form. The water-washed and dried extracts on evaporation *in vacuo* left a residue which after two recrystallizations from methanol melted at 212–214° (softening at 207°), $[\alpha]^{24}D$ −27 ± 2° (*c* 1.126); λ_{max}^{alc} 350 mμ (105); shoulder, 240–245 mμ (5800). The infrared spectrum showed bands at 2.85, 3.04 μ (OH) and at 7.31, 7.46 and 11.11μ (NO). The Liebermann reaction for nitrosamines with phenol–sulfuric acid was strongly positive (yellow → deep red → deep blue). It should be mentioned, however, that veratramine itself produces with these reagents a sequence of colors terminating in blue (deep yellow → dirty red → blue → green → blue), except that the latter is far less intense than with the nitroso derivative.

The compound contained solvent of crystallization which could not be completely removed by drying at 110° as prolonged heating led to decomposition. The analytical values obtained on a sample dried at 110° (0.1 mm.) for 3 hours fitted best for a hemihydrate.

Anal. Calcd. for $C_{27}H_{38}O_3N_2 \cdot {}^1/_2H_2O$ (447.6): C, 72.40; H, 8.80; N, 6.27. Found: C, 72.35; H, 8.75; N, 6.42.

Acknowledgments.—The authors gratefully acknowledge the coöperation of Mr. Norman Hosansky and of Miss Mildred Moore in checking on some of the experiments reported. They are also indebted to Mr. Joseph F. Alicino and his associates for the microanalyses, and to Dr. Nettie Coy for the ultraviolet and infrared measurements.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

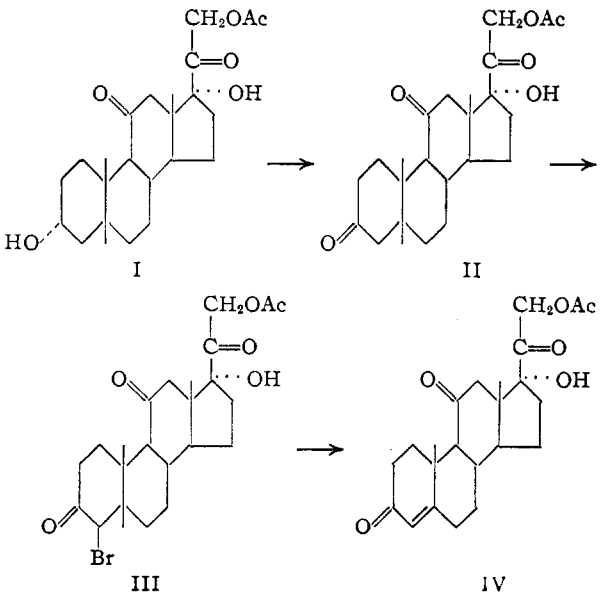
Simultaneous Oxidation and Bromination of 21-Acetoxypregnan-3α,17α-diol-11,20-dione

BY E. B. HERSHBERG, CORINNE GEROLD AND EUGENE P. OLIVETO

RECEIVED JANUARY 5, 1952

The oxidation of 21-acetoxypregnan-3α,17α-diol-11,20-dione (I) with N-bromosuccinimide in either aqueous acetone, aqueous *t*-butanol or a mixture of *t*-butanol, methylene chloride and pyridine, proceeded normally to the 3-ketone (II). Oxidation in methylene chloride and *t*-butanol solution in the absence of pyridine gave none of II, but instead, a mixture of bromides, 4-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (III) and 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V), with the former predominating. The same mixture was obtained from the action of bromine on 21-acetoxypregnan-3α, 17α-diol-11,20-dione (II) dissolved in methylene chloride and *t*-butanol mixture. Some transformations of the 21-bromide (V) are described.

