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BUXUS ALKALOIDS. PART XI.[1] THE SYNTHESIS OF CYCLOPROTOBUXINE-A (3β,20*S*-CHIRALITY) AND ITS TWO ISOMERIC ALKALOIDS WITH 3β,20*R*- AND 3α,20*R*- CONFIGURATION FROM LANOSTEROL.

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Abstract - The synthesis of cycloprotobuxine-A (**5**),representative of *Buxus* alkaloids, and its two isomeric alkaloids with 3β, 20*R*- and 3α,20*R*-configuration, from lanosterol, is described. In order to confirm the stereochemistries at C-3 and C-20 in these three alkaloids, the 3β-dimethylamino-(**27**) and the 3α-dimethylamino derivative (**28**) of cycloartanol (**24**) were also synthesised and their ^{1}H and ^{13}C n.m.r.spectra are discussed.

For more than two decades *Buxus* alkaloids[2] have been a subject of very intensive chemical investigation in various laboratories and as a result no less than 100 new alkaloids have now been isolated and their structures have been determined. They constitute a class of steroidal alkaloids which contain either a 9β,19-cyclo-5α-pregnane (**1**) or a 9(10-19)-*abeo*-5α-pregnane[+] (**2**) skeleton and which have a substitution pattern at C-4 and C-14, which is intermediate in the biosynthetic scheme between lanosterol- and cholesterol-type steroids. We have previously isolated more than 20 new alkaloids from several species of the genus *Buxus* which occur in Japan and Korea, and determined their chemical structures.[3] In contrast to a plethora of structural studies in this field, very little work towards the total synthesis of these alkaloids has been reported. In 1970 we published a first synthesis[1] of the fundamental skeleton (**3**) of cycloprotobuxine-A[#] (**5**), representative of *Buxus* alkaloids, from commercially available lanosterol (**4**). Almost all of the dibasic *Buxus* alkaloids so far isolated possess β-configuration of the amino group at C-3 and *S*-chirality of the amino group at C-20. However, there are a few exceptions. Cyclokoreanine, isolated from Korean *B. koreana*, possesses an α-oriented amino group at C-3, as demonstrated by our earlier work.[3c] Russian chemists[4] have presented evidence from the difference in the rates of hydrolysis of 3-*N*-acyl-derivatives that cycloprotobuxine-C,[§] originally isolated from *B. sempervirens*, should have the 3α-configuration and the unusual 20*R*-configuration. In completing the total synthesis of cycloprotobuxine-A (**5**), we have also attempted to obtain the other isomers at C-3 and C-20, and establish their absolute stereochemistries.

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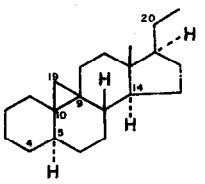
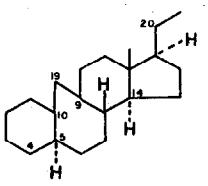
[+]For the nomenclature of these alkaloids, see I.U.P.A.C. Inform. Bull.,1968,N° 33,454.

[#]The letter suffix expresses the substitution pattern at nitrogen atoms at C-3 and C-20. 'A' indicates R^1=R^2=R^3=R^4=Me. See reference 2

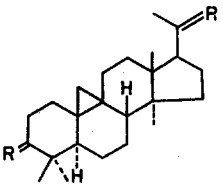
[§]The letter suffix 'C' indicates R^1=H,R^2=R^3=R^4=Me in the structure (**5**)



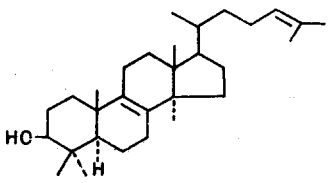
(1)



(2)



(3) R=O
(22) R=NOH
(23) R=NH_2, H



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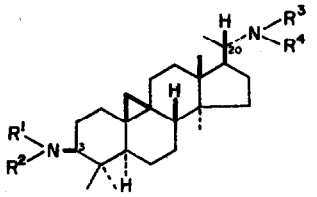
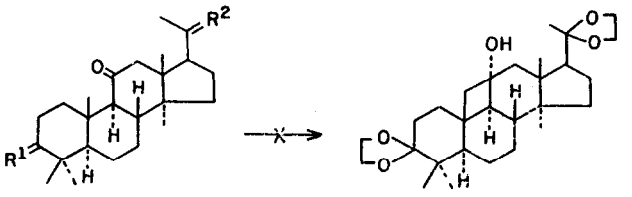


(5) $R^1 = R^2 = R^3 = R^4 = Me$

In this synthesis lanosterol (**4**) was employed as a starting material. It was first degraded to 3β-acetoxy-4,4,14α-trimethyl-5α-pregnane- 11,20-dione (**6**) according to the procedure of Ruzicka *et al.*[5] Our first attempt to construct a cyclopropane ring between C-9 and C-10 was based upon work on the u.v. irradiation of 11-oxo-lanostane derivatives by Schaffner *et al.*[6] Alkaline hydrolysis of compound (**6**), followed by oxidation with Jones reagent,[7] afforded the known 3,11,20-trione (**8**). Before photolysis the keto group at C-3

and C-20 were selectively protected as diethyleneketal derivatives. On treatment with ethylene glycol in the presence of *p*-toluenesulphonic acid the 3,11,20-trione (**8**) afforded the 11-oxo-3,20- diethyleneketal (**9**). When, however, this compound was irradiated in ethanol saturated with potassium carbonate under oxygen-free nitrogen with a 200W Hanovia medium pressure mercury lamp, the required 11α-hydroxy-11β,19- cyclobutane derivative (**10**) was not formed.

