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HIGHER ISOPRENOIDS—XI[a]

PARTIAL SYNTHESES FROM CYCLOARTENOL, CYCLOLAUDENOL—PART 3: CYCLOBUXOPHYLLININE-M, CYCLOBUXOPHYLLINE-K AND BUXANINE-M[b,c]

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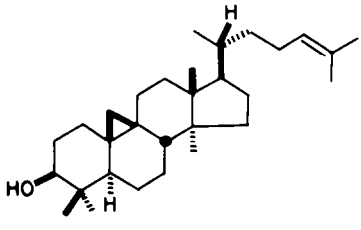
Abstract—3β-Acetoxy-9,19-cyclo-4,4,14α-trimethyl-5α-pregnan-20-one, an intermediate readily accessible from cycloartenol/cyclolaudenol has been transformed into cyclobuxophyllinine-M, an alkaloid isolated from certain *Buxus* Spp. This compound has been earlier converted into the closely related alkaloids cyclobuxophilline-K and buxanine-M. The present work formally constitutes the synthesis of these alkaloids from cycloartenol.

Buxus alkaloids[1] constitute an important group of cycloartenol-based natural products and, at present, no less than seventy members are known, a majority of which carry an oxygen function at C-16. In continuation of our earlier[2-4] work on the conversion of cycloartenol (**1**)/cyclolaudenol (**2**) into cycloartane derived naturally occurring compounds, specifically *Buxus* alkaloids,[3] we report a method for C-16 oxygenation, leading to the synthesis of cyclobuxophyllinine-M (buxenone-M) (**3**),[5,6] an alkaloid isolated from *Buxux microphylla* var. *Suffruticosa*[5] and *B. sempervirens*.[6] Since this compound has been earlier converted into the closely related *Buxus* alkaloids cyclobuxophylline-K (**4**)[5] and buxanine-M (**5**),[7] the present work, formally constitutes their synthesis as well. These conversions also formally serve to extend the total synthesis[8] of cycloartenol to these alkaloids.

[a]Part X: *Tetrahedron* **35**, 985 (1979).
[b]MRC Communication No. 24.
[c]Abstracted from the Ph.D. Theses (M.S. University, Baroda) of Joginder Singh (1977) and Manoj C. Desai (1980).

After considerable probing experiments,[9] the following strategy was envisaged for converting cycloartenol (**1**) to cyclobuxophyllinine-M (**3**), a typical C-16 oxygenated *Buxus* alkaloid. Degradation of side-chain of cycloartenol leading to 9,19 - cyclo - 4,4,14α - trimethyl - 3β - acetoxy - 5α - pregnan - 20 - one (**6**) was readily carried out by the method of Narula and Sukh Dev.[10] Further elaboration to **3** would involve: (i) generation of *E*-configurated $\Delta^{17(20)}$-16-keto system, and (ii) conversion of 3β-acetoxy group into 3β-methylamino function. For the introduction of the $\Delta^{17(20)}$-16-keto function, advantage was sought to be taken of the known[12] acid-catalyzed isomerization of pregn-16-en-20-ols to preg-17(20)-en-16-ols, while the introduction of the 3β-methylamino group appeared reasonably feasible by the stardard[13] reductive amination of the 3-keto function. However, sequence of reactions had to be so chosen that the oxygenated functions at C-3 and C-16/C-20 are properly differentiated. The series of reactions, which permitted the successful transformation of the hexanor ketone (**6**) into the targeted cyclobuxophyllinine-M (**3**) is outlined in Fig. 1.



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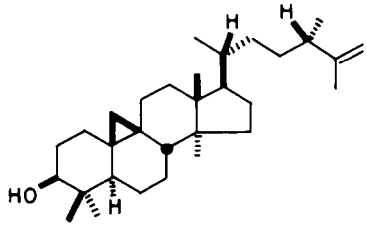

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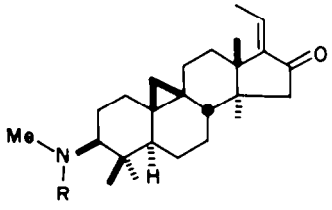


