## 930. *Use of* 20-*Oximes and* 20-*Semicarbazones in making Cortisol and* 4 : 5α-*Dihydrocortisol.*

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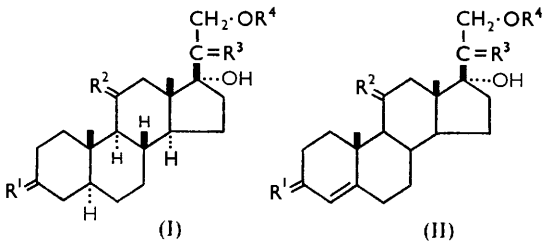
Experiments leading to satisfactory conversion of cortisone and its 21-acetate into cortisol, and of 4 : 5α-dihydrocortisone acetate into 4 : 5α-dihydrocortisol, have confirmed the utility of the 3 : 20-dioximes and 3 : 20-disemicarbazones as intermediates; in particular, the newly discovered reactivity of the 21-acetoxy-17α-hydroxy-20-ketones has been exploited. Treatment of the 20-hydroxyimino-steroids with nitrous acid yields nitrimino-compounds, which are probably mesoionic.

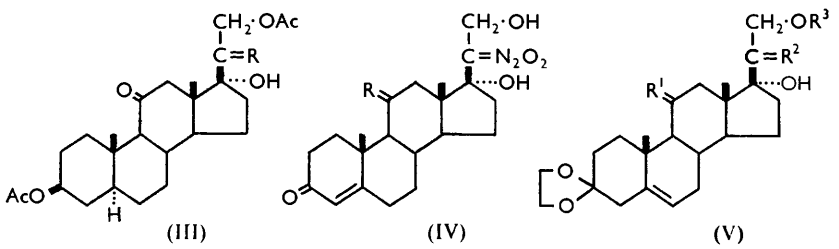
In continuing work on the synthesis of cortical hormones from 5α-steroids we have sought means of making cortisol and related 9α-halogeno-derivatives. Of various approaches open, the most attractive uses 4 : 5α-dihydrocortisone acetate (I; $R^1 = R^2 = R^3 = O$, $R^4 = Ac$) and its reduction product 4 : 5α-dihydrocortisol (I; $R^1 = R^3 = O$, $R^2 = H$, β-OH,

$R^4$ = H). A method for making the latter compound has already been described;[1] we discuss in this paper improved methods for this and related purposes.

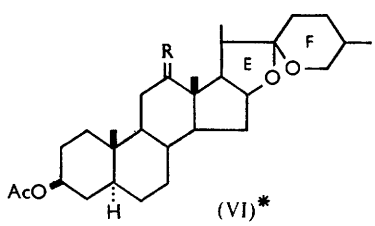


(I) (II)

4:5α-Dihydrocortisone: $R^1 = R^2 = R^3 = O$, $R^4 = H$ Cortisone: $R^1 = R^2 = R^3 = O$, $R^4 = H$
4:5α-Dihydrocortisol: $R^1 = R^3 = O$, $R^2 = H$, β-OH, $R = H$ Cortisol: $R^1 = R^3 = O$, $R^2 = H$, β-OH, $R^4 = H$
Substance D: $R^1 = H$, β-OH, $R^2 = R^3 = O$, $R^4 = H$; cf. (III) Substance S: $R^1 = R^3 = O$, $R^2 = H_2$, $R^4 = H$



(III) (IV) (V)



(VI)*

* Compounds with the same configuration in rings E and F as in tigogenin.
When R in (IV), and $R^1$ in (V) are H, OH, the 11β-hydroxy-group is implied.

Reduction of 3 : 11 : 20-trioxo-steroids to 11β-hydroxy-3 : 20-diones calls for selective protection at the 3- and the 20-position. Our experience confirms the difficulties in the acid-catalysed formation of ketals [1] and semicarbazones [2] of the 21-hydroxy-ketones, and earlier work proved the lack of reactivity of the 21-acetoxy-ketones.[3] However, one exception is noteworthy, for Reichstein's substance D 3 : 21-diacetate with semicarbazide base in hot acetic acid gave the derivative (III; R = N·NH·CO·$NH_2$), whereas pure 20-semicarbazones were not obtainable by this method from other 21-acetoxy-17α-hydroxy-20-ketones. We had recourse therefore to base-catalysed condensations with semicarbazide and hydroxylamine solutions,[4] utilising a tertiary base, preferably pyridine, as

[1] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[2] Wendler, Huang-Minlon, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 3818; cf. Wintersteiner and Pfiffner, *J. Biol. Chem.*, 1936, **116**, 291.
[3] Mancera, *J. Amer. Chem. Soc.*, 1950, **72**, 5752; Bernstein, Antonucci *et al.*, *J. Org. Chem.*, 1952, **17**, 1369; 1953, **18**, 70; Constantin, Haven, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 1716; Ralls and Riegel, *ibid.*, 1954, **76**, 4479; Sondheimer, Mancera, and Rosenkranz, *ibid.*, p. 5020; cf. Fleisher and Kendall, *J. Org. Chem.*, 1951, **16**, 556; von Euw, Neher, and Reichstein, *Helv. Chim. Acta*, 1955, **38**, 1423; ref. 2.
[4] Jones and Robinson, *J. Org. Chem.*, 1956, **21**, 586; Oliveto, Rausser, Weber, Shapiro, Gould, and Hershberg, *J. Amer. Chem. Soc.*, 1956, **78**, 1736; Joly, Nominé *et al.*, *Bull. Soc. chim. France*, 1956, 837, 1459.

solvent and catalyst.[5] Such conditions promote efficient condensations, even with the 21-acetoxy-ketones, and the semicarbazones so produced can be efficiently hydrolysed with solutions containing pyruvic acid [6] or, better, with mixtures of aqueous mineral acid and a solvent only slightly soluble in water.[7]

Comparison of the properties of the semicarbazones is made difficult by their insolubility and tendency to become solvated; further, attempted acetylation of the 20-semicarbazono-21-alcohols may be accompanied by removal of the basic group.[8] The infrared absorption due to the acetate group in the 21-acetoxy-semicarbazones is poorly resolved, but analyses and controlled hydrolysis of these compounds to 21-acetoxy-20-ketones prove that they are formed and hydrolysed with complete retention of the 21-acetate group. Present and already published evidence shows that the 11-keto-group does not form a semicarbazone,[9] and attempts at making a derivative of 3β-acetoxyergost-22-en-11-one failed. The 20-semicarbazones have $\lambda_{max.}$ 240 mμ, which coincides with the band due to a saturated 3-semicarbazone or may appear only as a shoulder in the absorption curve due to a $\Delta^4$-3 : 20-disemicarbazone.

This method of using basic media to form the 3 : 20-disemicarbazones, with subsequent reduction of the 11-oxo-group with a borohydride [2,4] and final acid-catalysed removal of the protecting groups, yielded efficient conversions of 4 : 5α-dihydrocortisone acetate and cortisone acetate into 4 : 5α-dihydrocortisol and cortisol respectively.

Tertiary bases such as pyridine might be expected to affect condensations with hydroxylamine, semicarbazide, or *O*-methylhydroxylamine differently, inasmuch as they would favour production of the ion $NH_2 \cdot O^-$; in practice such differences, if they exist, are of small account.[10] Evidence from paper chromatography indicates the possibility of oximating the 21-acetoxy-17α-hydroxy-20-oxo-system with acetic acid as catalyst, but only in conditions giving by-products.

Blatt [11] has shown that base-catalysed oximation favours the most strongly hydrogen-bonded forms of the derivatives of *o*-hydroxy-ketones in the aromatic series, and Schmidt-Thomé [12] has suggested that 20-hydroxyimino-steroids assume a configuration allowing the strongest hydrogen bonding with the substituent at the 21-position. In accordance with these observations our evidence for the existence of *syn*- and *anti*-forms comes only from the behaviour of the oxime *O*-methyl ethers and *O*-acetates (see Table 2), and the infrared spectra of the 20-hydroxyimino-21-acetates reveal marked intramolecular hydrogen bonding. We have not detected geometrical isomerism among the 3-oximes.[13] Analysis of the properties of the semicarbazones and oximes discloses inconsistent increments in molecular rotation, but good agreement in the $\Delta R_M$ values [14] for the oxime groups, except among the derivatives of cortisone. One of the last-named compounds, the dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$), is also exceptional in the ease with which its 11-keto-group is reduced (see below). In view of the marked influence [3] of the 21-acetate group on reactions involving the 20-ketones and on the stability of the 20-nitrimines (see below), its minor or erratic effect on the physical properties of the 20-oximes and 20-semicarbazones is surprising.

[5] Hopper, *J. Roy. Tech. Coll. Glasgow*, 1929, **2** (i), 52; Haller and La Forge, *J. Org. Chem.*, 1936, **1**, 38; Gulati and Ray, *Current Sci.*, 1936, **5**, 75; Jacquemain and Galliot, *Ann. Chim.*, 1946, **1**, 262; Greer and Pearson, *J. Amer. Chem. Soc.*, 1955, **77**, 6649; Campbell, McCallum, and Mackenzie, *J.*, 1957, 1922; cf. Cook, Hewett, and Lawrence, *J.*, 1936, 71.

[6] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.

[7] Kapp and Griffith, U.S.P. 2,530,334; Day, U.S.P. 2,781,367.

[8] Wolfrom, Georges, and Soltzberg, *J. Amer. Chem. Soc.*, 1934, **56**, 1794; Turner, *ibid.*, 1947, **69**, 875; Oliveto, Herzog, Weber, Tully, and Hershberg, *J. Org. Chem.*, 1956, **21**, 795.

