Synthesis of Steroidal Azides. Part 3.[1] Addition of Halogen Azides to Δ^6-Steroids

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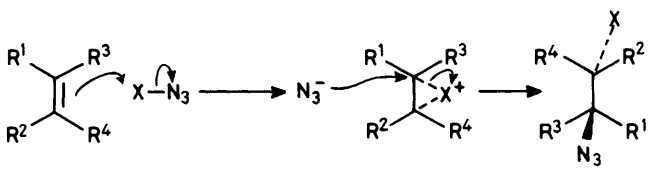
The reaction between halogen azides and Δ^6-steroids has been investigated. The addition of bromine azide to 3,20-dioxopregna-4,6-dien-17α-yl acetate (5), for example, is shown to give 7α-azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl acetate (10), whereas with 9α-fluoro-16α-methyl-20-oxo-2'-phenyl-2'*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazole-11β,17α,21-triol 21-acetate (27), the products are 6ξ-azido-7ξ-bromo-9α-fluoro-16α-methyl-20-oxo-2'-phenyl-2'*H*-pregna-2,4-dieno[3,2-*c*]pyrazole-11β,17α,21-triol 21-acetates (32). The differing regiospecificity of addition to the Δ^6-double bond, exhibited by these reactions, is rationalised in terms of conjugate addition of azide ion occurring in the former case and electrophilic addition of bromine in the latter. Addition of bromine azide to 17α-hydroxypregna-1,4,6-triene-3,20-dione (15) occurs primarily in the B ring under neutral conditions, whereas in the presence of hydrazoic acid, reaction takes place in ring A. Azide-ion-induced elimination from 7α-azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl acetate (10) generates 4-azido-3,20-dioxopregna-4,6-dien-17α-yl acetate (8) and 6-bromo-3,20-dioxopregna-4,6-dien-17α-yl acetate (9) in the ratio of 5 : 1. However, elimination of hydrazoic acid from the same compound promoted by tetramethylammonium fluoride yields compound (9) as the major product.

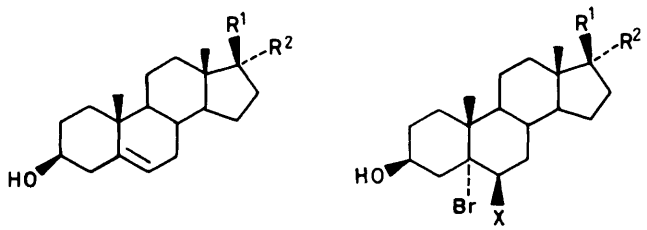
During our search for reagents which would convert steroidal 4,6-dien-3-ones into the pharmacologically valuable 6-azido-4,6-dien-3-ones,[2-4] we examined the utility of halogen azides for this purpose. Halogen azides have been described as convenient agents for the introduction of azide groups to a wide variety of organic molecules.[5] However, little work has been published on the reaction of these compounds with conjugated steroid enones.[6,7]

Hassner and his co-workers [8] have suggested that, in general, ionic additions of halogen azides to isolated cyclic olefins proceed through the intermediacy of cyclic halonium ions, with subsequent ring-opening by azide ion, leading to *trans* addition products (Scheme 1). This mechanism is therefore analogous to that proposed [9] for the addition of interhalogens to double bonds. For example, addition of bromine azide to cholesterol (1) gives the 6β-azido-5α-bromo adduct (3) [10] and addition of bromine fluoride to 17α-acetoxypregnenolone (2) leads to the corresponding 5α-bromo-6β-fluoro derivative (4),[11] both compounds arising by attack of positive bromine on the less hindered α-side of the steroid. The same mechanism has also been proposed by Ponsold,[6] Hassner,[12] and others [13] to explain the formation of products arising from halogen azide additions to conjugated enones.

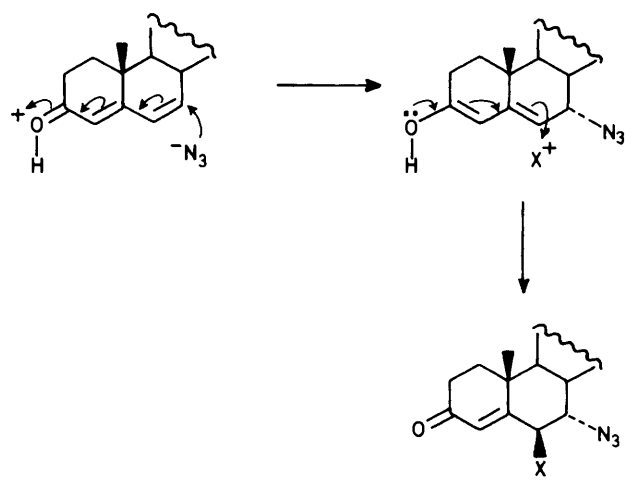
However, in the light of our experiences with the reactions of both chromium trioxide–sodium azide [14] and lead tetra-acetate–trimethylsilyl azide [1] with steroidal olefins *vis-à-vis* conjugated steroidal enones, we felt that an alternative mechanism, namely initial conjugate addition of azide ion followed by attack of the resulting azido dienol intermediate on positive halogen, should be considered as more likely (Scheme 2). Thus in the case of halogen azide additions to steroidal 4,6-dien-3-ones, the products formed by a conjugate-addition mechanism would be 7α-azido-6β-halogeno-4-en-3-ones (Scheme 2). Initial azide attack should occur on the less hindered α-face and electrophilic addition to the 3,5-dien-3-ol intermediate will lead to 6β-substitution.[15] We confirmed this hypothesis by observing the reaction of bromine azide with 17α-acetoxy-6,7-dehydroprogesterone (5) which gave exclusively the 7α-azido-6β-bromo adduct (10). The structure of the latter compound was evident from its spectral and analytical data.[1] This result contrasts with the addition of bromine fluoride to steroidal 4,6-dien-3-ones, which generates 6β-fluoro-7α-bromo adducts.[16]



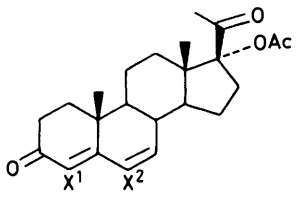
Scheme 1.



