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Reactions at Position 19 in the Steroid Nucleus. A Convenient Synthesis of 19-Norsteroids[1]

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A convenient synthesis of 19-norsteroids *via* the photolysis of the nitrites of 5α-halogeno-6β-hydroxy compounds has been developed. Alternative methods for the generation of 6β-alkoxy radicals have been investigated based on the photolysis of hypochlorites, hypobromites, and hypoiodites. The use of mercuric oxide and iodine for the *in situ* generation of hypoiodites has been recommended. By mixing *tert*-butyl hypochlorite with iodine or, alternatively, by treating potassium *tert*-butoxide with iodine, reagents considered to contain *tert*-butyl hypoiodite have been prepared. In an analogous procedure bromine and potassium *tert*-butoxide afford *tert*-butyl hypobromite. The use of these oxidant solutions for the generation of 6β-alkoxy radicals has been investigated. Convenient procedures for the synthesis of 19-hydroxy- and of 19-oxosteroids are also reported.

Considerable progress has been made recently in the study of reactions for the introduction of functional groups at "nonactivated" positions in the steroid nucleus.[2-5] The important salt-retaining hormone of the adrenal cortex, aldosterone,[6] and several of its derivatives,[7] have been conveniently synthesized by nitrite photolysis.[3]

The present paper deals with the synthesis of medically important 19-norsteroids and of 19-substituted steroids, as well as with new reagents and reactions for these purposes. Preliminary reports of part of our work have already appeared.[4,5] Related work in the field has recently been published[8] and we shall make specific reference to this where appropriate.

First, we report[5] on a convenient synthesis of 19-norsteroids starting with readily available $\Delta^{5,6}$-steroids of type I. Addition of hypobromous acid[9] to the 5,6-ethylenic linkage of Ia, Ib, Ic, Id, and Ie (all with R′ = Ac) gave the corresponding bromohydrins IIa, IIb, IIc, and IId (all with R′ = Ac, R″ = H, X = Br, and Y = H_2) in satisfactory yield. Similarly, the corresponding chlorohydrins can be prepared by the direct addition of hypochlorous acid[10] to $\Delta^{5,6}$-steroids. Alternately, in the present work, the above-mentioned bromohydrins were converted by treatment with methanolic potassium acetate into the corresponding 5,6-β-oxides which, on treatment with hydrogen chloride in the usual way, gave the desired chlorohydrins of type II (X = Cl, R″ = H, Y = H_2).

The bromohydrins IIa, IIb, IIc, and IId (R′ = Ac, R″ = H, X = Br, Y = H_2) were treated with nitrosyl chloride and pyridine to give the corresponding nitrites IIa, IIb, IIc, and IId (R′ = Ac, R″ = NO, X = Br, Y = H_2) which could be crystallized at low temperatures preferably using nonpolar solvents. Photolysis[3] of these nitrites in toluene at 4° gave, *via* the expected[3] nitroso dimers, the corresponding oximes IIa, IIb, IIc, and IId (R′ = Ac, R″ = H, X = Br, Y = NOH). On treatment with nitrous acid in aqueous acetic acid in the usual way the hemiacetals of type III (Y = H, OH) resulted. The corresponding acetates III (Y = H, OAc) were also formed in minor amount. We did not investigate optimum conditions to avoid the formation of the hemiacetal acetates, but this should obviously be possible. In general, the total product was oxidized with chromium trioxide in acetone.[11] Chromatography over alumina then afforded acetoxy lactones IIIa, IIIb, and IIId (R′ = Ac, X = Br, Y = O) and the unchanged hemiacetal acetates of type III (Y = H, OAc) referred to above. Hydrolysis of the acetoxy lactones with aqueous dioxane containing hydrochloric acid gave the corresponding hydroxy lactones IIIa, IIIb, and IIId (R′ = H, X = Br, Y = O) which with chromium trioxide in acetone[11] furnished the ketolactones IVa, IVb, and IVd (X = Br, Y = O). These compounds were not characterized, but on mild treatment with acid or base they furnished the expected unsaturated ketones Va, Vb, Vd, and Ve (Y = O). Reduction of these unsaturated lactones, or of their precursors, with zinc dust and acetic acid under defined conditions gave the desired 19-norandrostenedione[12] VIb (R′ = H), 19-norprogesterone[13] VId (R′ = H) and, in somewhat impure form, 19-norcholestenone VIa (R′ = H). The readily available intermediate

(1) For Contribution No. 28 see M. Akhtar, *Ann. Rev. Photochem.*, in press.

(2) *Inter alia*, E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958); **81**, 5209 (1959); P. Buchschacher, J. Kalvoda, D. Arigoni, and O. Jeger, *ibid.*, **80**, 2905 (1958); N. C. Yang and D. D. H. Yang, *ibid.*, **80**, 2913 (1958); P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959), and later papers; M. E. Wolff, J. F. Kerwin, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, and V. Georgian, *J. Am. Chem. Soc.*, **82**, 4117 (1960); J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, C. Karash, and V. Georgian, *J. Org. Chem.*, **27**, 3628 (1962).

(3) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961); M. Akhtar and M. M. Pechet, *ibid.*, **86**, 265 (1964).

(4) M. Akhtar and D. H. R. Barton, *ibid.*, **83**, 2213 (1961).

(5) M. Akhtar and D. H. R. Barton, *ibid.*, **84**, 1496 (1962).

(6) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); **83**, 4083 (1961).

(7) D. H. R. Barton and J. M. Beaton, *ibid.*, **83**, 750 (1961); M. Akhtar, D. H. R. Barton, J. M. Beaton, and A. G. Hortmann, **85**, 1512 (1963).

(8) (a) R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91**, 1420 (1961); **93**, 514 (1963). We regret that, at the time of submission of our preliminary Communication on the synthesis of 19-norsteroids (ref. 5), we were unaware of the earlier paper by Gardi and Pedrali. (b) A. Bowers, R. Villotti, J. A. Edward, E. Dent, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962); O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 39 (1963). (c) K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962); H. Ueberwasser, K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 344 (1963); J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *ibid.*, **46**, 1017 (1963). (d) T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 876 (1962); *Chem. Ind.* (London), 1194 (1962); R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963); N. Bhacca, M. E. Wolff, and R. Kwok, *J. Am. Chem. Soc.*, **84**, 4976 (1962); T. Jen and M. E. Wolff, *J. Org. Chem.*, **28**, 1573 (1963). (e) K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.*, **10**, 1126 (1962). (f) J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963). (g) J. Tadanier, *ibid.*, **28**, 1744 (1963).

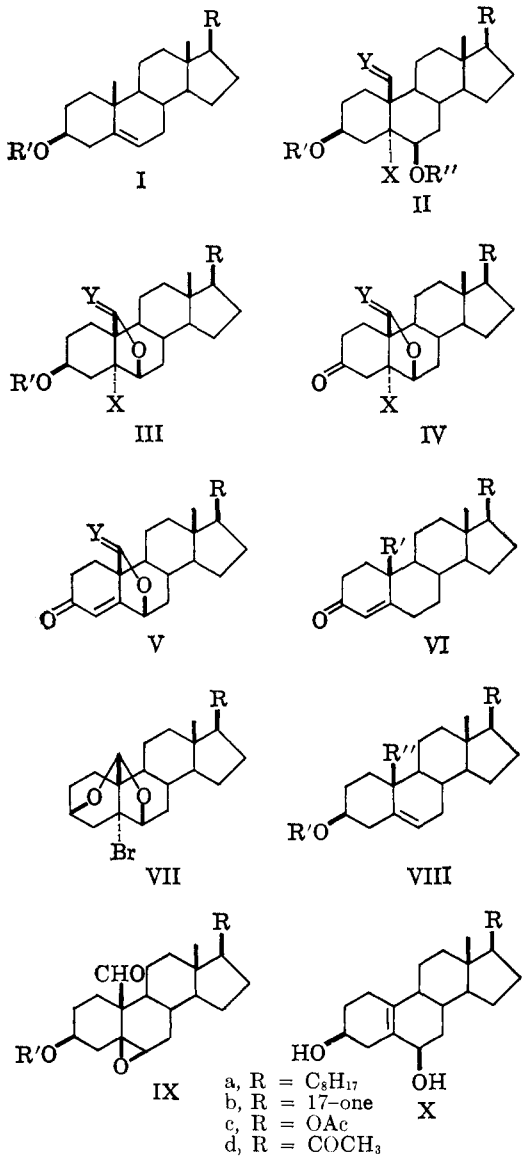
(9) E. M. Hicks, Jr., and E. S. Wallis, *J. Biol. Chem.*, **162**, 641 (1946); J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); **76**, 1455 (1954), and subsequent papers; L. B. Barkley, M. W. Farrer, W. S. Knowles, and H. Raffelson, *ibid.*, **76**, 5017 (1954); V. Grenville, D. K. Patel, V. Petrow, J. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

(10) S. Mori, *J. Chem. Soc. Japan*, **64**, 981 (1943); **71**, 600 (1950).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) H. Hagiwara, S. Naguchi, and M. Nishikawa, *Chem. Pharm. Bull. Japan*, **8**, 84 (1960).