3 : R = H

4 : R = Me

5 : R = COC_6H_5

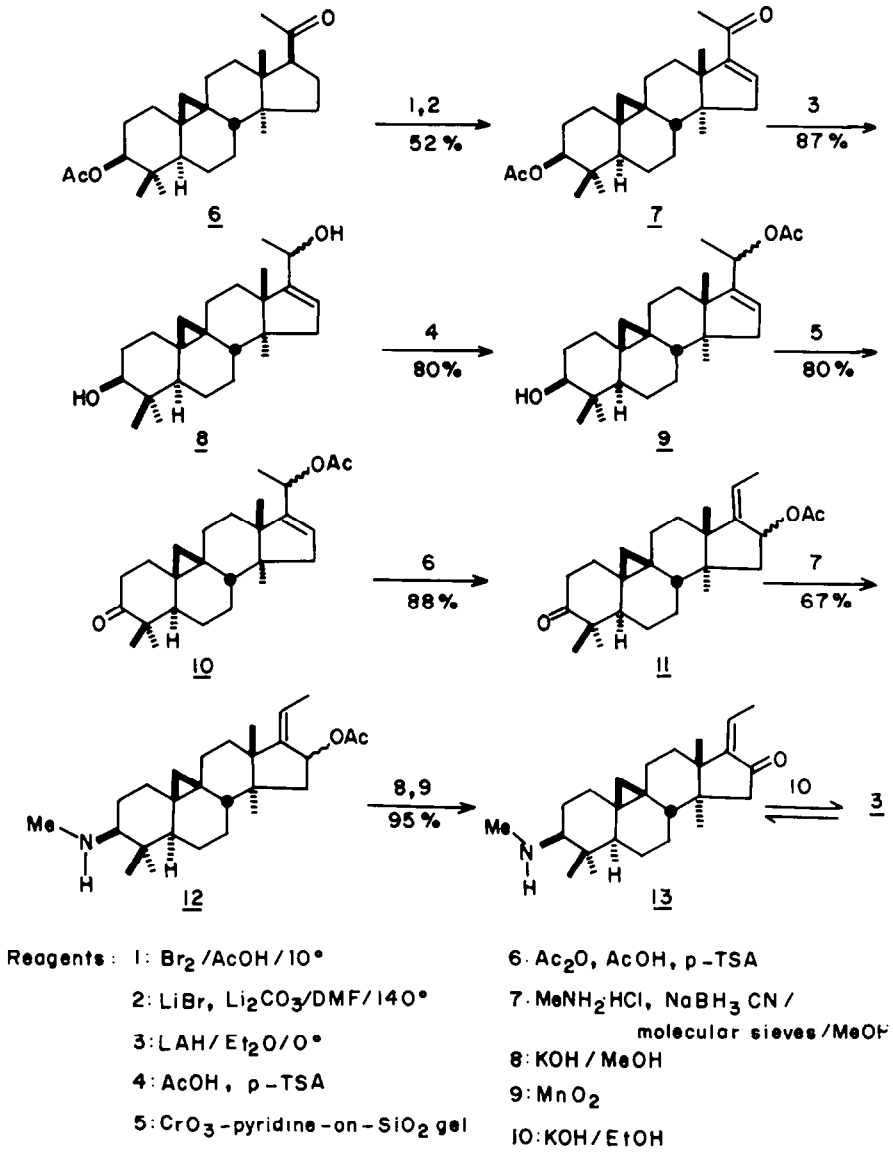
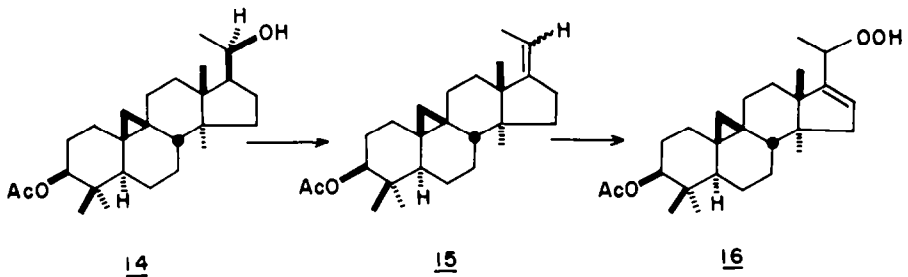
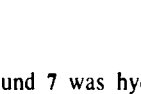


Fig. 1. Synthesis of cyclobuxophyllinine—M.

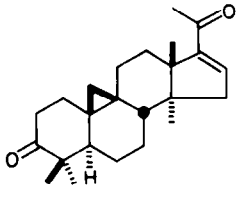
In the early stages of present investigation, conversion of the hexanor ketone **6** to the corresponding α,β-olefinic ketone (**7**) was sought to be achieved by a sequence of reactions avoiding use of a bromination–dehydrobromination step, as from prior analogy,[14] the cyclopropane ring in **6** was considered to be prone to cleavage during the bromination step. Thus, the sequence of reactions (**14** to **16**→**7**) was developed. The ketone **6** was reduced by $NaBH_4$ to furnish an essentially single alcohol (m.p. 205.5–207.5°. IR: OH 3520 and 1070 cm^{-1}; OAc 1720 and 1260 cm^{-1}. PMR: CHOH, 1H, m, 3.71 ppm) which, in analogy with the known[15] behaviour of 20-oxopregnanes on complex hydride reduction, is assigned 20*R*-configuration (**14**). The alcohol was next dehydrated



to the olefin mixture **15**, by refluxing its tosylate with *sym*-collidine.[16] Transformation of olefin **15** to the desired unsaturated ketone (**7**) was achieved by its photosensitized oxidation[17] to the hydroperoxide (**16**), which without isolation was converted to the desired ketone **7** (m.p. 234–236°, λ_{max} 242 nm, ϵ11300. IR: C=C–C=O 1665, 1590 cm^{-1} PMR: cyclopropane C$\underline{H}_2$, 1H doublets at 0.36 and 0.69 ppm, J = 4 Hz; $CH_3CO{\cdot}C{=}C\underline{H}$, 3H, s, 2.28 ppm, $CH_3CO{\cdot}C{=}C\underline{H}$, 1H, t, 6.68 ppm, J = 2.0 Hz), on exposure to acetic anhydride.[18] The overall yield of **7** by this route was ~40% based on **6**.

Subsequently, it was found possible to prepare the unsaturated ketone (**7**) by the much more convenient bromination–dehydrobromination sequence.[19] Exposure of the haxanor ketone (**6**) to Br_2 in acetic acid[20] at 10° furnished as the major product (~75%, PMR) the anticipated 17-bromo derivative (PMR: $CH_3CO{\cdot}C\underline{H}Br$, s, 2.36 ppm), which in analogy[21] to the bromination of pregnan-20-ones is considered 17α-configurated. The crude reaction product was immediately dehydrobrominated with LiBr/Li_2CO_3 in DMF[22] to yield the required enone **7** in an overall yield of 52% based on **6**. In a still another approach, the enone **7** was sought to be prepared from **6** by the application of the recently introduced method[23] involvong *syn*-elimination of β-ketoselenoxide; however, reaction of **6** with phenylselenenyl chloride, followed by H_2O_2 oxidation of the resulting selenenyl intermediate, led only to the net oxidation of the methyl ketone side chain to the corresponding carboxylic acid  [24]

