

BUXUS ALKALOIDS. PART I. THE STRUCTURES OF THREE NEW  
ALKALOIDS, CYCLOMICROPHYLLINE-A, B, AND C, FROM  
B. MICROPHYLLA SIEB. ET ZUCC.

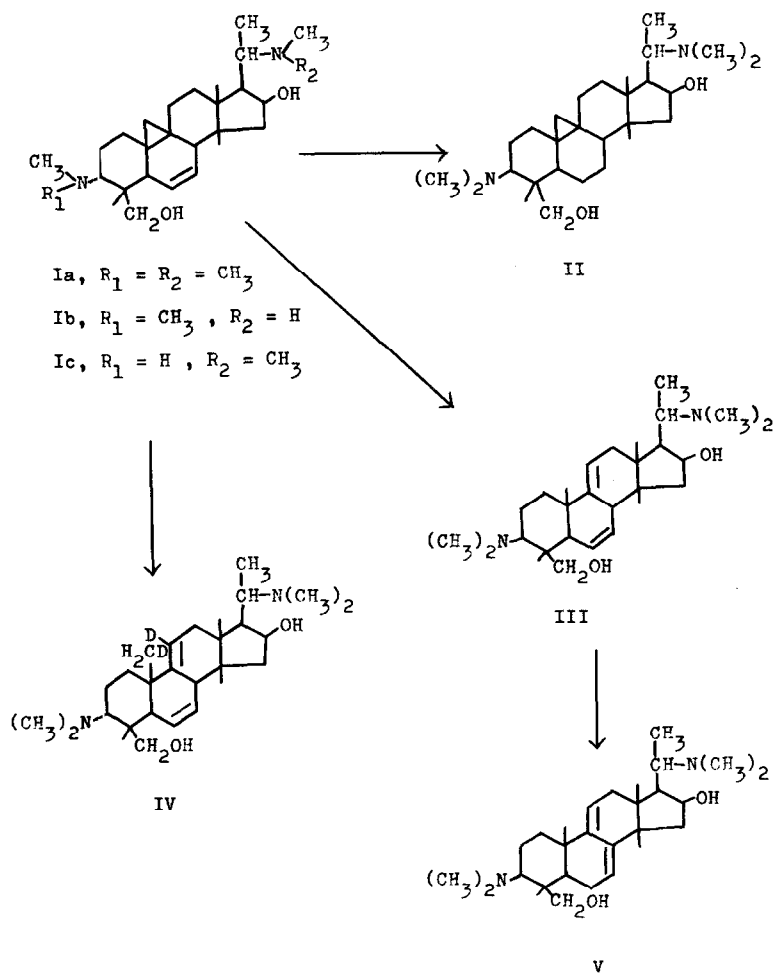
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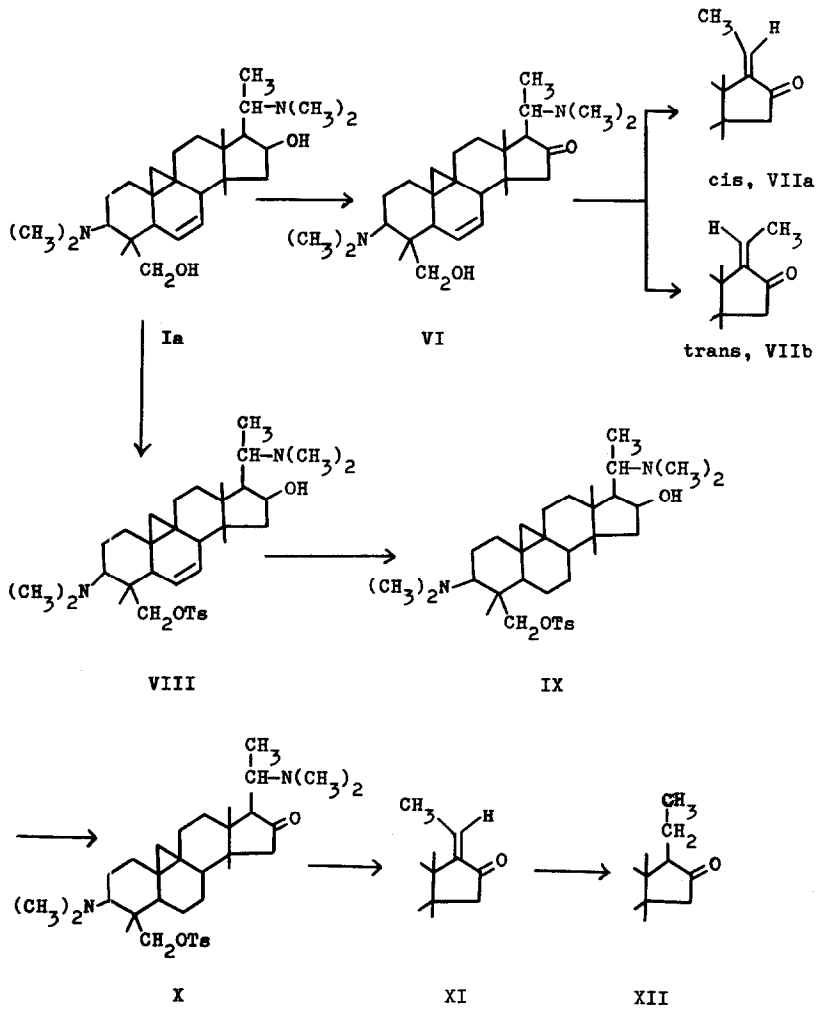
THE multicomponent nature of the alkaloid extract<sup>1</sup> of Buxus plants has been indicated by earlier studies by Schlittler et al. However, none of the structures of these alkaloids has been clarified until recently.<sup>2</sup> We shall present in this paper constitutions for three new alkaloids isolated from the strong base fraction of B. microphylla Sieb. et Zucc. var. suffruticosa Makino, collected in Kagoshima. These alkaloids have been named cyclomicrophylline-A, B, and C, and as will become clear in the sequel they represent a novel type of tetracyclic triterpenoid alkaloids with a cyclopropane ring.