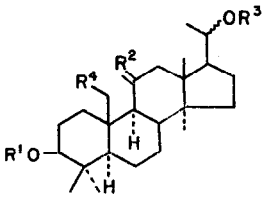


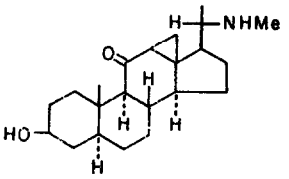
(10)

(6) R^1=α–H, β–OAc, R^2=O
(7) R^1=α–H, β–OH, R^2=O
(8) R^1=R^2=O
(9) R^1=R^2=

We therefore attempted to prepare a 9β,19-cyclopropane ring by the use of the method which Barton *et al.*[8] had developed in the nitrite ester photolysis. The 3,20,11-trione (**8**) was reduced with lithium aluminium hydride in ether to give a mixture of 3β,11β,20*S*- and 3β,11β,20*R*-triols (**11**). This mixture of triols, without separation, was subjected to acetylation with acetic anhydride-pyridine at room temperature, and the resulting acetates were separated by repeated crystallisation and subsequent chromatography over alumina to afford the 3β,20*R*-diacetate (**12**) and the 3β,20*S*-diacetate (**13**) in the ratio of *ca.* 4:1. There was no detectable formation of the 3,11,20-triacetoxy-derivatives. Since it is known that reduction of pregnane-20-ones[9] with lithium aluminum hydride gives predominantly 20-ols with *R*-chirality, the one which formed in a larger amount was regarded as the 20*R*-isomer.

The 3β,20*R*-diacetoxy-11β–ol (**12**) afforded the corresponding nitrite (**14**) on treatment with nitrosyl chloride in pyridine. Photolysis of the nitrite (**14**) in dry benzene containing iodine gave the 19-iodo-derivative (**15**), which, without separation, was at once oxidised with Jones reagent to the 11-oxo--19-iodo- derivative (**16**). On treatment with alumina (Merck, standardised, activity (II- III) in dry benzene the iodo-ketone (**16**) was smoothly transformed into the 9β,19-cyclo-11-oxo-derivative (**17**) in 65% overall yield from the nitrite (**14**). Alkaline hydrolysis of the compound (**17**) afforded the 3β,20*R*-diol (**18**). This compound exhibited positive n - π^* and $\pi - \pi^*$ Cotton effects in the o.r.d. and c.d. measurements. The 12β,18-cyclo-11-oxo-derivatives, such as (**19**), however, are known to display a negative n - π^* and a positive $\pi - \pi^*$ Cotton effect.[10]





(19)

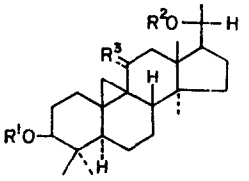
(11) 20R, S; $R^1 = R^3 = H$, $R^2 = \alpha - H$, $\beta - OH$, $R^4 = H$
(12) 20R; $R^1 = R^3 = Ac$, $R^2 = \alpha - H$, $\beta - OH$, $R^4 = H$
(13) 20S; $R^1 = R^3 = Ac$, $R^2 = \alpha - H$, $\beta - OH$, $R^4 = H$
(14) 20R; $R^1 = R^3 = Ac$, $R^2 = \alpha - H$, $\beta - ONO$, $R^4 = H$
(15) 20R; $R^1 = R^3 = Ac$, $R^2 = \alpha - H$, $\beta - OH$, $R^4 = I$
(16) 20R; $R^1 = R^3 = Ac$, $R^2 = O$, $R^4 = I$

Reduction of the 9β,19-cyclo-11-oxo-derivative (17) with an excess of lithium aluminium hydride[11] in boiling dioxane then afforded the 3β,20*R*-diol (20) and the 3β,11ξ,20*R*-triol (21) in the ratio of *ca.* 1:1. Subsequent oxidation of the diol (20) with Jones reagent furnished the 3,20-dione (3), identical with an authentic sample[12] kindly provided by Professor Romo.

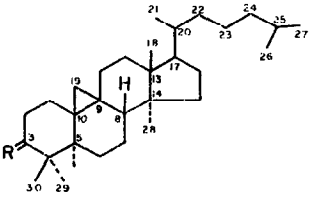
On treatment with hydroxylamine hydrochloride in pyridine the 3,20-dione (3) afforded the dioxime (22). Reduction of this dioxime with lithium aluminium hydride in dioxane then provided a mixture of isomeric 3,20-diamines (23), which, without separation, was immediately methylated with formic acid-formalin[13] to the 3,20-dimethylamino-derivatives. After careful chromatography over alumina there were obtained three products which were similar in polarity. The least polar (**A**) and the most polar dimethyl-diamine (**C**), which were obtained in the ratio of *ca.* 1.7:1, were the major products in this hydride reduction, and the second dimethyl-diamine (**B**) was formed only in small amount. Since the steric environment at C-20 in compound (3) is similar to that in pregnane-20-ones, it was reasonable to assume that lithium aluminium hydride reduction of the oxime (22), which is mechanistically akin[14] to the reduction of ketones, would afford predominantly the corresponding 20*R*-amine. Therefore, it was argued that dimethyl-diamines (**A**) and (**C**) should possess the same β-configuration at C-3, but the stereochemistry at C-20 is *R*-chiral in (**A**) and *S*-chiral in (**C**), and the dimethyl-diamine (**B**), obtained only as a minor product, should have the 3α- and 20*R*-configuration.* The ^1H n.m.r. spectra exhibited signals for two dimethylamino groups [2.28 and 2.12 (6H each, s) in (**A**); 2.28 and 2.18 (6H each, s) in (**C**); and 2.32 and 2.12 (6H each, s) in (**B**)], a secondary methyl group at C-20 [0.78 (3H, d)

*No detectable amount of the 3α,20*S*-isomer was formed.

in (**A**); 0.82 (3H, d) in (**C**); and 0.78 (3H,d) in (**B**)].The ^{13}C resonance for C-3 and C-20 were observed respectively at 71.93 and 60.91 [in (**A**)], 71.89 and 61.41 [in (**C**)],and 68.10 and 60.90[in (**B**)],whereas the methyl carbon at C-20 resonated at 9.25[in (**A**)],9.19[in(**C**)], and 9.24 [in (**B**)].



