Steroidal Sapogenins. LXIV. C-21 Acetoxylation of 12-Keto Steroids[2]

Procedural improvements in C-21 acetoxylation of steroids by iodine and calcium oxide followed by treatment of the resulting 21-iodo steroids with trimethylammonium acetate are described and the method is shown to be applicable to 12-keto steroids.

Ringold and Stork[3] reported a novel and useful procedure for the preparation of 21-acetoxylated steroids from a number of 20-keto pregnanes by reaction with iodine and calcium oxide followed by subsequent reaction of the 21-iodo intermediate with potassium acetate in acetone. In such a way they prepared the 21-acetoxy derivatives of 17α-hydroxyprogesterone, 17α-hydroxy-1,4-pregnadiene-3,20-dione, 11-keto progesterone, and 3α-hydroxypregnane-11,20-dione. More recently Halpern and Djerassi[4] applied similar reactions as the final stage of a cortisone acetate synthesis. We have found the Syntex method to be of great utility. The present paper presents several procedural improvements and in particular describes the extension of this reaction to 12-keto steroids.

It may be recalled that several attempts[5,6,7] to prepare 21-acetoxy-17α-hydroxy-4-pregnene-3,12,-20-trione ("12-keto S") from hecogenin failed when a variety of well known reactions, which ordinarily succeed when the 12-keto group is absent, were unsuccessful. The unfavorable effect of the 12-keto group was particularly demonstrated by the unsuccessful attempt[8] to obtain the 21-acetate derivative of 3β-acetoxy-17α-hydroxy-5-pregnene-12,20-dione by the Julian procedure.[9] Using the presently described method, 12-keto S was prepared by two routes, and the products agreed in physical properties with 12-keto S prepared from desoxycholic acid by Adams, Patel and Petrow.[10]

We followed Ringold and Stork's original procedure from details disclosed in a British patent.[3b] Later Halpern and Djerassi, in a footnote, recommended the use of aged tetrahydrofuran containing peroxides. In our hand the use of these techniques gave variable results and usually iodine uptake was very slow. On the assumption that the reaction was of the free radical type, mainly because of the above mentioned peroxide catalysis, we added small amounts of azobisisobutyronitrile to the reaction mixture as an initiator. Thereafter no further difficulties were encountered, although even with azobisisobutyronitrile induction periods of as long as one hour were sometimes observed.

In a further procedural modification, we used Moreland's excellent trimethylammonium acetate method[11] for replacing the C-21 iodine atom by the acetoxyl group. Moreland's procedure has several advantages over the more widely used potassium acetate method, in particular short reaction time and homogeneity of phase.

The experimental section describes the preparation of the following 21-acetoxy steroids: 21-acetoxy-3β,17α-dihydroxypregnane-20-one, 21-acetoxy-3β,17α-dihydroxy-5-pregnene-20-one, 21-acetoxy-16α,17α-epoxy-5-pregnene-20-one, 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, 21-acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione, and 21-acetoxy-17α-hydroxy-4-pregnene-3,12,20-trione.

By way of general comment it might be mentioned that the acetoxylation procedure gave variable results in the presence of the Δ^4-3-keto grouping. Good yields of 21-acetoxylated product were obtained in 12-keto S preparations, but, on the other hand, conversion of progesterone to 21-acetoxy progesterone consistently gave low yields. In general the maximal yields were obtained with 3β-hydroxy steroids. The iodinations are somewhat exothermic and in larger scale preparations sudden evolution of heat was occasionally observed capable of raising solvents to the boiling point unless a cooling bath was provided.

As a result of the availability of the key intermediate 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, IV, we were able to re-investigate the possibility of preparation of a cortisone analog, VI,

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Previous paper in this series, Steroidal Sapogenins LXIII, *J. Org. Chem.*, in press.

(3) (a) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, **80**, 250 (1958). (b) British patent **776,858** to Syntex Corp., June 12, 1957.

(4) O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 439 (1959).

(5) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 2209 (1954).

(6) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **78**, 1744 (1956).

(7) E. S. Rothman and M. E. Wall, *J. Org. Chem.*, **22**, 223 (1957).

