# Synthesis of Steroidal Azides. Part 1. Stereospecific Vicinal Azidohydroxylation of Steroidal Olefins

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A novel method for the direct conversion of steroidal olefins into vicinal azidohydrins has been discovered. Reaction of 20-oxopregn-5-en-3β-yl acetate (3) with chromium trioxide and sodium azide in glacial acetic acid is shown to give 6β-azido-20-oxopregnane-3β,5α-diol 3-acetate (4) as the major product, whereas 3,20-dioxopregna-4,6-dien-17α-yl acetate (8) leads to a mixture, containing 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12), together with smaller amounts of 6β,7α-diazido-3,20-dioxopregn-4-en-17α-yl acetate (10) and 7α-azido-3,6,20-trioxopregn-4-en-17α-yl acetate (11). Reaction mechanisms are proposed to interpret these results.

The 6-azido-$\Delta^6$ moiety is an important potency-modifying group, both in progesterones [1] and in corticosteroids.[1-3] Published methods of introducing this functionality into the steroid molecule include the acid-catalysed opening of a 6α,7α-epoxide with azide ion, followed by acetylation, and elimination of acetic acid with tetramethylammonium fluoride,[1] and *cis* hydroxylation of $\Delta^6$-steroids followed by reaction of the derived 6β,7β-dimesylate * with azide ion.[2] Both these reaction sequences have serious limitations. For example, in the former approach, epoxidation of 9-substituted 4,6-dien-3-ones with a variety of peroxy reagents gives poor yields of 6α,7α-epoxides, which in turn are extremely slow to open with azide ion.[1,4] In the latter route, *cis* hydroxylation of 9-unsubstituted 4,6-dien-3-ones gives mixtures of 6α,7α- and 6β,7β-diols and involves the expensive and toxic reagent osmium tetraoxide.[2] Finally, reaction of the derived 6β,7β-dimesylate with azide ion generates substantial quantities of 4-azido- and 6-mesyloxy-4,6-dien-3-ones, in addition to the desired product.[2]

With these considerations in mind, we undertook an investigation of alternative methods of introducing the $\Delta^6$-6-azido function into steroid molecules. In this and the following two papers we report the results of some of our work.

Since steroidal 6β-azido-7α-hydroxy-4-en-3-ones are readily converted into the desired 6-azido-4,6-dien-3-ones,[1] a one-step synthesis of these azidohydrins from the readily available 4,6-dien-3-ones [5,6] might represent an attractive alternative. Chromyl chloride is known to convert olefins into vicinal chlorohydrins, *via* the mechanism proposed by Cristol and Eilar,[7] which is illustrated in Scheme 1. Furthermore, in the case of cyclic olefins, chromyl chloride adds *trans* diaxially with regiospecificity opposite to that exhibited by hypohalous acid additions.[8] We thus speculated that an analogous reaction of chromyl azide (1) with steroidal olefins in general might occur to give *trans* diaxial azidohydrins having the azide group attached to the β-face of the molecule. Specifically, when treated with chromyl azide, it was anticipated that 4,6-dien-3-ones might yield 6β-azido-7α-hydroxy-4-en-3-ones which could then be readily converted into the desired 6-azido-4,6-dien-3-ones.

An examination of the literature revealed that chromyl azide (1) is a known compound, and that some details of its chemistry have been described.[9,10] However we are not aware of any work in which its utility in synthetic organic chemistry has been studied. Chromyl azide may be prepared [9] by adding a solution of hydrazoic acid in carbon tetrachloride to a mixture of chromium trioxide and phosphorus pentaoxide. The compound is unstable to light and explodes above −60 °C.[10] In order to minimise these drawbacks we sought to generate chromyl azide (1), or its precursor (2), and treat it with an appropriate olefin *in situ*.

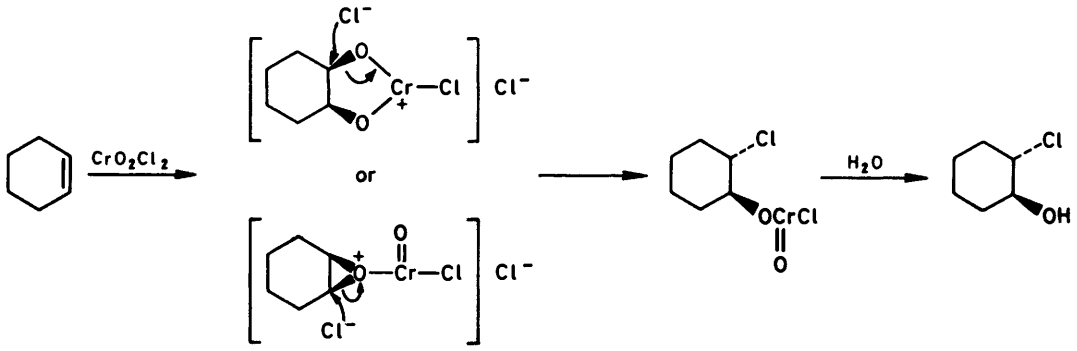
To our satisfaction, when a solution of pregnenolone acetate (3) in acetic acid was treated at room temperature with sodium azide and one equivalent of chromium trioxide, a rapid colour change from brown to green occurred, and after aqueous work-up and crystallisation, a homogenous product was obtained, which was identified as the azidohydrin (4) from the following evidence. The i.r. spectrum (Nujol) showed the presence of hydroxy ($\nu_{max.}$ 3 300 $cm^{-1}$) and azide ($\nu_{max.}$ 2 100 $cm^{-1}$) groups. The $^1H$ n.m.r. spectrum in [$^2H_6$]DMSO † revealed downfield resonances at δ 4.66 (1 H, s) exchangeable with $^2H_2O$ (tertiary hydroxy) and at δ 5.05 (1 H, br s, $w_{\frac{1}{2}}$ 23 Hz). The large half-band width of the latter signal shows 3-H to be axial and therefore the A/B junction is *trans*-fused. The resonance from 6-H appears at δ 3.48 (1 H, s, $w_{\frac{1}{2}}$ 8 Hz). The lack of axial–axial coupling to 6-H indicates a β-orientation for the azide group. Confirmation was obtained by acid-catalysed opening of the 5α,6α-oxide (5) [11] with azide ion, which gave an identical compound. This material is also described in a Shionogi patent which reports [12] its melting point. T.l.c. examination of the mother liquors from the chromium trioxide–sodium azide reaction revealed, in addition to (4), the presence of two other compounds in small amounts, which were tentatively identified as the enone (6) [13] and the allylic azide (7) [14] by t.l.c. comparison with authentic samples.