(13) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958).



IIIb (R′ = Ac, X = Br, Y = O) gave with peracetic acid the corresponding D-homolactone. On hydrolysis, oxidation, and zinc dust reduction as above this furnished 19-nortestolactone.[14]

The intermediates in the reaction sequence described above made available several other types of 19-substituted and 19-norsteroids. Some analogous work has been reported.[8] Mild acid treatment of the oximes IIa and IIb (R′ = Ac, R″ = H, X = Br, Y = NOH) gave the *gem*-dioxides VIIa and VIIb. A similar *gem*-dioxide was reported earlier.[3] On treatment with acetic acid–acetic anhydride containing perchloric acid the *gem*-dioxide VIIa gave the hemiacetal acetate IIIa (R′ = Ac, X = Br, Y = H, OAc) already mentioned above. On reduction with zinc dust and acetic acid the latter afforded the 19-aldehyde VIIIa (R′ = Ac, R″ = CHO) which on mild basic hydrolysis furnished the corresponding hydroxyaldehyde VIIIa (R′ = H, R″ = CHO). The *gem*-dioxides VIIa and VIIb were similarly reduced to give the hydroxyaldehydes VIIIa (R′ = H, R″ = CHO) (see above) and VIIIb (R′ = H, R″ = CHO) in moderate yield. These experiments made 19-aldehydes with 5,6-unsaturation readily available.

(14) G. M. Rickards, U. S. Patent 2,855,404; *Chem. Abstr.*, **53**, 8215*a* (1959).

Treatment of the diacetate IIIa (R′ = Ac, X = Br, Y = H, OAc) with aqueous methanolic alkali under mild conditions at room temperature gave the expected epoxide IXa (R′ = H), characterized as its acetate IXa (R′ = Ac). However, when the epoxide IXa (R′ = H) was treated with aqueous methanolic alkali at steam bath temperature it afforded the interesting 19-norcholest-5,10-ene-3β,6β-diol (Xa). Comparable transformations were carried out in the 17β-acetoxyandrostane series starting with the hemiacetal IIIc (R′ = Ac, X = Br, Y = H, OH).

While the work on the synthesis of 19-nor- and 19-substituted steroids outlined above was in progress we were also examining other methods for functionalizing "nonactivated" carbon. In our first communication on nitrite photolysis[3] we clearly adumbrated a series of photochemical reactions of the type XI → XII based upon the postulated capacity of alkoxyl radicals to abstract intramolecularly "nonactivated" hydrogen. The nitrite rearrangement was the first of these to be realized experimentally. We suggested specifically that when group X in XI was halogen, comparable rearrangements might be observable. In the first instance we decided[4] to examine the possible rearrangement of hypochlorites XI → XII (X = Cl). Both photochemical and thermal cleavage of hypochlorites to alkoxyl radicals and chlorine atoms are well known.[15] In order to preclude competitive oxidation of alcohol *via* hypochlorite to ketone we worked with tertiary alcohols. The known[16] 3β-acetoxy-20-methylallopregnan-20-ol (XIII, R = R′ = H) was converted to the crystalline hypochlorite XIII (R = H, R′ = Cl) with chlorine monoxide.[17] Photolysis of this hypochlorite using a mercury lamp gave a product which could not be crystallized. It must, however, have contained the desired chlorohydrin XIII (R = Cl, R′ = H) because treatment with alkali followed by reacetylation gave the 18,20-oxide XIV (X = H_2) in 25% yield. The constitution of this product was shown by its n.m.r. spectrum (disappearance of the 18-methyl signal) and by oxidation with chromic acid under vigorous conditions to the γ-lactone XIV (X = O). The oxide XIV (X = H_2) and its derived lactone were prepared also by Cainelli, *et al.*,[18] by a different method. Similarly, 3β-acetoxy-6α-methylcholestan-6β-ol[19] (XV, R = H) was converted into its hypochlorite (XV, R = Cl). Photolysis and treatment of the product with base gave the oxide XVI[20] in 50% yield. The constitution of XVI was confirmed by its n.m.r. spectrum (disappearance of 19-methyl signal).

In connection with these studies on steroid hypochlorites we should like to acknowledge a helpful and courteous discussion with Professor Cheves Walling (Columbia). Although we had studied the photolysis of steroid hypochlorites shortly after the appearance of our first communication on nitrite photolysis[3] we could not crystallize the products. Prof. Walling kindly informed

(15) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 386.

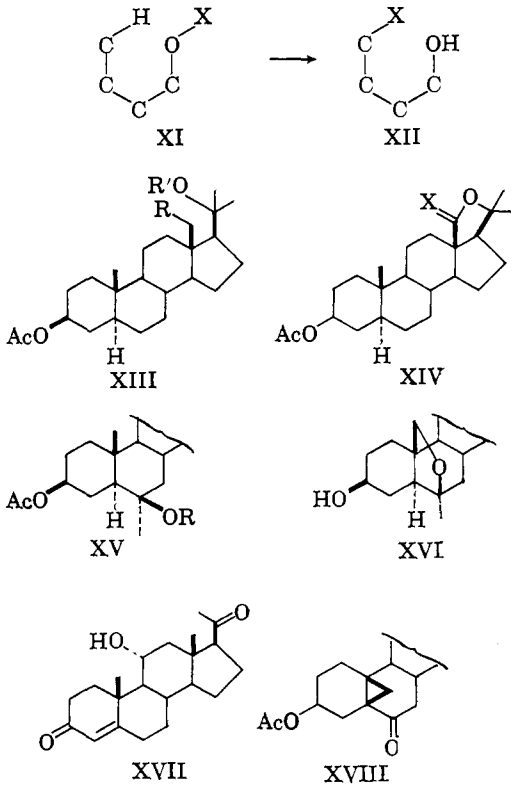
(16) A. Butenandt and H. Cobler, *Z. physiol. Chem.*, **234**, 218 (1935); see also B. Kolchlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

(17) M. Anbar and I. Dostrovsky, *J. Chem. Soc.*, 1105 (1959).

(18) G. Cainelli, B. Kamber, J. Keller, M. L. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961).

(19) L. F. Fieser and J. Rigaudy, *J. Am. Chem. Soc.*, **73**, 4661 (1951); see also R. A. Sneen, *ibid.*, **80**, 3982 (1958).