At this stage, compound **7** was hydrolysed (NaOH–MeOH) and the resulting hydroxy enone oxidised by Jones' reagent[25] to furnish the diketone (**17**); this compound has been reported earlier[26] as the Ruschig degradation product of cyclovirobuxine-D (**18**). Our product displayed properties (m.p., UV, IR) essentially identical to those reported in the literature.[26]



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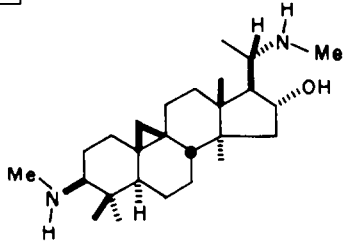

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Next, the enone (**7**) was reduced with LAH to get a product, which from its PMR spectrum was clearly a mixture of epimeric diols **8** ($CH_3CHOH{\cdot}C$: two discreet pairs of doublets at 1.36 and 1.39 ppm). As C-20 stereochemistry is of no consequence for the subsequent steps, no attempt was made to separate the epimers. At this stage, the strategic requirement for the selective oxidation of C-3 hydroxyl, demanded a selective protection of C-20 hydroxyl. This became possible when, treatment of diols (**8**) with dry acetic acid containing some *p*-toluenesulphonic acid furnished the monoacetates (**9**) in ~80% yield. Oxidation of this product with pyridinium chromate-on-silica gel[27] cleanly gave the desired 3-oxo derivative **10** in over 80% yield.

The next step was the generation of $\Delta^{17(20)}$-16-keto system, and to this effect, the mixture of Δ^{16}-20-acetates (**10**) was subjected to acid-catalyzed allylic rearrangement to get $\Delta^{17(20)}$-16-acetates (**11**). Benn and Dodson[12] have studied this rearrangement for a number of 20-hydroxy-16-pregnenes and arrived at the following conclusions: (i) $\Delta^{17(20)}$ is favoured over $\Delta^{16(17)}$ and the equilibrium is independent of the C-20 hydroxyl configuration, (ii) only *Z*-olefins are formed, and (iii) 16β-hydroxyl is favoured over the 16α-epimer. Since, the immediate environment of ring D in **10** is very similar to that in 20-hydroxy-16-pregnenes investigated by these authors, it is reasonable to assume that these generalizations remain valid for **10**. The anionotropic rearrangement of **10**, indeed, gave essentially the Z-olefin **11**; Z-configuration of the ethylidene side chain became evident from the PMR spectrum of the derived ketone (**13**), described below. Though *Z*-configuration is not desired for our target molecule, the situation is readily corrected at the last stage.

The above acetoxyketone (**11**) was subjected to reductive amination (methylamine sodium cyanoborohydride/MeOH/Type 4A molecular sieves)[13b] to furnish in 67% yield the corresponding 3-methylamino derivative. The product was essentially a single compound (tlc: solvent, EtOAc–NH_3, R_f 0.52; PMR: $NHC\underline{H}_3$, 2.84 ppm) with a trace of a second component (tlc: R_f 0.57; PMR: $NHC\underline{H}_3$, 2.73 ppm). That the major component would have the required 3β-configuration (**12**) follows from the expectation that the hydride attack on the intermediatory Schiff's base would occur from the less hindered α-face of the substrate, as is indeed the case for the hydride reduction of several 3-oxo-cycloartane derivatives.[28] The assignment of 3β-configuration (**12**) to the main product and α-stereochemistry to the very minor component is consistent with their tlc behaviour,[29] as well.

The 16-acetoxy-3β-methylamino derivative (**12**) was saponified and the resulting hydroxy compound oxidised with active MnO_2[30] to furnish **13** (m.p. 128–130°. IR: C=O 1708 cm^{-1}, C=C 1640 cm^{-1}) which differs from the targeted cyclobuxophyllinine-M (**3**) in being its *Z*-geometrical isomer. The *Z*-configuration of the ethylidene side-chain in **13** (and hence in **11**, because the configurational integrity would be maintained during saponification and subsequent MnO_2 oxidation) was obvious from a comparison of its PMR signals ($CH_3C\underline{H}{=}C{\cdot}CO$, d, 2.13 ppm, J = 7 Hz; $CH_3C\underline{H}{=}C{\cdot}CO$, q, 5.76 ppm, *J* = 7 Hz; $CH_3C\underline{H}{=}C{\cdot}CO$, q, 5.76 ppm, *J* = 7 Hz) with those reported[5] for cyclobuxophyllinine-M ($CH_3C\underline{H}{=}C{\cdot}CO$, d, 1.85 ppm, *J* = 7.5 Hz; $CH_3C\underline{H}$ = C·CO, q, 6.59 ppm, *J* = 7.5 Hz); the observed shifts are consistent[31] with the ethylidene side-chain geometries involved and as arising from anisotropy of the 16-oxo-group.

The *Z*-isomer (**13**) on equilibration[32] with ethanolic KOH yielded, in a 3:2 ratio (PMR), cyclobuxophyllinine-M (**3**) and *Z*-isomer, from which the required **3** could be isolated by fractional crystallization. The product thus obtained displayed characteristcs (m.p. 178–181°; $[\alpha]_D$ – 49.0°, $CHCl_3$; IR; PMR) essentially identical with those reported in the literature (m.p. 174°,[5] 181–182°;[6] $[\alpha]_D$ – 48°, $CHCl_3$;[5] IR;[5] PMR[5]).

EXPERIMENTAL

All m.ps are uncorrected. Light petroleum refers to fraction of b.p. 60–80°. Optical rotations were measured in $CHCl_3$ on a Schmidt–Haensch electronic polarimeter (model Polartronic-I).

The following instruments were used for spectral/analytical data: Perkin–Elmer spectrophtometer model 402(UV); Perkin–Elmer Infracord model 267; Perkin–Elmer model R32 (90 MHz) NMR spectrometer; Varian Mat CH7 mass spectrometer (70 eV, direct inlet system). While citing PMR data, the following abbreviations have been used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). While summarising mass spectral data, besides the molecular ion, nine most abundant ions (*m/e*) are reported with their relative intensities.