An essential sequence of reactions in one of the alternate syntheses of 11-dehydro-17α-hydroxycorticosterone acetate (cortisone acetate, IV) is the oxidation of 21-acetoxypregnan-3α,17α-diol-11,20-dione (I) to the corresponding 3-ketone, II, followed by bromination at C-4 and finally the introduction of the Δ^4-double bond by the elimination of hydrogen bromide.



I II III IV

Many reagents have been used for the oxidation of a 3α-hydroxyl group to a 3-ketone, among them chromic acid,[1] buffered and unbuffered potassium chromate,[2a] N-bromosuccinimide[3] and N-bromoacetamide.[2] However, no specific directions were available in the literature for the oxidation of I.

We had been privately advised that chromic acid[4] and N-bromoacetamide[5] were satisfactory for the oxidation of I to II. In our hands, the latter reagent gave somewhat better yields, probably because chromic acid is not specific for hydroxyl groups, but will also attack the ketol side-chain. It was important that as clean an oxidation as possible be obtained, for the purity of II is a factor in the success of the bromination step (II to III). The lack of adequate quantities of N-bromoacetamide at the time of this research led us to investigate the action of N-bromosuccinimide on I. Although in only one previous instance[3] had NBS[6] been reported to oxidize a 3α-hydroxy group to the corresponding ketone, we had reason to expect that the similarity of NBA[6] and NBS would allow a substitution of NBS in cases where NBA had been found to be useful. Such proved to be the case and NBS in *t*-butyl alcohol–methylene chloride, in the presence of pyridine, effected a smooth oxidation of I to II. Although the original investigators[7] of NBA had used aqueous *t*-butyl alcohol as the solvent, Sarett[2b] invariably added pyridine to remove the hydrogen bromide formed and to prevent possible attack by the acid on the ketol side-chain. In this particular oxidation, it had been reported[5] that NBA worked equally well either with or without

(1) L. H. Sarett, THIS JOURNAL, 71, 1169, 2443 (1949).

(2) (a) L. F. Fieser and S. Rajagopalan, *ibid.*, 72, 5530 (1950); (b) L. H. Sarett, *ibid.*, 71, 1165 (1949).

(3) L. F. Fieser and S. Rajagopalan, *ibid.*, 73, 118 (1951).

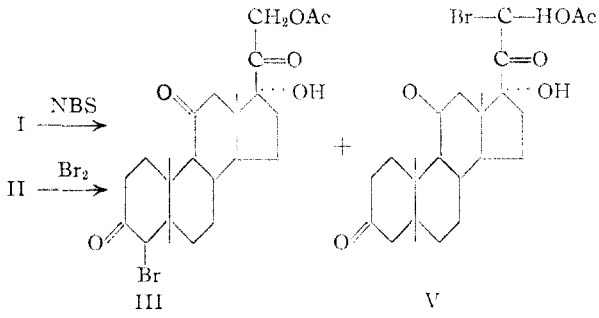
(4) E. C. Kendall, private communication.

(5) T. F. Gallagher, private communication.

(6) NBS = N-bromosuccinimide; NBA = N-bromoacetamide.

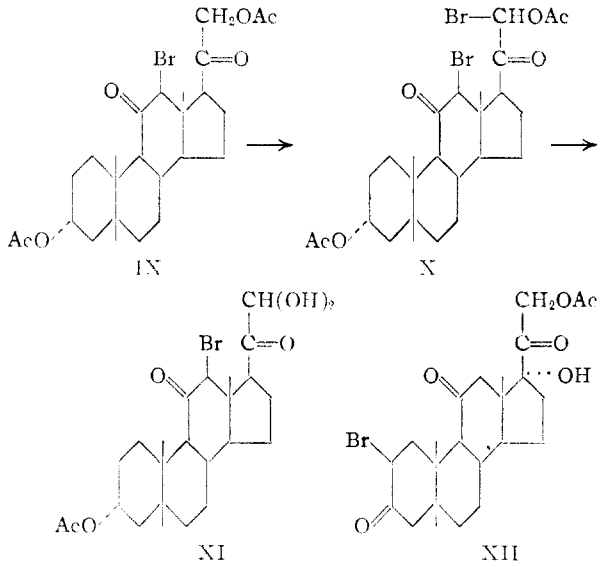
(7) H. Reich and T. Reichstein, *Helv. Chim. Acta*, 26, 562 (1943).

