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BUXUS ALKALOIDS. PART II. THE STRUCTURES AND THE STEREOCHEMISTRY OF CYCLOMICROPHYLLINE-A, B, AND C.

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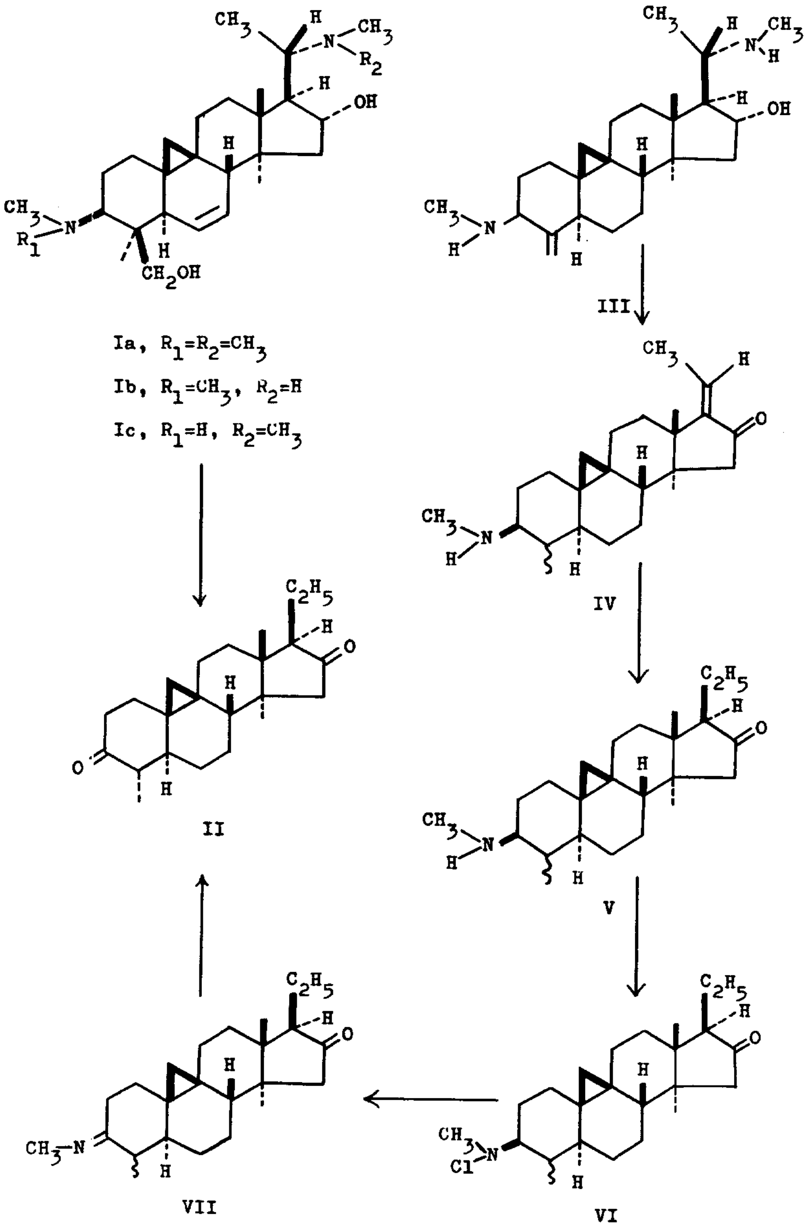
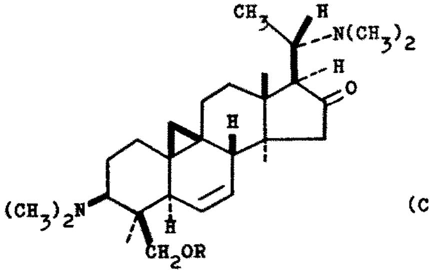
IN the present communication, we present further chemical evidence for the structures of cyclomicrophylline-A (Ia), B (Ib), and C (Ic), the major alkaloids from the strong base fraction of B. microphylla Sieb. et Zucc. var. suffruticosa Makino. In Part I,[1] it was shown that degradation of cyclomicrophylline-C (Ic) led to the diketone (II). This compound could be readily derived from the related alkaloid, cyclobuxine,[2] as shown below.

