Tetrahedron. Vol. 29, pp. 1109 to 1114. Pergamon Press 1973. Printed in Great Britain

STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—VIII[1]

REARRANGEMENTS OF 4,4,14α-TRIMETHYL-19(10 → 9β)*ABEO*-10α-PREGNA-1,5-DIENE-3,11,20-TRIONE

J. R. BULL and A. J. HODGKINSON

National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa

(*Received in the UK* 6 *November* 1972; *Accepted for publication* 14 *November* 1972)

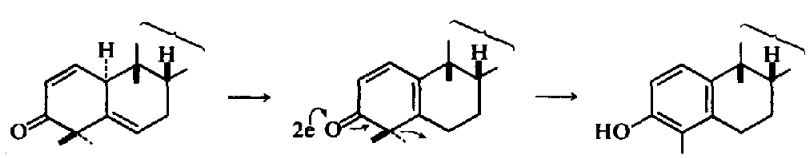
Abstract—Isomerisation of the $\Delta^{1,5}$-dien-3-one (1) under conditions of thermodynamic and kinetic control afforded the $\Delta^{1(10),5}$-isomer (2). The compound 1 underwent rearrangement in strong acids or acetyl bromide to give the aromatic derivatives 4 or 11, respectively. Further reactions of 1 and 4 are described.

The failure of earlier attempts[2,3] to utilise 6-alkoxy-radical processes for the degradation of the 4,4-dimethyl moiety of retro-pregnane analogues derived from the cucurbitacins, led to an investigation of more direct methods mediated by A-ring functionality. A plausible pathway for stepwise 4-Me loss is suggested by the reductive aromatisation of steroidal $\Delta^{1,4}$-3-ones, whereby treatment with zinc in aqueous pyridine or dimethylformamide (DMF),[4] or with lithium and biphenyl,[5] results in expulsion of the 10-Me group. Thus, isomerisation of the accessible $\Delta^{1,5}$-3,11,20-trione[6] (1) to the $\Delta^{1,5(10)}$-isomer would afford a linearly conjugated substrate in which the aberrant ring cleavage and rearrangement pathways[4] of the reductive aromatisation process would be suppressed by the nature of the substitution at the C(9) and C(10) positions. It was thus expected that reduction of a $\Delta^{1,5(10)}$-3,11,20-trione might lead to a phenol (Scheme 1) which could then undergo further A-ring modification.

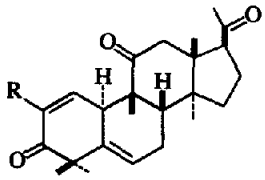
It has been reported[7] that mild alkaline treatment of a $\Delta^{1(10),5}$-3-one closely related to 1 gives the corresponding $\Delta^{1,5(10)}$-isomer. Accordingly a number of experiments were carried out upon 1 with UV monitoring, using similar and more drastic alkaline conditions. However, absorption suggestive of the formation or intermediacy of a $\Delta^{1,5(10)}$-3-one was not detected. Instead, the $\Delta^{1(10),5}$-isomer (2) was invariably formed. The role of the 11-CO group in establishing an equilibrium favouring deconjugation of C:C and C:O is not clear, but its importance is evidenced by the presence of an 11α-OH group in the cited case[7] where full conjugation is claimed to occur.

The compound 1 failed to react at all in the presence of certain acid catalysts (*e.g.* CF_3CO_2H, 0·4 M-H_2SO_4/MeOH, HCl in Et_2O or $CHCl_3$), but treatment with HCl/MeOH afforded the trienyl ether (3) together with the deconjugated product (2). Acidic hydrolysis of 3 also afforded 2. Obviously the C(2) position is more accessible for protonation than C(6), and it is suggested that in the absence of C-ring influences,[7] the deconjugated product (2) is both kinetically and thermodynamically favoured.

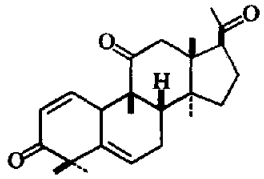
Treatment of 1 with toluene *p*-sulphonic acid in refluxing benzene afforded a new isomer (4) in 80% yield. This product was also formed, albeit less efficiently, by the reaction of 1 with BF_3-etherate in refluxing benzene or with conc H_2SO_4 in HOAc at 90°. The phenolic character of the product was confirmed by spectroscopy, and formation of an acetate (5) and a methyl ether (6). An NMR spectrum of 4 revealed that the A-ring is penta-substituted, and it was inferred from signals for identifiable C- and D-ring protons that no deep-seated rearrangement had taken place. Although an aromatisation mechanism involving skeletal C–C bond cleavage seemed unlikely, the spectroscopic data gave no clear indication of the pattern of A-ring substitution. However, NMR examina-