Cyclomicrophylline-A (Ia),  $C_{28}H_{48}N_2O_2$ , m.p. 232-233°,  $[\alpha]_D -93^\circ$ ,<sup>3</sup> shows  $\lambda_{max}$  2.98  $\mu^4$  (OH broad),  $\lambda_{max}^{Nujol}$  2.90  $\mu$  (OH broad) and n.m.r. peaks<sup>5</sup> 4.52-4.56 (2H;  $-\underline{CH}-\underline{CH}-$ ), 5.90 (1H, septet;  $CH_2-\underline{CHOH}-CH$ ), 6.30 (2H, doublets, J 10.5 cps;  $CH-C-\underline{CH}_2OH$ ), 7.66 (6H, two  $NCH_3$ ), 7.75 (6H, two  $NCH_3$ ), 8.88 (3H, one tertiary  $CH_3$ ), 9.07



(6H, two tert.  $\text{CH}_3$ ), 9.12 (3H, doublet, J 7 cps; one sec.  $\text{CH}_3$ ), and 9.20 and 10.16  $\tau^6$  (2H, doublets, J 4 cps; cyclopropyl methylene). Cyclomicrophylline-B (Ib),  $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_2$ , m.p. 251-252°,  $[\alpha]_D -65^\circ$ ,  $\lambda_{\text{max}}$  3.00  $\mu$  (NH and OH broad),  $\lambda_{\text{max}}^{\text{Nujol}}$  2.97 (OH broad) and 3.05  $\mu$  (NH sharp), and cyclomicrophylline-C (Ic),  $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_2$ , m.p. 283-284°,  $[\alpha]_D -40^\circ$ ,  $\lambda_{\text{max}}$  2.99  $\mu$  (NH and OH broad),  $\lambda_{\text{max}}^{\text{Nujol}}$  2.90 (OH broad) and 3.06  $\mu$  (NH sharp), are different from cyclomicrophylline-A only in that they possess three instead of four  $\text{NCH}_3$  groups. The interrelationship of these three alkaloids were established as follows. Heating of either Ib or Ic with formic acid-formalin led to Ia. Ic, on treatment with methyl iodide followed by silver oxide, also yielded Ia. Degradation of the diacetate of Ia with bromocyanide and subsequent hydrolysis with alkali furnished Ib. Since the  $-\text{NHCH}_3$  grouping in Ic is located at C-3 of ring A (vide infra), it follows that Ib should have the group at C-20 of the side chain of ring D.