Silica gel for column chromatography (−100, +200 mesh) was washed with hot water till sulphate-free, dried and activated at 125–130° for 6 hr and standardised.[33] Tlc was carried out on SiO_2-gel layers (0.25 mm) containing 15% gypsum and activated at 110–115° (2 hr).

(20R) - 3β - *Acetoxy* - 9,19 - *cyclo* - 4,4,14α - *trimethyl* - 5α - *pregnan* - 20 - *ol* (**14**)

$NaBH_4$ (0.2 g) in 80% ethanol aq (10 ml) was introduced dropwise during 15 min to a stirred soln of the hexanor ketone **6** (0.250 g) in $CHCl_3$ (5 ml) at 0° (N_2). The reaction mixture was stirred at the temp for 7 hr and then worked up in the usual manner to get a product (0.240 mg, m.p. 192–196°) which was chromatographed on silica gel (IIb; 1 cm × 15 cm) with tlc monitoring (solvent: 10% EtOAc in C_6H_6). After eluting with 20% C_6H_6 in light petrol (50 ml × 2), 50% C_6H_6 in light petrol (50 ml × 2), and C_6H_6 (50 ml), the required product (0.230 mg) was eluted with 25% EtOAc in C_6H_6 (50 ml × 3). This was crystallised from MeOH–isopropyl ether to furnish pure **14**, m.p. 205.5–207.5°, $[\alpha]_D + 52°$ (*c*, 1.5%). PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.34 ppm; 1H, d, 0.61 ppm, $J = 4$ Hz), C-Me's (singlets at 0.85, 0.88, 0.91 and 1.09 ppm), CH-Me (d, 1.16 ppm, $J = 6.5$ Hz), $OCOCH_3$ (3H, s, 2.04 ppm), CHOH (1H, m, 3.71 ppm), CHOAc (1H, m, 4.48 ppm). (Found: C, 77.29; H, 10.28. $C_{26}H_{42}O_3$ requires: C, 77.56; H, 10.52%).

3β - *Acetoxy* - 9,19 - *cyclo* - 4,4,14α - *trimethyl* - 5α - *pregn*-17(20) - *ene* (**15**)

The above alcohol (81 mg) in dry pyridine (7 ml) was converted to the corresponding tosylate by treatment with p-toluenesulphonyl chloride (39 mg), first at 0° (10 min) and later at 10–15° (30 hr). Usual work-up with $CHCl_3$ gave a product (112 mg, m.p. 120–122° dec.) which was crystallised from acetone to furnish pure tosylate, m.p. 121.5–122° (dec.). IR (CCl_4) $ArSO_2O$[34] 1370, 1190 and 1180 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.35 ppm; 1H, d, 0.58 ppm, $J = 4$ Hz), CH_3CHOTS (3H, d, 1.23 ppm, $J = 6.5$ Hz), CH_3CHOTs (1H, m, 4.78 ppm), $OSO_2C_6H_4CH_3$ (3H, s, 2.47 ppm).

The above tosylate (112 mg) was refluxed in dry *sym*-collidine (5 ml) for 3 hr (N_2), cooled, diluted with water (25 ml), the product taken up in $CHCl_3$ (20 ml × 4). The $CHCl_3$ extract was washed with 5% HCl aq, 5% $NaHCO_3$ aq, H_2O, brine and dried ($MgSO_4$). $CHCl_3$ was flashed off, the product taken up in light petrol–C_6H_6 (3:1; 10 ml), the solution passed through a column (2 cm × 5 cm) of Al_2O_3–III and the column eluted with the same solvent (100 ml). Removal of solvent from the eluates furnished the desired olefin **15** (52 mg, m.p. 118–121°), which was crystallised twice from isopropyl ether–MeOH, m.p. 144.5–147° IR (CCl_4): 1730, 1370, 1245, 1022 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.31 ppm; 1H, d, 0.67 ppm, $J = 4$ Hz), CH_3·CH=C (3H, d, 1.55 ppm, $J = 7$ Hz), $CH_3CH=C$ (1H, m, 4.99 ppm). (Found: C, 81.77; H, 11.13. $C_{26}H_{40}O_2$ requires: C, 81.20; H, 10.4%).

3β - *Acetoxy* - 9,19 - *cyclo* - 4,4,14α - *trimethyl* - 5α - *pregn* - 16 - *en* - 20 - *one* (**7**)

(i) *By singlet oxidation of olefin* **15**. The above olefin (100 mg) and methylene blue (46 mg) in dry pyridine (20 ml) were treated with a fine stream of O_2, which being illuminated with sunlight (Baroda, September, 10.00–17.00 hr). After 35 hr, Ac_2O (20 ml) was added and the reaction mixture allowed to stand at room temp. (30°) for 45 min and then at 60° for another 1 hr. The product was cooled, diluted with water (20 ml) and extracted with isopropyl ether (25 ml × 6). The organic phase was successively washed with cold 10% HCl aq, 5% aq $NaHCO_3$, brine and dried (Na_2SO_4). The solvent was flashed off to give a product (103 mg) which was chromatographed on silica gel (IIb; 1.5 cm × 18 cm), while monitoring with tlc (solvent; 5% EtOAc in C_6H_6): (i) 20% C_6H_6 in light petrol, 50 ml × 6, 50 mg of starting olefin; (ii) 40 to 70% C_6H_6 in light petrol, 50 ml × 4, 10 mg of mixture; (iii) C_6H_6, 50 ml × 5, 32 mg, m.p. 223–225° (dec.). The last fraction was crystallised from CCl_4 to furnish the desired ketone **7**, colorless needles, m.p. 229.5–231.5° (dec.). A somewhat purer material was obtained by method (ii).

