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The Synthesis of β-Carboline Derivatives. VIII.[1] Syntheses of Bisnorflavocarpine and Its Relatives

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In 1962, Büchi isolated a new alkaloid[3] in 0.0005% yield from the stem bark of *Pleiocarpa mutica* Benth. (*Apocyanaceae*), of which the crude extract had been reported to have hypotensive activity.[4,5] This alkaloid, beautiful yellow crystals, was named "flavocarpine" by Büchi[3] with reference to its yellow color.

The structure of flavocarpine was established to be Ia by Büchi, *et al.* and concurrently the alkaloid was synthesized by the same workers[3] by application of our synthetic method of β-carboline derivatives.[6]

Incidentally, we had been engaged in extention of this method[6] to syntheses of indoloquinolizidine with a substituent at C-2 in connection with the synthesis of *Hunteria* alkaloids, for instance, hunterburnine methochloride (II).[7]

Thus, the condensation of 3-(2-bromoethyl)indole (III) with methyl 2-chloroisonicotinate (IVa)[8] was conducted under several conditions to afford the indoloquinolizine (Va), red small needles, mp 328—331° (decomp.), in rather low yields (6—31%), results of which are listed in Table I. The Table indicates that the best yield was obtained by heating a mixture of III and IVa (molar ratio=1:2.5—3.0) without solvent under nitrogen at 90—95° for 15—20 hr.

Table I

Molar ratio of III to IVa	Solvent	Temperature (°C)	Reaction time (hr)	Yield of (%)
1/2	toluene	reflux (N_2)	12—14	6—14
2.8/1	dioxane	80—90	40—44	20
1.0/2.5—3.0	——	90—95 (N_2)	15—20	25—31

The ultraviolet spectrum of the compound (V) was bathochromically shifted on addition of alkali, which was considered to be corresponding to the conversion of the quaternary salt (V) into the anhydronium base (VII), as is well known with the similar compound[9] (See Fig. 1).

Subsequently, a solution of the ester (Va) in ethanol was refluxed with the excess of tetrachloro-*o*-benzoquinone for twenty hours to yield the dehydrogenation product (VIa, mp 334—336°, $\nu_{C=O}$ 1720 cm^{-1}), organge yellow needles, in 73% yield, during which time

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[1] Part VII: Y. Ban, R. Sakaguchi, and M. Nagai (née Seo), *Chem. Pharm. Bull.* (Tokyo), **13**, 931 (1965).

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[3] G. Büchi, R.E. Manning, and F.A. Hochstein, *J. Am. Chem. Soc.*, **84**, 3393 (1962).

