Organic Compounds with Reversible Red-Ox Potential as Oxidizers in Steroid Chemistry; I. Tetrazolium Salts

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Hitherto, reports on the application of organic red-ox systems in the chemistry of steroids are still rather limited[1]. The group of organic red-ox systems which can be recognized as thermodynamically reversible comprises, among others, tetrazolium salts such as triphenyltetrazolium chloride (TTC) and blue tetrazolium (BT)[2]. The reduction of tetrazolium compounds by the C-17 side-chain of corticosteroids is a classical reaction in the analysis of steroids[3].

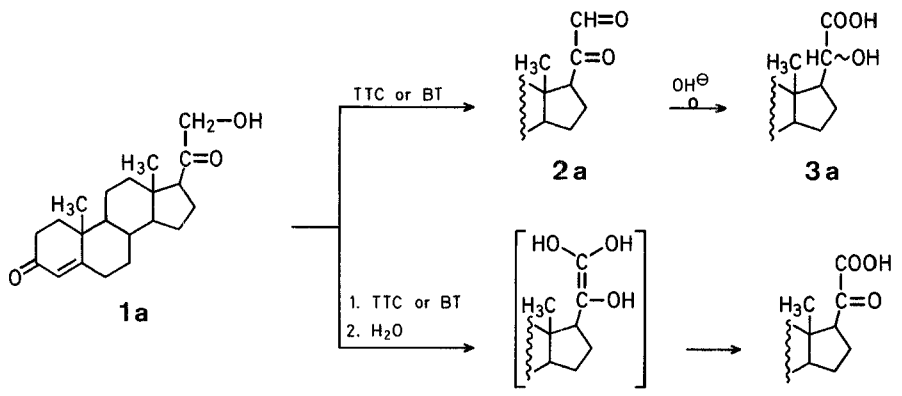
Earlier work by us[4,5] and others[6,7] has permitted the partial determination of the products of corticosteroid oxidation by TTC. Here, we report results on the preparative use of TTC and BT for obtaining steroid hydroxy acids from the respective corticosteroids. Hitherto, only microbiological methods[8] were satisfactory in this respect.

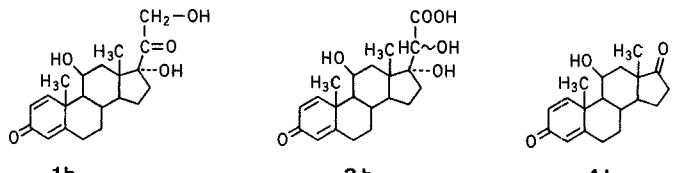
Under the conditions applied by us, in the oxidation of corticosteroids **1a–c** by tetrazolium salts, we obtained high yields of the respective steroid hydroxy acids **3a–c**. By thin layer analysis using standard compounds we found that the oxidation proceeded by way of dehydrogenation of the α-ketol group of the steroid, yielding glyoxal (20-oxo-21-formyl) derivatives as intermediate products **2**. In alkaline medium, as required for oxidation with tetrazolium salts, the glyoxal **2** derivatives underwent predominantly an intramolecular Cannizzaro rearrangement, leading to the respective steroid hydroxy acids **3a–c**.

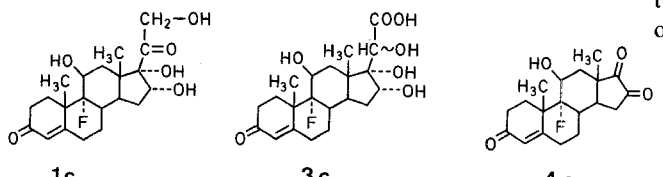
In aqueous medium, we found that the glyoxalic derivatives **2** undergo partial hydration to give intermediate products containing en-diol forms. The en-diol system favours the re-dehydrogenation of these compounds in the presence of tetrazolium salts leading to the α-oxo-acid **4a** (from desoxycorticosterone **1a**), the 17-oxo-steroid **4b** (from prednisolone **1b**), the α-dioxo-steroid **4c** (from 16α-hydroxy-9α-fluoro-hydrocortisone **1c**).