(ii) *By bromination-dehydrobromination of ketone* **6**. To a cooled (10°) soln of ketone **6** (6.0 g, 0.015 mole) in AcOH (70 ml), two drops of 48% HBr aq were added, followed by dropwise addition (1 hr) of a soln of Br_2 (2.64 g, 0.033 g atom) in AcOH (19 ml), precooled to 10°. After stirring the reaction mixture for 1 hr at 25 ± 3°, water (200 ml) was added and the precipitated solid taken up in ether (200 ml × 3). The extract was washed successively with water (200 ml × 3), 5% aq. $NaHCO_3$ (100 ml × 2), water (200 ml × 2), brine (100 ml × 1) and dried (Na_2SO_4). Removal of ether furnished the crude brominated product (6.7 g), PMR spectrum of which showed some 75% of the desired 17-bromo derivative (by comparison of CH_3CO–CBr signal at δ 2.36 ppm with that of $OCOCH_3$ signal at δ 2.02 ppm).

The above crude bromo derivative (6.7 g) was added to a stirred suspension of LiBr (6.1 g, 0.07 mole) and Li_2CO_3 (4.79, 0.07 mole) in dry DMF (200 ml) and the reaction mixture taken to 140° and heated at that temp for 8 hr (N_2). After cooling to room temp the reaction mixture was carefully poured into ice cold 10% HCl aq (100 ml) and worked up in the usual manner with ether. The solvent was flashed off to get a dark brown solid (5.2 g), which was crystallised from CH_2Cl_2–ether to get pure enone **7** (3.1 g), m.p. 234–236°. IR (CCl_4): 1730, 1665, 1590, 1450, 1390, 1370, 1245, 1090 and 1020 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.36 ppm; 1H, d, 0.69 ppm, $J = 4$ Hz), C-Me's (singlets at 0.89, 0.91, 0.99 and 1.21 ppm), $OCOCH_3$ (3H, s, 2.07 ppm), CH_3CO (3H, s, 2.28 ppm), CHOAc (1H, m, 4.67 ppm), C=CH (1H, t, 6.68 ppm, $J = 2$ Hz). Mass: *m/e* 398 (M^+, 29%), 338(52%), 323(37%), 295(31%), 135(46%), 107(35%), 93(30%), 69(37%), 49(68%) and 43(100%). (Found: C, 78.57; H, 9.61. $C_{26}H_{38}O_3$ requires: C, 78.35; H, 9.56%).

Methyl 3β - *acetoxy* - 9,19 - *cyclo* - 4,4,14α - *trimethyl* - 5α - *androstane* - 17β - *carboxylate*.

To a soln of hexanor ketone (**6**; 150 mg, 0.375 mole) in EtOAc (8 ml) was added phenylselenenyl chloride (86.2 mg, 0.45 mole) and a drop of conc HCl aq. The resulting orange soln was stirred at room temp (~28°) until it had turned yellow (4 hr), the EtOAc layer separated and washed with water (5 ml × 5). The EtOAc soln was, next, diluted with tetrahydrofuran (15 ml), and 30% H_2O_2 aq (5 ml) introuced with stirring at ~28° during 5 min and the stirring continued for an additional 1 hr. The reaction mixture was diluted with water (15 ml), the product taken up in ether (30 ml × 3), the extract washed with water, dried (Na_2SO_4), and freed of solvent to get a semi-solid, which was esterified (CH_2N_2). The product was crystallised from Et_2O–MeOH to furnish methyl 3β - acetoxy - 9,19 - cyclo - 4,4,14α - trimethyl - 5α - androstane - 17β - carboxylate (109 mg), m.p. 130–134°. IR (CCl_4): 1740, 1380, 1255, 1210, 1185, 1170, 1100, 1035 and 985 cm^{-1}. PMR (CCl_4): Cyclopropyl CH_2 (1H, d, 0.31 ppm; 1H, d, 0.64 ppm, $J = 4$ Hz), C-Me's (6H each, s, 0.87, 0.93 ppm), $OCOCH_3$ (s, 2.02 ppm), $COOCH_3$) (3H, s, 3.69 ppm), CHOAc (1H, m, 4.57 ppm). Mass: *m/e* 416 (M^+, 8%), 234(100%), 175(65%), 133(56%), 122(86%), 121(63%), 119(60%), 107(83%), 95(58%), 93(77%). (Found: C, 75.21; H, 9.87. $C_{26}H_{40}O_4$ requires: C, 74.96; H, 9.68%).

9,19 - *Cyclo* - 4,4,14α - *trimethyl* - 5α - *pregn* - 16 - *ene* - 3,20 - *dione* (**17**)

Enone **7** (106 mg) was saponified (10 ml of 10% NaOH in MeOH, reflux, 4 hr, N_2) and the product (100 mg, m.p. 178–182°)

crystallised from acetone to get the corresponding hydroxy ketone, m.p. 179.5–183°. IR ($CHCl_3$): OH 3610 and 1100 cm^{-1}. PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.33 ppm; 1H, d, 0.65 ppm, $J = 4$ Hz), C-Me's (3H singlets at 0.82, 0.97, 0.98 and 1.20 ppm), $COCH_3$ (3H, s, 2.27 ppm), CHOH (1H, m, 3.30 ppm). C=CH (1H, t, 6.69 ppm, $J = 2.4$ Hz).