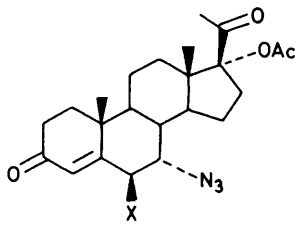
(1) R^1 = C_8H_{17}, R^2 = H (3) R^1 = C_8H_{17}, R^2 = H, X = N_3
(2) R^1 = Ac, R^2 = OAc (4) R^1 = Ac, R^2 = OAc, X = F
C_8H_{17} = $-CH(CH_3)[CH_2]_3CH(CH_3)_2$



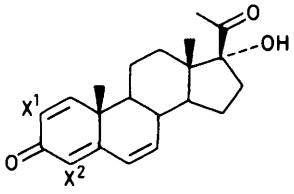
Scheme 2.



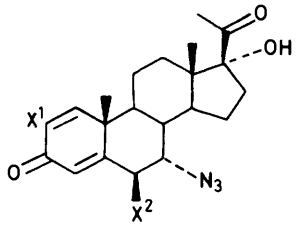
(5) $X^1 = X^2 = H$
(6) $X^1 = H$, $X^2 = Cl$
(7) $X^1 = H$, $X^2 = N_3$
(8) $X^1 = N_3$, $X^2 = H$
(9) $X^1 = H$, $X^2 = Br$



(10) X = Br
(11) X = I
(12) X = OH
(13) X = Cl
(14) X = N_3



(15) $X^1 = X^2 = H$
(16) $X^1 = Br$, $X^2 = H$
(17) $X^1 = H$, $X^2 = N_3$

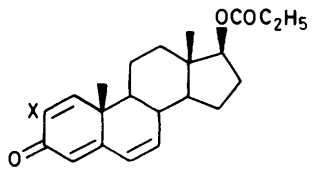


(18) $X^1 = H$, $X^2 = Br$
(19) $X^1 = X^2 = Br$
(20) $X^1 = H$, $X^2 = I$
(21) $X^1 = H$, $X^2 = OH$

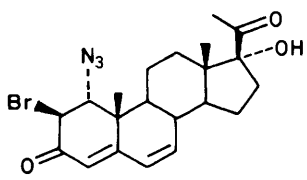
During the course of this work, Kocǒr and Gumulka [7] published similar results of their own investigation into the reaction of bromine azide with steroidal 4,6-dien-3-ones, although they did not speculate on the mechanistic aspects of this addition. It is pertinent to note at this point that others [17] have considered whether halogen additions to steroidal enones take place *via* halonium ion intermediates or by initial conjugate addition.

Similarly, reaction of 17α-acetoxy-6,7-dehydroprogesterone (5) with iodine azide rapidly gave the 7α-azido-6β-iodo adduct (11). Although this compound could be isolated, it was unstable in solution and attempts to crystallise it led to a new product which was identified as the previously prepared [14] 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12). This ready transformation presumably involves the 6α,7α-azidonium ion [18] arising by neighbouring-group-assisted elimination of iodide ion. Finally, under the same conditions we observed no reaction between 17α-acetoxy-6,7-dehydroprogesterone (5) and chlorine azide.

We also examined the addition of halogen azides to steroidal 1,4,6-trien-3-ones. Reaction of 17α-hydroxy-1,2:6,7-didehydroprogesterone (15) with one equivalent of bromine azide gave the corresponding ring-B adduct, namely 7α-azido-6β-bromo-17α-hydroxypregna-1,4-diene-3,20-dione (18) as the major product together with small amounts of starting material and 7α-azido-2,6β-dibromo-17α-hydroxypregna-1,4-diene-3,20-dione (19). This result contrasts with the work of Kocǒr and Gumulka [7] who report that the product from the reaction of bromine azide with 3-oxoandrosta-1,4,6-trien-17β-yl propionate (22) is the 2-bromo-1,4,6-trien-3-one (23). In view of this difference we decided to examine the reaction in greater detail. When the 1,4,6-trien-3-one (15) is permitted to react with two equivalents of bromine azide in the usual manner, the major product was still the ring-B adduct (18). If, however, the addition of one equivalent of bromine azide was carried out in the presence of excess of hydrazoic acid, the main



(22) X = H
(23) X = Br



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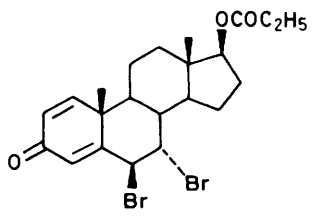

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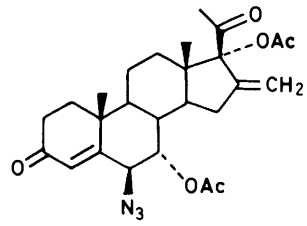


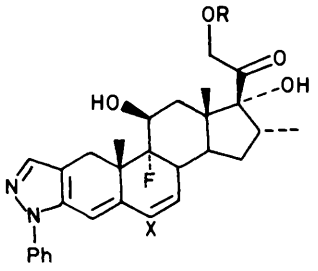
(26)

product was the ring-A adduct, namely 1α-azido-2β-bromo-17α-hydroxypregna-4,6-dien-3,20-dione (24), which was isolated by crystallisation. Examination of the mother liquors by t.l.c. indicated the presence of small quantities of two other less polar compounds having R_F values equivalent to those of the 7α-azido-2,6β-dibromo-1,4-dien-3-one (19) and the 2-bromo-1,4,6-trien-3-one (16) (*vide infra*). The structure of compound (24) followed from its u.v. ($\lambda_{max.}$ 301 nm, ε 22 300; 4,6-dien-3-one) and i.r. ($\nu_{max.}$ 2 100 cm^{-1}; azide) spectra and from its n.m.r. data in [$^2H_6$]DMSO.* The signals for 1-H and 2-H appeared at δ 4.59 and 4.86 respectively with a coupling constant of 2 Hz. The low value of $J_{1,2}$ indicates that both substituents in ring A are axially orientated. The chemical shifts for the vinyl protons at C-4, C-6, and C-7 were situated at δ 5.85, 6.30, and 6.30 respectively. Hydrazoic acid was readily eliminated from the latter compound to give the known [19] 2-bromo-1,4,6-trien-3-one (16) by treatment with sodium azide in dimethylformamide (DMF) at 60 °C. Finally, the 7α-azido-6β-bromo adduct (18) was stable in a methylene dichloride solution of hydrazoic acid, but on addition of *N*-bromosuccinimide (NBS), 7α-azido-2,6β-dibromo-17α-hydroxypregna-1,4-diene-3,20-dione (19) was formed. This pH-dependent, dual mode of addition to steroidal 1,4,6-trien-3-ones has been observed previously in the case of brominations. For example, addition of bromine to compound (22) gave the 6β,7α-dibromo-1,4-dien-3-one (25),[20] whereas bromination of (15) in propionic acid, followed by elimination of hydrogen bromide, yielded the 2-bromo-1,4,6-trien-3-one (16).[19]

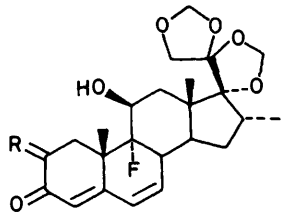
Addition of iodine azide to 17α-hydroxy-1,2:6,7-didehydroprogesterone (15) under neutral conditions gave the 7α-azido-6β-iodo adduct (20) which was readily hydrolysed, like its 1,2-dihydro analogue (11), and gave 7α-azido-6β,17α-dihydroxypregna-1,4-diene-3,20-dione (21). Chlorine azide again failed to react with the 1,4,6-trien-3-one (15).

