

perature overnight. The bulk of the solvents was removed *in vacuo* and the residue was distributed between ether-benzene (3:2) and water. The aqueous layer was back-extracted with benzene and the combined organic layers were extracted with a bicarbonate solution and then with a saturated solution of sodium chloride. The crude product contained only a small amount of the conjugated ketone as evidenced by $\log \epsilon$ 3.45 at 228 $m\mu$. Addition of a dilute solution of sodium methoxide immediately raised the $\log \epsilon$ to 4.12. An aliquot (75 mg.) was, therefore, dissolved in 15 ml. of methanol and isomerized for two hours by the addition of 1.5 ml. of a 0.86 *N* solution of sodium methoxide in methanol. Neutralization with acetic acid, removal of the solvent and addition of water gave 55 mg. of crude XIV. An analytical sample (m.p. 208–212°, λ_{\max} 229 $m\mu$ ($\log \epsilon$ 4.16); $\lambda_{\max}^{\text{Ni}}$ 5.86, 5.94 (shoulder), 6.11 μ ; $\lambda_{\max}^{\text{CH}_2}$ 5.85, 5.93, 6.11 μ) was prepared from acetone-Skellysolve B. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_6$: C, 68.02; H, 7.27. Found: C, 68.14; H, 7.00. In another experiment (40 mg. scale) the crude lead tetraacetate product did not show an absorption maximum at 228 $m\mu$ but the product gave a strong tetranitromethane test and showed one olefinic proton.¹⁵ Isomerization afforded XIV.

(b) From Acid A.—The lead tetraacetate oxidation was carried out on the lower melting acid (m.p. 198–200°) as described above for acid B on a 260-mg. scale. The crude product showed no selective absorption in the ultraviolet. Repeated recrystallization from acetone-Skellysolve B gave 5 ξ ,17 α ,21-trihydroxy-A-nor-pregnane-2,11,20-trione BMD, m.p. 259.2–260.2°, $\lambda_{\max}^{\text{Ni}}$ 2.91, 5.73, 5.92 μ which had no olefinic protons¹⁶ and gave a negative tetranitromethane test. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_7$: C, 65.01; H, 7.44. Found: C, 65.23; H, 7.76. Treatment with alkoxide carried out essentially as described above gave 205 mg., λ_{\max}

228 $m\mu$ ($\log \epsilon$ 4.14). One recrystallization from acetone-Skellysolve B gave XIV, m.p. 207–210°, identical with the specimen described above.

(c) From XI and XII.—The same compound XIV was obtained when 11.4 mg. of the 11 α -isomer XII or 9.4 mg. of the 11 β -isomer XI was treated, respectively, with 21 mg. and with 17.2 mg. of chromic oxide in aqueous acetic acid.

17 α ,21-Dihydroxy-A-nor-3(5)-pregnene-2,11,20-trione (XV).—A solution of 160 mg. of the A-norcortisone BMD XIV in 58 ml. of dilute acetic acid (50% v./v.) was heated on a steam-bath for about 14 hours. The mixture was poured on ice and extracted with chloroform. Removal of the solvent and crystallization from acetone-Skellysolve B gave crude XV which was purified further by paper chromatography on Whatman paper #4 using the solvent system employed in the purification of XIII. An analytical sample, m.p. ca. 200°, λ_{\max} 229 $m\mu$ ($\log \epsilon$ 4.12) was obtained from acetone-Skellysolve B. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{28}\text{O}_5$: C, 69.34; H, 7.56. Found: C, 69.07; H, 7.35.

17 α ,21-Dihydroxy-2-methoxy-1,4-pregnadiene-3,11,20-trione BMD (IV).—A solution of the sodio-derivative IIIb in a mixture of 100 ml. of acetone and 3 ml. of methyl iodide was refluxed in a nitrogen atmosphere. Solvents were removed *in vacuo* and the residue distributed between dilute aqueous sodium hydroxide and chloroform. The neutral fraction was recrystallized from acetone-Skellysolve B to give material melting at 262–264° dec. *Anal.* Calcd. for $\text{C}_{24}\text{H}_{30}\text{O}_7$: C, 66.96; H, 7.02. Found: C, 66.60; H, 7.00.

