Enolate Anions as Protecting Groups for Ketones during Reduction by Hydride †

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The selective formation of enolate anions provides protection for carbonyl groups against reduction by lithium aluminium hydride. Any carbonyl group not so protected is reduced in a synthetically useful manner.

THE selective reduction of a carbonyl group is a process often needed in steroid chemistry.[1] In general, any carbonyl group that should not be reduced is protected by formation of a derivative, especially the ethylene acetal.[1] Of course, the use of protecting groups adds two steps (protection and deprotection) to the overall reduction process.

Our particular interest in corticosteroids led us to consider ways of preventing reduction of a steroid 1,4-dien-3-one function, which is not readily converted into an acetal. Among the few reported selective reductions in the presence of this function, are that of an 11-ketone with lithium hydridotri-t-butylaluminate[2] and protection of the dienone system by semicarbazone formation followed by reduction at C-11.[3]

Previous experience with the enolate of the 1,4-dien-3-one system[4] prompted us to consider its use as a protecting device during reduction by hydride. Regeneration of the 1,4-dien-3-one would be expected on addition of water. Few examples of the use of enolates as protecting groups are known. Reduction of 2-ethoxycarbonylcyclopentanone with aluminium hydride gives 2-(hydroxymethyl)cyclopentanone,[5] presumably with intermediate formation of the 2-en-1-olate, which is inert to the reagent. An enol ester would be expected to react with lithium aluminium hydride to give the enolate, and this would then resist further reaction. An example of this process is known.[6] There are also some examples[7] where reduction of an enol ester with lithium aluminium hydride leads to the alcohol and not to the ketone.

(1) *Protection of the* 1,4-*dien*-3-*one function by enolate formation.* Bismethylenedioxyprednisone (1) is readily converted into its 3-enolate (2)[4] in tetrahydrofuran. Reduction with lithium aluminium hydride followed by work-up would be expected to give bismethylenedioxyprednisolone (3). In practice, the hydroxy-ketone (3) was formed, but together with other materials more and less polar than it. The less polar material was assumed to be the Δ^5-isomer (4) arising by kinetic protonation at C-4, a process which is well documented.[8] However, formation of the 5-ene (4) was not particularly troublesome since it readily isomerised to the 4-ene (3) on treatment with methanol–dichloromethane–hydrochloric acid. The more polar materials were less easily avoided. These appeared to be the result of reduction of compounds (3) and (4) on work-up, *i.e.* on protonating the enolate. Clearly, the necessary excess of hydride was causing over-reduction. Despite careful addition to a large volume of water these products were still formed.

† Preliminary communication, D. H. R. Barton, R. H. Hesse, M. M. Pechet, and C. Wilshire, *J.C.S. Chem. Comm.*, 1972, 1017.

[1] 'Steroid Reactions,' ed. C. Djerassi, Holden–Day, San Francisco, 1963; J. Fried and J. A. Edwards, 'Organic Reactions in Steroid Chemistry,' vols. 1 and 2, Van Nostrand–Reinhold Co. New York, 1972.

[2] J. Zderic and J. Iriarte, *J. Org. Chem.*, 1962, **27**, 1756.

[3] D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.

[4] D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 1497.

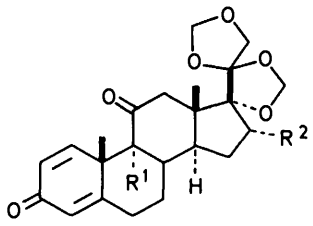
[5] N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, 1968, **90**, 2927.

[6] P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, 1960, **43**, 617.

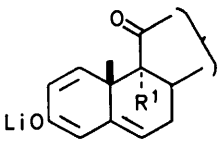
[7] W. G. Dauben and J. F. Eastham, *J. Amer. Chem. Soc.*, 1953, **75**, 1718; M. M. Rogic, *Tetrahedron*, 1965, **21**, 2823.

[8] S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, 1964, **86**, 1997.