(20) See also J. S. Mills and V. A. Petrow, *Chem. Ind.* (London), 946 (1961).



a, 1,2-dehydro XVII

us of his independent work[21] on aliphatic tertiary hypochlorites and encouraged us to repeat our experiments isolating the products (see above) as tetrahydrofurans.[22]

The application of the general principle[3] summarized in XI → XII has been skillfully exploited by the Ciba group using hypoiodites generated *in situ* from the action of lead tetraacetate and iodine on alcohols.[23] Although we had not foreseen this particular combination of reagents for the generation of hypoiodites, we had endeavored to make these unstable substances by the interaction of mercuric oxide with iodine in the presence of alcohols according to the general principle laid down by Petrov[24] in his studies of the addition of (formally) $RO^{\ominus}$ and $I^{\oplus}$ to the olefinic linkage. We have shown that a variety of steroidal alcohols react with mercuric oxide and iodine in either heat- or (preferably) light-induced reactions to give products which can be explained as having originated through hypoiodite intermediates. Thus the 6β-hydroxy compounds IIa (R′ = Ac, R″ = H, X = H, Y = H_2), IIc (R′ = Ac, R″ = H, X = Cl, Y = H_2), IId (R′ = Ac, R″ = H, X = Cl, Y = H_2), IIe (R′ = Ac, R″ = H, X = Cl, Y = H_2), and XV (R = H) with mercuric oxide–iodine in carbon tetrachloride all afforded on irradiation the corresponding 6,19-oxides IIIa (R′ = Ac, X = H, Y = H_2), IIIc (R = Ac, X = Cl, Y = H_2), IIId (R′ = Ac, X = Cl, Y = H_2), IIIe (R′ = Ac, X = Cl, Y = H_2) and, after the appropriate hydrolysis, XVI, respectively. The yields were in the range 60–80%. The intervention of a 19-iodo-6β-hydroxy compound in these reactions would be in keeping with the theoretical views of the Ciba group.[25]

The preparation of 6,19-oxides of type III (Y = H_2) from the corresponding alcohols of type II (R″ = H) was also studied using both the thermal reaction with lead tetraacetate[26] and the photochemical reaction with lead tetraacetate and iodine.[23] Insofar as comparisons have been made, the mercuric oxide–iodine procedure appears to be cleaner and to give a higher yield.

From our earlier work[5] on the synthesis of 19-norsteroids it was obvious that 5-halogeno-6,19-oxides of type III (X = halogen, Y = H_2) could serve as intermediates in an alternative synthesis of this type of compound. The alkaline hydrolysis of oxides of type III (R′ = Ac, X = halogen, Y = H_2) gave the corresponding alcohols readily oxidized to the derived ketones of type IV (X = halogen, Y = H_2). Mild basic treatment gave the corresponding unsaturated ketones of type V (Y = H_2). Reduction of the compounds of type IV (X = halogen, Y = H_2) or of type V (Y = H_2) with zinc dust and acetic acid under defined conditions furnished the appropriate 19-hydroxy compounds of type VI (R′ = CH_2OH). A convenient procedure for the conversion of such 19-hydroxy compounds into 19-norsteroids of type VI (R′ = H) has already been described.[12] After this work had been completed two other groups of workers[8b,8c] reported the synthesis of 19-norsteroids based on 6,19-oxides of type III (X = halogen, Y = H_2) and through essentially the same intermediates. We do not consider that it is possible to decide without development work which of the procedures described in the present paper is the best suited for the synthesis of 19-norsteroids in practice.

The mercuric oxide–iodine reagent can be applied to hydroxylic functions other than the 6β-OH. Thus, treatment of the tertiary alcohol XIII (R = R′ = H) gave the oxide XIV (X = H_2) already described above. Oxidation in the same way of 11α-hydroxyprogesterone XVII gave 1-dehydro-11α-hydroxyprogesterone XVIIa in 60% yield. The same reaction has been observed (and adequately discussed) using the lead tetraacetate iodine reagent.[27]

Photolysis of cyclopentanol nitrite gives glutaraldehyde monoxime.[28] Similarly, irradiation of cyclopentanol with mercuric oxide and iodine gave δ-iodovaleraldehyde characterized as its 2,4-dinitrophenylhydrazone. The δ-iodovaleraldehyde gave no C–Me group on Kuhn–Roth oxidation and afforded valeraldehyde on reduction with zinc dust and acetic acid. Its constitution was thus established. In both reactions the intermediate cyclopentyloxy radical undergoes ring fission smoothly.

In the reactions described above the hypoiodites are formed through the esterifying action of hypoiodous acid generated *in situ* from the mercuric oxide and iodine. We have also examined the possibility that

(21) C. Walling and A. Padma, *J. Am. Chem. Soc.*, **83**, 2207 (1961); **85**, 1597 (1963).

(22) See also F. D. Greene, M. L. Saritz, H. H. Law, F. D. Osterholtz, and W. N. Smith, *ibid.*, **83**, 2196 (1961); F. D. Greene, M. L. Saritz, F. D. Osterholtz, H. H. Law, W. N. Smith, and P. M. Zaret, *J. Org. Chem.*, **28**, 55 (1963); L. Denivelle, R. Fort, and J. P. Sassoulas, *Compt. rend.*, 1953 (1962); E. L. Jenner, *J. Org. Chem.*, **27**, 1031 (1962).

(23) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); *Helv. Chim. Acta*, **45**, 1317 (1962), and later papers.

(24) A. A. Petrov, *J. Gen. Chem. U.S.S.R.*, **10**, 819 (1940); *Chem. Abstr.*, **35**, 2112 (1941); and later papers.

(25) K. Heusler, J. Kalvoda, C. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2161 (1962); K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *ibid.*, **45**, 2575 (1962); J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *ibid.*, **46**, 618 (1963).

(26) G. Cainelli, M. L. Mihailovic, D. Arigoni, and O. Jeger, *ibid.*, **42**, 1124 (1959).

(27) J. Kalvoda, G. Enner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, L. M. Mihailovic, K. Schaffner, and A. Wettstein, *ibid.*, **44**, 186 (1961).

(28) P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, **27**, 2918 (1962).

steroid hypoiodites could be generated by a transfer process from the hypoiodite of a tertiary alcohol, suitably *tert*-butyl alcohol. In the initial experiments *tert*-butyl hypochlorite was mixed with iodine. This reagent, which presumably contains *tert*-butyl hypoiodite and iodine chloride, is a good oxidant for the purpose in hand. When the alcohols IIa (R′ = Ac, R″ = H, X = H, Y = H_2), IIa (R′ = Ac, R″ = H, X = Br, Y = H_2), and IId (R′ = Ac, R″ = H, X = Br, Y = H_2) were photolyzed in the presence of *tert*-butyl hypochlorite and iodine the corresponding 6,19-oxides IIIa (R′ = Ac, X = H, Y = H_2), IIIa (R′ = Ac, X = Br, Y = H_2), and IIId (R′ = Ac, X = Br, Y = H_2), respectively, were isolated in 60–80% yield. On the grounds of cost, *tert*-butyl hypochlorite may have some advantage over lead tetraacetate and mercuric oxide.

The oxidation of the alcohol IIa (R′ = Ac, R″ = H, X = H, Y = H_2) with *tert*-butyl hypochlorite–iodine was studied in more detail to establish if irradiation was essential. Interestingly, the reaction in the dark gave only the 6-ketone, 3β-acetoxycholestan-6-one, in high yield. It would seem that the reagent can react in either an ionic or a radical manner depending upon the absence or presence of light.

We then attempted the preparation of *tert*-butyl hypoiodite in the absence of iodine chloride. Treatment of potassium *tert*-butoxide with excess of iodine in dry benzene gave a solution which had powerful oxidizing properties consistent with the presence of *tert*-butyl hypoiodite. Reaction with the alcohol XV (R = H) under irradiation gave, after alkaline hydrolysis of the product, the oxide XVI. Similar treatment of the *tert*-alcohol XIII (R = R′ = H) afforded the γ-lactone XIV (X = O). Also 11α-hydroxprogesterone furnished the 1-dehydro derivative XVIIa. However, 3β-acetoxycholestan-6β-ol (IIa, R′ = Ac, R″ = H, X = H, Y = H_2) was very rapidly oxidized to the 6-ketone in high yield without formation of a significant amount of the 6,19-oxide derivative. It would appear that the reagent still has "basic" properties although prepared in the presence of excess iodine.