Acknowledgment.—The authors are pleased to acknowledge the able technical assistance of Mr. Nathan G. Steinberg.

RAHWAY, N. J.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY¹]

Steroidal Sapogenins. LI. Reaction of Steroidal Olefins with Acetyl Hypobromite^{2a,b}

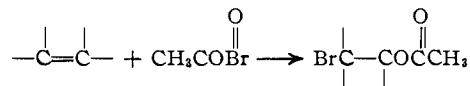
BY SAMUEL G. LEVINE AND MONROE E. WALL

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Treatment of various steroidal olefins with acetyl hypobromite has yielded stable bromohydrin acetate adducts which, on saponification, produced the corresponding β -oxides. This method is compared with certain alternative routes with regard to scope, limitations and possible general advantages.

In the course of studies on the conversion of steroidal sapogenins to cortical hormones it was necessary to prepare a number of β -oxides from the corresponding steroidal olefin. Conventionally, hypobromous acid has been the reagent used for this purpose^{3a–f} giving predominantly diaxial α -bromo- β -hydroxy compounds which yield the β -oxide on treatment with base. Several features of the hypobromous acid procedure seemed undesirable. This reaction is conducted in an acidic medium which, frequently, is incompatible with a spiroketal or other acid-labile functional grouping and at times other side reactions (*e.g.*, bromination) occur. Most important, in some cases, our wish to carry a stable intermediate through several stages

before closure to the β -oxide was precluded by the lability of bromohydrins toward oxidation or even the mildest base treatment. For these reasons, we have explored the olefin addition of acetyl hypobromite as a one-step method of preparing steroidal bromohydrin acetates as our epoxide precursors.



1,2-Addition of an acyl hypohalite is thought to be the first step of the familiar Prévost oxidation⁴ which, in cyclic olefins, leads to the corresponding *trans*-diol. The Winstein-Woodward modification leading to *cis*-diols has been similarly interpreted.⁵ In these cases, the intermediate iodohydrin ester is not ordinarily isolated⁶; such addition products have been obtained, though, from a variety of aliphatic and monocyclic olefins.⁴ However, the addition of acyl hypobromites to unsaturated polycyclic systems has received little attention.

(4) C. V. Wilson, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 350.

(5) R. B. Woodward and F. V. Brucher, Jr., *THIS JOURNAL*, **80**, 209 (1958).

(6) See, however, W. S. Knowles and Q. E. Thompson, *ibid.*, **79**, 3212 (1957).

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

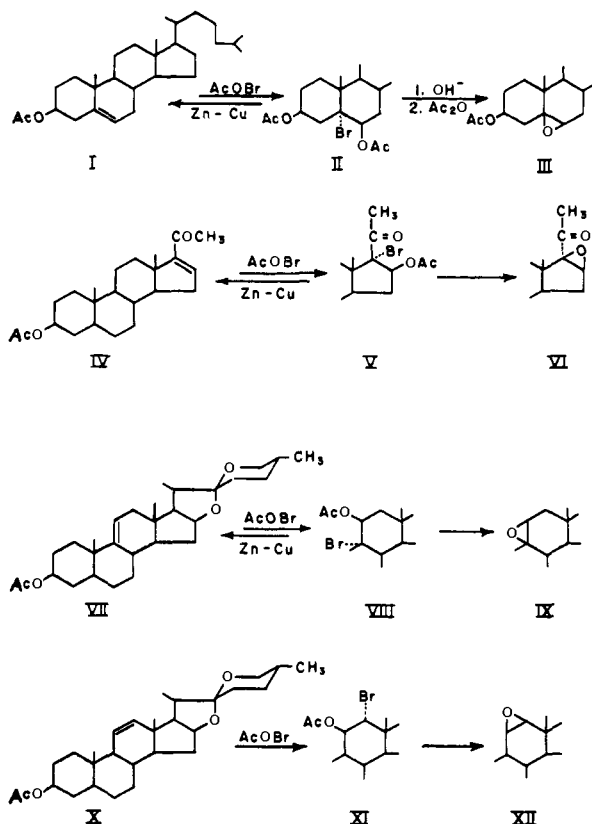
(2) (a) Presented in part at the 135th National A.C.S. Meeting, Boston, Mass., April 5–10, 1959; (b) Paper L, Walens and Wall, *THIS JOURNAL*, **81**, in press (1959).