The above hydroxyketone (56 mg) in acetone (3 ml) was cooled to 0° and treated with stirring with Jones' reagent[25] till a brown colour persisted (~ 1 ml). After stirring for another 30 min at 0°, the reaction mixture was worked up in the usual manner to get a product (54 mg, m.p. 151–160°) which on crystallization from acetone furnished pure **17**, m.p. 164–173° dec. (Lit.,[26] m.p. 165–178°) λ_{max}^{EtOH} 242.5 (7350). IR ($CHCl_3$): C=O 1700 cm^{-1}; C=C–C=O 1665 and 1590 cm^{-1}. PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.67 ppm, $J = 4$ Hz; second H under Me signal), C-Me's (3H singlets at 0.99, 1.07, 1.11 and 1.27 ppm), $COCH_3$ (3H, s, 2.27 ppm), C–CH (1H, t, 6.70 ppm, $J = 2.4$ Hz).

3β - Hydroxy - 9,19 - cyclo - 4,4,14α - trimethyl - 5α - pregn - 16 - en-20 - ols (**8**)

Enone **7** (5.0 g, 0.012 g mole) in dry ether (200 ml) was reduced at 0° (N_2) with LAH (80%, 2.37 g; 0.0625 mole) during 6 hr. After destroying the excess LAH with EtOAc (35 ml), followed by water (~ 10 ml), the precipitated salts were removed by filtration, washed with CH_2Cl_2 (100 ml) and the combined organic phase worked up in the usual manner to get a product (4.04 g) still containing a small amount of the unchanged enone. The product was chromatographed over silica gel (IIb; 3 cm × 35 cm) while monitoring with tlc (10% EtOAc in C_6H_6): (i) 5% EtOAc in C_6H_6, 100 ml × 4, 100 mg of **7**; (ii) 5% EtOAc in C_6H_6, 100 ml, 40 mg of mix. of **7** and **8**. (iii) 25% EtOAc in C_6H_6, 100 ml × 6, 3.9 g, m.p. 130–135°. Fraction (iii) was crystallised from Et_2O–MeOH to get 86.7% of **8**, m.p. 152–154°. IR (CCl_4): 3420, 1275, 1100, 1060, 1050, 1020, 985, 940, 910, 890, 860 and 800 cm^{-1}. PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.31 ppm; 1H, d, 0.69 ppm, $J = 4$ Hz), C-Me's (3H singlets at 0.82, 0.96, 1.0, and 1.16 + 1.22 ppm), $CHCH_3$ (3H, doublet at 1.36 + doublet at 1.39, $J = 7$ Hz), CHOH (1H, m, 3.33 ppm), CH_3·CHOH (1H, m, 4.18–4.51 ppm), C=CH (1H, t, 5.67 ppm, $J = 2$ Hz). Mass: *m/e* 358 (M^+, 18%), 313(23%), 173(26%), 119(31%), 107(36%), 105(24%), 93(24)%, 91(24%), 55(27%) and 43(100%). (Found: C, 80.13; H, 10.87. $C_{24}H_{38}O_2$ requires: C, 80.39; H, 10.68%).

3β-Hydroxy - 9,19 - cyclo - 4,4,14α - trimethyl - 5α - pregn - 16 - en - 20 - yl - acetates (**9**)

The above diol **8** (5.0 g, 0.014 mole) was dissolved in anhydrous AcOH (150 ml, freshly distilled from P_2O_5), soln cooled to ~ 12°, p-toluenesulphonic acid (220 mg) added and the reaction mixture set aside at the same temp. for 20 min. After this, water (200 ml) was added, the product taken up in ether (200 ml × 3) and the extract washed with water (150 ml × 3), 5% $NaHCO_3$ aq (150 ml × 3), water (150 ml) and brine (100 ml), and dried. Removal of solvent gave a semi-solid (4.45 g), which was chromatographed on silica gel (IIb; 2.7 cm × 52 cm) with tlc (Solvent: 10% EtOAc in C_6H_6) monitoring. After eluting with light petroleum (100 ml × 4) and, 3% EtOAc in C_6H_6 (100 ml × 5), the next 50 ml × 10 eluates with 3% EtOAc in C_6H_6, furnished 2.55 g (51%) of **9**, which partly crystallized; finally 25% EtOAc in C_6H_6, (100 ml × 5) eluted 1.6 g (m.p. 130–133°) of starting diol **8**. An analytical sample of **9** was obtained by crystallization from Et_2O–MeOH, m.p. 70–72°. IR (CCl_4): 3620, 3500, 1730, 1240, 1100, 1050, 1025 and 945 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.31 ppm; 1H, d, 0.69 ppm, $J = 4$ Hz), C-Me's (3H singlets at 0.82, 0.92, 0.99, and 1.13 + 1.2 ppm), $CHCH_3$ (3H, doublet at 1.37 + doublet at 1.39 ppm, $J = 6.5$ Hz), $OCOCH_3$ (3H, s, 2.07 ppm), CHOH (1H, m, 3.28 ppm), CHOAc (1H, m, 5.29–5.53 ppm), C=CH (1H, t, 5.6 ppm, $J = 2$ Hz). (Found: C, 78.22; H, 9.76. $C_{26}H_{40}O_3$ requires C, 77.95; H, 10.07%).