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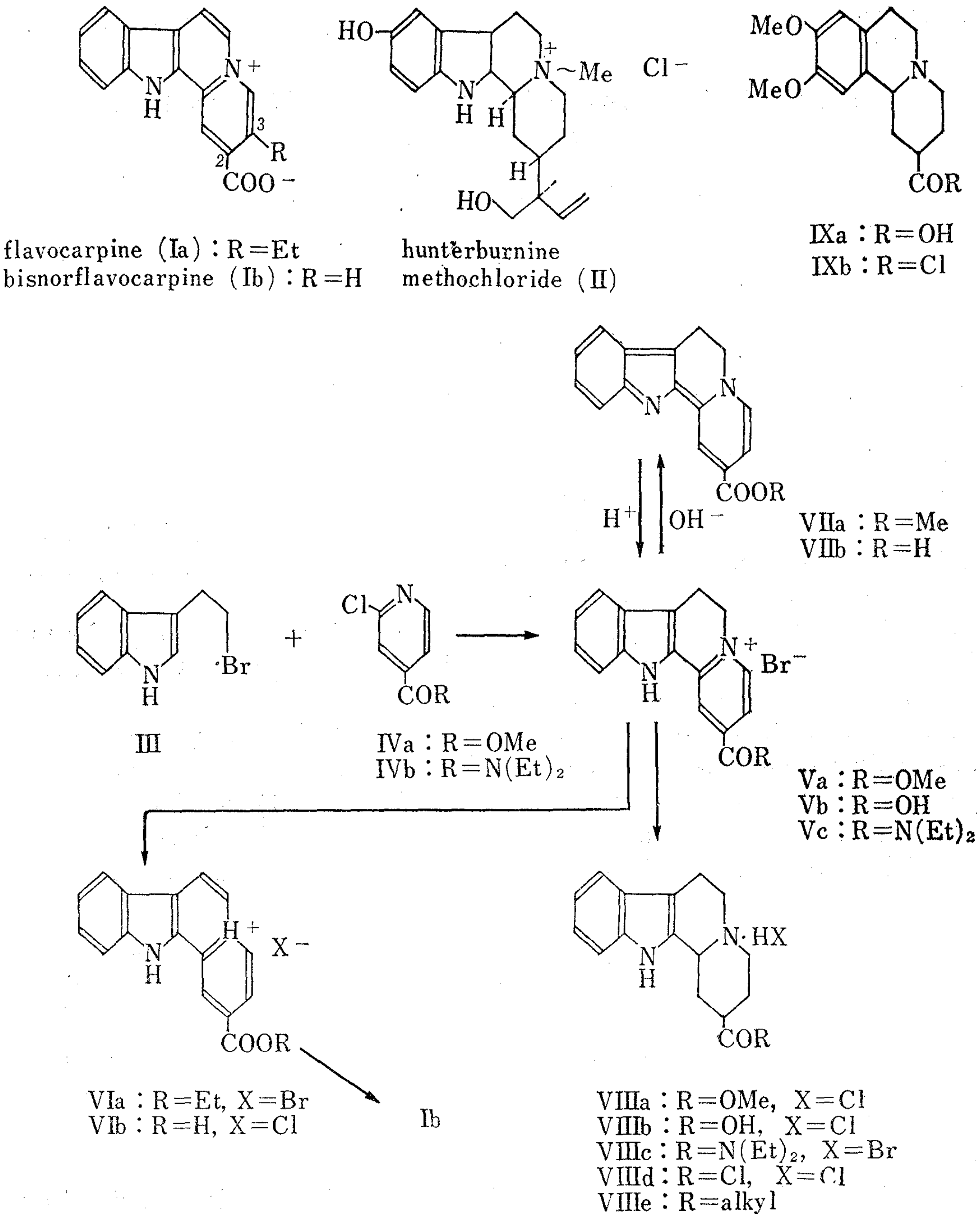

flavocarpine (Ia) : R=Et
bisnorflavocarpine (Ib) : R=H

hunterburnine
methochloride (II)

IXa : R=OH
IXb : R=Cl

VIIa : R=Me
VIIb : R=H

III

IVa : R=OMe
IVb : R=N(Et)$_2$

Va : R=OMe
Vb : R=OH
Vc : R=N(Et)$_2$

VIa : R=Et, X=Br
VIb : R=H, X=Cl

Ib

VIIIa : R=OMe, X=Cl
VIIIb : R=OH, X=Cl
VIIIc : R=N(Et)$_2$, X=Br
VIIId : R=Cl, X=Cl
VIIIe : R=alkyl

