[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. X. REVISION OF NOMENCLATURE OF PREVIOUSLY DESCRIBED COMPOUNDS[1]

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In a number of publications from this laboratory (1, 2, 3, 4, 5) various 5,6-oxides and 3,5,6-triols had been assigned arbitrary configurations at carbon atoms 5 and 6. Recent investigations performed in several laboratories, notably that of Ruzicka, now make it possible to define more accurately the configuration of these compounds. It appears that the necessary revisions are rather comprehensive.

The school of Ruzicka (6) established the configuration of the so-called α-cholesteryl oxide and of β-cholesteryl oxide. They should now be labelled 5,6(α)-oxidocholestane-3(β)-ol and 5,6(β)-oxidocoprostane-3(β)-ol respectively, designations which clearly express the configurations at both carbon atoms 5 and 6. The preceding arbitrary nomenclature was thus shown to be correct. Hattori (7) and later Baxter and Spring (8) studied the fission reactions of the two cholesteryl oxides, using water, hydrochloric acid, and glacial acetic acid. Fission of the oxide rings can also be brought about by catalytic hydrogenation (9, 9a, 10).[2] The opening of the oxide rings is known to be accompanied by a change of configuration at the carbon atom at which the bond with the oxygen atom is ruptured, as has been shown *e.g.* in the sugar series (lit. *cf.* 12). Applied to α or β-cholesteryl oxide such a rupture may lead in each case to two different

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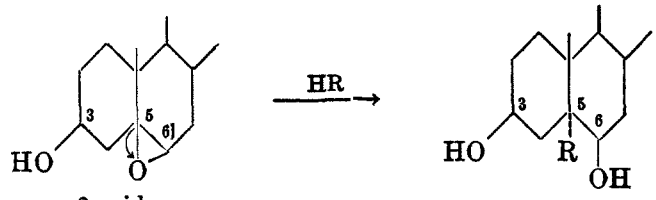
[2] Ruzicka (11) also studied the catalytic hydrogenation of the α-oxide and β-oxide of dehydroisoandrosterone acetate [3(β)-acetoxy-5,6(α)-oxidoandrostane-17-one and 3(β)-acetoxy-5,6(β)-oxidoetiocholane-17-one respectively]. The results were analogous to those obtained with the acetates of α-cholesteryl oxide and β-cholesteryl oxide respectively (9, 9a).

trans forms. It appears from the experiments that the one of the two possible stereoisomeric forms predominates. In each case the fission reaction leads to the predominant formation of cholestane derivatives. The equally possible coprostane derivatives are only produced in negligible amounts if at all. These reactions may be formulated in the following way (R = H, OH, Cl, OAc):

α-oxide.

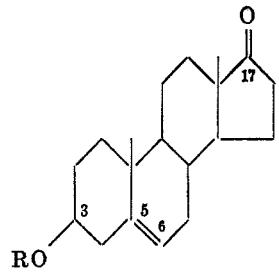


β-oxide.

Fission of the α-oxide ring, therefore, occurs mainly at carbon atom 6 and of the β-oxide ring chiefly at carbon atom 5.

In considering some of our previous publications (1, 2, 3, 4, 5) in the light of these recent findings, it appears necessary to alter the nomenclature and the configurational formulas in many instances. The changes follow by applying the above considerations to a number of reactions described in these publications. The configurational evidence stems from the fission products of the 5,6-oxides, to which are related the other compounds of the pertinent reaction scheme. Inasmuch as the reactions concerned have been discussed before, the material will be presented by way of formula schemes. Each compound will be characterized by its new configurational formula and nomenclature to which the previous names will be added in brackets. Previous names will be marked by a reference and by the Roman numeral given to the formula in that particular publication. It is to be noted that the configuration at carbon atom 5 is expressed by the general nomenclature; hence the additional marking by Greek letters is not necessary.

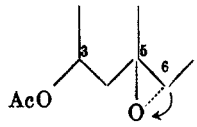
The first series of reactions are derived from dehydroisoandrosterone (I):



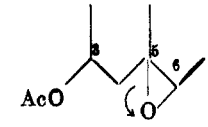
I. R = H, Dehydroisoandrosterone.
Ia. R = Ac, Dehydroisoandrosterone acetate.