(17) $R^1=R^2=Ac$, $R^3=O$
(18) $R^1=R^2=H$, $R^3=O$
(20) $R^1=R^2=H$, $R^3=H_2$
(21) $R^1=R^2=H$, $R^3=H,OH$



(24) $R=\alpha-H,\beta-OH$
(25) $R=O$
(26) $R=NOH$
(27) $R=\alpha-H,\beta-N(Me)_2$
(28) $R=\beta-H,\alpha-N(Me)_2$

In order to discuss these n.m.r. data in terms of the stereochemistries at C-3 and C-20 in these three isomers of cycloprotobuxine-A (**5**), we have synthesised as reference compounds 3β-and 3α-dimethylamino-derivatives of cycloartanol (**24**). The method of their preparation was essentially the same as that employed for the 3β- and 3α-dimethylamino-derivatives[15] of cyclolaudanol. Cycloartanol (**24**), obtained by catalytic hydrogenation of cycloartenol, was oxidised with Jones reagent to cycloartanone (**25**), which in turn was converted with hydroxylamine hydrochloride-pyridine to the oxime (**26**). Reduction of this oxime with lithium aluminium hydride in dioxane, followed by methylation with formic acid-formalin, afforded the 3β-dimethylamino-derivative (**27**) as a major product. On the other hand, catalytic hydrogenation of the oxime (**27**) with platinum oxide in acetic acid and subsequent methylation with formic acid-formalin gave predominantly the 3α-dimethylamino-derivative (**28**). The most significant differences in the ^1H and ^{13}C n.m.r. spectra of these two compounds (**27**) and (**28**) were that in (**27**) the dimethylamino signals appeared at 2.21 (6H, s), whereas in (**28**) the corresponding dimethylamino group resonated at 2.32 (6H, s). Furthermore, in (**27**) the carbon resonance for C-3 was observed at 72.03, but in (**28**) the same carbon signal occurred at higher field of 68.05. Comparison of these ^1H and ^{13}C n.m.r.data with those recorded for the three isomers (**A**), (**B**), and (**C**) of cycloprotobuxine-A (**5**) has allowed us to assign unambigously the signals of their two dimethylamino groups and also to confirm their stereochemistries at C-3 and C-20 which were predicted from the mode of the hydride reduction (See Table 1).

Table 1. Key ^{1}H and ^{13}C n.m.r. data[a] of 3β,20*R*-isomer (**A**), 3α,20*R*-isomer (**B**), 3β,20*S*-isomer (**C**), 3β-dimethylamino-(**27**) and 3α-dimethylamino-cycloartane (**28**).

Compound	3-N(Me)$_2$	20-N(Me)$_2$	20-Me		3-C	20-C
A	2.28(6H,s)	2.12(6H,s)	0.78(3H,d)	9.25	71.93	60.91
B	2.32(6H,s)	2.12(6H,s)	0.78(3H,d)	9.24	68.10	60.90
C	2.28(6H,s)	2.18(6H,s)	0.82(3H,d)	9.19	71.89	61.41
(27)	2.21(6H,s)				72.03	
(28)	2.32(6H,s)				68.05	

[a]The assignments[16] of all signals in the spectra of these five compounds are given in the Experimental Section. The differentiation of the CH_3, CH_2, CH, quaternary carbons was made by off-resonance proton decoupling and the DEPT sequence.

The identity of the 3β,20*S*-isomer (**C**), synthesised above, with cycloprotobuxine-A* (**5**), isolated from *B. microphylla* Sieb. *et* Zucc. *var. suffruticosa* Makino *forma major* Makino,[3b] was further established by direct comparison of all physical properties including optical rotations.

Finally, we would like to comment on the general rules for the relationship between structures and specific rotations of *Buxus* alkaloids, proposed earlier by A.-ur-Rahman *et al.*[2] It should be noted that while cycloprotobuxine-A (**5**) (3β,20*S*-chirality) possesses $[\alpha]_D$ + 76°, the isomeric two alkaloids (**A**) (3β,20*R*-chirality) and (**B**) (3α,20*R*-chirality) were found to exhibit $[\alpha]_D$ -75° and $[\alpha]_D$ -60°, respectively. Van de Woude *et al.*[17] have previously reported that the assignment of *R*- or *S*-configuration to epimeric 20-amino-steroids is possible by comparing the optical rotatory powers of the pure epimers since all known *R*-epimers are more levorotatory than their corresponding *S*-epimers, and the rotation increment for inversion *S* - *R* at C-20 is $\Delta[\alpha]_D$-11.5° and $\Delta[M]_D$ -40°. A.-ur-Rahman *et al.* stated that *Buxus* alkaloids possessing a cycloprotobuxine-type skeleton are dextrorotatory. However, in the case of cycloprotobuxine-A (**5**) (3β,20*S*-chirality) and its isomeric alkaloid (**A**) (3β,20*R*-chirality), the variation of rotation associated with the change of chirality of the 20-amino group from *S* to *R* is so pronounced ($\Delta[\alpha]_D$ -151° and $\Delta[M]_D$ -624°) as to invert the sign of rotation.+ We have also measured the specific rotations of 3β-dimethylamino-(**27**) and 3α-dimethylylamino-cycloartane (**28**) and found that both have positive signs of similar magnitude ($[\alpha]_D$ + 55° in (**27**) and $[\alpha]_D$ + 83° in

*Note that the configurations at C-3 and C-20 in this alkaloid have already been established as β and *S*, respectively.