pyridine. Although NBS in aqueous *t*-butyl alcohol or aqueous acetone was also an effective reagent for the oxidation of I to II, surprisingly, NBS in methylene chloride–*t*-butyl alcohol mixture without pyridine gave none of the expected product, II, but instead a mixture of brominated materials. It was possible by crystallization to separate the mixture into two components. The major fraction, with $[\alpha]_D$ *ca.* +100° in acetone, was easily identified as 4-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (III) by its conversion into cortisone acetate (IV) *via* the semicarbazone.[8] The second bromide, with a rotation of about 75°, was at first believed to be 2-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (XII), which is usually formed in smaller amount during the preparation[9] of the 4-bromide (III). However, treatment with semicarbazide hydrochloride, followed by pyruvic acid hydrolysis[8c] gave a bromine-free product with no α,β-unsaturated ketone, as shown by its ultraviolet spectrum. Since it is known that 11-keto-12-bromo compounds are stable to semicarbazide[10] and dinitrophenylhydrazine[8a] treatment, it seemed reasonable that this minor product was 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V).

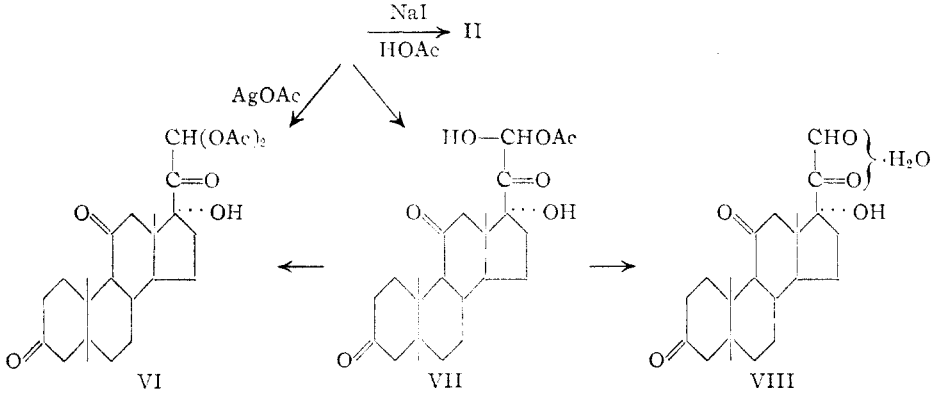


The only known example of a 21-bromo-21-acetoxy-20-keto compound is 12,21-dibromo-3α-21-diacetoxypregnan-11,-20-dione (X) which was prepared[11] by the direct bromination of 12-bromo-3α-21-diacetoxypregnan-11,20-dione (IX). In like fashion, we found that the direct bromination of 21-acetoxypregnan-17α-ol-3,11,20-trione (II) in *t*-butyl alcohol and methylene chloride gave the same mixture of 4-bromo (III) and 21-bromo (V) compounds obtained from the simultaneous NBS oxidation and bromination of I, again with the 4-bromo compound predominating.

The 21-bromo-21-acetoxy compound (V) is characterized by its facile reduction with sodium iodide in acetic acid to 21-acetoxypregnan-17α-ol-3,11,20-trione (II), and its very rapid hydrolysis in aqueous pyridine to 21-acetoxypregnan-17α,21-diol-3,11,20-trione (VII). This latter reaction was quite unexpected, for Fleisher and Kendall[11] have reported that a similar hydrolysis of (X) gave the hydrated glyoxal (XI). The retention of the acetate group was disclosed by the infrared spectrum; its presence was also indicated by analysis and the fact that compound VII could be further hydrolyzed to the glyoxal (VIII). The glyoxal was very difficult to obtain pure because of its tendency to form solvates.