Chart 1

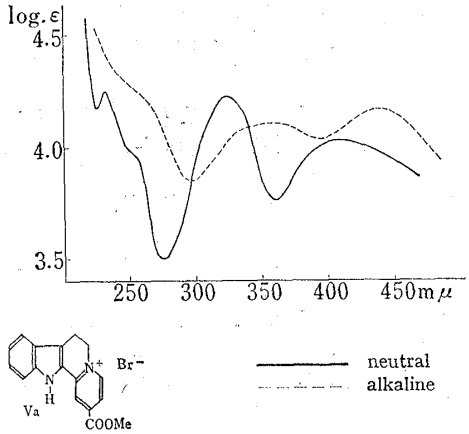

Fig. 1

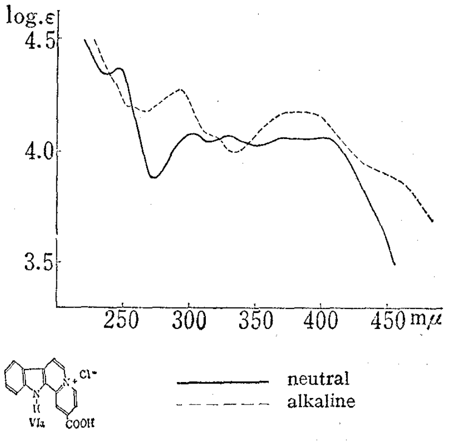

Fig. 2

the complete interchange of the methyl to the ethyl ester (VIa) occurred, that was confirmed by elemental analyses. The ultraviolet spectrum of the resulting product is remarkably different from that of the dihydro-compound (Va). The ethyl ester (VIa) was hydrolyzed to the corresponding acid (VIb), hygroscopic orange amorphous powders, mp 318—319° (decomp.), $\nu_{C=O}$ 1725 cm^{-1} (broad), in a quantitative yield, by refluxing VIa in methanol containing hydrochloric acid for forty hours.

The ultraviolet spectrum of VIb is in good accordance with that of flavocarpine hydrochloride reported by Büchi, and the bathochromic shift of the spectrum was observed in an alkaline solution (See Fig. 2).

An aqueous solution of this acid (VIb) was poured on the Amberlite IR–4B (acetate type), the elute was concentrated, and the residue was recrystallized from glacial acetic acid to afford bisnorflavocarpine (Ib), mp 307—308.5° (decomp.), yellow brownish needles, in 27.2% yield. The ultraviolet spectrum of this compound is nearly same as that of the starting carboxylic acid (VIb) in EtOH, and the absorption at 1725 cm^{-1} (COOH) in the infrared spectrum of the initial compound (VIb) disappeared and instead, a new broad band was observed at 1602 cm^{-1} ($-COO^-$).

On the other hand, the hydrogenation of the condensation product (Va) in the presence of the Adams' catalyst yielded the hydrogenated compound (VIIIa), colorless needles, mp 255—257°, which was hydrolyzed to the carboxylic acid (VIIIb).

For the synthesis of hunterburnine methochloride (II) type of compounds, the conversion of this acid (VIIIb) to the diethylamide (VIIIc) *via* the chloride (VIIId) was attempted, but preparation of the chloride with the usual reagents, for instance, thionyl chloride or oxalyl chloride *etc.*, resulted in failure. The reason why this chloride (VIIId) is difficult to be prepared, is not clear at present, but it makes us reminiscent of difficulty in preparing the chloride (IXb) from the acid (IXa) described by Sugasawas and Oka[10] who assumed that this difficulty is probably due to the amphoteric character of the acid. The relative positions of the basic and the acidic centers are quite same in both compounds (VIIIb and IXa). This diethylamide (VIIIc) would be expected to react with the Grignard reagent affording the ketone (VIIIe), which should be converted to hunterburnine derivatives.

Therefore, 3–(2–bromoethyl)indole (III) was condensed with N,N–diethyl–2–chloroisonicotinamide (IVb) to afford the quinolizinium bromide (Vc), yellow small scales, mp 280—281.5°, which was hydrogenated with the Adams' catalyst to the corresponding indoloquinolizidine hydrobromide (VIIIc), colorless needles, mp 289—291°, and the free base, pale yellow small prisms, mp 253—255°. This diethylamide (the free base of VIIIc) was subjected to the Grignard reaction along the above–mentioned line, but the objective compound (VIIIe) was not isolated. Thus, this project was changed to the other synthetic approaches which will be reported in the forthcoming paper. The pharmacological tests of these compounds are in progress.

Experimental[11]

2-Methoxycarbonyl-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium Bromide (Va)——A mixture of 3–(2–bromoethyl)indole (III, 5.60 g, 25 mmoles) and methyl 2–chloroisonicotinate (IVa, 10.81 g, 63 mmoles) was heated at 90±3° for 15 hr. On cooling, absolute ether was added to the reaction mixture of a dark red color, the whole was digested, and the precipitated material was collected and recrystallized from EtOH to afford 2.79 g (31.1%) of red small needles, mp 328—331° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}O_2N_2Br \cdot 0.5H_2O$: C, 56.11; H, 4.84; N, 7.70. Found: C, 56.09; H, 4.47; N, 8.19. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.24), 256 (3.94) (shoulder), 324 (4.22), 410 (4.02). λ_{min}^{EtOH} mμ (log ε): 225 (4.17), 275 (3.50), 360 (3.75). $\lambda_{max}^{EtOH \cdot NaOH}$ mμ: 265 (shoulder), 360, 438. $\lambda_{min}^{EtOH\ NaOH}$ mμ: 297, 390. IR ν_{max}^{Nujol} cm^{-1}: 1719, 1631, 1613.