[9] Cf. Elks and Phillipps, *J.*, 1956, 4326.

[10] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 688.

[11] Blatt, *J. Org. Chem.*, 1955, **20**, 591 and earlier papers.

[12] Schmidt-Thomé, *Chem. Ber.*, 1955, **88**, 895.

[13] Cf. Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744; 1940, **62**, 2459.

[14] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.

Reduction of cortisone dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = H$) with a borohydride is claimed in a patent [15] to give the dioxime of cortisol. However, the properties cited for the latter compound did not agree with those of the dioxime we made from cortisol, and we therefore studied the reduction of cortisone 3 : 20-dioxime and its 21-acetate. Paper chromatography of the products from the reduction of the 21-acetate with sodium borohydride showed that the ester was hydrolysed almost immediately and the ketone reduced with unexpected rapidity; generation of cortisol dioxime was accompanied by other reactions producing at least two contaminants, and indeed the yield of the required compound from such reductions was poor. Use of lithium borohydride in non-aqueous solvents gave from the dioxime of cortisone, or its 21-acetate, " infusible " material (m. p. >300°) with properties like those attributed in the patent to cortisol 3 : 20-dioxime. We found that this substance contained boron, which could be removed when it was heated in refluxing methanol,[16] with the production of the 3 : 20-dioxime also generated directly from cortisol.

The nature of such boron-containing substances, which have also been noticed in the reduction of 3 : 20-dioximes methyl ethers, is not clear, and we have not studied them further. Nevertheless, knowledge gained in the foregoing experiments made possible an efficient conversion of cortisone into cortisol, the oxime groups being removed from the reduction product either by persulphuric acid or by nitrous acid with subsequent hydrolysis of the 20-nitrimine (IV; R = H, β-OH) (see below). Cortisone 3 : 20-dioxime dimethyl ether (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = O$, $R^4 = H$) could also be reduced; the product, the cortisol derivative (II; $R^1 = R^3 = N{\cdot}OMe$, $R^2 = H$, β-OH, $R^4 = H$), slowly yielded cortisol on acid-catalysed hydrolysis.

Further adaptation of the properties of the new 20-oximes exploited the ease of hydrolysing them and the 3 : 3-ethylenedioxy-group [1] in dilute acid. The ketals of cortisone and its 21-acetate (V; $R^1 = R^2 = O$, $R^3 = H$ and Ac) gave 20-oximes, convertible into cortisol by borohydride reduction and subsequent acid-catalysed hydrolysis of both protecting groups.

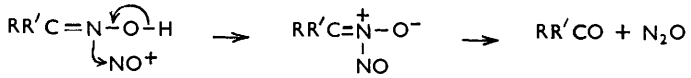
Attempts at regenerating cortisone acetate and similar 3 : 11 : 20-triones from their 3 : 20-dioximes showed that the action of aqueous mineral acid is generally limited to hydrolysis of the 20-hydroxyimino-group; [17] however, the 3- and the 20-oximes can be hydrolysed by aqueous persulphuric acid with simultaneous extraction of the ketones into methylene chloride. Persulphuric acid assists the hydrolysis by oxidising the liberated hydroxylamine; [18] in similar conditions or with dilute hydrochloric acid the hydrolysis of the 3 : 20-dioxime dimethyl ethers was completed very slowly. Aldehydes or ketones [6,17] failed to facilitate the hydrolysis in acid solution or in pyridine; sulphurous acid slowly but inefficiently removed the hydroxyimino-groups,[19] and bromine in polar solvents was unsatisfactory.[20] Nitrous acid regenerated the 3-oxo-group,[21] but converted the 20-hydroxyimino-groups into nitrimino-groups, recognisable in particular by their intense absorption at 1305—1330 and 1560—1580 $cm.^{-1}$. We have made pure specimens of the derivatives (IV; R = H, β-OH; and $R = H_2$) of cortisol and Reichstein's substance S and the nitrimine (V; $R^1 = O$, $R^2 = N_2O_2$, $R^3 = H$), but could not obtain their 21-acetates pure, because hydrolysis to the 20-ketone was unavoidable. Prolonged heating

[15] Graber and Wendler, U.S.P. 2,628,966.
[16] Cf. Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122; Abdel-Akker, Hamilton, and Smith, *ibid.*, 1951, **73**, 4691; Reid and Siegel, *J.*, 1954, 520.
[17] Cf. Hershberg, *J. Org. Chem.*, 1948, **13**, 542.
[18] Cf. Partington, " Textbook of Inorganic Chemistry," Macmillan & Co. Ltd., London, 1944, p. 556.
[19] von Pechmann, *Ber.*, 1887, **20**, 2904; Claisen and Manasse, *Ber.*, 1889, **22**, 530; Gluud, *Ber.*, 1915, **48**, 420.
[20] Piloty, *Ber.*, 1897, **30**, 3161; cf. Iffland and Yen, *J. Amer. Chem. Soc.*, 1954, **76**, 4083; Emmons and Pagano, *ibid.*, 1955, **77**, 4557.
[21] Cf. Goldschmidt and Veer, *Rec. Trav. chim.*, 1946, **65**, 796; 1947, **66**, 238; Hey and Morris, *J.*, 1948, 2319; Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781.

in polar solvents containing water converted the 20-nitrimino-17α : 21-dialcohols into 17α : 21-dihydroxy-20-ketones. Unless the nitrimine crystals were solvated with water, they showed no undue instability at raised temperatures. Attempts at facilitating hydrolysis of the 20-nitrimino-17α : 21-dialcohols by prior acetylation miscarried and caused blackening. Comparison of 3- and 20-monoximes has confirmed that only the latter yield isolable nitrimines, nitrous acid converting the former into ketones with a display of transient colours. Oxime methyl ethers did not give such products.

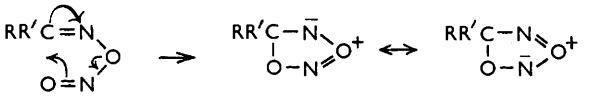
The action of nitrous acid on ketoximes does not generally yield nitrimines: they are generated (or, at least, isolable) only when the carbon atom on one side of the >C=N·OH group lacks hydrogen atoms. The terpenes provide a dozen or so examples and the steroids about half-a-dozen, the latter all 12-nitrimines.[22] In this connexion full substitution on the adjacent carbon atom, hitherto exemplified only with alkyl substituents in saturated and αβ-unsaturated oximes, does not imply a restriction on prototropy, since the terpenoid ketones and 12-oxo-steroids giving nitrimines can be brominated on the carbon atom not fully substituted.[23]

On the basis of differences between the derivatives of saturated and αβ-unsaturated oximes, Scholl [24] and Italian workers [25] have tried to classify the compounds and attribute structures to them. We can now extend the classification, since the nitrimines derived from camphor, hecogenin acetate, and the 20-oxo-steroids, which are hydrolysed to the parent ketones, display a pattern in their infrared absorption not obvious in the spectrum of the derivative of mesityl oxide, which is hydrolysed to the oxime or to other nitrogen-containing products. An attempted proof [26] of the structure >C=N·$NO_2$ for the camphor-derivative and its congeners being in our opinion inconclusive, we are tempted to speculate on the manner in which the ion $NO^+$ attacks the oximes. We assume that its usual action (for example, on 3-hydroxyimino-steroids) can be represented as an attack on the nitrogen atom:

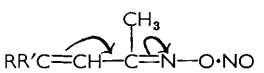


In heavily substituted oximes approach to the nitrogen atom may be hindered, so that attack at the oxygen atom predominates:

Subsequent cyclisation may then generate a mesoionic system, which offers a modern form of an expression first proposed by Foster, Trotter, and Weintroube [27] for the nitrimines:



We would then suppose that ring closure in the derivative from mesityl oxide is balked by the electron-accession, *viz.*:



[22] *E.g.*, Schenck and Reschke, *Ber.*, 1940, **73**, 200; Schenck, *Ber.*, 1942, **75**, 198; 1943, **76**, 874; 1944, **77**, 29, 501.

[23] *E.g.*, Simonsen and Owen, "The Terpenes," Cambridge Univ. Press, 1949, Vol. II, pp. 395 *et seq.*; Hershberg, Gerold, and Oliveto, *J. Amer. Chem. Soc.*, 1952, **74**, 3849; Elks, Phillipps, Walker, and Wyman, *J.*, 1956, 4330; cf. Gandini and Sparatore, *Chem. Abs.*, 1956, **50**, 7748.

[24] Scholl, *Annalen*, 1905, **338**, 1; 1906, **345**, 363.

[25] *E.g.*, Gandini, *Gazzetta*, 1942, **72**, 131, 232; Fusco, *ibid.*, 1943, **73**, 36.

[26] Suggitt, Myers, and Wright, *J. Org. Chem.*, 1947, **12**, 373.

[27] Foster, Trotter, and Weintroube, *J.*, 1911, **99**, 1982.

the powerfully hyperconjugative methyl groups in the nitrimine derived from pinacolone, which behaves like the unsaturated compound, probably stabilise the ester form similarly. The derivative of santonin has also been regarded as an oxime ester.[28]

A cyclic structure for nitrimines derived from ketones such as camphor satisfactorily accommodates their lack of colour, their hydrolysis to ketones, and the reduction of camphor nitrimine to bornylamine and *iso*bornylamine.[29] For the time being we are keeping the name nitrimine although, like the prefix pernitroso-, it no longer retains its precise meaning when applied to the compounds discussed herein.

