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BUXUS ALKALOIDS. VI.[a] THE CONSTITUTION OF CYCLOVIROBUXINE-D[b]

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Investigation by partition chromatography (1) of the acetone-insoluble fraction of the alkaloids of the common Box, Buxus sempervirens L., led to the isolation of three major new

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[a] Part V in the series: K. S. Brown, Jr., and S. M. Kupchan, J. Am. Chem. Soc., in press.

[b] The problem of the nomenclature of Buxus alkaloids was discussed by S. M. K. in Kyoto, Japan, on April 14, 1964, with Dr. D. Arigoni, Dr. R. Goutarel and Dr. T. Nakano. In order to avoid needless duplication and confusion it was proposed that each new alkaloid should be assigned a trivial name defining all of its structural features but for the substitution pattern of the C-3 and C-20 nitrogen functions. This substitution pattern is then designated by a letter suffix according to the following convention:

	C-3 N		C-20 N			C-3 N		C-20 N	
A	CH_3	CH_3	CH_3	CH_3	F	H	H	CH_3	CH_3
B	CH_3	CH_3	H	CH_3	G	H	CH_3	H	H
C	H	CH_3	CH_3	CH_3	H	H	H	H	CH_3
D	H	CH_3	H	CH_3	I	H	H	H	H
E	CH_3	CH_3	H	H					

On this basis cyclobuxine (I) (2) is renamed cyclobuxine-D, and cyclobuxamine (II) (3) is renamed cyclobuxamine-H.

[c] To whom inquiries concerning this paper should be directed.

bases. Two of these, cyclobuxine-D (I) (2) and cyclobuxamine-H (II) (3), have been shown to possess unusual variations of the steroid or triterpene structure, particularly at the 4-position. We now report on the constitution of the third, cyclovirobuxine-D[a] (IIIa, 3β, 20α-bis(methylamino)-4,4,14α-trimethyl-9β,19-cyclo-5α-pregnane-16α-ol), which represents biogenetically the fully methyl-substituted link of the group of bases (analogous to the typical triterpene substitution). Other Buxus alkaloids belonging to this type are cycloprotobuxine-C (4) and cycloprotobuxine-D (5).

Cyclovirobuxine-D, $C_{26}H_{46}ON_2$, m.p. 221-224° dec., $[\alpha]_D^{CHCl_3}$ +63°, has an infrared spectrum (in chloroform) essentially superimposable upon that of dihydrocyclobuxine-D (IVa) (2), and an n.m.r. spectrum[b] showing the presence of a proton under a hydroxyl group split by several neighboring protons (5.90 τ, poorly resolved multiplet), two N-methyl groups (7.58 τ, 6 protons), one secondary C-methyl (8.93 τ, doublet, J 6 c./s.), four tertiary C-methyls (8.90, 9.04, 9.05 and 9.27 τ), and a cyclopropyl methylene (2) (9.47 and 9.72 τ, AB doublets of J 4 c./s.). This spectrum showed many similarities to that of dihydrocyclobuxine-D (2) with two tertiary methyl groups instead of one secondary, and the chemical behavior of the two compounds was similarly parallel.

Cyclovirobuxine-D gave dibasic salts with common acids (e.g., the di-hydroiodide, $C_{26}H_{48}ON_2I_2$, m.p. 313-315° dec., and the di-perchlorate, $C_{26}H_{48}O_9N_2Cl_2$, m.p. 249-252° dec.). Acetic anhydride-pyridine acetylation gave the triacetyl derivative IIIb, $C_{32}H_{52}O_4N_2 \cdot H_2O$, m.p. 237-239° dec., $[\alpha]_D^{CHCl_3}$ -60°; infrared

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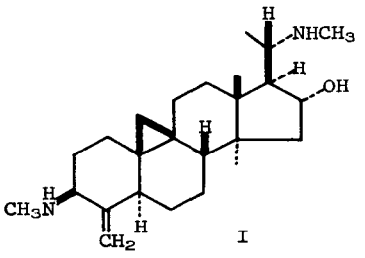
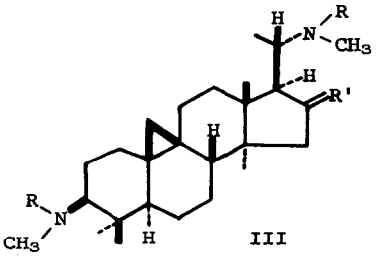
[a] Cyclovirobuxine-D is Band I, the alkaloid of R_f 0.76 in column 1 of Table II, ref. (1).

