Improved Syntheses of Aldosterone

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A convenient synthesis of 1,2-didehydroaldosterone acetate, from 11β-hydroxypregna-1,4-dien-3-one, is described. Photolysis of the 11-nitrite of the latter compound gives only the desired attack at C-18. The resulting 18-oxime is cyclised to the nitrone, and the oxidation level of the latter is conveniently used for the introduction of a 21-acetoxy-group. Similar experiments with 11β-hydroxypregna-1,4,6-trien-3-one afford 1,2,6,7-tetradehydroaldosterone acetate. Selective hydrogenation of 1,2-didehydro- or of 1,2,6,7-tetradehydroaldosterone acetate gives aldosterone acetate in unlabelled or labelled (tritium) form.

An interesting cleavage of steroid 18,20-nitrones with chromic acid (Jones reagent) has been discovered and shown to regenerate the masked aldehyde function of aldosterone-type compounds.

A systematic study of the photolysis of 11β-nitrites has defined the best solvent and other conditions for this reaction.

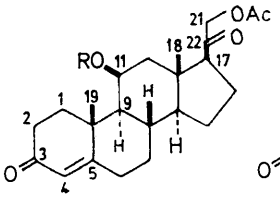
OUR earlier synthesis [1] of aldosterone 21-acetate (III) by photolysis of the 11β-nitrite (II) of corticosterone acetate (I) is convenient and simple, but the overall yield is rather low. The major reason for this is that radical attack on C-19 competes with the desired attack on C-18.

Functionalisation of an angular methyl group is sensitive to structural changes and requires generation of an alkoxyl radical 2.0—2.7 Å removed from and in a 1,3-diaxial relationship with the methyl group.[2] Thus the ratio of C-18 to C-19 attack in the 11β-nitrites (IVa)—(VI) increases in the order saturated lanostane derivative (VI) (0 : 1), 5(6) eneacetals (IVa and b) (1 : 2), 4-en-3-one (Va) (1 : 1), 4,6-dien-3-one (Vb) (>1 : 1), 1,4-dien-3-one (Vc) (1 : 0).[3] The relative increases of C-18 functionalisation with extended conjugation results from an increase in separation between C-19 and the 11β-oxygen atom. Comparison of the 18- and 19-proton shifts in the n.m.r. spectra of the parent alcohol and the 11-deoxy-compound can be used in an important method to predict the relative extent of C-18 and C-19 functionalisation.[4]

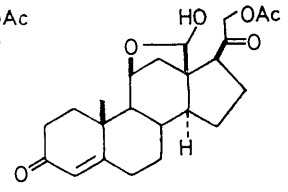
We now describe the synthesis of 1,2-didehydro- (XXd) and of 1,2,6,7-tetradehydro- (XXVIIIa) aldosterone 21-acetate from 11β-nitroso-oxypregna-1,4-diene-3,20-dione (Xe) and 1,2,6,7-tetradehydrocorticosterone 21-acetate 11-nitrite (XXIIId), respectively. The 1,2-double bond was incorporated into the nitrites (Xe) and (XXIIId) to ensure exclusive C-18 functionalisation. Radiolabelled aldosterone 21-acetate is thus conveniently available from (XXd) and (XXVIIIa) on hydrogenation with tritium.

[1] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1960, **82**, 2641; 1961, **83**, 4083.
[2] K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.
[3] R. H. Hesse, *Adv. Free-Radical Chem.*, 1969, **3**, 83, and references therein.
[4] R. B. Boar, *J.C.S. Perkin I*, 1975, 1275.

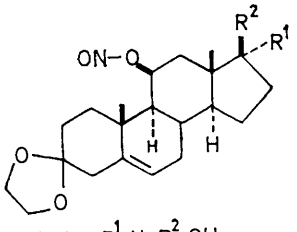
11β-Hydroxypregna-1,4-diene-3,20-dione (Xb) was prepared from the 11α-alcohol (VIIa) in five stages. Dehydration *via* the toluene-*p*-sulphonate (VIIb) gave the



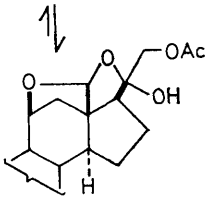
(I) R=H
(II) R=NO

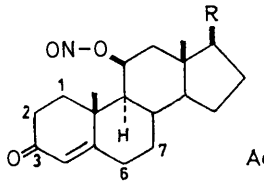


(III)

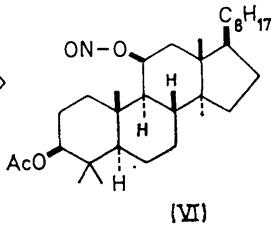


(IV) a; R^1=H, R^2=OH
b; R^1=H, R^2=COMe or CO·CH_2OAc





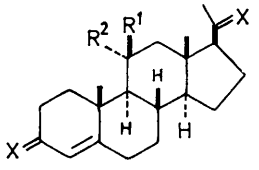
(Va)
(Vb) Δ^6
(Vc) Δ^1
(R variable)



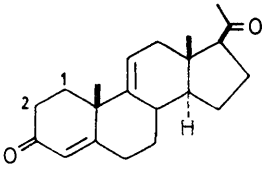
(VI)

dienone (VIII). Kinetically controlled [5] oxidation of the dienone (VIII) with dichlorodicyanobenzoquinone (DDQ) gave the trienone (IX). Attempts to oxidise the 11α-alcohol (VIIa) or the toluene-*p*-sulphonate (VIIb) resulted in appreciable formation of 4,6-dienones and 1,4,6-trienones, the 11α-substituent hindering removal of the 1α-proton.[5] Addition of hypobromous acid to the trienone (IX) and debromination by chromous acetate with hydrogen atom transfer gave 11β-hydroxypregna-1,4-diene-3,20-dione (Xb). The required alcohol (Xb) was also prepared by reduction of pregn-4-ene-3,11,20-trione (VIIc) with the oxo-groups at C-3 and C-20 protected by formation of the bis-semicarbazone (VIId) [6] or the bis-enolate (XIa) [7], followed by oxidation with DDQ. Reduction of the bis-semicarbazone (VIId) with borohydride and removal of the protecting groups with nitrous acid gave 11β-hydroxyprogesterone (VIIf). Oxidation with DDQ then afforded 11β-hydroxypregna-1,4-diene-3,20-dione (Xb). Alternatively the lithium bis-enolate (XIa), employed since sodium enolates of 3-ketones can rearrange to 11-enolates,[8] was reduced with lithium aluminium hydride or sodium bis-(2-methoxy ethoxy)aluminium hydride to give 11β-hydroxyprogesterone (VIIf). Recovery of the trione (VIIc) implied that some enolisation of the 11-ketone had occurred. An attempt to synthesis (Xb) from (VIIc) *via* (Xc) and (Xd) failed at the dehydrogenation stage. 4,5,6,7-Tetradehydro- and 1,2,4,5,6,7-hexadehydro-compounds were formed.

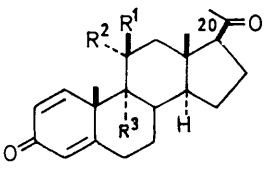
11β-Nitroso-oxypregna-1,4-diene-3,20-dione (Xe) was prepared in high yield from dienol (Xb) and nitrosyl chloride. Irradiation gave small amounts of alcohol (Xb) and of the ketone (Xc). The major product was the oxime (XIIa). On heating in propan-2-ol this was smoothly converted into the nitrone (XIIIa), the formation of which has precedent.[1] The yield of the nitrone (XIIIa) varied with the solvent used for photolysis in the order acetonitrile > tetrahydrofuran > chlorobenzene > toluene > benzene > acetone. Addition of base (1%



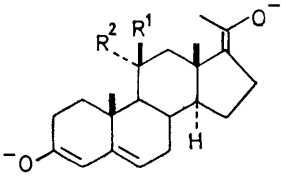
(VII) a; R^1=H, R^2=OH, X=O
b; R^1=H, R^2=SO_2·C_6H_4Me-*p*, X=O
c; R^1R^2=O, X=O
d; R^1R^2=O, X=N·NH·CO·NH_2
e; R^1=OH, R^2=H, X=N·NH·CO·NH_2
f; R^1=OH, R^2=H, X=O