The 21-acetoxy-21-hydroxy compound VII, gave the 21,21-diacetate (VI) upon treatment with one equivalent of acetic anhydride in pyridine. This compound was also obtained by reaction of the original 21-bromo-21-acetate (V) with silver acetate.



The normal procedure[9] for the bromination of 21-acetoxypregnan-17α-ol-3,11,20-trione involves the use of acetic acid as the solvent. The conditions of acidity, concentration, temperature, and final dilution with water must be carefully controlled to give a reasonable yield of the 4-bromo compound (III) which is satisfactory for the final step. Even so, there is always formed at least 15–25% of the 2-bromo compound (XII) which is of no value in

(8) (a) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); (b) B. Koechlin, T. Kritchevsky, and T. F. Gallagher, *ibid.*, **184**, 393 (1950); (c) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(9) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 593 (1950).

(10) Unpublished results, this Laboratory.

(11) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

the preparation of cortisone acetate (IV) and which must be separated from the 4-bromide and then reclaimed by debromination with zinc. Also, the hydrogen bromide–acetic acid solution in which the bromination is carried out is an ideal environment for the disproportionation[9] of the bromides formed and a concurrent increase in complexity of the reaction products.

The yields in the combined oxidation and bromination process described in this paper compare favorably with those which we obtained by using the two-step process. In our hands the delicate 4-bromination in buffered acetic acid solution did not give the yield claimed.[9]

The combined process has several potential advantages, the most obvious of which is the elimination of the isolation of the 3-keto compound (II). Second, the solvent mixture is of such a nature as to cut down the possibility of disproportionation. Third, the conditions of the reaction are not as critical and the by-product of the reaction, 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V) is easily converted into a usable material.

It is interesting that the bromination of II with bromine in acetic acid[9] produces a mixture of 4-bromide (III) and 2-bromide (XII), while in *t*-butyl alcohol–methylene chloride solution the 21-bromide (V) is isolated as the minor product rather than XII. The lability of the bromine in V probably precludes its isolation in the acetic acid procedure, and also points to the fallacy of assigning relative reactivities of various positions in the steroid nucleus toward bromine without specifying the nature of the solvent.

It is not possible to say whether or not the 21-bromide which we have isolated is a mixture of the two possible isomers. Although Fleisher and Kendall were able to separate 12,21-dibromo-3α,21-diacetoxypregnan-11,20-dione (X) into the two isomers at C-21 by crystallization, our material (V) and its hydrolysis product (VIII) both appeared to be homogeneous.

Experimental[12]

21-Acetoxypregnan-3α,17α-diol-11,20-dione (I).—A solution of 5 g. of pregnan-3α,17α-diol-11,20-dione[13] in 50 ml. of C.P. chloroform was brominated with one equivalent of bromine following the procedure of Gallagher.[14] The bromide was not isolated, but instead the solvent was removed under reduced pressure and the residue treated with 50 ml. of C.P. acetone and 20 g. of potassium acetate, and refluxed for five hours. One-half the solvent was removed under reduced pressure, water was added, and the mixture was extracted with methylene chloride. After drying and removal of the solvent, the residue was crystallized from ethyl acetate; yield 4.5 g., m.p. 229–232°, $[\alpha]_D$ +77.9° (acetone).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.70; H, 8.32.