Ia

$KMnO_4$, CH_3COOH

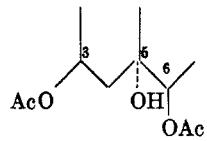


II. 3(β)-Acetoxy-5,6(α)-oxidoandrostane-17-one. m.p. 221–222.5°; $[\alpha]_D^{28}$ − 10.0°
[Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate. (3, V b)]
[Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate. (4, VIII)]



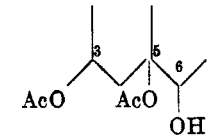
III. 3(β)-Acetoxy-5,6(β)-oxidoetiocholane-17-one. m.p. 188–190°; $[\alpha]_D^{28}$ + 58.4°
[Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate. (3, Va)
[Androstane-(5,6)(β)-oxide-17-one-3(β)-ol] acetate. (4, IX)]

glacial CH_3COOH



IV. 3(β),6(β)-Diacetoxyandrostane-5-ol-17-one.
[Androstane-17-one-3(β),5,6(trans)-triol 3,6-diacetate. (3, VIII) (4, X)]

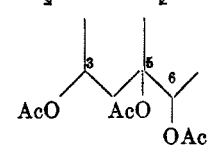
glacial CH_3COOH



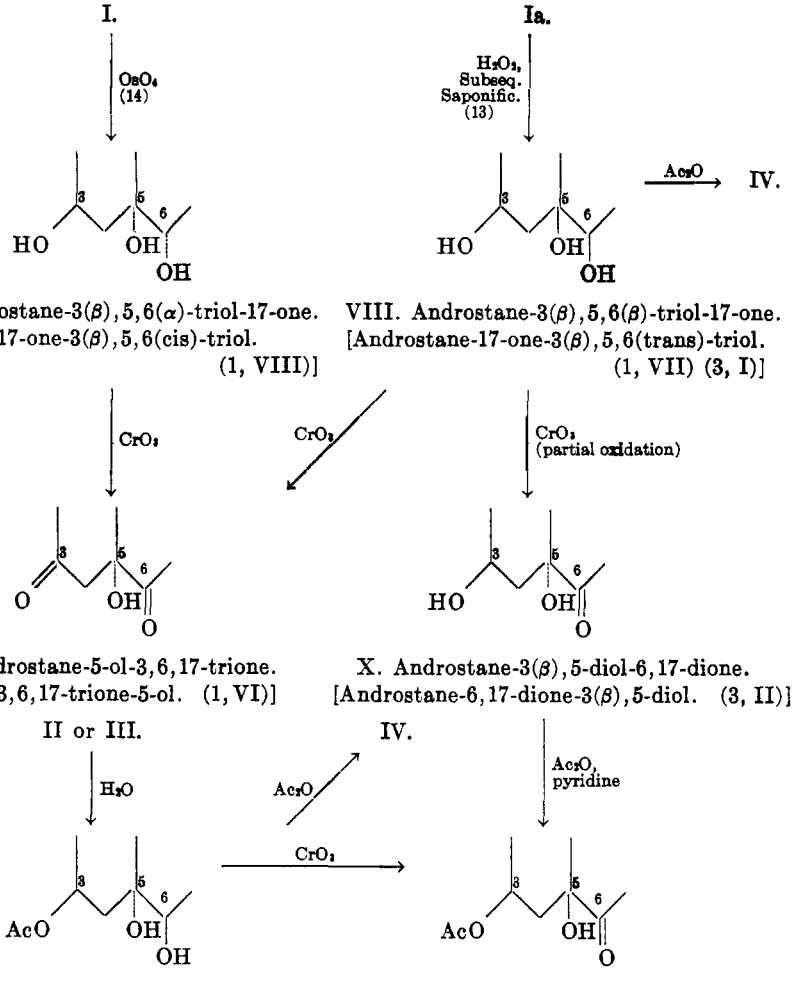
V. 3(β),5-Diacetoxyandrostane-6(β)-ol-17-one.
[Androstane-17-one-3(β),5,6(trans)-triol 3,5-diacetate. (4, XI)]

Ac_2O + HCl gas

Ac_2O



VI. 3(β),5,6(β)-Triacetoxyandrostane-17-one.
[Androstane-17-one-3(β),5,6(trans)-triol triacetate. (4, XII)]



VII. Androstane-3(β),5,6(α)-triol-17-one. [Androstane-17-one-3(β),5,6(cis)-triol. (1, VIII)]

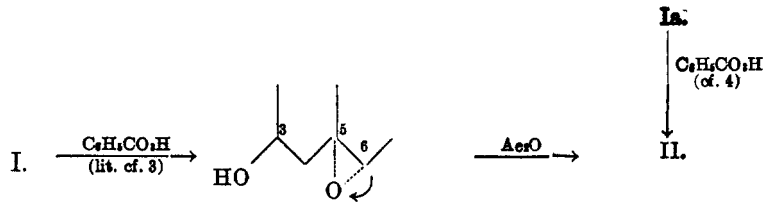
VIII. Androstane-3(β),5,6(β)-triol-17-one. [Androstane-17-one-3(β),5,6(trans)-triol. (1, VII) (3, I)]