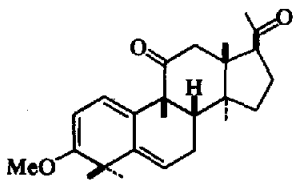
SCHEME 1



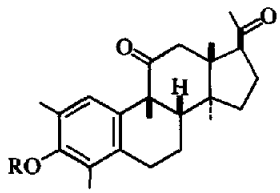
1: R = H
13: R = Br



2



3



4: R = H
5: R = Ac
6: R = Me

tion of 4 under the influence of added Eu(fod)$_3$,[8] revealed that the two aromatic Me groups experience small but very similar induced chemical shifts, while that of the aromatic proton is appreciably greater (Fig 1). This suggests that both aromatic Me groups are similarly disposed toward the OH group and, in so far as the magnitude of shift reflects the degree of complexation, it may be concluded that they occupy *ortho*-positions thereby hindering approach of the shift reagent to the OH group. The 11- and 20-CO groups are strongly complexed, as evidenced by induced shifts of proximate protons (Fig 1), and the former site

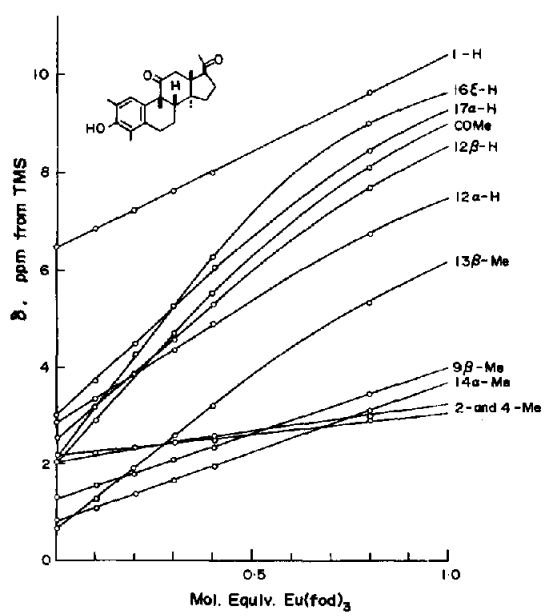


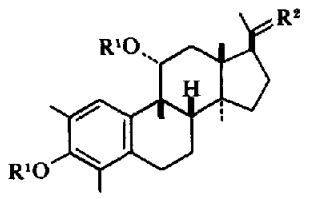
Fig 1.

(11) is well situated to influence the 1-position in the A-ring. This would account for the greater induced shift of the aromatic proton in the proposed structure (4).

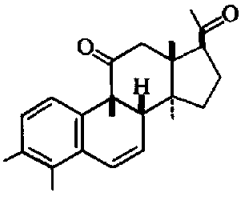
Confirmatory evidence for the assignment was obtained by Li-NH_3 reduction of 4 to give a separable mixture of 3,11α,20α- and 3,11α,20β-triols (7 and 8, respectively) which were converted to their respective triacetates (9 and 10). The assignment of 11α-configuration is in agreement with earlier work in this series,[9] and was supported by NMR examination, which showed sharp quartets ($J_{11\beta,12\alpha}$ 11–12 Hz and $H_{11\beta,12\beta}$ 4–5 Hz) for the 11β-proton. The signal for the aromatic proton in each of the derivatives (7–10) is substantially deshielded ($\Delta\delta$ 1·21–1·39) by comparison with the appropriate 11-ketones (4 or 5). This result is compatible with the assignment of the aromatic proton to C(1),[9] and it follows that the aromatic Me groups occupy C(2) and C(4).

A reasonable pathway for the formation of 4 from 1 involves a 1,2-shift of a 4-Me group to C(3) and isomerisation of the Δ^5-bond to the 5(10)-position.[10] Reorganisation to a $\Delta^{1(10),4}$-diene-2-carbonium ion would then enable the formed 3-Me group to undergo a second 1,2-shift to give the product (4) (Scheme 2). An unusual feature of the putative mechanism is the two-step Me migration "through" the 3-CO group. A formally related process is implicit in an acid-catalysed aromatisation of the A-ring in ψ-santonin.[11]

Interestingly, the reaction of 1 with acetyl bromide[12] at 20° afforded a benzene derivative (11) in high yield. The NMR spectrum of 11 showed two aromatic Me singlets at δ 2·23, an aromatic AB quartet (J 8 Hz) at δ 6·54 and 6·92, and olefinic proton signals at δ 5·85 (q, J 10 and 6 Hz) and 6·96 (q, J 10 and 1 Hz). Irradiation of either of the