(3) (a) B. Ellis and V. Petrow, *J. Chem. Soc.*, 4417 (1956); (b) R. K. Callow and V. H. T. James, *ibid.*, 4739 (1956); (c) J. Fried and E. F. Sabo, *THIS JOURNAL*, **75**, 2273 (1953); (d) B. Löken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 1738 (1956); (e) N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *ibid.*, **78**, 5027 (1956); (f) E. P. Oliveto, C. Gerold and E. B. Hershberg, *ibid.*, **79**, 3596 (1957).

The reagent was conveniently prepared by a modification of the procedure of Abbot and Arcus⁷ which entails the addition of bromine to a cold suspension of silver acetate in carbon tetrachloride. The hypobromite solution thus prepared was assayed iodometrically and then added, in slight excess, to a cold solution of the steroidal olefin in carbon tetrachloride.

The non-acidic nature of the acetyl hypobromite reaction conditions is illustrated by the two-step conversion of cholesteryl tetrahydropyranyl ether to the corresponding 5,6-oxide without loss of the acid-sensitive protecting group.

When cholesteryl acetate (I) was treated in this manner, a mixture of bromohydrin acetates, principally II, was obtained. Saponification of this material followed by acetylation yielded cholesteryl acetate β -oxide⁸ (III) as the major product, separable by crystallization from a smaller amount of the " α,β -oxide."⁸



Similar treatment of 3 β -acetoxy-5 α -pregn-16-en-20-one (IV)⁹ with acetyl hypobromite gave an addition product (V)¹⁰ which was saponified to the corresponding 16 β ,17 β -epoxy compound VI.

Two ring C unsaturated sapogenins were converted by this sequence into their corresponding β -oxides. Thus 3 β -acetoxy-5 α ,22 β ,25D-spirost-9-(11)-en(VII)^{11a} and 3 β -acetoxy-5 α ,22 β ,25D-spirost-

11-en(X)^{11b} yielded the adducts VIII and XI, respectively, the latter compound obtainable only in resinous form. Saponification of XI followed by acetylation produced 3 β -acetoxy-11 β ,12 β -epoxy-5 α ,22 β ,25D-spirostane (XII)¹² identical with an authentic sample; saponification of VIII gave the hitherto unknown 3 β -hydroxy-9 β ,11 β -epoxy-5 α ,22 β ,25D-spirostane (IX).¹³

An attempt was made to follow the progress of each of the above addition reactions by iodometric determination of unreacted acetyl hypobromite. However, in each case, the titer had reached a constant level (for 1 mole uptake) by the time the first two aliquots could be withdrawn. In contrast, it was found¹⁰ that the addition of hypobromous acid to the olefinic linkage of IV, under the usual conditions^{8a,b,c,e,f} required 5.5 hours for 80% completion.