Cyclobuxine (III), isolated from B. microphylla Sieb. et Zucc. var. suffruticosa Makino forma major Makino,[3] was degraded by the same reactions as carried out by Kupchan et al.[2] to IV, which, on catalytic hydrogenation with platinum oxide in acetic acid, afforded V, $C_{24}H_{37}NO$, m.p. 143-144°, $[\alpha]_D$ -57°,[4] $\lambda_{max}^{CHCl_3}$ 3.06 and 5.78 μ. Treatment of V with 1.2 molar equivalents of N-chlorosuccinimide in dry


Ia, $R_1=R_2=CH_3$
Ib, $R_1=CH_3$, $R_2=H$
Ic, $R_1=H$, $R_2=CH_3$
III
IV
V
VI
VII
II
CH_3
N
R_1
R_2
CH_2OH
OH
H
C_2H_5
O
Cl

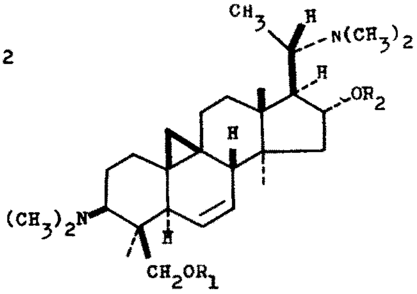
methylene chloride yielded the chloramine (VI), dec. $< 140^{\circ}$, $[\alpha]_D$ -60°, $\lambda_{max}^{CHCl_3}$ 5.78 μ, which, upon dehydrohalogenation with potassium methoxide in methanol, followed by hydrolysis with 2 N aqueous sulfuric acid at room temperature for 20 hours, led through the intermediate, VII, to the diketone (II). The identity of both these samples was proved by direct comparison (m.p., mixed m.p., rotation, and infrared and n.m.r. spectra). Since cyclobuxine (III) has been already related to a known triterpenoid, cycloeucalenol,[2] the foregoing result not only gives a strong support for the proposed structures for cyclomicrophylline-A, B, and C, but also establishes the absolute configuration at six of the eleven asymmetric centers (5α, 8β, 9β, 10β, 13β, and 14α) in their molecule.

Evidence is then advanced for the five remaining asymmetric centers. The β-orientation of the hydroxy methyl group at C-4 may be assigned on the basis of the n.m.r. spectra. In Ia and its diacetate, two protons due to the $-CH_2OH$ and the $-CH_2OAc$ group appear at 6.30 and 5.86 τ,[5] respectively, and this may be taken as evidence of the hydroxy methyl possessing axial conformation[6] (hence β-configuration). Furthermore, this hydroxy methyl is involved in strong intramolecular hydrogen bonding as is seen in the infrared spectrum of VIIIa, and hence the 3-dimethylamino group must be cis to it (equatorially oriented). Methylation of Ia with methyl iodide in acetone at room temperature took place at the 3-dimethylamino group and furnished the monomethiodide, $C_{29}H_{51}N_2O_2I$, mp. 265-270° (dec.), which