## Experimental

For general procedures see earlier papers.[1,14] In this paper the following conditions were observed, unless others are mentioned: m. p.s for samples on a Kofler block; optical rotations for semicarbazones in pyridine, for oximes and nitrimines in dioxan, and for other compounds in chloroform, all solutions being about 1% and at 20° ± 3°; infrared and ultraviolet absorption spectra for specimens in Nujol mulls and ethanolic solution respectively. The m. p.s of the semicarbazones vary according to the conditions and occur with darkening and decomposition at >200°; solid compounds whose m. p.s are not given melt at >300°. The m. p.s of the 20-oxo-17 : 21-dialcohols depend greatly on the size of the particles.[30] In the infrared spectra the semicarbazones showed peaks at 1680 and 1570, the oximes at 1645—1625, and the nitrimines at 1560—1580 and 1305—1330 cm.$^{-1}$. (See also the description below of the derivatives of mesityl oxide.)

The oximes and semicarbazones were prone to solvation, which was very difficult to reverse. Difficulties in combustion also made their analysis troublesome.[31]

The 20-oximes and 20-semicarbazones gave no colour with the TSTZ reagent (see below) and the rate of their formation could be confirmed by this test and polarimetry. Due allowance must be made for the colour given by hydroxylamine and semicarbazide with the TSTZ reagent;[32] *O*-methylhydroxylamine gave no colour. The identities of reaction products were confirmed by spectroscopy and paper chromatography.

*Paper Chromatography.*—The parent compounds and the oximes were run at 30° on Whatman No. 2 papers, with the following solvents (unless a system is mentioned, solvent L was used):

| Solvent system | Light petroleum, b. p. 60—80° | Methanol | Toluene | Water | Dioxan | Benzene |
|---|---|---|---|---|---|---|
| L | 75 | 200 | 325 | 75 | — | — |
| M | — | 200 | 200 | 100 | 25 | — |
| N | — | 55 | — | 45 | — | 100 |

The fractions were located with a spray consisting of a 1% solution of 2 : 5-diphenyl-3-*p*-styrylphenyltetrazolium chloride (M and B 1767, May and Baker Ltd., Dagenham) in ethanol diluted with water (4 parts); just before use this solution was mixed with half its volume of aqueous 10% sodium hydroxide. The spots reached their maximum intensity after about 10 min. at room temperature; the papers were best kept in the dark. The foregoing is referred to in this paper as the TSTZ reagent.

Compounds not giving colours with this reagent were detected by examination in ultraviolet light [33] or by the Komarowsky reagent [34] or with vanillin and perchloric acid.[35]

In the following list the $R_M$ values (°) [14] for each 21-alcohol and its 21-acetate and the $\Delta R_M$ value for the esterification are given in that order: substance S, −0·04, −0·87, −0·83; cortisone 0·63, −0·37, −1·00; cortisol, 0·91, −0·05, −0·96; 4 : 5α-dihydrocortisone, 0·31, −0·50, −0·81; 4 : 5α-dihydrocortisol, 0·58, −0·37, −0·95. The average $\Delta R_M$ for 21-acetylation is therefore −0·91 ±0·10. Values of $\Delta R_M$ for several other conversions are as follows: formation

[28] Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 270.
[29] Simonsen and Owen, ref. 23, p. 441.
[30] Reichstein and Shoppee, *Vitamins and Hormones*, 1943, **1**, 345.
[31] Cf. Ramirez and Stafiej, *J. Amer. Chem. Soc.*, 1955, **77**, 134; Davison and Christie, *J.*, 1955, 3389; Fabian, Legrand, and Poirier, *Bull. Soc. chim. France*, 1956, 1499.
[32] Snow, *J.*, 1954, 2588; Rogers, *J.*, 1955, 769.
[33] Bush, *Biochem. J.*, 1952, **50**, 370.
[34] Callow, Dickson, Elks, Evans, James, Long, Oughton, and Page, *J.*, 1955, 1966.
[35] Godin, *Nature*, 1954, **174**, 134.

of 3 : 20-dioxime dimethyl ethers (in $\Delta^4$-steroids), −1·37 (±0·10); 20-nitrimine formation, 0·25 (±0·04); 3-oximation in $\Delta^4$-steroids, 0·50 (±0·07), and in 5α-steroids (indirect calculation), 0·5—0·6; 20-oximation, 0·63 (±0·02); 3 : 20-dioximation (in $\Delta^4$-steroids), 1·12 (±0·04). Except for the oximation of cortisone these reactions gave consistent increments.

The following $R_F$ values were obtained with system L (the compound marked * being an otherwise unidentified component of mixtures). (*a*) Substance S, 0·52; 3-oxime, 0·28; 3 : 20-dioxime, 0·08; 3 : 20-dioxime dimethyl ether, 0·97; 20-nitrimine, 0·40. (*b*) Substance S 21-acetate, 0·88; 3-oxime,* 0·44; 3 : 20-dioxime, 0·34. (*c*) Substance D 3 : 21-diacetate, 0·93; 20-oxime, 0·76. (*d*) 4 : 5α-Dihydrocortisone 21-acetate, 0·76; 3 : 20-dioxime, 0·09. (*e*) Cortisone, 0·19; 3-oxime, 0·07; 3 : 20-dioxime, 0·10. (*f*) Cortisone 21-acetate, 0·70; 3-oxime, 0·44; 3 : 20-dioxime, 0·10. (*g*) Cortisol, 0·11; 3-oxime, 0·04; 3 : 20-dioxime, 0·01; 3 : 20-dioxime dimethyl ether, 0·69; 20-nitrimine, 0·06.

Solvents M and N give higher $R_F$ values.

*Preparation of Semicarbazones.*—The following description is of a typical example. Cortisone acetate (1 g.), dissolved in pyridine (25 ml.), was mixed with a solution of semicarbazide hydrochloride (5·4 g.) in water (6 ml.) to which a cool mixture of pyridine (25 ml.) and concentrated hydrochloric acid (6·2 ml.) had been added. The α decreased from +5·60° (after 1·75 min.) to +5·12° (64 hr.) (1 dm. tube), and then stayed constant. Aqueous sodium acetate was then added to neutralise the hydrochloric acid, and most of the solvents were evaporated off. Dilution with water then precipitated the disemicarbazone (1·23 g., 93%) (see Table 1). β-Picoline or *NN*-dimethylaniline could be used instead of pyridine.

Formation of the 20-semicarbazones of 17α : 21-dihydroxy-20-ketones was complete in <48 hr. Such products were purer than those made with acid catalysis.[2] 3β-Acetoxyergost-22-en-11-one was not converted into a semicarbazone, even after prolonged treatment in these conditions.

The 3-monosemicarbazones were obtained by terminating the condensation when the rotation reached its maximum (generally <5 min.). They were also made satisfactorily with the base hydrochloride and sodium acetate [36] or by the procedure typified in the following example. Semicarbazide hydrochloride (1 g.; finely ground) in *NN*-dimethylformamide (10 ml.) and pyridine (5 ml.) was added to cortisone acetate (0·5 g.) in pyridine (11 ml.). The

TABLE 1. *Properties of semicarbazones.*

(a) 3 : 20 - *Disemicarbazones* ($R^1 = R^3 =$ N·NH·CO·$NH_2$) of:

4 : 5α-*Dihydrocortisone* (I; $R^2 =$ O, $R^4 =$ H), $[\alpha]_D$ +17°, $\lambda_{max.}$ 229 mμ (ε 22,860) (Found: N, 16·7. $C_{23}H_{36}O_5N_6$,1·5$H_2O$ requires N, 16·7%); 21-*acetate* (I; $R^2 =$ O, $R^4 =$ Ac), $[\alpha]_D$ +21°, $\lambda_{max.}$ 231 mμ (ε 24,250) (Found: C, 54·5; H, 7·75; N, 15·5; OAc, 8·1. $C_{25}H_{38}O_6N_6$,1·5$H_2O$ requires C, 55·0; H, 7·6; N, 15·4; OAc, 7·9%).

17α : 21-*Dihydroxypregn*-4-*ene*-3 : 20-*dione* (substance S, II; $R^2 = H_2$, $R^4 =$ H), $[\alpha]_D$ +113°, $\lambda_{max.}$ 269 mμ (ε 34,100) (Found: C, 59·4; H, 8·1; N, 18·2. $C_{23}H_{36}O_4N_6$ requires C, 60·0; H, 7·9; N, 18·25%); 21-*acetate* (II; $R^2 = H_2$, $R^4 =$ Ac), $[\alpha]_D$ +108°, $\lambda_{max.}$ 269 mμ (ε 34,100) (Found: C, 58·2; H, 7·7; N, 16·35; OAc, 8·1. $C_{25}H_{38}O_5N_6$,0·5$H_2O$ requires C, 58·75; H, 7·7; N, 16·4; OAc, 8·4%).

Cortisone (II; $R^2 =$ O, $R^4 =$ H), $[\alpha]_D$ +195°, $\lambda_{max.}$ 270 mμ (ε 31,200), shoulder at 240 mμ (ε 19,500) (Found: N, 17·2. Calc. for $C_{23}H_{34}O_5N_6$: N, 17·7%); [2] 21-acetate (II; $R^2 =$ O, $R^4 =$ Ac), $[\alpha]_D$ +206°, $\lambda_{max.}$ 242·5 (ε 22,400) and 269 mμ (ε 28,950) (Found: C, 56·6; H, 7·3; N, 16·1; OAc, 8·1. Calc. for $C_{25}H_{36}O_6N_6$,0·5$H_2O$: C, 57·15; H, 7·1; N, 16·0; OAc, 8·3%).[4]

(b) 3-*Monosemicarbazones* ($R^1 =$ N·NH·CO·$NH_2$, $R^3 =$ O, $R^4 =$ Ac) of:

21-*Acetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (II; $R^2 = H_2$), $[\alpha]_D$ +157°, $\lambda_{max.}$ 269 mμ (ε 30,500) (Found: N, 9·2. $C_{24}H_{35}O_5N_3$,0·5$H_2O$ requires N, 9·25%).