Encouraged by this result, we then turned our attention to the more important 4,6-dien-3-one system. Reaction of 6,7-dehydro-17α-acetoxyprogesterone (8) with chromium trioxide and sodium azide as before gave three products, separable by column chromatography on silica gel. The mass spectrum of the least polar compound showed a molecular ion at *m/z* 454, corresponding to the addition of two azide groups which was supported by i.r. bands at 2 120 and 2 100 $cm^{-1}$. The $^1H$ n.m.r. spectrum in [$^2H_6$]DMSO revealed a lack of resonances associated with the $\Delta^6$-double bond, being replaced by signals at δ 4.72 (1 H, d, *J* 3 Hz) and 3.89 (1 H, br s, $w_{\frac{1}{2}}$, 7 Hz). Furthermore, the 4-H resonance appeared at δ 6.03 as a sharp singlet. The absence of coupling to 4-H [15] and the lack of any axial–axial proton coupling places both the 6- and 7-substituent in axial positions. Thus we assign the 6β,7α-diazide structure (10) to this compound.

The second product from the column failed to crystallise and decomposed with time (t.l.c. evidence). It too showed an azide band in the i.r. spectrum (2 150 $cm^{-1}$), exhibited a molecular ion at *m/z* 427, and u.v. absorption at 250 nm. The $^1H$ n.m.r. ($C^2HCl_3$) spectrum revealed downfield signals at

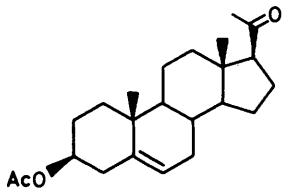
* Mesyl = methanesulphonyl.

† DMSO is dimethyl sulphoxide.




**Scheme 1.**


(1) X = $N_3$
(2) X = OH

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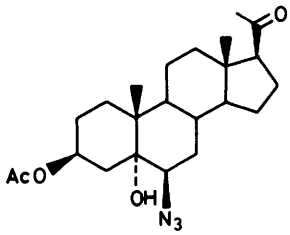


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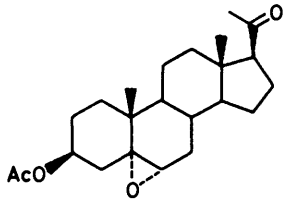


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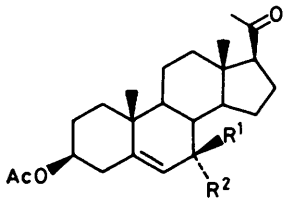
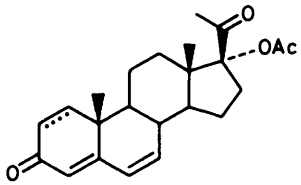
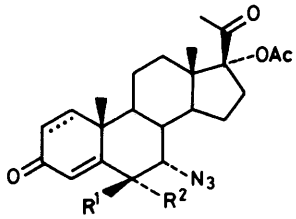