+It is pertinent to mention that in the *N*-salicylidene,[18] *N*-phthalyl,[19] and *N*-benzylidene[17] derivatives of 20-amino-steroids the 20*R*-epimers exhibit *negative* Cotton effect and its corresponding *negative* c.d. curves, but the 20*S*-epimers display *positive* Cotton effect and its corresponding *positive* c.d. curves.

(**28**); 3β-3α, $\Delta[\alpha]_D$ +28° and $\Delta[M]_D$ +127°).[#] Thus it may be concluded that *Buxus* alkaloids of the cycloprotobuxine-type with a 20*R*-amino group are levorotatory, but if the amino group is *S*-chiral they would be dextrorotatory, regardless of the configuration of the 3-amino group.[Φ] This may serve as good evidence that *1*-cycloprotobuxine-C ($[\alpha]_D$-62°),[4] isolated by Russian chemists from *B. sempervirens*, possesses *R*-chirality at C-20.

Experimental

M.p.s. were taken on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on Perkin-Elmer 337 and Nicolet 5DX FT-IR spectrometers in KBr discs. N.m.r. spectra were measured with Varian A-60 and Bruker AM-300 spectrometers in $CDCl_3$ solutions with tetramethylsilane as internal standard. Mass spectra were obtained on Hitachi-Perkin-Elmer RMU 6H and Kratos MS-250RFA instruments at an ionising voltage of 70 eV for electron-impact ionisation (unless otherwise specified) and for chemical ionisation. Rotations were determined at 23°C with a Zeiss polarimeter '0.01°' for solutions in chloroform. Alumina for chromatography refers to Merck standardised alumina, activity II-III. Thin layer chromatograms were prepared on silica gel G and the spots were observed by exposure to iodine vapour. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure below 60°C.

3β-*Hydroxy*-4,4,14α-*trimethyl*-5α-*pregnane*-11,20-*dione* (**7**).- 3β-Acetoxy-4,4,14α-trimethyl-5α-pregnane-11,20-dione (**6**) (15 g) in 5% methanolic sodium hydroxide (1000 ml) containing dioxane (50 ml) was heated under reflux for 2 h. Usual work-up afforded the 3β-alcohol (**7**) (12 g, 89%), m.p. 253-255°C (from methylene chloride-methanol) [lit.,[5] m.p. 241-247°C].

4,4,14α-*Trimethyl*-5α-*pregnane*-3,11,20-*trione* (**8**).- The 3β-hydroxy-11,20-dione (**7**) (4.9 g) in acetone (500 ml) was oxidised with Jones reagent. After usual work-up the 3,11,20-oxo-derivative (**8**) (4.2 g, 86%), m.p. 262-264°C (from methylene chloride-methanol) [lit.,[5] m.p. 265-267°C] was obtained.

3,20-*Diethylenedioxy*-4,4,14α-*trimethyl*-5α-*pregnane*-11-one (**9**).- A mixture of the 3,11,20-trione (**8**) (300 mg), *p*-toluene-sulphonic acid (150 mg), ethylene glycol (15 ml), and benzene (300 ml) was heated under reflux with a water separator for 22 h. The solution was washed with aqueous 5% sodium bicarbonate, and then with water. Removal of the solvent afforded the 11-*oxo*-3,20- *diethyleneketal* (**9**) (338 mg, 91%), m.p.221-223°C (from chloroform- methanol); *m/z* 460 (M^+); υ_{max} 1700 (CO)cm^{-1}; δ_H (60 MHz) 0.82, 0.85, 0.98 (3H each, s, Me), 1.18 (6H, s, 2xMe), 1.28 (3H, s, Me), and 4.05 (8H, br s, two ethyleneketal protons); $[\alpha]_D$ +33° (*c* 1.1) (Found: C, 73.25; H, 9.86. $C_{28}H_{44}O_5$ requires C, 73.00; H, 9.63%).

Photolysis of 3,20-*Diethylenedioxy*-4,4,14α-*trimethyl*-5α-*pregnane*-11-*one* (**9**).- The 11-oxo-3,20-diethyleneketal (**9**) (1.0 g) was dissolved in ethanol (900 ml). which had been saturated with potassium carbonate. The solution was then irradiated for 35 h at room temperature with a 200W Hanovia medium pressure mercury lamp under an atmosphere of dry nitrogen. After concentration of the solution to a small volume, water was added and the

[#]In the case of the *N*-phthalyl derivatives[19] of the 3-amino-5a-cholestanes, similar o.r.d. curves which, due to the effect of the strong positive background rotation, exhibited very weak Cotton effects, were observed in both 3β– and 3α– epimers.

[Φ]Note that dihydrocyclokoreanine-A (16α-hydroxy-3α,20*S*-cycloprotobuxine-A) and -B possess $[\alpha]_D$ +50° (its acetate,$[\alpha]_D$ +24°) and $[\alpha]_D$ +68°, respectively (see reference 3c).

product was extracted with chloroform. The chloroform extract was evaporated and the residue was chromatographed in benzene over alumina. Elution with benzene yielded unreacted starting material (420 mg). Elution with benzene-ether (9:1) afforded a fraction (200 mg), but attempts to identify it failed. Further elution with benzene-ether (1:1) gave a fraction (55 mg) which was not further investigated.

Reduction of 4,4,14α-*Trimethyl*-5α-*pregnane*-3,11-20-*trione* (**8**) *with Lithium Aluminium Hydride*.- The 3,11,20-trione (**8**) (700 mg) in dry ether (30 ml) was added dropwise to lithium aluminium hydride (760 mg) in dry ether (50 ml) with stirring and the stirring was continued overnight at room temperature. After addition of water and 20% aqueous sodium hydroxide, the product was worked up in the usual way. This crude triol (**11**) (650 mg) consisted of two epimeric alcohols at C-20, which, without separation, was submitted to the next acetylation.