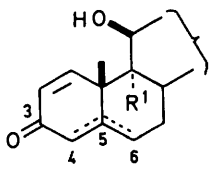
Thus it appeared desirable to destroy the excess of hydride before quenching the enolate. Ethyl acetate and carbon dioxide both reacted with enolate and hydride and were therefore unsatisfactory. However,



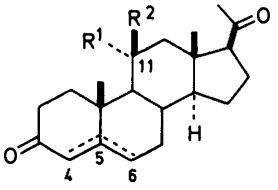
(1) $R^1 = R^2 = H$
(5) $R^1 = F, R^2 = Me$



(2) $R^1 = R^2 = H$
(6) $R^1 = F, R^2 = Me$

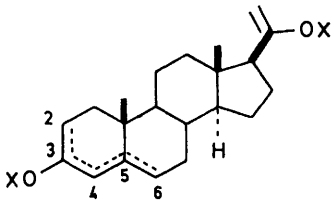


(3) $R^1 = R^2 = H, \Delta^4$
(4) $R^1 = R^2 = H, \Delta^5$
(7) $R^1 = F, R^2 = Me, \Delta^4$
(8) $R^1 = F, R^2 = Me, \Delta^5$



(9) $R^1 R^2 = O, \Delta^4$
(10) $R^1 = H, R^2 = OH, \Delta^4$
(14) $R^1 = H, R^2 = OH, \Delta^5$

$LiN(SiMe_3)_2$
(11)



(12) $\Delta^{2,4}$
(13) $\Delta^{3,5}$

anhydrous ammonia rapidly destroyed the excess of hydride but, as expected, was too weak an acid to protonate the enolate. With the modification of passing gaseous ammonia after reduction the over-reduction processes were prevented and work-up gave a 76% yield of hydroxy-ketone (3).

In a similar manner the 11-oxo-analogue (5) of dexamethasone (5) was converted into the 3-enolate (6) and thence into a mixture of the ketones (7) and (8). Isomerisation as before gave the ketone (7) in 60% yield.

(2) *Bis-enolate formation: protection of two carbonyl groups of a trione.* A logical extension of the above work is bis-enolate formation from a trione followed by selective reduction of the remaining oxo-group. Fortunately, a convenient case was to hand, namely the conversion of commercial 11-oxoprogesterone (9) into 11β-hydroxyprogesterone (10), an important intermediate in a synthesis of aldosterone.[9] Alternative routes to the 11β-ol (10) from the 11-ketone (9) or the 11α-ol involved several steps, and so there was considerable interest in a 'one-pot' preparation.

Bis-enolate formation from (9) was attempted by using a large excess of lithium bis(trimethylsilyl)amide (11) followed by trapping with an excess of acetic anhydride. This gave a mixture of bis-enol acetates which, from ^1H n.m.r. and u.v. data, were assigned the structures (12) and (13) (X = Ac). The absence of a C-21 methyl resonance showed that the 'kinetic' 20(21)-enolate had been formed and trapped.

With the above information in hand, reduction of the 11-ketone was attempted. Formation of the mixture [(12) + (13) (X = Li)] followed by reduction and work-up gave a modest yield of 11β-ol (10) together with the Δ^5-isomer (14), which readily isomerised to (10) during chromatography. At this point a preferred enolising base was sought. Trityl-lithium gave a distinct pink colouration at the enolisation end point in the above cases and on work-up triphenylmethane was easily removed. In contrast the silylamide did not show an obvious end point, so an excess was used. Furthermore, formation of a gelatinous product on work-up made isolation of the product tedious. Thus trityl-lithium was the reagent of choice. Even when this base was used, however, isolated yields of (10) were only 30—40%. A brief investigation showed that the enolate mixture [(12) + (13) (X = Li)] rapidly decomposed at room temperature. G.l.c. analysis of the trione (9) recovered on quenching the enolates showed that only 70% could be recovered directly after enolisation. After 3 h this figure was only 50%. Clearly a rapid low-temperature reaction was required. Since bis-enolate formation did not occur rapidly below room temperature, the bis-enolate was formed at room temperature and rapidly cooled to −78 °C. Reduction at this temperature followed by normal work-up enabled the 11β-ol (10) to be isolated in 50% yield.