(6) $R^1R^2$ = O
(7) $R^1$ = H, $R^2$ = $N_3$




(8) $\Delta^{4,6}$
(9) $\Delta^{1,4,6}$

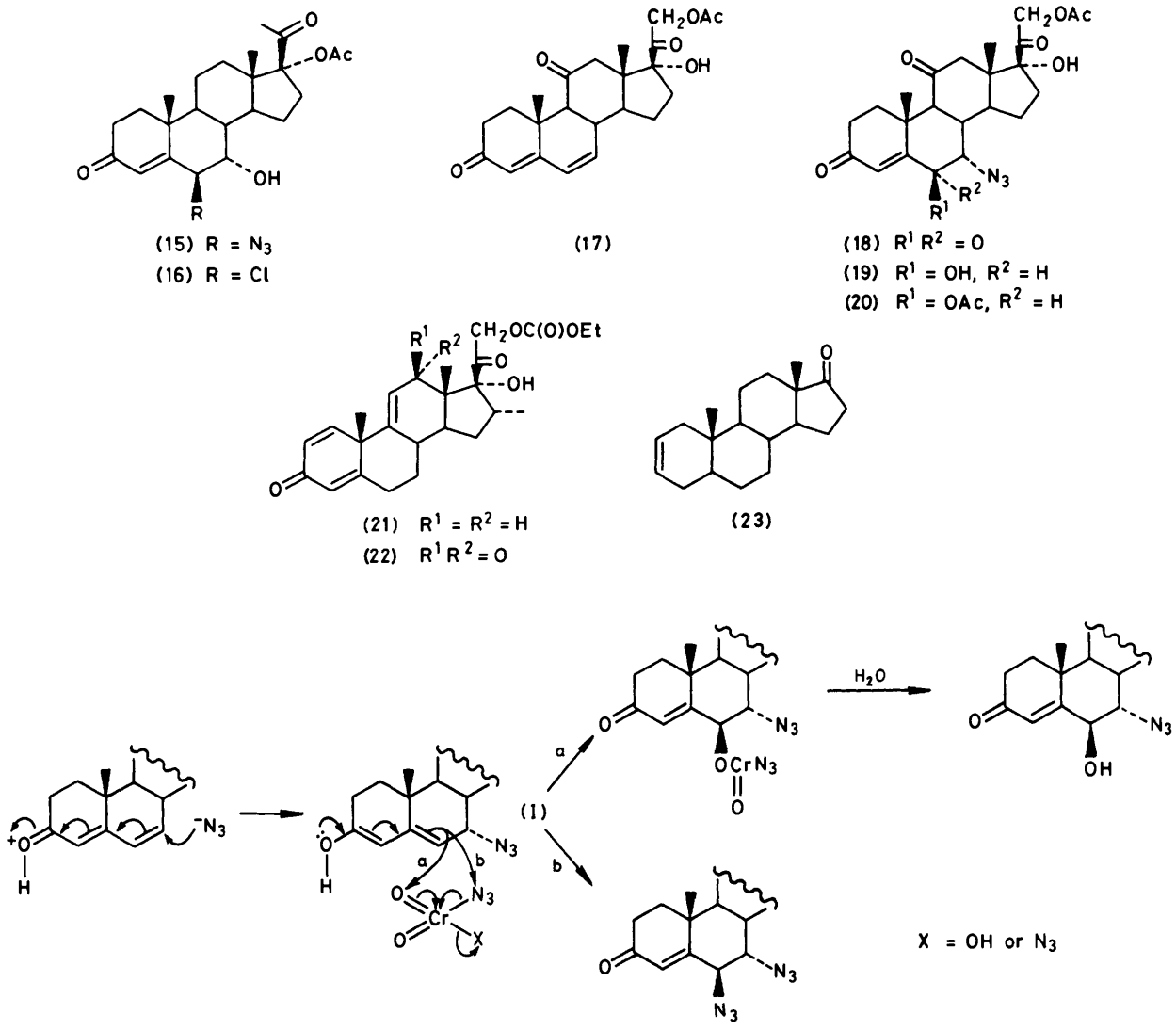



(10) $R^1$ = $N_3$, $R^2$ = H, $\Delta^4$
(11) $R^1R^2$ = O, $\Delta^4$
(12) $R^1$ = OH, $R^2$ = H, $\Delta^4$
(13) $R^1$ = OAc, $R^2$ = H, $\Delta^4$
(14) $R^1$ = OH, $R^2$ = H, $\Delta^{1,4}$

δ 6.32 (1 H, s) and 3.98 (1 H, d, *J* 2 Hz). This evidence and the observation that the same compound was obtained by oxidation of 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12) (*vide infra*), allowed us to assign the keto azide structure (11).

The most polar and major product had a molecular ion at *m/z* 429, corresponding to a derived azidohydrin, with i.r. bands at 3 450 $cm^{-1}$ (hydroxy) and 2 100 $cm^{-1}$ (azide). In the $^1H$ n.m.r. ([$^2H_6$]DMSO) spectrum were signals at δ 5.79 (1 H, s), 4.22 (1 H, t, collapsing to a doublet, *J* 3 Hz, upon $^2H_2O$ exchange), and 3.80 (1 H, br s, $w_{\frac{1}{2}}$ 8 Hz). The doublet character of the C*H*O$^2$H signal together with the absence of coupling to 4-H [15] places the hydroxy group in the 6β-position. Finally the lack of axial–axial coupling between 6-H and 7-H places the azide group at 7α. In addition the physical constants were clearly different from those of the isomeric 6β-azido-7α-hydrin (15) reported by Ponsold and his co-workers.[4] Thus we assign the unexpected structure (12) to the product. Oxidation with Kiliani's reagent [16] converted the latter compound into the previously obtained keto azide (11), while acetylation gave the corresponding diacetate (13) in which the 6α proton resonance had shifted downfield to δ 5.33 (1 H, d, *J* 3 Hz).

Only two compounds were isolated from the chromium trioxide–sodium azide treatment of 6,7-dehydrocortisone 21-acetate (17) and were separable by column chromatography on silica gel. These were identified as the keto azide (18) and




Scheme 2.