In marked contrast to the above cases, methyl 3 α -acetoxy- $\Delta^{9,11}$ cholenate was recovered mostly unchanged after treatment with acetyl hypobromite under the usual conditions. The particularly hindered nature of $\Delta^{9,11}$ -cholicates toward addition reactions is also manifested in their inertness toward catalytic hydrogenation¹⁴ and in the recovery of a preponderance of starting material from hypobromous acid addition conditions.¹⁵

We were also interested in testing the facility of iodohydrin acetate formation from two of the above-mentioned steroidal olefins. Accordingly, cholesteryl acetate (I) and the Δ^{16} -20-ketone IV were treated with iodine and silver acetate in glacial acetic acid using the procedure of Knowles and Thompson⁶ and, in both cases, starting material was the only identifiable reaction product. These results are in accord with Shoppee's conclusion¹⁶ that only disubstituted steroidal double bonds react easily under these conditions.¹⁷

Certain points of comparison may be made regarding the applicability of bromohydrin acetates as opposed to bromohydrins in a given reaction sequence. When the immediate conversion of a steroidal olefin to its β -oxide is intended, the over-all yields would seem to lie in the same range for the two methods; however, in cases where acid-catalyzed side reactions could occur, the acetyl hypobromite addition conditions (neutral and non-polar) are preferable. On the other hand, these adducts are clearly disadvantageous when oxidation to a

JOURNAL, **75**, 3252 (1953); (b) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *ibid.*, **76**, 4013 (1954).

(12) J. W. Cornforth, J. M. Osbond and G. H. Phillipps, *J. Chem. Soc.*, 907 (1954).

(13) The stereochemical course of these reactions can be rationalized in terms of an initial attack by Br⁺ on the less hindered (α) side of the steroidal double bond to give an intermediate bromonium ion which is then opened diaxially by β -attack of acetate ion. Saponification of the resulting bromohydrin acetate would then lead to β -oxides, as observed. This mechanism has been presented by Knowles and Thompson (ref. 6) in explanation of the mode of formation and saponification of an iodohydrin acetate.

(14) B. F. McKenzie, V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **175**, 249 (1948).

(15) E. M. Hicks, Jr., and E. S. Wallis, *ibid.*, **162**, 641 (1946).

(16) C. W. Shoppee, D. N. Jones and G. H. R. Summers, *J. Chem. Soc.*, 3100 (1957).

(17) In a preliminary experiment, we have determined that acetyl hypochlorite [M. Anbar and I. Dostrovsky, *J. Chem. Soc.*, 1105 (1954)] adds to the conjugated ketone IV, giving a product m.p. 216–219°, $[\alpha]_D^{20} + 61.3^\circ$, whose infrared spectrum is very similar to that of V.

(7) D. C. Abbot and C. L. Arcus, *J. Chem. Soc.*, 1515 (1952).

(8) Pl. A. Plattner, Th. Petrzilka and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

(9) R. E. Marker, H. M. Crooks, Jr., R. B. Wagner and E. L. Wittbecker, *THIS JOURNAL*, **64**, 2089 (1942).

(10) The structure and reactions of this compound are the subject of the following paper.

(11) (a) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, *THIS*

bromo-ketone is desired. A bromohydrin acetate would have particular advantage, though, when one is interested in carrying a *protected* olefin through one or more reaction steps prior to epoxide ring closure. In this regard we have found these adducts to be stable toward acid (2 *M* methanolic hydrogen chloride for 16 hours), mild alkali (aqueous alcohol at pH 9 for 16 hours or refluxing potassium acetate in acetone), and chromic acid oxidation. Indeed, since we have shown that by refluxing with zinc-copper in ethanol, the adducts III, V and VIII are efficiently reconverted to starting olefin, one may consider the addition reaction as an alternative (to bromine addition) olefin protective device.

Experimental¹⁸

Acetyl Hypobromite Reagent (Approx. 0.1 *M* in Carbon Tetrachloride).—Silver acetate (4.0 g.) was suspended in 160 ml. of carbon tetrachloride and stirred at 0° under anhydrous conditions. A solution of 1.00 ml. of bromine in 20 ml. of carbon tetrachloride was then added over 30 minutes with stirring and cooling. Stirring and cooling were continued for 90 minutes; by that time the red bromine color was no longer visible and the solution appeared light yellow-orange. Stirring was then stopped to allow the yellow precipitate (silver bromide) to settle. Portions of the clear supernatant liquid were withdrawn for iodometric titration and for use in the various addition reactions.

