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BUXUS ALKALOIDS. PART X (1). AN APPROACH TO THE TOTAL SYNTHESES OF BALEABUXINES AND CYCLOPROTOBUXINES.

THE CONSTRUCTION OF THEIR FUNDAMENTAL SKELETONS

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Baleabuxines, cycloprotobuxines, and buxamines (2) represent three major groups among a large family of the Buxus alkaloids (3) so far isolated which are characterized by the structures of (I), (II), and (III), respectively. We now report the elaboration of the fundamental skeletons of two of these three groups of alkaloids from readily available lanosterol.

3β-Acetoxy-4,4,14α-trimethyl-5α-pregnane-11,20-dione (IV), the synthesis of which from lanosterol has already been recorded (4), was transformed by alkaline hydrolysis and subsequent oxidation with Jones reagent (5) to the known 3,11,20-trione. Treatment of this compound with ethylene glycol in dry benzene in the presence of p-toluenesulfonic acid afforded the 11-oxo-3,20-diethyleneketal (V), m.p. 221-223° (from chloroform-methanol), $[\alpha]_D$ +33° (c, 1.17, $CHCl_3$), $\nu_{max.}$ (KBr) 1670 (11-ketone) $cm.^{-1}$, τ ($CDCl_3$) 5.95 (8H, s, two ethyleneketal protons), m/e 460 (M^+). Photolysis (6) of (V) in ethanol saturated with potassium carbonate under oxygen-free nitrogen using a 200 W Hanovia high pressure mercury lamp did not furnish any desired 11α-hydroxy-11β,19-cyclobutane derivative (VI) (7). Reduction of (IV) with lithium aluminum hydride in tetrahydrofurane afforded a mixture of the 3β,11β,20α- and 3β,11β,20β-triols (VII). This, without separation, was acetylated with acetic anhydride-pyridine in the usual manner and the resulting acetates were chromatographed on alumina to furnish a 3β,20α-diacetate (VIIIa), m.p. 205-207° (from chloroform-methanol), $\nu_{max.}$ (KBr) 3500 (OH) and 1720, 1700, and 1240 (acetate) $cm.^{-1}$, and a 3β,20β-diacetate (VIIIb), m.p. 236-237° (from chloroform-methanol), $[\alpha]_D$ +60°

(c, 1.21, $CHCl_3$), $\nu_{max.}$ (KBr) 3500 (OH) and 1720, 1705, and 1247 (acetate) cm.$^{-1}$, τ ($CDCl_3$) 7.94 (3H, s) and 7.91 (3H, s) (OAc), in a ratio of 1:4 (8). Treatment of (VIIIb) with nitrosyl chloride in pyridine afforded the corresponding 11β-nitrite (IXa), m.p. 167-169° (from ether), $[\alpha]_D$ +94° (c, 1.24, $CHCl_3$), $\nu_{max.}$ (KBr) 1730, 1720, and 1240 (acetate), and 1635 and 1595 (nitrite) cm.$^{-1}$, which was irradiated (9) in dry benzene containing iodine (1.3 mole) under oxygen-free nitrogen with a 200 W high pressure mercury lamp (Pyrex filter). The resulting iodo-derivative (IXb) (10) was immediately oxidized with Jones reagent (5) and the 11-oxo-19-iodo-compound (Xa), without isolation, was treated with alumina (Merck, standardized, activity II-III) in dry benzene. Subsequent chromatography on alumina furnished an 11-oxo-9β,19-cyclo-derivative (XIa) (60%) (11), m.p. (amorphous) ca. 110°, $\nu_{max.}$ (KBr) 1740 and 1247 (acetate) and 1670 (CO conjugated with a cyclopropane ring) cm.$^{-1}$ (12), further characterized by alkaline hydrolysis as the diol (XIb), m.p. 243-245° (from chloroform-ether), o.r.d. (dioxane) $[\Phi]_{314.5}$ +4526° (peak) and $[\Phi]_{230}$ +8162° (peak), (methanol) $[\Phi]_{315}$ +4477° (peak) and $[\Phi]_{238}$ +8650° (peak), c.d. (dioxane) $[\theta]_{302}$ +2846° and $[\theta]_{221}$ +10186°, (methanol) $[\theta]_{300}$ +2653° and $[\theta]_{225.5}$ +8060° (13). Reduction of (XIa) with an excess of lithium aluminum hydride in dioxane (14), followed by chromatography of the product on alumina, afforded a diol (XIII), m.p. 166-168° (from chloroform-hexane), $[\alpha]_D$ +37° (c, 0.93, $CHCl_3$), τ ($CDCl_3$) 9.67 and 9.40 (2H, AB quartet, J 4.5 c./sec., cyclopropyl protons), m/e 360 (M^+), and a triol (XIV) (15), in a ratio of 1:2. Oxidation of (XIII) with Jones reagent (5) furnished the ketone (XV), m.p. 190-192° (from ether-methanol), $\nu_{max.}$ (KBr) 1700 (ketone) cm.$^{-1}$, m/e 356 (M^+), identical with an authentic specimen (16) kindly provided by Professor Romo.

