COMMUNICATIONS TO THE EDITOR

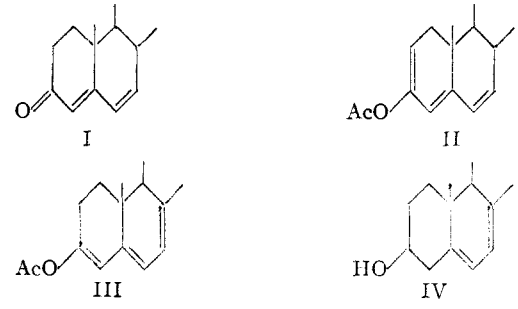
A NEW METHOD FOR THE PREPARATION OF 7-DEHYDROCHOLESTEROL

Sir:

Recently there have been reported methods for introducing an oxygenated function into the 11-position of the steroid nucleus using 7-dehydro compounds as starting material.[1] We wish to report a new method for the introduction of a double bond into the 7-position. Previous methods for introducing such unsaturation have involved the preparation of 7-substituted steroids with subsequent elimination of the elements of water or acid from the 7,8-positions.[2] The new method involves the transposition of the more easily formed Δ^6-double bond into the 7-position. As a model we have prepared 7-dehydrocholesterol, using as starting material $\Delta^{4,6}$-cholestadien-3-one (I). The latter compound can be prepared either from the Δ^5-3-ol system by oxidation[3] or from the Δ^4-3-one system by bromination and dehydrohalogenation.[4]

Depending upon conditions, acetylation of I yields one of the two possible enol acetates. Isopropenyl acetate and sulfuric acid, acetyl chloride and dimethylaniline or acetic anhydride and pyridine yield $\Delta^{2,4,6}$-3-acetoxycholestatriene (II); m. p. 89–91°; $[\alpha]^{25}D$ −21° ($CHCl_3$); $\lambda_{max.}^{EtOH}$ 302 mμ (log ε 4.1). Acetyl chloride and acetic anhydride (mixed) yields $\Delta^{3,5,7}$-3-acetoxycholestatriene (III); m.p. 91–93°; mixed with II m.p. 84–87°; $[\alpha]^{25}D$ −69° ($CHCl_3$); $\lambda_{max.}^{EtOH}$ 305, 316 (log ε 4.3), 330 mμ.[5] The assignment of structures II and III to the isomeric enol esters is made on the basis of the relative positions of the principal absorption maxima (302 and 316 mμ, respectively) and on the basis of the greater levorotary power of III. Confirmatory evidence for this assignment is the fact that III gives a positive Tortelli-Jaffé test[6] while II does not.

Reduction of III with sodium borohydride[7] in methanol-ether at room temperature proceeds rapidly and in high yield to a product which, on the basis of spectroscopic evidence, is essentially all in a $\Delta^{5,7}$-diene form; *i. e.*, the ultraviolet spectrum of the crude product is identical with that of 7-dehydrocholesterol. Presumably the reduction product is a mixture of the 3α- and 3β-hydroxy isomers. Over 70% of the crude material is precipitated by digitonin. Regeneration of the digitonide and crystallization of the product yields 7-dehydrocholesterol (IV); m.p. 142–143°; $[\alpha]^{25}D$ −115° ($CHCl_3$); $\lambda_{max.}^{EtOH}$ 271, 282 (log ε 4.1), and 293 mμ.



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(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); L. F. Fieser, J. E. Herz and Wei-Yuan Huang, *ibid.*, **73**, 2397 (1951); G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951).

(2) For leading references see v. J. Schmutz, H. Schaltegger and M. Sanz, *Helv. Chim. Acta*, **34**, 1111 (1951), and L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 179–182.

(3) C. Djerassi, "Organic Reactions," edited by R. Adams, Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 229–230.

(4) Ch. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946); H. H. Inhoffen, G. Stoeck and H. Martens, *Ann.*, **563**, 131 (1949).

(5) Compounds II and III have been further characterized by their carbon and hydrogen analyses, infrared spectra, and saponification equlvalents.

(6) Tortelli-Jaffé, *Chem. Z.*, **39**, 14 (1915); U. Westphal, *Ber.*, **72**, 1243 (1939).

(7) E. Schwenk, M. Gut and J. Belisle, *Arch. Biochem.*, **31**, 456 (1951); T. F. Gallagher and B. Belleau, THIS JOURNAL, **73**, 4458 (1951); W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951).

