

5*H*-Isoindolo[1,2-*b*][3]benzazepines

VIII.* Synthesis of derivatives of 5*H*-isoindolo[1,2-*b*]isoquinol-5-one

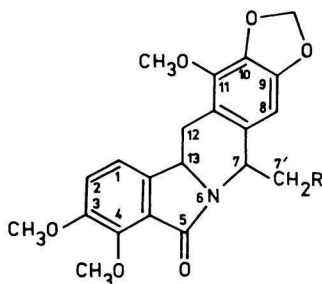
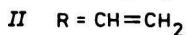
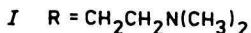
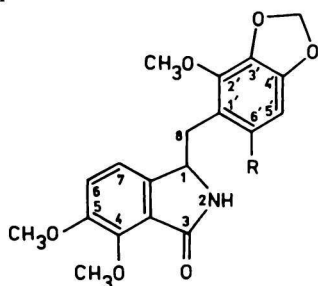
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Derivatives of 5*H*-isoindolo[1,2-*b*]isoquinol-5-one, isomeric with alkaloids related to 5*H*-isoindolo[1,2-*b*][3]benzazepine were synthesized from dihydronarceine imide.

(±)-Lennoxamine, a representative of the group of 5*H*-isoindolo[1,2-*b*][3]benzazepine alkaloids produced by the *Berberidaceae* plants family, biogenetically related to berberine [1] was the target of some synthetic studies [2—4]. In one of our preceding papers [5] a synthesis of 12-methoxylennoxamine derivatives by cyclization of dihydronarceine imide *N*-oxide was described. In the present study dihydronarceine imide (*I*) was utilized as a starting material for the preparation of 11-methoxylennoxamine isomers and further 5*H*-isoindolo[1,2-*b*]isoquinolines structurally isomeric with 5*H*-isoindolo[1,2-*b*][3]benzazepines.



Dihydronarceine imide (*I*) obtained by hydrogenation of (*Z*)-narceine imide in acetic acid over Adams catalyst was reacted with methyl iodide and the product was degraded *via* Hofmann reaction to dihydronarceone imide (*II*) [6]. The imide *II* heated in hydrochloric acid afforded a mixture of two substances giving on resolution by crystallization compounds *IIIa*, *IIIb*, isomeric with the

* For Part *VII* see *Chem. Papers* 45, 95 (1991).

starting imide *II*. The IR spectrum of *IIIa* and *IIIb* showed a band associated with a five-membered lactam-grouping at $\tilde{\nu} = 1696 \text{ cm}^{-1}$ and further vibrations due to the presence of an aromatic ring at $\tilde{\nu} = 1601$ and 1496 cm^{-1} ; on the other hand, bands corresponding to the vibrations characteristic of N—H and C=C bonds of the starting imide *II* were absent. The mass spectrum of *IIIa* and *IIIb* had quite a simple fragmentation pattern at 70 eV ionizing energy: the parent peak at $m/z = 368$ originated from the molecular radical ion by the loss of a methyl radical. The ^1H NMR spectrum of *IIIa* and *IIIb* lacked the proton signals of an ethylidene grouping and an imine group when contrasted with that of the starting imide *II*; nonetheless, signals of a methyl group split into a doublet by an interaction with the proton of the sp^3 hybridized carbon appeared. Presence of these signals — considering the reaction possibilities given by the structure of the starting material — is indicative of a 6,7,12,13-tetrahydro-5*H*-isoindolo[1,2-*b*]isoquinol-5-one skeleton of compounds under investiga-