Satisfactory elemental analyses were obtained for all compounds reported.

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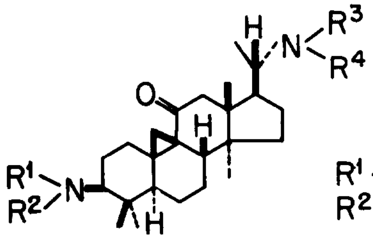
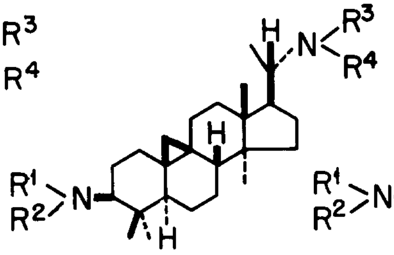
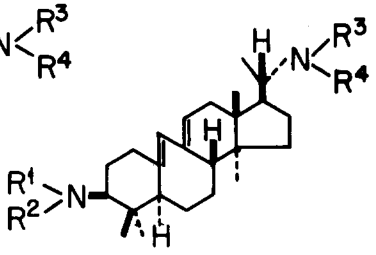

O
H
N
R3
R4
R1
R2
N
H
H

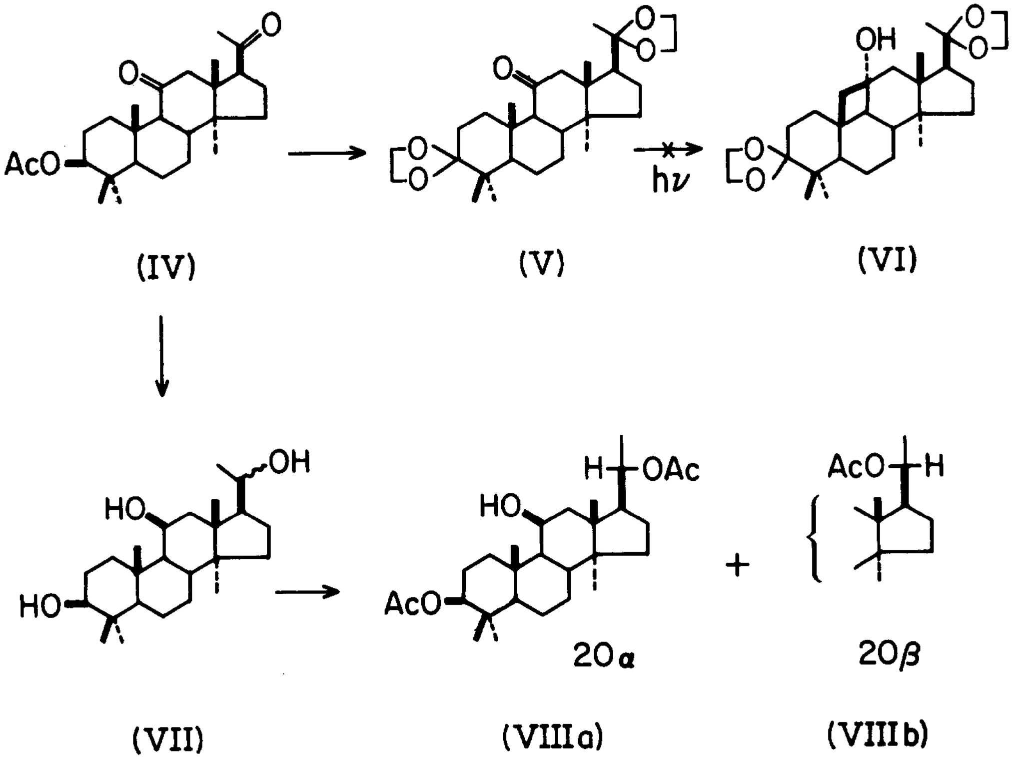
(I)