3β-20*R*-*Diacetoxy*-11β-*hydroxy*-4,4,14α-*trimethyl*-5α-*pregnane*- (**12**) and 3β-20*S*- *Diacetoxy*-11β-4,4,14α-*trimethyl*-5α-*pregnane* (**13**).- A mixture of the above triol (**11**) (2.257 g), pyridine (200 ml), and acetic anhydride (50 ml) was heated under reflux for 1 h. The usual work-up gave a crystalline mass (2.6 g), which after crystallisation from chloroform-methanol afforded the 3β-20*R*-*diacetate* (**12**) (1.46 g), m.p. 236-237°C; $[\alpha]_D$ +60° (*c* 1.2); *m/z* 462 (M^+); υ_{max} 3500 (OH), 1720, 1705, and 1247 acetate) cm^{-1} (Found: C,72.48; H, 9.78. $C_{28}H_{46}O_5$ requires C, 72.69; H, 10.02%). Repeated crystallisations of the mother liquor of the above 3β-20R-diacetate from chloroform-methanol yielded the 3β-20*S*-*diacetate* (**13**) (0.43 g, 15%), m.p. 205-207°C (chloroform-methanol); *m/z* 462 (M^+); υ_{max} 3500 (OH), 1720, 1700, and 1240 (acetate) cm^{-1} (Found: C,72.54; H, 9.83. $C_{28}H_{46}O_5$ requires C, 72.69; H, 10.02%). The mother liquors left after separation of the 3β,20S-diacetate was chromatographed in hexane over alumina. Elution with 20% benzene in hexane afforded an additional amount of the 3β-20*R*-diacetate (**12**) (0.29 g). The total yield of the 3β-20*R*-diacetate (**12**) was 1.75 g (63%).

3β,20*R*-*Diacetoxy*-4,4,14α-*trimethyl*-5α-*pregnane*-11β-*yl Nitrite* (**14**).- The 3β,20*R* diacetoxy-11β-ol (**12**) (0.309 g) in dry pyridine (10 ml) was treated at -70° with nitrosyl chloride until a permanent brown colour had developed. The solution was pured into water and extracted with ether, and the ether extract was washed with water. Removal of the ether afforded the 11β-*nitrite* (**14**) (0.260 g, 79%), m.p. 167-169°C(from ether); $[\alpha]_D$ +94° (*c* 1.2); *m/z* 491 (M^+); υ_{max} 1730, 1720, and 1240 (acetate), and 1635 and 1595 (nitrite)cm^{-1} (Found: C,68.28; H, 9.12; N, 2.75. $C_{28}H_{45}O_6N$ requires C, 68.40; H, 9.23; N, 2.83%).

3β,20*R*-*Diacetoxy*-4,4,14α-*trimethyl*-9β,19-cyclo-5α-*pregnane*-11-*one* (**17**).- The 11β-nitrite (**14**) (0.678 g) in dry benzene (200 ml) containing iodine (0.208 g) was irradiated at room temperature with a 200 W Hanovia medium pressure mercury lamp under nitrogen with use of Pyrex filter for 2 h (disappearance of starting material). The benzene solution was shaken with powdered sodium thiosulphate until the iodine colour had disappeared. The resulting 11β-hydroxy-19- iodo-derivative (**15**) in the benzene solution was, without isolation, at once treated with Jones reagent (4 ml). Washing of the benzene solution with water and removal of the solvent yielded the crude 19-iodo-11-ketone (**15**) (0.669 g) showing a positive iodine test. This crude product, without further purification, was treated in benzene solution with alumina (100 g). Elution with 10-20% ether in benzene afforded the 9β,19-*cyclo*-11-*ketone* (**17**) (0.414 g, 65% overall yield from the nitrite), m.p. 105°C (decomposition) (from methanol); *m/z* 458 (M^+); υ_{max} 1740 and 1247(acetate), and 1670 (CO conjugated with a cyclopropane ring) cm^{-1} (Found: C,73.15; H, 8.96. $C_{28}H_{42}O_5$ requires C, 73.32; H, 9.23%).

3β,20*R*-*Dihydroxy*-4,4,14α-*trimethyl*-9β,19-cyclo-5α-*pregnane*-11-*one* (**18**).- The 9β,19-cyclo-11-oxo-3β-20*R*-diacetate (**17**) (50 mg) was hydrolysed with 10% methanolic sodium

hydroxide (10 ml). Usual work-up afforded the *dihydroxy- derivative* (**18**) (35 mg, 85%), m.p. 243-245°C (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° (Found: C, 79.78; H, 10.11. $C_{24}H_{48}O_3$ requires C, 79.96; H, 10.23%).

Reduction of 3β,20*R*-*Diacetoxy*-4,4,14α-*trimethyl*-9β,19-cyclo-5a-*pregnane*-11-*one* (**17**) *with Lithium Aluminium Hydride*.- The 9β,19-cyclo-11-ketone (**17**) (0.690 mg) in dry dioxane (140 ml) containing lithium aluminium hydride (1.368 g) was heated under reflux for 30 h. After the usual work-up the product was chromatographed in benzene over alumina. Elution with ether afforded the 9β,19-*cyclo*-3β,20*R*-*diol* (**20**) (0.274 g, 51%), m.p. 166-168°C (from chloroform-hexane); $[\alpha]_D$ +37° (*c* 0.9); *m/z* 360 (M^+); δ_H (60 MHz) 0.33, 0.60 (1H each, d, *J* 4.5 Hz, cyclopropane), 0.81 (6H, s, 2xMe), and 0.93 (3H, s, Me), 1.00 (3H, d, *J* 6 Hz, 20-Me), 1.10 (3H, s, Me), and 3.3, 3.8 (1H each, m, C*H*OH) (Found: C, 79.77; H, 10.95. $C_{24}H_{40}O_2$ requires C, 79.94; C, 11.18%). Elution with 10% ether in methanol yielded the 9β,19-*cyclo*-3β,11ξ,20*R*-*triol* (21) (0.305 g) as a semi-solid; *m/z* 376 (M^+) (Found: C, 76.35; H, 10.45. $C_{24}H_{40}O_3$ requires C, 76.55; H, 10.71%).

