Notes

Lead Tetraacetate Oxidation of Steroidal Hydrazones

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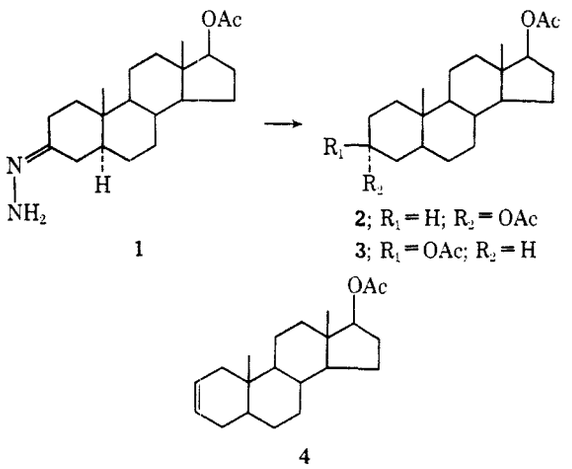
Received October 13, 1968

The purpose of this study is to examine the products formed when steroidal hydrazones are oxidized with lead tetraacetate, and compare these to products of other oxidative deamination reactions of steroidal amines.[1]



1

2; R_1 = H; R_2 = OAc

3; R_1 = OAc; R_2 = H

4

Oxidation of the 3-hydrazone of 17β-acetoxy-5α-androstan-3-one (1) with lead tetraacetate resulted in the immediate evolution of nitrogen.[2] The olefinic and ester products from this reaction were analyzed by vapor phase chromatography and then isolated by column chromatography. These products are tabulated in Table I.

TABLE I

	% olefin	% ester	% composn— 3α	3β
Reaction products from the oxidation of 1[a]	25[c]	52	65	35
3α-Nitrosoamide of cholestane decomposition products[b]	69–89	8–16	76–83	24–17

[a] Average of five runs. [b] Data reported by White and Bachelor; see ref 1. [c] A mixture of olefins containing 85% of the Δ^2 isomer.

The ratio of epimeric acetates in the present study shows a predominance of 3α-acetate 2 and is in qualitative agreement with the results obtained by White for nitrosoamide decompositions[1] (see Table I).

This reaction requires the conversion of the hydrazone into a reactive species which can readily lose nitrogen and either react with the acetic acid formed in the reaction to afford ester products or lose a proton to give olefinic products. Furthermore, the predominance of the 3α-acetate indicates that factors may be present which result in some measure of stereoselectivity in the formation of those esters, possibly in the protonation step.[3] Owing to the essentially instantaneous rate of reaction, no direct study of the mechanism could be made. Attempts to show solvent change effects by varying the acetic acid concentration and by using pyridine showed the product ratios quite unresponsive to changes in conditions (see Table II, Experimental Section).[4]

Experimental Section[5]

17β-Acetoxy-5α-androstan-3-one Hydrazone.—A solution of 5 g of 5α-androstan-17β-ol-3-one 17-acetate in 70 ml of EtOH, 1 ml of triethylamine, and 1 ml of hydrazine hydrate was refluxed for 2 hr and cooled.[6] The solvents were removed under vacuum, and the white residue was carefully recrystallized once from EtOH–H_2O to give 4 g of colorless crystals, mp 215–219°, which were suitable for subsequent oxidation: ir (mull) 3330, 3500 (-NH_2), 1640 cm^{-1} (C=N). Azine formation became apparent when this material was recrystallized several times. *Anal.* Calcd for $C_{21}H_{34}O_2N_2$: C, 72.79; H, 9.89; N, 8.09. Found: C, 72.38; H, 9.98; N, 7.82.