Table 1

 ^1H NMR chemical shifts in the spectra of compounds *III*, *V*, and *VI*

Position	Compound				
	<i>IIIa</i>	<i>IIIb</i>	<i>Va</i>	<i>Vb</i>	<i>VI</i>
H-1	7.15 dd	7.18 dd	7.16 dd	7.18 dd	7.21 dd
H-2	7.12 d	7.13 d	7.15 d	7.13 d	7.18 d
H-7	4.99 dddd	5.33 dddd	5.24 dddd	5.58 dddd	—
H-8	6.44 d	6.47 d	6.44 d	6.49 d	6.97 s
H-12ax	3.60 ddd	3.48 ddd	3.54 ddd	3.53 ddd	3.57 ddd
H-12eq	2.27 dd	2.17 dd	2.56 dd	2.12 dd	2.27 dd
H-13	4.31 dddd	4.50 dddd	4.33 dddd	4.89 dddd	4.53 ddd
H-7'	1.67 d	1.53 d	—	—	—
H-7'a	—	—	5.11 dd	4.11 dd	5.42 d
H-7'b	—	—	3.63 dd	3.85 dd	6.40 s
C-3—OCH ₃	3.90 s	3.90 s	3.91 s	3.92 s	3.92 s
C-4—OCH ₃	4.10 s	4.11 s	4.10 s	4.11 s	4.10 s
C-11—OCH ₃	4.06 s	4.01 s	4.06 s	4.03 s	4.02 s
OCH ₂ O	5.96 ABq	5.94 ABq	5.96 ABq	5.94 ABq	5.94 ABq

tion. The observed interactions of the H-7 proton with protons H-12ax and H-13 brought forward further evidence for the closure into an isoquinoline ring. Principal dissimilarities between compounds *IIIa* and *IIIb* in the ^1H NMR spectra (Tables 1 and 2) are in the position of proton signals bonded in the C ring; this was evoked by a different spatial arrangement, as proved by a NOE differential experiment [7] (Tables 3 and 4). The H-13 proton of compound *IIIa*

Table 2

Coupling constants *J*/Hz in the spectra of compounds *III*, *V*, and *VI*

$J_{H,H}$	Compound				
	<i>IIIa</i>	<i>IIIb</i>	<i>Va</i>	<i>Vb</i>	<i>VI</i>
1,2	8.1	8.1	8.2	8.2	8.1
1,13	0.9	0.8	0.8	0.8	0.7
7,8	0.4	0.7	0.5	0.6	—
7,12ax	0.9	1.1	0.8	1.2	—
7,13	0.9	0.8	0.8	0.5	—
7,7'	6.4	6.7	—	—	—
7,7'a	—	—	3.8	4.6	—
7,7'b	—	—	2.0	3.1	—
12ax,12eq	15.1	16.2	15.1	16.2	15.9
12ax,13	11.9	11.5	12.0	11.5	12.1
12eq,13	3.3	4.8	3.4	4.9	3.8
7'a,7'b	—	—	10.1	11.0	0.9

Table 3

 ^1H — ^1H nuclear Oberhauser effect (%) in the spectrum of compound *IIIa*

Proton irradiated	Proton observed						
	H-1	H-7	H-8	H-12ax	H-12eq	H-13	H-7'
H-7	—	—	26.9	—	—	2.3	1.6
H-8	—	16.7	—	—	—	—	0.4
H-12ax	1.2	—	—	—	35.4	—	—
H-12eq	5.5	—	—	34.2	—	15.8	—
H-13	2.0	3.8	—	—	6.2	—	—
H-7'	—	19.4	8.2	2.6	—	—	—

Table 4

 ^1H — ^1H nuclear Oberhauser effect (%) in the spectrum of compound *IIIb*

Proton irradiated	Proton observed						
	H-1	H-7	H-8	H-12ax	H-12eq	H-13	H-7'
H-7	—	—	10.7	—	—	—	2.0
H-8	—	13.2	—	—	—	—	0.8
H-12ax	0.5	—	—	—	36.9	—	—
H-12eq	2.6	—	—	28.8	—	14.8	—
H-13	2.1	—	—	—	5.6	—	1.0
H-7'	—	25.2	12.7	—	—	13.6	—

can occupy only an axial position and consequently, it interacts with H-1, H-7, and H-12eq protons, which means that the H-7 proton is in a *cis* position towards H-13 and is, therefore, axial. Irradiation of the H-13 proton in the ^1H NMR spectrum of *IIIb* resulted in an intensity increase of proton signals H-1, H-12eq, and the C-7' methyl group, which means that the latter must be in a *cis* position in regard to H-13. These findings are in line with the proposed structures *IIIa* and *IIIb* drawn in Fig. 1 showing the H-13 proton in a *trans* arrangement with respect to the lone electron pair at nitrogen N-6. Diastereomers *IIIa*, *IIIb*, isomeric with 12-methoxylennoxamine were analytically separated by liquid chromatography at a resolution $R_s = 1.4$ and a number of theoretical plates $N = 18\,000\text{ m}^{-1}$. This method served for estimation of the mutual ratio of compounds *IIIa*, *IIIb*, which was found to be 1.8 : 1 after an acid catalyzed cyclization of the imide *II*. This ratio dramatically changed upon treating the mixture in methanolic KOH, when compound *IIIa* was totally isomerized to *IIIb* after 1 h heating.