Cortisone 21-acetate (II; $R^2 =$ O), $[\alpha]_D$ +252° (in dioxan), $\lambda_{max.}$ 270 mμ (ε 30,800) (Found: N, 8·8. Calc. for $C_{21}H_{33}O_6N_3$,0·5$H_2O$: N, 9·0%) (crystallised from ethanolic methylene dichloride).[6]

α (0·5 dm. tube) +2·66° became 3·00° (constant) in 1 hr. The solution was diluted with water, and the precipitated semicarbazone (II; $R^1 =$ N·NH·CO·$NH_2$, $R^2 = R^3 =$ O, $R^4 =$ Ac) was collected.

A special procedure for use with substance D diacetate (III; R = O) is described below. We failed to make identifiable derivatives of the 20-ketones with Girard's reagents.[37]

The properties of the semicarbazones made in this work are listed in Table 1. They were

[36] Wild, "Characterisation of Organic Compounds," Cambridge Univ. Press, 1948, p. 121.
[37] Cf. McKinley, *Science*, 1955, **121**, 139.

all made in nearly quantitative yield. The 21-alcohols separated pure from aqueous pyridine; all the 21-acetates separated as needles from methanol.

Hydrolysis (see below) in high yield of representative semicarbazones to the parent ketones confirmed the structures of the derivatives.

3β : 21-*Diacetoxy*-17α-*hydroxy*-20-*semicarbazono*-5α-*pregnan*-11-*one* (III; R = $N{\cdot}NH{\cdot}CO{\cdot}NH_2$).—(i) The diacetate (III; R = O) (1 g.) and semicarbazide base (1 g.) in glacial acetic acid (10 ml.) were heated on a steam-bath for 15 min. The cooled mixture was poured into water, and the precipitate (1·12 g.), m. p. 244—246°, was collected. Crystallisation from aqueous acetic acid gave the *semicarbazone* (III; R = $N{\cdot}NH{\cdot}CO{\cdot}NH_2$), m. p. 252°, $[\alpha]_D \pm 0°$, $\lambda_{max.}$ 239·5 mμ (ε 9960) (Found: C, 61·45; H, 7·7; N, 8·0. $C_{26}H_{39}O_7N_3$ requires C, 61·75; H, 7·8; N, 8·3%). (ii) (With Dr. J. Oughton and Mr. L. Stephenson.) The diacetate (III; R = O) (0·50 g.) was shaken for 1 week with pyridine (32·5 ml.), concentrated hydrochloric acid (2·25 ml.), water (2·5 ml.), and ethyl acetate (10 ml.), during which time two phases were formed, the lower yellow. Most of the solvent was distilled off, and water added to the residue to precipitate plates of the semicarbazone (0·527 g., 93%), m. p. 244—246°, $[\alpha]_D \pm 0°$, $\lambda_{max.}$ 239·5 mμ (ε 9960), identified with the product described in (i) above. Omission of the ethyl acetate led to the generation of an inferior product, presumably owing to hydrolysis of the 3-acetate.

This semicarbazone (0·50 g.) was hydrolysed by suspension in ethyl acetate (100 ml.) to which 2N-hydrochloric acid (50 ml.) was added. The mixture was stirred at room temperature for 5 hr., during which all the solid dissolved. The aqueous layer was twice extracted with ethyl acetate, and the combined ethyl acetate phases were washed several times with 2N-hydrochloric acid, then with sodium hydrogen carbonate and water. Isolation and crystallisation from ethyl acetate gave prisms (0·34 g., 77%) of the pure diketone (III; R = O), m. p. 218—220°, $[\alpha]_D$ +69° {lit.,[30] m. p. 223—224°, $[\alpha]_D^{15}$ +72°}. Use of methylene dichloride instead of ethyl acetate in the hydrolysis led to the formation of intractable emulsions.

*Cortisol from the Disemicarbazone of Cortisone.*—The semicarbazone (II; $R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^2$ = O, $R^4$ = H) (3·0 g.), dissolved in *NN*-dimethylformamide (19 ml.) and anhydrous tetrahydrofuran (38 ml.), was added dropwise during 30 min. to lithium borohydride (1·9 g.) suspended in anhydrous tetrahydrofuran (94 ml.). The mixture was stirred at room temperature for another 2 hr., neutralised with aqueous acetic acid, evaporated to small bulk, and then diluted with much water. Part (2·0 g.) of the product (2·14 g.), which gave no colour with the TSTZ reagent, was dissolved in acetic acid (44 ml.), " 50—60% " pyruvic acid (British Drug Houses Ltd.) (7·3 ml.) and pyridine sulphate solution (22 ml.; see below) and stored at room temperature for 17 hr. The solution was then poured into much water, and isolation of the steroid with ethyl acetate gave cortisol (0·94 g., 62%), m. p. 207—214°, $[\alpha]_D$ +157° (in MeOH), $\lambda_{max.}$ 242 mμ (ε 15,400). A second crop (0·11 g., 7%) of m. p. 200—201° was also obtained.

4 : 5α-*Dihydrocortisol* 21-*Acetate*.—The disemicarbazone (I; $R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^2$ = O, $R^4$ = Ac) (5 g.), dissolved in ethanol (500 ml.), methylene dichloride (300 ml.), and water (100 ml.), was treated at room temperature with sodium borohydride (2·5 g.) in water (25 ml.). The solution was then refluxed for 2 hr., and cooled, and the excess of borohydride decomposed with aqueous acetic acid. The solvents were distilled off and the residue was acetylated with acetic anhydride (25 ml.) and pyridine (50 ml.). Evaporation of these left a solid, which was ground in a little water and transferred to a separating funnel. A cool solution of concentrated hydrochloric acid (133 ml.) and water (100 ml.) was added. After 1 minute's stirring the suspension cleared and it was then extracted with batches of ethyl acetate and methylene dichloride (1 : 1; 100 ml. each) until the extracts no longer had optical rotatory power and gave very weak colours with the TSTZ reagent. The washed and dried steroid (3·14 g.) from the combined extracts was acetylated with acetic anhydride (12·5 ml.) and pyridine (25 ml.) for 2 hr. at room temperature, giving a product (3·17 g.) that crystallised from ethyl acetate as 4 : 5α-dihydrocortisol acetate [1] (1·88 g., 48%), m. p. 220—222° (capillary), $[\alpha]_D$ +76°, with a second crop (0·81 g., 21%), m. p. 212—217° (capillary), $[\alpha]_D$ +74°.

*Removal of the Semicarbazone Groups by Hydrolysis.*—(i) The disemicarbazone (II; $R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^2$ = O, $R^4$ = Ac) (1 g.) of cortisone acetate and " 50—60% " pyruvic acid (British Drug Houses Ltd.) (3·7 ml.) was treated with a solution (11 ml.) of pyridine sulphate, made as follows: concentrated sulphuric acid (20 ml.) was poured into water (20 ml.), and the solution cooled and added slowly to pyridine (62 ml.); finally it was made up to 100 ml. with

water. The solution containing the steroid was kept at room temperature for 5 days, the rotation becoming constant. Dilution with water and extraction with ethyl acetate afforded cortisone acetate (0·815 g.), which crystallised from ethyl acetate to give a pure product (0·61 g., 79%), m. p. 241—244° (capillary), $[\alpha]_D$ +219°. The 3 : 20-disemicarbazones of the following were also hydrolysed in this manner (yields in brackets): 4 : 5α-dihydrocortisone (69%) and its 21-acetate (70%); substance S (66%) and its 21-acetate (81%), and 4 : 5α-dihydrocortisol acetate (48%; see above). Paper chromatography showed that in these circumstances the 21-acetates were not hydrolysed and that less polar compounds were not generally formed.[38]

(ii) This method is exemplified in the preparation of 4 : 5α-dihydrocortisol acetate and in the hydrolysis of the 20-semicarbazone of substance D diacetate (see above). The 3 : 20-disemicarbazones of 4 : 5α-dihydrocortisone 21-acetate (85%) and cortisone 21-acetate (62%) were hydrolysed similarly.

(iii) The powdered disemicarbazone (I; $R^1 = R^3 = N{\cdot}NH{\cdot}CO{\cdot}NH_2$, $R^2 = O$, $R^4 = Ac$) (1 g.) was suspended in water and cooled to 0°. Concentrated hydrochloric acid (20 ml.) mixed with water (5 ml.) was slowly run into the stirred suspension, and then a solution (1·1 ml.) made from sodium nitrite (5·45 g.) and water (10 ml.). Gas evolution subsided after 30 min., but the solution still gave a colour with starch–iodide. Urea was added until this test was negative, the solution diluted with water, and the precipitated steroid filtered off, dried, and acetylated with acetic anhydride (5 ml.) and pyridine (10 ml.). Evaporation and crystallisation of the residue from acetone gave 4 : 5α-dihydrocortisone 21-acetate (0·62 g., 80%), m. p. 224—227° (capillary), $[\alpha]_D$ +98°. This method generally gave slightly impure products.