(VIII)
(IX) Δ^1



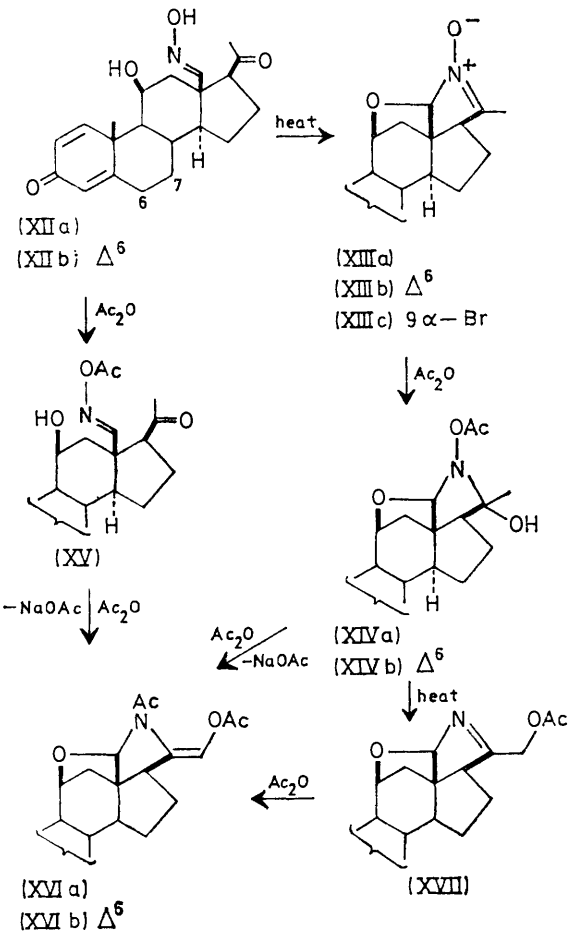
(X) a; R^1=OH, R^2=H, R^3=Br
b; R^1=OH, R^2=R^3=H
c; R^1R^2=O, R^3=H
d; R^1=OH, R^2=R^3=H, 20-H,OH
e; R^1=ONO, R^2=R^3=H
f; R^1=ONO, R^2=H, R^3=Br



(XI) a; R^1R^2=O
b; R^1=OH, R^2=H

[5] H. J. Ringold and A. Turner, *Chem. and Ind.*, 1962, 211; S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, 1964, **29**, 601.
[6] R. E. Jones and S. A. Robinson, *J. Org. Chem.*, 1956, **21**, 586; R. Joly, G. Nominé, and D. Bertin, *Bull. Soc. chim. France*, 1956, **23**, 1459; P. A. Diassi, J. Fried, R. M. Palmere, and E. F. Sabo, *J. Amer. Chem. Soc.*, 1961, **83**, 4249.
[7] D. H. R. Barton, R. H. Hesse, M. M. Pechet, and C. Wiltshire, *J.C.S. Chem. Comm.*, 1972, 1017.
[8] D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 1497.

solvent volume) gave improved yields. Since intramolecular functionalisation is favoured by rigidity in steroids, the expected intermolecular processes [9] do not

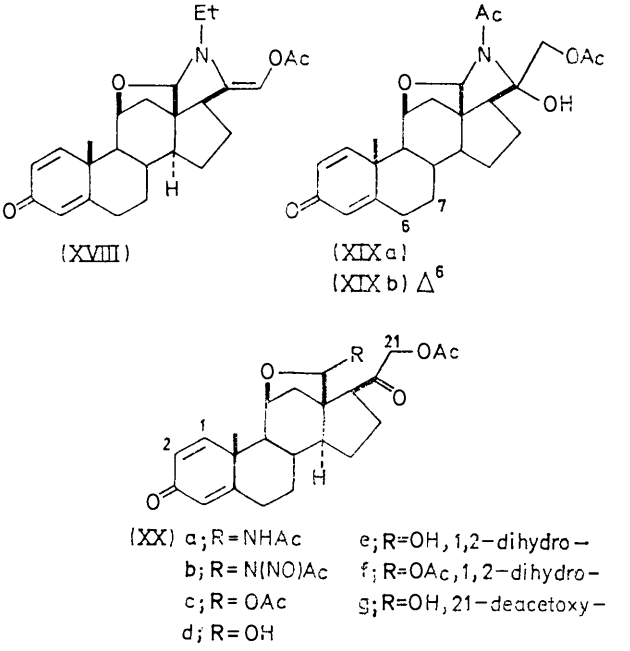


take place to a significant extent. Thus tetrahydrofuran and acetonitrile are preferred solvents for nitrite photolysis. The best yield of the nitrone (XIIIa) from the nitrite (Xe) was 55%.

The nitrone (XIIIa) was conceived to be a good intermediate for 21-acetoxylation. The functionalisation, by acylation, of a C–H bond α to a nitrone function has been reported previously.[10] We planned to convert the nitrone (XIIIa) into 1,2-didehydroaldosterone 21-acetate (XXd) by acetylation with rearrangement to give the 21-acetate (XVII), followed by hydrolysis by nitrosation of the imine function in the presence of water.

Low temperature acetylation of the nitrone (XIIIa) gave the hydroxymonoacetate (XIVa), which under more vigorous conditions gave the *N*-acetyl acetate (XVIa). Dehydration of the hydroxymonoacetate (XIVa) by refluxing in chlorobenzene gave the required imine (XVII). The imine (XVII) also gave the *N*-acetyl acetate (XVIa) on refluxing with acetic anhydride. During conversion of the nitrone (XIIIa) into the *N*-acetyl acetate (XVIa), a minor component, probably the oxime monoacetate (XV), was detected. This also gave the *N*-acetyl acetate (XVIa) with acetic anhydride–sodium acetate. Attempts to ring open the imine acetate (XVII) by nitrosation with nitrous acid, nitrosyl chloride, or nitrosyl tetrafluoroborate failed. Meerwein alkylation of the imine acetate (XVII) gave the vinyl acetate (XVIII). The proposed ring opening on alkylation, and by implication with alternate electrophilic attack, was prevented by ready double bond migration.

However, 1,2-didehydroaldosterone 18,21-diacetate (XXc) was prepared from the *N*-acetyl acetate (XVIa) *via* (XIXa) and (XXb). Basic hydrolysis of the *N*-acetyl acetate (XVIa) gave a mixture of products. However, hydration with acetic acid gave the hydroxy-*N*-acetyl acetate (XIXa) in high yield. Equilibration of the cyclic (XIXa) and acyclic (XXa) forms, presumably acid-catalysed, took place in chloroform. Nitrosation of the (XIXa)—(XXa) mixture with dinitrogen tetraoxide–chloroform–sodium acetate [11] gave the unstable *N*-nitroso-derivative (XXb). Pyrolysis afforded the required 1,2-didehydroaldosterone 18,21-diacetate (XXc). An alternative preparation of (XXc) from aldosterone 21-acetate (XXe) by oxidation with DDQ followed by acetylation gave identical material. Hydrolysis of the diacetate (XXc) with 90% aqueous acetic acid at 50 °C gave 1,2-didehydroaldosterone 21-acetate (XXd). Use of a



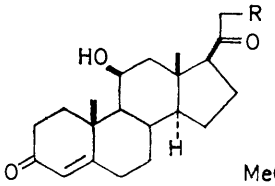
higher temperature also resulted in hydrolysis of the 21-acetate. Basic hydrolysis was avoided because of ready epimerisation at C-17. The cyclic–acyclic equilibration

[9] P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.*, 1962, **84**, 2711.

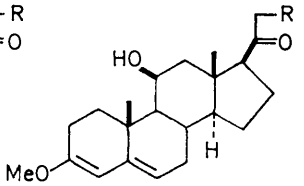
[10] T. Koenig, *J. Amer. Chem. Soc.*, 1966, **88**, 4045; R. Bodalski and A. R. Katritzky, *Tetrahedron Letters*, 1968, 257; R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 1959, 2094; D. H. R. Barton, N. J. A. Gutteridge, R. H. Hesse, and M. M. Pechet, *J. Org. Chem.*, 1969, **34**, 1473.

[11] E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6008, 6011, 6014.

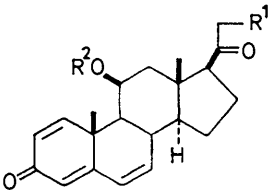
of (XXd) was apparent in the n.m.r. and i.r. spectra. Our n.m.r. assignments are in agreement with Genard's data [12] for aldosterone 21-acetate (XXe).



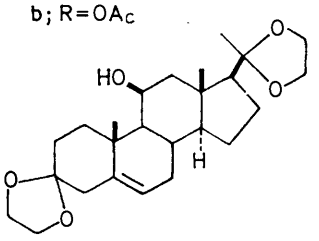
(XXI) a; R=H
b; R=OAc



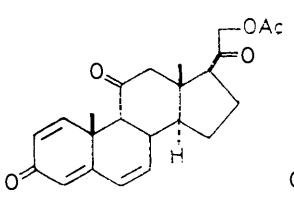
(XXII) a; R=H
b; R=OAc



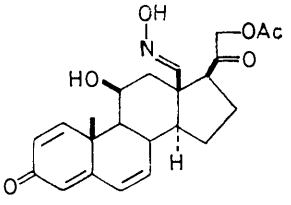
(XXIII) a; R^1=H, R^2=H
b; R^1=OAc, R^2=H
c; R^1=H, R^2=NO
d; R^1=OAc, R^2=NO



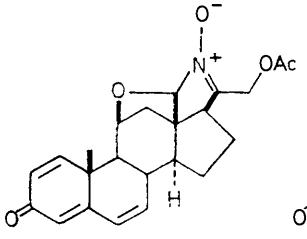
(XXIV)



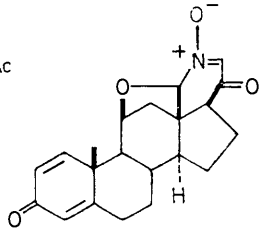
(XXV)



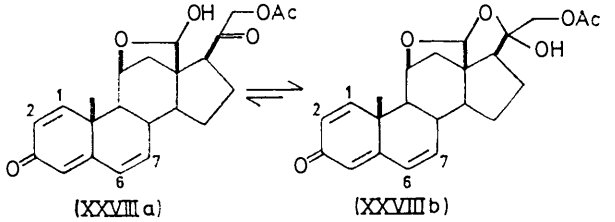
(XXVI)