STEROIDS. XXVIII.[1] INTRODUCTION OF THE 11-KETO AND 11α-HYDROXY GROUPS INTO RING C UNSUBSTITUTED STEROIDS (PART 2)

Sir:

Recently,[2] there was described the introduction of an oxygen function into position 11 of ring C unsubstituted steroids by performic acid oxidation of steroidal $\Delta^{7,9(11)}$-*allo*dien-3β-ols *via* 9α,11α-oxido-7-ones and thence $\Delta^{8(9)}$-11α-ol-7-ones (IV). We have now found that the by-products of the oxidation, which appear to be the isomeric $\Delta^{9(11)}$-7,8-oxides and/or $\Delta^{9(11)}$-7-ketone, are readily isomerized to $\Delta^{8(9)}$-7-ketones (I). A similar observation has already been recorded by Fieser and co-workers[3] in the bile acid series, where such derivatives represent the main products in the dichromate oxidation of steroidal $\Delta^{7,9(11)}$-dien-3-ols. The present communication deals with the facile conversion of such intermediates to 11-oxygenated steroids by a novel procedure, which promises to be of general applicability.

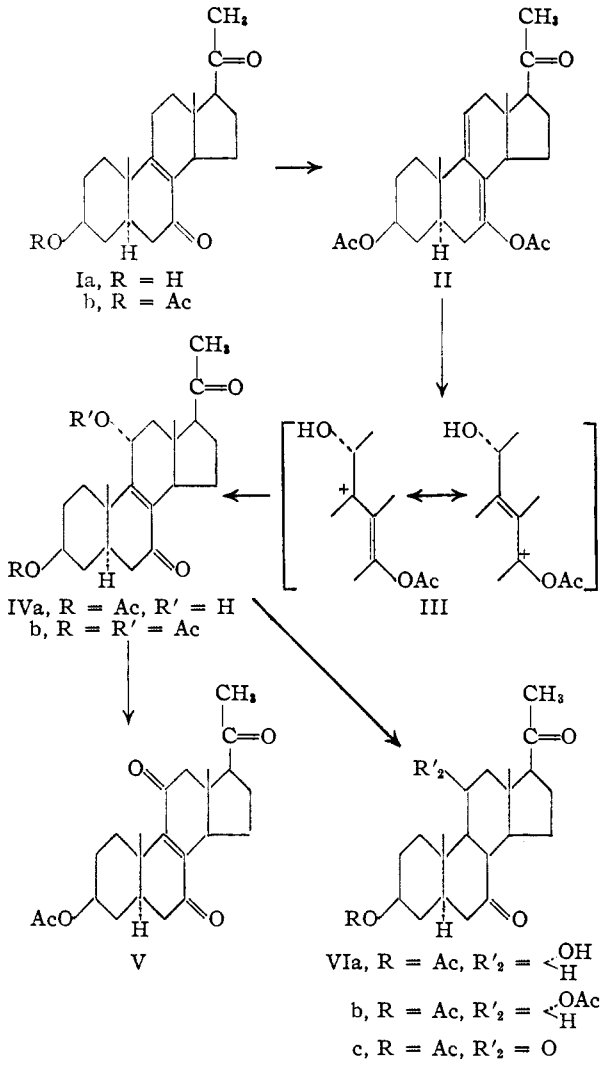
Performic acid oxidation of $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-acetate[4] proceeded exactly as described for the analogous 3β,20β-diol[2] yielding 9α,11α-oxidoallopregnane-7,20-dione-3β-ol acetate (m.p. 219–220°, $[\alpha]^{20}D$ −36° (all rotations in $CHCl_3$), $\lambda_{max.}^{CHCl_3}$ 1728 and 1700 cm.$^{-1}$, no free hydroxyl band, found: C, 71.06; H, 8.46), which was rearranged with alkali and acetylated to afford $\Delta^{8(9)}$-

(1) Paper XXVII, C. Djerassi, G. Rosenkranz, J. Pataki and St. Kaufmann, *J. Biol. Chem.*, in press.

(2) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951).

(3) L. F. Fieser, J. E. Herz and W. Huang, *ibid.*, **73**, 2397 (1951); L. F. Fieser, *et al.*, *ibid.*, **73**, 4053 (1951).

(4) C Djerassi, R. Romo and G, Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).



allopregnene-7,20-dione-3β,11α-diol diacetate (IVb) (m.p. 216–218°, $[\alpha]_D^{20}$ +55°, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 4.07, λ_{CHCl_3} 1728 (acetate), 1700 (20-ketone) and 1670 cm.$^{-1}$ (Δ^8-7-ketone), found: C, 69.65; H, 7.98) and then hydrogenated to allopregnane-7,20-dione-3β,11α-diol diacetate (VIb) (m.p. 156–157°, $[\alpha]_D^{20}$ ± 0°, $\lambda_{max.}^{CS_2}$ 1736 (acetate), 1718 (7-ketone) and 1710 cm.$^{-1}$ (20-ketone), found: C, 69.37; H, 8.52).

