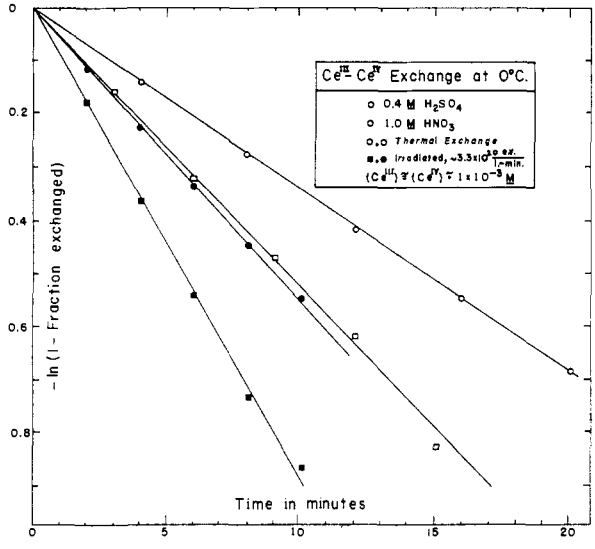


Fig. 1.

TABLE I

DOSIMETRY AND EXCHANGE DATA AT 0°

Observed rate of ferrous oxidation in 0.4 M H_2SO_4: 77.7 μmole/liter-minute $G_{Fe(III)}$ = 14 ions/100 ev. (assumed for low energy X-rays)

Medium	Rate Ce(IV) reduction (μmoles/l.-min.)	Radiation-induced exchange rate (μmols/l.-min.)	$G_{Ce(III)}$ (ions/100 ev.)	$G_{exchange}$ (ions/100 ev.)
0.8 N H_2SO_4	18.2	17.8	3.28	3.2
1.0 N HNO_3	46.1	9.6	8.32	1.7

All experiments were performed at 0° in order to minimize the contribution from the spontaneous thermal exchange process. G_{OH} values of 2.23–2.58 have been reported in the literature[5] for similar irradiation conditions at room temperature. This is certainly in the same range as our $G_{exchange}$ value found in H_2SO_4 and is highly suggestive that the inclusion of equation (1) in the ceric sulfate reduction mechanism is indeed valid.

In the HNO_3 system, the high $G_{Ce(III)}$ and low $G_{exchange}$ values are consistent with the above interpretation if it may be assumed that G_{OH} = 3.2, equal to the observed $G_{exchange}$ in the H_2SO_4 system. Since $G_{exchange}$ in HNO_3 is only 1.7, there remain about 1.5 OH radicals per 100 ev. which are free to react with the system in some other manner. If any of the following reactions occur, all of which are energetically possible under the experimental conditions employed, the additional reducing power of the solution would be sufficient to account for the large value of $G_{Ce(III)}$ in nitric acid.

$$OH + NO_3^- + H^+ = HO_2 + HNO_2 \qquad E^\circ = -0.16^6$$

$$2OH + NO_3^- + H_2O + H^+ = 2H_2O_2 + HNO_2 \qquad E^\circ = +0.22$$

$$3OH + NO_3^- + H_2O + H^+ = 3H_2O_2 + NO \qquad E^\circ = +0.24$$

We are currently engaged in extensive studies of the radiation-induced exchange in both the Ce(III)–Ce(IV) and Tl(III)–Tl(I) systems. Although Ce(III) and Ce(IV) possess opposite ionic charges in H_2SO_4 solutions,[7] the observed spontaneous exchange rate does not seem to differ greatly from that found for the nitric acid system,[8] in which both exist as cations. For this reason, a kinetic investigation of the spontaneous cerium exchange in H_2SO_4 is also planned.

(5) T. J. Hardwick, *Discussions Faraday Soc.*, **12**, 203 (1952).

(6) W. Latimer, "Oxidation Potentials," 2nd ed., Prentice-Hall Inc., New York, N. Y., 1952, pp. 45–50, 93.