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10) S. Sugasawa and K. Oka, *Chem. Pharm. Bull.* (Tokyo), 2, 85 (1954).
11) All melting points are not corrected.

2-Ethoxycarbonyl-12*H*-indolo[2,3-*a*]quinolizinium Bromide (VIa)——To a solution of the foregoing ester (Va, 600 mg) in absolute EtOH (60 ml) was added 2.70 g of tetrachloro-*o*-benzoquinone, and the whole mixture was refluxed on a water bath for 20 hr. On cooling, the precipitates were collected, the filtrate was concentrated to dryness and the residue was washed well with AcOEt, which was combined with the initial crop. The whole was recrystallized from EtOH-AcOEt to yield 436 mg (73%) of orange red samll needles, mp 334—336° (decomp.). *Anal.* Cacld. for $C_{18}H_{15}O_2N_2Br$: C, 58.23; H, 4.08; N, 7.55. Found: C, 58.51; H, 4.59; N, 7.84. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1639, 1615.

Bisnorflavocarpine Hydrochloride (VIb)——A solution of the ester (VIa, 300 mg) in MeOH (6 ml) containing concentrated hydrochloric acid (30 ml) was refluxed for forty hours in an oil bath, the resulting solution was concentrated to *ca.* 15 ml, and water was added. The precipitated crystals were collected and recrystallized from dil. aq. HCl-MeOH to afford hygroscopic orange amorphous powders, mp 318—319° (decomp.). *Anal.* Calcd. for $C_{16}H_{11}O_2N_2Cl \cdot H_2O$: C, 60.67; H, 4.14; N, 8.85. Found: C, 61.11; H, 4.57; N, 8.64. UV λ_{max}^{EtOH} mμ (log ε): 247.5 (4.23), 301 (4.12), 328 (4.12), 370 (4.12) (shoulder), 407 (4.12). λ_{min}^{EtOH} mμ (log ε): 236 (4.22), 272.5 (3.74), 314 (4.11), 349 (4.11). IR ν_{max}^{Nujol} cm^{-1}: 1725 (broad), 1640, 1626.

Bisnorflavocarpine (Ib)——An aqueous solution of the carboxylic acid (VIb, 200 mg) was poured on 20 ml of the anion exchange resin (Amberlite IR-4B, acetate form), which was eluted with 5% AcOH. The elute was concentrated and the residue was recrystallized from glacial acetic acid to afford 48 mg (27.2%) of yellow brownish needles, mp 307—308.5° (decomp.). *Anal.* Calcd. for $C_{16}H_{11}O_2N_2 \cdot \frac{1}{2}CH_3COOH$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.64; H, 4.06; N, 9.85. IR ν_{max}^{Nujol} cm^{-1}: 1637, 1603 (brood). An absorption at 1725 cm^{-1} disappeared.

2-Methoxycarbonyl-1,2,3,4,5,6,7-hexahydro-12*H*,12b*H*-indolo[2,3-*a*]quinolizine Hydrochloride (VIIIa)——A methanolic solution of the foregoing bromide (Va, 1.80 g) was refluxed with AgCl to yield the corresponding chloride (mp 325—327° (decomp.)), which was dissolved in MeOH·H$_2$O (6:1, 350 ml) and conc. HCl (1.5 ml) was added. The whole solution was subjected to hydrogenation with the Adams' catalyst (200 mg) at room temperature in atmospheric pressure of hydrogen, and 3 mole eq. of H$_2$ was absorbed in 8 hr. After removal of the catalyst and solvent, the residual hydrochloride was recrystallized from MeOH to give 1.256 g (78%) of colorless small needles, mp 255—257° (decomp.). *Anal.* Calcd. for $C_{17}H_{20}O_2N_2 \cdot HCl$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.29; H, 6.41; N, 8.95.