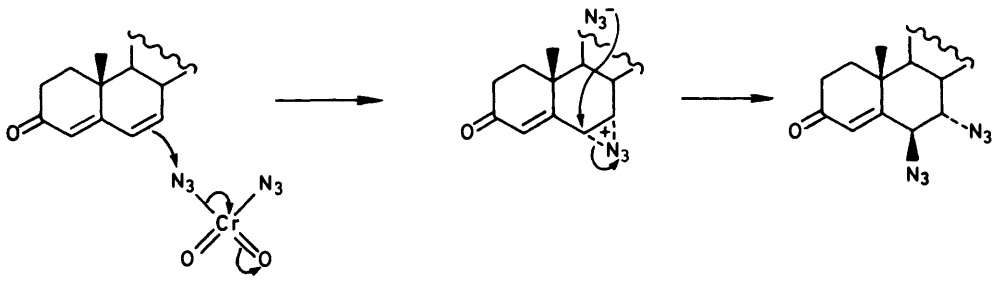
the azidohydrin (19) by analogy with the previous reaction. Acetylation of the latter compound gave the corresponding acetate (20). Similarly 1,2:6,7-didehydro-17α-acetoxyprogesterone (9) gave the azidohydrin (14) with only traces of other contaminants, which were not isolated.

Surprisingly, the triene (21) with chromium trioxide and sodium azide gave a single compound containing no azide group, and which was identified as the product of allylic oxidation in ring C, (22), whereas androst-2-en-17-one (23) yielded a complex mixture from which no pure products were isolated.

The conversion of pregnenolone acetate (3) into the azidohydrin (4) would argue for the involvement of chromyl azide (1) or its precursor (2) reacting on the α-side of the steroid *via* a mechanism analogous to that proposed for chromyl chloride. However, isolation of 6β-hydroxy-7α-azido compounds from 4,6-dien-3-ones, rather than the expected isomeric 6β-azido-7α-hydrins, indicates that either Scheme 1 is operating with initial attack of a chromium(VI) species on the β-face, followed by ring-opening with azide ion on the α-side at C-7, or that an alternative mechanism takes place. The former possibility might be the case, since it is known that osmium tetraoxide, for example, reacts with 9-unsubstituted 4,6-dien-3-ones to give the 6β,7β-diols with only minor amounts of the isomeric α-diols.[3] But it is not clear why a 6β,7β-cyclic chromium intermediate should be opened exclusively by attack at C-7. Compare, for example, ring-opening of 6β,7β-epoxides which yields mixtures.[17] Furthermore when compound (8) is treated with chromyl chloride in methylene dichloride, the sole product is the expected 6β-chloro-7α-hydrin (16),[18] m.p. 128—130 °C; $[\alpha]_D$ +1.4° (lit.,[18] m.p. 133—135 °C; $[\alpha]_D$ +2°).

Such a result might best be rationalised in terms of greater nucleophilicity of azide ion relative to chloride ion, together with the decreased electron density in the dienone double bonds, allowing conjugate addition of azide ion to C-7. A similar proposal has been made by Mitsuhashi *et al.*[19] in discussing the reaction of conjugated enones with hydrazoic acid. The intermediate (I) thus formed may then be oxidised by a chromium(VI) species (Scheme 2, path a). Other dienol derivatives of this type are known [20] to undergo electrophilic additions at C-6 to the β-face of the molecule.

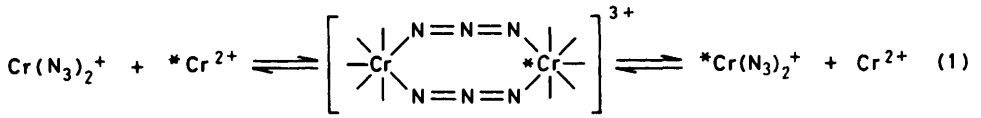
The 6β,7α-diazides must arise by the transfer of ' positive azide ' at some point. This can be achieved by electrophilic attack of chromyl azide (1) or its precursor (2), either on the dienol intermediate (I) (Scheme 2, path b), or on the dienone itself, followed by ring-opening of the derived cyclic azidonium [21] ion with azide (Scheme 3). We prefer the former route,



Scheme 3.

since intermediacy of such a cyclic ion would predict the formation of a 5α,6β-diazide in the reaction of pregnenolone acetate (3). This is not observed. The azide group acts as a medium for the flow of electrons from steroid to chromium, and this finds analogy in the redox equilibrium (1) observed

**CAUTION! Although we did not experience any untoward reactions whilst using chromium trioxide and sodium azide in glacial acetic acid, the reported [10] explosive properties of chromyl azide in the solid state and of hydrazoic acid [26] dictate the observance of appropriate safety precautions.**



by Snellgrove and King.[22] Furthermore, this mechanism is analogous to the lead tetra-acetate–trimethylsilyl azide reaction with 4,6-dien-3-ones discussed in the following paper.[23]

Although azide ion is readily converted into azide radical by a variety of oxidants,[24] it is unlikely that they are involved in this reaction to any appreciable extent, since treatment of $\Delta^5$-steroids with a reagent system known to produce free azide radicals yields 5α,6β-diazides.[24]

The scope of this reaction and the synthetic utility of chromyl azide for converting olefins in general into azidohydrins remains unknown. However, the subject warrants further investigation, since there is only one other method, of which we are aware, that directly results in the simultaneous vicinal addition of nitrogen and oxygen functions to a double bond; namely the use of alkylimido-osmium compounds.[25]

## Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 257 spectrometer and u.v. spectra in methanol with a Cary 118 spectrometer. $^1$H N.m.r. spectra were measured in [$^2H_6$]DMSO solution on a Varian CFT-20 instrument operating at 79.5 MHz, unless otherwise stated, and chemical shifts are expressed in p.p.m. downfield from tetramethylsilane as internal standard. Mass spectrometry was carried out on a Varian Mat CH5 instrument using a 70 eV source. Optical rotations were measured at 26 °C as 0.3% chloroform solutions (unless otherwise specified) with an Autopol III automatic polarimeter. All evaporations were carried out under reduced pressure with a rotary evaporator, whilst solutions were dried over anhydrous magnesium sulphate, followed by filtration. The silica gel used in column chromatography was 60—200 mesh, grade 62, obtained from the Davison Chemical Division of Grace Inc. The silica gel G.F. preparative (1 000 μ) and analytical (250 μ) t.l.c. plates were supplied by Analtech Inc. Light petroleum refers to that fraction with b.p. 40—60 °C. Ether is diethyl ether. Yields are of isolated crystallised compounds unless otherwise stated.