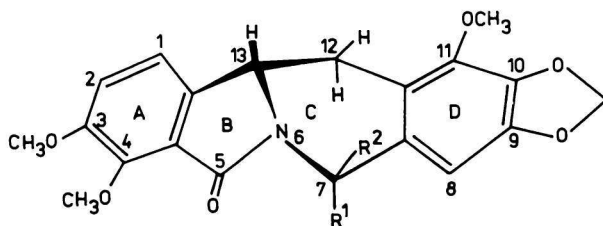
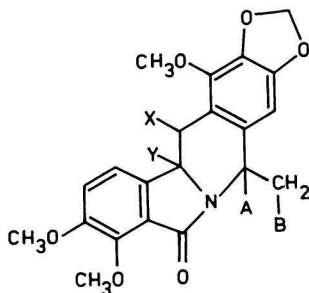


Fig. 1. Relative configuration of compounds *IIIa* ($R^1 = \text{CH}_3$, $R^2 = \text{H}$), *IIIb* ($R^1 = \text{H}$, $R^2 = \text{CH}_3$), *Va* ($R^1 = \text{CH}_2\text{Br}$, $R^2 = \text{H}$), and *Vb* ($R^1 = \text{H}$, $R^2 = \text{CH}_2\text{Br}$).

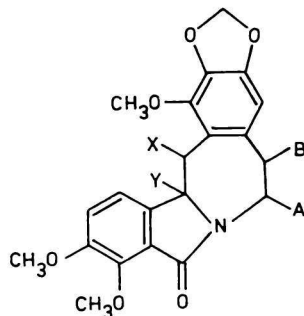
Dihydronarceone imide (*II*) added bromine to the ethylidene double bond. Bromination with an equivalent amount of bromine at 0°C afforded after 1 h a mixture of compounds *IV* and *V*, which were chromatographically separated. Compound *IV* is, according to spectral evidence, the required 1',2'-dibromodihydronarceone imide. The IR spectrum of compound *V* lacked, like spectra of *IIIa* and *IIIb*, bands of vibrations of N—H and C=C bonds. The mass spectrum of compound *V* contained peaks indicative of isotopic ions at $m/z = 463$ and at $m/z = 461$ and 381, the latter resulting from elimination of hydrogen bromide. The pairs of peaks of highest intensity at $m/z = 94$ and 96 belonged to isotopes of methyl bromide. The ^1H NMR spectrum revealed compound *V* to be a mixture of diastereomers of 7-bromomethyl-6,7,12,13-tetrahydro-5*H*-isoindolo[1,2-*b*]isoquinol-5-one; these were not separated, but — in view of its further utilization — only analyzed employing findings obtained when solving the structure of compounds *IIIa* and *IIIb* (Tables 1 and 2). Proton

H-13 of the major constituent *Va* is in a *cis* position towards the proton H-7, whilst in the minor constituent *Vb* the bromomethyl group is in a *cis* position with regard to H-13.



VI AB = double bond; X = Y = H

VII A = B = H; XY = double bond



VIII A = B = H; XY = double bond

IX AB = double bond; X = Y = H

Dehydrobromination of the mixture *Va*, *Vb* in methanolic KOH afforded compound *VI* with an exocyclic methylene group attached to C-7, as evidenced by proton signals in the ^1H NMR spectrum at $\delta = 6.40$ and 5.43 . Compound *VI* ($\text{C}_{21}\text{H}_{19}\text{NO}_6$) is so far the fourth tetracyclic derivative of isoindole obtained from (*Z*)-narcaine imide. The isomeric compounds *VI*—*IX* [1, 6] differ *inter alia* in their UV spectra: the highest conjugation between rings A and D was displayed by compounds *VII* ($\lambda_{\text{max}} = 397$ nm, $\log \epsilon = 3.42$ m 2 mol $^{-1}$) and *VIII* ($\lambda_{\text{max}} = 380$ nm, $\log \epsilon = 3.49$ m 2 mol $^{-1}$); the conjugation decreases in compound *IX* ($\lambda_{\text{max}} = 342$ nm, $\log \epsilon = 3.02$ m 2 mol $^{-1}$) and the lowest one was shown by compound *VI* ($\lambda_{\text{max}} = 284$ nm, $\log \epsilon = 3.09$ m 2 mol $^{-1}$).