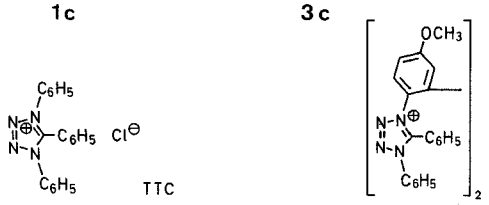
In a previous paper[5], we pointed out the possibility of compounds of the type **4b** and **4c** arising by decomposition of hypothetical steroid hydroxy-oxo-acids, by analogy to the formation of the stable α-oxo-acid **4a**.

No compounds of the type of steroid hydroxy-oxo-acids have as yet to our knowledge been described in the literature. In Table 1 we give the yields of the oxidation products of the respective corticosteroids **1a–c** by TTC and BT.









Generally, the yield of the steroid hydroxy acid **3** is higher with BT than with TTC. On the contrary, use of TTC results in a higher yield of the products of secondary dehydrogenation i.e., **4a**, **4b**, and **4c**, respectively.

The proposed method of oxidation of corticosteroids applying tetrazolium salts is very simple. It permits the easy

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Table 1. Yields of Oxidation Products

Substrate		Products		Yield [%]	
				with TTC	with BT
1a	21-hydro-3,20-dioxopregn-4-ene (desoxycorticosterone)	**3a**	20-hydroxy-3-oxo-pregn-4-en-21-oic acid	62	74
		4a	3,20-dioxopregn-4-en-21-oic acid	11	6
1b	11β,17α,21-trihydroxy-3,20-dioxopregna-1,4-diene (prednisolone)	**3b**	11β,17α,20-trihydroxy-3-oxopregna-1,4-dien-21-oic acid	61	70
		4b	11β-hydroxy-3,17-dioxoandrost-1,4-diene	19	8
1c	9-fluoro-11β,16α,17α,21-tetrahydroxy-3,20-dioxopregn-4-ene (16α-hydroxy-9α-fluorohydrocortisone)	**3c**	9-fluoro-11β,16α,17α,20-tetrahydroxy-3-oxopregn-4-en-21-oic acid	57	63
		4c	9-fluoro-11β-hydroxy-3,16,17-trioxoandrost-4-ene	9	4

Table 2. Physical Data for Products **3a–c** and **4a–c**

Product	m.p. [°C]	Molecular formula[a]	pK_a	I.R. (KBr) ν [cm⁻¹]	¹H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
3a	162–165°	$C_{21}H_{30}O_4$ (346.5)	5.8	3390; 2620; 2650; 1725; 1660; 1615; 1260	0.7 (s, 18-CH_3); 1.15 (s, 19-CH_3); 3.6–3.8 (m, OH-acid); 5.75 (s, 1H, H—C-4)
4a	159–163°	$C_{21}H_{28}O_4$ (344.4)	5.2	3050; 1730; 1715; 1660; 1615; 1250	0.75 (s, 18-CH_3); 1.2 (s, 19-CH_3); 4.3 (s, OH-acid); 5.75 (s, 1H, H—C-4)
3b	236–239°	$C_{21}H_{28}O_6$ (376.4)	5.15	3390; 3250; 2680; 2590; 1730; 1660; 1600; 1250	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	157–159°	$C_{19}H_{24}O_3$ (300.4)	—	3400; 1735; 1655; 1610	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	261–264°	$C_{21}H_{29}FO_7$ (412.5)	4.95	3320; 3240; 2610; 1735; 1660; 1615	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	224–226°	$C_{19}H_{23}FO_4$ (334.4)	—	3400; 1710–1725; 1660; 1615	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)

[a] All compounds gave satisfactory microanalyses (C ±0.31%; H ±0.25%), analyses were performed with a Perkin-Elmer 240 Microanalyzer.

separation of the reduction products of the tetrazolium salts from the steroid products of the oxidation process. Appropriate extraction, according to changes in the pH of medium, permits the separation of the individual products of oxidation, **3** and **4**, which do not require chromatographic purification.