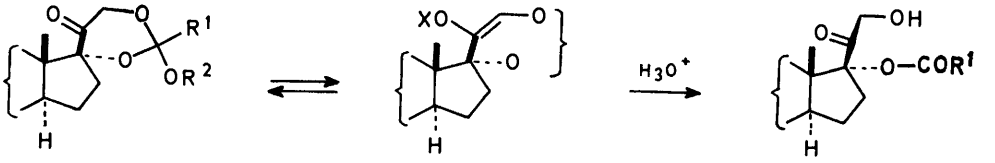
A further example of bis-enolate formation and use arose from our interest in finding alternatives to the use of two methylenedioxy-groups for protecting the 17,21-dihydroxy-20-one side chain of the corticosteroids. 17,21-Orthoesters of these compounds were known,[10] and it seemed possible that enolate formation might be achieved (Scheme 1). Furthermore, neutral aqueous work-up would regenerate the orthoester whereas acidic work-up would lead to the medicinally important 17-ester. An appropriate model was the 11-oxo-analogue (15) of dexamethasone 17,21-(n-butyl orthopropionate), which was readily prepared from the diol (16) and tri-n-butyl orthopropionate. We considered that 3,20-bis-enolate formation followed by reduction at C-11 might be feasible.

In fact the trione (15) gave a pink colouration after

[9] D. H. R. Barton, N. K. Basu, M. J. Day, R. H. Hesse, M. M. Pechet, and A. N. Starrett, *J.C.S. Perkin I*, 1975, 2243.

[10] R. Gardi, R. Vitalli, and A. Ercoli, *Tetrahedron Letters*, 1961, 448.

addition of 2 equiv. of trityl-lithium, presumably forming the bis-enolate (17). Normal reduction and work-up gave two products, indicated by n.m.r. to be the Δ^4- and Δ^5-compounds (18) and (19). Isomerisation of (19) giving (18) could not be achieved without also cleaving the orthoester system, so the orthoester was itself first cleaved under controlled conditions to give a mixture of 17-propionates, (20) and (21). Conjugation was then effected by using methanol–dichloromethane–hydrochloric acid as before, and the yield of isolated dexamethasone 17-propionate (20) was 41%.

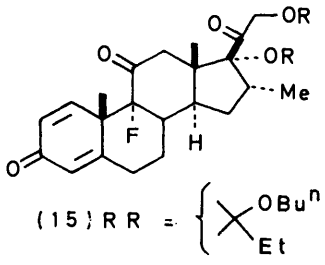


SCHEME 1

(3) *Selective formation of a monoenolate.* Selective mono-enolate formation from a polycarbonyl compound is, in principle, possible under appropriately controlled conditions (kinetic or thermodynamic). Our final example illustrates selective enolate formation by abstraction of the most acidic proton, followed by reduction of the remaining carbonyl groups. Reduction of the dioxo-ester (22) is utilized in the synthesis of cortisol; the published procedure [11] involves protection of the 4-en-3-one system as the enamine, reduction, and deprotection.

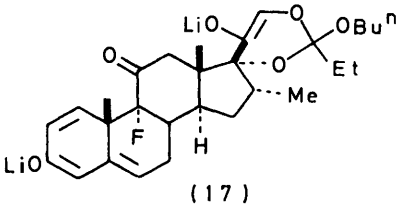
Using our procedure we anticipated formation of the 3-enolate (23) selectively (ketones are normally *ca.* 3 pK_a units more acidic than esters) [12] followed by reduction at the remaining sites. Addition of 1 equiv. of trityl-lithium at −78 °C followed by reduction and work-up gave a mixture of two diols; by analogy with previous results these were taken to be (24) and the Δ^5-isomer (25). Isomerisation of (25) to (24) occurred readily in methanolic potassium acetate, and the diol (24) was isolated (43% yield) and identified as its 21-acetate (26).

As shown in this paper, metal enolate systems resist reduction by hydride and represent convenient protecting groups for carbonyl groups during such reactions. In general, the yields are similar to those obtained by the multi-step protection–deprotonation procedure.