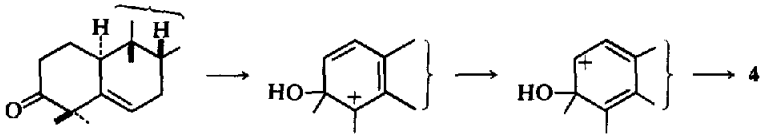


7: $R^1 = H, R^2 = \alpha$-OH, β-H
8: $R^1 = H, R^2 = \beta$-OH, α-H
9: R^1= Ac, $R^2 = \alpha$-OAc, β-H
10: R^1 = Ac, $R^2 = \beta$-OAc, α-H



11

6 Hz) at δ 6·5 to collapse to a doublet (J 10 Hz). These data and the observed shift rates (Fig 2) are entirely compatible with the 3,4-dimethyl-1,3,5(10)6-tetraene structure **11**. This rearrangement of **1** is assumed to proceed through an initial 1,2-shift of a 4-Me group (*cf* first step of Scheme 2) at which juncture, elimination of the 3–O function (OH or OAc) intervenes to prevent a further 1,2-Me shift. Under the reaction conditions, this elimination must be highly favoured since no trace of **4** was detected in the crude product.



SCHEME 2

latter signals collapsed the 10 Hz splitting in the other, thus confirming the presence of a disubstituted olefinic bond flanked by an isolated allylic proton. Confirmation of the structure **11** was obtained by NMR spectroscopy with Eu(fod)$_3$[8] additions (Fig 2). Thus, the lower field aromatic proton signal underwent paramagnetic displacement comparable to that experienced by the C(1) proton in **4**, while the signal at δ 6·92 and those of the aromatic Me groups were only slightly affected. Furthermore, at 0·4 mol. Eu(fod)$_3$ a doublet (J 6 Hz) was seen at δ 3·92 for the 8β-proton. Irradiation of this signal caused the quartet (J 10 and

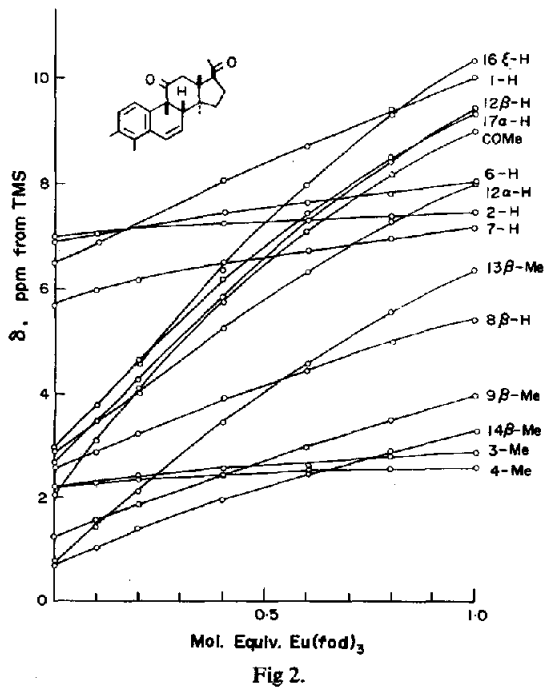


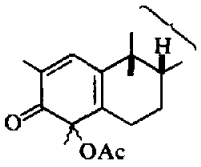
Fig 2.

Although the desired goal of a 4-Me expulsion had not been achieved, it was reasoned that further A-ring modification of the phenol (**4**) might lead to interesting retroprogesterone analogues. Predictably, an attempted Birch reduction of the methyl ether (**6**) under forcing conditions failed to attack the A-ring, owing to steric interference by the 2- and 4-Me groups. Accordingly, the application of a reported method[13] whereby an aromatic 1-Me group was converted to the corresponding aldehyde which underwent ready decarbonylation, was examined. Model experiments on 3-methoxy-1-methyl-oestra-1,3,5(10)-trien-17-one revealed that Ce(IV) oxidation of the Me group is difficult to control, and confirmed that several side reactions intervene.[14,15]

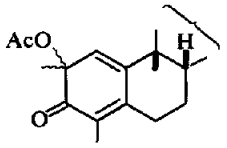
The attempted Ce(IV) oxidation of **6** in acetic acid proceeded rapidly (TLC monitoring) and after 5 min, gave a complex mixture containing two major components, which underwent mutual interconversion during chromatography. MS examination of the mixture showed a molecular ion of 440 with a strong M-60 peak, suggestive of acetoxylated derivatives of **4**. This was further evidenced by an NMR spectrum which exhibited an extra Me singlet at δ 2·1, and ill-defined multiplets at δ 5·5–6·2. No trace of a signal for a CHO group was seen, and it was concluded that the major components of the mixture are the 6α- and 6β-OAc derivatives[15] of **6**.