Experimental

The melting points were estimated on a Kofler micro hot-stage, the IR spectra of chloroform solutions of the prepared compounds were measured with a Perkin—Elmer, model 983, spectrophotometer, the respective electron impact mass and ^1H NMR spectra of deuteriochloroform solutions containing tetramethylsilane as an internal standard were recorded with Jeol JMS 100 D ($E = 70$ eV, $I = 300$ μA) and Bruker AM-300 ($\nu = 300$ MHz) instruments. A column (150 mm \times 3 mm) packed with Separon SGX C18, 7 μm (Tessek, Prague) was employed for high-performance liquid chromatography; mobile phase methanol—water ($\phi_r = 6 : 4$), flow rate 0.4 cm 3 min $^{-1}$, UV detector ($\lambda = 254$ nm). Silufol UV 254 sheets in chloroform—methanol ($\phi_r = 9 : 1$) were used for analytical thin-layer chromatography.

Cyclization of dihydronarceone imide (II)

Concentrated hydrochloric acid (10 cm³) was added to a solution of the imide *II* (280 mg, 0.72 mmol) dissolved in methanol (100 cm³) and the solution was refluxed for 1.5 h. (Course of this reaction was monitored by thin-layer chromatography.) The mixture was concentrated and the residue dissolved in chloroform was shaken with aqueous NaHCO₃ ($\rho = 50 \text{ g dm}^{-3}$), the organic layer was dried with sodium sulfate, filtered, the solvent was distilled off and the residue was six times recrystallized from methanol to give the chromatographically pure *IIIa* (checked by high-performance liquid chromatography, $t_r = 29.4 \text{ min}$ for *IIIa*, $t_r = 26.6 \text{ min}$ for *IIIb*). The mother liquors were combined, the solvent was distilled off and the residue was crystallized from benzene—heptane ($\varphi_r = 1 : 1$) to furnish *IIIb*.

Compound IIIa: Yield = 131.2 mg, m.p. 196—196.5°C. For C₂₁H₂₁NO₆ ($M_r = 383.4$) $w_i(\text{calc.})$: 65.79% C, 5.52% H, 3.65% N; $w_i(\text{found})$: 65.82% C, 5.44% H, 3.48% N. IR spectrum, $\tilde{\nu}/\text{cm}^{-1}$: 3003, 2943, 2886, 2839, 1696, 1601, 1496. Mass spectrum, m/z ($I_r/\%$): 383 (10), 382 (37), 368 (100), 252 (5), 192 (2), 191 (19), 190 (5). ¹H NMR spectrum — Tables 1 and 2.

Compound IIIb: Yield = 29.6 mg, m.p. 188—189°C. For C₂₁H₂₁NO₆ ($M_r = 383.4$) $w_i(\text{calc.})$: 65.79% C, 5.52% H, 3.65% N; $w_i(\text{found})$: 65.70% C, 5.48% H, 3.60% N. IR spectrum, $\tilde{\nu}/\text{cm}^{-1}$: 3000, 2885, 2839, 1696, 1601, 1496. Mass spectrum, m/z ($I_r/\%$): 383 (10), 382 (36), 368 (100), 252 (6), 192 (3), 191 (17), 190 (2). ¹H NMR spectrum — Tables 1 and 2.

Reaction of dihydronarceone imide (II) with bromine

A solution of bromine (166 mg, 1.04 mmol) in chloroform (5 cm³) was added dropwise to a cooled (0°C) and stirred solution of the imide *II* (400 mg, 1.04 mmol) in chloroform (25 cm³). Then, when the temperature rose to about 20°C, the solution was evaporated to dryness and the residue was chromatographed on a silica gel-packed column with chloroform—methanol ($\varphi_r = 99 : 1$) and the fractions were combined according to thin-layer chromatography. Those having the R_f value 0.81 were worked up and crystallized from benzene to furnish the mixture *Va*, *Vb* (382 mg). Fractions of $R_f = 0.49$ gave by an analogous procedure compound *IV* (126 mg) which was crystallized from toluene—methanol ($\varphi_r = 19 : 1$).

