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BUXUS ALKALOIDS. VII.[a] THE STRUCTURE OF BUXENINE-G, A NEW AND NOVEL STEROIDAL ALKALOID FROM BUXUS SEMPERVIRENS L.[b]

S. Morris Kupchan and Wady L. Asbun

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison 6, Wisconsin

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In 1962, we reported the elucidation of the structure and configuration of cyclobuxine-D (I) (1) an alkaloid isolated from Buxus sempervirens L. (2). Cyclobuxine-D was shown to be the prototype of a new class of steroidal alkaloids which contain a cyclopropane ring and which have a substitution pattern at C-4 and C-14 which is intermediate in the biogenetic scheme, between lanosterol- and cholesterol-type steroids. Subsequent studies have characterized the following structurally-related alkaloids: II, $R^1=R^2=CH_3$ (3); II, $R^1=H$, $R^2=CH_3$ (3); II, $R^1=CH_3$, $R^2=H$ (3,4); III (4); IV, $R^1=R^2=H$ (5); IV, $R^1=R^2=CH_3$ (6); V, $R=CH_3$ (7); and V, R=H (8). We report herewith the isolation and characterization of buxenine-G, a new alkaloid from Buxus sempervirens L. which contains a conjugated diene

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[a] Part VI in the series: K. S. Brown, Jr., and S. M. Kupchan, Tetrahedron Letters, previous communication. The convention on use of letter suffixes to designate substitution pattern at C-3 and C-20 nitrogen functions is described in Part VI.

[b] This report summarizes part of a Dissertation submitted by Wady L. Asbun on January 9, 1964 in partial fulfillment of the requirements for the Ph.D. degree at the University of Wisconsin; cf. Dissertation Abstracts, XXIV, no. 11, 4415 (1964).

system and lacks the cyclopropane ring characteristic of all Buxus alkaloids described earlier.

Buxenine-G was isolated from the acetone-soluble portion of the strong bases obtained by the fractionation procedure described earlier (9). Further fractionation, via sulfate salt precipitation to a soluble sulfate salt fraction, oxalate-salt precipitation to an oxalate-insoluble fraction, and partition chromatography of the regenerated free bases using Phenol Red in the stationary phase (10), yielded a band which crystallized from acetone to yield buxenine-G isopropylidene-imine, $C_{28}H_{46}N_2$, m.p. 186-188° (m.p. after vacuum sublimation, 194-196°); $[\alpha]_D^{e2}$ +51° (c 0.72, $CHCl_3$); λ_{max}^{EtOH} 238 mμ (ε 24,400), 247 mμ (ε 26,800), 256 mμ (ε 16,800), shoulders at 230 and 280 mμ; $\lambda_{max}^{CHCl_3}$ 6.02 μ; mass spectral molecular ion, 410.[a] The n.m.r. spectrum (CCl_4 solution with TMS internal standard) shows the presence of two vinyl protons (3.88 τ, singlet, and 4.50 τ, multiplet), one N-methyl group (7.55 τ, 3H), two C-methyl groups on olefinic carbon (8.08 τ, 3H, 8.20 τ, 3H), one secondary C-methyl group (9.02 τ, 3H, doublet, J 6 c./s.), and four tertiary C-methyl groups (9.00, 9.20, 9.25, 9.33 τ, 12H). Treatment of the isopropylidene-imine with dilute hydrochloric acid followed by ammonia yielded acetone (isolated as 2,4-dinitrophenylhydrazone) and chromatographically-homogeneous buxenine-G, which resisted attempts at crystallization. Buxenine-G shows λ_{max}^{EtOH} 238 mμ (ε 27,200), 247 mμ (ε 29,100), 255 mμ (ε 18,650) shoulders at 215, 230 and 290 mμ; $\lambda_{max}^{CHCl_3}$ 6.14, (w, double bond), 6.33 μ (w, NH_2). The n.m.r. spectrum

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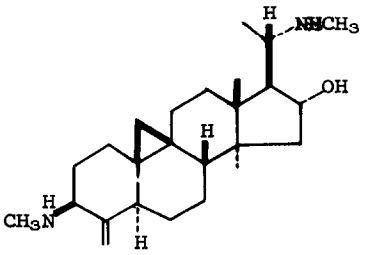
[a] We thank Professor C. Djerassi and Dr. H. Budzikiewicz, Stanford University, for the mass spectral and circular dichroism data.



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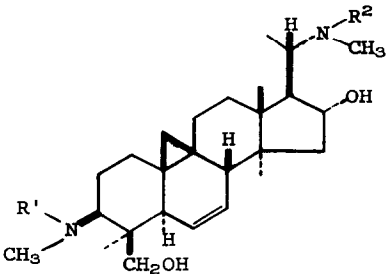

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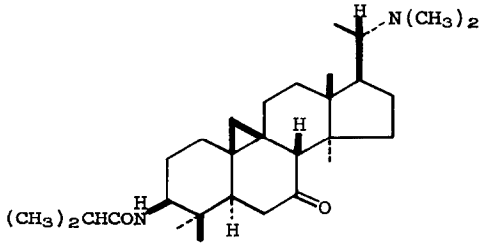