(XXVII)



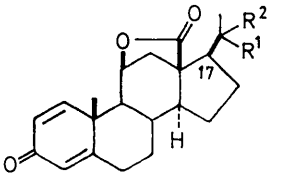
(XXIX)



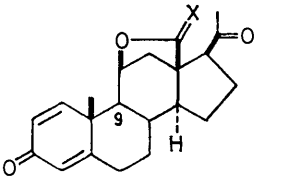
(XXVIII a) (XXVIII b)
(XXVIII c) 1,2-dihydro (XXVIII d) 1,2-dihydro
(XXVIII e) 1,2,6,7-tetrahydro (XXVIII f) 1,2,6,7-tetrahydro

The nitrone (XIIIa) on oxidation gave diverse products. Treatment with selenium dioxide gave the nitrone (XXIX), presumably formed by oxidation at C-21 to the aldehyde and subsequent ring expansion.[13] Use of lead tetra-acetate gave the nitroso-acetate (XXXa) and the oxime (XXXb). Reduction of the nitroso-acetate (XXXa) with zinc–acetic acid gave the oxime (XXXb), which was also formed, along with the lactone (XXXc), on treatment of the nitroso-acetate (XXXa) with potassium hydroxide in methanol–water. Presumably solvent methanol is the reductant. The nitrone (XIIIa) on oxidation with manganese dioxide gave the lactone oxime (XXXIa) and the cyclic imidate (XXXIc); the former was readily acetylated. Jones oxidation of the nitrone (XIIIa) gave the lactone (XXXId) with acetone–dichloromethane as solvent, the lactone oxime (XXXIa) with acetone, and 1,2-didehydro-21-deoxyaldosterone (XXg) with aqueous acetone. Treatment of the lactone (XXXId) with base gave a C-17 epimer mixture (XXXc) identical with that from the nitroso-acetate (XXXa).

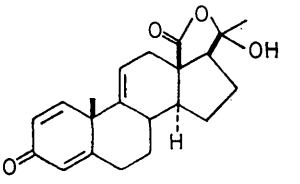
Having completed the synthesis of 1,2-didehydroaldosterone 21-acetate (XXd) and of 1,2-didehydro-21-deoxyaldosterone (XXg), we undertook that of 1,2,6,7-tetradehydroaldosterone 21-acetate (XXVIIIa). Oxidation of 11β-hydroxy-3-methoxypregna-3,5-dien-20-one (XXIIa) with DDQ [5] gave the trienone (XXIIIa) in 56% yield. Since ethylene acetals undergo α-bromination



(XXX) a; R^1=OAc, R^2=NO
b; R^1R^2=NOH
c; R^1R^2=O, mixture of 17-epimers



(XXXI) a; X=NOH
b; X=NOAc
c; X=NH
d; X=O
e; X=O, 9α-Br
f; X=NOH, 9α-Br
g, X=H,OH, 9α-Br



(XXXII)

via equilibration with the 2-hydroxyethyl vinyl ether,[14] oxidation of 11β-hydroxyprogesterone 3,20-bisethylene acetal (XXIV) with DDQ was expected to give, after hydrolysis, the 1,4,6-trienone (XXIIIa). This prediction was borne out, a yield of 60% being obtained. Photolysis of the derived nitrite (XXIIIc) in acetonitrile, *etc.*, gave the nitrone (XIIIb). Acetylation of the nitrone (XIIIb) gave the *N*-acetyl acetate (XVIb) *via* the hydroxymonoacetate (XIVb). Although the *N*-acetyl acetate (XVIb)

[12] P. Genard, *Org. Magnetic Resonance*, 1971, **3**, 759.
[13] R. F. C. Brown, V. M. Clark, and A. Todd, *J. Chem. Soc.*, 1959, 2105.
[14] A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. Soc. chim. France*, 1961, 1822.

gave, on hydrolysis with acetic acid, the required hydroxy-*N*-acetyl acetate (XIXb), attempted deamination with dinitrogen tetraoxide resulted in attack on the trienone in addition to *N*-nitrosation. Pyrolysis of the products gave an intractable mixture. Dinitrogen tetraoxide is well known to react with olefins especially in the presence of oxygen.[15]

The alternative approach *via* Jones oxidation of the nitrone (XXVII) derived from corticosterone 21-acetate (XXIb) was examined. Oxidation of 21-acetoxy-11β-hydroxy-3-methoxypregna-3,5-dien-20-one (XXIIb) gave the required tetradehydroketone (XXIIIb). Room temperature photolysis of the nitrite derivative (XXIIId) in tetrahydrofuran–triethylamine gave the 11-ketone 21-acetate (XXV), 1,2,6,7-tetradehydrocorticosterone 21-acetate (XXIIIb), and, as main product, the required oxime (XXVI). In chloroform solution the oxime (XXVI) gave the nitrone (XXVII). The u.v. spectra of the oxime (XXVI) and the nitrone (XXVII) were identical and consistent with overlap of the two chromophores. Presumably the oxime (XXVI) gave the nitrone (XXVII) in methanol. The required 1,2,6,7-tetradehydroaldosterone 21-acetate (XXVIIIa) was obtained from Jones oxidation of the nitrone (XXVII) or deamination of the oxime (XXVI) with nitrous acid. The n.m.r. spectrum of 1,2,6,7-tetradehydroaldosterone 21-acetate was consistent with the presence of an equilibrium mixture of the cyclic form (XXVIIIa) (80—90%) and the hemiacetal (XXVIIIb) (10—20%), the major difference being the 21-H signal, which appeared as a singlet at τ 5.20 in the case of (XXVIIIa) and as an AB quartet at τ 5.88 in that of (XXVIIIb). Tristriphenylphosphinerhodium(I) chloride-catalysed hydrogenation of 1,2,6,7-tetradehydroaldosterone 21-acetate (XXVIIIa) gave 6,7-didehydroaldosterone 21-acetate (XXVIIIc). Prolonged hydrogenation gave aldosterone 21-acetate (XXVIIIe). Dreiding models indicated that the observed selectivity resulted from steric approach control.

Of the two foregoing syntheses of aldosterone, the first, affording 1,2-didehydroaldosterone 21-acetate (XXd), although lengthy, utilised low-cost starting material. Nitrone oxidation in the second approach proved an easy route to 1,2,6,7-tetradehydroaldosterone 21-acetate (XXVIIIa). Both syntheses are convenient for the preparation of tritium-labelled aldosterone acetate.

A further example of the Jones oxidation of nitrones was demonstrated in another series of compounds. The 9α-bromo-nitrone (XIIIc), prepared from 9α-bromo-11β-hydroxypregna-1,4-diene-3,20-dione (Xa) *via* the 11-nitrite (Xf) and irradiation and cyclisation, was oxidised with Jones reagent. In aqueous acetone 9α-bromo-1,2-didehydro-21-deoxyaldosterone (XXXIg) was smoothly formed. In contrast, oxidation in dichloromethane–acetone in the absence of water gave the lactone (XXXIe) and the lactone oxime (XXXIf). Reduction of the bromo-lactone (XXXIe) with a zinc–copper couple gave the lactol (XXXII). Ordinary Jones oxidation of the aldosterone derivative (XXXIg) gave the lactone (XXXIe). This seems to prove that in the Jones oxidation of the nitrone there is formed an intermediate relatively stable to oxidation, but easily hydrolysed to an aldosterone derivative on work-up. Further studies of this nitrone oxidation have shown that optimal yields are obtained at room temperature with a short oxidation time and 1 : 1 v/v aqueous acetone as solvent. The mechanism of this unusual chromic acid cleavage of steroidal 18(20)-nitrones deserves further study. *

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. Unless otherwise stated i.r. spectra were recorded for KBr discs, u.v. spectra for solutions in methanol, n.m.r. spectra for solutions in deuteriochloroform, and optical rotations for solutions in chloroform. Organic solutions were dried over anhydrous sodium sulphate. Preparative layer chromatography (p.l.c.) was carried out on Merck silica GF_{254}.

11α-*p*-Tolylsulphonyloxypregn-4-ene-3,20-dione [16] (VIIb), pregna-4,9(11)-diene-3,20-dione [17] (VIII), pregna-1,4,9(11)-triene-3,20-dione [18] (IX), 9α-bromo-11β-hydroxypregna-1,4-diene-3,20-dione [19] (Xa), 11β-hydroxypregna-1,4-diene-3,20-dione [20] (Xb), and pregna-1,4-diene-3,11,20-trione [21] (Xc) were prepared according to the references cited.

Pregn-4-ene-3,11,20-trione 3,20-*Bis-semicarbazone* (VIId).—Semicarbazide hydrochloride (54 g) in water (400 ml) was added to 11-oxoprogesterone (40 g) in pyridine (50 ml) in hot methanol (1 200 ml). Next day the bis-semicarbazone (VIId) (52 g, 97%) was filtered off, washed, and dried; m.p. (from CH_2Cl_2–MeOH) >350°, $\nu_{max.}$ 3 400m, 3 250m, 1 710—1 680br, s, and 1 580—1 565s cm^{-1}; determination of optical rotation and u.v. and n.m.r. data was precluded by insolubility.