(7) T. J. Hardwick and E. Robertson, *Can. J. Chem.*, **29**, 828 (1951).

(8) J. W. Gryder and R. W. Dodson, THIS JOURNAL, **73**, 2890 (1951).

UNIVERSITY OF CALIFORNIA GEORGE E. CHALLENGER
LOS ALAMOS SCIENTIFIC LABORATORY BURTON J. MASTERS
LOS ALAMOS, NEW MEXICO

RECEIVED JANUARY 13, 1955

STEROIDS AND RELATED PRODUCTS. II.[1] THE SYNTHESIS OF 11-DEHYDRO-17α-METHYLCORTICOSTERONE ACETATE

Sir:

The important biological properties of 17-methylated estradiol,[2] testosterone[3a,b,c] and other androgens, such as Δ^5-3β,17β-dihydroxy-17α-methylandrostene[3a,4] and the recently described 17aα-methyl-D-homotestosterone[5] and 17α-methyl-19-nortestosterone,[6] of progesterone[7a,b,c] and desoxycorticosterone[1,8a,b] made the synthesis of 17-methyl adducts of 11-oxygenated adrenal cortical hormones desirable. I now wish to record the synthesis of 11-dehydro-17α-methylcorticosterone acetate (IV), a biologically active homolog of 11-dehydrocorticosterone acetate and analog of cortisone acetate.

Reaction of 3α-acetoxy-11,20-diketopregnane (I) with one mole of bromine gave a product from which the 17-monobromo derivative Ia[9] [m.p. 168–170°, $[\alpha]^{25}D$ 0.8° (c 0.864, $CHCl_3$); calcd. for $C_{23}H_{33}O_4Br$: C, 60.92; H, 7.34; Br, 17.63. Found: C, 60.86, 61.14; H, 7.47, 7.43; Br, 17.51, 17.45], a dibromide to which, according to present evidence, structure Ib should be assigned [m.p. 177°, $[\alpha]^{24}D$ 22.3° (c 1.121, $CHCl_3$); calcd. for $C_{23}H_{32}O_4Br_2$: C, 51.89; H, 6.06; Br, 30.03. Found:

(1) Paper I of this series: Ch. R. Engel and G. Just, THIS JOURNAL, **76**, 4909 (1954).

(2) B. C. Bocklage, H. J. Nicholas, E. A. Doisy, Jr., W. H. Elliott, S. A. Thayer and E. A. Doisy, *J. Biol. Chem.*, **202**, 27 (1953).

(3) (a) L. Ruzicka, M. W. Goldberg and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935); (b) K. Miescher and E. Tschopp, *Schweiz. Med. Wochenschrift*, **68**, 1258 (1938); (c) *cf.* also E. J. Foley, *Proc. Soc. Exp. Biol. Med.*, **75**, 811 (1950); A. T. Kenyon, K. Knowlton and I. Sandiford, *Ann. Int. Med.*, **20**, 632 (1944).

(4) *Cf.* for instance E. Henderson and M. Weinberg, *J. Clin. Endocrinol.*, **11**, 641 (1951); see also the literature discussed in a recent paper by P. M. Hyde, W. H. Elliott, E. A. Doisy, Jr., and E. A. Doisy [*J. Biol. Chem.*, **207**, 287 (1954)].

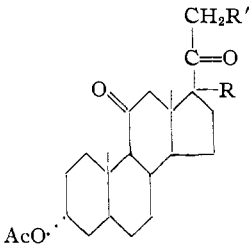
(5) H. Heusser, Nagi Wahba and F. Winternitz, *Helv. Chim. Acta*, **37**, 1052 (1954).

(6) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954).

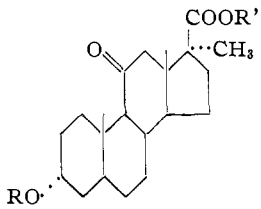
(7) (a) Pl. A. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta*, **32**, 270 (1949); (b) H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *ibid.*, **33**, 2229 (1950); (c) Hs. H. Günthard, E. Beriger, Ch. R. Engel and H. Heusser, *ibid.*, **35**, 2437 (1952).