2-Carboxy-1,2,3,4,6,7-hexahydro-12*H*,12b*H*-indolo[2,3-*a*]quinolizine Hydrochloride (VIIIb)——To an ethanolic solution of the foregoing ester (VIIIa, 600 mg) was added 5.0 ml of 10% ethanolic solution of KOH, and the whole solution was refluxed for ten hr. On cooling, the ethanol was evaporated, the residue was dissolved in 10 ml of water, then washed with ether. The aqueous layer was neutralized with conc. HCl (0.9 ml) to separate the white precipitate, the whole mixture was kept in a refrigerator overnight, and the precipitate was collected. Recrystallization from water gave 410 mg of colorless prisms, mp 292—294° (decomp.) in 71.4% yield. *Anal.* Calcd. for $C_{16}H_{18}O_2N_2 \cdot HCl \cdot H_2O$: C, 59.16; H, 6.52; N, 8.63. Found: C, 59.05; H, 6.60; N, 9.04. IR ν_{max}^{Nujol} cm^{-1}: 3200 (broad), 2700 (broad), 1730.

N,N-Diethyl-2-chloroisonicotinamide (IVb)——To a solution of Et$_2$NH (18.0 g) in dry benzene (45 ml) was added under ice-cooling in 3 hr a benzene solution (25 ml) of 2-chloroisonicotinyl chloride which had been prepared from the reaction of 14.0 g of the acid with 65.1 ml of SOCl$_2$, and the whole mixture was allowed to stand overnight.

The benzene-layer was washed with water, saturated sodium bicarbonate solution, then with water and dried over Na$_2$SO$_4$. The solvent was removed and the product was purified by distillation to afford 16.7 g of the diethylamide (IVb), colorless liquid, bp 134—135° (3.5 mmHg). *Anal.* Calcd. for $C_{10}H_{13}ON_2Cl$: C, 56.47; H, 6.13; N, 13.17. Found: C, 56.76; H, 6.53; N, 13.18. IR ν_{max}^{Film} cm^{-1}: 1640, 1593.

2-(N,N-Diethylcarbamoyl)-6,7-dihydro-12*H*-indolo[2,3*a*]quinolizinium Bromide (Vc)——A mixture of 3-(2-bromoethyl)indole (III, 2.19 g, 13 mmoles) and the foregiong amide (IVb, 8.30 g, 39 mmoles) was heated at 90±4° for 26 hr. On cooling, absolute ether was added, triturated, and the solid was collected by filtration.

Recrystallization from ethanol gave 1.019 g (19.6%) of yellow small scales, mp 280—281.5° (decomp.). *Anal.* Calcd. for $C_{20}H_{22}ON_3Br$: C, 60.00; H, 5.54; N, 10.51. Found: C, 59.79; H, 5.66; N, 10.4. UV λ_{max}^{EtOH} mμ (log ε): 254 (4.07), 320 (4.24).

2-(N,N-Dimethylcarbamoyl)-1,2,3,4,6,7-hexahydro-12*H*,12b*H*-indolo[2,3-*a*]quinolizine (The free base of VIIIc)——A solution of 1.223 g of the foregoing quaternary bromide (Vc) in 80 ml of MeOH was hydrogenated over 122 mg of Adams' catalyst at room temperature in atmospheric pressure of hydrogen, and 3 molar equivalent of hydrogen was absorbed in 8 hr. Worked up in the usual manner, the hydrobromide (VIIIc) was obtained as colorless needles (960 mg, 77.4% yield), mp 289—291°, which was liberated to the free base. The crude base was recrystallized from ethanol-hexane to afford small pale-yellow prisms, mp 253—255°. *Anal.* Calcd. for $C_{20}H_{27}ON_3$: C, 73.80; H, 8.37; N, 12.92. Found: C, 74.09; H, 8.46; N, 12.94.

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