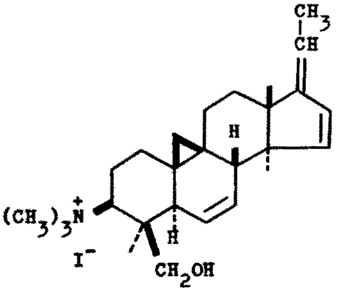
VIIIa, R=H

VIIIb, R=Ts

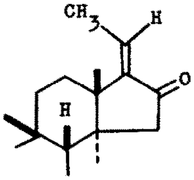


XIa, R_1=Ts, R_2=H

XIb, R_1=R_2=Ts

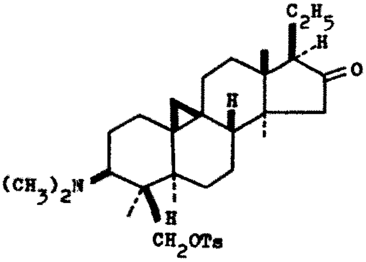


IX

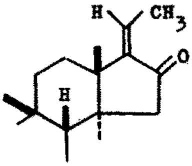


XIIa

XIIb



X



XII'a

XII'b

failed to undergo Hofmann degradation, giving under vigorous conditions as employed by Corey et al.[7] more than a 90% recovery of Ia and no detectable olefin. On the other hand, heating of Ia with methyl iodide in methanol yielded in small amount the dimethiodide, $C_{30}H_{54}N_2O_2I_2$, m.p. >320°. Hofmann degradation by Corey's procedure[7] afforded trimethylamine, characterized as the picrate, and a non-volatile fraction. The latter, after chromatography on alumina and subsequent methylation with methyl iodide, gave IX, $C_{27}H_{42}NOI$, m.p. >325° (sublime), λ_{max}^{Nujol} 3.00 (OH) and 6.13 μ (C=C), λ_{max}^{EtOH} 219.5 mμ (ε 20300). This behavior upon Hofmann degradation also favors assignment of equatorial conformation[8] to the 3-dimethylamino group.

The o.r.d. curves of 16-ketones (VIIIa) and (X) showed strong negative Cotton effects (VIIIa, trough M_{320} = -12000°, peak M_{280} = +10600°; X, trough M_{320} = -8200°, peak M_{280} = +17000°)[9]. This favors assignment of the 13β,14α,17β-configuration.[10]

The α-orientation of the 16-hydroxy group was suggested by the results upon acetylation as well as tosylation of Ia. The differences in molecular rotation between the monotosylate (XIa) and ditosylate (XIb) of Ia, and Ia and its diacetate, were found to be -166° and -90°, respectively. These values are characteristic of the 16α-hydroxyl grouping with a 17β-side chain.[11]

Finally, the α-configuration[12] of the 20-methylamino group was deduced as follows. The infrared spectrum of XIa suggests that the 16α-hydroxy group also is hydrogen bonded with the 20-methylamino group. Inspection of molecular models indicates that such hydrogen bonding can more readily occur when the 20-methylamino group assumes α- rather than β-configuration since in the latter case there is very considerable steric compression between the angular 18-methyl group and the 21-methyl group. Assignment of α-configuration to the 20-methylamino group was further confirmed by pyrolytic cis elimination of VIIIa in which a cis cyclopentenone (XIIa) was obtained. VIIIb, on passing in methylene chloride solution through neutral alumina,[1] rapidly lost dimethylamine to give exclusively a cis isomer (XIIb). Mild alkaline treatment[1] of VIIIa led to a mixture of two isomers (XIIa) and (XII'a). In the latter case, the product which initially formed seems to be a cis cyclopentenone (XIIa), which is then converted by base into a trans isomer (XII'a), giving a 1:1 composition of the equilibrium mixture.[13] Such an example of base-catalyzed bimolecular cis elimination[14] is rather rare, but the preference for cis rather than trans elimination in this system may be ascribed to the influence of the carbonyl group at C-16 (and the basic nitrogen at C-20), which greatly increases the acidity of the 17α-hydrogen being eliminated.

On the basis of the present chemical evidence together with a series of degradation reactions already described in Part I,[1] cyclomicrophylline-A, B, and C, should be assigned stereochemical formulas, Ia, Ib, and Ic, respectively.

Acknowledgements

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References

Satisfactory analyses were obtained for all compounds reported herein.

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2. K. S. Brown, Jr. and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590, 4592 (1962).
3. This species is a variety of *B. microphylla* Sieb. *et* Zucc. *var. suffruticosa* Makino.
4. All rotations were determined at 10-20° in chloroform.
5. The n.m.r. spectra were taken on a Varian Associates recording spectrometer (A-60) at 60 Mc. in deuterated chloroform. Chemical shifts are reported in τ values, using tetramethylsilane as the internal reference.
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9. The o.r.d. curves refer to methanol solutions.
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11. Average, when there is a 17β-side chain, for 16α-OH to 16α-OAc, -240°; for 16β-OH to 16β-OAc, +65° (see D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951)). It is also pertinent to mention that

the molecular rotation difference for the transformation of N,N'-dimethylcyclobuxine to its acetate is -96° (see reference 2).

12. All known 20-amino steroids possess the α-configuration at that center: see R. Goutarel, *Tetrahedron*, **14**, 126 (1961), and O. Jeger and V. Prelog, in "*The Alkaloids*", ed. R. H. F. Manske, Vol. VII, Academic Press, New York, N.Y., 1960, pp. 319-342.
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