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OXIDATION OF CORTICOSTEROIDS BY FLAVINS

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Abstract: The new reaction is reported between corticosteroids and flavins leading to the steroid-21-oic acids.

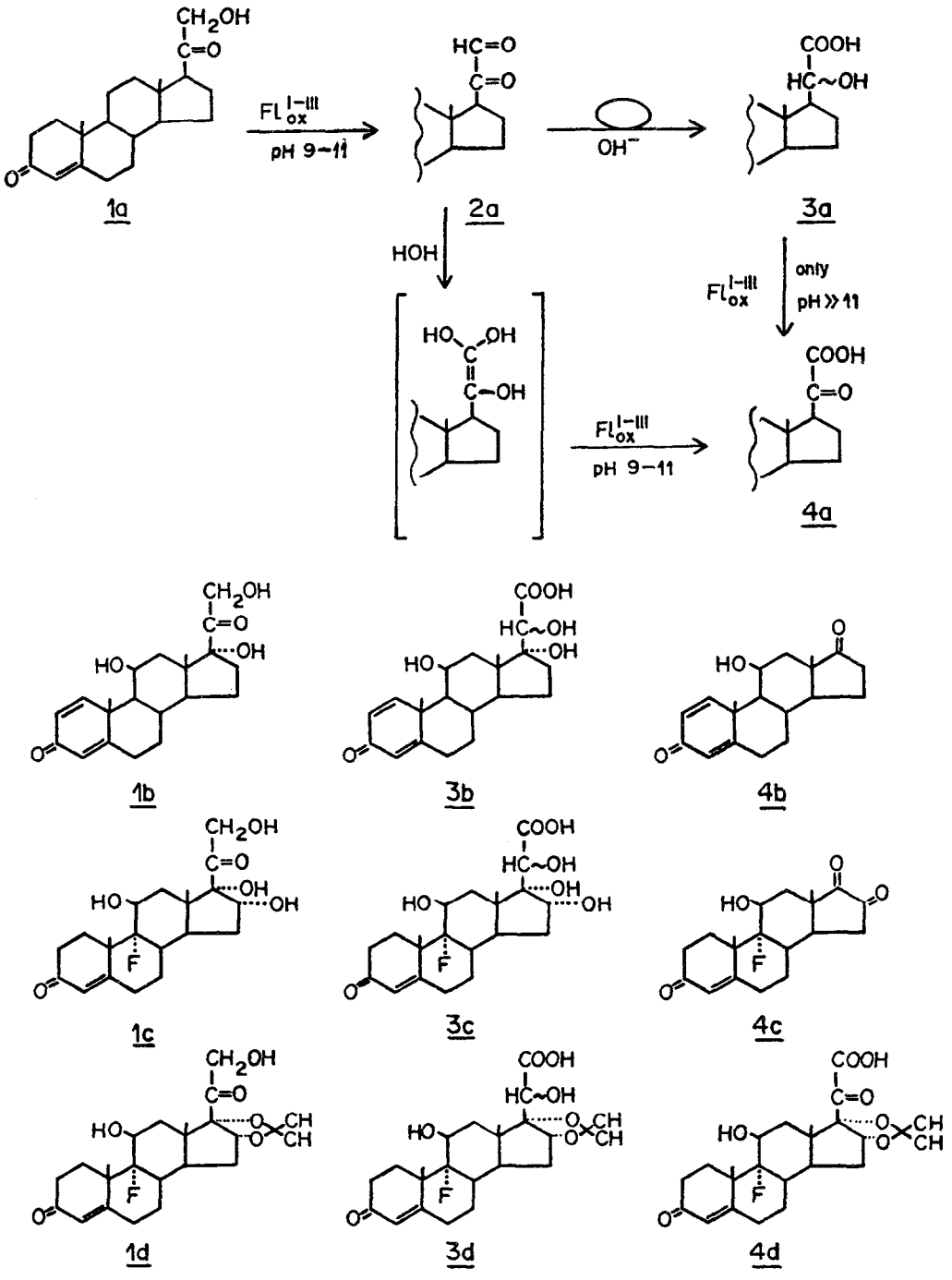
Until now, reports concerning synthesis of steroid 20-hydroxy-21-oic acids from the corticosteroids are still limited[1-3]. The possibility that corticosteroids are oxidized in vivo or in vitro to 21-oic acids has never been seriously considered. Only Monder et al. have shown that carboxylic acids are quantitatively important products of corticosteroid metabolism in man in vivo[4].

