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OXIDATION OF 3-KETO STEROIDS IN ALKALINE MEDIUM

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WE have described in preceding publications [1,2] the preparation of 4-hydroxy-3-keto-Δ^4-steroids from the corresponding 3-keto-4,5-epoxides.

In this paper we report a new method for the synthesis of this class of compounds, consisting in the oxidation of 3-keto-5β-steroids in alkaline solution in the presence of air.

Transformations of ketones by the action of potassium alcoholate and oxygen have already been published: Doering[3] and Elkik[4] by oxidation in alkaline solution of ketones having α hydrogen obtained acids formed by breaking of C-C bonds. Barton obtained a diosphenol from a ketone present in the citrus bitter principle limonin[5] and introduced a 17α-hydroxy group in 20-keto saturated steroids.[6]

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[1] B. Camerino, B. Patelli and A. Vercellone, J.Amer.Chem.Soc. 78, 3540 (1956).

[2] B. Camerino, B. Patelli, A. Vercellone and F. Meda, Il Farmaco (Ed.Sc.) 11, 586 (1956); B. Camerino, R. Modelli and B. Patelli, Ibid. 13, 52 (1958).

[3] W. Doering and R.M. Haines, J.Amer.Chem.Soc. 76, 482 (1954).

[4] E. Elkik, Bull.Soc.Chim.Fr. 933 (1959).

[5] D.H.R. Barton, S.K. Pradham, S. Sternhell and J.F. Templeton, J.Chem.Soc. 255 (1961); see also Experientia 16, 41 (1960).

[6] D.H.R. Barton, E.J. Bailey and J. Elks, Proc.Chem.Soc. 214 (1960).

5β-Androstan-17β-ol-3-one[7] was dissolved in t-butanol containing potassium t-butylate and left at room temperature for 40 hours. After usual work-up we isolated 4-hydroxy-testosterone,[1] m.p. 221-223°, $[\alpha]_D^{22}$ + 102° ($CHCl_3$), ϵ_{278}^{EtOH} 11,900 in 50% yield. Since the isolation of pure 3-keto-5β-steroids is not always easy, we have in other instances used the crude products obtained by catalytic reduction of the corresponding 3-keto-Δ^4-steroids.

The reaction was followed by observing the increase of the U.V. absorption maximum at 278 mμ and required usually 18-50 hours. The yields were in the range of 20-60% of pure 4-hydroxy-Δ^4-3-keto-steroids, isolated by direct crystallization. All the compounds showed the expected enolic properties (ultra-violet, infra-red, ferric chloride) and were identified by comparison with authentic samples prepared as already described.[1,2] The steroids which were subjected to the reaction and the physical properties of the products isolated are reported in Table 1.

We have also applied this reaction to 3-keto-5α-steroids and we have isolated the corresponding 2-keto derivatives in enolic form. The structure of these compounds, which was different from the corresponding 4-hydroxy-3-keto-Δ^4-steroids, was deduced from the following facts:
(1) elementary analysis, (2) maximum at 267-270 mμ in the U.V., (3) red colour developed with $FeCl_3$, (4) H_2O_2 - NaOH oxidation of 17α-methyl-5α-androstane-17β-ol-2,3-dione to 2,3-seco-17α-methyl-5α-androstane-17β-ol-2,3-dioic acid identical with the acid obtained by oxidation of 17α-methyl-5α-androstane-17β-ol-3-one with CrO_3 - AcOH.[8]

In Table 2 are shown the products subjected to the reaction and the physical properties of the compounds obtained.

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[7] V. Prelog, L. Ruzicka, P. Meister and P. Wieland, Helv.Chim.Acta 28, 618 (1945).

[8] L.F. Fieser and M. Fieser, Steroids p.64. Reinhold, New York (1959).

TABLE 1 [a,b]

Properties of 4-Hydroxy-3-keto-Δ^4-derivatives

Starting material[c]	4-Hydroxy-3-keto-Δ^4-derivatives		
	m.p.	$[\alpha]_D^{22}$ in $CHCl_3$	ϵ_{278}^{EtOH}
17α-Methyltestosterone	173-175°	+ 70°	12,950
11β-Hydroxy-17α-methyltestosterone[9]	183-185°	+111°	12,380
19-Nortestosterone[10]	188-190°	+ 50°	11,600
17α-Methyl-19-nortestosterone[11]	168-170°	+ 26°	12,820
Progesterone	233-235°	+191°	12,200
17α-Hydroxyprogesterone	229-231°	+185°	11,850
Δ^4-Pregnen-3-one-BMD[d] [12]	280-285°	- 25°	12,900
Cortisone-BMD[13]	275-277°	+152°	10,200
Hydrocortisone-BMD[13]	268-270°	+ 13°	9,900

[a] Satisfactory analytical and spectral properties have been obtained for the new substances reported herein.

[b] All the 4-hydroxy-3-keto-Δ^4-steroids give with $FeCl_3$ in aqueous ethanol a dark green colour.

[c] Crude 4,5 dihydroderivatives obtained by Pd/C reduction of the following 3-keto-Δ^4-steroids.

[d] The designation BMD signifies bismethylenedioxy.