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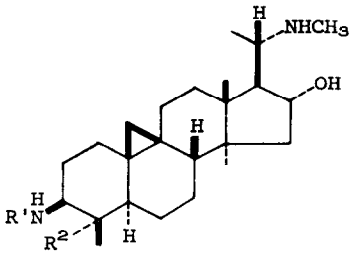

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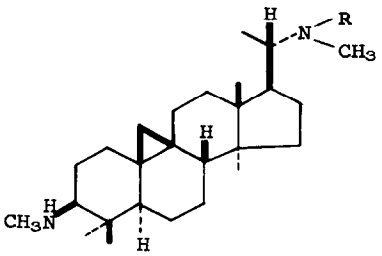


V

shows the presence of two vinyl protons (4.17 τ, singlet, and 4.55 τ, multiplet), one N-methyl group (7.60 τ, 3H), one secondary C-methyl group (8.96 τ, 3H, doublet, J 6 c./s.), and four tertiary C-methyl groups (9.02, 9.27, 9.30, 9.37 τ, 12H). Crystallization of buxenine-G from acetone readily re-formed the isopropylidene-imine derivative.

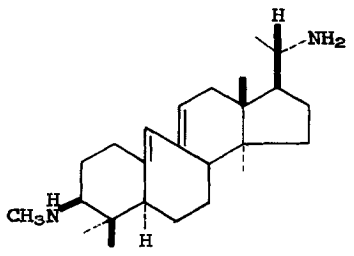
The foregoing data indicate that buxenine-G has a $C_{25}H_{42}N_2$ molecular formula and that it contains a heteroannular diene group, four carbocyclic rings, four tertiary methyl groups, one secondary methyl group, one N-methyl group and one primary amino group, but no cyclopropane ring. Furthermore, the vinyl proton signals best accord with the following diene partial structure: $-CH_2-CH=\overset{|}{C}-CH=\overset{|}{C}-CH-$.

Catalytic hydrogenation of buxenine-G in the presence of platinum and acetic acid led to consumption of two molar equivalents of hydrogen and formation of tetrahydrobuxenine-G, characterized as the isopropylidene-imine, $C_{28}H_{50}N_2$, m.p. 140-143°; $[\alpha]_D^{29}$ +3° (c 0.60, $CHCl_3$). The compound shows no absorption in the ultraviolet. The n.m.r. spectrum shows the presence of one N-methyl group (7.50 τ, 3H), two C-methyl groups on olefinic carbon (8.08 τ, 3H, 8.20 τ, 3H), one secondary C-methyl group (9.03 τ, 3H, doublet, J 7 c./s.), and four tertiary C-methyl groups (9.02, 9.10, 9.17, 9.35 τ, 12H). Similar hydrogenation of buxenine-G isopropylidene-imine gave a hexahydro derivative, $C_{28}H_{52}N_2$, m.p. 113-115°; $[\alpha]_D^{36}$ +39° (c 1.30, $CHCl_3$).

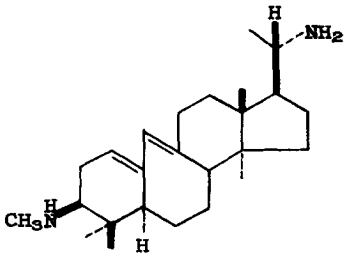
Ruschig degradation of buxenine-G using one molar equivalent of N-chlorosuccinimide yielded a methyl ketone derivative, $C_{25}H_{39}ON$, m.p. 174-175°; $[\alpha]_D^{20}$ +23° (c 1.00, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3.00 (w), 5.86 (s), 6.30 μ (s); $\lambda_{max}^{cyclohexane}$ 239 mμ (ε 24,300), 248 mμ (ε 27,800), 257 mμ (ε 17,600). The n.m.r. spectrum

shows signals for an N-methyl group at 7.65 τ and a methyl peak at 7.98 τ ($COCH_3$).

The physical and chemical data summarized above and biogenetic considerations have led us to propose formulas VI and VII as the most likely alternatives for the structure of



VI



VII

buxenine-G. Treatment of buxenine-G with salicylaldehyde in methanol readily yielded buxenine-G salicylaldimine, $C_{32}H_{46}ON_2$, m.p. 216-220°; $[\alpha]_D^{24}$ +130° (c 1.10 $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 6.02 (w), 6.15 (s), 6.35 (m), 6.71, 6.89 μ; $\lambda_{max}^{cyclohexane}$ 227 mμ (ε 16,030), 238 mμ (ε 17,920), 245 mμ (ε 24,900), 253 mμ (ε 18,200), 280 mμ (ε 4,680), 314 mμ (ε 3,260), 400 mμ (ε 1,695); C.D. in dioxane: c 0.42 (380-340 mμ); c 0.084 (350-320 mμ); c 0.042 (330-280 mμ); c 0.0168 (300-270 mμ); $[\theta]_{312.5}$ +5460. The positive C.D. maximum at 312.5 mμ indicates that the primary amino function at C-20 possesses the α-configuration (11), in good accord with biogenetic precedent. Studies in progress are aimed at confirming the novel skeletal structure and at making possible a choice between the alternative diene formulations.

D. Stauffacher has recently described (12) the isolation and characterization of an alkaloid from Buxus sempervirens L.

("nor-buxamine") which appears to be identical with buxenine-G. We note with gratification that Dr. Stauffacher has independently reached essentially the same conclusions concerning the structure of buxenine-G.

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