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HIGHER ISOPRENOIDS—VI

PARTIAL SYNTHESES FROM CYCLOARTENOL, CYCLOLAUDENOL—PART 2: BUXANDONINE, CYCLOPROTOBUXINE-F AND CYCLOPROTOBUXINE-A[a,b]

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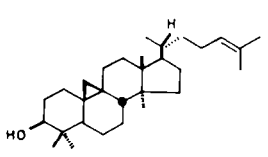
Abstract—Stereospecific conversion of 9,19-cyclo-4,4,14α-trimethyl-3β-acetoxy-5α,9β-pregnan-20-one, readily accessible from cycloartenol/cyclolaudenol, into three closely related *Buxus* alkaloids—buxandonine, cyclo-protobuxine-F and cycloprotobuxine-A—is described.

In continuation of our studies[1] on the conversion of cycloartenol (**1**)/cyclolaudenol (**2**) into cycloartane-based naturally occurring compounds, we report transformations leading to three closely related *Buxus* alkaloids—buxandonine (**3**),[2] cycloprotobuxine-F (**4**)[3] and cyclo-protobuxine-A (**5**).[4] These conversions formally serve to extend the total synthesis[5] of cycloartenol to these alkaloids. *Buxus* alkaloids[6] constitute an important group of cycloartenol derived natural products and, at present, no less than 65 members are known. Very limited synthetic activity has been reported[7] in this field and with the exception of transformation[8] of cycloartenol into cycloprotobuxine-C (**6**), no other synthesis/conversion has been published.



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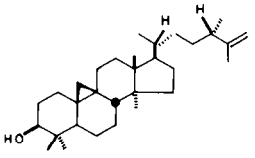

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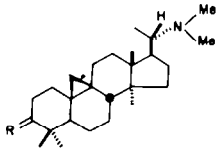


3 R=O
4 R=H(∝), NH_2
5 R=H(∝), NMe_2
6 R=H(∝), NHMe
7 R=H(∝), OH

9,19-Cyclo-4,4,14α-trimethyl-3β-acetoxy-5α,9β-pregnan-20-one (**8**), for which we have already described[9] an efficient and expeditious preparation from cycloartenol (**1**), is a key-intermediate for possible elaboration of a number of *Buxus* alkaloids. Many of these alkaloids have an amino function at C_{20} and this has always *S*-chirality.[6] All the three alkaloids (**3**, **4**, **5**), selected for synthesis from **8** have a dimethylamino function at C_{20}. Hence, the first objective was a stereoselective transformation of C_{20}-carbonyl into carbylamino function with the desired *S*-chirality.

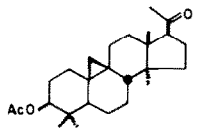
Since, the reduction of 20-oxo-pregnanes with complex metal hydrides is known[10] to furnish predominantly *R*-configurated alcohols and since, the immediate environment at C_{20} in **8** is similar to that in 20-oxo-pregnanes, it was argued that a similar hydride reduction of **8** should furnish as the predominant product 20*R*-alcohol (**9**). Also, since the reduction of oximes or imines is mechanistically akin[11] to the reduction of ketones, routes to C_{20}-amine using such intermediates, would result predominantly in the unwanted *R*-chirality. Hence, the most promising approach appeared to be one involving a single S_N2 displacement of a suitable derivative of **9**.

Ketone **8** was reduced with $NaBH_4$ to furnish a mixture of epimeric alcohols (9:1), which were readily separated on SiO_2-gel. The major product, m.p. 199–204°, is considered to be **9**, in view of the reasoning given earlier. This was tosylated and the crystalline derivative (**11**) exposed to NaN_3 in hexamethylphosphoramide[12] (HMPT), when the desired azide (**12**; 65%), accompanied by the elimination product[12b] **14** (35%), was obtained; *S*-chirality at C_{20} in **12** follows from the known chemistry[13] of such displacement reactions. At this stage, it may be pointed out that the use of the usual solvents recommended[14,15] for this reaction resulted in either low yields (28–40%; DMSO, 35–40°, 12 hr; 10% H_2O in DMF, 90°, 7 hr) of the azide (balance being olefin **14**) or no reaction (CH_3CN, 30°, 72 hr) occurred.

Azide **12** was reduced with LAH[13b] to the corresponding amine (**13**), which on N-methylation (HCHO–HCOOH)[16] and subsequent alkaline hydrolysis yielded N,N-dimethylamino alcohol **7**.