4,4,14α-*Trimethyl*-9β,19-*cyclo*-5α-*pregnane*-3,20-*dione* (**3**).- The 9β,19-cyclo- 3β,20*R*-diol (**20**) (70 mg) in acetone (20 ml) was treated with Jones reagent at 0°C. After usual work-up and crystallisation of the crude product from ether-methanol, the 3,20-diketone (**3**) (62 mg, 90%), m.p. 190-192°C, was obtained; *m/z* 356 (M^+); υ_{max} 1704 (CO) cm^{-1}; δ_H (300 MHz) 0.57, 0.82 (1H each, d, *J* 4.4 Hz, cyclopropane), 0.92 0.97, 1.05, 1.09 (3H each, s, Me), 2.11 (3H, s, 20-Me), 2,25-2.39, 2.65-2.79, and 2.94-3.3 (1H each, m, 2-and 7-protons) (Found: C, 80.67; H, 9.91. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.18%).

The Dioxime (**22**) *of* 4,4,14α-*Trimethyl*-9β,19-*cyclo*-5α-*pregnane*-3,20-*dione* (**3**).- A solution of the 3,20-dione (**3**) (0.352 g) and hydroxylamine hydrochloride (1.094 g) in pyridine (15 ml) was refluxed for 4 h. After addition of water the product was taken up in ether and the ether extract was washed with water, dried, and evaporated, yielding the *dioxime* (**22**) (0.345 g, 90%), m.p. 277-278°C (from ether-methanol); *m/z* 386 (M^+); υ_{max} 3275 (OH), 1658 (C=N), and 964, 953, 930, 906 (N-O) cm^{-1} (Found: C, 74.34; H, 9.86; N, 7.02. $C_{24}H_{38}O_2N_2$ requires C, 74.75; H, 9.91; N, 7.25%).

Cycloprotobuxine-A (**5**) *and its Isomeric Alkaloids with* 3α,20*R*- *and* 3β,20*R*-*Configuration*.- A mixture of the dioxime (**22**) (1.079 g), lithium aluminium hydride (2.0 g), and dry dioxane (50 ml), was heated under reflux for 20 h. The excess reagent was decomposed with water and the complex was treated with 40% aqueous sodium hydroxide (1 ml). Then anhydrous sodium sulphate was added and the mixture was filtered. Evaporation of the filtrate gave the crude *diamine* (**23**) (1.096 g) as an oil. This diamine was dissolved in dioxane (55 ml) and heated under reflux with 35% aqueous formalin (11 ml) and 85% formic acid (11 ml) for 24 h. The solution was then basified with 10% aqueous potassium hydroxide, diluted with water, and extracted with ether. Evaporation of the ether extract gave a residue (1.38 g), which was chromatographed over alumina (90 g). Elution with hexane afforded 3β,20*R*-*dimethylamino*-4,4,14α-*trimethyl*-9β,19-*cyclo*-5α-*pregnane* (200 mg, 17%), m.p. 183-185°C (from chloroform-acetone-ether); $[\alpha]_D$ -75° (*c* 2.1); *m/z* (C.I.) 413 (M^+-1, 14%),344 (11), 343 (29), 131 (10), 119 (13), 117 (10), 109 (10), 107 (14), 105 (20), 98 (17), 95 (16), 93 (22), 91 (30), 86 (16), 85 (31), 84 (70), 81 (20), 79 (25), 77 (15), 73 (61), 72 (100), 71 (78), and 70 (27); υ_{max} 2983, 2958, 2942, 2929, 2870, 2865, 2818, 2775, 2761, 1459, 1440, 1459, 1382, 1371, 1360, 1263, 1156, 1098, 1051, 1042, 1027, 1005, 966, 957, 940, 921, 894, 888, 865, 800, and 759; δ_H (300 MHz) 0.23, 0.54 (1H each, d, *J* 3.8 Hz, cyclopropane), 0.78 (3H, d, *J* 6.3 Hz, 20-Me), 0.79, 0.89, 0.95, 1.00 (3H each, s, Me), 1.97 (1H, m, 3-H), 2.45 (1H, m, 20-H), 2.12 [6H, s, 20-N(Me)$_2$], and 2.28 [6H, s, 3-N(Me)$_2$]; δ_C (75.47 MHz) 33.41 (1), 20.43 (2), 71.93 (3), 41.81 (4), 49.32 (5), 21.34 (6), 31.20 (7), 49.40 (8), 20.06 (9), 26.84 (10), 27.29 (11), 30.00 (12), 44.37 (13), 48.45 (14), 35.57 (15), 26.04 (16), 48.45 (17), 17.03 (18), 29.70 (19), 60.91 (20), 9.25 (21), 19.31 (28),

26.63 (29), 15.92 (30), 40.09 [20-N(Me)$_2$], and 45.54 [3-N(Me)$_2$] (Found: C, 80.86; H, 12.26; N, 6.54. $C_{28}H_{50}N_2$ requires C, 81.09; H, 12.15; N, 6.76%).