5 α -Bromo-3 β ,6 β -diacetoxycholestane (II).—Cholesteryl acetate (10.07 g.) was dissolved in 20 ml. of carbon tetrachloride and cooled to 0°. To it was added 250 ml. of 0.1 *M* acetyl hypobromite at 0°. After 5 minutes, the resulting solution was shaken with 5 ml. of cold 5% sodium bisulfite solution. The organic layer was then washed twice with water, dried over sodium sulfate, and concentrated to an oily residue which was crystallized from warm methanol yielding 10.55 g. (80%) of crude product, m.p. 78–88°, $[\alpha]_D^{25} - 58.0^\circ$; characteristic infrared bands at 1740 (broad, 3- and 6-acetate), 1240 (3-acetate), 1225 (6-acetate), 750 (halogen). Several crystallizations from methanol afforded a sample, m.p. 89–91°. *Anal.* Calcd. for C₃₁H₅₁O₄Br: Br, 14.1. Found: Br, 14.7.

17 α -Bromo-3 β ,16 β -diacetoxy-5 α -pregnan-20-one (V).—3 β -Acetoxy-5 α -pregn-16-en-20-one (0.74 g.) was dissolved in 10.0 ml. of carbon tetrachloride and treated with 25.0 ml. of 0.095 *M* acetyl hypochlorite reagent in the manner described above. The product (0.725 g., 71%) was obtained as prisms from methanol, m.p. 202–206°. Two recrystallizations from methanol and one from hexane gave an analytical sample, m.p. 213.5–215.5°, $[\alpha]_D^{25} + 68.8^\circ$; characteristic infrared absorption bands at 1710 (20-ketone), 1730 (3-acetate), 1744 (16 β -acetate), 1250 and 1230 (acetates), 760 (halogen). *Anal.* Calcd. for C₂₉H₄₇O₅Br: C, 60.35; H, 7.48. Found: C, 60.15; H, 7.66.

9 α -Bromo-3 β ,11 β -diacetoxy-5 α ,22 β ,25D-spirostane (VIII).—A solution of 0.60 g. of 3 β -acetoxy-5 α ,22 β ,25D-spirost-9(11)en in 25 ml. of carbon tetrachloride was cooled to 0° and treated with 20 ml. of 0.10 *M* acetyl hypobromite reagent as described for compound II. Following the usual work-up, the product was obtained as plates from methanol, 0.43 g. (56%), m.p. 170–175°, $[\alpha]_D - 19.8^\circ$; characteristic infrared bands at 1737 (broad, 3- and 11-acetate), 1230–1250 (3- and 11-acetates), 760 and 730 (halogen). *Anal.* Calcd. for C₃₁H₄₇O₅Br: Br, 13.4. Found: Br, 13.2.

12 α -Bromo-3 β ,11 β -diacetoxy-5 α ,22 β ,25D-spirostane (XI).—A solution of 0.45 of 3 β -acetoxy-5 α ,22 β ,25D-spirost-11-en in 10 ml. of carbon tetrachloride was treated with 10.0 ml. of 0.11 *M* acetyl hypobromite reagent as described for compound II. After the usual work-up followed by filtration through a short column of Florisil,¹⁸ the product was obtained as a viscous oil; characteristic infrared absorption

bands at 1735 (broad, 3- and 11-acetates), 1245 (3-acetate), 1230 (11-acetate), 762 and 735 (halogen).