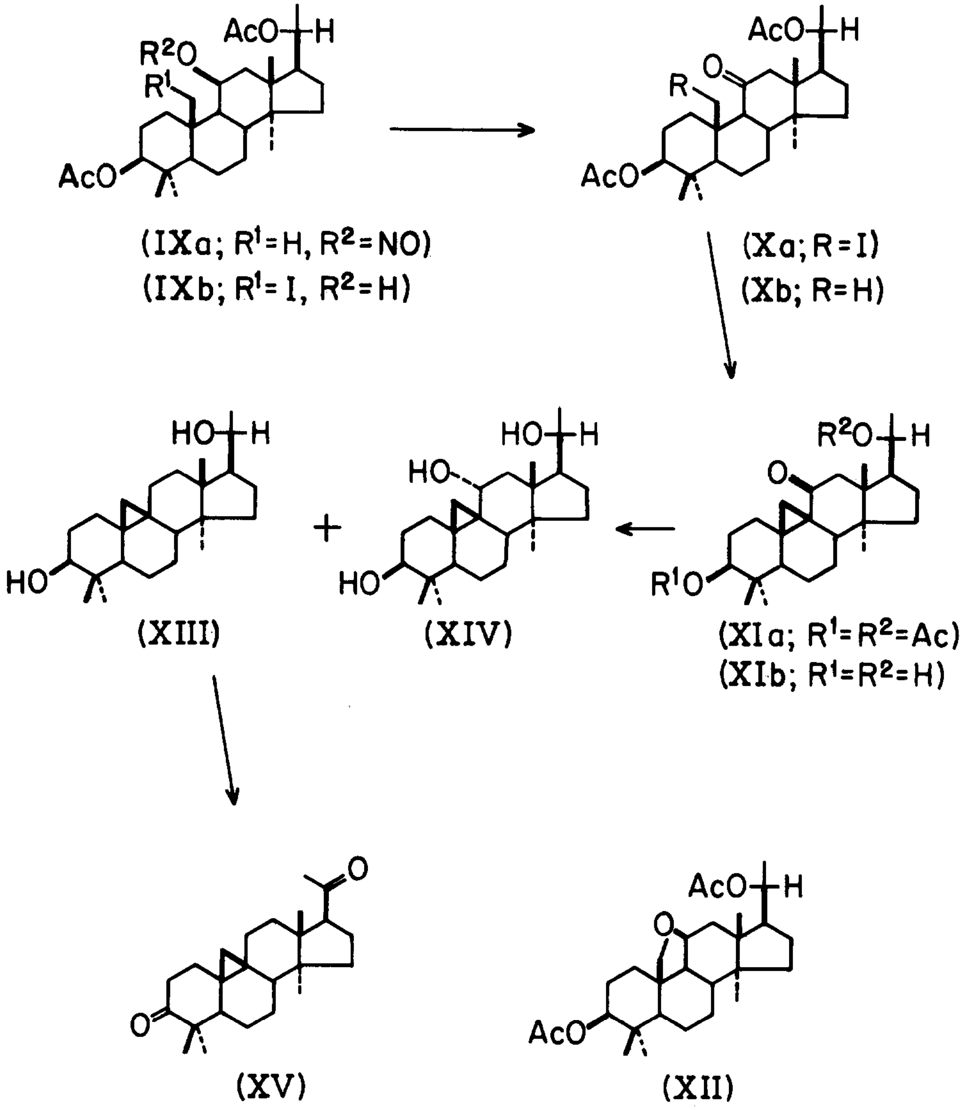

H
N
R3
R4
H
R1
R2
N
H

(II)


H
N
R3
R4
H
R1
R2
N
H

(III)