Further elution with hexane gave 3α,20*R*-*dimethylamino*-4,4,14α-*trimethyl*-9β,19-*cyclo*-5α-*pregnane* (30 mg, 2.6%), m.p. 166-168°C (from chloroform-acetone- ether); $[\alpha]_D$-60°(*c* 0.9); *m/z* (C.I.) 413 (M^+-1, 2%), 119 (5), 107 (6), 105 (7), 98 (5), 95 (7), 93 (8), 91 (10), 85 (8), 84 (35), 81 (8), 79 (9), 77 (5), 73 (15), 72 (100), 71 (66), and 70 (9); υ_{max} 2963, 2942, 2931 2913, 2873, 2864, 2851, 2817, 2773, 1471, 1459, 1437, 1370, 1264, 1156, 1142, 1095, 1048, 1038, 1029, 1023, 1006, 984, 958, 924, 886, 879, 820, 796, and 770; δ_H (300 MHz) 0.20, 0.54 (1H each, d, *J* 3.9 Hz, cyclopropane), 0.78 (3H each, d, *J* 6.3 Hz, 20-Me), 0.89, 0.90, 0.94, 1.01 (3H each, s, Me), 2.0 (1H, m, 3-H), 2.45 (1H, m, 20-H), 2.12 [6H, s, 20-N(Me)$_2$], and 2.32 [6H, s, 3-N(Me)$_2$]; δ_C (75.47 MHz) 31.66 (1), 17.63 (2), 68.10 (3), 40.07 (4), 43.62 (5), 22.10 (6), 31.27 (7), 48.58 (8), 18.90 (9), 24.27 (10), 25.83 (11), 31.41 (12), 45.57 (13) 48.43 (14), 35.72 (15), 26.52 (16), 49.47 (17), 17.27 (18), 27.28 (19), 60.90 (20), 9.24 (21), 18.32 (28), 24.15 (29), 23.77 (30), 40.07 [20-N(Me)$_2$], and 44.99 [3-N(Me)$_2$]' (Found: C, 81.36; H, 12.46; N, 6.46. $C_{28}H_{50}N_2$ requires C, 81.09; H, 12.15; N, 6.76%).

Elution was further continued with hexane, whereupon cycloprotobuxine-A (3β,20*S*-dimethylamino-4,4,14α-trimethyl-9β,19-cyclo-5α-pregnane) (**5**) (130 mg, 11%), m.p. 212-214°C (from chloroform-acetone- ether); $[\alpha]_D$ +76° (*c* 1.2) (lit.,[3b] m.p. 207-208°C, $[\alpha]_D$ +76°); *m/z* (C.I.) 413 (M^+-1, 4%), 145 (5), 133 (5), 131 (5), 121 (5), 119 (6), 109 (6), 107 (8), 105 (10), 98 (10), 95 (10), 93 (10), 91 (13), 86 (6), 85 (10), 84 (54), 83 (5), 82 (5), 81 (11), 79 (11), 77 (6), 73 (19), 72 (100), 71 (73), and 72 (12); υ_{max} 2975, 2961, 2928, 2871, 2854, 2827, 2781, 1260, 1470, 1457, 1441, 1384, 1370, 1260, 1175, 1156, 1097, 1059, 1046, 1026, 1005, 985, 971, 953, 920, 890, 861, 837, and 794; δ_H (300 MHz) 0.29, 0.52 (1H each, d, *J*, 3.9 Hz, cyclopropane), 0.82 (3H, d, *J*, 6.3 Hz, 20-Me), 0.79, 0.92 (3H each, s, Me), 0.95 (6H, s, 2xMe), 1.95 (1H, m, 3-H), 2.43 (1H, m, 20-H), 2.18 [6H, s, 20-N(Me)$_2$], and 2.28 [6H,s, 3-N(Me)$_2$]; δ_C (75.47 MHz) 33.52 (1), 20.41 (2), 71.89 (3), 41.82 (4), 48.30 (5), 21.51 (6), 32.67 (7), 49.30 (8), 19.93 (9), 26.06 (10), 26.40 (11), 27.37 (12), 44.29 (13), 48.97 (14), 35.40 (15), 26.57 (16), 50.74 (17), 18.31 (18),29.85 (19), 61.41 (20), 9.19 (21), 19.43 (28), 26.11 (29), 15.95 (30), 39.93 [20-N(Me)$_2$], and 44.35 [3-N(Me)$_2$] (Found: C, 80.75; H, 12.36; N, 6.49. $C_{28}H_{50}N_2$ requires C, 81.09; H, 12.15; N, 6.76%).

Elution with hexane-ether and ether yielded fractions which consisted of a complex mixture of incompletely methylated diamines, as detected by the analysis of the n.m.r. and mass spectra. Attempts to separate each component by repeated chromatography failed.

Cycloartanone (**25**).- Cycloartanol (**24**) (1.05 g), obtained by the hydrogenation of cycloartenol,[20] was dissolved in acetone (50 ml) and oxidised with Jones reagent at 0°C. Usual work-up afforded cycloartanone (**25**) (0.80 g, 81%), m.p. 103-104°C (chloroform-methanol-ether) [lit.,[21] m.p. 110°C].

The Oxime (**26**) of *Cycloartanone* (**25**).- A solution of cycloartanone (**25**) (0.60 g) and hydroxylamine hydrochloride (0.90 g) in pyridine (15 ml) was refluxed for 4 h to furnish the *oxime* (**26**) (0.50 g 81%), m.p. 208-210°C (from chloroform-ether-hexane); *m/z* 441 (M^+); υ_{max} 3266 (OH), 1655 (C=N), and 940, 933 (N-O) cm^{-1} (Found: C, 81.36; H, 11.47; N, 2.91. $C_{30}H_{51}ON$ requires C, 81.53; H, 11.64; N, 3.17%).