1'',2''-Dibromodihydronarceone imide (IV): M.p. = 163—165°C. For C₂₁H₂₁Br₂NO₆ ($M_r = 543.2$) $w_i(\text{calc.})$: 46.43% C, 3.90% H, 2.58% N; $w_i(\text{found})$: 46.48% C, 3.82% H, 2.56% N. IR spectrum, $\tilde{\nu}/\text{cm}^{-1}$: 3440, 3001, 2940, 2899, 2840, 1690, 1492, 1480. Mass spectrum, m/z ($I_r/\%$): 463 (1.9), 461 (2.3), 448 (2), 446 (2.5), 382 (25), 381 (79), 369 (19), 368 (81), 252 (50), 190 (100). ¹H NMR spectrum, δ : 7.09 (d, 1H, H-6) $J_{6,7} = 8.2 \text{ Hz}$, 6.83 (dd, 1H, H-7) $J_{1,7} = 0.8 \text{ Hz}$, 6.72 (s, 1H, H-5'), 6.48 (s, 1H, NH), 5.95 (ABq, 2H, OCH₂O) $J = 1.5 \text{ Hz}$, 4.75 (dd, 1H, H-1'') $J_{1',2'a} = 8.5 \text{ Hz}$, $J_{1',2'b} = 3.5 \text{ Hz}$, 4.72 (ddd, 1H, H-1) $J_{1,9a} = 6.9 \text{ Hz}$, $J_{1,9b} = 6.6 \text{ Hz}$, 4.07, 4.03, 3.89 (3 × s, 3 × 9H, 3 × OCH₃), 3.40 (dd, 1H,

H-9a) $J_{9a,9b} = 10.5$ Hz, 3.21 (dd, 1H, H-9b), 3.1 (dd, 1H, H-2''a) $J_{2''a,2''b} = 10.5$ Hz, 3.0 (dd, 1H, H-2''b).

7-Bromomethyl-3,4,11-trimethoxy-9,10-methylenedioxy-6,7,12,13-tetrahydro-5*H*-isoindolo[1,2-*b*]isoquinol-5-ones (*Va*, *Vb*): M.p. = 195—198°C. For $C_{21}H_{20}BrNO_6$ ($M_r = 462.3$) w_i (calc.): 54.56% C, 4.36% H, 3.03% N; w_i (found): 54.50% C, 4.37% H, 3.00% N. IR spectrum, $\tilde{\nu}/\text{cm}^{-1}$: 2920, 2860, 2826, 1680, 1611, 1493, 1480. Mass spectrum, m/z ($I_r/\%$): 448 (2), 446 (2.8), 382 (16), 381 (100), 366 (28), 352 (12). ^1H NMR spectrum — Tables 1 and 2.

Dehydrobromination of the mixture Va, Vb

Mixture of *Va*, *Vb* (162.3 mg, 0.35 mmol) was stirred in methanolic KOH ($\rho = 10 \text{ g dm}^{-3}$) for 12 h, neutralized with dilute acetic acid, the solvent was evaporated and the residue was extracted with chloroform. The extract was dried with sodium sulfate, concentrated and crystallized from acetone—hexane ($\phi_r = 1:1$). Yield = 88 mg of compound *VI*, m.p. = 196—198°C. For $C_{21}H_{19}NO_6$ ($M_r = 381.4$) w_i (calc.): 66.14% C, 5.02% H, 3.67% N; w_i (found): 66.08% C, 4.92% H, 3.64% N. IR spectrum, $\tilde{\nu}/\text{cm}^{-1}$: 3000, 2929, 2840, 1696, 1640, 1598, 1480. Mass spectrum, m/z ($I_r/\%$): 381 (100), 380 (10), 366 (6), 352 (12), 338 (7), 191 (7), 190 (21). ^1H NMR spectrum — Tables 1 and 2.

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