Oxidation of **7** with CrO_3-pyridine in CH_2Cl_2 was carried out with the hope of getting buxandonine (**3**), but instead the N-formyl ketone **15** was obtained, almost exclusively. Such oxidations of the N-Me function by CrO_3 are on record.[17] However, selective oxidation of **7** to the desired **3** could be achieved with Jones CrO_3 reagent. The product was duly identified by comparision of its characteristics (m.p., $[\alpha]_D$, IR, PMR), with those reported in the literature[18] for **3**, obtained from cycloprotobuxine-C (**6**) by Ruschig degradation. Compound **3** (Buxandonine) has since been isolated from *Buxus sempervirens*.[2]

[a] MRC Communication No. 6.
[b] Abstracted from the Ph.D Thesis (Poona University, 1976) of Chandan Singh.



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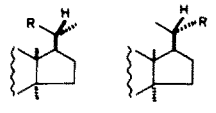
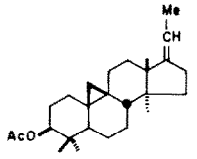


9 R = OH
11 R = OTs

10 R = OH
12 R = N_3
13 R = NH_2, 3β-OH



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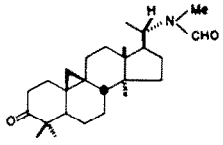

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Compound **3** was oximated and the oxime reduced by LAH to furnish cycloprotobuxine-F (**4**), which was further characterised as the known[8] N-3-isopropylidene derivative. Methylation (HCHO–HCOOH) of **4** yielded cycloprotobuxine-A (**5**). The physical characteristics (m.p., $[\alpha]_D$, IR, PMR) of these compounds were found to be essentially identical with those reported for the naturally occurring alkaloids.

EXPERIMENTAL

For general remarks, see Part V of This Series.

3β - *Acetoxy* - 20 - *hydroxy* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregnane* (**9**, **10**). A mixture of **8** (2.0 g) and $NaBH_4$ (0.20 g) in 95% EtOH aq (150 ml) was stirred for 8 hr at 25 ± 2° and then worked up in the usual manner to furnish a gum (2.0 g) showing on TLC (SiO_2-gel; solvent: 10% EtOAc in C_6H_6) two spots of R_f 0.33 and 0.40. The product was chromatographed on SiO_2-gel/II (100 cm × 2 cm); the following pooled fractions were collected:

Fraction 1	C_6H_6	100 ml × 5	—
Fraction 2	C_6H_6	50 ml × 5	1.7 g, m.p. 195–198°, R_f 0.40
Fraction 3	C_6H_6	50 ml × 1	150 mg, gum, mixture.
Fraction 4	C_6H_6	50 ml × 4	150 mg, solid, R_f 0.33.

20R-*Alcohol* (**9**). Fraction 2 was recrystallised from CCl_4 to furnish colorless needles, m.p. 199–204°, $[\alpha]_D$ +50.3 (*c*, 1.3%). IR (KBr): OH 3540, 1030 cm^{-1}; OAc 1725, 1270 cm^{-1}. PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.33 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (3H singlets at 0.84, 0.89, 0.94 and 1.09 ppm), CHMeOH (3H, d, 1.16 ppm, J = 6 Hz), OAc (3H, s, 2.04 ppm), CHMeOH (1H, m, 3.76 ppm), CHOAc (1H, m, 4.56 ppm). Mass: *m/e* 342 (M^+–AcOH), 327, 283, 216, 171, 157, 143, 129, 118, 116. (Found: C, 77.77; H, 9.91. $C_{26}H_{42}O_3$ requires: C, 77.56; H, 10.52%).

20S- *Alcohol* (**10**). Fraction 4 was crystallised from ether–MeOH to give **10**, m.p. 160–165°. IR (Nujol): OH 3330, 1025 cm^{-1}; OAc 1730, 1250 cm^{-1}. PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.30 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (3H singlets at 0.84, 0.88, 0.90 and 0.96 ppm), CHMeOH (3H, d, 1.19 ppm, J = 6 Hz), OAc (3H, s, 2.02 ppm), CHMeOH (1H, m, 3.69 ppm), CHOAc (1H, m, 4.56 ppm). Mass: *m/e* 342 (M^+–AcOH), 327, 299, 283, 220, 203, 175, 173, 161, 149. (Found: C, 77.20; H, 10.04. $C_{26}H_{42}O_3$ requires: C, 77.56; H, 10.52%).