11β-*Hydroxypregn-4-ene-3,20-dione Bis-semicarbazone* (VIIe).—Sodium borohydride (17 g)–water (50 ml) slurry was added to a suspension of the bis-semicarbazone (VIId) (52 g.) in tetrahydrofuran (THF) (1 500 ml)–water (750 ml). After the vigorous reaction had subsided, sodium borohydride (17 g) was added, and the mixture was stirred (1 h) and heated to reflux (7 h). Removal of THF, extraction with water (750 ml) at 70 °C for 0.5 h, and filtration gave *compound* (VIIe) (49 g, 96%), m.p. (from CH_2Cl_2–MeOH) >350°, $\nu_{max.}$ 3 400m, 3 150m, 1 695—1 675s, and 1 565s cm^{-1} (Found: C, 62.0; H, 8.15; N, 18.75. $C_{23}H_{36}N_6O_3$ requires C, 62.15; H, 8.15; N, 18.9%).

The reduction was only *ca.* 75% complete when carried out with a large excess of sodium borohydride in THF–propan-2-ol–water (10 : 5 : 1).

11β-*Hydroxyprogesterone* (VIIf).—Sodium nitrite (25 g) in water (250 ml) was added in portions to a stirred solution of the bis-semicarbazone (VIIe) (49 g) in hydrochloric acid

* Work on the acylative rearrangement of related 18(20)-nitrones has recently been published (J. P. Alazard, B. Khemis, and X. Lusinchi, *Tetrahedron*, 1975, **31**, 1427).

[15] For example, W. K. Seifert, *J. Org. Chem.*, 1963, **28**, 125.

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(3N; 2 000 ml); the temperature was maintained at 5 °C for 20 min. Urea (150 g) in water (250 ml) was added and the crude product (37 g) filtered off. Chromatography on grade III alumina gave 11β-hydroxyprogesterone (VIIf) (30.2 g, 83%), m.p. (from Me_2CO) 185—186° (lit.,[22] 186—188°), $[\alpha]_D^{21}$ +218° (*c* 0.95 in Me_2CO) (lit.,[22] +217°), $\nu_{max.}$ 3 500m, 1 700s, 1 660s, 1 620m, and 1 350m cm^{-1}, $\lambda_{max.}$ 241 nm (ε 14 500) (Found: C, 76.2; H, 8.9. Calc. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.15%).

11β-Hydroxypregna-1,4-diene-3,20-dione (Xb).—Oxidation of 11β-hydroxyprogesterone (VIIf) (660 mg) in dioxan (30 ml) containing benzoic acid (488 mg) with DDQ (568 mg) and chromatography on Fluorisil gave the title compound (491 mg, 75%), identical with that previously prepared.

11β-Hydroxyprogesterone (VIIf).—*Alternative methods.* (*A*) 11-Oxoprogesterone (VIIc) (656 mg) in THF (5 ml) was added to sodium bistrimethylsilylamide (878 mg) in THF (5 ml) giving a yellow suspension of the bis-enolate (XIa). The suspension was added to anhydrous lithium chloride (1.6 g) in THF (5 ml). After stirring for 20 min sodium bis-(2-methoxyethoxy)aluminium hydride (70% in benzene; 2.5 ml) was added. After 1 h the excess of reducing agent was destroyed with ammonia, the dianion (XIb) was quenched with sulphuric acid (4M; 20 ml), and the mixture was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and evaporated. Chromatography on alumina gave compound (VIIf) (345 mg, 52%) and unchanged 11-oxoprogesterone (VIIc) (170 mg, 26%).

Low-temperature (−20 °C) reactions, prolonged reaction times and (inverse) addition of base to steroid gave similar results. When only 2 equiv. of base were employed the 11β-alcohol (VIIf) (51%) and unchanged ketone (VIIc) (11%) were obtained. A large excess of base gave the 11β-alcohol (VIIf) (23%) and unchanged ketone (VIIc) (61%).

(*B*) n-Butyl-lithium (23% in hexane; 2.05 ml) was added to triphenylmethane (1.22 g) in THF (20 ml). After 30 min the deep red solution was added over 10 min to 11-oxoprogesterone (VIIc) (656 mg) in THF (15 ml) until a permanent pink colouration was observed. Sodium bis-(2-methoxyethoxy)aluminium hydride in benzene (70%; 2 ml) was added. Work-up as previously described, extraction of the crude product with hot cyclohexane to remove triphenylmethane, and chromatography on grade III alumina gave 11β-hydroxyprogesterone (VIIf) (338 mg, 51%) and unchanged 11-oxoprogesterone (66 mg, 10%).

11β-Nitroso-oxypregna-1,4-diene-3,20-dione (Xe).—Nitrosyl chloride was passed through an ice-cooled solution of 11β-hydroxypregna-1,4-diene-3,20-dione (Xb) (656 mg) in pyridine (5 ml) until a permanent brown colour was observed. The mixture was poured into ice–water (100 ml) and the crude nitrite (Xe) was filtered off, dissolved in dichloromethane, and washed with aqueous sodium hydrogen carbonate and water. Evaporation gave *compound* (Xe) (664 mg, 93%), m.p. (from EtOAc with a trace of pyridine) 175—176° (decomp.), $[\alpha]_D^{22}$ +216° (*c* 0.87), $\nu_{max.}$ 1 705s, 1 665s, 1 630m, and 1 605m cm^{-1}, $\lambda_{max.}$ 242 nm (ε 13 000) (Found: C, 70.35; H, 7.75. $C_{21}H_{27}NO_4$ requires C, 70.55; H, 7.6%).

Photolysis of the 11β-Nitrite (Xe).—The nitrite (Xe) (0.75 g, 4 mmol) in the appropriate solvent was deoxygenated with argon prior to and during irradiation ($\lambda > 300$ nm; Pyrex filter) with a 200 W medium-pressure mercury arc. Irradiation was continued until t.l.c. indicated the absence of starting material (Xe). The solvent was removed and the residue taken up in propan-2-ol and heated to reflux for 30 min. P.l.c. on alumina gave *2′,11β-epoxy-2′,4′α-dihydro-5′-methyl-18-norandrosta-1,4-dieno*[13,17-c]*pyrrol-3-one* N-*oxide* (XIIIa), m.p. (from CH_2Cl_2–hexane) 285—288° (decomp.), $[\alpha]_D^{23}$ 118° (*c* 0.79), $\nu_{max.}$ 1 665s, 1 625m, 1 600w, 1 580m, and 1 240s cm^{-1}, $\lambda_{max.}$ 239 nm (ε 23 800), τ 2.85 (1 H, d, *J* 10 Hz, 1-H), 3.80 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.85br (1 H, s, 4-H), 4.70 (1 H, s, 2′-H), 4.95 (1 H, d, *J* 6 Hz, 11α-H), 7.95 (3 H, s, 5′-Me), and 8.65 (3 H, s, 19-H_3) (Found: C, 74.4; H, 7.35; N, 4.3. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.45; N, 4.15%). Yields of nitrone (XIIIa) were as follows: 20% (benzene), 38% (benzene; nitrone filtered off and filtrate reirradiated), 32% (toluene), 35—40% (chlorobenzene), 40—45% (THF), 50% (acetonitrile), and 18% (acetone). The yields of nitrone (XIIIa) from irradiation of the nitrite (Xe) in THF showed little variation with temperature (−65 to 15 °C). Addition of triethylamine or pyridine (0.3—1.5% solvent volume) gave increased yields of the nitrone (XIIIa); 40% (chlorobenzene, 0.3% pyridine), 47% (THF, 1.4% pyridine), 55% (acetonitrile, 1% pyridine or Et_3N). Excess of base was detrimental to yield.

1′-Acetoxy-2′,11β-epoxy-5′-hydroxy-5′-methyl-4′αH-18-norandrosta-1,4-dieno[13,17-c]*pyrrolidin-3-one* (XIVa).—The nitrone (XIIIa) (500 mg) in acetic anhydride (4 ml) was kept at 0 °C (16 h) and stirred with water (50 ml) (1 h). *Compound* (XIVa) (450 mg, 77%) was filtered off; m.p. (from EtOAc) 170—173°, $[\alpha]_D^{21}$ +136° (*c* 0.86), $\nu_{max.}$ 3 500m, 1 750s, 1 660s, 1 625m, and 1 240s cm^{-1}, $\lambda_{max.}$ 243 nm (ε 1 6300), τ 2.80 (1 H d, *J* 10 Hz, 1-H), 3.75 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.95br (1 H, s, 4-H), 5.00 (1 H, d, *J* 6 Hz, 11α-H), 5.26 (1 H, 2, 2′-H), 5.85 (1 H, exch. D_2O, OH), 7.80 (3 H, s, NAc), 8.64 (3 H, s, 5′-Me), and 8.68 (3 H, s, 19-H_3) (Found: C, 69.1; H, 7.25; N, 3.7. $C_{23}H_{29}NO_5$ requires C, 69.15; H, 7.3; N, 3.5%). Attempted chromatography of (XIVa) gave the nitrone (XIIIa).