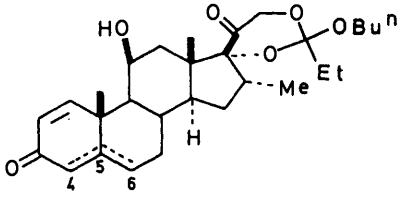


(15) R R = $\left\{\begin{array}{l} \\ \end{array}\right.$ OBu^n, Et

(16) R = H

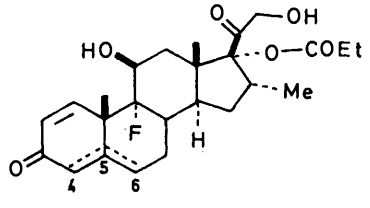


(17)



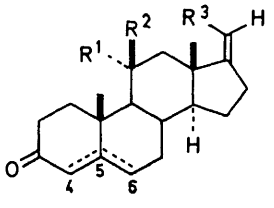
(18) Δ^4

(19) Δ^5



(20) Δ^4

(21) Δ^5

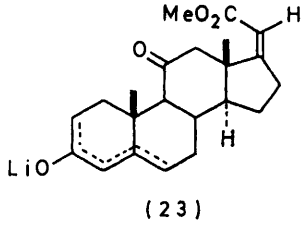


(22) R^1 R^2 = O, R^3 = CO_2Me, Δ^4

(24) R^1 = H, R^2 = OH, R^3 = CH_2·OH, Δ^4

(25) R^1 = H, R^2 = OH, R^3 = CH_2·OH, Δ^5

(26) R^1 = H, R^2 = OH, R^3 = CH_2·OAc, Δ^4



(23)

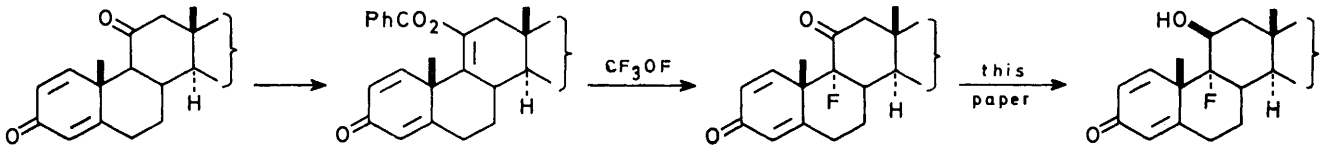
These reductions have the advantage of being ' one-pot ' processes which can be performed in 1—2 h. Furthermore, the 1,3,5-trien-3-olate system is an excellent protecting group for a 1,4-dien-3-one, which is difficult to protect by other means. The 20,21-enolate system of the corticosteroid 17,21-orthopropionate is also a good protecting group, with the advantage of easy removal.

[11] F. W. Heyl and M. H. Herr, *J. Amer. Chem. Soc.*, 1953, **75**, 1918.

[12] H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, New York, 1972, p. 494 and references therein.

Reduction of the 11-oxo-group of 9α-fluoro-corticosteroids now formally completes a process [13] (Scheme 2) in which the fluorine is introduced electrophilically to give the medicinally important 9α-fluoro-11β-ol function. This function has been previously introduced by way of cleavage of 9β,11β-epoxides with hydrogen fluoride.

In conclusion, it seems likely that metal enolate formation should be convenient for protecting carbonyl groups during other transformations, such as Grignard reactions, Wittig reactions, *etc.*, possibilities which have yet to be explored.



SCHEME 2

EXPERIMENTAL

General Methods for Preparation of Enolates.—Enolates were prepared by using either triphenylmethyl-lithium, or lithium or sodium bis(trimethylsilyl)amide in redistilled, deoxygenated tetrahydrofuran under an atmosphere of argon.

Method (1); *normal addition, base to ketone.* The substrate was stirred in deoxygenated tetrahydrofuran under argon at the desired temperature. The enolising base was added dropwise *via* a syringe to the substrate until the desired amount had been introduced or the end point was reached. The enolate solution was then ready for subsequent reaction.

Method (2); *inverse addition, ketone to base.* The required amount of base in solution was stirred under argon at the desired temperature. The substrate was then added in solution, dropwise by syringe.