IX. Androstane-5-ol-3,6,17-trione. [Androstane-3,6,17-trione-5-ol. (1, VI)]

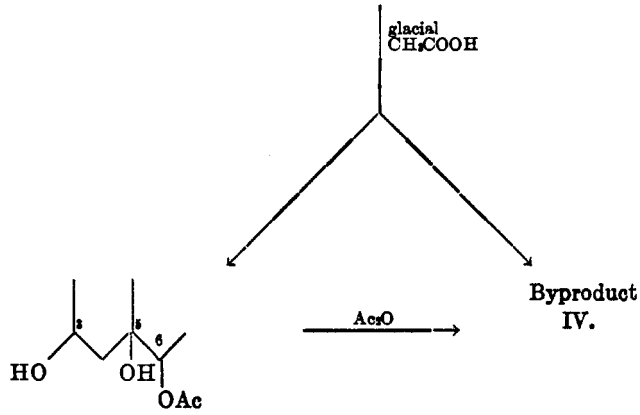
X. Androstane-3(β),5-diol-6,17-dione. [Androstane-6,17-dione-3(β),5-diol. (3, II)]

XII. 3(β)-Acetoxyandrostane-5,6(β)-diol-17-one. [Androstane-17-one-3(β),5,6(trans)-triol 3-monoacetate. (3, VI)]

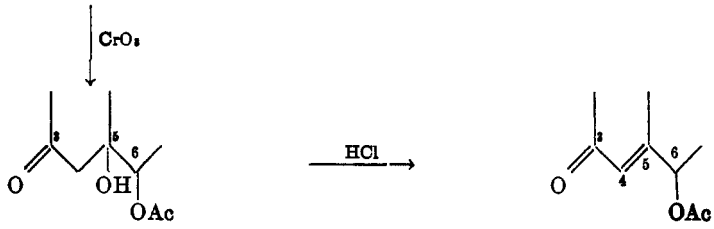
XI. 3(β)-Acetoxyandrostane-5-ol-6,17-dione. [Androstane-6,17-dione-3(β),5-diol 3-monoacetate. (3, VII)]



XIII. 5,6(α)-Oxidoandrostane-3(β)-ol-17-one.
[Dehydroisoandrosterone oxide,
Androstane-(5,6)(β)-oxide-17-one-3(β)-ol. (3, IX)]
[Androstane-(5,6)(α)-oxide-17-one-3(β)-ol. (4, XIV)]



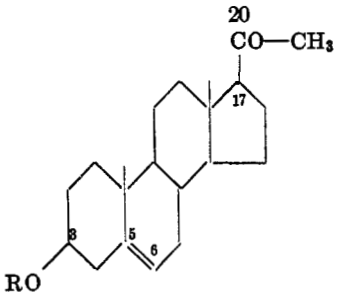
XIV. 6(β)-Acetoxyandrostane-3(β), 5-diol-17-one.
[Androstane-17-one-3(β),5,6(trans)-triol 6-monoacetate. (4, XV)]



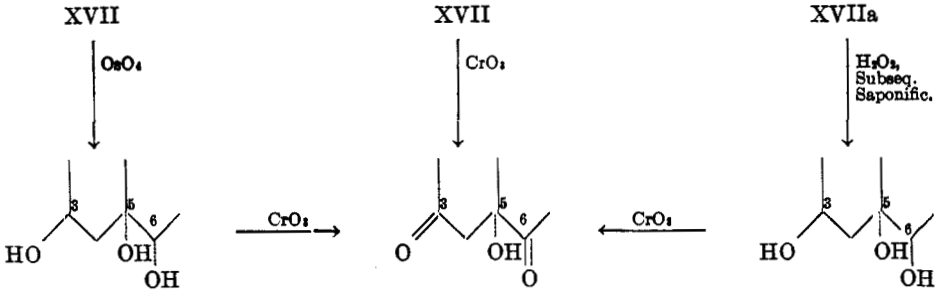
XV. 6(β)-Acetoxyandrostane-5-ol-3,17-dione.
[Androstane-3,17-dione-5,6(trans)-diol 6-monoacetate. (4, XVI)]