*Preparation of Oximes.*—(i) The following is a typical example. Cortisone acetate (1 g.), dissolved in anhydrous pyridine (20 ml.), was mixed with a solution of hydroxylamine hydrochloride (1 g.) in anhydrous pyridine (10 ml.), and the solution set aside at room temperature. The α (1 dm. tube) +7·83° changed to +6·70° in *ca.* 64 hr. and did not change thereafter. Careful dilution with water then precipitated the dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = O$, $R^4 = Ac$) nearly quantitatively. For further details of this and related preparations, see Table 2.

Such products were generally pure. Attempts at crystallisation may lead to decomposition.

The oxime methyl ethers were made similarly. Dioximation of the 21-alcohols was complete within 24 hr.

(ii) Substance S (0·56 g.) in methanol (12 ml.) and methylene dichloride (6 ml.) was treated with a filtered mixture of hydroxylamine hydrochloride (0·472 g.) and 0·339N-sodium methoxide in methanol (24 ml.). The alkaline solution was set aside at room temperature for a weekend. Subsequent acidification with acetic acid and dilution with water precipitated the dioxime (II; $R^1 = R^3 = N{\cdot}OH$, $R^2 = H_2$, $R^4 = H$) (0·48 g.), with a second crop (0·07 g.), identified with the oxime so described in Table 2.

(iii) 4 : 5α-Dihydrocortisone acetate (0·5 g.) in ethanol (50 ml.) was treated with hydroxylamine hydrochloride (0·5 g.) and crystalline potassium acetate (0·9 g.), the two last being dissolved in ethanol (12·5 and 15 ml. respectively) and mixed just before use. The mixture was left at room temperature for 20 hr., and the oxime (I; $R^1 = N{\cdot}OH$, $R^2 = R^3 = O$, $R^4 = Ac$) isolated by extraction into ether or methylene dichloride or by precipitation with water. This product (0·49 g.) was crystallised from ethyl acetate to give a pure specimen (0·30 g.) (see Table 2).

This method did not give pure 20-oximes from the 21-acetates, since forcing conditions produced mixtures. 20-Oximation in this manner of the 21-alcohols was very slow.

The oximes listed in Table 2 were made by method (i) with a few exceptions (see footnote) or by selective hydrolysis (see below). A blank in the yield column denotes preparation by hydrolysis or, in the case of a derivative, by acylation. The yields are for material purified by precipitation from aqueous pyridine until it gave only one spot on a paper chromatogram.

The following oximes, not mentioned in Table 2, were made by the methods mentioned above: (+)-Camphor oxime (methods i and iii), m. p. 117—118° (cap.), $[\alpha]_D$ −41° (in EtOH) {lit.,[39] m. p. 119°, $[\alpha]_D$ −42° (in EtOH)}. 4-Hydroxyimino-2-methylpent-2-ene (from mesityl oxide by method iii), b. p. 92—94°/15 mm., $\lambda_{max.}$ 233 mμ (ε 8760) (lit.,[40] b. p. 95°/11 mm. for

[38] Cf. Slates and Wendler, *J. Org. Chem.*, 1957, **22**, 498.

[39] " Dictionary of Organic Compounds," ed. Heilbron and Bunbury, Eyre and Spottiswood, London, 1943, Vol. I, p. 384.

[40] *Op. cit.*, 1936, Vol. II, p. 593.

TABLE 2. *Properties of the oximes.*

| No. | Compound | Yield (%) | Cryst. habit (solvent) | M. p. | $[\alpha]_D$ | $\lambda_{max.}$ (mμ) | ε |
|---|---|---|---|---|---|---|---|
| Substance S | | | | | | | |
| 1 | 3 : 20-Dioxime | 95 | Prisms (MeOH) | 225—227° | +123° | 241 | 19,200 |
| 2*a* | 3 : 20-Dioxime $Me_2$ ether | 87 | (i) Needles (Aq. $COMe_2$) [a,b] | 164, 180 | +167 | 249 | 17,600 |
| 2*b* | | | (ii) Plates ($COMe_2$) [b] | 194—196 | +132 | 249 | 23,000 |
| Substance S 21-acetate | | | | | | | |
| 3 | 3 : 20-Dioxime | 88 | Needles (Aq. MeOH) | 174—176 | +136 | 240 | 21,400 |
| Substance D 3 : 21-diacetate | | | | | | | |
| 4 | 20-Oxime | 100 | Nacreous (EtOAc) | 231—232 | +13 | — | — |
| 5 | 20-Oxime acetate [c] | — | Needles (Aq. $COMe_2$) | 176—178 | +23 | — | — |
| 4 : 5α-Dihydrocortisone 21-acetate | | | | | | | |
| 6 | 3-Oxime [d] | 95 | Prisms (EtOAc) | 276—279 | +97 | — | — |
| 7 | 3 : 20-Dioxime | 89 | Needles (EtOAc) | 203—204 | +41 | — | — |
| Cortisone | | | | | | | |
| 8 | 3-Oxime | — | Needles (Aq. EtOH) | 149—150 | +220 | 240 | 18,400 |
| 9 | 3 : 20-Dioxime [c] | 91 | Needles (Aq. $COMe_2$) | 200 | +167 | 240 | 20,700 |
| Cortisone 21-acetate | | | | | | | |
| 10 | 3-Oxime [d] | 91 | Needles (Aq. EtOH) | 250—252 | +235 | 240 | 20,400 |
| 11 | 3 : 20-Dioxime | 98 | Needles (EtOAc–$CH_2Cl_2$–hexane) [e,f] | 207—209 | +162 | 240 | 22,600 |
| 12 | 3 : 20-Dioxime $Me_2$ ether | 85 | Needles (Aq. EtOH) [b] | 159·5—162·5 | +203 | 249 | 20,200 |
| Cortisone, 3-ethylene ketal [c] | | | | | | | |
| 13 | 20-Oxime | 91 | Needles (MeOH) | 233—234 | −2 | — | — |
| Cortisone 21-acetate, 3-ethylene ketal | | | | | | | |
| 14 | 20-Oxime | 69 | Prisms (Aq. EtOH) | 218—223 | +9 | — | — |
| Cortisol | | | | | | | |
| 15 | 3-Oxime [a] | — | Needles (Aq. $COMe_2$) | 146—148, 190 | +121 | 240 | 18,500 |
| 16 | 3 : 20-Dioxime [c] | 83 | Needles (Aq. MeOH) | 205—207 | +125 | 240 | 22,700 |
| 17 | 3 : 20-Dioxime $Me_2$ ether [c] | — | Crystals (EtOAc–*cyclo*-hexane) | 78—83 | +167 | 249 | 30,000 |
| Cortisol, 3-ethylene ketal | | | | | | | |
| 18 | 20-Oxime | — | Rods (Aq. $COMe_2$) | 231—234 | −37 | — | — |

| | | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|---|
| No. | Formula | C | H | N | C | H | N |
| 1 | $C_{21}H_{32}O_4N_2$ | 66·7 | 8·6 | 7·3 | 67·0 | 8·6 | 7·4 |
| 2*a* | $C_{23}H_{36}O_4N_2$ | 67·7 | 8·8 | 7·1 | 68·3 | 9·0 | 6·9 |
| 2*b* | $C_{23}H_{36}O_4N_2$ | 68·35 | 8·7 | 7·1 | 68·3 | 9·0 | 6·9 |
| 3 | $C_{23}H_{34}O_5N_2$ | 65·4 | 7·9 | 6·5 | 66·0 | 8·2 | 6·7 |
| 4 | $C_{25}H_{37}O_7N$ | 64·8 | 8·0 | 3·1 | 64·8 | 8·05 | 3·0 |
| 5 | $C_{27}H_{39}O_8N$ | 64·7 | 7·6 | 2·8 | 64·2 | 7·8 | 2·8 |
| 6 | $C_{23}H_{33}O_6N$ | 65·8 | 7·9 | 3·2 | 65·85 | 7·9 | 3·3 |
| 7 | $C_{23}H_{34}O_6N_2$ | 63·9 | 7·75 | 5·8 | 63·6 | 7·9 | 6·45 |
| 8 | $C_{21}H_{29}O_5N,H_2O$ | 64·0 | 7·6 | 3·0 | 64·1 | 7·9 | 3·6 |
| 9 | $C_{21}H_{30}O_5N_2,H_2O$ | 61·95 | 7·9 | 6·7 | 61·7 | 7·9 | 6·9 |
| 10 | $C_{23}H_{31}O_6N$ | 66·4 | 7·3 | 3·5 | 66·2 | 7·5 | 3·4 |
| 11 | $C_{23}H_{32}O_6N_2$ | 63·9 | 7·1 | 6·7 | 63·9 | 7·4 | 6·5 |
| 12 | $C_{25}H_{36}O_6N_2$ | 65·5 | 8·05 | 6·5 | 65·2 | 7·9 | 6·1 |
| 13 | $C_{23}H_{33}O_6N$ | 65·6 | 7·7 | 3·4 | 65·9 | 7·9 | 3·3 |
| 14 | $C_{25}H_{36}O_7N$ | 65·25 | 7·8 | 3·3 | 65·05 | 7·6 | 3·0 |
| 15 | $C_{21}H_{31}O_5N,0·5H_2O$ | 65·4 | 8·1 | 3·5 | 65·3 | 8·3 | 3·6 |
| 16 | $C_{21}H_{32}O_5N_2,H_2O$ | 61·7 | 8·2 | 7·0 | 61·4 | 8·35 | 6·8 |
| 17 | $C_{23}H_{36}O_5N_2,2C_6H_{12}$ | 70·6 | 9·6 | 4·6 | 71·4 | 10·3 | 4·8 |
| 18 | $C_{23}H_{35}O_6N$ | 65·4 | 8·5 | 3·4 | 65·5 | 8·4 | 3·3 |

[a] Double m. p. [b] $\alpha_D$ for $CHCl_3$ solution. [c] For further information, see below. [d] Made by method (iii). [e] M. p. variable. [f] For published data on this compound, see ref. 4.