The 7α-azido-6β-bromo-4-en-3-one (10) in contact with sodium azide in DMF at 60 °C gave the 4-azido-4,6-dien-3-one (8) and the 6-bromo-4,6-dien-3-one (9) in the ratio 5 : 1. An analogous initial S_N2' reaction of azide ion at C-4 has been reported by Shapiro [2,21] with compound (26) as substrate. The 7α-azido-6β-iodo-4,6-dien-3-one (11) under identical conditions gave only the 4-azido-4,6-dien-3-one (8) together with some of the previously observed hydrolysis product (12). No 6-iodo-4,6-dien-3-one was observed.

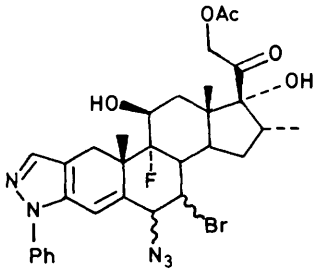
* DMSO is dimethyl sulphoxide.



(27) R = Ac, X = H
(28) R = Ac, X = N_3
(29) R = X = H



(30) R = H_2
(31) R = CHOH



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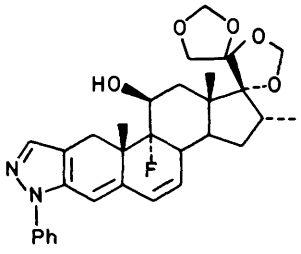

(33)

These results contrast with the sodium azide treatment of the analogous 7α-azido-6β-chloro-4-en-3-one (13) and the 6β,7α-diazido-4-en-3-one (14) which undergo a simple elimination of hydrazoic acid to yield exclusively the 6-chloro- and 6-azido-4,6-dien-3-ones (6) and (7) respectively.[1] Since the functionality at C-7 is identical in each case, the particular pathway taken by the reaction must be determined by the ease at which the 6-substituent acts as a leaving group, relative to that at C-7. As the electronegativity of the 6-substituent decreases, its leaving ability is enhanced, so favouring the S_N2' mechanism.

If, however, the 7α-azido-6β-bromo-4-en-3-one (10) is treated with tetramethylammonium fluoride, a non-nucleophilic base,[2] then the major product becomes the 6-bromo-4,6-dien-3-one (9). Two minor products are the 4-azido-4,6-dien-3-one (8) and the unsubstituted 4,6-dien-3-one (5). Compound (8) is presumably formed by reaction of azide ion generated by the elimination of hydrazoic acid, but it is not clear by what mechanism the unsubstituted 4,6-dien-3-one arises. However, a similar base-promoted elimination of halogen to give a $\Delta^{9(11)}$ steroidal olefin has also been observed by Heller *et al.*[22]

Similarly the 7α-azido-6β-bromo-1,4-dien-3-one (18) and the 7α-azido-6β-iodo-1,4-dien-3-one (20) in contact with sodium azide in DMF gave exclusively the product of an S_N2' reaction, *viz.* the 4-azido-1,4,6-trien-3-one (17).

In view of these results, it was apparent that halogen azides were not suitable reagents for the convenient transformation of steroidal 4,6-dien-3-ones into their 6-azido-substituted analogues. We felt, however, that the addition to a Δ^6-steroid might be accomplished in the desired regiochemical sense if the polarity of the olefinic bond in ring B could be reversed by the introduction of an electron-donating system at C-3. For example, addition of bromine azide to dihydropyran results in the exclusive formation of 2-azido-3-bromo adducts.[23] Such a suitable steroid substrate is the 2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazole (27), a member of a class of potent anti-inflammatory corticosteroids.[24] The latter compound was prepared from the bis(methylenedioxy)-4,6-dien-3-one (30)[25] utilising the procedures described by the Merck group[24] (see Experimental section). Indeed reaction of (27) with bromine azide was complete within ten minutes and the product exhibited a single spot on t.l.c. The mass spectrum exhibited ions at *m/z* 655 and 657 corresponding to the addition of bromine azide, and the u.v. spectrum ($\lambda_{max.}$ 264 nm, ε 13 600) was typical of the pregna-2,4-dieno[3,2-*c*]-pyrazole system.[24] However, it was evident from the ^1H n.m.r. spectrum in [$^2H_6$]DMSO that this material contained at least two products (10β-methyl signals at δ 1.13 and 1.23). This mixture was readily dehydrobrominated by tetramethylammonium fluoride in acetonitrile to give only the corresponding 6-azidopregna-2,4,6-trieno[3,2-*c*]pyrazole (28), thus defining the regiochemistry of addition of bromine azide to the pregna-2,4,6-trieno[3,2-*c*]pyrazole system. The point of attachment of the azide group in compound (28) was apparent from the ^1H n.m.r. spectrum in [$^2H_6$]DMSO, with signals for 4-H and 7-H appearing at δ 6.67 (sharp singlet) and 5.39 ($w_{\frac{1}{2}}$ 5 Hz, coupling between 7- and 8-H) respectively. We did not observe any 6-bromopregna-2,4,6-trieno[3,2-*c*]-pyrazole and therefore assign structures (32) to the products arising from the bromide azide addition to (27).

Thus, only in this one particular instance were we able to utilise a halogen azide to achieve a simple conversion of a steroidal 4,6-diene into its 6-azido-substituted analogue.

Experimental

For general experimental details see the preceding two papers.[1,14] NBS was recrystallised from hot water prior to use, as described[26] previously. Preparative layer chromatographic (p.l.c.) separations were accomplished with silica gel GF_{254} 1 000 μ plates using chloroform–ethyl acetate (4 : 1) as developer. Bands were visualised with u.v. light and extracted with ethyl acetate. In n.m.r. data, dd refers to doublet of doublet.