Cholesteryl-Acetate β -Oxide (III).—The bromodiacetate II (3.0 g.) was heated under reflux for one hour with 80 ml. of 5% methanolic sodium hydroxide. The solution was then cooled, neutralized with glacial acetic acid, concentrated to low volume at reduced pressure, and mixed with 100 ml. of water. After collecting, washing, and drying, the total crude product (2.2 g.) was acetylated with pyridine-acetic anhydride at 90° for 40 minutes. Following the usual work-up, the product was crystallized from methanol. Several fractional crystallizations from the same solvent yielded 0.8 g. (34%) of prisms, m.p. 111–113°, $[\alpha]_D^{25} + 1^\circ$, and 0.4 g. (17%) of plates, m.p. 102–110°, $[\alpha]_D - 17.3^\circ$; lit.⁸ gives cholesteryl acetate β -oxide, m.p. 112–113°, $[\alpha]_D - 0.2^\circ$; cholesteryl acetate " α,β -oxide," m.p. 114–115°, $[\alpha]_D - 23.4^\circ$.

Preparation of Cholesteryl Oxide Tetrahydropyranyl Ether (as Stereoisomeric Mixture).—Cholesteryl tetrahydropyranyl ether¹⁹ (0.40 g.) in 10 ml. of carbon tetrachloride was treated with 10 ml. of 0.11 *N* acetyl hypobromite reagent in the usual manner. The reaction solution was then washed with cold, dilute sodium bisulfite followed by water, dried over sodium sulfate, and concentrated to an oil. The residue was saponified with methanolic potassium hydroxide and the product crystallized from methanol to give 0.28 g. (68%) of wide melting (105–135°) blades. The infrared spectrum was devoid of absorption in the hydroxyl region. The material was not further separated or characterized.

16 β ,17 β -Epoxy-3 β -acetoxy-5 α ,17-iso-pregnan-20-one (VI).—17 α -Bromo-3 β ,16 β -diacetoxy-5 α -pregnan-20-one (V) (0.15 g.) was heated under reflux for one hour with 10 ml. of methanol, 2 ml. of water and 0.25 g. of potassium carbonate. The solution was then concentrated at reduced pressure, diluted with water, and the product extracted with ether. The residue from the dried, concentrated ether extract was acetylated with acetic anhydride-pyridine at room temperature. Following the usual work-up the acetate was twice crystallized from methanol to yield 75 mg. (71%) of product, m.p. 158–159°, $[\alpha]_D^{25} - 64.2^\circ$; infrared spectrum: 1705 (20-ketone), 1735 (acetate), 860 and 900 (oxide?). *Anal.* Calcd. for C₂₈H₄₄O₄: C, 73.76; H, 9.15. Found: C, 74.04; H, 9.64.

9 β ,11 β -Epoxy-3 β -hydroxy-5 α ,22 β ,25D-spirostane (IX).—The bromodiacetate VIII (0.152 g.) was heated under reflux with 5.0 ml. of 4% methanolic potassium hydroxide for 90 minutes. Solvent was mostly removed at reduced pressure and the concentrate taken up in ether, washed and dried. Removal of solvent and crystallization of the residue from hexane gave 69 mg. (62%) of needle crystals, m.p. 174–176°, $[\alpha]_D^{25} - 13^\circ$. *Anal.* Calcd. for C₂₇H₄₂O₄: C, 75.31; H, 9.83. Found: C, 75.09; H, 9.88.

The corresponding α -oxide²⁰ is reported to have m.p. 213–215°, $[\alpha]_D - 70^\circ$.

11 β ,12 β -Epoxy-3 β -acetoxy-5 α ,22 β ,25D-spirostane (XII).—Amorphous bromodiacetate XI (0.16 g.) was saponified by the above procedure and then acetylated with acetic anhydride and pyridine at room temperature. The mixture melting point and infrared spectrum of the product were identical with an authentic sample of the β -oxide XII, m.p. 200–206°.