3 - Oxo - 9,19 - cyclo - 4,4,14α - trimethyl - 5α - pregn - 16 - en - 20 - yl - acetates (**10**)

To a soln of the above hydroxy acetate (**9**; 1.0 g, 0.0025 mole) in CH_2Cl_2 (10 ml), pyridinium chromate-on-silica gel[27] (7.2 g ≡ 1.0 g CrO_3) and AcOH (150 mg) were added and the reaction mixture mechanically shaken for 6 hr at room temp (30–35°). At the end of this period, ether (10 ml) was added, shaking continued for another 5 min and the reaction mixture filtered and the solids washed with ether (75 ml). The combined filtrate and washings were successively washed with 5% aq. HCl (20 ml × 1), water (20 ml × 2), 5% aq. $NaHCO_3$ (25 ml × 2), water (30 ml × 2), brine and dried. Removal of ether furnished a light yellow solid (807 mg, 81%), which was crystallised from Et_2O–MeOH to furnish the required **10**, m.p. 132–135°. IR (CCl_4): 1740, 1712, 1250, 1210, 1115, 1055, 1040, 1025 and 950 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.56 ppm, $J = 4$ Hz; second H under Me signal), C-Me's (3H singlets at 0.94, 0.99, 1.04, 1.11 and 1.17 + 1.22 ppm), $CHCH_3$ (3H, doublet at 1.37 + doublet at 1.39 ppm, $J = 6$ Hz), CHOAc (1H, m, 5.41 ppm), C = CH (1H, 5.67 ppm). Mass: *m/e* 398 (M^+, 26%), 336(53%), 322(37%), 134(41%), 120(33%), 119(95%), 107(30%), 105(33%), 93(25%), 91(32%) and 43(100%). (Found: C, 78.73; H, 9.81. $C_{26}H_{38}O_3$ requires: C, 78.35; H, 9.16%).

3 - Oxo - 9,19 - cyclo - 4,4,14α - trimethyl - 5α - pregn-17(20) - en - 16 - yl - acetates (**11**)

A soln of the above compound (**10**; 3.1 g, 0.0078 mole) in AcOH (45 ml) containing acetic anhydride (6 ml) and p-toluene sulphonic acid (200 mg) was set aside (N_2) at room temp (30–35°) till tlc showed almost complete conversion of **10** (R_f 0.37) into **11** (R_f 0.42) (48 hr; tlc solvent: 5% EtOAc in C_6H_6, 27°). At this stage the dark brown reaction mixture was worked up by dilution with water and extraction with ether, to get crude **11** as a dark semi-solid (2.9 g). This was dissolved in C_6H_6 and filtered through SiO_2-gel (IIb; 3 cm × 10 cm); elution with 10% EtOAc in C_6H_6 furnished **11** as a light yellow semi-solid (2.74 g, 88.4%). An analytical sample was obtained by crystallisation from Et_2O–MeOH, m.p. 148–150°. IR(CCl_4): 1740, 1712, 1250, 1120, 1040 and 950 cm^{-1}. PMR (CCl_4): cyclopropyl CH_2 (1H, d, 0.53 ppm, $J =$ 4 H; second H under Me signal), C-Me's (3H singlets at 0.81, 1.01, 1.08 and 1.27 ppm), CH_3–C=C (3H, d, 1.63 ppm, $J = 7$ Hz), C=CH (1H, q, 5.38 ppm, $J = 7$ Hz), CHOAc (1H, m, 5.75 ppm) (Found: C, 78.20; H, 9.71. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.61%).

Cyclobuxophyllinine-M (**3**)

To a soln of **11** (150 mg, 0.377 mmole) in dry MeOH (10 ml) were added sodium cyanoborohydride (28.5 mg, 0.452 mmole), methylamine hydrochloride (67 mg, 1 mmole) and Type 4A molecular sieves (1.5 g; powder, activated). The reaction mixture was stirred for 80 hr at room temp. (25–30°), filtered ad the seives washed with hot MeOH (5 × 15 ml). The combined filtrate and washings were cooled (0°), acidified (pH < 2) with conc. HCl aq and MeOH removed under vacuum at room temp. The residue was taken up in water (20 ml), extracted with ether (15 ml × 2) to remove any neutral products and the aq. soln basified (pH > 10) with powdered KOH, satured with NaCl and extracted with CH_2Cl_2 (20 ml × 4). The extract was washed with water, brine, dried (Na_2SO_4) and freed of solvent to get crude **12** (105 mg, 67%; tlc pure, R_f 0.45, EtOAc saturated with NH_3) which was directly used in the next step.

The above product (107 mg) was saponified (5 ml, 10% KOH in MeOH; reflux, 4 hr) to get the corresponding alcohol (100 mg), which was dissolved in C_6H_6 (10 ml) and the soln stirred (12 hr) with activated MnO_2[35] (500 mg) at room temp (~ 27°). Usual work-up furnished a solid (94 mg, ~ 100%), which was crystallised from acetone to get pure **13**, m.p. 128–130°. IR ($CHCl_3$): 2800, 1708, 1640, 1160, 1094 and 920 cm^{-1}. PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.36 ppm; 1H, d, 0.64 ppm, $J = 4$ Hz), C-Me's (3H singlets at 0.78, 0.93, 0.98 and 1.27 ppm), CH_3–C=C (3H, d, 2.13 ppm, $J = 7$ Hz), $NHCH_3$ (3H, s, 2.47 ppm), C=CH (1H, q, 5.76 ppm, $J = 7$ Hz).

The above *Z*-isomer (**13**; 90 mg, 0.244 mmole) in 80% EtOH aq (5 ml) containing KOH (200 mg) was kept at room temp. (27°) for 2 hr (N_2). Usual work-up gave a mixture of *Z*- and *E*-isomers (81 mg; *Z*:*E*/2:3, PMR) which was fractionally crystallised from ether to get pure **3** (17 mg), m.p. 178–181°, $[\alpha]_D$ – 49.0° (*c*, 0.49%). IR ($CHCl_3$): 2800, 1712, 1643, 1191, 1097, 981 and 920 cm^{-1}. PMR ($CDCl_3$): cyclopropyl CH_2 (1H, d, 0.40 ppm; 1H, d, 0.67 ppm, $J = 4$ Hz), C-Me's (3H singlets at 0.80, 0.98, 0.98 and 1.36 ppm),

CH_3–C=C (3H, d, 1.87 ppm, $J = 7$ Hz), $NHCH_3$ (3H, s, 2.49 ppm), C=CH (1H, q, 6.62 ppm, $J = 7$ Hz). Mass: *m/e* 369(M^+, 52%), 354(14%), 326(8%), 135(10%), 107(6%), 105(6%), 93(6%), 91(6%), 80(42%), 58(12%) and 57(100%).