Saponification of the performic acid oxidation mother liquors yielded $\Delta^{8(9)}$-allopregnene-7,20-dione-3β-ol (Ia) (m.p. 191–193°, $[\alpha]_D^{20}$ −8°, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 4.10, $\lambda_{max.}^{nujol}$ 1700 and 1656 cm.$^{-1}$ and free hydroxyl band, found: C, 76.50; H, 9.28); acetate (Ib), (m.p. 159–161°, $[\alpha]_D^{20}$ −12°, found: C, 74.13; H, 8.91), which presumably arose from a mixture of $\Delta^{9(11)}$-7,8-oxides and/or $\Delta^{9(11)}$-7-one, since chromatography of the mother liquors produced in a fair state of purity two isomers ($C_{23}H_{32}O_4$) giving a yellow color with tetranitromethane (*A*: m.p. 139–142°, $[\alpha]_D^{20}$ +33°, found: C, 74.49; H, 9.03; *B*: 213–215°, $[\alpha]_D^{20}$ −35°, found: C, 73.43; H, 8.79), which were rearranged by alkali in high yield to the identical unsaturated ketone Ia. *Taking advantage of the fact that isopropenyl acetate*[4a] *reacts readily with α,β-unsaturated ketones but not at all with saturated 20-ketosteroids*, the acetate Ib was converted to the oily enol acetate II, which without isolation was treated with 1.1 moles of monoperphthalic acid in ether solution at room temperature. After 40 hours, there *crystallized directly*[5] from the ether solution in over 70% over-all yield (based on Ib) $\Delta^{8(9)}$-allopregnene-7,20-dione-3β,11α-diol 3-monoacetate (IVa) (m.p. 192–194°, $[\alpha]_D^{20}$ +14°, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 4.12, $\lambda_{max.}^{CHCl_3}$ 1728, 1700 and 1670 cm.$^{-1}$ and free hydroxyl band, found: C, 71.29; H, 8.39), which upon acetylation gave the identical diacetate IVb described above. Hydrogenation of IVa with palladized charcoal afforded 81% of allopregnane-7,20-dione-3β,11α-diol 3-acetate (VIa) (m.p. 184–186°), $[\alpha]_D^{20}$ −10°, $\lambda_{max.}^{nujol}$ 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band, found: C, 70.96; H, 8.85), identified further by conversion to the known (*vide supra*) 3,11-diacetate VIb.

A particularly attractive feature of the present process is the facile preparation of 3-acylated-11α-ols (*e.g.*, IVa, VIa), which allows interconversion with intermediates employed by other workers[3,6] for the introduction of an 11-keto group. As an illustration, chromium trioxide oxidation of the monoacetate IVa smoothly yielded $\Delta^{8(9)}$-allopregnene-7,11,20-trione-3β-ol acetate (V) (m.p. 171–173°, $[\alpha]_D^{20}$ +50°, $\lambda_{max.}^{EtOH}$ 268 mμ, log ϵ 3.82, found: C, 71.63; H, 8.06), while similar treatment of VIa afforded allopregnane-7,11,20-trione-3β-ol acetate (VIc) (m.p. 209–211°, $[\alpha]_D^{20}$ +20°, found: C, 71.25; H, 8.40).

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(4a) In benzene solution, using *p*-toluenesulfonic acid as catalyst.

(5) The reaction presumably involves attack of the unhindered 11α-position by positively charged hydroxyl ion (*cf.* D. Swern, *Chem. Revs.*, **45**, 48 (1949)) through species such as III to yield ultimately IVa and possibly the mixed anhydride of phthalic and acetic acids. An analogous change is involved in the conversion of thebaine to 14-hydroxycodeinone (M. Freund and E. Speyer, *J. prakt. Chem.*, **94**, 135 (1916)) by peracetic acid.

(6) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951).

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THERMAL DECOMPOSITION OF CYCLOBUTANE

Sir:

Cyclobutane has been found to undergo a homogeneous, first order decomposition in the temperature range 430–480°. The cyclobutane which was prepared by the photolysis of cyclopentanone[1,2] was purified by fractionation in a Podbielniak column. Samples obtained by fractionation and subjected to different purification treatments have given similar results. Infrared absorption curves[3] and vapor pressure measurements have been used to confirm the identity and purity of the cyclobu-

(1) S. Benson and G. Kistiakowsky, THIS JOURNAL, **64**, 80 (1942).

(2) This preparation was undertaken jointly with Drs. L. H. Jones and A. B. F. Duncan.

(3) The infrared absorption measurements have been made by Mr. Carl Whiteman.