Lead Tetraacetate Oxidation of 1.—A solution of 1.39 g (2.9 mmol) of lead tetraacetate (dried under vacuum over KOH) was dissolved in 75 ml of dry CH_2Cl_2 and cooled to 0° in an ice bath. A solution of 1.0 g (2.8 mmol) of 1 in 75 ml of CH_2Cl_2 was added dropwise. Instantaneous evolution of nitrogen resulted, and a white precipitate of lead acetate formed. The theoretical volume of nitrogen was evolved. After the addition was complete, the ice bath was removed; the reaction mixture was allowed to warm with stirring for 0.5 hr. H_2O was added, stirring continued for a few minutes, and the mixture was filtered through a cake of filter aid. CH_2Cl_2 was added to the filtrate, as well as additional H_2O; the organic layer was separated, washed with saturated $NaHCO_3$ solution, saturated salt solution, and dried over $MgSO_4$. Evaporation of solvent gave an oily solid. The crude oil (0.962 g) was chromatographed on 20 g of Florisil (100–200 mesh). Three major components were isolated: 5α-androst-2- (and 3-) en-17β-ol 17-acetate (4) from petroleum ether (bp 30–60°) (cuts 4–83, 0.22 g, mp 96–106°); 5α-androstan-3α,17β-diol diacetate (2), 5% through 30% benzene in petroleum ether (cuts 84–302, 0.356 g, mp 159–160°[7] 32.4%); 5α-androstane-3β,17β-diol diacetate (3), 30% through 50% benzene in petroleum ether (cuts 302–1063, mp 126–127°,[8] 19%). This isolation was monitored by glpc; combination of cuts were made on this basis.

(1) E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, 77 (1965), and references cited therein.

(2) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, **83**, 747 (1961).

(3) A recent study by W. Kirmse and R. Siegfried, *J. Amer. Chem. Soc.*, **90**, 6564 (1968), illustrates that 2-diazonorpinane can undergo *exo* protonation stereospecifically to give reaction products that are best explained by the occurrence of 2-*endo*-norpinyldiazonium ion as an intermediate.

(4) The low activation energy for this type of reaction minimizes the effect of solvation. See G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(5) All melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were taken on a Varian HR-60 instrument with tetramethylsilane as an internal standard. Ir spectra were obtained on a Beckman IR-9 spectrophotometer. A Barber–Coleman gas chromatograph, equipped with 1% XE-60 on Gas Chrom 80/100 column in the vicinity of 200°, was used.

(6) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962).

(7) A. Butenandt and K. Tscherning, *Z. Physiol. Chem.*, **234**, 224 (1935).

(8) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940).

The oxidation was carried out with several concentrations of AcOH in CH_2Cl_2 and also in pyridine. Some representative runs are shown in Table II. Estimates of ester ratios were made by glpc.

TABLE II

	% olefin	% ester	% composn 3α	% composn 3β
10 mol % acetic acid–CH_2Cl_2	28.9	60.7	65	35
100 mol % acetic acid–CH_2Cl_2	31.8	53.2	70	30
Pyridine	23.8	50.3	70	30

Registry No.—Lead tetraacetate, 546-67-8; **1**, 19640-01-8.

Acknowledgments.—The authors are grateful to Mr. G. Maciak and associates for microanalyses, to Mr. D. O. Woolf for physicochemical data, to Mr. C. Snell for gas chromatographic determinations, and to our colleagues, Dr. E. Farkas and Dr. R. T. Rapala, for helpful discussion of this work.

Tetramethyl Bismethylenedioxy Steroids. I. A Novel Protective Group

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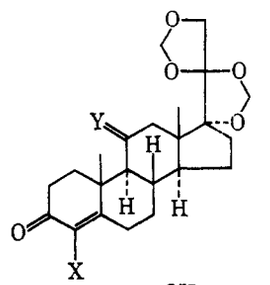
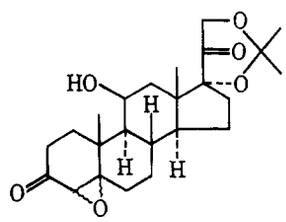
Received November 6, 1968