An alternative approach to degrading **4** *via* *p*-acetoxylation with Pb(OAc)$_4$[16] or Tl(OCOCF$_3$)$_3$[17] was considered, since stepwise reduction of the resultant cross-conjugated dienone could also lead to Δ^4-3-ones. The reaction of **6** with Pb(OAc)$_4$ proceeded slowly, but afforded a complex mixture which was not examined. However, the free phenol (**4**) reacted rapidly to give a mixture which showed two spots on TLC. Although the higher R_f spot was shown by multiple development

methods to comprise two products, an attempted preparative isolation of the components was unsuccessful. Spectroscopic data on the mixture [λ_{max} 360 (ϵ *ca* 1500) and 319 nm (ϵ *ca* 3500); ν_{max} 1738, 1700, 1675 (CO), 1645 and 1585 cm^{-1} (C:C); *m/e* 384 ($M^+ - 42$) and 366 ($M^+ - 60$); δ 6·72 (br. s, 1-H)] were incompatible with a $\Delta^{1,4}$-3-one, but suggested linear dienones of the type A or B. The product distribution reflects epimerically



A

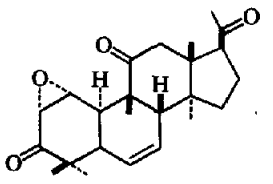


B

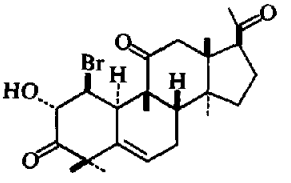
indiscriminate attack on **4** at C(2) and C(4). Similarly, the reaction of **4** with Tl $(OCOCF_3)_3$ in CF_3CO_2H gave a mixture [λ_{max} 320 nm (ϵ *ca* 5000); ν_{max} 1790 and 1700 cm^{-1}; M^+, 480] suggestive of trifluoroacetoxylation at C(2) and C(4).

It is evident that suppression of *p*-attack by these reagents is a consequence of A-ring substitution in **4**, and that steric interference at C(10) contributes in directing attack toward the *ortho*-positions.

The development of other pathways to 4-desmethyl derivatives of **1** may be envisaged through the introduction of further functionality in the A-ring, and with this in view, a preliminary study was made of the selective reactivity of the Δ^1-bond. Thus, treatment of **1** with alkaline H_2O_2 afforded the 1α,2α-epoxide (**12**). Since prolonged exposure of **1** to the reagent caused losses of the product, the reaction was stopped before proceeding to completion. An NMR spectrum of **12** revealed that the 1β- and 10α-protons are not coupled to each other and must therefore lie in a mutually orthogonal relationship. Such an arrangement is best accommodated by an α-epoxide. This was further evidenced by treatment of **12** with HBr-HOAc to give the 2-Br-Δ^1-compound (**13**) and the bromohydrin (**14**). The former product (**13**) arose from Br^- attack at C(2) and subsequent β-elimination, and although a transient intermediate assumed to be the 2β-Br,1α-OH compound was detected during TLC monitoring it could not be isolated. The bromohydrin (**14**) showed NMR signals at δ 4·44 (br. d, *J* 2·5 Hz) and 4·67 (d, *J* 2·5 Hz) ascribed to the 1α- and 2β-protons respectively. These signals provide indisputable evidence for a diaxial relationship between the two substituents and, since UV examination of an alkaline solution of **14** revealed the development of diosphenol absorption, a 1β-Br,2α-OH structure for **14** and hence α-configuration for the epoxide **12** follows. A feature of the NMR spectrum of **14** is the very weak coupling between the



12



14

1α- and 10α-protons as evidenced by slight broadening of the 1α-H signal.

Attempted *cis*-hydroxylation of the Δ^1-bond of **1** with 1 mole OsO_4 was considerably less selective than expected; chromatography of the product mixture afforded an oily but apparently pure fraction (13%), the NMR spectrum of which suggests a 1β,2β-diol structure. No other pure products were isolated.

EXPERIMENTAL

For general directions see Ref 2.