Without knowledge of recent work on the preparation of *tert*-butyl hypobromite,[29] we attempted to obtain this compound by the action of bromine on potassium *tert*-butoxide in dry benzene. The resultant solution undoubtedly contains *tert*-butyl hypobromite. On reaction with the alcohol IIa (R′ = Ac, R″ = H, X = H, Y = H_2) in diffuse daylight this reagent, after chromatography of the product over alumina, gave the 6,19-oxide IIIa (R′ = Ac, X = H, Y = H_2). In order to ascertain if an isolable 19-bromohydrin was involved, the experiment was repeated and the crude product was oxidized with chromium trioxide. Subsequent chromatography over alumina gave 3β-acetoxycholestan-6-one and the 5,19-cyclopropanone XVIII as major products with minor amounts of the 6,19-oxide IIIa (R′ = Ac, X = H, Y = H_2) and the corresponding 6,19-lactone IIIa (R′ = Ac, X = H, Y = O). The 5,19-cyclopropane XVIII was prepared in collaboration with Dr. H. R. Browning by the following route. The aldehyde VIIIa (R′ = Ac, R″ = CHO) was reduced with sodium borohydride to the corresponding alcohol VIIIa (R′ = Ac, R″ = CH_2OH) which was converted into its toluene-*p*-sulfonate. Solvolysis of the latter in aqueous acetone containing potassium acetate gave an alcohol which we formulate as 3β-acetoxy-6α-hydroxy-5,19-cyclocholestane. Oxidation of this alcohol gave the ketone XVIII referred to above.

The formation of the cyclopropane XVIII is good evidence for a 19-bromo-6-hydrin as an intermediate in the reaction with *tert*-butyl hypobromite. In the dark 3β-acetoxycholestan-6β-ol was not attacked rapidly by the *tert*-butyl hypobromite solution. Treatment of 11α-hydroxyprogesterone XVII with the *tert*-butyl hypobromite reagent in diffuse daylight gave the expected 1-dehydro derivative XVIIa.

(29) C. Walling and A. Padua, *J. Org. Chem.*, **27**, 2976 (1962); A. Kergomard, *Bull. soc. chim.*, 2360 (1961); J.-M. Geneste and A. Kergomard, *ibid.*, 470 (1963).

Experimental

Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were determined using an Infracord Model 137 spectrophotometer. Spectra were taken for all compounds and were in agreement with the assigned constitutions, but we only report data when of special significance. Unless stated otherwise, ultraviolet spectra were determined in methanol and optical rotations in chloroform. Melting points were taken on a Kofler-type hot stage. Merck acid-washed alumina was used for chromatography unless stated to the contrary.

Preparation of 5α-Bromo-6β-hydroxy Compounds.—The following example is illustrative. Cholesteryl acetate (Ia, R′ = Ac; 50 g.) in purified diozane (400 ml.) and aqueous perchloric acid (23 ml., 0.28 *M*) was stirred vigorously in a dark flask at room temperature. N-Bromoacetamide (43.2 g.) was added in four portions during 30 min. and stirring then continued for 30 min. After cooling to 0°, water (200 ml.) was added and then aqueous sodium sulfite (10%, 300 ml.). The product was extracted into ether and the organic layer washed with water, dried (sodium sulfate), and evaporated. Crystallization from methylene chloride gave the bromohydrin IIa (R′ = Ac, R″ = H, X = Br, Y = H_2; 34.4 g., 61%), m.p. 172–174° (lit.[30] m.p. 177–179°).

The following compounds were prepared by the same procedure: 5α-bromo-3β,6β-dihydroxyandrostan-17-one 3-acetate (IIb, R′ = Ac, R″ = H, X = Br, Y = H_2; 75%), m.p. (from hexane or methanol) 171–172°, $[\alpha]_D$ +2° (*c* 1.19) (lit.[31] m.p. 173–175°, $[\alpha]_D$ 0°, but no analysis given). *Anal.* Calcd. for $C_{21}H_{31}O_4Br$: C, 59.00; H, 7.30; O, 14.95; Br, 18.75. Found: C, 58.65; H, 7.45; O, 15.00; Br, 19.05.

5α-Bromo-3β,6β-trihydroxyandrostane 3,17-diacetate (IIc, R′ = Ac, R″ = H, X = Br, Y = H_2; 70%), m.p. (from acetone–hexane) 168–172°, $[\alpha]_D$ −49° (*c* 1.09) (lit.[31] m.p. 159°, $[\alpha]_D$ −58°). *Anal.* Calcd. for $C_{23}H_{35}O_5Br$: C, 58.60; H, 7.50; Br, 16.95. Found: C, 58.80; H, 7.25; Br, 16.25.

5α-Bromo-3β,6β-dihydroxypregnan-20-one 3-acetate (IId, R′ = Ac, R″ = H, X = Br, Y = H_2; 75%), m.p. (from hexane–methylene dichloride) 171–174°, $[\alpha]_D$ +7° (*c* 0.93). *Anal.* Calcd. for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.75; O, 14.05; Br, 17.55. Found: C, 60.82; H, 7.82; O, 14.21; Br, 17.55.

5α-Bromo-3β,6β,17α-trihydroxypregnan-20-one 3,17-diacetate (55%), m.p. (from ether–methylene dichloride) 190–196°, $[\alpha]_D$ −49° (*c* 1.12). *Anal.* Calcd. for $C_{25}H_{37}O_6Br$: C, 58.47; H, 7.26; O, 18.70; Br, 15.56. Found: C, 58.75; H, 7.24; O, 18.21; Br, 15.30.

Conversion of Bromhydrins into 5,6β-Epoxides.—The following example is illustrative. The bromohydrin IIc (R′ = Ac, R″ = H, X = Br, Y = H_2; 10 g.) was refluxed for 2 hr. in a 5% methanolic potassium acetate solution (1 l.). After removal of most of the solvent *in vacuo*, water was added and the product extracted into methylene dichloride. The organic phase was washed with water, dried (sodium sulfate), and the solvent removed *in vacuo*. Crystallization of the residue from methylene dichloride–methanol afforded 5β,6β-epoxyandrostane-3β,17β-diol diacetate (6.7 g.), m.p. 139–141°, $[\alpha]_D$ −244° (*c* 0.76).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.76; O, 20.49. Found: C, 71.01; H, 8.56; O, 20.35.

The following compounds were prepared by the same procedure: 5β,6β-epoxy-3β-acetoxypregnan-20-one (70%), m.p. (from

(30) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 4224 (1954).

(31) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, ref. 9.

methanol) 132–136°, $[\alpha]_D$ +50° (*c* 1.03). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 74.06; H, 8.97; O, 16.73.

5β,6β-Epoxy-3β,17α-dihydroxypregnan-20-one diacetate (81%) m.p. (from methylene dichloride–ether) 177–179°, $[\alpha]_D$ −20° (*c* 1.09). *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; O, 22.19. Found: C, 69.34; H, 8.40; O, 22.30.

Preparation of 5α-Chloro-6β-hydroxy Compounds.—The following example is illustrative. 5β,6β-Epoxyandrostane-3β,17β-diol diacetate (see above; 6.0 g.) in chloroform (100 ml.) containing hydrogen chloride (0.3 *N*) was left for 1 hr. at 0°. After washing with water, then with saturated aqueous sodium hydrogen carbonate, and drying (sodium sulfate), the chloroform was removed *in vacuo*. Crystallization from methylene dichloride–methanol gave the chlorohydrin IIc (R′ = Ac, R″ = H, X = Cl, Y = H_2; 5.0 g.), m.p. 195–200°, $[\alpha]_D$ −41° (*c* 0.81).

Anal. Calcd. for $C_{23}H_{35}O_5Cl$: C, 64.69; H, 8.26; O, 18.74; Cl, 8.31. Found: C, 64.48; H, 8.18; O, 18.54; Cl, 8.30.

The following compounds were prepared by the same procedure: 3β-acetoxy-5α-chloro-6β-hydroxypregnan-20-one (IIb, R′ = Ac, R″ = H, X = Cl, Y = H_2; 80%), m.p. (from methanol) 203–210°, $[\alpha]_D$ +21° (*c* 0.64). *Anal.* Calcd. for $C_{23}H_{35}O_4Cl$: C, 67.21; H, 8.58; Cl, 8.63. Found: C, 67.05; H, 8.39; Cl, 8.86.