3β - *Acetoxy* - (20R) - 20 - *tosyloxy* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregnane* (**11**). A soln of **9** (1.42 g) and *p*-toluenesulfonyl chloride (3.0 g) in anhyd pyridine (30 ml) was kept at 10–15° for 30 hr, then diluted with ice-water (100 ml), extracted with ether (100 ml × 3) and the combined extracts washed successively with chilled 10% HCl aq (50 ml × 2), 5% $NaHCO_3$ aq and ice-water (50 ml × 3). After drying (Na_2SO_4), the solvent was flashed off under vacuum to furnish a white solid (1.6 g, m.p. 116–119°), which was recrystallised from acetone, m.p. 125–126° (dec). IR (Nujol): Ar·SO_2·O 1180, 1190, 1363 cm^{-1}; OAc 1730, 1250 cm^{-1}. PMR (CCl_4): tertiary Me's (3H, singlets at 0.84, 0.87, 0.89 and 1.04 ppm), CHMeOTs (3H, d, 1.22 ppm, J = 6 Hz), OAc (3H, s, 2.0 ppm), Me·$C_6H_4SO_3$ (3H, s, 2.48 ppm), CHOAc (1H, m, 4.53 ppm), CHOTs (1H, m, 4.80 ppm), Me·C_6H_4·SO_3 (2H, d, 7.31 ppm; 2H, d, 7.78 ppm; J = 8 Hz). Mass: *m/e* 384 (M^+–TsOH, 1%) 324 (8%), 172 (18%), 107 (32%), 95 (22%), 91 (100%), 81 (16%), 79 (26%), 77 (23%), 65 (30%).

Azidolysis of **11**. A mixture of the above tosylate (1.9 g), NaN_3 (4.0 g) in HMPT (30 ml) was stirred at 30 ± 2° for 8 hr, then diluted with water (100 ml), extracted with ether (100 ml × 3), and the total extract washed successively with water (100 ml), 10% Na_2CO_3 aq (50 ml) and water (100 ml), and dried (Na_2SO_4). Solvent was flashed off to give a yellowish gum (1.4 g), which on TLC (solvent: 50% C_6H_6 in hexane) showed two spots of R_f 0.55 and 0.60. This mixture could be easily separated by column chromatography on SiO_2-gel/II (100 × 2 cm) using light petroleum as an eluant.

3β - *Acetoxy* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregn* - 17(20) - *ene* (**14**). Initial fractions of the above chromatography yielded material (450 mg) of R_f 0.60; this was crystallised from ether–MeOH to give **14**, m.p. 132–135°. IR (Nujol): OAc 1735, 1250 cm^{-1}. PMR (CCl_4): cyclopropane CH_2 (1H, d, 0.30 ppm; 1H, d, 0.60 ppm; J = 4 Hz), tertiary Me's (9H, s, 0.87 ppm; 3H, s, 1.16 ppm), MeCH=C (dt, 1.62 ppm; J_1, J_2 = 7.5, 1.0 Hz),[19] OAc (3H, s, 1.99 ppm), CHOAc (1H, m, 4.51 ppm), MeCH=C (1H, m, 5.17 ppm). Mass: *m/e* 384 (M^+, 15%), 187 (65%), 161 (60%), 147 (62%), 135 (50%), 133 (55%), 121 (100%), 119 (45%), 107 (50%), 105 (47%), 93 (55%). (Found: C, 81.77; H, 11.13. $C_{26}H_{40}O_2$ requires: C, 81.20; H, 10.48%).

3β - *Acetoxy* - (20S) - 20 - *azido* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregnane* (**12**). Later chromatographic fractions on solvent removal furnished the desired azide (950 mg), which was crystallised from light petroleum, m.p. 85–88°. IR (Nujol): N_3 2090 cm^{-1}; OAc 1735, 1250 cm^{-1}. PMR (CCl_4): cyclopropane CH_2 (1H, d, 0.33 ppm; 1H, d, 0.58 ppm; J = 4 Hz), tertiary Me's (3H singlets at 0.84, 0.87, 0.90 and 0.96 ppm), CHMeN$_3$ (3H, d, 1.24 ppm; J = 7 Hz), OAc (3H, s, 1.98 ppm), CHMeN$_3$ (1H, m, 3.36 ppm), CHOAc (1H, m, 4.51 ppm). (Found: C, 74.69; H, 9.45; N, 8.75. $C_{26}H_{41}O_2N_3$ requires: C, 73.02; H, 9.66; N, 9.83%).