(8) (a) H. Heusser, E. Beriger and Ch. R. Engel, *ibid.*, **37**, 2166 (1954); (b) *cf.* also a forthcoming publication on the biological activities of this substance.

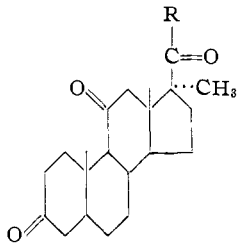
(9) Compare P. L. Julian, *Recent Progr. in Hormone Research*, **6**, 195 (1951). Recently, H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan and J. A. Hogg reported [THIS JOURNAL, **76**, 743 (1954)] the preparation of Ia by the action of hypobromous acid on the 17-enol acetate of I.



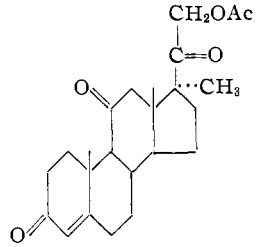
I, R = R′ = H
Ia, R = Br, R′ = H
Ib, R = R′ = Br



II, R = R′ = H
IIa, R = H, R′ = CH_3
IIb, R = Ac, R′ = CH_3



III, R = OH
IIIa, R = OCH_3
IIIb, R = Cl
IIIc, R = CHN_2
IIId, R = CH_2Cl
IIIe, R = CH_2I
IIIf, R = CH_2OAc



IV

C, 51.85; H, 6.24; Br. 29.82] and the starting material I were isolated. The crude, not easily separable bromination product was subjected to a rearrangement of the Aston–Greenburg type[10a,b,c] and, after debromination and reacetylation, methyl 3α-acetoxy-11-keto-17α-methyletianate (IIb) [m.p. 184°, $[\alpha]^{25}D$ 63.7° (*c* 0.982, $CHCl_3$); calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.99. Found: C, 71.21; H, 8.80] obtained in approximately 40% yield from the neutral fraction of the reaction product. From the acid fraction the hydroxy acid II [m.p. 285–286°, $[\alpha]^{25}D$ 29.5° (*c* 1.099, dioxane); calcd. for: $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.34; H, 9.04] was isolated. The pure monobromide Ia gave under similar conditions a higher yield of ester IIb and acid II. Refluxing of IIb with methanolic potassium hydroxide gave the hydroxy ester IIa [m.p. 165°, $[\alpha]^{22}D$ 41.5° (*c* 1.012, $CHCl_3$); calcd. for $C_{22}H_{34}O_4$: C, 72.80; H, 9.45. Found: C, 72.78; H, 9.30], also obtained upon methylation of acid II and easily reacetylated to the ester IIb. Prolonged treatment of the latter with methanolic potassium hydroxide in a sealed tube at 170° gave a high yield of the free acid II. Oxidation of acid II with chromic acid afforded the keto acid III [m.p. 288.5°, $[\alpha]^{22}D$ 45.1° (*c* 0.941, dioxane); calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.68; H, 8.75. Yield 85–90%], further characterized by its methyl ester IIIa [m.p. 185°, $[\alpha]^{23}D$ 49.8 (*c* 1.002, $CHCl_3$); calcd. for $C_{22}H_{32}O_4$: C, 73.27; H, 8.95. Found: C, 73.49; H, 8.81] which was also obtained by chromic acid oxidation of IIa. Acid III was transformed to its chloride IIIb with oxalyl chloride, using Reichstein's modification[11] of Wilds' method.[12] The crude acid chloride reacted with diazomethane, giving the diazo ketone IIIc, which, upon decomposition with hydrochloric acid, yielded the chloroketone IIId [m.p. 151°, $[\alpha]^{25}D$ 48.1° (*c* 0.890, $CHCl_3$); calcd. for $C_{22}H_{31}O_3Cl$: C, 69.73; H, 8.25; Cl, 9.36. Found: C, 69.93; H, 8.38; Cl, 9.32. Yield from III 65–70%]. The chloride IIId was converted to the iodide IIIe and thence, using a method previously described,[1,8a] with silver acetate in boiling pyridine, in the presence of small amounts of acetic anhydride and under nitrogen, to the ketol acetate IIIf [m.p. 191.5–192.5°, $[\alpha]^{24}D$ 45.9° (*c* 1.051, $CHCl_3$); calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.67; H, 8.44. Yield from IIId 65–70%]. Introduction of the Δ^4-double bond, according to Kendall's procedure,[13] through the 4-bromide (m.p. 163–164°) and the Δ^4-3-semicarbazone (m.p. 210–215°) of IIIf, gave 11-dehydro-17α-methylcorticosterone acetate (IV) [m.p. 157–158°, $[\alpha]^{24}D$ 170° (*c* 0.79, $CHCl_3$); λ_{max}^{EtOH} 237 mμ (log ϵ 4.44); $\nu_{max}^{CHCl_3}$ 1750 and 1720 cm.$^{-1}$ (21-acetoxy-20-ketone doublet); 1710 cm.$^{-1}$ (11-ketone); 1670 and 1620 cm.$^{-1}$ (Δ^4-3-ketone doublet); calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.23; H, 7.96. Yield from IIIf approximately 60%].