Reduction of Bismethylenedioxyprednisone (1) *to Bismethylenedioxyprednisolone* (3).—Bismethylenedioxyprednisone (1) [prepared by the literature method; [14] m.p. 215 °C (lit.,[14] 214—217 °C)] (1.0 g) in tetrahydrofuran (30 ml) under argon was treated with triphenylmethyl-lithium until a pink colouration was observed. Method (1) was used at room temperature. The solution of the 3-enolate (2) was cooled to −78 °C and a solution of lithium aluminium hydride in tetrahydrofuran (1.0 ml, 5 mmol) was added. The mixture was allowed to warm to room temperature and ammonia was bubbled through until the vigorous reaction had subsided. Hydrochloric acid (0.5N; 20 ml) was added and the mixture was extracted with methylene chloride (2 × 50 ml). The extracts were washed to neutrality with water, dried ($MgSO_4$), and evaporated to dryness. Silica gel t.l.c. (3% acetone in methylene chloride) showed the presence of triphenylmethane and two polar products, the more polar of which corresponded in R_F to bismethylenedioxyprednisolone (3). Trituration of the crude residue with hot hexane left a colourless solid (820 mg). I.r. absorptions at 1 680 (enone), and 1 660 (dienone) cm^{-1} were consistent with the latter solid being a mixture of the expected isomeric reduction products which differ only in the position of the double bond. Treatment of the mixture with chloroform–ethanol–hydrogen chloride resulted in rapid isomerisation of deconjugated to conjugated product. The solution was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness. Recrystallisation from ethyl acetate gave bismethylenedioxyprednisolone (3) (0.75 g), m.p. 267—271 °C (lit.,[14] 270—274 °C). A mixed m.p. with genuine (3) was not depressed (270 °C).

Reduction of the 11-Oxo-analogue (5) *of Bismethylenedioxydexamethasone to Bismethylenedioxydexamethasone* (7).—The 11-ketone (5) [prepared by the literature method; [15] m.p. 312 °C (lit.,[15] 305—310 °C)] (0.5 g) was dissolved in redistilled tetrahydrofuran (20 ml) and the solution was deoxygenated. By using method (1) at room temperature, the solution was treated with triphenylmethyl-lithium until a pink colouration was attained. The solution was cooled to −78 °C and a solution of lithium aluminium hydride in tetrahydrofuran (0.5 ml, 2.5 mmol) was added. The mixture was warmed to room temperature and ammonia was passed through until the vigorous reaction had ceased. Hydrochloric acid (0.5N; 10 ml) was added and the mixture was extracted with methylene chloride (2 × 30 ml). The extracts were washed to neutrality with water, dried ($MgSO_4$), and evaporated to dryness. The residue was washed with hexane to remove triphenylmethane. The presence of bismethylenedioxydexamethasone (7) and its Δ^5-isomer (8) was confirmed by i.r. absorptions at 1 680 and 1 660 cm^{-1} and by t.l.c. (silica gel; 3% acetone in methylene chloride). Isomerisation of (8) to (7) was effected with chloroform–ethanol–hydrogen chloride. The acid was neutralised by washing with aqueous sodium hydrogen carbonate and the solvents were removed to give bismethylenedioxydexamethasone (7) (0.3 g). Recrystallisation from methanol–methylene chloride gave a sample, m.p. and mixed m.p. 305—312 °C (lit.,[14] 310—320 °C).

Reduction of 11-Oxoprogesterone (9) *to 11β-Hydroxyprogesterone* (10).—(a) *Preparation of the bis-enolate* [(12) + (13) (X = Li)] *and bis-enol acetate* [(12) + (13) (X = Ac)]. 11-Oxoprogesterone (9) (100 mg) was dissolved in redistilled tetrahydrofuran (5 ml) and the solution was deoxygenated and then flushed with argon. The steroid was treated with lithium bistrimethylsilylamide (1.2 g) in tetrahydrofuran [method (1)] at room temperature. The mixture was quenched with acetic anhydride (0.5 ml) in tetrahydrofuran (5 ml). The solution was poured into water and the product was extracted into methylene chloride (2 × 50 ml). The extracts were washed with water, dried ($MgSO_4$), and evaporated at reduced pressure to leave the product [(12) + (13) (X = Ac)] as a light yellow oil, δ 0.5 (3 H, s, 18-H_3), 1.1 (3 H, s, 19-H_3), 2.0 (6 H, s, OAc), and 4.6—5.6 (4 H, m, vinylic), $\nu_{max.}$ (film) 1 750vs (acetate C=O) and 1 700s cm^{-1} [C(11)=O], $\lambda_{max.}$ (EtOH) 274 nm (ε 6 000).