9 M.E. Herr, U.S.Pat. 2.793.218; Chem.Abstr. 52, 1298d (1958).

10 A.L. Wilds and N.A. Nelson, J.Amer.Chem.Soc. 75, 5366 (1953).

11 C. Djerassi, L. Miramontes, G. Rosenkraz and F. Sondheimer, J.Amer.Chem.Soc. 76, 4092 (1954).

12 R. Beyler and L.H. Sarett, U.S.Pat. 2.888.457.

13 R.E. Beyler, R.M. Moriarty, F. Hoffman and L.H. Sarett, J.Amer.Chem.Soc. 80, 1517 (1958).

TABLE 2

Properties of 2,3-Diketo-5α-derivatives [a]

Starting material	2,3-diketo-5α-derivatives			
	m.p.	$[\alpha]_D^{22}$ in $CHCl_3$	λ_{max}	ϵ
17α-Methyl-5α-androstane-17β-ol-3-one[14]	183-186°	+28°	270	7900
19-Nor-5α-androstane-17β-ol-3-one[15]	158-162°	+37°	237	8700[b]
5α-Pregnane-11β-ol-3-one-BMD[c]	260-262°	-38°	267	9340

[a] See Table 1, note a.

[b] The product of the reaction has been purified as the diacetate.

[c] Prepared from 5α-pregnane-11β,17α,21-triol-3,20-dione-21-acetate[16] by saponification and treatment with hydrochloric acid and formalin; the product had m.p. 235-240°.

It was also interesting to see if 3-keto-Δ^4-steroids reacted when submitted to the action of potassium t-butylate in the presence of air. When a solution of Δ^4-cholestene-3-one in t-butanol was subjected to the action of potassium t-butylate for 36 hours at 25° in an open flask, the absorption maximum at 240 mμ disappeared and two new maxima appeared at 255 and at 315 mμ. After the usual work-up and chromatography, we were able to isolate (15% yield) $\Delta^{4,6}$-cholestadiene-4-ol-3-one (diosterol 1),[17] m.p. 160-163°;

[14] L. Ruzicka, M.W. Goldberg and H.R. Rosenberg, Helv.Chim.Acta 18, 1487 (1953).

[15] A. Bowers, H.J. Ringold and E. Denot, J.Amer.Chem.Soc. 80, 6115 (1958).

[16] J. Pataki, G. Rosenkranz and C. Djerassi, J.Biol.Chem. 195, 751 (1952).

[17] H.H. Inhoffen, Ber.Dtsch.Chem.Ges. 69, 1702 (1936); A. Butenandt and G. Schramm, Ibid. 69, 2289 (1936).

TABLE 3

Properties of 4-Hydroxy-Δ^{6}-3-Keto-$\Delta^{4,6}$- and 3,6-Diketo-Δ^{4}-Derivatives[a]

Starting material	4-Hydroxy-Δ^{6}-dehydro-derivatives			6-Keto-derivatives		
	m.p.	$[\alpha]_D^{22}$	ϵ_{318}^{EtOH}	m.p.	$[\alpha]_D^{22}$	ϵ_{250}^{EtOH}
Testesterone	210-215°	+ 80°[b]	21,200	205-210°	-49°[c]	10,600[19]
17α-Hydroxyprogesterone-20-ethylenketal[20] [e]	263-265°	+102°[d]	23,760	250-252°	-60°[b]	10,300[22]
Cortisone-BMD[13]	310-315°	+145°[b]	20,300	248-250°	-11°[d]	10,460
Hydrocortisone-BMD[13]	288-290°	+ 23°[d]	20,670	288-290°	-79°[b]	10,760
9α-Fluorohydrocortisone-BMD[12]	300-305°	+ 44°[d]	21,480	-	-	-

[a] See Table 1, note a.

[b] In chloroform solution.

[c] In acetone solution.

[d] In dioxane solution.

[e] The data reported for the 4-hydroxy-Δ^{6}-dehydro- and 6-keto-derivatives refer to the products obtained after acid hydrolysis of the ketal group.

ε_{315}^{EtOH} 21.400; $[\alpha]_D^{22}$ +36° ($CHCl_3$) and (5% yield) Δ^4-cholestene-3,6-dione;[18] m.p. 123-125°; ε_{251}^{EtOH} 10.500; $[\alpha]_D^{22}$ -37°.

The same reaction was applied to the following steroids (see Table 3).

It is possible to reduce selectively the Δ^6 double bond of 4-hydroxy-$\Delta^{4,6}$-3-keto-steroids; in fact 4-hydroxy-Δ^6-testosterone yields by hydrogenation with Pd/C 4-hydroxy-testosterone.[1]

The 3,6-diketo-Δ^4-steroids possess characteristic I.R. absorption spectra which will be the subject of a future communication by one of us (R.S.).

The oxidations described probably proceed through the attack of oxygen on the anion formed by enolization of the ketone in alkaline medium. It is well known[21] that 3-keto-5β-steroids enolize to 3-hydroxy-Δ^3-compounds while the 5α epimers give 3-hydroxy-Δ^2-steroids; the attack of oxygen takes place on the former at C_4 and on the latter at C_2. In the case of 3-keto-Δ^4-steroids which by enolization give a 3-hydroxy-$\Delta^{3,5}$-diene, the attack of oxygen takes place in position 4 or 6.

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[18] J. Mauthner and W. Suida, Monatsh. 17, 579 (1896); W.C.J. Ross, J.Chem.Soc. 737 (1946).

[19] A. Butenandt and B. Riegel, Ber.Dtsch.Chem.Ges. 69, 1163 (1936).

[20] P.L. Julian, E.W. Meyer and I. Ryden, U.S.Pat. 2.648.662; Chem.Abstr. 48, 7651 (1954).

[21] See ref. 8, p.282.

[22] P.D. Meister, D.H. Peterson, H.C. Murray, G.B. Spero, S.H. Eppstein, A. Weintraub, L.M. Reineke and H.M. Leigh, J.Amer.Chem.Soc. 75, 416 (1953); Makoto Shirasaka, Chem.Pharm.Bull.(Japan) 9, 152 (1961).