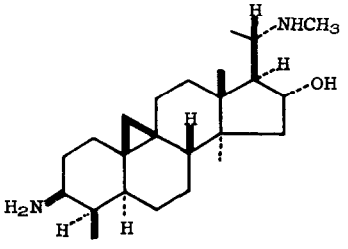
[b] N.m.r. spectra were measured in deuteriochloroform solution on a Varian A-60 spectrometer (tetramethylsilane = 10.00 τ); we thank Mr. Roy Matsuo and Mr. Arnold Krubsack for these determinations.



I



III



II

	R	R'
a.	H	OH
b.	$COCH_3$	$OCOCH_3$
c.	$COCH_3$	OH
d.	CH_3	OH
e.	$COOCH_2$-C_6H_4-NO_2	OH
f.	$COOCH_2$-C_6H_4-NO_2	O
g.	Cl	OH
h.	$COCH_3$	O
i.	CH_3	$OCOCH_3$

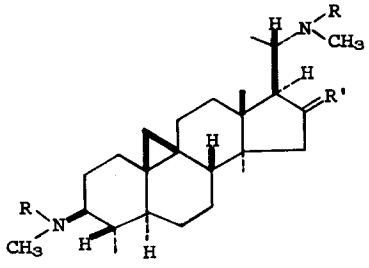
spectrum showing bands for one ester (5.78 μ) and two tertiary amide (6.14 μ, vs) functions, confirming the presence in the parent alkaloid IIIa of an hydroxyl group and two secondary amino groups. Mild basic hydrolysis of the triacetyl derivative, or mild acetylation of the parent alkaloid with acetyl chloride-potassium carbonate in benzene (2), gave the N,N'-diacetamide IIIc, $C_{30}H_{50}O_3N_2 \cdot H_2O$, m.p. 265-266°, $[\alpha]_D^{CHCl_3}$ -43°, $\lambda_{max}^{CHCl_3}$ 2.95 μ (m), 6.15 μ (vs). Methylation of cyclovirobuxine-D gave the N,N'-dimethyl-derivative IIId, $C_{28}H_{50}ON_2$, m.p. 240-241° dec., $[\alpha]_D^{CHCl_3}$ +44°.

Oxidation of N,N'-di-p-nitrobenzyloxycarbonyl-cyclovirobuxine-D (IIIe, $C_{42}H_{56}O_9N_4$, m.p. 227-229°, $[\alpha]_D^{CHCl_3}$ -8°,

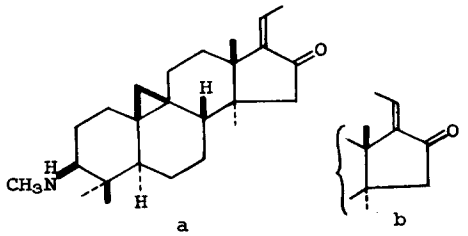
$\lambda_{max}^{CHCl_3}$ 2.90 μ (m), 5.92 μ (vs)), with chromic acid gave the ketone IIIf, $C_{42}H_{54}O_9N_4 \cdot 0.5H_2O$, m.p. 231-233°, $[\alpha]_D^{CHCl_3}$ -36°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (s), 5.92 μ (vs), which upon hydrogenolysis and base-catalyzed elimination of methylamine (2) gave the cyclopentenone mixture V: trans isomer (Va), $C_{25}H_{39}ON \cdot 0.5H_2O$, m.p. 138-141°, $[\alpha]_D^{CHCl_3}$ -60°, $\lambda_{max}^{CHCl_3}$ 5.83 μ (s), 6.08 μ (s), λ_{max}^{EtOH} 244.5 mμ (ε 8, 500); cis isomer (Vb), $C_{25}H_{39}ON \cdot 0.5H_2O$ m.p. 164-169°, $[\alpha]_D^{CHCl_3}$ -63°, $\lambda_{max}^{CHCl_3}$ 5.83 μ (s), 6.08 μ (s), λ_{max}^{EtOH} 244.5 mμ (ε 8,000). The isomers were separated by partition chromatography and the configurations assigned by analogy with those derived from dihydrocyclobuxine-D (1,2).