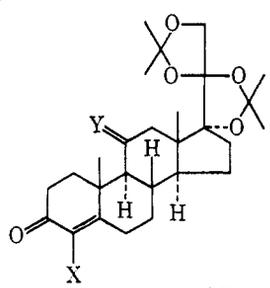
It is widely known that a bismethylenedioxy group (BMD)[3] has outstanding advantages as a protective group for the dihydroxyacetone side chain of adrenocortical hormones. Regarding the limitations, Sarett, *et al.*,[3a] noticed that a ketonic group at C_{11} retarded the BMD hydrolysis to a marked extent. We have noticed that 4-chlorohydrocortisone-BMD (**1b**), 4-chlorohydrocortisone-BMD-11-methoxy methyl ether (**1d**), and 4-chlorocortisone-BMD (**1f**) could not be hydrolyzed by acetic acid, formic acid, or perchloric acid to the corresponding 4-chlorocorticoids. This finding supports Hirschmann's observation[4] that "a variation at an even more remote position of the corticoid—for example, in the A ring—can have a marked effect on the rate of BMD hydrolysis." It may be mentioned in this connection that a chloro substituent at C_4 did not affect the hydrolysis of a 17α,21-acetonide linkage. In fact, 4-chlorohydrocortisone[5] could be prepared directly by the hydrogen chloride treatment of 4ξ,5ξ-oxido-11β-hydroxy-17α,21-isopropylidenedioxypregnane-3,20-dione (**2**). Now we have discovered that the hydrolysis of a tetramethyl bismethylenedioxy (TMBMD) group (or in other words 17,20-20,21-acetonides) is unaffected by an 11-ketone and also by a 4-chloro substituent in a steroid molecule. In fact, hydrocortisone-TMBMD (**3a**), 4-chlorohydrocortisone-TMBMD (**3b**), cortisone-TMBMD (**3c**), and 4-chlorocortisone-TMBMD (**3d**) could smoothly be hydrolyzed by acetic acid (50%) on a steam bath (3–4 hr) to the corresponding corticoids (yields, 80–90%). The faster rate of hydrolysis of the TMBMD grouping may be attributed to the hypercon-





2

1a, X = H; Y = α-OH, β-H
b, X = Cl; Y = α-OH, β-H
c, X = H; Y = α-OCH_2OCH_3, β-H
d, X = Cl; Y = α-OCH_2OCH_3, β-H
e, X = H; Y = O
f, X = Cl, Y = O



3a, X = H; Y = α-OH, β-H
b, X = Cl; Y = α-OH, β-H
c, X = H; Y = O
d, X = Cl; Y = O

jugation effect of the acetonide methyl groups. The nmr spectrum ($CDCl_3$) of the TMBMD compounds showed signals which supported the presence of six methyl groups (τ 8.2–9.1) and one OCH_2 group (5.9–6.0). **3a** and **3c** also showed the vinyl proton (τ 4.3–4.35). The ultraviolet (uv) absorptions of the 4-chloro derivatives (**1b**, **1d**, **1f**, **3b**, and **3d**) were in the region of 254–255 mμ. The TMBMD compounds showed absorptions at 1370–1390 (*gem*-dimethyl) and 1220–1230 cm^{-1} (asymmetric C—O—C stretching) in addition to the symmetric stretching around 1070 cm^{-1}. The BMD derivatives, on the other hand, exhibit only symmetric C—O—C stretching at 1100 cm^{-1}.[3a] The chlorine substituent at C_4 of the corticoids and their derivatives (BMD and TMBMD) makes significant shifts (20–25 cm^{-1}) of Δ^4-3-keto band toward higher and C=C band toward lower frequencies. Satisfactory elemental analyses were obtained for all the new compounds.

In the preparation of the TMBMD compounds, steroids were dissolved in dry acetone, a few drops of perchloric acid (70%) were added, and the solution was stirred overnight at room temperature (yield 60–65%). Chlorination of the corticoid derivatives was effected

(1) To whom all enquiries regarding this paper should be directed.

(2) Recipient of a Roswell Park Memorial Institute summer fellowship from The National Institute of Health, Training Grant CA06183, 1967.

(3) (a) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961), and other papers in this series; (b) *ibid.*, **26**, 2426 (1961); (c) *J. Amer. Chem. Soc.*, **81**, 1235 (1959); (d) *ibid.*, **82**, 170 (1960).

(4) See ref 7 on p 2423 of ref 3a.

(5) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).