Preparation of Methylene Dichloride Solutions of Hydrazoic Acid.—A solution containing hydrazoic acid (*ca.* 1 mmol) in methylene dichloride (10 ml) was prepared by dissolving sodium azide (65 mg, 1 mmol) in hydrochloric acid (1 ml) and extracting with methylene dichloride (2 × 5 ml). The extracts were dried and added to the reaction vessel.

7α-Azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl Acetate (10).—To a solution of 3,20-dioxopregna-4,6-dien-17α-yl acetate (5) (370 mg, 1 mmol) in methylene dichloride (15 ml) and t-butyl alcohol (2 ml) was added NBS (178 mg, 1 mmol) and a solution of hydrazoic acid (1 mmol) in methylene dichloride (10 ml). The mixture was kept for 16 h, washed in turn with 0.05M aqueous sodium thiosulphate and water, then dried and concentrated under reduced pressure to give a gum. Crystallisation from ether–light petroleum gave 7α-azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl acetate (10) (271 mg, 55%), m.p. 150—152 °C (decomp.); $[\alpha]_D$ −37°; identical with material prepared previously.[1]

7α-Azido-6β-iodo-3,20-dioxopregn-4-en-17α-yl Acetate (11) *and 7α-Azido-3,20-dioxopregn-4-en-6β,17α-diol 17-Acetate* (12).—To a solution of 3,20-dioxopregna-4,6-dien-17α-yl acetate (5) (370 mg, 1 mmol) in methylene dichloride (15 ml) and t-butyl alcohol (2 ml) was added *N*-iodosuccinimide (NIS) (226 mg, 1 mmol) and a solution of hydrazoic acid (1 mmol) in methylene dichloride (10 ml). The reaction mixture was kept for 1 h, washed in turn with 0.05M aqueous sodium thiosulphate and water, then dried and concentrated under

reduced pressure to give a gum. Purification by p.l.c. gave 7α-*azido*-6β-*iodo*-3,20-*dioxopregn*-4-*en*-17α-*yl acetate* (11), as a yellow gum (366 mg, 69%), δ 6.13 (1 H, s, 4-H), 5.61 (1 H, d, $J_{6,7}$ 3 Hz, 6-H), 4.19 (1 H, t, $J_{7,8}$ 2 Hz, 7-H), 2.05 (3 H, s, 17α-OCOCH$_3$), 1.95 (3 H, s, 21-H$_3$), 1.53 (3 H, s, 19-H$_3$), and 0.62 (3 H, s, 18-H$_3$) (Found: M^+, 539. $C_{23}H_{30}IN_3O_4$ requires M, 539).

A solution of this gum (350 mg) in ether (25 ml) was kept overnight during which time a wine-red colour developed. The solution was washed in turn with 0.05M aqueous sodium thiosulphate and water, and dried. Evaporation of the solvent under reduced pressure gave an oil which was chromatographed (p.l.c.) to give an oil (184 mg, 65%). Crystallisation from ether gave 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12), m.p. 115—116 °C; $[\alpha]_D$ −42°; identical with material previously prepared.[14]

7α-*Azido*-2,6β-*dibromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (19) *and* 7α-*Azido*-6β-*bromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (18).—To a solution of 17α-hydroxypregna-1,4,6-triene-3,20-dione (15) (652 mg, 2 mmol) in methylene dichloride (25 ml) and t-butyl alcohol (4 ml) was added NBS (356 mg, 2 mmol) and a solution of hydrazoic acid (2 mmol) in methylene dichloride (20 ml). The mixture was stirred at room temperature overnight, washed in turn with 0.05M sodium thiosulphate and water, then dried. The residue obtained on evaporation of the solvent was chromatographed on a silica gel column and eluted (gradient) with light petroleum–ether to give the following products in order of increasing polarity; (i) 7α-*azido*-2,6β-*dibromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (19) (71 mg, 7%), crystallised from ether, m.p. 199—201 °C (decomp.); $[\alpha]_D$ −20°; $\lambda_{max.}$ 255 nm (ε 14 100); $\nu_{max.}$ 3 450, 2 100, 1 700, and 1 660 cm^{-1}; δ 7.72 (1 H, s, 1-H), 6.69 (1 H, s, 4-H), 5.43 (1 H, d, $J_{6,7}$ 2 Hz, 6-H), 5.30 (1 H, br s, exchanges with ^2H_2O, 17-OH), 4.23 (1 H, t, $J_{7,8}$ 2 Hz, 7-H), 2.11 (3 H, s, 21-H$_3$), 1.49 (3 H, s, 19-H$_3$), and 0.60 (3 H, s, 18-H$_3$) (Found: C, 47.6; H, 4.8; Br, 29.7; N, 7.7%; M^+, 525, 527, and 529. $C_{21}H_{25}Br_2N_3O_3$ requires C, 47.83; H, 4.78; Br, 30.31; N, 7.79%; M, 525, 527, and 529), (*ii*) 7α-*azido*-6β-*bromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (18) (544 mg, 61%), crystallised from ether, m.p. 177—178 °C (decomp.); $[\alpha]_D$ +12°; $\lambda_{max.}$ 248 nm (ε 16 700); $\nu_{max.}$ 3 350, 2 100, 1 720, 1 700, 1 670, and 1 620 cm^{-1}; δ 7.21 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.52 (1 H, d, $J_{2,4}$ 3 Hz, 4-H), 6.15 (1 H, dd, 2-H), 5.42 (1 H, d, $J_{6,7}$ 3 Hz, 6-H), 5.31 (1 H, s, exchanges with ^2H_2O, 17-OH), 4.21 (1 H, t, $J_{7,8}$ 3 Hz, 7-H), 2.12 (3 H, s, 21-H$_3$), 1.44 (3 H, s, 19-H$_3$), and 0.61 (3 H, s, 18-H$_3$) (Found: C, 55.9; H, 5.65; N, 8.95%; M^+, 447 and 449. $C_{21}H_{26}BrN_3O_3$ requires C, 56.25; H, 5.85; N, 9.37%; M, 447 and 449), and (iii) 17α-hydroxypregna-1,4,6-triene-3,20-dione (15) (78 mg, 12%), identified by comparison with starting material.