5α-Chloro-3β,6β,17α-trihydroxypregnan-20-one 3,17-diacetate (93%), m.p. (from methylene dichloride–ether) 213–223°, $[\alpha]_D$ −47° (*c* 0.86). *Anal.* Calcd. for $C_{25}H_{37}O_6Cl$: C, 64.02; H, 7.95; O, 20.47; Cl, 7.56. Found: C, 64.18; H, 7.92; O, 20.21; Cl, 7.87.

Preparation and Photolysis of Bromohydrin Nitrites.—The following example is illustrative. 3β-Acetoxy-5α-bromocholestan-6β-ol (IIa, R′ = Ac, R″ = H, X = Br, Y = H_2; 25 g.) in dry pyridine (300 ml. of Karl Fischer reagent) was treated with nitrosyl chloride gas at −20° until a blue color persisted. Addition of ice–water (500 ml.) gave a precipitate which was filtered, taken up in the minimum of methylene dichloride, and dried (sodium sulfate). Crystallization by cautious addition of methanol afforded 3β-acetoxy-5α-bromocholestan-6β-ol nitrite (IIa, R′ = Ac, R″ = NO, X = Br, Y = H_2; 22.4 g., 90%), m.p. 110–112°, $[\alpha]_D$ −70° (*c* 0.97).

Anal. Calcd. for $C_{29}H_{48}O_4NBr$: C, 62.80; H, 8.70; N, 2.55; Br, 14.40. Found: C, 62.45; H, 8.40; N, 2.55; Br, 14.60.

This nitrite (22 g.) in toluene (700 ml.) was irradiated with a 200-w. high pressure mercury arc lamp as detailed previously[3] at 0°. After 3 hr. (disappearance of nitrite infrared bands) the precipitated nitroso dimer was filtered, washed with hexane, taken up in 2-propanol (300 ml.), and heated on the steam until the green color (nitroso monomer) had disappeared. Removal of the solvent *in vacuo* and crystallization from methanol gave 3β-acetoxy-5α-bromo-19-oximinocholestan-6β-ol (IIa, R′ = Ac, R″ = H, X = Br, Y = NOH; 55%), m.p. 176–180°, $[\alpha]_D$ −35° (*c* 0.86).

Anal. Calcd. for $C_{29}H_{48}O_4NBr$: C, 62.80; H, 8.70; N, 2.55; Br, 14.40. Found: C, 62.75; H, 8.75; N, 2.45; Br, 14.30.

Total precipitates (essentially quantitative) of nitrites prepared as described above were used for the photolytic preparation of the following compounds according to the procedure given above (the yields, in parentheses, are based on starting bromohydrin): 5β-bromo-19-oximinoandrostane-3β,6β-diol-17-one 3-acetate (IIb, R′ = Ac, R″ = H, X = Br, Y = NOH; 38%), m.p. (from acetone–hexane) 178–180°, $[\alpha]_D$ −11° (dioxane, *c* 0.45). *Anal.* Calcd. for $C_{21}H_{30}O_5NBr$: C, 55.25; H, 6.65; O, 17.55; N, 3.05. Found: C, 55.15; H, 6.65; O, 17.45; N, 3.00.

5α-Bromo-19-oximinoandrostane-3β,6β,17β-triol 3,17-diacetate (IIc, R′ = Ac, R″ = H, X = Br, Y = NOH; 56%), m.p. (from ethyl acetate–hexane) 175–176°. *Anal.* Calcd. for $C_{23}H_{34}O_6NBr$: C, 55.20; H, 6.85; N, 2.80; Br, 15.95. Found: C, 54.90; H, 6.90; N, 2.75; Br, 16.20.

5α-Bromo-19-oximinopregnane-3β,6β-diol-20-one 3-acetate (IId, R′ = Ac, R″ = H, X = Br, Y = NOH; 74%), m.p. (from acetone–hexane) 173–178°, $[\alpha]_D$ −5° (*c* 1.09). *Anal.* Calcd. for $C_{23}H_{34}O_5NBr$: C, 57.02; H, 7.07; O, 16.51; N, 2.89; Br, 16.50. Found: C, 56.81; H, 7.29; O, 16.85; N, 2.80; Br, 16.48.

Further Processing of the 19-Oximes.—The following example is illustrative. The oxime IIa (R′ = Ac, R″ = H, X = Br, Y = NOH; 5 g.) in glacial acetic acid (850 ml.) and water (170 ml.) was treated at 70° with sodium nitrite (5 g.). After 2 min. the reaction mixture was poured onto ice and water (2 l.) and extracted with methylene dichloride. After washing with water and with aqueous sodium hydrogen carbonate the organic layer was dried (sodium sulfate) and the solvent removed *in vacuo*. The residue in acetone (250 ml.) was treated with a slight excess of chromium trioxide in acetone at room temperature for 3 min. and the excess of oxidant destroyed with aqueous methanol. Dilution with water and extraction into ether gave, after washing with water, drying (sodium sulfate), and evaporation, a residue which was chromatographed over alumina by eluting with hexane containing increasing proportions of benzene. Crystallization of the more easily eluted fractions from methanol gave the lactone IIIa (R′ = Ac, X = Br, Y = O; 1.9 g., 32%), m.p. 170–172°, $[\alpha]_D$ −16° (*c* 1.05).

Anal. Calcd. for $C_{29}H_{45}O_4Br$: C, 64.80; H, 8.45; Br, 14.87. Found: C, 64.95; H, 8.35; Br, 14.75.

Crystallization of the more difficulty eluted fractions afforded the hemiacetal acetate IIIa (R′ = Ac, X = Br, Y = H, OAc; 900 mg., 16%), m.p. (from aqueous acetic acid) 151–156°, $[\alpha]_D$ +21° (*c* 1.10).

Anal. Calcd. for $C_{31}H_{49}O_5Br$: C, 64.00; H, 8.50; O, 13.75; Br, 13.75. Found: C, 64.25; H, 8.50; O, 13.85; Br, 13.90.

The following lactones of type III (Y = O) were prepared by the same procedure: the 5α-bromoandrostane derivative IIIb (R′ = Ac, X = Br, Y = O; 59%), m.p. (from methylene dichloride–hexane) 221–229°, $[\alpha]_D$ −13° (*c* 1.03). *Anal.* Calcd. for $C_{21}H_{27}O_5Br$: C, 57.40; H, 6.20; Br, 18.20. Found: C, 57.10; H, 6.05; Br, 18.05.

The 5α-bromopregnane derivative IIId (R′ = Ac, X = Br, Y = O; 46%), m.p. (from acetone–hexane) 153–157° and 161–164° (different crystalline forms), $[\alpha]_D$ +13° (*c* 0.84). *Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.69; O, 17.12; Br, 17.10. Found: C, 58.92; H, 6.69; O, 17.19; Br, 17.20.

The intermediate hemiacetal for lactone preparation was characterized in one series. The oxime IIb (R′ = Ac, R″ = H, X = Br, Y = NOH; 2 g.) in glacial acetic acid (100 ml.) and water (20 ml.) was treated with sodium nitrite (2 g.) at 70° for 3 min. The reaction mixture was worked up as in the experiment detailed above and the product was chromatographed over alumina (60 g.) eluting with hexane containing increasing proportions of benzene. Crystallization from methylene dichloride–hexane and from ether–hexane gave the hemiacetal IIIb (R′ = Ac, X = Br, Y = H, OH; (270 mg.), m.p. 184–186°, $[\alpha]_D$ +41° (*c* 1.04).

Anal. Calcd. for $C_{21}H_{29}O_5Br$: C, 57.15; H, 6.60; O, 18.10; Br, 18.10. Found: C, 56.85; H, 6.45; O, 17.75; Br, 18.10.

The ketolactone IIIb (R′ = Ac, X = Br, Y = O; 5.0 g.) in glacial acetic acid (25 ml.) containing toluene-*p*-sulfonic acid (400 mg.) was treated with peracetic acid (5 ml.) in the same solvent (20 ml.) in the dark at room temperature for 24 hr. The solution was poured into ice water and the product crystallized from methylene dichloride–hexane to give to corresponding bislactone (4.1 g.), m.p. 268–272, $[\alpha]_D$ −58° (*c* 1.01).