Oxidation of Steroids 1a–c with Tetrazolium Salts; General Procedure:

The steroid **1** (3 mmol) and the tetrazolium salt (6 mmol of TTC or 4 mmol of BT) are dissolved in 96% ethanol (200 ml). A stream of oxygen-free nitrogen is maintained over the solution. A solution of potassium hydroxide (0.7 g) in water (20 ml) is added (potassium hydroxide concentration of reaction solution: 0.056 normal). The mixture is allowed to stand for 0.5 h at room temperature, water (50 ml) is then added, the mixture cooled to 0 °C, and the precipitated, coloured formazans (reduction product of tetrazolium salt) removed by filtration. The filtrate is neutralised with 0.2 normal sulphuric acid (~50–60 ml) and last traces of formazans removed by extraction with petroleum ether (b.p. 45–55 °C; 3 × 50 ml). The aqueous solution of the oxidation products of the steroid is made basic (pH 11) by addition of 0.1 normal potassium hydroxide (to form potassium salts of the steroid acids which are then not extracted by weakly polar solvents). The solution is then extracted with benzene (3 × 70 ml) and both phases are separated.

Benzene phase: The benzene extract is dried with sodium sulphate and evaporated to give the crude, non-acidic, oxidation products **4**. The solid is recrystallised from benzene/petroleum ether (3:2) to give pure **4b** from **1b** or pure **4c** from **1c**.

Aqueous phase: The aqueous phase is adjusted to pH 5 by addition of 2 normal sulphuric acid (to produce free steroid acids) and extracted with chloroform (3 × 70 ml). The combined chloroform extract is dried with sodium sulphate and evaporated to give the crude steroid acids **3a–c** and **4a**. The crude solid is recrystallised from acetone/water (1:1) to give pure **3a–c**. Acid **4a** does not crystallise from acetone/water. Thus, the mother liquor from the crystallisation of **3a** is evaporated to dryness and the residue recrystallised from chloroform/petroleum ether (2:1) to give pure **4a**.

Received: March 7, 1980

[1] J. Fried, J. Edwards, *Organic Reactions in Steroid Chemistry*, Vol. I, Van Nostrand, New York, 1972, pp. 222–250.

[2] F. P. Altman, *An Introduction to the Use of Tetrazolium Salts in Quantitative Enzyme Cytochemistry*, Koch-Light Laboratories Ltd., Colnbrook, Bucks., England, 1972.

[3] S. Görög, Gy. Szász, *Analysis of Steroid Hormone Drugs*, Elsevier, Amsterdam, 1978, pp. 331–343.

[4] A. Smoczkiewicz, J. Jasiczak, *Zesz. Nauk. Wyzsza Szk. Ekon. Poznan. Ser. 1*, **46**, 181 (1972); *C. A.* **80**, 60071 (1974).

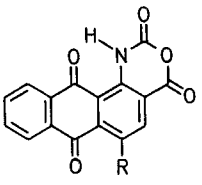
[5] A. Smoczkiewicz, J. Jasiczak, *Zesz. Nauk. Wyzsza Szk. Ekon. Poznan. Ser. 2* **53**, 125 (1973); *C. A.* **81**, 136360 (1974).

[6] H. Möhrle, D. Schittenhelm, E. Federolf, *Arch. Pharm. (Weinheim, Ger.)* **305**, 587 (1972).

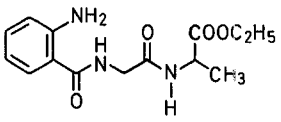
[7] S. Görög, P. Horváth, *Analyst* **103**, 346 (1978).

[8] K. O. Martin, C. Monder, *Biochemistry* **15**, 576 (1976).

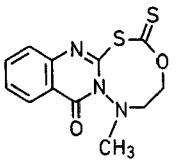
G. M. Coppola, *Synthesis* **1980** (7), 505–536;
The structures of compounds **43** (p. 511), **122** (p. 520), and **241** (p. 533) should be as shown below:



43

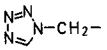


122



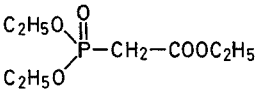
241

J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, A. Zugaza-Bilbao, *Synthesis* **1980** (7), 547–551;
The substitutent R^1 in Table 1 entries 2 and 20 and Table 2, entry 1 should be:



A more correct name for reagent **4** (as used in index) is **3,3'-(Chlorophosphinylidene)-bis[2-oxo-1,3-oxazolidine].**

J. Becher, *Synthesis* **1980** (8), 589–612;
The structure of compound **36** (p. 593) should be:



36

H. Paulsen, F. R. Heiker, J. Feldmann, K. Heyns, *Synthesis* **1980** (8), 636–638;
The correct name for reagent **1** is **3-methyl-2-selenoxo-2,3-dihydro-1,3-benzothiazole.**