5′-Acetoxymethyl-2′,11β-epoxy-2′,4′α-dihydro-18-norandrosta-1,4-dieno[13,17-c]*pyrrol-3-one* (XVII).—The hydroxy-monoacetate (XIVa) [crude; from the nitrone (XIIIa) (100 mg)] in chlorobenzene (30 ml) was heated to reflux under argon (30 min). Removal of solvent and p.l.c. gave *compound* (68 mg, 61%), m.p. (from EtOAc–hexane) 136—137°, $[\alpha]_D^{21}$ +28° (*c* 0.5), $\nu_{max.}$ 1 745m, 1 660s, 1 625m, 1 610w, and 1 240s cm^{-1}, $\lambda_{max.}$ 243 nm (ε 16 800), τ 2.80 (1 H, d, *J* 10 Hz, 1-H), 3.72 (1H, dd, *J* 10 and 2 Hz, 2-H), 3.93br (1 H, s, 4-H), 4.60 (1 H, s, 2′-H), 5.12 (1 H, d, *J* 6 Hz, 11α-H), 5.29br (2 H, s, 5′-CH_2), 7.87 (3 H, 2, OAc), and 8.60 (3 H, s, 19-H_3) (Found: C, 72.25; H, 7.3; N, 3.55. $C_{23}H_{27}NO_4$ requires C, 72.4; H, 7.15; N, 3.65%).

Alkylation of the Imino-acetate (XVII).—Triethyloxonium tetrafluoroborate (136 mg) was added to the imino-acetate (XVII) (68 mg) in dichloromethane (5 ml). After stirring for 30 min the solution was washed with aqueous sodium hydrogen carbonate and water. Evaporation and p.l.c. gave *5′-acetoxymethylene-2′,11β-epoxy-1′-ethyl-4′αH-18-norandrosta-1,4-dieno*[13,17-c]*pyrrolidin-3-one* (XVIII) as an amorphous solid, $[\alpha]_D^{23}$ +174° (*c* 0.4), $\nu_{max.}$ 1 740s, 1 660s, 1 620m, 1 225s, 1 060s, and 1 040s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 16 500), τ 2.76 (1 H, d, *J* 10 Hz, 1-H), 3.50br (1 H, s, 5′-CH), 3.70 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.90br (1 H, s, 4-H), 5.13 (1 H, d, *J* 6 Hz, 11α-H), 5.20 (1 H, s, 2′-H), 7.00 and 8.63 (5 H, q and t, NEt), 7.90 (3 H, s, OAc), and 8.64 (3 H, s, 19-H_3), *m/e* 409 (M^+) (Found: C, 72.95; H, 8.0; N, 3.1. $C_{25}H_{31}NO_4$ requires C, 73.3; H, 7.65; N, 3.4%).

1′-Acetyl-5′-acetoxymethylene-2′,11β-epoxy-4′αH-18-nor-

[22] G. Rosenkranz, J. Pataki, and C. Djerassi, *J. Org. Chem.*, 1952, **17**, 290.

androsta-1,4-*dieno*[13,17-c]*pyrrolidin*-3-*one* (XVIa).—The hydroxy-monoacetate (XIVa) [crude; from the nitrone (XIIIa) (1.0 g)] and sodium acetate (80 mg) in acetic anhydride (20 ml) were heated to reflux (20 min). The mixture was poured into aqueous sodium hydrogen carbonate; the solid was filtered off, taken up in dichloromethane, and washed with water. P.l.c. gave *compound* (XVIa) (668 mg, 55%), m.p. (from EtOAc) 257—260°, $[\alpha]_D^{23}$ +211 (*c* 0.75), $\nu_{max.}$ 1 740s, 1 680s, 1 660s, 1 625m, 1 605w, and 1 225s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 17 000), τ 1.80 (1 H, d, *J* 17 Hz., 5'-CH), 2.82 (1 H, d, *J* 10 Hz, 1-H), 3.80 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.97br (1 H, s, 4-H), 4.60 (1 H, s, 2'-H), 5.07 (1 H, d, *J* 6 Hz, 11α-H), 7.77 and 7.90 (6 H, 2s, NAc and OAc), and 8.64 (3 H, s., 19-H_3), *m/e* 423 (M^+) (Found: C, 70.7; H, 7.0; N, 3.3. $C_{25}H_{29}NO_5$ requires C, 70.9; H, 6.9; N, 3.3%).

1'-*Acetyl*-5'-*acetoxymethyl*-2',11β-*epoxy*-5'-*hydroxy*-4'βH-18-*norandrosta*-1,4-*dieno*[13,17-c]*pyrrolidin*-3-*one* (XIXa).—The *N*-acetyl acetate (XVIa) (125 mg) in acetic acid (4.75 ml) and water (0.25 ml) was kept at 20 °C for 36 h. Partition between water and dichloromethane gave, on evaporation, *compound* (XIXa) (112 mg), m.p. (from EtOAc) 230—235°, $[\alpha]_D^{23}$ +144° (*c* 0.5), $\nu_{max.}$ 3 400m, 1 735s, 1 655s, 1 620m, 1 600w, and 1 225s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 17 300), τ 2.90 (1 H, d, *J* 10 Hz, 1-H), 3.80 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.98br (1 H, s, 4-H), 4.80 (1 H, s, 2'-H), 5.12 (1 H, d, *J* 6 Hz, 11α-H), 5.30 (2 H, ABq, *J* 17 Hz, 5'-CH_2), 7.87 and 7.94 (6 H, 2s, NAc and OAc), and 8.67 (3 H, s, 19-H_3) (Found: C, 65.65; H, 7.05; N, 3.15. $C_{25}H_{31}NO_6,H_2O$ requires C, 65.35; H, 7.25; N, 3.05%). In chloroform the cyclic isomer (XIXa) reached equilibrium with the acyclic form (XXa), $\nu_{max.}$ 3 350m, 3 250m, 1 740m, 1 725m, 1 660s, 1 625m, 1 530m, 1 230s cm^{-1}, τ 2.93 (1 H, d, *J* 10 Hz, 1-H), 3.77 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.97br (1 H, s, 4-H), 3.40, 3.56, 4.25, and 4.38 (2 H, ABq, NH, and 18-H), 5.15 (1 H, d, *J* 6 Hz, 11α-H), 5.34 (2 H, ABq, *J* 17 Hz, 21-H_2), 7.84 and 7.94 (6 H, 2s, NAc and OAc), and 8.70 (3 H, s, 19-H_3).

1,2-*Didehydroaldosterone* 18,21-*Diacetate* (XXc).—*Compound* (XIXa) (250 mg) was added to sodium acetate (1.0 g) in chloroform (1.5 ml) saturated with dinitrogen tetra-oxide at −10 °C. After 20 min stirring the solution was diluted with chloroform, washed with aqueous sodium hydrogen carbonate and water, and evaporated (<5 °C) to leave the crude *N*-nitroso-derivative (XXb), $\nu_{max.}$ ($CHCl_3$) 1 740s, 1 660s, 1 620m, and 1 530m $cm.^{-1}$ The product in dioxan (5 ml) was heated to reflux (16 h), diluted with water, and extracted with dichloromethane. Evaporation and p.l.c. gave starting material (XIX) (93 mg, 36%) and compound (XXc) (132 mg, 52%), as an oil identical (i.r. and n.m.r.) with that prepared from the oxidation with DDQ of aldosterone 18,21-diacetate (XXf); $\nu_{max.}$ ($CHCl_3$) 1 750s, 1 740m, 1 720m, 1 660s, 1 625m, and 1 225s cm^{-1}.

1,2-*Didehydroaldosterone* 21-*Acetate* (XXd).—The diacetate (XXc) (132 mg) was hydrolysed with 90% aqueous acetic acid at 55 °C for 3 h. Partition between dichloromethane and aqueous sodium hydrogen carbonate and p.l.c. gave the diacetate (XXc) (26 mg, 20%), and compound (XXd) (76 mg, 64%) [identical with authentic material (mixed m.p., i.r., and n.m.r.)], m.p. (from Me_2CO–hexane) 187.5—189.5°, $[\alpha]_D^{21}$ +75° (*c* 1.01), $\nu_{max.}$ 3 450m, 1 740s, 1 660s, 1 620m, 1 605w, and 1 225s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 13 900), τ 2.97 (1 H, d, *J* 10 Hz, 1-H), 3.87 (1 H, dd, *J* 10 and 2 Hz, 2-H), 4.00br (1 H, s, 4-H) 4.60 (0.8H, s, 18-H), 5.00 (0.2H, s, 18-H), 5.12 (1 H, d, J 6 Hz, 11α-H), 5.30 (0.4—0.5 H, s, 21-H, open form), 6.00 (1.5—1.6 H, dd, *J* 11 Hz, 21-H, closed form), 6.80 (1 H, s, exch. D_2O, OH), 7.90 and 7.93 (3 H, 2s, OAc), and 8.70 and 8.73 (3 H, 2s, 19-H_3) (Found: C, 68.9; H, 6.75. Calc. for $C_{23}H_{28}O_6$: C, 69.0; H, 7.05%).