3β - *Hydroxy* - (20S) - 20 - N,N - *dimethylamino* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregnane* (**7**). To a cooled (0°) and stirred slurry of LAH (0.60 g) in dry ether (100 ml), a soln of **12** (0.90 g) in dry ether (10 ml) was added dropwise (10 min), the mixture stirred for 10 hr at reflux, cooled to 0°, and the excess reagent and complex decomposed by cautious addition of water (1 ml), followed by 20% NaOH aq (2 ml). After stirring for 10 min, the mixture was filtered, the residue washed with warm $CHCl_3$ (50 ml × 3). The combined filtrates were washed with water (50 ml × 2), dried (Na_2SO_4) and freed of solvent to give a white solid (0.76 g, m.p. 146–48°), which was clearly **13** from its PMR spectrum ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.26 ppm; 1H, d, 0.50 ppm; J = 4 Hz), tertiary Me's (3H singlets at 0.73, 0.84, 0.90 and 0.98 ppm), CHNH$_2$ (1H, m, 2.71 ppm), CHOH (1H, m, 3.22 ppm). This was used as such in the next step.

A soln of the above amine (0.18 g), 30% HCHO aq (1 ml) and 85% HCOOH aq (1 ml) dioxane (10 ml) was refluxed (24 hr), made just alkaline with 10% NaOH aq and extracted with $CHCl_3$ (50 ml × 3), the combined extracts washed with water (25 ml × 2) and dried (Na_2SO_4). The solvent was flashed off and the residue refluxed with 10% alcoholic NaOH (10 ml) for 1 hr. The mixture was cooled, diluted with water (50 ml), extracted with $CHCl_3$ (50 ml × 3), the extract washed with water (20 ml × 2), dried (Na_2SO_4) and freed of solvent to give a residue (200 mg), which was chromatographed on SiO_2–gel/II (10 cm × 1 cm). 10% MeOH in $CHCl_3$ (50 ml × 3) eluted the required compound (180 mg; m.p. 155–160°), which was crystallised from acetone, m.p. 170–175°. IR (KBr): 3340, 1340, 1260, 1198, 1170, 1102, 1030, 925 cm^{-1}. PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.33 ppm; 1H, d, 0.58 ppm; J = 4 Hz), C–Me's (singlets at 0.80, 0.82, 0.88, 0.94, 0.99 ppm), NMe$_2$ (6H, s, 2.22 ppm), CHOH (1H, m, 3.33 ppm). Mass: *m/e* 387 (M^+, 0.2%), 105 (1.8%), 95 (1.6%), 93 (1.8%), 91 (2.4%), 84 (2.4%), 81 (1.5%), 79 (2.0%), 77 (1.3%), 72 (CHMe=$\dot{N}$Me$_2$, 100%), 67 (1.6%). (Found: N, 3.53%. $C_{26}H_{45}ON$ requires: N, 3.61%).

3 - *Oxo* - (20S) - 20 - N - *methyl* - 20 - N - *formylamino* - 4,4,14α - *trimethyl* - 9,19 - *cyclo* - 5α - *pregnane* (**15**). To a stirred soln of

CrO_3 (0.2 g) and pyridine (1 ml) in CH_2Cl_2 (20 ml), a soln of **7** (100 mg) in CH_2Cl_2 (5 ml) was added in one lot and stirred for 1 hr at 25 ± 2°. The mixture was diluted with 2% NaOH aq (20 ml), the product taken up in ether (25 ml × 3), washed with water and dried (Na_2SO_4). Solvent was removed to give a solid (100 mg), which was crystallised from acetone, m.p. 201–205°. IR (Nujol): HCON– 1675 cm^{-1}; C=O 1703 cm^{-1}. PMR ($CDCl_3$): tertiary Me's (singlets at 0.93, 1.06, 1.11 and 1.11 ppm), N<u>Me</u> (3H, s, 2.78 ppm; s, 2.83 ppm), <u>H</u>CON (1H; s, 8.04 ppm; s, 8.17 ppm). (Found: N, 3.32. $C_{26}H_{41}O_2N$ requires: N, 3.51%).