6β-*Azido*-20-*oxopregnane*-3β,5α-*diol* 3-*Acetate* (4).—(i) *From* 20-*oxopregn*-5-*en*-3β-*yl, acetate* (3). Sodium azide (2.6 g, 40 mmol) and then chromium trioxide (200 mg, 2.0 mmol) were added to a magnetically stirred solution of 20-oxopregn-5-en-3β-yl acetate (3) (716 mg, 2.0 mmol) in glacial acetic acid (15 ml) and the mixture was stirred for 30 min at room temperature. The mixture was diluted with water and extracted with ether. The combined extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, and dried. The solvent was evaporated off and the residue was crystallised from ethyl acetate to give 6β-azido-20-oxopregnane-3β,5α-diol 3-acetate (4) (420 mg, 50%), m.p. 236—238 °C (lit.,[12] 236—239 °C); $[\alpha]_D$ −46°; $\nu_{max.}$ 3 300, 2 100, 1 730, 1 700, and 1 250 cm$^{-1}$; δ 5.05 (1 H, br s, $w_{\frac{1}{2}}$ 23 Hz, 3α-H), 4.66 (1 H, s, OH), 3.48 (1 H, s, $w_{\frac{1}{2}}$ 8 Hz, 6α-H), 2.04 (3 H, s, $COCH_3$), 1.96 (3 H, s, $COCH_3$), 1.04 (3 H, s, 19-$H_3$), and 0.52 (3 H, s, 18-$H_3$) [Found: C, 66.0; H, 8.45; N, 10.0%; ($M^+$ − 43), 374. Calc. for $C_{23}H_{35}N_3O_4$: C, 66.16; H, 8.45; N, 10.06%; *M*, 417].

(ii) *From* 5α,6α-*epoxy*-20-*oxopregnan*-3β-*yl acetate* (5). A solution of sodium azide (1 g, 15.4 mmol) in water (3 ml) was added to a solution of 5α,6α-epoxy-20-oxopregnan-3β-yl acetate (5) (290 mg, 0.75 mmol) in dioxane (10 ml) and glacial acetic acid (7 ml). The mixture was maintained at room temperature for 4 d, then diluted with water and extracted with ethyl acetate. The combined extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, and dried. The solution was concentrated and allowed to crystallise to yield 6β-azido-20-oxopregnane-3β,5α-diol 3-acetate (4) (135 mg, 42%), m.p. 237—239 °C, identical with the material previously obtained.

*Reaction of* 3,20-*Dioxopregna*-4,6-*dien*-17α-*yl Acetate* (8) *with Chromium Trioxide and Sodium Azide*.—Sodium azide (5.2 g, 80 mmol), then chromium trioxide (0.2 g, 2.0 mmol) were added to a magnetically stirred solution of 3,20-dioxopregna-4,6-dien-17α-yl acetate (8) (0.74 g, 2.0 mmol) in acetic acid (25 ml) and the mixture was stirred for 30 min at room temperature. The mixture was diluted with water and extracted well with ether. The combined extracts were washed in turn

with saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation of the solvent gave a green oil which was chromatographed on a silica gel column. Gradient elution with light petroleum–ether gave three products in the following order: (i) 6β,7α-*diazido*-3,20-*dioxopregn*-4-*en*-17α-*yl acetate* (10), crystallised from ether (49 mg, 5%), m.p. 161—162 °C; $[\alpha]_D$ −100°; $\lambda_{max.}$ 234 and 286 nm (ε 11 400 and 1 900); $\nu_{max.}$ 2 120, 2 100, 1 740, 1 720, 1 690, and 1 250 $cm^{-1}$; δ 6.03 (1 H, s, 4-H), 4.72 (1 H, d, $J_{6,7}$ 3 Hz, 6α-H), 3.89 (1 H, br s, $w_{\frac{1}{2}}$ 7 Hz, 7β-H), 2.08 (3 H, s, $COCH_3$), 1.97 (3 H, s, $COCH_3$), 1.27 (3 H, s, 19-$H_3$), and 0.60 (3 H, s, 18-$H_3$) (Found: C, 60.9; H, 6.35; N, 18.4%; $M^+$, 454. $C_{23}H_{30}N_6O_4$ requires C, 60.77; H, 6.55; N, 18.49%; *M*, 454); (ii) 7α-*azido*-3,6,20-*trioxopregn*-4-*en*-17α-*yl acetate* (11) as a yellow oil (92 mg, 10%) which decomposed with time, $\lambda_{max.}$ 250 nm; $\nu_{max.}$ 2 150 1 735, 1 725, 1 700, and 1 250 $cm^{-1}$; δ ($C^2HCl_3$) 6.32 (1 H, s, 4-H), 3.98 (1 H, d, $J_{7,8}$ 2 Hz, 7β-H), 2.16 (3 H, s, $COCH_3$), 2.07 (3 H, s, $COCH_3$), 1.18 (3 H, s, 19-$H_3$), and 0.68 (3 H, s, 18-$H_3$) (Found: $M^+$, 427. $C_{23}H_{29}N_3O_5$ requires *M*, 427); (iii) 7α-*azido*-3,20-*dioxopregn*-4-*ene*-6β,17α-*diol* 17-*acetate* (12), crystallised from ether (413 mg, 48%), m.p. (crystals fragment 85—86 °C) 115—117 °C; $[\alpha]_D$ −41°; $\lambda_{max.}$ 234 nm (ε 11 100); $\nu_{max.}$ 3 450, 2 100, 1 735, 1 720, 1 680, and 1 250 $cm^{-1}$; δ 5.81 (1 H, d, exchanges with $^2H_2O$, 6β-OH), 5.79 (1 H, s, 4-H), 4.22 [1 H, t (d with $^2H_2O$), $J_{6,7}$ 3, $J_{6,6\beta\text{-OH}}$ 3 Hz, 6α-H], 3.80 (1 H, br s, $w_{\frac{1}{2}}$ 8 Hz, 7β-H), 3.88 (4 H, q, ether), 2.09 (3 H, s, $COCH_3$), 1.28 (3 H, s, 19-$H_3$), 1.09 (6 H, t, ether), and 0.60 (3 H, s, 18-$H_3$) [Found (after being dried at 100 °C *in vacuo*): C, 64.6; H, 7.0; N, 9.95%; $M^+$, 429. $C_{23}H_{31}N_3O_5$ requires C, 64.31; H, 7.28; N, 9.78%; *M*, 429].