In the present paper, we report results concerning synthesis in vitro of the respective steroid-21-oic acids from desoxycorticosterone 1a, prednisolone 1b, 9-fluoro-16α-hydroxyhydrocortisone 1c, acetonide of 9-fluoro-16α-hydroxyhydrocortisone 1d in redox reaction with lumiflavin Fl^{I}_{ox}, 3-methyllumiflavin Fl^{II}_{ox} and 8-carboxylumiflavin Fl^{III}_{ox}.

Synthesis of steroid acids: aqueous or aqueous/ethanol solutions of respective flavins (1mmol) and respective corticosteroids (0.5mmol) in modified Thunberg cuvette were deoxygenated by bubbling N_2 and reaction was achived using 150W lamp. After irradiation stopped (0.5h) the solution were neutralised, then products isolated using column chromatography (silica gel, ethyl acetate - ethanol 3:1).

Under the conditions applied by us, in the oxidation of corticosteroids 1a-d by flavins Fl^{I-III}_{ox}, we obtained high yields of the respective steroid hydroxyacids 3a-d. We found that the oxidation proceeded by way of dehydrogenation of the α-ketol group of the steroid, yielding glyoxal derivatives as intermediate products 2. In alkaline medium, as required for reaction with flavins (pH 9-11), the glyoxal 2 underwent predominantly an intramolecular Cannizzaro rearrangement, leading to the respective steroid hydroxyacids 3a-d.

In aqueous medium, we found that the glyoxalic derivatives 2 undergo partial hydration to give intermediate products containing en-diol forms. The en-diol system favours the re-dehydrogenation of these compounds in the presence of flavins leading to the α-oxoacid 4a (from 1a), the 17-oxosteroid 4b (from 1b), the α-dioxosteroid 4c (from 1c) and the α-oxoacid 4d (from 1d).



In strongly alkaline medium (pH» 11), the isolated steroid hydroxyacids 3a-d partialy underwent further oxygenation in presence of flavines to the derivatives 4a-d, respectively. This reactions did not take place under standard conditions (pH 9-11).

In the previous paper[2], we pointed out the possibility of compounds of the type 4b and 4c arising by decomposition of hypothetical steroid hydroxy-oxo-acids, by analogy to formation of the stable α-oxoacid 4a and acetonide of α-oxoacid 4d. Acetonide blocking of the hydroxy groups at C-16 and C-17 (steroid 1d) lowers the lability of the side chain in corticosteroids. As a result, the side chain at C-17 is not cleaved in the oxidation of steroid 1d. This result is analogous to the result obtained from the oxidation of 1a which contains no hydroxyl group at C-16 or C-17, and is in contrast to the results of the oxidation of steroids 1b and 1c which contain hydroxy groups at C-17 and C-16 + C-17, respectively.

In table we give the yields of the oxidation products 3a-d and 4a-d.

Table

Oxidizing agent	Potential[5,6] $E_{m7(mV)}$	Yields (%) of oxidation products							
		3a	3b	3c	3d	4a	4b	4c	4d
Fl_{ox}^{I}	- 0.207	41	37	40	32	16	8	11	15
Fl_{ox}^{II}	- 0.223	46	43	38	34	11	15	20	14
Fl_{ox}^{III}	- 0.457	67	56	52	46	9	12	10	19

The data in table show that in case when Fl_{ox}^{III} was applied as oxidizing agent, yields of steroid acids 3a-d are better then results obtained with Fl_{ox}^{I} and Fl_{ox}^{II}. This fact may be rationalized by the tendency of the reagents having a more negative potential to react at a higher rate[7]. When Fl_{ox}^{III} is used as the oxidizing agent, rapid dehydrogenation of the hydroxymethyl ketone take place with formation of the intermediate 20,21-dioxo derivative 2. Hence, the rate of this reaction stage essentially controls the yield of the steroid hydroxyacid 3 which is formed from the 20,21-dioxo derivative 2 by an intramolecular Cannizzaro reaction. Detailed results of the studies on the mechanism of this redox reaction will published later.