(b) *Preparation and properties of the bis-enolate* [(12) +

[13] D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804.

[14] R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarrett, *J. Org. Chem.*, 1961, **26**, 2421.

[15] L. J. Danks, Ph.D. Thesis, London University, 1968; the method is essentially that of ref. 13.

(13) (X = Li)] *with triphenylmethyl-lithium*. 11-Oxoprogesterone (9) (1.0 g) in dry deoxygenated tetrahydrofuran (20 ml) was treated with triphenylmethyl-lithium [method (1)] at room temperature until a pink colouration was attained. At this stage a voluminous precipitate was formed.

Half the above mixture was quenched with deoxygenated water. G.l.c. analysis (0.7% SE 30 column at 220 °C with cholestanone as internal standard) showed that 70 ± 5% of the initial 11-oxoprogesterone (9) had been recovered. The remaining half of the solution was left at room temperature for 3 h under argon. Quenching with water and subsequent g.l.c. analysis indicated that 50 ± 5% of the starting ketone (9) had been recovered.

(c) *Reduction of the bis-enolate* [(12) + (13) (X = Li)]. The bis-lithium enolate, prepared from 11-oxoprogesterone (9) (3.0 g) as above, was cooled to −78 °C. A solution of lithium aluminium hydride (10 ml, 50 mmol) was added and the mixture was warmed to room temperature. Ammonia was passed through the solution until the vigorous reaction had ceased and hydrochloric acid (0.5N; 50 ml) was added. The aqueous layer was extracted with methylene chloride (2 × 100 ml). The extracts were separated, washed to neutrality with water, dried ($MgSO_4$), and evaporated to dryness. The residue was triturated with hexane to leave an insoluble oil, which was chromatographed on alumina (grade 3). Elution with methylene chloride gave a solid (1.5 g) which on recrystallisation from ethyl acetate–hexane gave 11β-hydroxyprogesterone (10), m.p. 183—186 °C (lit.,[16] 186—188°), $[\alpha]_D$ +213° (in Me_2CO) {lit.,[16] [α] +212° (in Me_2CO)}, $\nu_{max.}$ 3 500s (OH), 1 700s, and 1 660vs cm^{-1} (C=O).

Reduction of Methyl 3,11-*Dioxopregna*-4,17(20)-*dien*-21-*oate* (22).—Methyl 3,11-dioxopregna-4,17(20)-dien-21-oate (22) (500 mg) in dry, deoxygenated tetrahydrofuran (10 ml) was treated with triphenylmethyl-lithium solution (1 equiv.) by method (1) at −78 °C. A solution of lithium aluminium hydride in tetrahydrofuran (1.5 ml, 7 mmol) was added and the solution was warmed to room temperature. Ammonia was bubbled through the solution to destroy the excess of lithium aluminium hydride and the mixture was quenched with water (20 ml). The aqueous layer was extracted with methylene chloride (2 × 50 ml) and the extracts were washed to neutrality with water, dried ($MgSO_4$), and evaporated to dryness. Trituration with hexane left a residue, t.l.c. of which showed two spots; the less polar did not quench the u.v. fluorescence of the plate. The residue was dissolved in methanol (4 ml) containing potassium acetate (500 mg) and left at room temperature overnight. T.l.c. showed that the less polar product had been completely converted into the more polar product. Acetylation with pyridine (0.5 ml) and acetic anhydride (0.5 ml) at 0 °C for 24 h followed by pouring onto ice–water gave a solid which was filtered off, washed with water, and dried. Recrystallisation from ethyl acetate–hexane gave crystals of 21-acetoxy-11β-hydroxypregna-4,*cis*-17(20)-dien-3-one (26), m.p. 188—190° (lit.,[11] 190—191°), $\nu_{max.}$ 3 400s (OH), 1 730s (acetate), and 1 660vs cm^{-1} (enone), $[\alpha]_D$ +122° (in CH_2Cl_2) (lit.,[11] $[\alpha]_D$ +128°).