Oxidation of 21-Acetoxypregnan-3α,17α-diol-11,20-dione (I) with N-Bromosuccinimide.—A solution of 15 g. of 21-acetoxypregnan-3α,17α-diol-11,20-dione in 300 ml. of *t*-butyl alcohol and 60 ml. of water was cooled to 2° with agitation, and 16.5 g. (2.5 moles per mole I) of N-bromosuccinimide was added. Stirring at 1–2° was continued for six hours with the flask protected from light. At the end of the reaction time, the suspension was poured into 3 l. of ice-water containing 25 g. of sodium sulfite. The precipitate was collected, washed and dried. This material weighed 11.50 g. and melted at 211–215°. An additional 3.02 g., m.p. 223–226°, precipitated from the aqueous filtrate upon standing overnight. Both precipitates were combined and recrystallized from ethyl acetate and gave two crops: 9.72 g., m.p. 228–232°, and 2.89 g., m.p. 226–229° (total, 84%). This material was identical with 21-acetoxypregnan-17α-ol-3,11,20-trione (II) obtained by NBA[6] or chromic acid[4] oxidation of I, or as prepared according to Sarett.[1]

Oxidation and Bromination of 21-Acetoxypregnan-3α,-17α-diol-11,20-dione (I) with N-Bromosuccinimide.—A solution of 5.0 g. of 21-acetoxypregnan-3α,17α-diol-11,20-dione in 100 ml. of dry *t*-butanol was combined with a solution of 5.5 g. of N-bromosuccinimide in 100 ml. of methylene chloride. The solution was allowed to stand overnight at room temperature. It was then shaken with an excess of dilute sodium sulfite solution and washed twice with water. After drying over sodium sulfate the solvent was removed under reduced pressure. The residue, 5.78 g., $[\alpha]_D$ +69.0° (acetone), was sludged for ten minutes with 20 ml. of acetone; 80 ml. of ether was added and the sludging was continued for ten minutes longer. The suspension was chilled, filtered, and the solid washed with cold ether: weight 2.70 g., m.p. 200–203° dec., $[\alpha]^{21}_D$ +97.2° (acetone).

Anal. Calcd. for $C_{23}H_{31}O_6Br$: Br, 16.53. Found: Br, 16.40.

This was shown to be 4-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (III) by its conversion to cortisone acetate via the semicarbazone.[8]

The acetone–ether filtrate was evaporated to dryness under reduced pressure and the residue was sludged as before with 2.5 ml. of acetone and 5 ml. of ether. This left a residue of 0.88 g. of material, $[\alpha]_D$ +78.7° (acetone). Upon recrystallization from methylene chloride–hexane there was obtained 0.70 g. of 21-bromo-21-acetoxypregnan-17α-ol-11,20-dione (IV); $[\alpha]^{20}_D$ +74.7° (acetone), m.p. 202–204° dec.

Anal. Calcd. for $C_{23}H_{31}O_6Br$: Br, 16.5. Found: Br, 15.45.

It was not possible to obtain an analytically pure sample, presumably because of the facile replacement of the 21-bromine. Successive crystallizations resulted in a further decrease of the bromine value.

Reduction of 21-Bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (IV).—To a solution of 0.25 g. of 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V) in 4 ml. of glacial acetic acid was added 0.25 g. of sodium iodide. After 2.5 hours, the deep red solution was poured into water and the tan solid collected, washed with water and dried. Recrystallization from ethyl acetate gave 0.12 g. of white crystals, m.p. 224–226°, $[\alpha]^{25}_D$ +86.5° (acetone). Two further recrystallizations, from ethyl acetate and from aqueous methanol, did not change the melting point. The infrared spectrum of this material was identical with that of authentic 21-acetoxypregnan-17α-ol-3,11,20-trione (II) which had been prepared by NBS oxidation of I. A melting point of the mixture was not depressed.

21-Acetoxypregnan-17α,21-diol-3,11,20-trione (VII).—A solution of 0.50 g. of 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V) in 4 ml. of 80% aqueous pyridine was allowed to stand 15 minutes at room temperature; the solution was then poured into ice-water containing 4 ml. of 10 *N* sulfuric acid and the precipitate was collected, washed thoroughly with water and dried. Recrystallization from benzene gave 0.42 g., m.p. 204.8–206°, $[\alpha]^{24}_D$ +102.6° (chloroform). The material showed no strong ultraviolet absorption, contained no bromine, and an infrared spectrum showed that the acetate group had not been removed.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.38; H, 7.50.