The adrenal cortical activity exhibited by the new hormone analog, 11-dehydro-17α-methylcorticosterone acetate, will be the subject of a separate communication.

I wish to express sincere thanks to the Canadian Life Insurance Officers Association for financial support; to the Ciba Company Limited, Basel, Switzerland, for the generous gift of starting material, to Dr. E. H. Venning, Royal Victoria Hospital, Montreal, for the biological tests; to Dr. R. N. Jones, National Research Council, Ottawa, for the infrared spectral analysis; and to Dean J. B. Collip for his continued encouragement. The author also wishes to express his appreciation to Mr. J. F. Alicino, Metuchen, New Jersey, who carried out the micro analyses.

(10) (a) J. G. Aston and R. B. Greenburg, THIS JOURNAL, **62**, 2590 (1940). (b) See also Al. Faworsky, *J. prakt. Chem.*, [2] **88**, 658 (1913). (c) Comparable rearrangements of 17-bromo-20-ketosteroids have been described by R. E. Marker and R. B. Wagner [THIS JOURNAL, **64**, 216, 1273 (1942)]; Pl. A. Plattner, H. Heusser and S. F. Boyce [*Helv. Chim. Acta*, **31**, 603 (1948)]; H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner [*ibid.*, **33**, 2229 (1950)].

(11) F. Reber, A. Lardon and T. Reichstein, *ibid.*, **37**, 45 (1954). A. Lardon and T. Reichstein, *ibid.*, **37**, 388, 443 (1954).

(12) A. L. Wilds, U. S. Patent 2,538,611. A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948). Compare also R. Adams and L. H. Ulich, *ibid.*, **42**, 599 (1920).

(13) W. F. McGuckin and E. C. Kendall, *ibid.*, **74**, 5811 (1952).

COLLIP MEDICAL RESEARCH LABORATORY
UNIVERSITY OF WESTERN ONTARIO CH. R. ENGEL
LONDON, ONTARIO, CANADA

RECEIVED JANUARY 14, 1955

FORMATION OF A NEW DINUCLEOTIDE FROM COZYMASE BY ENZYMIC DESTRUCTION OF THE "ONIUM" LINKAGE

Sir:

Recently it has been shown[1] that certain enzymatically catalyzed syntheses derive their energy from the reduction of quaternary ammonium or sulfonium salts, rather than from the usual mechanism of cleavage of energy-rich phosphate esters. One such "onium" salt, *viz.*, cozymase (DPN) was proposed as a suitable substrate from which to derive dinucleotides by this mechanism. We wish to record the realization of such a reaction. The substrate was DPN and the acceptor amine was

(1) D. W. Woolley, *Nature*, **171**, 323 (1953).