1α-*Azido*-2β-*bromo*-17α-*hydroxypregna*-4,6-*diene*-3,20-*dione* (24).—To a solution of hydrazoic acid (10 mmol) in methylene dichloride (25 ml) were added t-butyl alcohol (1.2 ml), 17α-hydroxypregna-1,4,6-triene-3,20-dione (15) (326 mg, 1 mmol), and NBS (178 mg, 1 mmol). The mixture was maintained at room temperature for 2 h, then washed in turn with aqueous sodium thiosulphate and water, then dried. Evaporation of the solvent under reduced pressure left a solid residue which was crystallised from ether to give 1α-*azido*-2β-*bromo*-17α-*hydroxypregna*-4,6-*diene*-3,20-*dione* (24) (210 mg, 47%), m.p. 165—166 °C (decomp.); $[\alpha]_D$ −234°; $\lambda_{max.}$ 301 nm (ε 22 300); $\nu_{max.}$ 3 500, 2 100, 1 700, 1 650, 1 610, and 1 580 cm^{-1}; δ 6.30 (2 H, s, 6- and 7-H), 5.85 (1 H, s, 4-H), 5.31 (1 H, s, exchanges with ^2H_2O, 17-OH), 4.86 (1 H, d, $J_{1,2}$ 2 Hz, 2-H), 4.59 (1 H, d, 1-H), 2.13 (3 H, s, 21-H$_3$), 1.44 (3 H, s, 19-H$_3$), and 0.62 (3 H, s, 18-H$_3$) [Found: C, 56.3; H, 5.7; Br, 17.85; N, 9.2%; (M^+ − 43), 404 and 406. $C_{21}H_{26}BrN_3O_3$ requires C, 56.25; H, 5.85; Br, 17.82; N, 9.37%; (M − 43), 404 and 406].

2-*Bromo*-17α-*hydroxypregna*-1,4,6-*triene*-3,20-*dione* (16).—A solution of 1α-azido-2β-bromo-17α-hydroxypregna-4,6-diene-3,20-dione (24) (179 mg, 0.4 mmol) in DMF (4 ml) containing sodium azide (26 mg, 0.4 mmol) was heated to 60 °C for 2 h. The mixture was diluted with water and extracted with ether. The extracts were combined and washed with water, dried, and concentrated to give 2-*bromo*-17α-*hydroxypregna*-1,4,6-*triene*-3,20-*dione* (16), crystallised from ether–light petroleum (113 mg, 70%), m.p. 194—196 °C; $[\alpha]_D$ +11°; $\lambda_{max.}$ 222 (ε 15 100), 270 (11 700), and 308 nm (9 600); $\nu_{max.}$ 3 460, 1 715, 1 640, 1 610, and 1 590 cm^{-1}; δ 7.71 (1 H, s, 1-H), 6.36 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 2 Hz, 7-H), 6.11 (1 H, d, 6-H), 6.11 (1 H, s, 4-H), 5.26 (1 H, s, exchanges with ^2H_2O, 17-OH), 2.10 (3 H, s, 21-H$_3$), 1.21 (3 H, s, 19-H$_3$), and 0.62 (3 H, s, 18-H$_3$) (Found: C, 61.8; H, 6.0; Br, 19.6%; M^+, 404 and 406. $C_{21}H_{25}BrO_3$ requires C, 62.22; H, 6.22; Br, 19.72%; M, 404 and 406).

7α-*Azido*-2,6β-*dibromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (19) *from* 7α-*Azido*-6β-*bromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (18).—To a solution of 7α-azido-6β-bromo-17α-hydroxypregna-1,4-diene-3,20-dione (18) (448 mg, 1 mmol) in methylene dichloride (15 ml) and t-butyl alcohol (2 ml) was added NBS (178 mg, 1 mmol) and a solution of hydrazoic acid (5 mmol) in methylene dichloride (20 ml). The mixture was kept for 5 h, then washed in turn with aqueous sodium hydrogen carbonate and water, dried, and concentrated under reduced pressure. Crystallisation of the residue from ether afforded 7α-azido-2,6β-dibromo-17α-hydroxypregna-1,4-diene-3,20-dione (19) (348 mg, 66%), m.p. 198—200 °C (decomp.).

7α-*Azido*-17α-*hydroxy*-6β-*iodopregna*-1,4-*diene*-3,20-*dione* (20).—To a solution of 17β-hydroxypregna-1,4,6-triene-3,20-dione (15) (326 mg, 1 mmol) in methylene dichloride (20 ml) and t-butyl alcohol (2 ml) was added NIS (225 mg, 1 mmol) and a solution of hydrazoic acid (1 mmol) in methylene dichloride (10 ml). The mixture was kept at room temperature for 5 h. T.l.c. indicated *ca.* 50% conversion of starting material. The reaction mixture was washed in turn with 0.05M aqueous sodium thiosulphate and water and was then dried and concentrated to give a gum. Purification (p.l.c.) gave a pale yellow gum (215 mg, 43%). Concentration of an ether–light petroleum solution of this residue under reduced pressure gave 7α-*azido*-17α-*hydroxy*-6β-*iodopregna*-1,4-*diene*-3,20-*dione* (20) as an amorphous solid, $[\alpha]_D$ +58°; $\lambda_{max.}$ 244 nm (ε 20 200); $\nu_{max.}$ 3 450, 2 100, 1 715, 1 670, and 1 625 cm^{-1}; δ 7.18 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.51 (1 H, d, $J_{2,4}$ 2 Hz, 4-H), 6.12 (1 H, dd, 2-H), 5.60 (1 H, d, $J_{6,7}$ 2 Hz, 6-H), 5.30 (1 H, s, exchanges with ^2H_2O, 17-OH), 4.21 (1 H, t, $J_{7,8}$ 2 Hz, 7-H), 2.10 (3 H, s, 21-H$_3$), 1.53 (3 H, s, 19-H$_3$), and 0.62 (3 H, s, 18-H$_3$) (Found: M^+, 495. $C_{21}H_{26}IN_3O_3$ requires M, 495).

7α-*Azido*-6β,17α-*dihydroxypregna*-1,4-*diene*-3,20-*dione* (21).—A solution of 7α-azido-17α-hydroxy-6β-iodopregna-1,4-diene-3,20-dione (20) (130 mg, 0.26 mmol) in ether (25 ml) was maintained for 1 d during which time a wine-red colour developed. The solution was washed in turn with 0.05M aqueous sodium thiosulphate and water, dried, and evaporated. The residue was purified by p.l.c. and crystallisation from ether gave 7α-*azido*-6β,17α-*dihydroxypregna*-1,4-*diene*-3,20-*dione* (21) (43 mg, 43%), m.p. 230—231 °C; $[\alpha]_D$ −116°; $\lambda_{max.}$ 252 nm (ε 11 100); $\nu_{max.}$ 3 550, 3 400, 2 120, 1 700, 1 670, and 1 630 cm^{-1}; δ 7.13 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.16 (1 H, s, 4-H), 6.07 (1 H, dd, $J_{2,4}$ 2 Hz, 2-H), 5.86 (1 H, d, $J_{6\alpha,6\beta\text{-OH}}$ 3 Hz,

exchanges with ^2H_2O, 6β-OH), 5.26 (1 H, s, exchanges with ^2H_2O, 17-OH), 4.38 (1 H, t, collapses to doublet with ^2H_2O, $J_{6,7}$ 3 Hz, 6-H), 3.81 (1 H, t, $J_{7,8}$ 2 Hz, 7-H), 2.09 (3 H, s, 21-H_3), 1.30 (3 H, s, 19-H_3), and 0.58 (3 H, s, 18-H_3) (Found: C, 64.3; H, 7.0; N, 10.4%; M^+, 385. $C_{21}H_{27}N_3O_4 \cdot \frac{1}{2}H_2O$ requires C, 63.93; H, 7.15; N, 10.65%; *M*, 385).