21,21-Diacetoxypregnan-17α-ol-3,11,20-trione (VI). A.—A mixture of 0.50 g. of 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V), 5 ml. of benzene, 10 ml. of glacial acetic acid and 0.35 g. of silver acetate was shaken for 65 hours at room temperature. The solution was then filtered from the solids which were thoroughly washed with chloroform. The combined organic extracts were washed neu-

(12) All melting points are corrected. All rotations were taken in a one decimeter tube at a concentration of 1%. We are indebted to Mr. Edwin Conner and his staff for the microanalytical data, and to Dr. William Tarpley and his staff for the infrared spectra and interpretations.

(13) L. H. Sarett, THIS JOURNAL, **71**, 1169 (1949).

(14) B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 189 (1951).

tral, dried, and evaporated to dryness. Recrystallization of the residue from aqueous methanol gave 0.45 g., m.p. 209–211°. A second recrystallization from methanol raised the melting point to 211–213°; $[\alpha]^{24}D$ +98.5° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 64.92; H, 7.41. Found: C, 64.94; H, 7.51.

B.—A solution of 0.10 g. of 21-acetoxypregnan-17α-21-diol-3,11-dione (VII) in 2 ml. of pyridine was treated with 1 equivalent of acetic anhydride (0.45 ml. of a solution of acetic anhydride in pyridine, containing 0.0054 g. of acetic anhydride per ml.). After six hours at room temperature the solution was poured into water and the white crystals which separated were collected with suction, washed and dried: weight 0.09 g., m.p. 210–212°. There was no change in m.p. on crystallization from ether. A mixed melting point with the diacetate obtained in (A) above showed no depression, and the infrared spectra of the two compounds were identical.

Pregnan-17α,21,21-triol-3,11,20-trione (VIII).—A solution of 0.09 g. of crude 21,21-diacetoxypregnan-17α-ol-3,-11,20-trione in 8 ml. of methanol was combined with a solution of 0.20 g. of potassium bicarbonate in 2 ml. of water. A white precipitate which formed immediately was dissolved by gentle warming for five to ten minutes. The solution was allowed to stand at room temperature for five hours, diluted with water and extracted several times with methylene chloride. The combined organic extracts were washed once with water and the wash reëxtracted once with methylene chloride. The solution was dried with magnesium sulfate and evaporated, leaving 0.06 g. of a light tan solid. Crystallization from aqueous isopropyl alcohol gave the hydrated glyoxal VIII, m.p. 169–170.4° (with bubbling), $[\alpha]^{21}D$ +87.0° (ethanol).

Anal. Calcd. for $C_{21}H_{28}O_5 \cdot H_2O$: C, 66.64; H, 7.99. Found: C, 67.50; H, 7.95.

Crystallization from benzene gave the unhydrated form, m.p. 187–188°.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.53; H, 8.50.

Solutions of VIII in non-polar solvents such as benzene gave a yellow color characteristic of glyoxals.

Bromination of 21-Acetoxypregnan-17α-ol-3,11,20-trione (II) in *t*-Butyl Alcohol–Methylene Chloride.—A solution of 1.00 g. of 21-acetoxypregnan-17α-ol-3,11,20-trione in 10 ml. of methylene chloride and 10 ml. of *t*-butyl alcohol was combined with a solution of 0.40 g. of bromine in 5 ml. of methylene chloride and 5 ml. of *t*-butyl alcohol. After 1.5 hours at room temperature, the red bromine color had discharged. The methylene chloride was removed by distillation under reduced pressure until crystallization began and the residual solution was poured into 200 ml. of cold water. The precipitate was collected, washed with water and dried at 50°; weight 1.11 g., $[\alpha]^{21}D$ +87.1° (acetone). Recrystallization of 1.00 g. from aqueous acetone gave two crops. The first crop which weighed 0.65 g. was 4-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (III), $[\alpha]^{26}D$ +100.7° (acetone); while the second crop of 0.17 g. was 21-bromo-21-acetoxypregnan-17α-ol-3,11,20-trione (V), $[\alpha]^{26}D$ +74.5° (acetone).