Isomerisation of the enone (**1**) *with alkali*

The enone **1** (0·048 g) in MeOH (3 ml) was added to a soln of NaOMe (2% in MeOH; 50 ml) at 25° in N_2. After 1·5 hr the soln was cooled to 0° and M-HSO_4 (25 ml) was added. The product was extracted with chloroform (20 ml). Evaporation of the solvent gave a residue which was adsorbed on silica gel (10 g). Elution with benzene-EtOAc (9:1; 200 ml) gave 4,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1(10),5-*diene*-3,11,20-*trione* (**2**) (0·022 g) as an amorphous product, $[\alpha]_D$ + 133° (*c* 1·1), ν_{max} 1700 cm^{-1}, λ_{max} 239 nm (ϵ 11300), δ 0·66, 0·96, 1·20, 1·22 and 1·25 (5 × Me), 2·07 (COMe), 2·54 (1H, d, *J* 13 Hz, 12β-H), 5·19 (1H, br, $w_{1/2}$ *ca* 10 Hz, 1-H) and 5·80 (1H, m, 6-H) (Found: C, 78·1; H, 8·6%; M^+, 368. $C_{24}H_{32}O_3$ requires: C, 78·2; H, 8·75%; M, 368).

Treatment of the enone (**1**) *with methanolic hydrogen chloride*

The enone **1** (0·1 g) was treated with a methanolic soln of HCl (2%; 85 ml) at 20° for 1 hr. Solid $NaHCO_3$ was added, followed by water (20 ml). The material was extracted with chloroform and evaporation of the solvent gave a residue which was adsorbed on silica gel (12 g). Elution with benzene-EtOAc (9:1, 50 ml) gave 3-*methoxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1(10),2,5-*triene*-11,20-*dione* (**3**) (0·03 g), m.p. 216–220° (from MeOH), $[\alpha]_D$ + 589° (*c* 0·6), ν_{max} 1698, 1650 and 1575 cm^{-1}, λ_{max} 328 nm (ϵ 10400), δ 0·63, 1·04, 1·12, 1·18 and 1·23 (5 × Me), 2·05 (COMe), 2·48 (1H, d, *J* 13·5 Hz, 12β-H), 3·03 (1H, t, *J* 8·5 Hz, 17α-H), 3·04 (1H, d, *J* 13·5 Hz, 12α-H), 4·83 (1H, d, *J* 7 Hz, 2-H), 5·21 (1H, d, *J* 7 Hz, 1-H), and 5·67 (1H, m, 6-H) (Found:

C, 78·2; H, 8·8%; M⁺, 382. $C_{25}H_{34}O_3$ requires: C, 78·5; H, 9·0%; M, 382).

Further elution gave the 1(10),5-diene **2** (0·055 g) identified by TLC and spectral analysis.

Acidic hydrolysis of the trienyl ether (**3**)

(a) The ether **3** (0·005 g) in MeOH (0·5 ml) was treated with 2·5N-HCl (0·4 ml) for 2 hr at 20°. The material was extracted with chloroform. TLC showed the presence of one major product which was isolated and shown by spectral analysis to be the 1(10),5-diene (**2**).

(b) The ether **3** (0·005 g) was dissolved in AcOH (60%; 0·8 ml) and allowed to stand for 2 hr at 20°. Chloroform extraction afforded the 1(10),5-diene (**2**).

Isomerisation of the enone (**1**) *with toluene-p-sulphonic acid*

The enone **1** (0·175 g) in dry benzene (70 ml) was refluxed with toluene *p*-sulphonic acid (1 g) for 5 hr in a Dean-Stark apparatus. The soln was washed with $NaHCO_3$aq and water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (30 g). Elution with benzene-EtOAc (17:3, 300 ml) gave 3-*hydroxy*-2,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1,3,5(10)-*triene*-11,20-*dione* **4** (0·136 g), m.p. 206–209° (from aqueous MeOH), $[\alpha]_D$+218° (*c* 1·1), ν_{max} 1698 cm^{-1}, λ_{max} 219 (ε 10200) and 278 nm (ε 1900), $\Delta\epsilon_{max}$+10·74 (294 nm, MeOH), δ 0·67, 0·81 and 1·31 (3 × Me), 2·05 (COMe), 2·08 and 2·14 (2 × ArMe), 2·55 (1H, d, *J* 13·5 Hz, 12β-H), 2·86 (1H, d, *J* 13·5 Hz, 12α-H), 2·99 (1H, t, *J* 8·5 Hz, 17α-H), and 6·51 (1H, s, 1-H) (Found: C, 78·15; H, 8·7%; M⁺, 368. $C_{24}H_{32}O_3$ requires: C, 78·2, H, 8·75%; M, 368).