REFERENCES

[1]See e.g.: J. Tomko and Z. Voticky in *The Alkaloids* (Edited by R. H. F. Manske), Vol. 14, pp. 1–82. Academic Press, New York (1973).

[2]C. Singh and Sukh Dev, *Tetrahedron* **33**, 817 (1977).

[3]C. Singh and Sukh Dev, *Ibid.* **33**, 1053 (1977).

[4]M. C. Desai, C. Singh, H. P. S. Chawla and Sukh Dev, *Tetrahedron Letters* 5047 (1979).

[5]T. Nakano, S. Terao and Y. Saeki, *J. Chem. Soc.* (*C*) 1412 (1966).

[6]W. Dopke, B. Muller and P. W. Jeffs, *Pharmazie* **21**, 643 (1966).

[7]W. Dopke and B. Muller, *Ibid.* **21**, 769 (1966).

[8]D. H. R. Barton, D. Kumari, P. Welzel, L. J. Danks and J. F. McGhie, *J. Chem. Soc.* (*C*) 332 (1969).

[9]Unsuccessful attempts included the action of $Pb(OAc)_4/I_2(h\nu)$ on alcohols (a, b), obtained by hydroboration of the corresponding olefins;[10] this reaction resulted in fragmentation[11] to the iodide (c), with none of the expected ethers (d/e), being formed.

[10]A. S. Narula and Sukh Dev, *Tetrahedron* **27**, 1119 (1971).

[11]See e.g.: K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Edit.* **3**, 524 (1964); M. Lj. Mihailovic and Z. Cekovic, *Synthesis* 209 (1970).

[12]W. R. Benn and R. M. Dodson, *J. Org. Chem.* **29**, 1142 (1964).

[13]See e.g.: [a]W. S. Emerson, *Organic Reactions* **4**, 174 (1948); [b]R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).

[14]See e.g.: J. H. Turnbull and E. S. Wallis, *J. Org. Chem.* **21**, 663 (1956); M. Gaitonde, P. A. Vatakencherry and Sukh Dev, *Tetrahedron Letters* 2007 (1964).

[15]See e.g.: D. N. Kirk and M. P. Hartshorn, *Steroid Reactions Mechanisms*, p. 139. Elsevier, Amsterdam (1968); D. M. S. Wheeler and M. M. Wheeler in *Organic Reactions in Steroid Chemistry* (Editors: J. Fried and J. A. Edwards), Vol. I, p. 61. Van Nostrand Reinhold, New York (1972).

[16]See e.g.: R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.* **26**, 2883 (1961).

[17]See e. g.: R. W. Denny and A. Nickon, *Organic Reactions* **20**, 133 (1973).

[18]See e.g.: A. M. Krubiner, G. Saucy and E. P. Oliveto, *J. Org. Chem.* **33**, 3548 (1968).

[19]C. C. Beard, *Organic Reactions in Steroid Chemistry* (Edited by J. Fried and J. A. Edwards), Vol. I, pp. 267–306. Van Nostrand Reinhold, New York (1972).

[20]R. E. Marker, H. M. Crooks, Jr. and R. B. Wagner, *J. Am. Chem. Soc.* **64**, 210 (1942).

[21]See e.g.: L. F. Fieser and M. Fieser, *Steroids*, pp. 561–563. Reinhold, New York (1959).

[22]R. Joly, J. Warnant, G. Nomine and D. Bertin, *Bull. Soc. Chem. Fr.* 366 (1958).

[23]K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Am. Chem. Soc.* **95**, 6137 (1973); For a general review see: D. L. J. Clive, *Tetrahedron* **34**, 1049 (1978).

[24]It would appear that selenenylation with sterically bulky phenylselenenyl cation took place at the less hindered C-21 position to give α-phenylselenoketone (f) which on oxidation with H_2O_2 would give the corresponding β-ketoselenoxide (g). The latter carries no β-hydrogen atom for elimination and is instead converted to the carboxylic acid (h). The mechanism of the reaction is being investigated.

[25]K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946); R. G. Curtis, I. M. Heilbron E. R. H. Jones and G. F. Woods, *Ibid.* 457 (1953).

[26]K. S. Brown and S. M. Kupchan, *Tetrahedron Letters* 2895 (1964).

[27]R. P. Singh, H. N. Subbarao and Sukh Dev, *Tetrahedron* **35**, 1789 (1979).

[28]S. Corsano and E. Mincione, *Chem. Comm.* 738 (1968); N. L. Dutta and C. Quasim, *Indian J. Chem.* **7**, 1276 (1969); Y. Tachi, S. Taga, Y. Kamano and M. Komatsu, *Chem. Pharm. Bull.* **19**, 2193 (1971).

[29]L. Labler and V. Cerny, *Coll. Czech. Chem. Comm.* **28**, 2932 (1963); L. Labler and V. Cerny, *Thin Layer Chromatography* (Edited by M. Bettolo). Elsevier, Amsterdam (1964).

[30]See e.g.: J. S. Pizey, *Synthetic Reagents*, Vol. II, p. 143. Wiley, New York (1974); C. Beard, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.* **86**, 269 (1964).

[31]See e.g.: L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, pp. 222–225. Pergamon Press, Oxford (1969).

[32]K. S. Brown and S. M. Kupchan, *J. Am. Chem. Soc.* **86**, 4414 (1964).

[33]R. Hernandez, R. Hernandez, Jr., and L. R. Axelrod, *Analyt. Chem.* **33**, 370 (1961).

[34]R. S. Tipson, *J. Am. Chem. Soc.* **74**, 1354 (1952).

[35]J. Attenburow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).