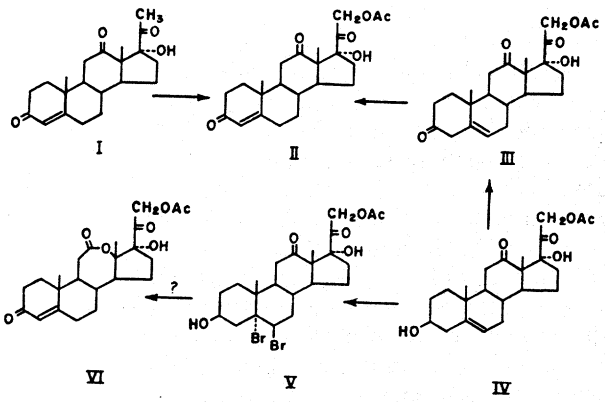
(8) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **77**, 2229 (1955).

(9) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *J. Am. Chem. Soc.*, **72**, 5145 (1950).

(10) W. J. Adams, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 4688 (1954).

(11) W. T. Moreland, Jr., *J. Org. Chem.*, **21**, 820 (1956).

wherein the C-ring is expanded to a 12,13-*seco*-lactone system.[8] The Δ^5 double bond of IV was protected by bromination to give the crystalline product, 21-acetoxy-5α,6β-dibromo-3β,17α-dihydroxyallopregnane-12,20-dione[12] which was submitted to the Baeyer-Villiger reaction conditions.[8] Regeneration of the olefinic bond with sodium iodide gave a product exhibiting the expected lactonic infrared spectrum[13] but the product resisted crystallization.



EXPERIMENTAL[14]

Melting points were determined on the Kofler block but are otherwise not corrected. Rotations were measured in a 2 dm. tube containing 25 mg. of steroid dissolved in 1.5 ml. of chloroform.

21-Acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione. Preparation by generalized acetoxylation procedure. A solution of 11.5 g. of 3β,17α-dihydroxy-5-pregnene-12,20-dione, IV, in 85 ml. of tetrahydrofuran and 85 ml. of methanol was treated with 17 g. of powdered calcium oxide and 575 mg. of azobisisobutyronitrile. The mixture was surrounded by a 25° water bath and stirred during addition of 11.4 g. of iodine dissolved in a mixture of 55 ml. of tetrahydrofuran and 35 ml. of methanol. The iodine solution was added rapidly in a dropwise manner to just exceed the rapid decolorization rate. Typically a 5 to 60-min. induction period was observed and thereafter iodine absorption was continuous until an abrupt stop occurred at the indicated 50% excess point.[15] The mixture was then diluted with 450 ml. of methylene chloride and was filtered. The residue was washed on the filter with 200 ml. of methylene chloride and was discarded. The filtrate, diluted with 600 ml. of ether, often became turbid but shaking with as little as 2 ml. of water produced clarification. The organic layer was washed free of excess iodine with 15% aqueous sodium iodide solution, was dried with sodium sulfate, and solvents evaporated under reduced pressure. The 21-iodo residue, without purification, was redissolved in 150 ml. of acetone, mixed with 51.5 ml. of acetic acid and 79 ml. of triethylamine (exothermic reaction), and refluxed for 45 min. After cooling and carefully diluting with 250 ml. of water, the mixture was let stand to deposit crystals of the acetoxylated product in 66% yield, m.p. 185–186°. Recrystallization from ether-hexane and from aqueous ethanol gave the analytical sample, m.p. 187–188°, $[\alpha]^{25}_{D}$ −13.7°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.43; H, 8.16.

In runs on cruder material it was necessary to extract the reaction mixture with benzene and to chromatograph the crude product. The desired product was rapidly eluted from Florisil with benzene and crystallized in the earliest eluate residues on treatment with ether-hexane.

21-Acetoxy-16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one (VII). Using the above procedure 5 g. of 16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one[16] gave 2.10 g. of the known compound,[17] VII, m.p. 190–192°, previously reported[17] m.p. 190–192°.