By treatment of the 21-bromide with sodium iodide in acetic acid as described previously, the starting material (II) was regenerated.

Repetition of the above reaction in darkness, with a trace of benzoyl peroxide, required four hours and a higher percentage of the 4-bromide was formed. Upon recrystallization the first crop weighed 0.75 g., $[\alpha]D$ +104.5° (acetone). The second crop weighed 0.17 g., $[\alpha]^{24}D$ +88.4° (acetone). From this rotation it was apparent that only about half of the second crop consisted of the 21-bromide.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

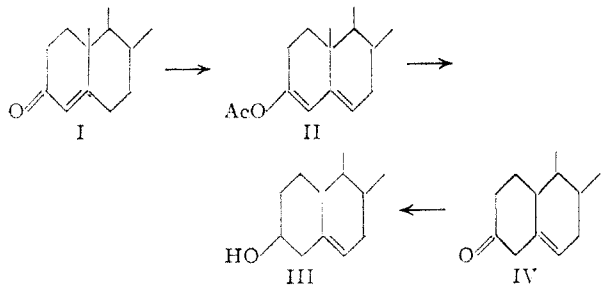
The Reduction of Steroidal Enol Acetates with Lithium Aluminum Hydride and Sodium Borohydride

BY WILLIAM G. DAUBEN, ROBERT A. MICHELI AND JEROME F. EASTHAM

RECEIVED JANUARY 22, 1952

The enol acetates of cholestanone and coprostanone were prepared using isopropenyl acetate and their structures were shown to be Δ^2 and Δ^3, respectively. Each enol acetate was reduced with lithium aluminum hydride and it was found that carbon–carbon double bond reduction occurred. The ratio of α- and β- isomers formed from the enol acetates was different from that obtained by reduction of the parent ketones; a larger amount of the less available isomer was always formed from the enol acetate. The same enol acetates were reduced with sodium borohydride and it was found that the product composition was identical with that obtained by direct reduction of the ketone. The reduction of Δ^4-cholesten-3-one was reinvestigated and it was found that approximately 70% of the β-isomer was formed, a result in contrast to the previously reported equal amounts of the α- and β-compounds.

It has recently been reported that both lithium aluminum hydride[1] and sodium borohydride[2–4] reduce 3-acetoxy-$\Delta^{3,5}$-cholestadiene (Δ^4-cholesten-3-one enol acetate, II) to cholesterol (III). The presence of two double bonds in II makes it atypical as an enol acetate and raises the question of the structural requirements for the above type of reaction. If the reduction could be applied to simple enol acetates, then the reaction might be of utility for a purpose more general than the rather unique task of transforming an α,β-unsaturated ketone into a β,γ-unsaturated alcohol.[5] For example, in the reduction of a steroidal ketone to an alcohol, there exists the possibility that both isomeric alcohols will be formed. It was found in the above enol acetate case, however, that whereas sodium borohydride reduction gave an isomer ratio similar



(1) W. G. Dauben and J. F. Eastham, THIS JOURNAL, 73, 3260 (1951).

(2) E. Schwenk, M. Gut and J. Belisle, *Arch. Biochem. Biophys.*, 31, 456 (1951).

(3) B. Belleau and T. F. Gallagher, THIS JOURNAL, 73, 4458 (1951).

(4) W. G. Dauben and J. F. Eastham, *ibid.*, 73, 4463 (1951).

(5) For an extension of the method to the transformation of an α, β, γ-, δ-unsaturated ketone into a β, γ-, δ, ε-unsaturated alcohol, see W. G. Dauben, J. F. Eastham and R. A. Micheli, *ibid.*, 73, 4496 (1951).