Reaction of 7α-*Azido*-6β-*bromo*-3,20-*dioxopregn*-4-*en*-17α-*yl Acetate* (10) *with Sodium Azide*.—A solution of 7α-azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl acetate (10) (376 mg, 0.76 mmol) in DMF (10 ml) containing sodium azide (50 mg, 0.76 mmol) was heated to 60 °C for 3 h. The mixture was cooled, diluted with ether, and washed with water. The ether solution was dried and the residue, obtained on evaporation of the solvent, was purified by p.l.c. to give 4-*azido*-3,20-*dioxopregna*-4,6-*dien*-17α-*yl acetate* (8) (160 mg, 51%), crystallised from ether, m.p. 305—306 °C (decomp.); $[\alpha]_D$ +38°; $\lambda_{max.}$ 206 (ε 9 700), 243sh (5 400), and 322 nm (18 600); $\nu_{max.}$ 2 120, 1 735, 1 720, 1 680, 1 610, 1 570, and 1 260 cm^{-1}; δ 6.55 (1 H, dd, $J_{6,7}$ 9, $J_{7,8}$ 2 Hz, 7-H), 6.17 (1 H, dd, $J_{6,8}$ 1.5 Hz, 6-H), 2.07 (3 H, s, 17-OCOCH_3), 1.98 (3 H, s, 21-H_3), 1.06 (3 H, s, 19-H_3), and 0.65 (3 H, s, 18-H_3) [Found: C, 67.1; H, 7.15; N, 10.25%; (M^+ − 28), 383. $C_{23}H_{29}N_3O_4$ requires C, 67.13; H, 7.10; N, 10.21%; (*M* − 28), 383], and 6-*bromo*-3,20-*dioxopregna*-4,6-*dien*-17α-*yl acetate* (9) (30 mg, 9%), crystallised from ether, m.p. 215—216 °C; $[\alpha]_D$ +8.7°; $\lambda_{max.}$ 287 nm (ε 20 000); $\nu_{max.}$ 1 730, 1 715, 1 660, 1 600, and 1 250 cm^{-1}; δ 6.62 (1 H, d, $J_{7,8}$ 2 Hz, 7-H), 6.00 (1 H, s, 4-H), 2.08 (3 H, s, 17-OCOCH_3), 1.98 (3 H, s, 21-H_3), 1.13 (3 H, s, 19-H_3), and 0.64 (3 H, s, 18-H_3) (Found: C, 61.5; H, 6.45; Br, 17.5%; M^+, 448 and 450. $C_{23}H_{29}BrO_4$ requires C, 61.47; H, 6.50; Br, 17.78%; *M*, 448 and 450).

Reaction of 7α-*Azido*-6β-*iodo*-3,20-*dioxopregn*-4-*en*-17α-*yl Acetate* (11) *with Sodium Azide*.—Treatment of 7α-azido-6β-iodo-3,20-dioxopregn-4-en-17α-yl acetate (11) (348 mg, 0.65 mmol) with sodium azide as described in the preceding experiment gave, following p.l.c., 4-azido-3,20-dioxopregna-4,6-dien-17α-yl acetate (8) (163 mg, 61%), m.p. 303—304 °C (decomp.) and 7α-azido-3,20-dioxopregn-4-ene-6β,17α-diol 17-acetate (12) (22 mg, 8%), m.p. 115—116 °C; both products were identified by comparison with authentic materials.

Reaction of 7α-*Azido*-6β-*bromo*-3,20-*dioxopregn*-4-*en*-17α-*yl Acetate* (10) *with Tetramethylammonium Fluoride*.—To a solution of 7α-azido-6β-bromo-3,20-dioxopregn-4-en-17α-yl acetate (10) (178 mg, 0.36 mmol) in acetonitrile (10 ml) under nitrogen was added tetramethylammonium fluoride pentahydrate (66 mg, 0.36 mmol). The mixture was heated at 60 °C for 2 h and was then diluted with water and extracted with ether. The extracts were washed with water, dried, and concentrated to give a gum. P.l.c. gave the following products in order of increasing polarity; (i) 4-azido-3,20-dioxopregna-4,6-dien-17α-yl acetate (8) (18 mg, 12%), m.p. 305—306 °C (decomp.), (ii) 6-bromo-3,20-dioxopregna-4,6-dien-17α-yl acetate (9) (66 mg, 41%), m.p. 214—215 °C, and (iii) 3,20-dioxopregna-4,6-dien-17α-yl acetate (5) (32 mg, 24%), m.p. 220—222 °C).

Reaction of 7α-*Azido*-6β-*bromo*-17α-*hydroxypregna*-1,4-*diene*-3,20-*dione* (18) *with Sodium Azide*.—A solution of 7α-azido-6β-bromo-17α-hydroxypregna-1,4-diene-3,20-dione (18) (224 mg, 0.5 mmol) in DMF (10 ml) containing sodium azide (33 mg, 0.5 mmol) was heated at 60 °C for 2 h. The reaction mixture was diluted with water and extracted with ether. The extracts were combined, washed with water, dried, and concentrated to give a residue which was purified by p.l.c. to give 4-*azido*-17α-*hydroxypregna*-1,4,6-*triene*-3,20-*dione* (17), crystallised from ether (95 mg, 51%), m.p. 142—143 °C (decomp.); $[\alpha]_D$ +118°; $\lambda_{max.}$ 229 (ε 12 000), 240 (12 000), 266sh (5 700), and 337 nm (6 300); $\nu_{max.}$ 3 450, 2 120, 1 725, 1 700, 1 650, 1 600, and 1 560 cm^{-1}; δ 7.28 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 6.61 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 3 Hz, 7-H), 6.24 (1 H, d, 2-H), 6.09 (1 H, dd, $J_{6,8}$ 2 Hz, 6-H), 5.23 (1 H, s, exchanges with ^2H_2O, 17-OH), 2.10 (3 H, s, 21-H_3), 1.15 (3 H, s, 19-H_3), and 0.61 (3 H, s, 18-H_3) [Found: C, 68.35; H, 6.6; N, 11.15%; (M^+ − 28), 339. $C_{21}H_{25}N_3O_3$ requires C, 68.64; H, 6.86; N, 11.44%; (*M* − 28), 339].