Oxidation of the Nitrone (XIIIa) *with Selenium Dioxide*.—The nitrone (XIIIa) (296 mg) and selenium dioxide (149 mg) in t-butyl alcohol (25 ml) were heated to reflux for 2½ h under nitrogen. Dichloromethane and precipitated silver were added and the refluxing continued (15 min). After filtration water was added and the mixture extracted with dichloromethane. The extract was washed with saturated aqueous sodium hydrogen carbonate, aqueous ammonium sulphide, water, and brine. Evaporation and chromatography on grade III alumina(eluant benzene–dichloromethane, 1 : 1) gave 2',11β-*epoxy*-2'H-18-*norandrosta*-1,4-*dieno*-[13,17-c]*pyridine*-3,5'(4'αH)-*dione* N-*oxide* (XXIX) (190 mg), m.p. (from CH_2Cl_2–EtOAc) 273—276° (decomp.), $[\alpha]_D^{24}$ +131° (*c* 0.82), $\nu_{max.}$ 1 660s, 1 630, 1 605, and 1 537s cm^{-1}, $\lambda_{max.}$ 242 (ε 18 000) and 280 nm (ε 17 000) (Found: C, 71.35; H, 6.75. $C_{21}H_{23}NO_4$ requires C, 71.35; H, 6.55%).

Oxidation of the Nitrone (XIIIa) *with Lead Tetra-acetate*.—Lead tetra-acetate (550 mg) was added to the nitrone (XIIIa) (277 mg) in dichloromethane (25 ml). After 15 min at room temperature the solution was decanted and washed with water. Evaporation gave 20-*acetoxy*-20-*nitroso*-3-*oxo*-*pregna*-1,4-*dien*-18,11β-*olactone* (XXXa) as pale blue crystals, m.p. (from EtOH and CH_2Cl_2–EtOAc) 197—199° (decomp.), $[\alpha]_D^{22}$ −225° (*c* 0.43) and −259° (*c* 0.52), $\nu_{max.}$ 1 780, 1 745, 1 670, 1 635, 1 605, and 1 570 cm^{-1}, $\lambda_{max.}$ 240 nm (ε 17 700) (Found: C, 65.6; H, 6.5. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.6%). Chromatography of the mother liquors on neutral grade III alumina (eluant benzene) gave additional (XXXa) (128 mg total) and (eluant Me_3CO) the *oxime* (XXXb) (12 mg), m.p. (from CH_2Cl_2–EtOAc) 272—275°, $[\alpha]_D^{22}$ +135° (*c* 0.66), $\nu_{max.}$ 3 400, 1 788, 1 685, and 1 630 cm^{-1}, $\lambda_{max.}$ 242 nm (ε 14 100) (Found: C, 71.0; H, 7.15. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.35%).

Reaction of the Nitroso-acetate (XXXa) *with Potassium Hydroxide*.—Aqueous methanolic potassium hydroxide (10%; 1 : 1; 1 ml) was added to the nitroso-acetate (XXXa) (66 mg) in methanol (4 ml). After 1 h the solution was extracted with dichloromethane and the aqueous phase was acidified and re-extracted with dichloromethane. Evaporation of the neutral extract left a residue (18 mg), and chromatography on neutral grade V alumina gave the oxime (XXXb). P.l.c. of the acidic extract (23 mg) gave the 20-*ketone* (XXXc), m.p. (from CH_2Cl_2–EtOAc) 218–220°, $[\alpha]_D^{22}$ 0° (*c* 0.55), $\nu_{max.}$ 1 780s, 1 715s, 1 670s, 1 625m, and 1 610m cm^{-1}, $\lambda_{max.}$ 241 nm (ε 19 000) (Found: C, 74.25; H, 7.3. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%). The oxime (XXXb) was alternatively prepared by reduction with zinc–acetic acid of the nitroso-acetate (XXXa). The $[\alpha]_D$ value for the lactone (XXXc) indicates the presence of a mixture of 17-epimers.

Oxidation of the Nitrone (XIIIa) *with Manganese Dioxide*.—The nitrone (XIIIa) (518 mg) in chloroform (50 ml) was stirred with active manganese dioxide at room temperature for 24 h. Filtration, extraction with 2N-hydrochloric acid, evaporation, and chromatography on neutral grade V alumina (eluant benzene) gave 3,20-*dioxopregna*-1,4-*dien*-18,11β-*olactone* 18-*oxime* (XXXIa), m.p. (from CH_2Cl_2–EtOAc) 255—257°, $[\alpha]_D$ +93° (*c* 0.85); $\nu_{max.}$ 3 510s, 1 697s, 1 630m, and 1 602m cm^{-1} (Found: C, 70.6; H, 6.95. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1%). The concentrated mother liquors gave 11β,18-*epoxy*-18-*iminopregna*-1,4-*diene*-3,20-*dione* (XXXIc), m.p. (from CH_2Cl_2–EtOAc) 314—316°, $[\alpha]_D$ +117° (*c* 0.78), $\nu_{max.}$ 3 300m, 1 702s, 1 670s, 1 635m, and

1 603s, cm^{-1} (Found: C, 74.2; H, 7.1. $C_{21}H_{35}NO_3$ requires C, 74.3; H, 7.4%).

Acetylation of Lactone Oxime (XXXIa).—Acetylation [acetic anhydride (1 ml)–pyridine (1 ml); 4 h at room temperature] of the oxime (XXXIa) (49 mg) gave the acetate (XXXIb), m.p. (from CH_2Cl_2–EtOAc) 203—206°, $[\alpha]_D^{23}$ +133° (*c* 1.0), $\nu_{max.}$ 1 780s, 1 720s, 1 675s, 1 635m, and 1 605m cm^{-1} (Found: C, 69.35; H, 6.75. $C_{23}H_{27}NO_5$ requires C, 69.5; H, 6.85%).

Oxidation of the Nitrone (XIIIa) *with Chromic Acid.*—(*A*) The nitrone (XIIIa) (73 mg) in acetone (15 ml) and dichloromethane (15 ml) was stirred at room temperature with Jones reagent (0.25 ml) for 15 min. Partition between brine and dichloromethane, evaporation, and chromatography on grade V alumina (eluant benzene) gave 3,20-*dioxopregna*-1,4-*dien*-18,11β-*olactone* (XXXId), m.p. (from hexane) 199—202°, $[\alpha]_D^{23}$ +106° (*c* 0.69), $\nu_{max.}$ 1 785, 1 725, 1 680, 1 640, and 1 615 cm^{-1} (Found: C, 73.95; H, 6.95. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%). Oxidation of the lactone oxime (XXXIa) also gave the lactone (XXXId).

(*B*) Jones reagent (0.25 ml) was added to the nitrone (XIIIa) (57 mg) in acetone (8 ml) and water (8 ml). After 7 min at room temperature the mixture was poured into water and extracted with dichloromethane. Evaporation and chromatography on neutral grade V alumina (eluant benzene–CH_2Cl_2) gave 1,2-*didehydro*-21-*deoxyaldosterone* (XXg) (46 mg), m.p. (from CH_2Cl_2–EtOAc) 188—192°, $[\alpha]_D^{19}$ +122° (*c* 0.90), $\nu_{max.}$ 3 440, 1 715, 1 665, and 1 620 cm^{-1} (Found: C, 73.65; H, 7.45. $C_{21}H_{26}O_4$ requires C, 73.65; H, 7.65%).

(*C*) Jones reagent (0.25 ml) was added to the nitrone (XIIIa) (20 mg) in acetone (20 ml) at room temperature. After 5 min stirring, work-up and chromatography on neutral grade V alumina (eluant benzene) gave the lactone oxime (XXXIa) (12 mg), identical (m.p., t.l.c., and i.r.) with that previously prepared.

11β-*Hydroxy*-3-*methoxypregna*-3,5-*dien*-20-*one* (XXIIa).—11β-Hydroxyprogesterone (XXIa) (300 mg), toluene-*p*-sulphonic acid monohydrate (8 mg), and methanol (0.1 ml) in 2,2-dimethoxypropane (2.5 ml)–DMF (2.5 ml) were heated to reflux (4 h) with addition of methanol (0.1 ml) after 2 h. Neutralisation with sodium hydrogen carbonate (45 mg), dilution with water, partition between water and dichloromethane, and evaporation gave *compound* (XXIIa) (279 mg, 89%), purified by chromatography; m.p. (from 0.1% pyridine–MeOH) 150—155°, $[\alpha]_D^{21}$ −18° (*c* 0.95), $\nu_{max.}$ 3 500m, 1 700s, 1 660w, and 1 630w cm^{-1}, $\lambda_{max.}$ 239 nm (ε 20 700) (Found: C, 76.8; H, 9.45. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.35%).

11β-*Hydroxypregna*-1,4,6-*triene*-3,20-*dione* (XXIIIa).—(*A*) DDQ (450 mg) was added to a stirred solution of the foregoing enol ether (XXIIa) [from (XXIa) (300 mg)] in dioxan (100 ml). After 15 min, work-up and repeated chromatography gave the *trienedione* (XXIIIa) (167 mg, 56%), m.p. (from CH_2Cl–EOAc) 208—209°, $[\alpha]_D^{23}$ +173° (*c* 0.82), $\nu_{max.}$ 3 350m, 1 705s, 1 645s, and 1 595m cm^{-1}, $\lambda_{max.}$ 223 (ε 12 500), 257 (9 800), and 300 nm (12 800) (Found: C, 77.25; H, 7.95. $C_{21}H_{26}O_3$ requires C, 77.25; H, 8.05%).

