
8) T. Kametani, K. Fukumoto, S. Shibuya, and T. Nakano, *Chem. Pharm. Bull.* (Tokyo), **11**, 1299 (1963).

the chemical shift of C-12a proton in NMR spectrum (in deuterochloroform) was 5.40 τ as a quartet, which was a characteristic of cularine type compounds.[9]

Subsequent debromination and debenzylation of (XII) with hydrogen over 10% palladium-charcol gave *dl*-cularidine (Id), melted at 201—203°, whose IR and NMR spectra were superimposable with those of natural cularidine.

As a conclusion, it was confirmed that 7,8-dioxygenated isoquinoline, which was easily obtained from corresponding phenolic bromo amide by the usual Bischler–Napieralski reaction, could be converted to cularine type compounds by the intramolecular Ullmann reaction. And the structure of cularidine (Id), which was proposed by Manske and Kametani, was fully supported through these works.

Experimental[10]

N-(4-Benzyloxy-2-bromo-5-hydroxyphenethyl)-2-(2-bromo-4,5-dimethoxyphenyl) Acetamide (VIII)——A solution of 2-bromo-4,5-dimethoxyphenylacetyl chloride (VII) [prepared from 2-bromo-4,5-dimethoxyphenylacetic acid (5 g) and thionyl chloride (2 g)] in dry benzene (30 ml) was added to a mixture of 4-benzyloxy-2-bromo-5-hydroxyphenethylamine (VI) hydrochloride (3.2 g), ether (100 ml), and 5% sodium hydroxide (30 ml) at 0—10° with stirring, and the mixture was stirred at room temperature for 2 hr. The aqueous layer was then separated and acidified with 10% hydrochloric acid and extracted with chloroform. The $CHCl_3$ extract was washed with water, 10% HCl, water, 5% $NaHCO_3$, and water again, dried over Na_2SO_4, and evaporated to yield 3 g of VIII as a pale yellow solid. Recrystallization of the residue from EtOH gave colorless needles, mp 160—161°. *Anal.* Calcd. for $C_{25}H_{25}O_5NBr_2$: C, 51.83; H, 4.35; N, 2.42. Found: C, 52.03; H, 4.28; N, 2.23. IR cm^{-1} ($CHCl_3$): ν_{OH} 3550, ν_{NH} 3420; $\nu_{C=O}$ 1670. NMR (τ) (in $CDCl_3$): 2.55 (5H, singlet, aromatic protons), 2.94 (2H, singlet, aromatic protons), 3.19 (1H, singlet, aromatic proton), 3.25 (1H, singlet, aromatic proton), 4.93 (2H, singlet, $C_6H_5CH_2O$), 6.13 (6H, singlet, $2\times OCH_3$). Mass Spectrum *m/e*: 579 (M^+).

7-Benzyloxy-5-bromo-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-8-hydroxyisoquinoline(X)——A mixture of the phenolic amide (VIII) (2 g), $POCl_3$ (8 g), and CH_3CN (50 ml) was heated under reflux for 50 min. Excess reagents were then removed under reduced pressure. The residue was washed with *n*-hexane and dissolved in methanol (20 ml). To this solution, $NaBH_4$ (2 g) was added in portions with stirring at 0—10° within 30 min, the mixture was stirred at room temperature for another **30** min. The solvent was evaporated off *in vacuo*. The residue was decomposed with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated to yield 0.8 g of X as a pale yellow solid. Recrystallization of the product from EtOH–$CHCl_3$ gave colorless needles, mp 166—168°. *Anal.* Calcd. for $C_{25}H_{25}O_4NBr_2$: C, 53.30; H, 4.47; N, 2.49. Found: C, 53.62; H, 4.56; N, 2.30. IR cm^{-1} ($CHCl_3$): ν_{OH} 3650. NMR (τ) ($CDCl_3$): 2.56 (5H, singlet, aromatic protons), 2.92 (1H, singlet, aromatic proton), 3.00 (1H, singlet, aromatic proton), 3.12 (1H, singlet, aromatic proton), 5.50 (1H, quartet, $J=5$ and $J=10$ Hz, C-1 proton), 6.18 (6H, singlet, $2\times$O–CH_3). Mass Spectrum *m/e*: 563 (M^+).