" β "-form). 2-Hydroxyimino-3 : 3-dimethylbutane (from pinacolone by method iii), m. p. 74—77° (capillary) (Found: N, 10·4. Calc. for $C_6H_{13}ON,H_2O$: N, 10·5%) (lit.,[41] m. p. 74—75°). 12-*Hydroxyiminotigogenin acetate* (from hecogenin acetate by methods i and iii), laminæ (from ethyl acetate), m. p. 303—310° (decomp.), $[\alpha]_D$ +0·5° (in $CHCl_3$) (Found: C, 70·9; H, 8·95; N, 3·0. $C_{29}H_{45}O_5N$ requires C, 71·4; H, 9·3; N, 2·9%).

3β : 21-*Diacetoxy*-20-*acetoxyimino*-17α-*hydroxy*-5α-*pregnan*-11-*one* (III; R = N·OAc).—The 20-oxime (III; R = N·OH) (0·25 g.) of substance D 3 : 21-diacetate was heated on the water-bath for 5 min. with acetic anhydride (3 ml.) and pyridine (2 ml.). Evaporation with subsequent crystallisation from methanol of the dry residue gave needles of the *oxime acetate* (0·25 g., 92%) with the properties set out in Table 2.

Attempts at acetylating the 3 : 20-dioxime (II; $R^1 = R^3 =$ N·OH, $R^2 =$ O, $R^4 =$ H) likewise or with acetic anhydride and acetic acid, gave mixtures with up to four components detectable by paper chromatography.

*Cortisone* 3 : 20-*Dioxime* (II; $R^1 = R^3 =$ N·OH, $R^2 =$ O, $R^4 =$ H).—The 21-acetate (II; $R^1 = R^3 =$ N·OH, $R^2 =$ O, $R^4 =$ Ac) (1·0 g.) was suspended in methylene dichloride (20 ml.) under nitrogen, and 0·04N-sodium hydroxide in ethanol (27·3 ml., 1·0 mol.) added. Dioxan (22 ml.) and water (5 ml.) were run in, and the solution stirred for 10 min., and then neutralised (Congo-red) with acetic acid. Evaporation and washing of the product left a dried steroidal residue (0·89 g.), crystallising from aqueous acetone as needles (0·84 g., 89%), m. p. 198—203° (decomp.), identified with those obtained by direct oximation of cortisone (see Table 2).

Hydrolysis by means of water (1 mol.) in methanolic sodium methoxide was a little less efficient.[42]

*Cortisol* 3 : 20-*Dioxime* (II; $R^1 = R^3 =$ N·OH, $R^2 =$ H, β-OH, $R^4 =$ H).—(i) Cortisol (5·0 g.) in anhydrous pyridine (30 ml.) was treated with a solution of hydroxylamine hydrochloride (5·0 g.) in dry pyridine (50 ml.). The solution was kept at room temperature for 24 hr., evaporated to small bulk, and diluted with 50% aqueous methanol. The gum that separated was isolated by decanting the supernatant fluid; it was triturated with aqueous acetone to yield a white solid (4·47 g., 83%), m. p. 184—186° (decomp.), $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1cm.}$ 499) (Found: N, 7·0%). It was purified by dissolving it in methanolic sodium methoxide (2 mol.), setting the solution aside overnight at 0°, and precipitating the sodium salt by addition of benzene. This gave a white gelatinous solid, m. p. 174—175°, that was washed with light petroleum (b. p. 40—60°). Treatment of this salt in aqueous suspension with carbon dioxide gave a precipitate, m. p. 202—205° (decomp.), $[\alpha]_D$ +125°, characterised (after crystallisation from aqueous methanol) by the properties set out in Table 2.

(ii) Cortisone 3 : 20-dioxime (II; $R^1 = R^3 =$ N·OH, $R^2 =$ O, $R^4 =$ H) (1·0 g.) was reduced with lithium borohydride according to the instructions given by Wendler *et al.*[2,15] The water-washed product (0·87 g.) was got as rhombs, m. p. >330°, becoming brown at >240°. Precipitation from methanol gave a purer solid (0·53 g.), m. p. >310°, $[\alpha]_D$ +154° (*c* 0·58; acetic acid), $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1cm.}$ 414), devoid of carbonyl absorption in its infrared spectrum (Found: B, 4·1%) (Graber and Wendler [15] isolated a compound with similar m. p., $[\alpha]_D$, and ultraviolet absorption, and called it the 3 : 20-dioxime of cortisol).

The foregoing boron-containing compound (0·28 g.) was heated in refluxing methanol until the vapour over the solution no longer burnt with a green-edged flame (*ca.* 5 hr.). Evaporation of the solvent left a residue (0·28 g.), sintering at *ca.* 123°, and fusing to a varnish at *ca.* 180°. Two crystallisations from ethyl acetate–*n*-hexane afforded a fine powder (0·22 g.), shrinking at 158—162°, m. p. 171—177° (capillary) (to a varnish), decomp. >213°, of the *dioxime* (II; $R^1 = R^3 =$ N·OH, $R^2 =$ H, β-OH, $R^4 =$ H) (Found: C, 63·8; H, 8·5; N, 6·7. $C_{21}H_{32}O_5N_2$ requires C, 64·3; H, 8·2; N, 7·1%). Crystallisation from aqueous methanol gave a hydrate, m. p. 199° (decomp.), $[\alpha]_D$ +123°, $\lambda_{max.}$ 240·5 mμ (ε 19,800), identified with the compound described in Table 2.

[The action of lithium borohydride in anhydrous solvents on the 3 : 20-dioxime (II; $R^1 = R^3 =$ N·OH, $R^2 = H_2$, $R^4 =$ H) of substance S produced an infusible compound, from which the original dioxime was regenerated by refluxing methanol. Sodium borohydride in methanol at 20° or refluxing did not change this dioxime; it was also stable in aqueous alcoholic

[41] *Op. cit.*, 1937, Vol. III, p. 493.
[42] Huang-Minlon and Tishler, U.S.P. 2,634,277.

alkali. The dioxime and boric acid in refluxing aqueous tetrahydrofuran did not yield a boron-containing steroid.]

*Cortisol* 3 : 20-*Dioxime Dimethyl Ether* (II; $R^1 = R^3 =$ N·OMe, $R^2 =$ H, β-OH, $R^4 =$ H).—The 3 : 20-dioxime dimethyl ether of cortisone acetate (II; $R^1 = R^3 =$ N·OMe, $R^2 =$ O, $R^4 =$ Ac) (1·27 g.) in ethanol (20 ml.) containing N-sodium hydroxide (2·75 ml.) was treated with sodium borohydride (0·6 g.) in water (0·5 ml.), the cloudy mixture then being refluxed for 4 hr. More borohydride (0·6 g.) in water (0·5 ml.) was added, and the refluxing continued for another 2 hr. Neutralisation of the cooled mixture with 10% (v/v) aqueous acetic acid and extraction with methylene dichloride yielded a steroid (1·03 g.) almost devoid of infrared carbonyl absorption. This steroid was heated in refluxing methanol (25 ml.) for 4 hr., after which the vapours no longer burnt with a green flame. The boron-free residue left after evaporation was still almost devoid of carbonyl absorption, and crystallised to give the non-ketonic dioxime dimethyl ether (0·32 g., 20%). Its properties (Table 2) suggest that it is a clathrate compound.[43]

*Substance S* 20-*Nitrimine* (IV; R = $H_2$).—The dioxime (II; $R^1 = R^3 =$ N·OH, $R^2 = H_2$, $R^4 =$ H) (1·0 g.) was dissolved in acetic acid (25 ml.) containing crystalline potassium acetate (0·05 g.). 15% Aqueous sodium nitrite (5 ml.) was added, and then more if the starch–iodide test had become negative. Aliquot portions taken during 3 hr. showed that the nitrogen content of the steroid never dwindled to $<6{\cdot}5\%$. Precipitation with water then yielded the *nitrimine* which, crystallised from acetic acid, had m. p. 186—187°, $[\alpha]_D$ +80°, $\lambda_{max.}$ 240 mμ (ε 18,000) (0·68 g., 74%) (Found: C, 64·8; H, 7·8; N, 7·1. $C_{21}H_{30}O_5N_2$ requires C, 64·6; H, 7·7; N, 7·2%).

*Cortisol* 20-*Nitrimine* (IV; R = H, β-OH).—Cortisol dioxime (0·95 g.) in acetic acid (30 ml.) was treated at room temperature with 5% aqueous sodium nitrite (20 ml.). The solution was set aside for 2 hr. during which a bright yellow colour developed rapidly and faded slowly. Dilution with aqueous sodium acetate precipitated a white solid (0·8 g., 71%), crystallisation of which from aqueous acetic acid yielded the *nitrimine* (0·40 g., 35%), m. p. 166—168° (decomp.), $[\alpha]_D^{24}$ +98°, $\lambda_{max.}$ 240 mμ (ε 17,200) (Found: C, 61·1; H, 7·3; N, 7·1. $C_{21}H_{30}O_6N_2,0{\cdot}5H_2O$ requires C, 60·8; H, 7·5; N, 6·8%).