Ruschig degradation of cyclovirobuxine-D proceeded via the highly crystalline dichloramine IIIg, $C_{26}H_{44}ON_2Cl_2$, m.p. 190° dec. to the one-enone VI (obtained by basic hydrolysis in 85% ethylene glycol and 170° for 2 hr., to hydrolyze the highly hindered 3-imine), m.p. 165-178°, $\lambda_{max}^{CHCl_3}$ 5.89 μ (s), 6.02 μ (s), 6.28 μ (m), λ_{max}^{EtOH} 242 mμ (ε 6,400). Selective hydrogenation of the one-enone VI gave the diketone VII (4,4,14α-trimethyl-9β,19-cyclo-5α-pregnane-3,20-dione), $C_{24}H_{36}O_2$, m.p. 194-196°, $[\alpha]_D^{CHCl_3}$ +67° $\lambda_{max}^{CHCl_3}$ 5.87 μ (vs) 7.03 μ (s), 7.37 μ (s). Through the kind cooperation of Professor D. Arigoni in Zurich, the diketone VII was compared with the same compound obtained via degradation (6) of the known steroid cycloartenyl acetate (VIII) (7,8); the two were completely identical by infrared spectrum, rotation, and mixture melting point (9). This provided strong confirmation for structure IIIa for cyclovirobuxine-D, and established its absolute configuration at positions 5, 8, 9, 10, 13 and 14.

The configuration at C-16 was indicated by the n.m.r. signal typical of the 16β-proton in this series (2) in the spectrum of N,N'-dimethylcyclovirobuxine-D (IIId) (see above), as well as the large negative molecular rotation increments observed upon acetylation of the 16α-hydroxyl group (-110° for IIIc to IIIb, -62° for IIId to IIIi) (2). The ketone IIIh ($C_{30}H_{48}O_3N_2$ $0.5H_2O$,

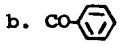


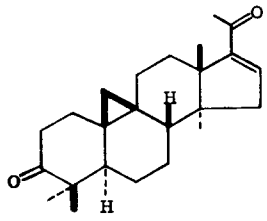
IV



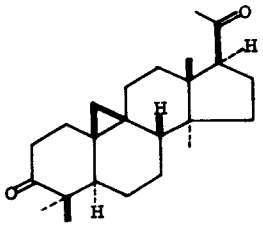
a b

V

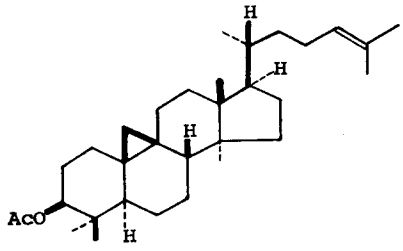
	R	R'
a.	H	
b.		O



VI



VII



VIII

m.p. 233-236°, $[\alpha]_D^{CHCl_3}$ -91°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (s), 6.15 μ (vs)), derived from the diacetyl derivative IIIc, showed an o.r.d. curve (in methanol) essentially identical through the first extremum (the limit of the instrument used) to that of N,N'-dibenzoyl-dehydrodihydrocyclobuxine-D (IVb): trough at 332 mμ, M -5650° (IVb, 331 mμ, M -6300°), shoulder at 327-322 mμ, M -5100° (IVb, 225-220 mμ, M -5950°). This indicated stereochemical identity of the two at position 17, and probably position 20 as well. The completely parallel molecular rotation changes in various transformations of cyclovirobuxine-D to those observed for the analogous transformations in the dihydrocyclobuxine-D series support assignment of like configuration (3β, 20α) to the amino functions of cyclovirobuxine-D.

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