(*B*) DDQ (289 mg) and 11β-hydroxyprogesterone 3,20-bisethylene acetal (XXIV) (250 mg) in benzene (20 ml) were heated to reflux (40 min). Work-up gave the trienedione (XXIIIa) (117 mg, 60%).

11β-*Nitroso-oxypregna*-1,4,6-*triene*-3,20-dione (XXIIIc)—*Compound* (XXIIIc), prepared from the 11β-ol (XXIIIa) (750 mg) and nitrosyl chloride, had m.p. (from EtOAc–hexane) 183—185°, $[\alpha]_D^{21}$ +287° (*c* 0.35), $\nu_{max.}$ 1 705s, 1 660s, 1 620m, 890s, 795s, 770s, and 740s cm^{-1}, $\lambda_{max.}$ 222 (ε 13 800), 250 (11 500), and 299 nm (12 800) (Found: C, 71.0; H, 7.15; N, 3.75. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%).

Irradiation of the Nitrite (XXIIIc).—Irradiation of the nitrite (XXIIIc) in acetonitrile and p.l.c. gave 2′,11β-*epoxy*-2′,4′α-*dihydro*-5′-*methyl*-18-*norandrosta*-1,4,6-*trieno*[13,17-c]*pyrrol*-3-*one* N-*oxide* (XIIIb) (60%), m.p. (from CH_2Cl_2) 258—263° (decomp.; sealed tube), $[\alpha]_D^{21}$ +183° (*c* 0,81), $\nu_{max.}$ 1 650s, 1 600w, 1 580m, and 1 230m cm^{-1}, $\lambda_{max.}$ 229 (ε 18 300), 247sh (16 200), and 299 nm (13 000), τ 2.90 (1 H, d, *J* 10 Hz, 1-H), 3.77 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.90, and 4.05 (3 H, 4, 6-, and 7-H), 4.65br (1 H, s, 2′-H), 4.95 (1 H, d, *J* 6 Hz, 11α-H), 7.97br (3 H, s, 5′-Me), and 8.65 (3 H, s, 19-H_3), *m/e* 337 (M^+) (Found: C, 74.75; H, 6.75; N, 3.95. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.85; N, 4.15%).

1′-*Acetyl*-5′-*acetoxymethylene*-2′,11β-*epoxy*-4′αH-18-*norandrosta*-1,4,6-*trieno*[13,17-c]*pyrrolidin*-3-*one* (XVIb).—*Compound* (XVIb) (62 mg, 50%) was prepared from the nitrone (XIIIb) (100 mg) *via* the hydroxymonoacetate (XIVb); m.p. (from EtOAc) 233—237°, $[\alpha]_D^{22}$ +208° (*c* 1.26), $\nu_{max.}$ 1 740s, 1 680m, 1 650br, s, 1 600w, and 1 220s, cm^{-1}, $\lambda_{max.}$ 225 (ε 18 800), 250—251 (20 600), and 299—300 nm (14000) *m/e* 421 (M^+) (Found: C, 71.1; H, 6.55; N, 3.1. $C_{25}H_{27}NO_5$ requires C, 71.25; H, 6.45; N, 3.3%).

1′-*Acetyl*-5′-*acetoxymethyl*-2′,11β-*epoxy*-5′-*hydroxy*-4′βH-18-*norandrosta*-1,4,6-*trieno*[13-17,c]*pyrrolidin*-3-*one* (XIXb).—*Compound* (XIXb), from the hydrolysis (95%; aqueous acetic acid; 30 h, 20 °C) of the *N-acetyl* acetate (XVIb) followed by repeated chromatography, was obtained as an amorphous solid, $[\alpha]_D^{22}$ +160° (*c* 0.55), $\nu_{max.}$ 35 00w, 3 400w, 1 735m, 1 680m, 1 655s, and 1 235m cm^{-1}, $\lambda_{max.}$ 227 (ε 16 200), 250 (17 400), and 300 nm (12 800), *m/e* 439 (M^+) (Found: C, 66.7; H, 6.75; N, 2.95. $C_{25}H_{29}NO_6$, 0.5 H_2O requires C, 66.95; H, 6.75; N, 3.1%).

Treatment of the title compound (XIXb) with dinitrogen tetraoxide resulted in considerable attack at the triene system in addition to *N*-nitrosation. Heating at 50 °C gave an intractable mixture.

21-*Acetoxy*-11β-*hydroxy*-3-*methoxypregna*-3,5-*dien*-20-*one* (XXIIb).—Corticosterone 21-acetate (XXIb) (10 g), 2,2-dimethoxypropane (100 ml), DMF (100 ml), pyridinium chloride (0.5 g), and methanol (5 ml) were heated to reflux under nitrogen for 16 h. Sodium hydrogen carbonate (2 g) and water (3 000 ml) were added and the crude solid product was partitioned between dichloromethane and water. Evaporation and trituration (methanol and a trace of pyridine) gave *compound* (XXIIb) (8.6 g, 83%), m.p. (from MeOH with a trace of pyridine) 189—191°, $[\alpha]_D^{26}$ −3° (*c* 0.85), $\nu_{max.}$ 3 650m, 1 745s, 1 720s, 1 655m, 1 635m, 1 245s, and 1235s cm^{-1}, $\lambda_{max.}$ 239 nm (ε 21 100) (Found: C, 71.55; H, 8.45. $C_{24}H_{34}O_5$ requires C, 71.6; H, 8.5%).

1,2,6,7-*Tetradehydrocorticosterone* 21-*Acetate* (XXIIIb).—*oxidation* of the enol ether (XXIIb) (2.0 g) with DDQ and chromatography on Fluorisil gave *compound* (XXIIIb) (1.16 g, 61%), m.p. (from EtOAc) 170—171°, $[\alpha]_D^{19}$ +188° (*c* 0.86), $\nu_{max.}$ 3 500m, 1 745s, 1 720s, 1 645s, 1 600m, and 1 230s cm^{-1}, $\lambda_{max.}$ 223 (ε 12 400), 253 (10 100), and 300 nm (12 500) (Found: C, 72.05; H, 7.2. $C_{23}H_{28}O_5$ requires C, 71.85; H, 7.35%).

Preparation and Irradiation of 1,2,6,7-*Tetradehydrocorticosterone* 21-*Acetate* 11-*Nitrite* (XXIIId).—The title nitrite (3.97 g, 95%), obtained from the 11β-alcohol (XXIIIb) and nitrosyl chloride, had m.p. (from EtOAc) 172—175°

(decomp.), $[\alpha]_D^{19}$ +256° (*c* 0.92), $\nu_{max.}$ 1 750s, 1 710s, 1 655s, 1 600m, and 1 235s cm^{-1}, $\lambda_{max.}$ 224 (ε 14,500), 249 (12 200), and 298 nm (13 600). The nitrite (XXIIId) (3.8 g) and triethylamine (1 ml) in THF (160 ml) under argon were irradiated for 45 min. Evaporation and chromatography on Fluorisil (eluant CH_2Cl_2–MeOH, 1 : 0—17 : 3) gave (a) 21-*acetoxypregna*-1,4,6-*triene*-3,11,20-*trione* (XXV) (750 mg, 21%), m.p. (from EtOAc) 156—157°, $[\alpha]_D^{32}$ +322° (*c* 1.08), $\nu_{max.}$ 1 765m, 1 735s, 1 705s, 1 655s, 1 605m, 1 245s, 1 230s, and 1 210s cm^{-1}, $\lambda_{max.}$ 225 (ε 12 000), 254—255 (11 000), and 298 nm (13 400) (Found: C, 72.2; H, 6.8. $C_{23}H_{26}O_5$ requires C, 72.25; H, 6.85%); (b) 1,2,6,7-*tetradehydrocorticosterone* 21-*acetate* (XXIIIb); and (c) the 18-*hydroxyimino*-*derivative* (XXVI) of the latter (1.41 g, 38%), m.p. (from CH_2Cl_2–EtOAc) 157—159° (sealed tube), $[\alpha]_D^{23}$ +177° (*c*, 1.08 in CH_2Cl_2), $\nu_{max.}$ 3 300m, 1 740s, 1 650s, 1 600s, and 1 220s cm^{-1}, $\lambda_{max.}$ 245 (ε 20 000) and 300 nm (14 000), τ 2.37br (1 H, s, 18-H), 2.69 (1 H, d, *J* 10 Hz, 1-H), 3.60—4.05 (4 H, m, 2-, 4-, 6-, and 7-H), 5.50 (1 H, m, 11 α-H), 5.70 (2 H, s, 21-H_2), 7.90 (3 H, s, OAc), 8.55 (3 H, s, 19-H_3), *m/e* 413 (M^+) (Found: C, 66.8; H, 6.45; N, 3.3. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.5; N, 3.4%). When kept in chloroform for 90 min the oxime (XXVI) gave 5′-*acetoxymethyl*-2′,11β-*epoxy*-2′,4′α-*dihydro*-18-*norandrosta*-1,4,6-*trieno*[13,17-c] *pyrrol*-3-*one* N-*oxide* (XXVII), m.p. (from $CHCl_3$–EtOAc) 226—228° (decomp.; sealed tube), $[\alpha]_D^{22}$ +142° (*c* 0.98), $\nu_{max.}$ 1 745s, 1 655s, 1605m, 1 585m, and 1 230s cm^{-1}, $\lambda_{max.}$ 245—246 (ε 19 400) and 299 nm (13 400), τ 2.82 (1 H, d, *J* 10 Hz, 1-H), 3.60—4.05 (4 H, m, 2-, 4-, 6-, and 7-H), 4.60br (1 H, s, 2′-H), 4.89 (1 H, d, *J* 6 Hz, 11α-H), 5.00br (2 H, s, 5′-CH_2), 7.90 (3 H, s, OAc), and 8.65 (3 H, s, 19-H_3), *m/e* 395 (M^+) (Found: C, 69.75; H, 6.3; N, 3.45. $C_{23}H_{25}NO_5$ requires C, 69.85; H, 6.35; N, 3.55%).