Reaction of 7α-*Azido*-17α-*hydroxy*-6β-*iodopregna*-1,4-*diene*-3,20-*dione* (20) *with Sodium Azide*.—Treatment of 7α-azido-17α-hydroxy-6β-iodopregna-1,4-diene-3,20-dione (20) (248 mg, 0.5 mmol) with sodium azide as described in the preceding experiment gave, following p.l.c., 4-azido-17α-hydroxypregna-1,4,6-triene-3,20-dione (17), crystallised from ether (119 mg, 65%), m.p. 141—142 °C (decomp.), identical with the material prepared previously.

9α-*Fluoro*-11β-*hydroxy*-2-(*hydroxymethylene*)-16α-*methyl*-17α,20:20,21-*bis*(*methylenedioxy*)*pregna*-4,6-*dien*-3-*one* (31).—To a solution of 9α-fluoro-11β-hydroxy-16α-methyl-17α,20:20,21-bis(methylenedioxy)pregna-4,6-dien-3-one [25] (30) (1.58 g, 3.64 mmol) in dry tetrahydrofuran (THF) (133 ml) and benzene (67 ml) under nitrogen were added sodium hydride (970 mg, 20.6 mmol; 51% dispersion in mineral oil), sodium methoxide (970 mg, 18.0 mmol), and freshly distilled ethyl formate (3 ml, 37 mmol). The mixture was stirred at room temperature for 2.5 h then diluted with saturated aqueous potassium dihydrogen phosphate. Most of the solvent was distilled off under reduced pressure and the residue was partitioned between benzene and water. The benzene phase was then washed with 5% aqueous sodium hydrogen carbonate, and extracted three times with 2% aqueous sodium hydroxide. The sodium hydroxide extracts were combined, washed with benzene, and acidified with 2% hydrochloric acid. The resulting precipitate was filtered off, washed with water, and air-dried to yield 9α-*fluoro*-11β-*hydroxy*-2-(*hydroxymethylene*)-16α-*methyl*-17α,20:20,21-*bis*(*methylenedioxy*)*pregna*-4,6-*dien*-3-*one* (31) (1.1 g, 65%) which could be used without further purification. Crystallisation from methanol–ethyl acetate afforded a methanol solvate, $\lambda_{max.}$ 288 nm (ε 17 100); δ (C^2HCl_3) 7.70 (1 H, s, C*H*OH), 6.25 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 2 Hz, 7-H), 5.88 (1 H, dd, $J_{6,8}$ 1.5 Hz, 6-H), 5.81 (1 H, s, 4-H), 5.23—4.94 (4 H, m, 2 × OCH_2O), 4.26 (1 H, br d, 11α-H), 4.00 (2 H, s, 21-H_2), 1.31 (3 H, s, 19-H_3), 1.19 (3 H, s, 18-H_3), and 0.96 (3 H, d, *J* 7 Hz, 16α-CH_3) (Found: C, 63.4; H, 7.15; F, 3.7%; M^+, 462. $C_{25}H_{31}FO_7 \cdot CH_3OH$ requires C, 63.14; H, 7.13; F, 3.84%; *M*, 462).

9α-*Fluoro*-11β-*hydroxy*-16α-*methyl*-17α,20:20,21-*bis*-(*methylenedioxy*)-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]-*pyrazole* (33).*—A solution of 9α-fluoro-11β-hydroxy-2-(hydroxymethylene)-16α-methyl-17α,20:20,21-bis(methylenedioxy)pregna-4,6-dien-3-one (31) (1.1 g, 2.38 mmol) in absolute ethanol (15 ml) containing phenylhydrazine (0.6 ml, 6.1 mmol) under nitrogen was refluxed for 1 h. The solution was concentrated under reduced pressure and the residue was dissolved in ether and washed with 2% hydrochloric acid. The residue, obtained on concentrating the dried ethereal solution, was chromatographed on a silica gel column (25 × 2.5 cm). Elution with chloroform gave 9α-*fluoro*-11β-*hydroxy*-16α-*methyl*-17α,20:20,21-*bis*(*methylenedioxy*)-2′-

* 9α-Fluoro-16α-methyl-17α,20:20,21-bis(methylenedioxy)-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-11β-ol.

phenyl-2′H-*pregna*-2,4,6-*trieno*[3.2-c]*pyrazole* (33) (539 mg, 42%), m.p. 264—266 °C; $[\alpha]_D$ −179°; $\lambda_{max.}$ 223 (ε 10 150), 286 (14 600), and 314 nm (17 200); $\nu_{max.}$ 3 270, 1 715, 1 600, and 1 510 cm^{-1}; δ (C^2HCl_3) 7.46 (6 H, s, aromatics), 6.27 (1 H, s, 4-H), 6.18 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 2 Hz, 7-H), 5.55 (1 H, d, 6-H), 5.22—4.94 (4 H, m, 2 × OCH_2O), 4.25 (1 H, br d, 11α-H), 3.98 (2 H, s, 21-H_2), 1.27 (3 H, s, 19-H_3), 1.18 (3 H, s, 18-H_3), and 0.94 (3 H, d, *J* 7 Hz, 16α-CH_3) (Found: C, 69.5; H, 6.85; F, 3.34; N, 5.15%; M^+, 534. $C_{31}H_{35}FN_2O_5$ requires C, 69.64; H, 6.66; F, 3.53; N, 5.24%; *M*, 534).