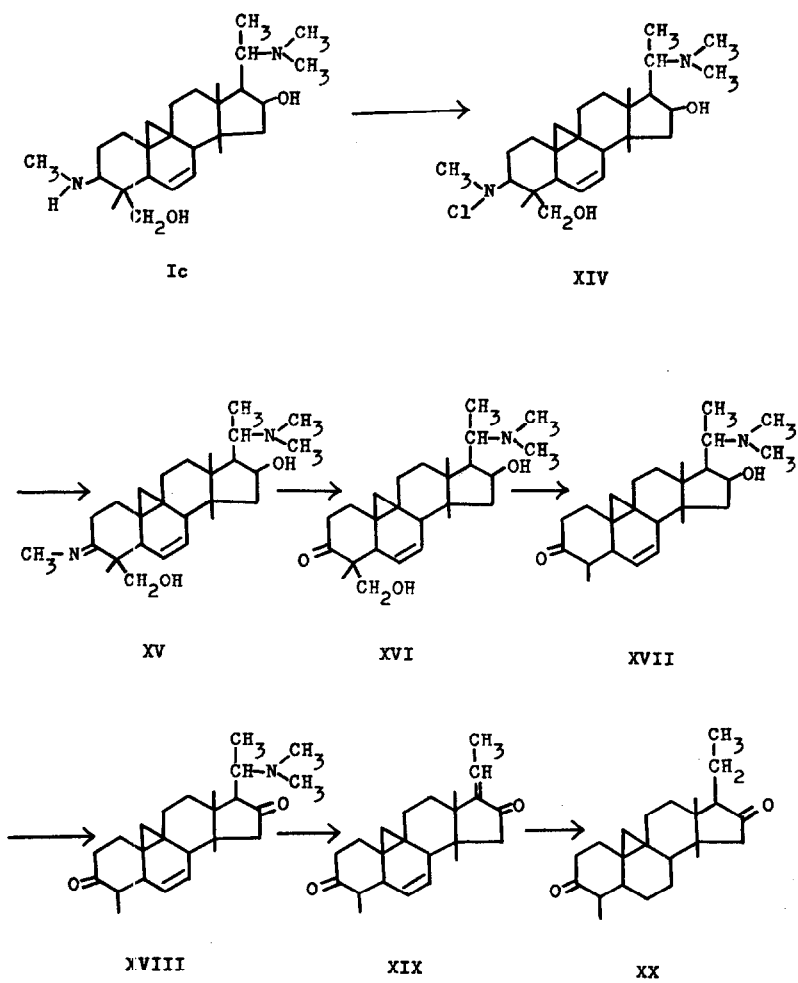
Ia, on catalytic hydrogenation with platinum oxide in acetic acid, absorbed one molar equivalent of hydrogen at room temperature for 10 hours and furnished the dihydro-derivative (II),  $\text{C}_{28}\text{H}_{50}\text{N}_2\text{O}_2$ , m.p. 265-266°,  $[\alpha]_D +37^\circ$ , n.m.r. peaks at 9.40 and 9.69  $\tau$  (2H, doublets, J 4 cps; cyclopropyl methylene). Decyclization of Ia by heating with either hydrogen chloride in chloroform or hydrochloric acid for 10 minutes afforded III,<sup>7</sup>  $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}_2$ , m.p. 306°,  $[\alpha]_D -78^\circ$ ,  $\lambda_{\text{max}}$  11.66 (trisubstituted double bond) and 14.10  $\mu$  (disubstituted cis double bond). The n.m.r. spectrum