XVI. 6(β)-Acetoxy-Δ⁴-androstene-3,17-dione.
[4-Androstene-3,17-dione-6(α)-ol acetate; 6(α)-acetoxy-4-androstene-3,17-dione. (4, XVII)]

The second series of reactions are derived from pregnenolone (XVII):



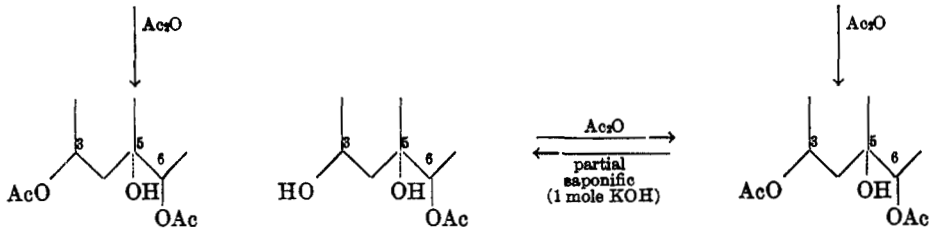
XVII. R = H, Δ^5-Pregnene-3(β)-ol-20-one.
XVIIa. R = Ac, 3(β)-Acetoxy-Δ^5-pregnene-20-one.



XVIII. Allopregnane-3(β),5,6(α)-triol-20-one. [Pregnane-20-one-3(β),5,6(cis)-triol. (1, XII) (2, III)]

XX. Allopregnane-5-ol-3,6,20-trione. [Pregnane-3,6,20-trione-5-ol. (1, XIII) (5)]

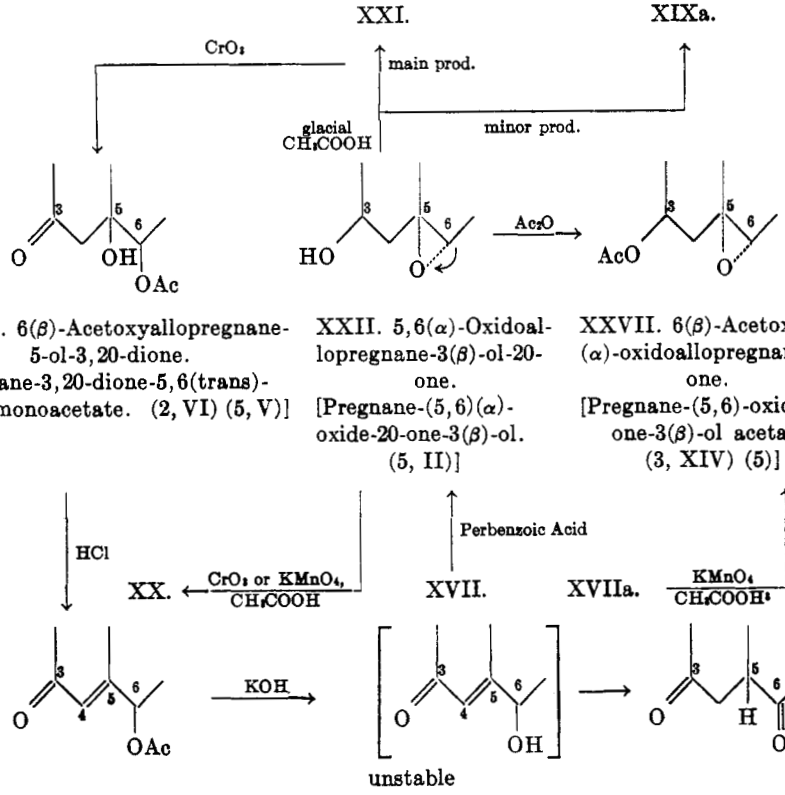
XIX. Allopregnane-3(β),5,6(β)triol-20-one. [Pregnane-20-one-3(β),5,6 (trans)-triol. (1, XI) (2, II) (5)]



XVIIIa. 3(β),6(α)-Diacetoxy-allopregnane-5-ol-20-one. [Pregnane-20-one-3(β),5,6(cis)-triol 3,6-diacetate. (2) (3)]

XXI. 6(β)-Acetoxyallopregnane-3 (β),5-diol-20-one. [Pregnane-20-one-3(β),5,6 (trans)-triol 6-monoacetate. (2, V)(5, III)]

XIXa. 3(β),6(β)-Diacetoxyallopregnane-5-ol-20-one. [Pregnane-20-one-3(β),5,6(trans)-triol 3,6-diacetate. (2, IV) (5, IV)