Treatment of **4** with Ac_2O-pyridine at 25° afforded the 3-*acetate* (**5**), m.p. 174–177° (from cyclohexane-ether), $[\alpha]_D$+197° (*c* 1·2), δ 0·69, 0·81 and 1·33 (3 × Me), 1·96 and 2·04 (2 × ArMe), 2·06 (COMe), 2·29 (OCOMe), 2·57 (1H, d, *J* 13·5 Hz, 12β-H), 2·87 (1H, d, *J* 13·5 Hz, 12α-H), 3·00 (1H, t, *J* 8·0 Hz, 17α-H), and 6·63 (1H, s, 1-H) (Found: C, 76·3; H, 8·5%; M⁺, 410. $C_{26}H_{34}O_4$ requires: C, 76·1; H, 8·35%; M, 410).

Methylation of the phenol **4** (0·04 g) in MeOH (5 ml) with 2N-NaOH (10 ml) and dimethyl sulphate (2 ml) for 1 hr gave a colourless product. The material was filtered, washed with water and recrystallised from aqueous MeOH to give the 3-*methyl ether* **6** (0·035 g), m.p. 154–156°, $[\alpha]_D$+212° (*c* 1·3), δ 0·67, 0·78 and 1·31 (3 × Me), 2·05 (COMe), 2·08 and 2·16 (2 × ArMe), 3·62 (OMe), 2·55 (1H, d, *J* 13·5 Hz, 12β-H), 2·86 (1H, d, *J* 13·5 Hz, 12α-H), 2·98 (1H, t, *J* 8·5 Hz, 17α-H), and 6·53 (1H, s, 1-H) (Found: C, 78·5; H 9·0%; M⁺, 382. $C_{25}H_{34}O_3$ requires: C, 78·5; H 9·0%; M, 382).

Lithium-liquid ammonia reduction of the phenol (**4**)

The phenol **4** (0·11 g) in dry THF (100 ml) was added dropwise to Li (0·18 g) in liquid ammonia (freshly distilled from sodium; *ca* 150 ml). After stirring for 20 min NH_4Cl (5 g) was added. The ammonia was evaporated, water was added, and the product was extracted with chloroform. Evaporation of the solvent gave a residue which was adsorbed on silica gel (40 g). Elution with benzene-EtOAc (7:3, 350 ml) gave 3,11α,20α-*trihydroxy*-2,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1,3,5(10)-*triene* **1** (0·035 g), m.p. 208–210° (from chloroform-cyclohexane), $[\alpha]_D$+35° (*c* 0·8), δ 0·92, 1·22 and 1·30 (3 × Me), 2·06 and 2·18 (2 × ArMe), 1·19 (3H, d, *J* 6 Hz, 21-H), 3·70 (1H, oct, $w_{1/2}$ *ca* 24 Hz, 20β-H), 4·13 (1H, q, *J* 12 and 4 Hz, 11β-H), and 7·89 (1H, s, 1-H) (Found: C, 77·5; H, 9·8%; M⁺, 372. $C_{24}H_{36}O_3$ requires: C, 77·4; H, 9·7%; M, 372).

Further elution with the same solvent gave 3,11α,20β-*trihydroxy*-2,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1,3,5(10)-*triene* **8** (0·075 g) as an amorphous product, $[\alpha]_D$+25° (*c* 1·0), δ 1·02, 1·11 and 1·32 (3 × Me), 2·07 and 2·16 (2 × ArMe), 1·08 (3H, d, *J* 6 Hz, 21-H), 3·78 (1H, oct, $w_{1/2}$ *ca* 28 Hz, 20β-H), 4·19 (1H, q, *J* 11·5 and 5 Hz, 11β-H) and 7·92 (1H, s, 1-H) (Found: C, 77·4; H, 9·8%; M⁺, 372).

Treatment of **7** with Ac_2O-pyridine at 25° afforded the 3,11α,20α-*triacetate* (**9**), m.p. 164–166° (from aqueous MeOH), $[\alpha]_D$+30° (*c* 1·4), δ 1·09, 1·18 and 1·18 (3 × Me), 1·16 (3H, d, *J* 6 Hz, 21-H), 1·95 and 1·95 (2 × ArMe), 2·12, 2·12 and 2·29 (3 × OCOMe), 4·97 (1H, oct, *J* 8·5 and 6 Hz, 20β-H), 5·40 (1H, q, *J* 12 and 4 Hz, 11β-H) and 7·73 (1H, s, 1-H) (Found: C, 72·1; H, 8·3%; M⁺, 498. $C_{30}H_{42}O_6$ requires: C, 72·3; H, 8·5%; M, 498).