Debromoacetoxylation of the Adducts II, V and VIII.—Zinc-copper couple was prepared according to the procedure of Elks, *et al.*²¹; 47 mg. of the bromodiacetate VIII was dissolved in 6.0 ml. of ethanol and heated with stirring and under reflux with zinc-copper (from 0.9 g. of zinc dust) for 3 hours. Solids were then removed by filtration through Super-cel¹⁸ and the clear solution evaporated to dryness. The residue, in benzene solution, was washed with water, dried, and filtered through a short column of Florisil.¹⁸ Crystallization of the concentrate from methanol afforded a halogen-free product (25 mg., 70%) identical in mixture melting point and infrared spectrum with 3 β -acetoxy-5 α ,22 β ,25D-spirost-9(11)en, m.p. 204–207°. Similar treatment of II and of V effected the regeneration of cholesteryl acetate (I) and of 3 β -acetoxy-5 α -pregn-16-en-20-one (IV), respectively.

(19) W. G. Dauben and H. L. Bradlow, *THIS JOURNAL*, **74**, 559 (1952).

(20) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(21) J. Elks, G. H. Phillips, T. Walker and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956).

(18) Infrared spectra were obtained in carbon disulfide solution, 10.0 g./liter. Optical rotations were measured in chloroform using a 2 decimeter tube, approximately 12.5 g./liter. We wish to thank C. S. Fenske and C. T. Leander for infrared data, S. Serota for optical rotation measurements, and Ruth B. Kelly for elemental analyses. Specification of brand names of materials used does not imply endorsement over other similar commercial products.

Attempted Conversion of I and IV to their Iodohydrin Acetates.—Cholesteryl acetate (I) (0.240 g., 0.00056 mole) and 0.200 g. (0.00056 mole) of 3β -acetoxy- 5α -pregn-16-en-20-one each were allowed to react with 0.101 g. of silver acetate and 0.148 g. of iodine in 1.8 ml. of glacial acetic acid and 0.6 ml. of chloroform according to the procedure of Knowles

and Thompson.⁶ The starting olefins were recovered in approximately 65% yield in both experiments. Resinous, halogenated material was also formed, in each case, which on treatment with base gave little indication (infrared spectrum) of epoxide formation.
PHILADELPHIA 18, PENNA.

(CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY¹)

Steroidal Sapogenins. LII. Structure and Properties of the Acetyl Hypobromite Adduct from a Δ^{16} -Pregnen-20-one^{2a,b}

BY SAMUEL G. LEVINE AND MONROE E. WALL

RECEIVED NOVEMBER 17, 1958

The adduct from acetyl hypobromite and 3β -acetoxy- 5α -pregn-16-en-20-one is shown to be $3\beta,16\beta$ -diacetoxy- 17α -bromo- 5α -pregnan-20-one. The marked resistance of this compound toward C_{21} -bromination is described and the possible utility of this property is indicated.

The addition of acetyl hypobromite to 3β -acetoxy- 5α -pregn-16-en-20-one (I) to give a bromohydrin acetate was described in the previous communication.² Since the double bond involved in this facile reaction is part of a conjugated ketone system,³ we felt unjustified in adducing, in this case, the same mechanistic principles² which aided in our assignment of structures to the adducts from isolated double bonds.⁴ This paper records the evidence on which the 16β -acetoxy- 17α -bromo structure (II) was assigned to this addition product.

When II was treated with zinc dust or with Raney nickel, the conjugated ketone I was regenerated, indicating that the acetyl hypobromite addition was accompanied by no gross structural change. Saponification of II, followed by mild acetylation produced an epoxyketone formulated as 3β -acetoxy- $16\beta,17\beta$ -epoxy- 17 -iso- 5α -pregnan-20-one (III), since it was not identical with the known, corresponding α -oxide.⁵ The two oxides are also known in the Δ^5 -series⁶ and, in both series, the molecular rotation of the β -oxide is the more positive by $400 \pm 35^\circ$.⁷ Since these data are consistent with a 16α -bromo- 17β -acetoxy structure as well as with II, additional structure evidence was required.

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Article not copyrighted.

(2) (a) Presented in part at the 135th National A.C.S. Meeting, Boston, Mass., April 5-10, 1959; (b) paper LI, S. G. Levine and M. E. Wall, *THIS JOURNAL*, **81**, 2826 (1959).