Physical data for oxidation products:

- their structure was confirmed by ^{1}H-NMR(DMSO-d_6,TMS, δ ppm) and IR (cm^{-1}),
- all compounds gave satisfactory elemental analysis,
- melting points are uncorrected.

3a (20-hydroxy-3-oxo-pregn-4-en-21-oic acid) : m.p. 160-163°C,
molecular formula $C_{21}H_{30}O_4$ (346.5); IR: 3395, 1725, 1660, 1615, 1265;
NMR: 0.7(s,18-CH_3), 1.20(s,19-CH_3), 3.4-3.7(m,OH-acid), 5.8(s,1H,H-C-4).

4a (3,20-dioxopregn-4-en-21-oic acid) : m.p. 157-161°C,
molecular formula $C_{21}H_{28}O_4$ (344.4); IR: 3050, 1730, 1715, 1660, 1250;
NMR: 0.75(s,18-CH_3), 1.15(s,19-CH_3), 4.4(s,OH-acid), 5.75(s,1H,H-C-4).

3b (11β,17α,20-trihydroxy-3-oxopregn-1,4-dien-21-oic acid) : m.p. 235-238°C, molecular formula $C_{21}H_{28}O_4$ (376.4); IR: 3390, 1730, 1660, 1600, 1250; NMR: 1.0(s,18-CH_3), 1.4(s,19-CH_3), 3.8-4.1(m,OH-acid), 4.5(m,1H,H-C-11), 5.9(s), 6.1(d), 7.3(d,H-C-4,H-C-1).

4b (11β-hydroxy-3,17-dioxoandrost-1,4-diene) : m.p. 157-158°C, molecular formula $C_{19}H_{24}O_3$ (300.4); IR: 3400, 1735, 1655, 1610; NMR: 0.95(s,18-CH_3), 1.5(s,19-CH_3), 4.6(m,1H,H-C-11), 5.9(s), 6.1(d), 7.3(d,H-C-4,H-C-1).

3c (9-fluoro-11β,16α,17α,20-tetrahydroxy-3-oxopregn-4-en-21-oic acid) : m.p. 261-263°C, molecular formula $C_{21}H_{29}FO_7$ (412.5); IR: 3320, 2610, 1735, 1660, 1615; NMR: 1.1(s,18-CH_3), 1.4(s,19-CH_3), 3.9-4.2(m,OH-acid), 4.8(m,H-C-11), 5.75(s,H-C-4).

4c (9-fluoro-11β-hydroxy-3,16,17-trioxoandrost-4-ene) : m.p. 225-227°C, molecular formula $C_{19}H_{23}FO_4$ (334.4); IR: 3400, 1710-1725, 1660, 1615; NMR: 0.95(s,18-CH_3), 1.4(s,19-CH_3), 4.7(m,1H,H-C-11), 5.75(s,H-C-4).

3d (O,O-isopropylidene-9-fluoro-11,20-dihydroxy-3-oxopregn-4-en-21-oic acid) : m.p. 267-270°C, molecular formula $C_{24}H_{33}FO_7$ (452.5); IR: 3380, 2690, 1735, 1660, 1615sh, 1245, 1055; NMR: 1.1(s,18-CH_3), 1.5-1.7(m,3CH_3), 4.05-4.15(m,OH-acid), 4.7(m,1H,H-C-11), 5.75(s,H-C-4).

4d (O,O-isopropylidene-9-fluoro-11-hydroxy-3,20-dioxopregn-4-en-21-oic acid) : m.p. 252-254°C, molecular formula $C_{24}H_{31}FO_7$(450.5); IR: 3500, 1735sh, 1725, 1660, 1620sh, 1240, 1070; NMR: 1.1(s,18-CH_3), 1.6-1.8(m,3CH_3), 4.9(m,1H,H-C-11), 5.8(s,H-C-4).

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