On double the above scale, the acetate (26) was obtained in 43% yield (450 mg).

11-*Oxo-analogue* (15) *of Dexamethasone* 17,21-(*Butyl Orthopropionate*).—The dihydroxy-trione (16) [prepared by the literature method;[17] m.p. 249—251 °C (lit.,[17] 249—252 °C)] (100 mg) in benzene (25 ml) was refluxed with removal of water (Dean–Stark head). Tributyl orthopropionate (250 mg) and toluene-*p*-sulphonic acid monohydrate (1.5 mg) were added and the refluxing was continued for 1 h. Sodium hydrogen carbonate (10 mg) and pyridine (1 drop) were added and the solvent was evaporated off under reduced pressure. The residue was extracted with ether and the extracts were evaporated to dryness. The solid was triturated with methanol at −50 °C, filtered off, and dried under vacuum. Recrystallisation from methylene chloride–hexane gave 9-*fluoro*-17,21-*dihydroxy*-16α-*methylpregna*-1,4-*diene*-3,11,20-*trione* 17,21-(*butyl orthopropionate*) (15), m.p. 191—194°, δ 0.7 (3 H, s, 18-H_3), 1.6 (3 H, s, 19-H_3), 4.0 (2 H, q, *J* 18 Hz, 21-H_2), 6.1—6.3 (2 H, m, 2- and 4-H), 7.3 (1 H, d, *J* 10 Hz, 1-H), and 1.0—1.3 (9 H, m, remaining 3 × Me), $\nu_{max.}$ 1 720 and 1 660 cm^{-1} (C=O) $\lambda_{max.}$ (MeOH) 237 nm (ε 16 500), $[\alpha]_D$ +84° (*c* 1.6 in $CHCl_3$), *m/e* 502 (M^+) (Found: C, 69.25; H, 7.7; F, 3.75. $C_{29}H_{39}FO_6$ requires C, 69.3; H, 7.8; F, 3.85%).

Reduction of the Orthopropionate (15).—The orthopropionate (15) (251 mg) in dry, redistilled tetrahydrofuran (10 ml) was degassed under vacuum and flushed with argon. Triphenylmethyl-lithium was added at *ca.* −20 °C until a pink colouration was obtained. The solution was then chilled to −78 °C and a solution of lithium aluminium hydride in tetrahydrofuran (0.4 ml; 2 mmol) was added. The mixture was then warmed to room temperature and ammonia was passed until the vigorous reaction ceased. Water was added and the product extracted into methylene chloride; the solution was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography on alumina (grade 3) gave triphenylmethane on elution with 50% hexane in methylene chloride. The mixture of major products was eluted with 10% hexane in methylene chloride. The mixture of the two steroidal products (225 mg) was dissolved in acetic acid (5 ml) containing water (1 drop) and left at room temperature overnight. The solution was poured onto ice–water and the products extracted into methylene chloride; the extracts were washed with aqueous sodium hydrogen carbonate. [T.l.c. of the organic layer showed two new products, the more polar of which corresponded exactly with dexamethasone 17-propionate (20).] The solvent was evaporated off under reduced pressure and the residue was dissolved in methylene chloride (50 ml) and ethanol (50 ml). A saturated solution of hydrogen chloride in methylene chloride (5 ml) was added dropwise over 5 min. The mixture was then diluted with methylene chloride (50 ml) and combined organic phase was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The residue was recrystallised from ether–acetone–hexane to give dexamethasone 17-propionate (20) (185 mg, 41%). Further recrystallisation gave a sample, m.p. 215—222 °C (lit.,[18] 219—233°, mixed m.p. 216—222°), $[\alpha]_D$ −5.5° (*c* 1.27 in $CHCl_3$) {lit.,[18] $[\alpha]_D$ −6° (*c* 1.0 in $CHCl_3$)}.

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