XXIII. 6(β)-Acetoxyallopregnane-5-ol-3,20-dione. [Pregnane-3,20-dione-5,6(trans)-diol 6-monoacetate. (2, VI) (5, V)]

XXII. 5,6(α)-Oxidoallopregnane-3(β)-ol-20-one. [Pregnane-(5,6)(α)-oxide-20-one-3(β)-ol. (5, II)]

XXVII. 6(β)-Acetoxy-5,6(α)-oxidoallopregnane-20-one. [Pregnane-(5,6)-oxide-20-one-3(β)-ol acetate. (3, XIV) (5)]

XXIV. 6(β)-Acetoxyprogesterone, 6(β)-Acetoxy-Δ^4-pregnene-3,20-dione. [6(α)-Hydroxyprogesterone acetate, 4-Pregnene-3,20-dione-6(α)-ol acetate. (2, VII) (5, VI)]

XXV. 6(β)-Hydroxyprogesterone, Δ^4-Pregnene-6(β)-ol-3,20-dione. [6(α)-Hydroxyprogesterone, 4-Pregnene-3,20-dione-6(α)-ol. (2, VIII)]

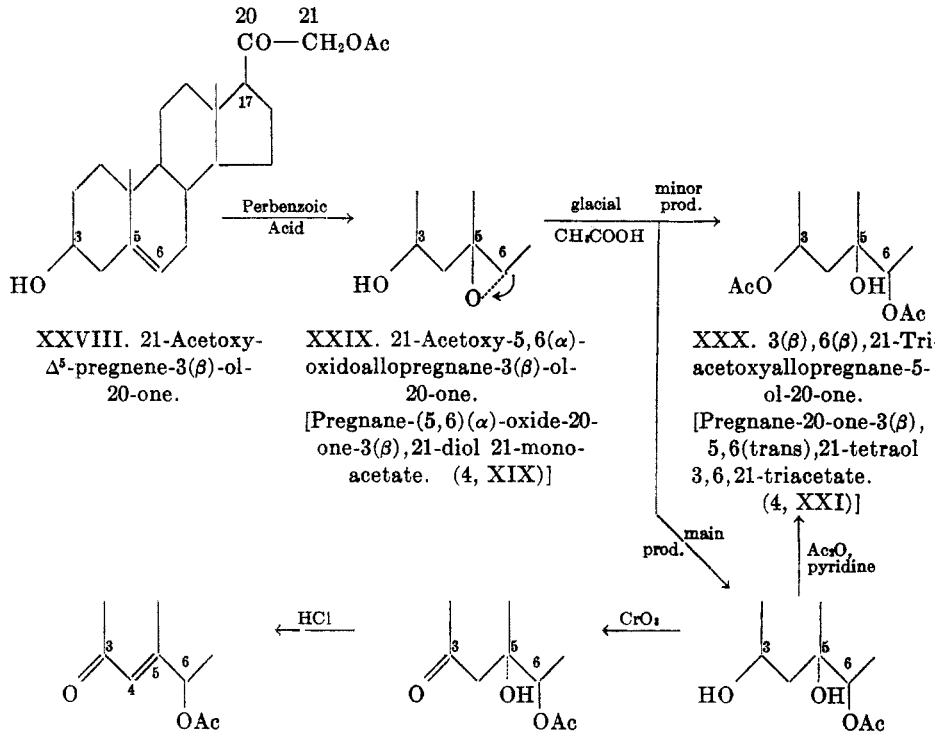
XXVI. Allopregnane-3,6,20-trione. [Pregnane-3,6,20-trione or Allopregnane-3,6,20-trione. (2 IX)]

It is noteworthy that 3(β),6(β)-diacetoxyallopregnane-5-ol-20-one (XIX a) can be partially saponified in position 3 (2, 5). This is in good agreement with its newly assigned configuration which places the acetoxy group at carbon atom 6 in cis position to the methyl group at carbon atom 10. It should therefore be sterically hindered (*cf.* 6), which explains its somewhat slower saponification. In 3(β),6(α)-diacetoxyallopregnane-5-ol-20-one (XVIII a) the saponification of the two acetoxy groups proceeds at an approximately equal rate (2). This is likewise in agreement with the newly assigned configuration, which places the acetoxy group at carbon atom 6 in trans position to the methyl group at carbon atom 10. It should, therefore, not be sterically hindered.