showed the presence of a new tertiary methyl group (8.94  $\tau$ ) and a new vinyl hydrogen (4.84  $\tau$ , multiplet). Treatment of Ia with deuterium chloride in deuterium oxide led to IV, m.p. 293-294°,  $[\alpha]_D -87^\circ$ . In the n.m.r. spectrum a diffused triplet<sup>8</sup> corresponding to  $-\text{CH}_2\text{D}$  appears at 8.98  $\tau$ , while, in the infrared spectrum either in solution or in solid state, absorption bands of both  $-\text{C}=\text{CD}-$  and  $-\text{CH}_2\text{-D}$  groups due to the C-D stretching vibration<sup>9</sup> are observed at 4.41 and 4.53  $\mu$ , respectively. Isomerization of III with concentrated hydrochloric acid for 6 hours led to the conjugated diene (V),  $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}_2$ , m.p. 320°,  $[\alpha]_D +50^\circ$ ,  $\lambda_{\text{max}}^{\text{Nujol}}$  10.04  $\mu$ , with the triple ultraviolet absorption bands characteristic of  $\Delta^{7,9(11)}$ -lanostadiene-3 $\beta$ -ol at  $\lambda_{\text{max}}$  236 (14100), 243.5 (16200) and 252  $m\mu$  ( $\epsilon$  10600),<sup>10</sup> and n.m.r. peaks at 4.53 and 4.79  $\tau$  (2H, multiplet;  $\text{CH}=\text{C}-\text{C}=\text{CH}$ ).

Oxidation of Ia with 1.2 molar equivalents of chromium trioxide in acetic acid-water (9:1) at room temperature furnished the cyclopentanone (VI),  $\text{C}_{28}\text{H}_{46}\text{N}_2\text{O}_2$ , m.p. 156-157° (dec.),  $[\alpha]_D^{\text{MeOH}} -170^\circ$ ,<sup>11</sup>  $\lambda_{\text{max}}$  5.78  $\mu$ . Treatment of VI with 0.1% methanolic potash led to the formation of an unseparable mixture (1:1)<sup>12</sup> of two cisoid cyclopentenones (VIIa) and (VIIb),  $\text{C}_{26}\text{H}_{39}\text{NO}_2$ , m.p. 191-194°,  $[\alpha]_D -171^\circ$ ,  $\lambda_{\text{max}}$  5.84 ( $\alpha,\beta$ -unsaturated five-membered ketone) and 6.07  $\mu$  (C=C),  $\lambda_{\text{max}}$  244  $m\mu$  ( $\epsilon$  8300). Ozonolysis of this mixture in acetic acid gave rise to acetaldehyde, characterized as the 2,4-dinitrophenylhydrazone.

Treatment of Ia with 1.2 molar equivalents of tosyl



chloride in pyridine gave the monotosylate (VIII),  $C_{35}H_{54}N_2SO_4$ , m.p. 176-177°,  $[\alpha]_D +12^\circ$ ,  $\lambda_{max}^{Nujol} 2.93 \mu$  (OH broad),  $\lambda_{max} 2.98 \mu$  (OH broad). Catalytic hydrogenation of VIII with platinum oxide in acetic acid led to the dihydro-derivative (IX),  $C_{35}H_{56}N_2SO_4$ , m.p. 188-189°,  $[\alpha]_D +37^\circ$ , which, on oxidation with chromium trioxide in acetic acid at room temperature, furnished the cyclopentanone (X), m.p. 165-167°,  $\lambda_{max} 5.78 \mu$ . Passage of X in methylene chloride solution through neutral alumina afforded exclusively a cis cyclopentenone (XI),<sup>13</sup> m.p. 206-207°,  $[\alpha]_D -31^\circ$ ,  $\lambda_{max} 5.82 \mu$ ,  $\lambda_{max} 244 m\mu$  ( $\epsilon$  9300), n.m.r. peaks at 3.45 (1H, quartet, J 7.5 cps; vinyl proton coupled with  $CH_3$ ) and 8.16  $\tau$  (3H, doublet, J 7.5 cps; vinyl  $CH_2$ ). Hydrogenation of XI with platinum oxide in ethanol-acetic acid (9:1) led to XII, m.p. 186°,  $[\alpha]_D -20^\circ$ ,  $\lambda_{max} 5.78 \mu$ .

Treatment of Ic with N-chlorosuccinimide<sup>14</sup> in dry methylene chloride gave the chloramine (XIV),  $C_{27}H_{45}N_2O_2Cl$ , m.p. 255-260° (dec.),  $[\alpha]_D -38^\circ$ , which, upon dehydrohalogenation followed by hydrolysis with dilute sulfuric acid, led through the intermediate, XV to the six-membered ketone (XVI),  $C_{26}H_{41}NO_3$ , m.p. 216-217°,  $\lambda_{max} 2.95$  and  $5.84 \mu$ . Mild alkaline treatment of XVI brought about a retro-aldol type reaction<sup>15</sup> to yield formaldehyde and XVII,  $C_{25}H_{39}NO_2$ , m.p. 188-190°,  $\lambda_{max} 2.95$  and  $5.84 \mu$ . The n.m.r. spectrum indicates the absence of the protons of a hydroxy methyl group. Oxidation of XVII with chromium trioxide in acetic acid led to the diketone (XVIII),  $\lambda_{max} 5.78$  and