(3) Reaction of the same reagent with another conjugated ketone, progesterone, resulted in the formation of an intensely colored, intractable product mixture from which only a small amount of starting material could be recovered. Cf. the addition of hypobromous acid to the conjugated double bond of cortisone acetate [E. P. Oliveto, C. Gerold and E. B. Hershberg, *ibid.*, **79**, 3596 (1957)].

(4) In particular, a mechanism based on initial electrophilic attack by "Br⁺" from the less hindered (α) side of the molecule may not be operative with Δ^{16} -20-ketones which have been shown to be particularly labile toward nucleophilic addition [E.g., see D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951)].

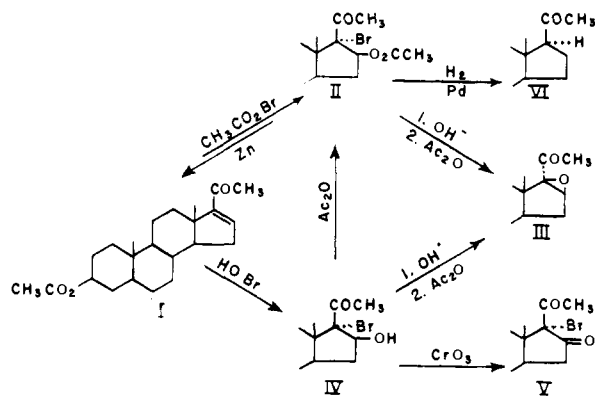
(5) Pl. A. Plattner, L. Ruzicka, N. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

(6) B. Löcken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, *THIS JOURNAL*, **78**, 1738 (1956).

(7) Physical properties of 3β -acetoxy- $16,17$ -epoxy-pregnan-20-ones:

	M.p., °C.	[M] _D	Ref.	
$5\alpha H$	$16\beta,17\beta$	157-159	-240°	Present study
	$16\alpha,17\alpha$	186-187	+193°	
	$16\beta,17\beta$	176-178	-402°	
Δ^5	$16\alpha,17\alpha$	156-158	-37.2°	6

Treatment of I with N-bromoacetamide under the usual⁸ conditions of hypobromous acid addition gave a halohydrin (IV) which, on acid-catalyzed acetylation, produced II in high yield. The structural correspondence between these two compounds was also manifested in the ready conversion of IV to the same β -oxide (III) as was obtained from II.



The position of attachment of the new oxygen function in these adducts could now be ascertained. Chromic acid oxidation of the bromohydrin IV yielded a bromodione-3-acetate V showing no hydroxyl absorption in the infrared but possessing a new carbonyl band at 1742 cm^{-1} (5-ring ketone⁹). This establishes the secondary (16β)-alcohol structure IV for the bromohydrin¹⁰ and, consequently, fixes II as the structure of the acetyl hypobromite adduct.

(8) See paper cited in ref. 3.

(9) The unshifted position of this absorption band is not surprising in view of the quasi-axial orientation of the 17α -bromine atom. The failure of this substituent to exert a hypsochromic effect on 20-ketone absorption is also illustrated in V, ν_{max} 1710 cm^{-1} , as well as in II, ν_{max} 1705 cm^{-1} , and has already been commented on by R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *THIS JOURNAL*, **74**, 2828 (1952).

(10) Sondheimer, *et al.* (ref. 6), have prepared the corresponding bromohydrin in the Δ^5 -pregnene series to which these authors assign an identical ring D structure based on a different line of evidence. It may be noted that their bromohydrin was apparently stable toward zinc reduction whereas the similar bromohydrin acetate II is converted, under these conditions, to the conjugated ketone I. Also, palladium hydrogenation of their bromohydrin yielded a 16β -hydroxy-20-ketone in contrast to the ring D unsubstituted 20-ketone obtained by hydrogenation of II.