Buxandonine (**3**). A soln of **7** (100 mg) in acetone (20 ml) was treated with Jones reagent[20] (2 ml; 2.67 g CrO_3, 2.3 ml H_2SO_4 conc., diluted to 10 ml with H_2O) at 0–5° and the mixture stirred for 20 min at the same temp, after which it was diluted with water (20 ml), made alkaline with 10% NaOH aq and worked up in the usual manner, using $CHCl_3$. Removal of solvent gave a solid (95 mg, m.p. 163–175°), which was recrystallised from acetone to give **3**, m.p. 188–92°, $[\alpha]_D$ + 14 (lit.[18] m.p. 197, $[\alpha]_D$ + 14). IR ($CHCl_3$): C=O 1700 cm^{-1}. PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.57 ppm; second d, unclear at 0.80 ppm; J = 4 Hz), CH<u>Me</u>NMe_2 (3H, d, 0.86 ppm, J = 6 Hz), tertiary Me's (3H singlets at 0.93, 0.99, 1.06 and 1.10 ppm), N<u>Me_2</u> (6H, s, 2.21 ppm). Mass: *m/e* 385 (M^+, 0.1%), 105 (1.1%), 95 (0.9%), 93 (1.1%), 91 (1.4%), 84 (2.0%), 81 (0.9%), 79 (1.6%), 72 (CHMe = $\dot{N}Me_2$, 100%), 69 (1.1%), 67 (1.3%).

Cycloprotobuxine-F (**4**). A soln of **3** (218 mg) and $NH_2OH \cdot HCl$ (300 mg) in pyridine (5 ml) was refluxed (4 hr), cooled to 0°, made alkaline with 10% NaOH aq and the product taken up in $CHCl_3$ (25 ml × 3). After water (20 ml × 3) washing and drying (Na_2SO_4), the solvent was removed to give the oxime (210 mg, m.p. 218–20°), which was recrystallised from ether–MeOH, m.p. 235–239°. (lit.[8]: m.p. 236–238°). IR (Nujol): OH 3200 cm^{-1}; C=N 1660 cm^{-1}; N–O 950, 940 cm^{-1}.

The above oxime (140 mg) was reduced with LAH (200 mg) in dry dioxane (10 ml) by refluxing for 24 hr. Usual work-up gave the required amine (**4**) as a solid (130 mg), m.p. 150–160° (lit.[3]: m.p. 163°; the base is best characterised as the isopropylidene derivative, described below). PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.29 ppm; 1H, d, 0.60 ppm; J = 4 Hz), C-Me's (singlets at 0.89, 0.91, 0.94, 0.99 and 1.07 ppm), N<u>Me_2</u> (6H, s, 2.27 ppm). Mass: *m/e* 386 (M^+, 0.34%), 105 (1.4%), 95 (1.1%), 93 (1.1%), 91 (1.5%), 84 (2.2%), 79 (1.2%), 72 (CHMe=$\dot{N}Me_2$, 100%), 70 (1.1%), 69 (1.1%), 67 (1.1%).

The amine (**4**, 100 mg) in acetone (10 ml) was refluxed for 6 hr, then concentrated till crystallisation started. The product, colourless needles, m.p. 183–185° (lit.[8]: m.p. 180–182°), was collected after several hr at 25°.

Cycloprotobuxine-A (**5**). A soln of **4** (200 mg), 30% HCHO aq (2 ml) and 85% HCOOH aq (2 ml) in dioxane (10 ml) was refluxed (48 hr) and then worked up as already described for **7** to furnish **5** (200 mg), which was recrystallised from acetone, m.p. 200–205°, $[\alpha]_D$ +77.6°. (lit.[18b]: m.p. 206–207°, $[\alpha]_D$ +77). IR (Nujol): 2780, 1265, 1160, 1097, 1050, 1030, 925, 810 cm^{-1}. PMR ($CDCl_3$): cyclopropane CH_2 (1H, d, 0.29 ppm; 1H, d, 0.54 ppm; J = 4 Hz), CH<u>Me</u>NMe_2 (3H, d, 0.86 ppm, J = 6 Hz), tertiary Me's (singlets at 0.92, 0.98, 0.98 and 1.01 ppm), two N<u>Me_2</u> (6H, s, 2.32 ppm; 6H, s, 2.36 ppm).

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