5.86  $\mu$ , which readily eliminated in basic solution dimethylamine to give XIX,  $C_{23}H_{30}O_2$ , m.p. 140-144 $^{\circ}$ ,  $\lambda_{max}$  5.85 and 6.06  $\mu$ ,  $\lambda_{max}$  244 m $\mu$  ( $\epsilon$  8400). XIX, on hydrogenation with platinum oxide in acetic acid, afforded XX,  $C_{23}H_{34}O_2$ , m.p. 134-135 $^{\circ}$ ,  $[\alpha]_D -97^{\circ}$ ,  $\lambda_{max}$  5.78 and 5.86  $\mu$ .

The degradative evidence so far presented is well explained if cyclomicrophylline-A, B, and C, are assumed to have structures, Ia, Ib, and Ic, respectively. The establishment of the identity of the diketone (XX) with the corresponding derivative of the related known alkaloid, cyclobuxine,<sup>2</sup> will be forthcoming in the succeeding communication.

#### Acknowledgements

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#### References

- All compounds reported in this communication gave satisfactory elementary analyses.
1. E. Schlittler, K. Heusler and W. Friedrich, Helv. Chim. Acta, 32, 2209 (1949); K. Heusler and E. Schlittler, ibid., 32, 2226 (1949); W. Friedrich and E. Schlittler, ibid., 33, 873 (1950); E. Schlittler and W. Friedrich, ibid., 33, 878 (1950).
  2. K. S. Brown, Jr. and S. M. Kupchan, J. Am. Chem. Soc., 84, 4590, 4592 (1962).
  3. Rotations were measured at 10-20 $^{\circ}$  in chloroform solution, unless otherwise specified.



4. Infrared spectra refer to chloroform solution unless otherwise stated.
5. All n.m.r. spectra were determined on a Varian Associates recording spectrometer (A-60) at 60 Mc. in deuterated chloroform. Chemical shifts are reported in  $\tau$  values, using tetramethylsilane as the internal reference.
6. The unusual high field shift must arise from long range shielding by the double bond of ring B. See E. Mueller, H. Kessler, H. Fricke and H. Suhr, Tetrahedron Letters, No. 16, 1047 (1963); E. J. Corey and R. L. Dawson, J. Am. Chem. Soc., 85, 1782 (1963); E. Vogel, W. Wiedemann, W. F. Harrison and H. Kiefer, Tetrahedron Letters, No. 11, 673 (1963).
7. III was accompanied by a small amount of V (5-6%) as detected by the ultraviolet spectrum.
8. D. H. Williams and N. S. Bhacca, J. Am. Chem. Soc., 85, 2861 (1963).
9. E. G. Hoffmann, Ann., 618, 276 (1959).
10. All ultraviolet spectra are in 95% ethanol.
11. This  $[\alpha]_D$  was taken from the value at 589 m $\mu$  of the o.r.d. curve.
12. The distinction between cis isomer, VIIa and trans isomer, VIIb, and its ratio were made on the basis of the n.m.r. data (see L. M. Jackman and R. H. Wiley, J. Chem. Soc., 2887 (1960); for cis isomer, VIIa, 3.51 (1H, quartet, J 7.5 cps; vinyl proton coupled with CH<sub>3</sub>) and 8.19  $\tau$  (3H, doublet, J 7.5 cps; vinyl methyl), and for trans isomer, VIIb, 4.35 (1H, quartet, J 7.5 cps) and 7.92  $\tau$  (3H, doublet, J 7.5 cps).
13. The configuration was assigned on the basis of the n.m.r. spectrum (see reference 12).
14. H. Ruschig, W. Fritsch, J. Schmidt-Thome and W. Haede, Chem. Ber., 88, 883 (1955); L. Lahler and F. Sorm, Coll. Czech. Chem. Comm., 24, 2975 (1960).
15. D. H. R. Barton and P. de Mayo, J. Chem. Soc., 887 (1953)