9α-*Fluoro*-11β,17α,21-*trihydroxy*-16α-*methyl*-20-*oxo*-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]*pyrazole* (29).*—A solution of 9α-fluoro-11β-hydroxy-16α-methyl-17α,20:20,21-bis-(methylenedioxy)-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]-pyrazole (33) (539 mg, 1.01 mmol) in 60% aqueous formic acid (25 ml) was heated on a steam-bath for 30 min. The solution was concentrated under reduced pressure and the residue was diluted with 10% aqueous sodium hydrogen carbonate solution. After extraction with ether, the combined extracts were washed with water and concentrated to dryness. The residue was dissolved in ethanol (50 ml) and THF (25 ml) and stirred under nitrogen with 1M aqueous potassium hydroxide (3 ml). After dilution with water (200 ml), the pH of the mixture was adjusted to 7 by the addition of dilute acetic acid. The precipitate was filtered off, washed with water, and dried. Crystallisation from methylene dichloride–di-isopropyl ether gave 9α-*fluoro*-11β,17α,21-*trihydroxy*-16α-*methyl*-20-*oxo*-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]*pyrazole* (29) (193 mg, 36%), m.p. 275—280 °C; $[\alpha]_D$ −97° (dioxane); $\lambda_{max.}$ 220 (ε 13 100), 285 (17 800), and 313 nm (19 500); $\nu_{max.}$ 3 570, 3 340, 1 720, 1 600, and 1 515 cm^{-1}; δ 7.51 (6 H, s, aromatics), 6.36 (1 H, s, 4-H), 6.22 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 2 Hz, 7-H), 5.53 (1 H, d, 6-H), 5.08 (1 H, d, *J* 3 Hz, exchanges with ^2H_2O, 11β-OH), 4.94 (1 H, s, exchanges with ^2H_2O, 17α-OH), 4.84—4.04 [2 H, m, collapses to AB q (J_{gem} 19 Hz) with ^2H_2O, 21-H_2], 4.20 (1 H, br s, 11α-H), 1.22 (3 H, s, 19-H_3), 0.92 (3 H, s, 18-H_3), and 0.84 (3 H, d, *J* 7 Hz, 16α CH_3) (Found: C, 70.95; H, 7.05; F, 3.7; *N*, 5.65%; M^+, 492. $C_{29}H_{33}FN_2O_4$ requires C, 70.70; H, 6.74; F, 3.85; N, 5.69%; *M*, 492).

9α-*Fluoro*-16α-*methyl*-20-*oxo*-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]*pyrazole*-11β,17α,21-*triol* 21-*Acetate* (27).—To a solution of 9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-20-oxo-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazole (29) (886 mg, 1.8 mmol) in pyridine (10 ml) was added acetic anhydride (1.2 ml) and the mixture was kept at room temperature overnight. The reaction mixture was poured into 10% hydrochloric acid (100 ml) and the precipitate was filtered off, washed with water, and dried. Recrystallisation from ether gave 9α-*fluoro*-16α-*methyl*-20-*oxo*-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]*pyrazole*-11β,17α,21-*triol* 21-*acetate* (27) (882 mg, 92%), m.p. 168—170 °C (solidifies and remelts 248—250 °C); $[\alpha]_D$ −55°; $\lambda_{max.}$ 220 (ε 14 400), 285 (19 000), and 314 nm (22 400); $\nu_{max.}$ 3 500, 3 250, 1 765, 1 730, 1 600, 1 510, and 1 230 cm^{-1}; δ 7.55 (1 H, s, 5′-H), 7.52 (5 H, s, Ph), 6.36 (1 H, s, 4-H), 6.23 (1 H, dd, $J_{6,7}$ 10, $J_{7,8}$ 2 Hz, 7-H), 5.54 (1 H, d, 6-H), 5.22 (1 H, d, *J* 6 Hz, exchanges with ^2H_2O, 11β-OH), 5.16 (1 H, s, exchanges with ^2H_2O, 17α-OH), 4.94 (2 H, AB q, J_{gem} 18 Hz, 21-H_2), 4.20 (1 H, br s, 11α-H), 2.11 (3 H, s, $OCOCH_3$), 1.23 (3 H, s, 19-H_3), 0.95 (3 H, s, 18-H_3), and 0.83 (3 H, d, *J* 7 Hz, 16α-CH_3) (Found: C, 69.8; H, 6.65; F, 3.3; N, 5.05%; M^+, 534. $C_{31}H_{35}FN_2O_5$ requires C, 69.64; H, 6.66; F, 3.53; N, 5.24%; *M*, 534).

* 9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-20-one.

6-*Azido*-9α-*fluoro*-16α-*methyl*-20-*oxo*-2′-*phenyl*-2′H-*pregna*-2,4,6-*trieno*[3,2-c]*pyrazole*-11β,17α,21-*triol* 21-*Acetate* (28).—To a solution of 9α-fluoro-16α-methyl-20-oxo-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazole-11β,17α,21-triol 21-acetate (27) (267 mg, 0.5 mmol) in methylene dichloride (10 ml) was added NBS (89 mg, 0.5 mmol) and a solution of hydrazoic acid (0.5 mmol) in methylene dichloride (5 ml). The mixture was kept for 30 min at room temperature, then evaporated to an oil, and the product was purified by p.l.c. to give a non-crystalline solid (280 mg), $[\alpha]_D$ +35°; $\lambda_{max.}$ 264 nm (ε 13 600). This solid was dissolved in acetonitrile (20 ml), tetramethylammonium fluoride pentahydrate (156 mg, 0.85 mmol) was added, and the mixture was stirred at 50 °C overnight. 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 a brown gum which was purified by p.l.c. to give 6-azido-9α-fluoro-16α-methyl-20-oxo-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazole-11β,17α,21-triol 21-acetate (28), crystallised from ether (175 mg, 61%), m.p. 230 °C (decomp.); $[\alpha]_D$ +23°; $\lambda_{max.}$ 222 (ε 14 300), 293 (18 000), and 318 nm (20 900); $\nu_{max.}$ 3 400, 3 200, 2 100, 1 735, 1 720, 1 600, 1 500, and 1 270 cm^{-1}; δ 7.63 (1 H, s, 5′-H), 7.55 (5 H, s, Ph), 6.67 (1 H, s, 4-H), 5.39 (1 H, d, $J_{7,8}$ 2 Hz, 7-H), 5.33 (1 H, d, exchanges with ^2H_2O, 11β-OH), 5.20 (1 H, s, exchanges with ^2H_2O, 17α-OH), 4.25 (1 H, br s, 11α-H), 4.97 (2 H, q, J_{gem} 18 Hz, 21-H_2), 2.13 (3 H, s, $OCOCH_3$), 1.27 (3 H, s, 19-H_3), 0.98 (3 H, s, 18-H_3), and 0.87 (3 H, d, *J* 7 Hz, 16α-CH_3) (Found: C, 64.55; H, 6.05; F, 3.3; N, 12.25%; M^+, 575. $C_{31}H_{34}FN_5O_5$ requires C, 64.68; H, 5.95; F, 3.30; N, 12.17%; *M*, 575).

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