[3] The two other oxidation products probably have to be interpreted as 3(β)-acetoxyallopregnane-5,6(α)-diol-20-one [pregnane-20-one-3(β),5,6-triol 3-monoacetate (3, XV)] and 3(β)-acetoxyallopregnane-5-ol-6,20-dione [pregnane-6,20-dione-3(β),5-diol 3-monoacetate (3 XVI)] respectively.

As was stated in a previous communication (2), the alkaline hydrolysis of 6(β)-acetoxyprogesterone (XXIV) does not yield the 6(β)-hydroxyprogesterone (XXV) which is obviously unstable and rearranges to a compound which is identical with the allopregnane-3,6,20-trione (XXVI) obtained from hyodesoxycholic acid in the laboratory of Hoehn (15). These authors observed that pregnane-3,6,20-trione undergoes rearrangement to allopregnane-3,6,20-trione under the influence of mineral acid or alkali.

A third series of reactions are derived from 21-acetoxypregnenolone (XXVIII):



XXVIII. 21-Acetoxy-Δ⁵-pregnene-3(β)-ol-20-one.

XXIX. 21-Acetoxy-5,6(α)-oxidoallopregnane-3(β)-ol-20-one. [Pregnane-(5,6)(α)-oxide-20-one-3(β),21-diol 21-monoacetate. (4, XIX)]

XXX. 3(β),6(β),21-Triacetoxyallopregnane-5-ol-20-one. [Pregnane-20-one-3(β),5,6(trans),21-tetraol 3,6,21-triacetate. (4, XXI)]

XXXIII. 6(β)-Hydroxy-11-desoxycorticosterone 6,21-diacetate; 6(β),21-Diacetoxy-Δ⁴-pregnene-3,20-dione. [6(α)-Hydroxy-11-desoxycorticosterone diacetate; 4-Pregnene-3,20-dione-6(α),21-diol diacetate. (4, XXIII)]

XXXII. 6(β),21-Diacetoxyallopregnane-5-ol-3,20-dione. [Pregnane-3,20-dione-5,6(trans),21-triol 6,21-diacetate. (4, XXII)]

XXXI. 6(β),21-Diacetoxyallopregnane-3(β),5-diol-20-one. [Pregnane-20-one-3(β),5,6(trans),21-tetraol 6,21-diacetate. (4, XX)]

With the above changes of nomenclature complete analogy exists regarding the behavior of the 5,6-oxides and 3,5,6-triols derived from cholesterol (6, 16) and those derived from dehydroisoandrosterone (I), pregnenolone (XVII) and 21-acetoxypregnenolone (XXVIII) respectively.[4]

[4] No definite configurations can as yet be assigned to some compounds obtained from a 5,6-oxide of Δ⁵-pregnene-3(β),20,21-triol by means of a Grignard reaction (17).

Addition: Lardon (18) in Reichstein's laboratory recently studied the partial saponification of methyl 3(α), 7(α), 12(α)-triacetoxyetiocholanate. He presented convincing evidence that the monoacetoxy compound present in the resulting mixture of reaction products is methyl 3(α), 12(α)-dihydroxy-7(α)-acetoxyetiocholanate. In a paper dealing with some degradation products of cholic acid (19) we described the partial saponification of 3(α), 7(α), 12(α)-triacetoxypregnane-20-one which yielded a monoacetoxy compound interpreted to be 12(α)-acetoxypregnane-3(α), 7(α)-diol-20-one. The identical substance was subsequently described by others (20). On account of his findings in connection with the partial hydrolysis of methyl 3(α), 7(α), 12(α)-triacetoxyetiocholanate Lardon (18) presumes that the 12-acetoxypregnane-3(α), 7(α)-diol-20-one described by us (19) and Miescher (20) is in reality 7(α)-acetoxypregnane-3(α), 12(α)-diol-20-one. This assumption is probably correct and hence the product of the oxidation of the latter compound with chromic acid (19) should be called 7(α)-acetoxypregnane-3,12,20-trione rather than 12(α)-acetoxypregnane-3,7,20-trione. In like manner the product of the partial dehydrogenation of the compound by means of the Oppenauer method (19) should be named 7(α)-acetoxypregnane-12(α)-ol-3,20-dione rather than 12(α)-acetoxypregnane-7(α)-ol-3,20-dione.

The author is indebted to Dr. William H. Pearlman for his valuable suggestions.

SUMMARY

The naming of a number of compounds described in previous publications (1, 2, 3, 4, 5, 19) has been revised to conform with the latest nomenclature.

PHILADELPHIA 4, PA.

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