Anal. Calcd. for $C_{21}H_{27}O_6Br$: C, 55.39; H, 5.98. Found: C, 55.51; H, 5.92.

Preparation of 19-Norsteroids.—The first step in this sequence was the hydrolysis of the acetoxylactones of type III (R′ = Ac, X = Br, Y = O) to the corresponding alcohols. The following example is illustrative. The 5α-bromolactone IIIa (R′ = Ac, X = Br, Y = O; 120 mg.) in dioxane (10 ml.) was heated on a steam bath for 2 hr. with water (5 ml.) and concentrated hydrochloric acid (1.0 ml.) under nitrogen. Dilution with water, extraction into ether, and crystallization of the product from acetone–hexane gave the corresponding hydroxylactone IIIa (R′ = H, X = Br, Y = O; 73%), m.p. 174–179°, $[\alpha]_D$ −18° (*c* 0.89).

Anal. Calcd. for $C_{27}H_{43}O_3Br$: C, 65.45; H, 8.75; O, 9.70; Br, 16.15. Found: C, 65.50; H, 8.85; O, 9.75; Br, 16.45.

The following hydroxylactones of type III (R′ = H, X = Br, Y = O) were prepared by the same procedure: the 5α-bromoandrostane derivative IIIb (R′ = H, X = Br, Y = O; 52%), m.p. 221–232°, $[\alpha]_D$ +10° (*c* 1.06). *Anal.* Calcd. for $C_{19}H_{15}O_3Br$: C, 57.45; H, 6.35; O, 16.10; Br, 20.10. Found: C, 57.65; H, 6.50; O, 16.20; Br, 19.85.

The 5α-bromopregnane derivative IIId (R′ = H, X = Br, Y = O; 66%), m.p. (from methanol) 210–214°, $[\alpha]_D$ +18°. *Anal.* Calcd. for $C_{21}H_{29}O_4Br$: C, 59.30; H, 6.87; O, 15.05; Br, 18.79. Found: C, 58.73; H, 6.27; O, 15.61; Br, 19.44.

5α-Bromo-3β,6β-dihydroxy-17α-oxa-D-homoandrostan-17-one-19-oic acid 6β,19-lactone (75%), m.p. (from acetone) 224–247°, $[\alpha]_D$ −66° (*c* 0.86).

Anal. Calcd. for $C_{19}H_{25}O_5Br$: C, 55.21; H, 6.09; O, 19.36; Br, 19.33. Found: C, 55.29; H, 6.00; O, 19.58; Br, 19.47.

The formation of the 4,5-unsaturated 3-ketones of type V (Y = O) was the next step in the sequence. The following example is illustrative. The hydroxylactone IIIa (R′ = H, X = Br, Y = O; 340 mg.) in acetone (25 ml.) was treated with a slight excess of chromium trioxide in acetone for 3 min. After dilution with aqueous methanol and extraction into ether the product was crystallized cautiously from methanol to give the bromo ketone IVa (X = Br, Y = O), m.p. 176–181° dec., $[\alpha]_D$ +19°. Since this compound decomposed on attempted recrystallization, it (100 mg.) was heated on the steam bath for 10 min. in glacial acetic acid (10 ml.) containing concentrated hydrochloric acid (1 drop). Dilution with water, extraction into ether, and crystallization of the product from chloroform–methanol gave the lactone Va (Y = O), m.p. 179–184°, $[\alpha]_D$ −102° (*c* 0.98), λ_{max} 238 mμ (ε 12,500).

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 78.59; H, 9.75; O, 11.65. Found: C, 78.00; H, 9.70; O, 12.05.

The following compounds of type V (Y = O) were prepared by the same procedure: the androstene derivative Vb (Y = O; 65%), m.p. (from ether–hexane) 291–293°, λ_{max} 235 mμ (ε 12,000). *Anal.* Calcd. for $C_{19}H_{22}O_4$: C, 72.60; H, 7.05; O, 20.35. Found: C, 72.45; H, 7.05; O, 20.50.

The pregnene derivative Vd (Y = O), m.p. (from methylene dichloride–hexane) 236–239°, $[\alpha]_D$ −246° (*c* 0.77), λ_{max} 237 mμ (ε 12,700). *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65; O, 18.69. Found: C, 73.59; H, 7.45; O, 18.85.

6β-Hydroxy-17α-oxa-D-homoandrost-4-ene-3,17-dion-19-oic acid 6β,19-lactone, m.p. (from methylene dichloride–hexane) 294–299°, $[\alpha]_D$ −191° (*c* 1.80), λ_{max} 233 mμ (ε 16,200).

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71; O, 24.22. Found: C, 69.15; H, 6.70; O, 24.27.

The following example is illustrative of the final step in the synthesis of 19-nor steroids. The ketone IVa (X = Br, Y = O), obtained from hydrolysis and oxidation of the acetoxylactone IIIa (R′ = Ac, X = Br, Y = O), in glacial acetic acid (28 ml.) was refluxed with stirring while zinc dust (5.6 g.) was added in two portions; the refluxing was continued for 15 min. The excess zinc was removed by filtration and the acetic acid was evaporated *in vacuo*. The product was taken up in ether and the organic layer was washed with water, dried (sodium sulfate), and the ether removed. The residue in chloroform (50 ml.) and methanolic hydrogen chloride (12 ml., 1.2 *N*) was refluxed for 15 min. After dilution with water, the chloroform layer was evaporated and the residue chromatographed over alumina (30 g.). Elution with hexane containing increasing proportions of benzene gave (fractions having 1660 cm.$^{-1}$ carbonyl band) 19-norcholestenone (VIa, R′ = H). After sublimation at 200° (1 mm.) this (47% over-all from the acetoxylactone IIIa (R′ = Ac, X = Br, Y = O)) had $[\alpha]_D$ +44° (*c* 1.05), λ_{max} 240 mμ (ε 14,000).

Anal. Calcd. for $C_{26}H_{42}O$: C, 84.25; H, 11.40; O, 4.30. Found: C, 83.45; H, 11.80; O, 4.60.

The following 19-nor-steroids of type VI (R′ = H) were prepared by the same procedure: 19-norandrostene-3,17-dione[12] (VIb, R′ = H; 70% based on the hydroxylactone IIIb (R′ = H, X = Br, Y = O)), m.p. (from ether–hexane) 164–169°, $[\alpha]_D$ +136° (*c* 1.01), λ_{max} 241 mμ (ε 17,000). *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.35; H, 8.90; O, 11.75. Found: C, 79.25; H, 8.65; O, 12.25.

19-Norprogesterone[13] (VId, R′ = H), m.p. (from methylene dichloride–hexane) 143–146°, $[\alpha]_D$ +142°, λ_{max} 240 mμ (ε 17,000). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.40. Found: C, 79.82; H, 9.80. 19-Nortestolactone[14] (83%, based on the precursor 4-en-3-one), m.p. (from methylene dichloride–hexane) 194–198°, $[\alpha]_D$ −17° (*c* 0.92), λ_{max} 238 mμ (ε 17,000). *Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39; O, 16.64. Found: C, 74.98; H, 8.18; O, 16.26.

The residue from the crystallization of 19-norprogesterone gave, on chromatography over alumina, a further compound regarded as 19-nor-17-isoprogesterone. Recrystallized from methylene dichloride–hexane, this had m.p. 143–144°, $[\alpha]_D$ +6° (*c* 0.72).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.40. Found: C, 79.64; H, 9.22.

5α-Bromo-3β,19-6β,19-diepoxycholestane (VIIa) and 5α-Bromo-3β,19-6β,19-diepoxyandrostan-17-one (VIIb).—The oxime IIa (R′ = Ac, R″ = H, X = Br, Y = NOH; 14 g.) in acetone (560 ml.), water (112 ml.), and peroxide-free dioxane (140 ml.) was treated with concentrated hydrochloric acid (56 ml.) under reflux for 3 hr. The solvent was partially removed *in vacuo* and, after cooling, the crystalline precipitate of 5α-bromo-3β,19-6β,19-diepoxycholestane (VIIa) was collected (86%); m.p. 140–143°, $[\alpha]_D$ +11° (*c* 1.00) after recrystallization from hexane.