7α-*Azido*-3,6,20-*trioxopregn*-4-*en*-17α-*yl Acetate* (11).—To a magnetically stirred solution of 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12) (43 mg, 0.1 mmol) in acetone (5 ml) was added Kiliani's reagent [16] (0.13 ml) and the mixture was stirred for 30 min. The reaction mixture was diluted with water and extracted with ether. The combined extracts were washed with water and dried. Evaporation of the solvent gave (11) as a yellow gum (40 mg, 93%), whose i.r., and $^1H$ n.m.r. spectra and t.l.c. behaviour were identical with those previously obtained.

7α-*Azido*-3,20-*dioxopregn*-4-*ene*-6β,17α-*diol* 6,17-*Diacetate* (13).—Acetic anhydride (0.1 ml) was added to a solution of 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12) (100 mg, 0.23 mmol) in pyridine (2 ml) and the mixture was maintained at room temperature overnight. The solution was poured into ice-cold 3% hydrochloric acid and extracted with ether. The extracts were dried and concentrated to give an oil which was chromatographed on 2 × 1 000 μ silica gel GF preparative plates [developer chloroform–ethyl acetate (4 : 1)]. Extraction with ethyl acetate gave 7α-*azido*-3,20-*dioxopregn*-4-*ene*-6β,17α-*diol* 6,17-*diacetate* (13), crystallised from ether (75 mg, 68%), m.p. 201—202 °C; $[\alpha]_D$ −4°; $\lambda_{max.}$ 233 nm (ε 13 300); $\nu_{max.}$ 2 100, 1 740, 1 730, 1 715, 1 670, 1 640, 1 250, and 1 225 $cm^{-1}$; δ 5.91 (1 H, s, 4-H), 5.33 (1 H, d, $J_{6,7}$ 3 Hz, 6α-H), 3.99 (1 H, br s, $w_{\frac{1}{2}}$ 7 Hz, 7α-H), 2.10 (3 H, s, $COCH_3$), 2.05 (3 H, s, $COCH_3$), 1.98 (3 H, s, $COCH_3$), 1.23 (3 H, s, 19-$H_3$), and 0.62 (3 H, s, 18-$H_3$) (Found: C, 63.9; H, 7.1; N, 8.95%; $M^+$, 471. $C_{25}H_{33}N_3O_6$ requires C, 63.67; H, 7.05; N, 8.91%; *M*, 471).