1,2,6,7-*Tetradehydroaldosterone* 21-*Acetate* (XXVIIIa).—Sodium nitrite (350 mg total; 100 mg after 15 min) was added to the oxime (XXVI) (250 mg) in acetic acid (10 ml)–water (5 ml) and the solution was stirred for 25 min at 20 °C. Neutralisation ($NaHCO_3$), dilution with water, extraction with ethyl acetate, and evaporation gave *compound* (XXVIIIa) (142 mg, 59%), m.p. (from CH_2Cl_2–EtOAc) 207.5—209°, $[\alpha]_D^{22}$ +71° (*c* 0.97), $\nu_{max.}$ 3 600m, 1735s, 1 645s, 1 600m, and 1 225s cm^{-1}, $\lambda_{max.}$ 224 (ε 11 800), 254—255 (10 000), and 301 nm (12 500), *m/e* 398 (M^+), τ [open form (XXVIIIa)] 2.80 (1 H, d, *J* 10 Hz 1-H), 3.55—4.00 (4 H, m, 2-, 4-, 6-, and 7-H), 4.60 (1 H, s, 18-H), 4.95 (1 H, d, *J* 6 Hz, 11α-H), 5.20 (2 H, s, 21-H_2), 7.84 (3 H, s, OAc), and 8.70 (3 H, s, 19-H_3), τ [closed form (XXVIIIb)] 2.80 (1 H, d, *J* 10 Hz, 1-H), 3.55—4.00 (4 H, m, 2-, 4-, 6-, and 7-H), 4.50 (1 H, s, 18-H), 4.95 (1 H, d, *J* 6 Hz, 11α-H), 5.88 (2 H, ABq, *J* 11 Hz, 21-H), 7.86 (3 H, s, OAc), and 8.67 (3 H, s, 19-H_3) (Found: C, 69.1; H, 6.45. $C_{23}H_{26}O_6$ requires C, 69.35; H, 6.6%).

The acetate (XXVIIIa) was alternatively prepared from the nitrone (XXVII). Jones reagent (1 ml) was added to the nitrone (XXVII) (100 mg) in acetone (5 ml)–water (5 ml). After 7 min at 20 °C, water and sodium hydrogen carbonate were added, the mixture was extracted with ethyl acetate, and the extract was washed with water. Evaporation and p.l.c. gave compound (XXVIIIa) (56 mg, 56%).

6,7-*Didehydroaldosterone* 21-*Acetate* (XXVIIIc).—The 21-*acetate* (XXVIIIa) (100 mg) and tristriphenylphosphinerhodium(I) chloride (350 mg) in benzene (15 ml)–ethanol (15 ml) were stirred under hydrogen at 1 atm for 2 h. Evaporation, chromatography on Fluorisil–alumina, and p.l.c. gave 6,7-didehydroaldosterone 21-acetate (XXVIIIc) (67 mg, 67%), m.p. (from CH_2Cl_2–EtOAc) 203—205° (lit.,[23] 204—207°), $[\alpha]_D^{29}$ +90° (*c* 0.74) (lit.,[23] +86°), $\nu_{max.}$ 3 600s, 1 745s, 1 660s, 1 620m, 1 585m, and 1 225s cm^{-1} $\lambda_{max.}$ 284 nm (ε 23 600), *m/e* 400 (M^+) (Found: C, 68.75; H, 7.0. Calc. for $C_{23}H_{28}O_6$: C, 69.0; H, 7.1%).

Aldosterone 21-*Acetate* (XXVIIIe).—Hydrogenation of the 21-acetate (XXVIIIa) (50 mg) over tristriphenylphosphinerhodium(I) chloride (200 mg) for 20 h gave compound (XXVIIIe) (28 mg, 56%) m.p. (from CH_2Cl_2–EtOAc) 196.5—198° (lit.,[1] 194—201°), $[\alpha]_D^{28}$ +126° (*c* 0.5) (lit.,[1] +127°), $\nu_{max.}$ 3 600m, 1 735s, 1 665s, 1 620m, and 1 225s cm^{-1} $\lambda_{max.}$ 239—240 nm (ε 15,100) (Found: C, 68.6; H, 7.4. Calc. for $C_{23}H_{30}O_6$: C, 68.6; H, 7.5%).

9α-*Bromo*-2′,11β-*epoxy*-2′,4′α-*dihydro*-5′-*methyl*-18-*norandrosta*-1,4-*dieno*[13,17-c]*pyrrol*-3-*one* N-*Oxide* (XIIIc).—9α-*Bromo*-11β-*nitroso*-*oxypregna*-1,4-*diene*-3,20-*dione* (Xf), prepared from the 11β-alcohol (Xa) (3.85 g), had m.p. (from Me_2CO–hexane with a trace of pyridine) 165—168° (decomp.) $[\alpha]_D^{22}$ +244° (*c* 0.76) (Found: C, 58.05; H, 6.25. $C_{21}H_{26}BrNO_4$ requires C, 57.8; H, 6.0%). Irradiation of the nitrite (Xf) (total product) and pyridine (0.1 ml) in benzene (450 ml) for 45 min, partition between water and benzene, and extraction of the aqueous phase with dichloromethane gave, on evaporation, the *bromo-nitrone* (XIIIc) (1.09 g.) as needles, decomp. >225° (from CH_2Cl_2–EtOAc), $[\alpha]_D^{23}$ +63° (*c* 0.58), $\nu_{max.}$ 1 675s, 1 640m, 1 615w, and 1 595m cm^{-1} (Found: C, 60.4; H, 6.0. $C_{21}H_{24}BrNO_3$ requires C, 60.3; H, 5.8%).

Oxidation of the Bromonitrone (XIIIc).—(*A*) Oxidation with Jones reagent (0.50 ml) of the bromo-nitrone (XIIIc) (74 mg) in acetone (50 ml)–dichloromethane (25 ml) and chromatography on neutral grade V alumina gave (eluant benzene) the *bromo-lactone* (XXXIe) (42 mg) m.p. (from CH_2Cl_2–EtOAc) 240—242°, $[\alpha]_D^{22}$ +34° (*c* 1.17), $\nu_{max.}$ 1 790s, 1 715s, 1 675s, 1 640s, and 1 605m cm^{-1} (Found: C, 60.2; H, 5.65. $C_{21}H_{23}BrO_4$ requires C, 60.15; H, 5.55%), and (eluant CH_2Cl_2) the *bromo-lactone oxime* (XXXIf) (22 mg), decomp. >200° (from CH_2Cl_2–EtOH), $[\alpha]_D^{23}$ +32° (*c* 0.53), $\nu_{max.}$ 3 400, 1 715, 1 670, 1 630, and 1 610 cm^{-1} (Found: C, 58.1; H, 5.55. $C_{21}H_{24}BrNO_4$ requires C, 58.05; H, 5.55%).

(B) Jones reagent (0.25 ml) and the bromo-nitrone (XIIIc) (38 mg) in acetone (10 ml)–water (10 ml) (7 min at room temperature) gave 9α-*bromo*-1,2-*didehydro*-21-*deoxyaldosterone* (XXXIg), m.p. (from CH_2Cl_2–EtOAc) 195—198° (decomp.), $[\alpha]_D^{22}$ +81° (*c* 0.79), $\nu_{max.}$ 3 360, 1 710, 1 665, and 1 610 cm^{-1} (Found: C, 60.05; H, 6.05. $C_{21}H_{25}BrO_4$ requires C, 59.85; H, 6.0%). Jones reagent and (XXXIg) gave the lactone (XXXIe), identical (mixed m.p., t.l.c., and i.r.) with that previously prepared.

Reduction of the Bromo-lactone (XXXIe).—The bromo-lactone (XXXIe) (53 mg) was stirred with acetic acid (5 ml) and zinc–copper couple at room temperature for 35 min. Work-up gave the alkali-soluble 20-hydroxy-3-oxopregna-1,4,9(11)-*trien*-18,20-*olactone* (XXXII), m.p. (from CH_2Cl_2–EtOAc) 203—206°, $[\alpha]_D^{30}$ −35°, $\nu_{max.}$ 3 460, 1 770, 1 670, 1 645, and 1 605 cm^{-1} (Found: C, 74.15; H, 7.25. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%).

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