Anal. Calcd. for $C_{27}H_{43}O_2Br$: C, 67.62; H, 9.04; O, 6.67; Br, 16.66. Found: C, 68.15; H, 9.09; O, 6.68; Br, 16.49.

In the same way the oxime IIb (R′ = Ac, R″ = H, X = Br, Y = NOH) gave 5α-bromo-3β,19-diepoxyandrostan-17-one (VIIb), m.p. 243–244°, $[\alpha]$ +59° (*c* 0.89).

Anal. Calcd. for $C_{19}H_{25}O_3Br$: C, 59.85; H, 6.61; O, 12.59; Br, 20.96. Found: C, 60.14; H, 6.67; O, 12.58; Br, 20.82.

When the diepoxide VIIa (6.3 g.) in glacial acetic acid (315 ml.) and acetic anhydride (94.5 ml.) cooled to 6° in an ice bath was treated with 70% perchloric acid (3.8 ml.) and kept at 6° for 2 hr. it gave, on addition of water and working up in the usual way, the hemiacetal acetate IIIa (R′ = Ac, X = Br, Y = H, OAc; 81%) already described above.

Preparation of 19-Aldehydes.—The following example is illustrative. The 5α-bromodiepoxide VIIa (1.0 g.) was converted to the hemiacetal acetate IIIa (R′ = Ac, X = Br, Y = H, OAc) as described above and the total crude product in acetic acid (100 ml.) and water (30 ml.) was refluxed with zinc dust (30 g.) for 40 min. Working up in the usual way and crystallization from methanol gave 19-oxocholesterol acetate (VIIIa, R′ = Ac, R″ = CHO; 70%), m.p. 106–107°, $[\alpha]_D$ −199° (*c* 1.56).

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.48; O, 10.86. Found: C, 78.60; H, 10.51; O, 10.88.

Crystallization from methanol containing sodium hydroxide (2 *N*) afforded 19-oxocholesterol (VIIIa, R′ = H, R″ = CHO), m.p. 138–141°, $[\alpha]_D$ −175° (*c* 1.52); $\nu_{max}^{CHCl_3}$ 3800, 2600, 2750, 1720, and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07; O, 7.99. Found: C, 80.99; H, 10.66; O, 8.31.

This hydroxyaldehyde was also obtained in the following way. The diepoxide VIIa (1.0 g.) in glacial acetic acid (35 ml.) and water (5 ml.) was refluxed with zinc dust (10 g.) for 1 hr. Crystallization of the product from methanol gave the hydroxyaldehyde VIIIa (R′ = H, R″ = CHO; 51%).

In the same manner as above the diepoxide VIIc was converted *via* the hemiacetal acetate IIIc (R′ = Ac, X = Br, Y = H, OAc) into the corresponding acetate aldehyde VIIIc (R′ = Ac, R″ = CHO). Recrystallized from hexane this had m.p. 137–143°, $[\alpha]_D$ −251° (*c* 0.95).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30; O, 20.59. Found: C, 70.84; H, 8.20; O, 20.80.

The diepoxide VIIb was also reduced directly as above to the hydroxyaldehyde VIIIc (R′ = H, R″ = CHO). Recrystallized from acetone–hexane this had m.p. 187–193°, $[\alpha]_D$ −268° (*c* 0.49 in dioxane).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.68; H, 9.11; O, 15.92.

3β-Acetoxy-19-hydroxycholest-5-ene (with Dr. H. R. Browning).—The 19-aldehyde VIIIa (R′ = Ac, R″ = CHO; 1.0 g.) in ethanol (50 ml.) was treated with sodium borohydride (1.0 g.) for 15 min. Addition of water, extraction into ether, and crystallization from methanol afforded the 19-alcohol VIIIa (R′ = Ac, R′ = CH_2OH; 87%), m.p. 125°, $[\alpha]_D$ −30° (*c* 0.55).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.89; O, 10.79. Found: C, 78.41; H, 10.78; O, 11.18.

This alcohol (1.17 g.) and toluene-*p*-sulfonyl chloride (2.50 g.) were left in pyridine (30 ml.) for 6 days. Addition of water, extraction into ether, and crystallization from chloroform–methanol gave the toluene-*p*-sulfonate VIIIa (R′ = Ac, R″ = $CH_2OSO_2C_6H_4Me$ (*p*); 57%), m.p. 144–145°, $[\alpha]_D$ −55° (*c* 0.60).

Anal. Calcd. for $C_{36}H_{54}O_5S$: C, 72.20; H, 9.09; S, 5.36; O, 13.36. Found: C, 71.86; H, 8.93; S, 6.49; O, 12.96.

3β-Acetoxy-5,19-cyclocholestan-6-one (XVIII) (with Dr. H. R. Browning).—3β-Acetoxy-19-hydroxycholest-5-ene toluene-*p*-sulfonate (see above; 4.25 g.) and potassium acetate (3.30 g.) were refluxed in acetone (135 ml.) and water (34 ml.) for 42 hr. The acetone was removed *in vacuo* and the residue extracted with hexane. Chromatography over Florisil (40 g.), eluting with benzene–ether (9:1), gave an oil. Crystallization from acetone afforded 3β-acetoxy-5,19-cyclocholestan-6α-ol (48%), m.p. 112–113°, $[\alpha]_D$ +44° (*c* 0.70), tetranitromethane test negative.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88; O, 10.79. Found: C, 78.52; H, 10.76; O, 11.00.

This alcohol (787 mg.) was oxidized with a slight excess of chromium trioxide in acetone.[11] Addition of methanol, removal of the solvents *in vacuo*, and extraction into ether gave 3β-acetoxy-5,19-cyclocholestan-6-one (70%); m.p. 124°, $[\alpha]_D$ −33° (*c*

0.87), λ_{max} 208 mμ (ε 3500) after recrystallization from chloroform–methanol.

Anal. Calcd. for $C_{39}H_{46}O_3$: C, 78.68; H, 10.47; O, 10.84. Found: C, 78.81; H, 10.45; O, 11.08.

Preparation of 3β,6β-Dihydroxy-5(10)-olefins.—The diacetate IIIa (R′ = Ac, X = Br, Y = H, OAc; 100 mg.) in methanol (5 ml.) was treated with aqueous sodium hydroxide (1 ml., 1 *N*) at 0° for 5 min. and then left at ambient temperature for 35 min. Filtration and crystallization from methylene dichloride–methanol gave 5β,6β-epoxy-19-oxocholestan-3β-ol (IXa, R′ = H; 70 mg.), m.p. 138–140°, [α]D −10° (*c* 1.09).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65; O, 11.52. Found: C, 77.63; H, 10.36; O, 11.79.

The derived acetate IXa (R′ = Ac), prepared with excess of pyridine–acetic anhydride at room temperature, had m.p. (from hexane) 138–140°, [α]D +34° (*c* 0.98).

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.95; H, 10.10. Found: C, 75.70; H, 9.91.

5β,6β-Epoxy-19-oxocholestan-3β-ol (865 mg.) in methanol (55 ml.) and aqueous potassium hydroxide (20%, 10 ml.) was refluxed for 2 hr. under nitrogen. Dilution with water, extraction into methylene dichloride, and crystallization from methanol gave 19-norcholest-5(10)-ene-3β,6β-diol (Xa), m.p. 165–168°, [α]D +98° (*c* 0.89).

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.34; H, 11.41; O, 8.23. Found: C, 80.22; H, 11.49; O, 8.56.

5α-Bromo-3β,19-6β,19-diepoxyandrostan-17-one (VIIb, 4.3 g.) in methanol (600 ml.) was treated with sodium borohydride (5 g.) at room temperature for 2 hr. The product (500 mg.) in glacial acetic acid (20 ml.) and acetic anhydride (6 ml.) was treated at 5° with 70% perchloric acid (0.16 ml.) for 2 hr. After working up as in comparable experiments above, the crude triacetate IIIc (R′ = Ac, X = Br, Y = H, OAc) in methanol (20 ml.) and aqueous potassium hydroxide (20%, 4 ml.) was refluxed under nitrogen for 2 hr. Crystallization of the product from ethyl acetate–hexane gave 19-norandrost-5(10)-ene-3β,6β,17β-triol, m.p. 179–182°, [α]D −23° (*c* 0.93 in methanol).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.41. Found: C, 74.03; H, 9.71; O, 16.38.