3 : 3-*Ethylenedioxy*-17α : 21-*dihydroxy*-20-*nitriminopregn*-5-*en*-11-*one* (V; $R^1 =$ O, $R^2 = N_2O_2$, $R^3 =$ H).—The oxime (V; $R^1 =$ O, $R^2 =$ N·OH, $R^3 =$ H) (0·25 g.) in acetic acid (5 ml.) was treated with 5% aqueous sodium nitrite (5 ml.) for 4 hr., during which there separated irregular crystals of the *nitrimine* (V) (0·058 g.), m. p. 176—179° (decomp.) (Found: N, 6·2. $C_{23}H_{32}O_7N_2$ requires N, 6·25%).

The oxime acetate (III; R = N·OAc) and oxime methyl ethers were stable in such nitrosating conditions.

The 21-acetoxy-17α-hydroxy-20-oximes did not yield pure 20-nitrimines, owing to ready hydrolysis. The apparent thermal decomposition of an impure specimen of the 20-nitrimine of cortisone acetate could be attributed to hydration of the crystals. Attempts at acetylating the 21-hydroxy-20-nitrimines led to blackening.

12-*Nitriminotigogenin Acetate* (VI; R = $N_2O_2$).—The oxime (VI; R = N·OH) (0·50 g.) in pure dioxan (30 ml.) and acetic acid (5 ml.) was treated with a solution of sodium nitrite (1 g.) in water (5 ml.). A precipitate separated almost at once, but redissolved in 5 hr. Isolation of the product (0·53 g.), m. p. 185—187° (decomp.; capillary), by dilution with water and subsequent crystallisation from ethanol gave prisms of the *nitrimine* (VI; R = $N_2O_2$) (0·383 g.), m. p. 189° (decomp.), $[\alpha]_D$ +4° (in $CHCl_3$) (Found: C, 68·1; H, 8·8; N, 5·2. $C_{29}H_{44}O_6N_2$ requires C, 67·4; H, 8·6; N, 5·4%).

(+)-*Camphor Nitrimine*.—(+)-Camphor oxime (1·0 g.) in acetic acid (30 ml.) was treated with 5% aqueous sodium nitrite (15 ml.). A bright yellow colour developed and dispersed slowly, and the $[\alpha]_D$ (no correction for alterations in mol. wt.) rose from −50° to −43° in 0·5 hr.; thereafter it was constant. After another 1·5 hr. the product (0·90 g., 77%), m. p. 34—36° (capillary), was precipitated by the addition of water. Crystallisation from ethanol yielded the pure nitrimine (0·447 g.), m. p. 41—43° (capillary), $[\alpha]_D$ −32° (lit.,[44] m. p. 43°).

4-*Methyl*-2-*nitriminopent*-3-*ene*.—The oxime of mesityl oxide (5·0 g.) in acetic acid (7·5 ml.) was treated with pentyl nitrite (7·3 ml.). A vigorous reaction ensued and crystals were deposited. These were collected, washed with ethanol, and dried (3·81 g.; m. p. 138°). Three

[43] Cf. Baker, Gilbert, and Ollis, *J.*, 1952, 1443; Newman and Powell, *ibid.*, p. 3747.
[44] Angeli and Rimini, *Ber.*, 1895, **28**, 1078; *Gazzetta*, 1899, **29**, 36.

crystallisations from ethanol yielded a specimen of constant m. p. 136° (decomp.), 137—138° (capillary), $\lambda_{max.}$ 212·5 (ε 8910) and 310 mμ (ε 4460) (Found: C, 50·9; H, 7·1; N, 19·6. Calc. for $C_6H_{10}O_2N_2$: C, 50·7; H, 7·1; N, 19·7%) (lit.,[45] m. p. 155—156°). The infrared absorption of this compound lacked the usual bands attributed to the nitrimine system in the foregoing compounds but presented a powerful new maximum at 1480 cm.$^{-1}$.

*Decomposition of Nitrimines.*—(i) Cortisol nitrimine (IV; R = H, β-OH) (0·46 g.) was heated in dioxan (10 ml.) and water (10 ml.) for 5 hr. on the steam-bath, then evaporated under reduced pressure to small bulk. Methanol (20 ml.) was added, and evaporation under reduced pressure again carried out until precipitation began. Water was added; a product (0·30 g., 73%), m. p. 202—208°, $[\alpha]_D$ +149° (in dioxan), crystallised. Recrystallisation from methanol yielded cortisol as rhombs, m. p. 207—210°, $[\alpha]_D$ +164° (in MeOH), +154°, $\lambda_{max.}$ 241 mμ (ε 16,700) {lit.,[46] m. p. 215·5—221°, $[\alpha]_D^{24}$ +163° (in MeOH), $\lambda_{max.}$ 242 mμ (ε 16,100 in MeOH)}.

(ii) The nitrimine (IV; R = $H_2$) (0·16 g.) of substance S was decomposed similarly in dioxan (5 ml.) and water (5 ml.). The product, m. p. 197—205°, $[\alpha]_D$ +120° (in dioxan), $\lambda_{max.}$ 240·5 mμ (ε 16,000), was identified with substance S made by hydrolysis of its 21-acetate {lit.,[47] m. p. 202—213°, $[\alpha]_D^{23}$ +132°, $\lambda_{max.}$ 240 mμ (ε 16,600)}.

Similar decompositions could also be brought about with ethanol or acetonitrile containing water. No decomposition occurred in anhydrous solvents or on heating. The nitrimine derived from cortisone acetate (see below) contained water of crystallisation; when heated it melted, losing water, solidified, and finally melted as pure cortisone acetate. Attempts at acetylating the 21-hydroxy-20-nitrimines gave tars.

(iii) The nitrimine (VI; R = $N_2O_2$) (0·20 g.) derived from hecogenin acetate was heated for 1 hr. in refluxing dioxan (4·5 ml.) and water (1·5 ml.) containing urea (23·5 mg.). Crystals separated early and were isolated after dilution with water. This product (0·171 g., 93%), m. p. 243—249° (capillary), $[\alpha]_D$ −3° (in $CHCl_3$), was hecogenin acetate (VI; R = O) {lit.,[48] m. p. 245°, $[\alpha]_D^{25}$ −1° (in $CHCl_3$)}.

(iv) Camphor nitrimine (0·50 g.) was heated at 100° with water (5 ml.) containing urea (0·77 g.) in a Carius tube. The top of the tube was not heated, so that a sublimate (0·096 g.), m. p. 158—160°, collected where it could be easily removed. The infrared spectrum of this specimen was almost indistinguishable from that of pure camphor. It was resublimed at 150—160°/76 cm., giving a pure specimen, m. p. 174—175° (capillary).

(v) The nitrimine (0·50 g.) derived from mesityl oxide was heated with water (5 ml.) at 100° in a Carius tube for 24 hr. The subliming crystals (0·21 g.), m. p. 150—154°, were combined with material (0·16 g.), m. p. 149—150°, isolated by extraction with ether, and crystallised twice from chloroform, to give a product (0·12 g.), m. p. 150—153° (with a phase change at 125°), 155° (capillary), $\lambda_{max.}$ 262·5 mμ ($E_{1\,cm.}^{1\%}$ 595), $\nu_{max.}$ (Nujol) 1650 and 3250 cm.$^{-1}$ (Found: C, 50·8; H, 7·0; N, 18·9. Calc. for $C_6H_{10}O_2N_2$: C, 50·7; H, 7·1; N, 19·7%). This appears to be the compound described by Harries [45] with m. p. 156—157°, arising by the action of water at 120° on the nitrimine. We thank Mr. K. Bowden for doing this experiment.

*Other Reactions with Nitrous Acid.*—(i) To the 20-oxime (III; R = N·OH) (0·25 g.) of substance D 3 : 21-diacetate in acetic acid (8 ml.), 5% sodium nitrite (4 ml.) was added. The solution was left for 2 hr. at room temperature, then diluted with water and filtered. The washed and dried precipitate (0·22 g.), m. p. 180—195°, gave a weak test with TSTZ, and bands at 1310 and 1580 cm.$^{-1}$ in its infrared spectrum showed that it contained much nitrimine (Found: N, 4·2%). It was treated with refluxing 50% aqueous dioxan for 2 hr.; isolation then yielded the diacetate (III; R = O) (0·15 g., 62%), m. p. 215—220°, $[\alpha]_D$ +68°.

(ii) The dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = O, $R^4$ = Ac) (3 g.) of cortisone acetate in acetic acid (60 ml.) was treated during 10 min. with 5% sodium nitrite solution (60 ml.). The solution became yellow at first and evolved a colourless gas (probably nitrous oxide), but after 20 min. it was colourless and still. During the ensuing 100 min. crystals separated. Water precipitated a first crop (1·98 g.), $[\alpha]_D$ +156°, $\lambda_{max.}$ 237 mμ ($E_{1\,cm.}^{1\%}$ 358), melting at 125—140° with gas evolution, solidifying, and remelting at 218—223°, with $\nu_{max.}$ 1566 and 1305 cm.$^{-1}$;

[45] Harries and Gley, *Ber.*, 1899, **32**, 1330; Harries, *Annalen*, 1901, **319**, 230.
[46] Ref. 30; Wendler, Graber, Jones, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 3630.
[47] Ref. 30; Dorfman, *Chem. Rev.*, 1953, **53**, 47; Meystre, Vischer, and Wettstein, *Helv. Chim. Acta*, 1954, **37**, 1549.
[48] Wall, Krider, Rothman, and Eddy, *J. Biol. Chem.*, 1952, **198**, 533; cf. Sannié and Lapin, *Bull. Soc. chim. France*, 1952, 1080.

it gave a weak test with TSTZ [Found: $H_2O$ (K. Fischer) 4·5; N, 3·15%]. A second crop (0·50 g.), m. p. 220—225°, was crude cortisone acetate, purifiable by crystallisation from acetone.