O
O
AcO
(IV)
O
O
O
O
O
(V)
hν
OH
O
O
O
O
(VI)
OH
HO
HO
(VII)
H
OAc
HO
AcO
20α
(VIIIa)
+
AcO
H
20β
(VIIIb)


AcO
R²O
R¹
AcO
(IXa; R¹=H, R²=NO)
(IXb; R¹=I, R²=H)
AcO
O
R
AcO
(Xa; R=I)
(Xb; R=H)
HO
HO
(XIII)
+
HO
HO
HO
(XIV)
R²O
O
R¹O
(XIa; R¹=R²=Ac)
(XIb; R¹=R²=H)
O
O
(XV)
AcO
O
AcO
(XII)

REFERENCES

1. Part IX, T. Nakano and Z. Votický, J. Chem. Soc. (C), 590 (1970).
2. The plural form is used to indicate various derivatives at C-3 and C-20 nitrogen functions of each skeletal type [see formulas (I), (II), and (III)]
3. V. Černý and F. Šorm, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press Inc., New York, 1967, pp. 375-426, and references cited therein.
4. W. Voser, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, **35**, 503 (1952).
5. A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, J. Chem. Soc., 2548 (1953).
6. E. Altenburger, H. Wehrli, and K. Schaffner, Helv. Chim. Acta, **48**, 704 (1965) and related references.
7. After chromatography on alumina there were isolated various other products, besides an 11-hydroxy-3,20-diethyleneketal. The structures of these abnormal products are now being analyzed by the X-ray method.
8. There was no detectable formation of a 3,11,20-triacetate [see J. Romo, G. Stork, G. Rosenkranz, and C. Djerassi, J. Am. Chem. Soc., **74**, 2918 (1952)]. Since it is known that reduction of pregnane-20-ones with lithium aluminum hydride gives predominantly a 20β-ol [L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, p. 5670; D. N. Kirk and A. Mudd, J. Chem. Soc. (C), 968 (1969)], the one which formed in a larger amount may be regarded as the 20β-epimer.
9. M. Akhtar, D. H. R. Barton, and P. G. Sammes, J. Am. Chem. Soc., **86**, 3394 (1964); **87**, 4601 (1965); D. H. R. Barton, D. Kumari, P. Welzel, L. J. Danks, and J. F. McGhie, J. Chem. Soc. (C), 332 (1969).
10. There was no detectable formation of an 18-iodo-derivative.
11. The minor product from the reaction sequence was the 11-oxo-compound (Xb), m.p. 209-211° (from chloroform-methanol). In one case, there was also isolated a very minute amount of the 11β,19-oxide (XII), m.p. 234-236° (from chloroform-methanol).
12. L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1958, p. 138.
13. See K. Schaffner and G. Snatzke, Helv. Chim. Acta, **48**, 347 (1965) and R. Imhof, W. Graf, H. Wehrli, and K. Schaffner, Chem. Comm., 852 (1969). Also see K. Kuriyama, H. Tada, Y. K. Sawa, S. Itô, and I. Itoh, Tetrahedron Letters, 2539 (1968).
    In the o.r.d. and c.d. curves of 11-oxo-9β,10-cyclo-derivatives, positive n-π* and π-π* Cotton effects are observed, whereas 11-oxo-12β,18-cyclo-derivatives exhibit a negative n-π* and a positive π-π* Cotton effects.
    We are indebted to Dr. K. Kuriyama, Shionogi Research Laboratory, Shionogi & Co., Ltd., Osaka, for determination of the o.r.d. and c.d. curves.

14. D. Herlem-Gaulier, F. Khuong-Huu-Laine, and R. Goutarel, *Bull. Soc. chim. France*, 3478 (1966); S. M. Kupchan, R. M. Kennedy, W. R. Schleigh, and G. Ota, *Tetrahedron*, **23**, 4563 (1967).
15. For the assignment of the α-configuration to the 11-hydroxy group, see S. P. Acharya and H. C. Brown, *J. Am. Chem. Soc.*, **89**, 1925 (1967) and S. S. Corsano and G. Nicita, *Ricerca Sci.*, **37**, 351 (1967).
16. L. Rodríguez-Hahn, A. Romo de Vivar, A. Ortega, M. Aguilar, and J. Romo, *Revista Latinoamericana de Química*, **1**, 24 (1970).