Treatment of **8** with Ac_2O-pyridine at 25° afforded the 3,11α,20β-*triacetate* (**10**), m.p. 176–177° (from aqueous MeOH), $[\alpha]_D$+78° (*c* 1·3), δ 1·02, 1·18 and 1·18 (3 × Me), 1·10 (3H, d, *J* 6 Hz, 21-H), 1·96 and 1·99 (2 × ArMe), 2·11, 2·11 and 2·29 (3 × OCOMe), 4·84 (1H, oct, *J* 10 and 6 Hz, 20α-H), 5·33 (1H, q, *J* 12 and 4·5 Hz, 11β-H), and 7·74 (1H, s, 1-H) (Found: C, 72·4; H 8·4%; M⁺, 498).

Isomerisation of the enone (**1**) *with acetyl bromide*

The enone **1** (0·04 g) was treated with acetyl bromide (10 ml) at 20° for 20 hr. The soln was cooled to −80°, water was added and the product extracted with chloroform. Evaporation of the solvent gave a residue which was adsorbed on silica gel (10 g). Elution with benzene-EtOAc (9:1, 50 ml) gave 3,4,14α-*trimethyl*-19(10 → 9β)abeo*pregna*-1,3,5(10),6-*tetraene*-11,20-*dione* **11** (0·035 g), m.p. 196–199° (from aqueous MeOH), $[\alpha]_D$+140° (*c* 1·4), ν_{max} 1698 cm^{-1}, λ_{max} 224 (ε 19000), 231 (sh, ε 15600) and 272 nm (ε 5600), δ 0·74, 0·74 and 1·27 (3 × Me), 2·08 (COMe), 2·23 and 2·23 (2 × ArMe), 2·64 (1H, d, *J* 14 Hz, 12β-H), 2·92 (1H, d, *J* 14 Hz, 12α-H), 2·96 (1H, t, *J* 8·5 Hz, 17α-H), 5·85 (1H, q, *J* 10 and 6 Hz, 7-H), 6·54 (1H, *J* 8 Hz, 1-H), 6·92 (1H, d, *J* 8 Hz, 2-H) and 6·96 (1H, q, *J* 10 and 1 Hz, 6-H) (Found: C, 82·5; H, 8·9%; M⁺, 350. $C_{24}H_{30}O_2$ requires: C, 82·2; H, 8·6%; M, 350).

1α,2α-*Epoxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-10α-*pregn*-5-ene-3,11,20-*trione* (**12**)

The enone **1** (0·25 g) in MeOH (30 ml) was treated with 2N NaOH (5 ml) and H_2O_2 (30%; 9 ml) at 0°. After 40 min the soln was acidified with AcOH, chloroform was added, and the organic layer was washed with water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (50 g). Elution with benzene-EtOAc (9:1; 500 ml) gave the *epoxy-trione* **12** (0·12 g), m.p. 212–215° (from benzene-cyclohexane), $[\alpha]_D$+179° (*c* 0·9), ν_{max} 1705 cm^{-1}, $\Delta\epsilon_{max}$+5·94 (290 nm) and −0·91 (330 nm), δ 0·70, 1·10, 1·16, 1·21 and 1·37 (5 × Me), 2·11 (COMe), 2·62 (1H, d, *J* 14 Hz, 12β-H), 3·06 (1H, t, *J* 8·5 Hz, 17α-H), 3·25 (1H, d, *J* 4 Hz, 2β-H), 3·30 (1H, d, *J* 14 Hz, 12α-H), 3·62 (1H, d, *J* 4 Hz, 1β-H) and 5·72 (1H, quin, *J* 2 Hz, 6-H) (Found: C, 74·8; H, 8·4%; M⁺, 384. $C_{24}H_{32}O_4$ requires: C, 75·0; H, 8·4%; M, 384).

Further elution gave unchanged enone **1** (0·1 g).

Acid treatment of the 1α,2α-*epoxy*-3,11,20-*trione* (**12**)