*Reaction of* 3,11,20-*Trioxopregna*-4,6-*diene*-17α,21-*diol* 21-*Acetate* (17) * *with Chromium Trioxide and Sodium Azide*.—To a suspension of sodium azide (1.95 g, 30 mmol) in glacial acetic acid (50 ml) at room temperature was added 3,11,20-trioxopregna-4,6-diene-17α,21-diol 21-acetate (17) (1.2 g, 3 mmol) followed by chromium trioxide (300 mg, 3 mmol) in portions during 30 min. The mixture was stirred for an additional 90 min, then poured into water and extracted with ether. The combined extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, and dried. The residue, after evaporation of the solvent, was chromatographed on a silica gel column and eluted (gradient) with light petroleum–ether to afford 7α-*azido*-3,6,11,20-*tetraoxopregn*-4-*ene*-17α,21-*diol* 21-*acetate* (18) as an unstable oil (164 mg, 12%), $[\alpha]_D$ +15°; $\lambda_{max.}$ 232 nm (ε 11 000); δ 6.07 (1 H, s, 4-H), 5.90 (1 H, s, 17-OH), 4.87 (2 H, q, $J_{gem}$ 18 Hz, 21-$H_2$), 4.29 (1 H, s, 7β-H), 2.08 (3 H, s, 21-$OCOCH_3$), 1.32 (3 H, s, 19-$H_3$), and 0.48 (3 H, s, 18-$H_3$) (Found: C, 59.9; H, 6.05; N, 9.4%; $M^+$, 457. $C_{23}H_{27}N_3O_7$ requires C, 60.38; H, 5.95; N, 9.19%; *M*, 457), followed by 7α-*azido*-3,11,20-*trioxopregn*-4-*ene*-6β,17α,21-*triol* 21-*acetate* (19), crystallised from ether (512 mg, 37%), m.p. 160—162 °C; $[\alpha]_D$ +77°; $\lambda_{max.}$ 230 nm (ε 13 200); $\nu_{max.}$ 3 450, 2 100, 1 740, 1 730, 1 710, 1 670, and 1 250 $cm^{-1}$; δ 5.88 (1 H, d, *J* 3 Hz, exchanges with $^2H_2O$, 6β-OH), 5.85 (1 H, s, exchanges with $^2H_2O$, 17α-OH), 4.84 (2 H, q, $J_{gem}$ 17 Hz, 21-$H_2$), 4.23 [1 H, t (d with $^2H_2O$), $J_{6,7}$ 3, $J_{6,6\beta\text{-OH}}$ 3 Hz, 6α-H], 3.90 (1 H, br s, $w_{\frac{1}{2}}$ 7 Hz, 7β-H), 2.08 (3 H, s, 21-$OCOCH_3$), 1.45 (3 H, s, 19-$H_3$), and 0.50 (3 H, s, 18-$H_3$) (Found: C, 60.35; H, 6.3; N, 8.75%; $M^+$, 459. $C_{23}H_{29}N_3O_7$ requires C, 60.12; H, 6.36; N, 9.15%; *M*, 459).

7α-*Azido*-3,11,20-*trioxopregn*-4-*ene*-6β,17α,21-*triol* 6,21-*Diacetate* (20).—Acetic anhydride (7 ml) was added to a solution of 7α-azido-3,11,20-trioxopregn-4-ene-6β,17α,21-triol 17-acetate (19) (459 mg, 1.0 mmol) in pyridine (20 ml) and the mixture was maintained at room temperature for 3 h. The solution was poured into ice-cold 3% hydrochloric acid and the precipitated solid was filtered off, washed with water, and dried. Crystallisation from ethyl acetate gave 7α-*azido*-3,11,20-*trioxopregn*-4-*ene*-6β,17α-21-*triol* 6,21-*diacetate* (20) (352 mg, 70%), m.p. 235—236 °C; $[\alpha]_D$ +90°; $\lambda_{max.}$ 230 nm (ε 12 800); $\nu_{max.}$ 3 500, 3 300, 2 100, 1 750, 1 725, 1 700, 1 675, and 1 250 $cm^{-1}$; δ 5.92 (1 H, s, 4-H), 5.90 (1 H, s, exchanges with $^2H_2O$, 17-OH), 5.35 (1 H, d, $J_{6,7}$ 3 Hz, 6α-H), 4.87 (2 H, q, $J_{gem}$ 17 Hz, 21-$H_2$), 4.08 (1 H, br s, $w_{\frac{1}{2}}$ 7 Hz, 7β-H), 2.10 (3 H, s, $OCOCH_3$), 2.06 (3 H, s, $OCOCH_3$), 1.41 (3 H, s, 19-$H_3$), and 0.53 (3 H, s, 18-$H_3$) (Found: C, 59.85; H, 6.35; N, 8.25%; $M^+$, 501. $C_{25}H_{31}N_3O_8$ requires C, 59.87; H, 6.23; N, 8.38%; *M*, 501).

*Reaction of* 3,20-*Dioxopregna*-1,4,6-*trien*-17α-*yl Acetate* (9) *with Chromium Trioxide and Sodium Azide*.—Sodium azide (2.6 g, 40 mmol), then chromium trioxide (0.2 g, 2.0 mmol) were added to a magnetically stirred solution of 3,20-dioxopregna-1,4,6-trien-17α-yl acetate (9) (0.736 g, 2.0 mmol) in acetic acid (25 ml) and the mixture was stirred for 1 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed in turn with saturated aqueous sodium hydrogen carbonate solution and water, and dried. Evaporation of the solvent gave a green oil which was chromatographed on a silica gel column. Gradient elution with light petroleum–ether gave pure 7α-*azido*-3,20-*dioxopregna*-1,4-*diene*-6β,17α-*diol* 17-*acetate* (14), crystallised from ether (326 mg, 38%), m.p. 243—245 °C (decomp.); $[\alpha]_D$ −99°; $\lambda_{max.}$ 243 nm (ε 15 700); $\nu_{max.}$ 3 400, 2 100, 1 730, 1 720, 1 670, 1 650, 1 620, and 1 250 $cm^{-1}$; δ 7.16 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.17 (1 H, s, 4-H), 6.11 (1 H, dd, $J_{2,4}$ 2 Hz, 2-H), 5.92 (1 H, d, *J* 3 Hz, exchanges with $^2H_2O$, 6β-OH), 4.41 (1 H, t, $J_{6,7}$ 3, $J_{6,6\beta\text{-OH}}$ 3 Hz, 6α-H), 3.85 (1 H, t, $J_{7,8}$ 3 Hz, 7β-H), 2.07 (3 H, s, $COCH_3$), 1.99 (3 H, s, $COCH_3$), 1.37 (3 H, s, 19-$H_3$), and 0.65 (3 H, s, 18-$H_3$) (Found: C, 64.75;

* 6,7-Dehydrocortisone acetate.