Part (0·25 g.) of the first crop was heated on the water-bath in dioxan (5 ml.) for 1 hr. Water was then added until steroid began to separate. This product (0·18 g.), m. p. 228—235°, $[\alpha]_D$ +225° (in $CHCl_3$), $\lambda_{max.}$ 237 mμ (ε 15,300), was cortisone acetate, the total corrected recovery of which was 69%.

(iii) The 3-oxime (II; $R^1$ = N·OH, $R^2$ = $R^3$ = O, $R^4$ = Ac) (0·10 g.) was treated in acetic acid (3 ml.) with 5% aqueous sodium nitrite (1 ml.). The solution darkened immediately, then became yellow after 3 min., a colourless gas being evolved. After a further 2 min., crystals (0·087 g., 90%), m. p. 222—232°, of cortisone acetate separated. Recrystallisation from acetone gave a purer specimen, m. p. 238—242°.

(iv) The dioxime (I; $R^1$ = $R^3$ = N·OH, $R^2$ = O, $R^4$ = Ac) (0·60 g.) of 4 : 5α-dihydrocortisone acetate was treated in the foregoing manner with acetic and nitrous acid. The solution, after an early green hue, became colourless. The product (0·34 g.) isolated after 2 hours' treatment melted at 160°, resolidified, and remelted at 195—198°. It gave a weak colour with TSTZ and its infrared spectrum included bands at 1580 and 1310 $cm.^{-1}$. Part (0·20 g.) was heated in refluxing dioxan (5 ml.) and water (5 ml.) for 90 min.; the cold solution deposited colourless plates (0·11 g., 33%), m. p. 233—237°, of 4 : 5α-dihydrocortisone 21-acetate.

*Decompositions with Sulphurous Acid.*—The dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = $H_2$, $R^4$ = H) (0·30 g.) of substance S in dioxan (10 ml.) was treated with a saturated aqueous solution of sulphur dioxide (10 ml.). The whole was heated on a steam-bath for 15 hr., sulphur dioxide being bubbled in all the time. Most of the solvent was evaporated and the residue diluted with water. Plates (0·197 g.), m. p. 180—200°, $[\alpha]_D$ +128°, separated; recrystallisation from aqueous ethanol gave pure substance S (0·14 g., 52%), m. p. 190—202°.

In a similar experiment in which sodium acetate was added as a buffer a more polar product was also detected. It was possibly the 3-oxime.

*Partial Hydrolysis of 3 : 20-Dioximes.*—(i) The dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = $H_2$, $R^4$ = H) (0·50 g.) of substance S was dissolved in warm 2N-hydrochloric acid (*ca.* 20 ml.) and set aside at room temperature for 2 days. Neutralisation of the solution and addition of water precipitated the 3-oxime (II; $R^1$ = N·OH, $R^2$ = $H_2$, $R^3$ = O, R = H), whose properties after crystallisation are given in Table 2.

(ii) After a similar experiment in which the dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = O, $R^4$ = H) (0·30 g.) of cortisone was stirred for 0·75 hr. with 2N-hydrochloric acid (30 ml.), the 3-oxime (II; $R^1$ = N·OH, $R^2$ = $R^3$ = O, $R^4$ = H) (0·261 g., 88%) was obtained (see Table 2).

(iii) Cortisol 3 : 20-dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = H, β-OH, $R^4$ = H) (0·50 g.) was hydrolysed in 0·75 hr. in solution in 2N-hydrochloric acid (25 ml.). The product (0·44 g., 89%), m. p. 145—150°, was mainly the 3-oxime (II; $R^1$ = N·OH, $R^2$ = H, β-OH, $R^3$ = O, $R^4$ = H), crystallisation of which gave the compound whose properties are given in Table 2.

*Further Methods for Hydrolysing Oximes and their Methyl Ethers.*—(i) The dioxime (II; $R^1$ = $R^3$ = N·OH, $R^2$ = H, β-OH, $R^4$ = H) (0·25 g.) of cortisol was dissolved in warm N-sulphuric acid (50 ml.) to which ammonium persulphate (0·16 g.) was added. Purified methylene dichloride (50 ml.) was added and the mixture shaken for 8 days at room temperature. A starch–iodide test on the aqueous phase was then still positive. Isolation of the steroid yielded cortisol (0·191 g.), crystallising from ethyl acetate with m. p. 205—208°, $[\alpha]_D$ +163° (*c* 1·64; MeOH), $\lambda_{max.}$ 242 mμ (ε 15,600). Ferric salts could not be used effectively instead of the persulphate.

With the following potential acceptors of the liberated hydroxylamine and in mild or vigorous conditions of acid hydrolysis the oxime groups were not removed or the reactions resulted in general destruction: pyruvic acid, acetone, benzaldehyde, 2 : 4-dinitrobenzaldehyde, furfural, chloral, and formaldehyde. With these acceptors catalysis by pyridine was also unsatisfactory. Pure products could not be isolated after the action of cupric acetate in acetic acid, Raney nickel in acetone, nitric acid in acetic acid, or selenium dioxide. Bromine in acetic acid failed to remove all the nitrogen, and *N*-bromosuccinimide in acetic acid, and *N*-bromoacetamide in dioxan containing perchloric acid, yielded substances containing nitrogen and bromine.

(ii) The dimethyl ether (II; $R^1$ = $R^3$ = N·OMe, $R^2$ = H, β-OH, $R^4$ = H) (75 mg.) of cortisol, mixed with 2N-hydrochloric acid (50 ml.), was shaken with methylene dichloride (50 ml.) for 5 days. A steroid (62 mg.) was then isolated and acetylated with acetic anhydride

(2 ml.) and pyridine (2 ml.) overnight at room temperature. The product was purified by chromatography over neutral alumina [49] to remove a less polar fraction ($R_F$ 0·81) from the main fraction ($R_F$ 0·50), which was cortisol 21-acetate, crystallising from acetone as rhombs (22 mg., 43%), m. p. 214—219°, $[\alpha]_D$ +158°. (Solvent N was used for the paper chromatography.)

21-*Acetoxy*-3 : 3-*ethylenedioxy*-17α-*hydroxypregn*-5-*ene*-11 : 20-*dione* (V; $R^1 = R^2 = O$; $R^3$ = Ac).—This compound was made in 97% yield from cortisone acetate with ethylene glycol refluxing at 20 mm. and toluene-*p*-sulphonic acid as catalyst.[1] The material so obtained, m. p. 272—280°, $[\alpha]_D^{23}$ +59° (in pyridine), was good enough for most purposes; crystallisation from aqueous pyridine gave a pure specimen, m. p. 286—288°, $[\alpha]_D$ +46° (in pyridine) (Found: C, 67·4; H, 7·6. Calc. for $C_{25}H_{34}O_7$: C, 67·3; H, 7·7%) {lit.,[50] m. p. 268—272°, $[\alpha]_D$ +49° (in pyridine)}.

The above acetate (5 g.) was suspended in methylene dichloride (200 ml.) and stirred under nitrogen. A solution of sodium hydroxide in methanol [made by adding 40% aqueous sodium hydroxide (5 ml.) to dry methanol (500 ml.); 0·114N; 98·0 ml., 1 mol.] was added in one lot. The steroid dissolved in 1·5 min., and stirring was continued for a total of 15 min.; the solution was then neutralised with acetic acid (phenolphthalein). Evaporation and subsequent dilution with water gave the crude 21-*hydroxy-ketal* (V; $R^1 = R^2 = O$, $R^3$ = H) (4·27 g., 94%, m. p. 191—198° (capillary). Crystallisation from ethyl acetate yielded prisms (3·2 g., 71%), m. p. 221—224°, $[\alpha]_D$ +32° (in pyridine). Further crystallisation gave the pure compound, m. p. 225—226°, $[\alpha]_D$ +32° (in pyridine) (Found: C, 68·2; H, 8·1. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%).

3 : 3-*Ethylenedioxy*-20-*hydroxyiminopregn*-5-*ene*-11β : 17α : 21-*triol* (V; $R^1$ = H, β-OH, $R^2$ = N·OH, $R^3$ = H).—The ketal oxime (V; R = O, $R^2$ = N·OH, $R^3$ = H) (0·50 g.) (see Table 2) in refluxing ethanol (11 ml.) was reduced in 3 hr. with sodium borohydride (0·40 g.) in water (2 ml.) and N-sodium hydroxide (5·2 ml.). Acidification with acetic acid and extraction with chloroform yielded an oxime (0·375 g., 75%), m. p. 200—204° (decomp.; capillary), which crystallised from aqueous acetone as rods (0·13 g., 61%) with the properties given in Table 2 for the ketal-oxime (V; $R^1$ = H, β-OH, $R^2$ = N·OH, $R^3$ = H).

The foregoing ketal oxime (0·371 g.) was dissolved in ethanol (40 ml.), and 2N-hydrochloric acid (40 ml.) was added. The $[\alpha]_D$ rose from +97° (3 min.) to +160° (22 hr.), at which it stayed constant. After 26 hr. the solution was neutralised with sodium hydrogen carbonate and extracted with chloroform, to yield a product (0·243 g.) which from ethyl acetate gave cortisol (0·105 g., 33%), m. p. 207—209° (decomp.), $[\alpha]_D$ +166° (in MeOH), $\lambda_{max.}$ 241 mμ (ε 15,300).

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[49] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.
[50] Sondheimer *et al.*, ref. 3.