G. Sosnovsky, J. A. Krogh, *Synthesis* **1980** (8), 654–656;
The first line of the text should read:
In 1978, Olah and Vankar reported[1] the conversion of

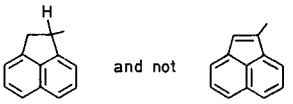
D. A. Walsh, *Synthesis* 1980 (9), 677–688;
The correct name for compound **39** (p. 680) is ***N'*-(2-Carboxyphenyl)-*N,N*-dimethylformamidine.**

M. A. Smoczkiewicz, J. Jasiczak, *Synthesis* **1980** (9), 739–740;
Compounds **2** should be named as **20,21-dioxo derivatives**; the name for compound **1a** (p. 740, Table 1) should be **21-hydroxy-3,20-dioxopregn-4-ene.**

Abstract 5878, *Synthesis* **1980** (9), 759;
The title should be: **Hydrofluorination, Halofluorination, and Nitrofluorination of Alkenes and Alkynes by Pyridinium Poly(Hydrogen Fluoride).**

Abstract 5885, *Synthesis* **1980** (9), 761;
The title should be: **Alkylation of *S*-Methyl 3-Oxoalkanethioates.**

T. Wagner-Jauregg, *Synthesis* **1980** (10), 769–798;
The name of compounds **552a** and **b** (p. 772) should be ***cis*-** and ***trans*-1-methyl-3-phenylindan.**
The heading for Table 2 (p. 784) should be:
Tabelle 2. Herstellung von 1-Arylacenaphthen-Derivaten durch Photocyclisierung von 1-(1-Arylethenyl)-naphthalin-Derivaten in Abwesenheit von Oxidationsmitteln[441].
The structures of the products in this Table should be of the type:



and not

The first paragraph on p. 785 (right-hand side) should read:
Aus den konjugierten 1,2-Diiminen **667** und Phenyl-isocyanaten oder Benzoyl-isocyanat entstehen criss-cross-Addukte (**668**, Schema **2.2.1.-E**)[480,481].

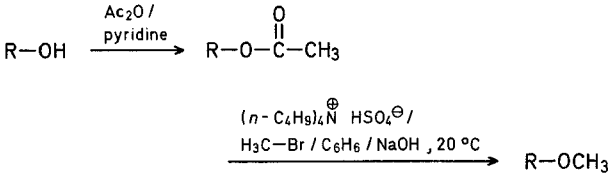
The last line on p. 794 should read:
und der Hydroxamsäuren[552] deutlich gesteigert[553].

Reference 441 (p. 796) should be:
[441] R. Lapougade, R. Koussini, H. Bouas-Laurent, *J. Am. Chem. Soc.* **99**, 7374 (1977).

H. Alper, D. E. Laycock, *Synthesis* **1980** (10), 799;
The last structure for R^1-R^2 in the Table should be:

T. Takajo, S. Kambe, *Synthesis* **1980** (10), 833–836;
Products designated as **4a,b,c,d** in Table 1 (p. 834) and Table 2 (p. 835) should be designated as **4a,b,f,g,** respectively.

P. Di Cesare, P. Duchaussoy, B. Gross, *Synthesis* **1980** (11), 953–954;
The first formula scheme (p. 954) should be:



Z. H. Kudzin, W. J. Stec, *Synthesis* **1980** (12), 1032–1034;
The heading for the first procedure (p. 1033) should be: **3-(Tris-[*t*-butoxy]silylthio)-propanal [3; R = (*t*-$C_4H_9O)_3Si$].**

R. E. Zipkin, N. R. Natale, I. M. Taffer, R. O. Hutchins, *Synthesis* **1980** (12), 1035–1036;
The substituents R^1-R^2 in the Table for product **4e** should be:
—$(CH_2)_2$—C[=$C(CH_3)_2$]—CH_2—

Abstract 5948, *Synthesis* **1980** (12), 1040;
Compounds **2** should be named **carboximidium dichlorides.**

Abstract 5963, *Synthesis* **1980** (12), 1045;
The title should be: **Acyl Fluorides, Chlorides, Bromides, and Iodides from Carboxylic Acids.**

Abstract 5973, *Synthesis* **1980** (12), 1047;
The title should be: **Acetoxylation-Arylselenylation of Alkenes.**