H, 6.85; N, 10.0%; $M^+$, 427. $C_{23}H_{29}N_3O_5$ requires C, 64.62; H, 6.84; N, 9.83%; *M*, 427).

*Reaction of* 3,20-*Dioxopregna*-4,6-*dien*-17α-*yl Acetate* (8) *with Chromyl Chloride*.—To a magnetically stirred solution of 3,20-dioxopregna-4,6-dien-17α-yl acetate (8) (740 mg, 2.0 mmol) in methylene dichloride (50 ml) was added chromyl chloride (0.18 ml, 2.2 mmol). After being stirred at room temperature for 3 h the brown suspension was diluted with aqueous sodium hydrogen sulphite (2%; 50 ml) and the mixture was stirred until the solid had dissolved. The mixture was then extracted with methylene dichloride and the combined extracts were washed with water, dried, and evaporated to leave an oil. T.l.c. showed a single product contaminated with starting material. Separation was effected by chromatography on 8 × 1 000 μ preparative silica gel plates, developer chloroform–ethyl acetate (3 : 1). The least polar band was extracted with ethyl acetate to give starting material (8) (95 mg). The more polar band was extracted with ethyl acetate and the residue, obtained upon evaporation of the solvent, was crystallised from ether to give 6β-*chloro*-3,20-*dioxopregn*-4-*ene*-7α,17α-*diol* 17-*acetate* (16) (480 mg, 65%), m.p. 128—130 °C $[\alpha]_D$ +1.4°; $\lambda_{max.}$ 239 nm (ε 13 300); δ 5.91 (1 H, s, 4-H), 5.46 (1 H, d, *J* 5 Hz, exchanges with $^2H_2O$, 7α-OH), 4.56 (1 H, d, $J_{6,7}$ 3 Hz, 6α-H), 3.70 (1 H, br s, $w_{\frac{1}{2}}$ 9 Hz, 7β-H), 3.32 (4 H, q, ether), 2.08 (3 H, s, $COCH_3$), 1.96 (3 H, s, $COCH_3$), 1.34 (3 H, s, 19-$H_3$), 1.08 (6 H, t, ether), and 0.60 (3 H, s, 18-$H_3$) (Found: C, 65.35; H, 7.55; Cl, 8.35%; $M^+$, 422. $C_{23}H_{31}ClO_5$ requires C, 65.31; H, 7.39; Cl, 8.38%; *M*, 422).

16α-*Methyl*-3,12,20-*trioxopregna*-1,4,9(11)-*triene*-17α,21-*diol* 21-(*Ethoxyformate*) (22).*—To a magnetically stirred solution of 16α-methyl-3,20-dioxopregna-1,4,9(11)-triene-17α,21-diol 21-(ethoxyformate) (21) (856 mg, 2.0 mmol) in acetic acid (15 ml) at room temperature was added sodium azide (2.6 g, 40 mmol) followed by chromium trioxide (200 mg, 2.0 mmol). After 4 h t.l.c. indicated a 1 : 1 mixture of starting material and product. Additional chromium trioxide (200 mg, 2.0 mmol) was added and the mixture was stirred overnight, then diluted with water and extracted with ether and the extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation of the solvent gave an oil which was chromatographed over a silica-gel column. Elution with ether–light petroleum (1 : 1) gave 16α-*methyl*-3,12,20-*trioxopregna*-1,4,9(11)-*triene*-17α,21-*diol* 21-(*ethoxyformate*) (22), crystallised from ethyl acetate (550 mg, 62%), m.p. 232–233 °C; $[\alpha]_D$ +46°; $\lambda_{max.}$ 238 nm (ε 25 700); $\nu_{max.}$ 3 400, 1 760, 1 740, 1 670, 1 660, 1 625, 1 600, and 1 240 $cm^{-1}$; δ 7.43 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.17 (1 H, dd, $J_{2,4}$ 2 Hz, 2-H), 6.10 (1 H, d, 4-H), 5.71 (1 H, s, 11-H), 5.37 (2 H, q, $J_{gem}$ 18 Hz, 21-$H_2$), 5.20 (1 H, s, exchanges with $^2H_2O$, 17-OH), 4.12 (2 H, q, $J_{gem}$ 7 Hz, $OCH_2CH_3$), 1.50 (3 H, s, 19-$H_3$), 1.21 (3 H, t, $OCH_2CH_3$), 0.87 (3 H, s, 18-$H_3$), and 0.84 (3 H, d, *J* 7 Hz, 16α-$CH_3$) (Found: C, 67.5; H, 6.85%; $M^+$, 442. $C_{25}H_{30}O_7$ requires C, 67.85; H, 6.83%; *M*, 442).

*Reaction of Androst*-2-*en*-17-*one* (23) *with Chromium Trioxide and Sodium Azide*.—To a magnetically stirred solution of androst-2-en-17-one (23) (272 mg, 1.0 mmol) in glacial acetic acid (10 ml) at room temperature was added sodium azide (1.3 g, 20 mmol) and chromium trioxide (100 mg, 1.0 mmol) and the mixture was stirred for 30 min, then diluted with water and extracted with ether. The extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation of the solvent gave a green oil which contained at least eight components (t.l.c.). Chromatography on a silica gel column, with gradient elution with light petroleum–ether, failed to yield any pure compounds.

* Ethyl 17α-hydroxy-16α-methyl-3,12,20-trioxopregna-1,4,9(11)-trien-21-yl carbonate.

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