7-Benzyloxy-5-bromo-1-(2-bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-8-hydroxy-2-methylisoquinoline (XI)——A mixture of tetrahydro isoquinoline (X) (1.5 g), 37% HCHO (1.5 ml), and 30 ml of MeOH–$CHCl_3$ (1: 1 v/v) was stirred at room temperature for 30 min. To this mixture, $NaBH_4$ (1.5 g) was added in portions with stirring at 0—10° within 30 min, the mixture was stirred at room temperature for another 30 min. Solvent was then removed. The residue was dissolved in water and extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to give 1.3 g of XI as a pale brownish syrup, whose hydrochloride was recrystallized to afford 1.2 g, mp 203—205° (decomp.) (from MeOH–ether). *Anal.* Calcd. for $C_{26}H_{27}O_4NBr_2\cdot HCl\cdot H_2O$: C, 49.42; H, 4.59; N, 2.21. Found: C, 49.41; H, 4.64; N, 2.26. IR cm^{-1} ($CHCl_3$): ν_{OH} 3550. NMR (τ) ($CDCl_3$): 2.55 (5H, singlet, aromatic protons), 2.88 (1H, singlet, aromatic proton) 3.00 (1H, singlet, aromatic proton), 3.10 (1H, singlet, aromatic proton), 6.13 (3H, singlet, O–CH_3), 6.15 (3H, singlet, O–CH_3), 7.61 (3H, singlet, N–CH_3). Mass Spectrum *m/e*: 577(M^+).

6-Benzyloxy-4-bromo-1-methyl-9,10-dimethoxy-1,2,3,12,12a-pentahydrobenzoxepino[2,3,4-*i*,*j*]isoquinoline (XII)——A mixture of the N-methyltetrahydroisoquinoline (XI) (1.2 g), anhydrous pyridine (60 ml), K_2CO_3 (1 g), and CuO (1.5 g) was heated at 160—170° with stirring under N_2 atmosphere for 3 hr. After cooled, the mixture was dissolved in $CHCl_3$ and the solution was filtered. The solvent was distilled off *in vacuo*, to give a reddish brown residue, which was purified by chromatography on silica gel eluted with $CHCl_3$

9) N.S. Bhacca, J.C. Craig, R.H.F. Manske, S.K. Roy, M. Shamma, and W.A. Slusarchyk, *Tetrahedron*, **22**, 1467 (1967).
10) All melting points were not corrected.

to yield 600 mg pale yellow solid. Recrystallization of the product from EtOH gave colorless needles, mp 151—152°. *Anal.* Calcd. for $C_{26}H_{26}O_4NBr$: C, 62.91; H, 5.28; N, 2.82. Found: C, 63.28; H, 5.18; N, 2.66. NMR (τ) ($CDCl_3$): 2.60 (5H, singlet, aromatic protons), 2.83 (1H, singlet, aromatic proton), 3.22 (1H, singlet, aromatic proton), 3.48 (1H, singlet, aromatic proton), 6.20 (3H, singlet, O–CH_3), 6.30 (3H, singlet, O–CH_3), 7.40 (3H, singlet, N–CH_3). Mass Spectrum *m/e*: 495 (M^+).

***dl*-Cularidine (Id)**——A mixture of XII (500 mg), and EtOH (50 ml) was stirred at room temperature on 10% Pd-C in a current of hydrogen. After absorption of the calculated amount of hydrogen, the catalyst was filtered off, and the solvent was distilled off *in vacuo*. The residue was basified with aqueous ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to yield 200 mg pale yellow solid. Recrystallization of the product from MeOH gave colorless needles, mp 201—203°. *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.46; N, 4.28. Found: C, 69.50; H, 6.61; N, 3.94. IR (in $CHCl_3$) and NMR (in $CDCl_3$) spectra of this compound were completely identical with those of the natural product. NMR (τ) ($CDCl_3$): 3.18 (2H, singlet, aromatic protons), 3.24 (1H, singlet, aromatic proton), 3.42 (1H, singlet, aromatic proton), 5.60 (1H, quartet, $J=4$ and $J=12$ Hz, C_{12a}–H), 6.18 and 6.20 (6H, singlet, $2\times$O–CH_3), 7.41 (3H, singlet, N–CH_3). Mass Spectrum *m/e*: 327 (M^+).

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