21-Acetoxy-3β,17α-dihydroxypregnan-20-one (VIII). In like manner, 2 g. of 3β,17α-dihydroxy pregnan-20-one[18] gave 1 g. of VIII,[18] m.p. 201–205°. The 3-acetate of VIII[18,19] exhibited a double melting point, 90–100°; 153–155°, previously reported, 154–157°[18] and 149–151°.[19]

21-Acetoxy-3β,17α-dihydroxy-5-pregnen-20-one (IX). Similarly, 15.26 g. of 3β,17α-dihydroxy-5-pregnen-20-one[16] gave 10 g. of IX,[20] m.p. 210–212°, previously reported[20] m.p. 211–213°.

21-Acetoxy-17α-hydroxy-4-pregnene-3,12,20-trione (II). A suspension of 300 mg. of 17α-hydroxy-4-pregnen-3,12,20-trione,[6] I, in 2.25 ml. of tetrahydrofuran and 1.5 ml. of methanol was treated with 450 mg. of iodine under the conditions described in the generalized acetoxylation procedure described above. After chromatography on Florisil with 1:1 hexane-benzene 148 mg., m.p. 189–192°, was obtained after crystallization from hexane containing a trace of acetone. The analytical sample of II recrystallized from hexane melted from 190–193°, $[\alpha]^{23}_{D}$ +109° in reasonably good agreement with the reported values,[10] m.p. 189.5–190.5°, $[\alpha]^{20}_{D}$ +125°.

Conversion of 3β-acetoxy-5,16-pregnadiene-12,20-dione[7] *to 3β,17α-dihydroxy-5-pregnene-dione.* The indicated pregnadiene was converted with alkaline hydrogen peroxide as previously described[7] to the 16α,17α-epoxide, the alkalinity of the oxidant concomitantly saponifying the 3-acetate group. Attempts to open the oxirane ring with hydrobromic acid in tetrahydrofuran and in methanol failed[21]; thus 33 g. of the epoxide in 1.32 l. of tetrahydrofuran treated with 45 ml. of 48% hydrobromic acid was recovered unchanged after standing 18 hr. at 25°. In methanolic-aqueous hydrobromic acid, no reaction occurred in 3 days time. However, using precisely the conditions for oxirane opening described for the 11-keto analog,[22] namely anhydrous hydrobromic acid in

(12) The dibromide structure is assigned on the basis that sodium iodide treatment liberated iodine and regenerated the olefinic bond. The dibromide had an optical rotation more negative than the olefin as is the relationship of the 5α,6β-dibromide of cholesterol to cholesterol, whereas the other *trans* dibromide, 5β,6α-, is more dextrorotatory than its olefin precursor, cholesterol (see L. F. and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, 1959, p. 39).

(13) See Fig. 1 of reference 9 and compare curve D with curve E.

(14) Specification of brand names of materials used does not imply endorsement over similar commercial products.

(15) This point probably has no stoichiometric significance. The rate or amount of iodine uptake seems to be in some way affected by the nature of the surface of the calcium oxide surface. After iodine uptake stopped at about the 50% molar excess point, uptake could be reinduced by addition of a fresh quantity of calcium oxide even though there was already an apparent excess of solid calcium oxide in the system.

(16) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, 72, 367 (1950).

(17) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. Ryden, *J. Am. Chem. Soc.*, 71, 3574 (1949); 72, 5145 (1950).

(18) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, 73, 189 (1951).

(19) R. B. Wagner and J. A. Moore, *J. Am. Chem. Soc.*, 72, 5301 (1950).

(20) J. Heer and K. Miescher, *Helv. Chim. Acta*, 34, 359 (1951).

(21) Under similar conditions 16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one gives an excellent yield of bromohydrin.

(22) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, 81, 411 (1959), see compound V of that reference.

acetic acid, complete reaction occurred in 25 min. Unlike the 11-ketone case, a substantial amount of 3-acetylation occurred during the reaction. The debromination was carried out as previously described.[7] The mixed 3-alcohol and 3-acetate, 22.2 g. in 1.11 l., of methanol was treated with 22.2 g. of potassium bicarbonate in 222 ml. of water and refluxed in a nitrogen atmosphere for 1 hr. The cooled mixture was diluted with 7 l. of ice-water and after standing overnight was filtered. The 18.9 g. of crystalline product was collected and recrystallized from acetone to give 17.1 g. of diol, m.p. 203–205°, $[\alpha]_D^{25}$ −19.3°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.83; H, 8.85.