(a) HBr was bubbled through a soln of **12** (0·045 g) in chloroform (10 ml) at 25°. After 5 min the soln was washed with water. Evaporation of the solvent gave a residue which was adsorbed on silica gel (6 g). Elution with benzene-EtOAc (17:3; 150 ml) gave 2-*bromo*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-10α-*pregna*-1,5-*diene*-3,11,20-*trione* **13** (0·04 g), m.p. 216–217° (from chloroform-cyclohexane), $[\alpha]_D$ + 56° (*c* 1·3), ν_{max} 1700 and 1610 cm^{-1}, λ_{max} 255 nm (ε 5000), δ 0·70, 1·00, 1·14, 1·21 and 1·34 (5 × Me), 2·10 (COMe), 2·60 (1H, d, *J* 14 Hz, 12β-H), 3·03 (1H, t, *J* 8·5 Hz, 17α-H), 3·15 (1H, d, *J* 14 Hz, 12α-H), 3·42 (1H, q, *J* 2·5 and 2 Hz, 10α-H), 5·82 (1H, m, 6-H) and 7·09 (1H, d, *J* 2·5 Hz, 1-H) (Found: C, 64·5; H, 7·0%; M^+, 446 and 448. $C_{24}H_{31}BrO_3$ requires: C, 64·4; H, 7·0%, M, 446 and 448).

Further elution with the same solvent gave 1β-*bromo*-2α-*hydroxy*-4,4,14α-*trimethyl*-19(10 → 9β)abeo-10α-*pregn*-5-*ene*-3,11,20-*trione* **14** (0·008 g) m.p. 222–224° (from chloroform-cyclohexane), $[\alpha]_D$ + 80° (*c* 0·9), ν_{max} 1740 and 1700 cm^{-1}, λ_{max} 298 nm (ε 2200) (2 hr after addition of 2N NaOH, δ 0·76, 1·11, 1·14, 1·30 and 1·40 (5 × Me), 2·07 (COMe), 2·50 (1H, d, *J* 14 Hz, 12β-H), 3·02 (1H, t, *J* 8·5 Hz, 17α-H), 3·26 (1H, d, *J* 14 Hz, 12α-H), 3·28 (1H, d, *J* 2·5 Hz, 10α-H), 4·44 (1H, br. d, *J* 2·5 Hz, 1α-H), 4·67 (1H, d, *J* 2·5 Hz, 2β-H) and 5·78 (1H, m, 6-H) (Found: C, 62·2; H, 7·1%; M^+ −18, 446 and 448. $C_{24}H_{33}BrO_4$ requires: C, 61·9; H, 7·15%; M, 464 and 466).

(b) HBr was bubbled through a soln of **12** (0·08 g) in chloroform (freshly distilled from P_2O_5, 20 ml) at 0°. After 3 min the soln was worked up and chromatographed as in the previous experiment to give **13** (0·02 g) m.p. and mixed m.p. 215–217° (from chloroform-cyclohexane), and the bromohydrin **14** (0·06 g), m.p. and mixed m.p. 222–224° (from chloroform-cyclohexane).

REFERENCES

[1]Part VII. *Tetrahedron* **29**, 1101 (1973).

[2]J. R. Bull, P. R. Enslin and H. H. Lachmann, *J. Chem. Soc.* (C), 3929 (1971).

[3]J. R. Bull and C. J. Van Zyl, *Tetrahedron* **28**, 3957 (1972).

[4]M. Morisaki, H. Izawa and K. Tsuda, *Chem. Pharm. Bull.* **14**, 866 (1966); K. Tsuda, E. Ohki and S. Nozoe, *J. Org. Chem.* **28**, 783, 786 (1963).

[5]H. L. Dryden, G. M. Webber and J. J. Wieczorek, *J. Am. Chem. Soc.* **86**, 742 (1964); J. S. Baran, *J. Med. Chem.* **10**, 1188 (1967).

[6]J. R. Bull and A. J. Hodgkinson, *Tetrahedron* **28**, 3969 (1972).

[7]J. W. ApSimon and J. M. Rosenfeld, *Chem. Comm.* 1271 (1970).

[8]R. E. Rondeau and R. E. Sievers, *J. Am. Chem. Soc.* **93**, 1522 (1971).

[9]J. W. ApSimon, R. R. King and J. J. Rosenfeld, *Canad. J. Chem.* **47**, 1989 (1969).

[10]P. Bey and G. Ourisson, *Bull. Soc. Chim. Fr.* 1402, 1411 (1968).

[11]W. G. Dauben, P. D. Hance and W. K. Hayes, *J. Am. Chem. Soc.* **77**, 4609 (1955).

[12]J. Libman and Y. Mazur, *Chem. Comm.* 729, 730, 1146 (1971).

[13]S. B. Laing and P. J. Sykes, *J. Chem. Soc.* (C), 2915 (1968).

[14]P. J. Sykes and F. J. Rutherford, *Tetrahedron Letters* 3393 (1971).

[15]D. M. Piatak and L. S. Eichmeier, *Chem. Comm.* 772 (1971).

[16]A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.* **80**, 5683 (1958).

[17]M. M. Coombs and M. B. Jones, *Chem. & Ind.* 169 (1972).