3β-*Dimethylamino-cycloartane* (**27**).- A mixture of the oxime (**26**) (0.70 g) and lithium aluminium hydride (0.70 g) in dry dioxane (30 ml) was heated under reflux for 24 h and then worked up as already described for the dioxime (**22**). A mixture of 3β-and 3α-amino-cycloartanes, thus obtained, was directly methylated with 85% formic acid (4 ml) and 35% aqueous formalin (4 ml) in dioxane (20 ml) for 20 h. The solution was basified with 5% aqueous sodium hydroxide and the product was isolated in the usual way. The resulting dimethylamino- derivatives (0.86 g) were chromatographed over alumina (30 g) and elution with hexane yielded 3β-*dimethylamino-cycloartane* (**27**) (487 mg,68%),m.p. 123-124°C (from chloroform- ether-methanol); $[\alpha]_D$+55° (*c* 2.0); *m/z* (C.I.) 454 (M^+-1, 15%), 440 (12), 426

(12), 412 (6), 397 (4), 384 (4), 369 (7), 356 (5), 341 (4), 327 (3), 313 (4), 299 (4), 147 (13), 133 (14), 121 (21), 107 (29), 95 (55),84 (100), 83 (25), 82 (16), 81 (35), 79 (30), 77 (16), 72 (61), 71 (92), and 70 (64); υ_{max} 2961, 2948, 2929, 2898, 2863, 2838, 2818, 2778, 2759, 1471, 1456, 1444, 1384, 1374, 1261, 1152, 1094, 1040, 1025, 1004, and 803; δ_H (300 MHz) 0.22, 0.45 (1H each, d, *J* 4.4 Hz, cyclopropane), 0.73, 0.82 (3H each, s, Me), 0.89 (6H, s, 2xMe), 0.80 (9H, d, *J* 6 Hz, 3x*Me*CH), 1.95(1H, m, 3-H), and 2.21 [6H, s, $N(Me)_2$]; δ_C (75.47 MHz)33.64 (1), 20.51 (2), 72.03 (3), 41.95 (4), 48.40 (5), 21.59 (6), 33.05 (7), 49.52 (8), 20.09 (9), 26.59 (10), 26.15 (11), 28.21 (12), 45.32 (13), 48.85 (14), 35.72 (15), 26.63 (16), 52.51 (17), 18.13 (18), 29.85 (19), 36.15 (20), 19.41 (21), 36.54 (22), 24.17 (23), 39.60 (24), 28.02 (25), 22.56 (26), 22.82 (27), 18.36 (28), 26.09 (29), 15.99 (30), and 44.35 [$N(Me)_2$] (Found: C, 84.16; H, 12.44; N, 2.86. $C_{32}H_{57}N$ requires C, 84.32; H, 12.61; N, 3.07%).

Further elution with hexane afforded 3α-dimethylamino-cycloartane (**28**) (59 mg, 8%), m.p. 116-117°C (from chloroform-ether-methanol) (see below).

3α-*Dimethylamino-cycloartane* (**28**).- The oxime (**26**) (0.50 g) in glacial acetic acid (20 ml) containing ether (10 ml) was hydrogenated with platinum oxide (100 mg) at atmospheric pressure at 23°C. After addition of water the product was extracted with ether and evaporation of the ether extract afforded a mixture of 3β- and 3α-amino-cycloartanes (0.60 g). They were at once methylated with 85% formic acid (3 ml) and 35% aqueous formalin (3 ml) as described above, and the resulted dimethylamino-derivatives (0.47 g) were chromatographed over alumina (30 g). Elution with hexane yielded 3β-dimethylamino-cycloartane (**27**) (55 mg, 10.7%), m.p. 123-124°C (from chloroform-ether-methanol) (see above).

Further elution with hexane afforded 3α-*dimethylamino-cycloartane* (**28**) (240 mg, 46.6%), m.p. 116-117°C (from chloroform-ether-methanol); $[\alpha]_D$ +83° (*c* 1.2); *m/z* (C.I.) 454 (M^+-1, 12%), 412 (12), 369 (15), 189 (10), 187 (11), 175 (15), 173 (15), 163 (12), 161 (19), 159, (20), 152 (10), 149 (17), 148 (10), 147 (25), 145 (23), 143 (10), 137 (12), 136 (14), 135 (23), 134 (14), 133 (30), 131 (22), 129 (12), 125 (15), 124 (11), 123 (25), 122 (16), 121 (40), 120 (16), 119 (41), 117 (19), 115 (11), 111 (13), 110 (18), 109 (47), 108 (18), 107 (50), 106 (16), 105 (50), 99 (10), 98 (25), 97 (22), 96 (18), 95 (63), 94 (22), 93 (54), 92 (16), 91 (56), 86 (14), 85 (66), 84 (75), 83 (75), 82 (22), 80 (57), 79 (12), 78 (53), 77 (13), 76 (31), and 71 (100); υ_{max} 2961, 2950, 2929, 2878, 2865, 2817, 2805, 2771, 1467, 1459, 1377, 1364, 1265, 1164, 1150, 1100, 1091, 1074, 1056, 1038, 1023, 984, 971, 930, 882, 820, and 800; δ_H (300 MHz) 0.25, 0.62 (1H each, d, *J* 4.2 Hz, cyclopropane), 0.92 (6H, s, 2xMe), 0.96, 0.98, 0.99 (3H each, s, Me), 0.89 (6H, d, *J* 6 Hz, 2x *Me*CH), 0.91 (3H, d, *J*, 6 Hz,(*Me*CH), 2.0 (1H, m, 3-H), and 2.32 [6H, s, $N(Me)_2$]; δ_C (75.47 MHz) 31.85 (1), 17.57 (2), 68.05 (3), 40.05 (4), 43.76 (5), 22.29 (6), 31.22 (7), 48.91 (8), 18.77 (9), 23.74 (10), 25.88 (11), 33.05 (12), 45.27 (13), 48.74 (14), 35.81 (15), 26.52 (16), 52.46 (17), 18.29 (18), 28.18 (19), 36.09 (20), 19.49 (21), 36.46 (22), 24.14 (23), 39.54 (24), 28.00 (25), 22.55 (26), 22.84 (27), 18.32 (28), 24.14 (29), 23.77 (30), and 44.94 [$N(Me)_2$] (Found: C, 84.09; H, 12.51; N, 2.78. $C_{32}H_{57}N$ requires C, 84.32; H, 12.61; N, 3.07%).

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