21-Acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione, III. The trioldione monoacetate, IV, 135 mg. dissolved in 25 ml. of acetone (redistilled from potassium permanganate), was cooled to 10° and stirred with 0.10 ml. of an aqueous solution containing 26.7 mg. of chromium trioxide and 0.023 ml. of sulfuric acid.[23] Within 1 min. a gray-green precipitate formed. Stirring was continued an additional 2 min. and the reaction mixture was diluted to 150 ml. with nearly saturated sodium chloride solution. The crystalline precipitate filtered off weighed 130 mg., melted at 155°, and showed no selective ultraviolet absorption maximum and no band at 6 μ in the infrared. The analytical sample was recrystallized from water containing 20% of acetone and finally from hexane, m.p. 172–175°, $[\alpha]_D^{25}$ +8.2°.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.30; H, 7.71.

Isomerization of 21-acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione (III) *to the corresponding 4-ene* (II). The 5-ene, III, 600 mg. was stirred and refluxed 2 hr. in 30 ml. of dry acetone with 1.2 g. of potassium acetate. The mixture was cooled, diluted with 60 ml. of water, and concentrated under reduced pressure to 60 ml. final volume. The crystalline precipitate was collected and recrystallized from hexane containing a small proportion of acetone. The product, II, needles melted from 191–193°, $[\alpha]_D^{25}$ +123°, $\lambda_{max}^{CH_3OH}$ 238 mμ, log ε = 4.23, agreed well with the product described above and with the preparation reported by the British group.[10]

21-Acetoxy-5α,6β-dibromo-3β,17α-dihydroxy allopregnane-12,20-dione (V). A solution of 1 g. of 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, α_D −13.7°, in 25 ml. of methylene chloride at 4° was treated with 10.72 ml. of a carbon tetrachloride solution containing a molar equivalent of bromine. The bromine solution was added at a controlled rate during 75 min. time. The mixture was stirred an additional 2 min., solvents were removed *in vacuo* at room temperature and 10 ml. of methanol was added. On stirring, 955 mg. of colorless crystals of V, α_D −28.8°, m.p. 140–141° dec., deposited. A small additional crop separated from the decanted supernatant solution. Some preparations of the dibromide developed coloration on standing due to decomposition. Purer preparations were more stable.

Anal. Calcd. for $C_{23}H_{32}O_6Br_2$: C, 48.95; H, 5.72; Br, 28.32. Found: C, 49.12; H, 5.86; Br, 28.77.

Treatment of the dibromide, V, *with perbenzoic acid.* The dibromide, V, 1.17 g., dissolved in 7.9 ml. of cold chloroform, was treated with 11 ml. of a solution of perbenzoic acid in the same solvent (1 ml. = 11.52 ml. 0.1*N* sodium thiosulfate) 0.2 ml. of water, and 0.45 ml. of 10% sulfuric acid in acetic acid and was let stand with occasional shaking for 113 hr. in the dark at room temperature. The resulting orange solution was shaken with 100 ml. of ether and 100 ml. of water. Decolorization occurred and the aqueous phase was discarded. The organic layer was washed with aqueous sodium iodide to destroy peroxyacid and was washed cautiously with just enough dilute sodium thiosulfate to decolorize the large excess of liberated iodine, with dilute sodium bicarbonate to remove acids and with saturated sodium chloride solution. Solvents were evaporated under reduced pressure. The residue, dissolved in 25 ml. of acetone, was stirred with 2 g. of potassium iodide and refluxed for 1 hr. After dilution with water, extraction with ether, and removal of liberated iodine by treatment with dilute sodium thiosulfate, the isolated steroid was chromatographed on Florisil.[14] Elution with methylene chloride gave unchanged starting material identified by its infrared spectrum. Further elution with 1:1 methylene chloride gave an intermediate cut rich in unreacted starting material. Elution with 4% methanol in methylene chloride gave 250 mg. of a material yielding an amorphous powder on treatment with ether and having a single broad carbonyl infrared absorption band from 5.7 to 5.8 μ with a weak shoulder at 5.91 μ (in methylene chloride solution). The carbonyl area resembled that of the similarly obtained known 5α—C ring lactonoid corticoid.[13] The substance gave a strong tetrazolium color reaction.

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(23) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).