When the crude triacetate IIIc (R′ = Ac, X = Br, Y = H, OAc; see above; 660 mg.) in methanolic potassium hydroxide (7 ml., 5%) was left at 15° for 15 min., it afforded, after crystallization of the product from acetone–hexane, 5β,6β-epoxy-19-oxoandrostane-3β,6β-diol 17-acetate (Xc, 430 mg.), m.p. 188–193°, [α]D −47° (*c* 0.80).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.36; O, 22.0. Found: C, 69.97; H, 8.59; O, 21.41.

Reactions of Steroidal Hypochlorites.—The acetoxy alcohol[16] XIII (R = R′ = H; 752 mg.) in dry carbon tetrachloride (40 ml.) containing anhydrous potassium carbonate (2.0 g.) was treated with chlorine monoxide[17] in the same solvent (6 ml., 1 *N*) at 0° for 30 min. Filtration, removal of the solvent at 5° *in vacuo*, and crystallization in the cold from carbon tetrachloride–hexane gave the crystalline hypochlorite XIII (R = H, R′ = Cl), m.p. 145–147°, [α]D 0° (*c* 1.51 in carbon tetrachloride), $\lambda_{max}^{CCl_4}$ 258 and 318 mμ (ε 107 and 9.5, respectively). This compound titrated for one atom of "active" chlorine and the resultant solution gave the parent acetoxy alcohol XIII (R = R′ = H) in high yield.

The hypochlorite XIII (R = H, R′ = Cl), prepared from parent alcohol (752 mg.), in dry benzene (80 ml.) was photolyzed for 1 hr. in the usual apparatus[3] (Pyrex filter). After washing with aqueous sodium carbonate, the solvent was removed *in vacuo* and the residue refluxed with methanolic potassium hydroxide (5%, 50 ml.) for 2 hr. Acetylation of the product with pyridine–acetic anhydride and chromatography of the resultant acetates over alumina, eluting with benzene and with benzene–ether mixtures, gave firstly the 18,20-oxide XIV (X = H_2; 154 mg.). Recrystallized from chloroform–methanol this had m.p. 152–154°, [α]D +17° (*c* 1.16).

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.95; H, 10.20. Found: C, 77.00, 76.98; H, 10.15, 10.20.

Eluted secondly was the parent acetate alcohol XIII (R = R′ = H; 142 mg.).

The 18,20-oxide XIV (X = H_2; 90 mg.) in glacial acetic acid (10 ml.) was added under reflux to chromium trioxide (200 mg.) in aqueous acetic acid (90%, 10 ml.) and the solution refluxed for 15 min. After working up in the usual way the product was crystallized from methanol to give the lactone XIV (X = O; 17 mg.), m.p. 209–210°, [α]D +7° (*c* 0.60), ν_{max}^{KBr} 1760 and 1745 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.20; H, 9.35. Found: C, 74.25; H, 9.40.

3β-Acetoxy-6α-methylcholestan-6β-ol[19] (XV, R = H) was converted to the hypochlorite XV (R = Cl) as in the example given above. The crude hypochlorite, which could not be crystallized, had [α]D −13° (*c* 1.76 in carbon tetrachloride) and on titration showed one active chlorine atom giving back the starting alcohol XV (R = H). This hypochlorite (1.8 g.) in dry benzene (80 ml.) was photolyzed and further processed as in the example above. Chromatography of the product (after the alkali treatment but before acetylation) over alumina eluting with ether and ether–methanol gave firstly the oxido alcohol XVI (760 mg.), m.p. (from methanol) 179–181°, [α]D +19° (*c* 0.68).

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.70; H, 11.60. Found: C, 80.45; H, 11.35.

Eluted later was 6α-methylcholestane-3β,6β-diol.[19]

Oxidation of 6β-Hydroxysteroids with Mercuric Oxide and Iodine.—The following example is illustrative. 3β-Acetoxycholestan-6β-ol (500 mg.) in dry carbon tetrachloride (100 ml.) was stirred for 20 min. with finely divided mercuric oxide (900 mg.) and iodine (1.07 g.), while being irradiated with a high pressure mercury lamp in the usual way.[3] The mixture was filtered, washed with aqueous sodium thiosulfate, and the solvent removed *in vacuo*. Crystallization from methanol gave the oxide IIIa (R′ = Ac, X = H, Y = H_2; 330 mg.), m.p. 114–116°, [α]D +4° (*c* 1.13).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88; O, 10.79. Found: C, 78.22; H, 10.64; O, 10.88.

The experiment was repeated under reflux in a black flask without irradiation. The same oxide IIIa (R′ = Ac, X = H, Y = H_2; 350 mg.) was obtained.

The following 6β,19-oxides of type III (Y = H_2) were prepared from alcohols of type II (Y = H_2) by the same (photolytic) procedure: 6α-methyl-6β,19-epoxycholestan-3β-ol (XVI; alkaline hydrolysis with 5% methanolic potassium hydroxide prior to crystallization; 56%), m.p. (from chloroform–methanol) 179–180°, [α]D +19° (*c* 0.68). *Anal.* Calcd. for $C_{28}H_{48}O_2$: C, 80.70; H, 11.60. Found: C, 80.45; H, 11.35.

5α-Chloro-6β,19-epoxyandrostane-3β,17β-diol 3,17-diacetate (IIIc, R′ = Ac, X = Cl, Y = H_2; 78%), m.p. (from chloroform–methanol) 154–158°, [α]D −18° (*c* 0.62). *Anal.* Calcd. for $C_{23}H_{33}O_5Cl$: C, 65.00; H, 7.83; O, 18.83; Cl, 8.34. Found: C, 64.85; H, 7.91; O, 18.59; Cl, 8.31.

5α-Chloro-6β,19-epoxypregnan-3β-ol-20-one acetate (IIId, R′ = Ac, X = Cl, Y = H_2; 75%), m.p. (from methanol) 131–133°, [α]D +65° (*c* 0.60). *Anal.* Calcd. for $C_{23}H_{33}O_4Cl$: C, 67.54; H, 8.13; O, 15.65; Cl, 8.67. Found: C, 67.38; H, 8.22; O, 15.44; Cl, 8.43. (The same yield (75%) of the latter compound was obtained under reflux conditions without irradiation.)

5α-Chloro-3β,17α-dihydroxy-6β,19-epoxypregnan-20-one 3,17-diacetate (76%), m.p. (from methylene dichloride–ether) 208–210°, [α]D −6° (*c* 0.82). *Anal.* Calcd. for $C_{25}H_{35}O_6Cl$: C, 64.29; H, 7.55; O, 20.56; Cl, 7.59. Found: C, 64.56; H, 7.74; O, 19.90; Cl, 8.10.

Some comparative experiments were made using lead tetraacetate and iodine as oxidant. The following example is illustrative. The bromohydrin IIc (R′ = Ac, R″ = H, X = Br, Y = H_2; 5.0 g.) in anhydrous benzene (250 ml.) was photolyzed with lead tetraacetate (15 g.; previously washed with acetic acid and dried overnight *in vacuo* over potassium hydroxide and calcium chloride) and iodine (8.58 g.) for 6 hr. in the usual way[3] and with constant stirring at reflux. Addition of water, extraction into ether, washing the ether layer with aqueous sodium thiosulfate (10%) and then with water, drying (sodium sulfate), and evaporation *in vacuo* gave, after crystallization from methanol, 5α-bromo-6β,19-epoxyandrostane-3β,17β-diol 3,17-diacetate[32] (IIIc, R′ = Ac, X = Br, Y = H_2; 63%), m.p. 179–181°, [α]D −7° (*c* 0.72).

Anal. Calcd. for $C_{23}H_{33}O_5Br$: C, 58.85; H, 7.09; O, 17.04; Br, 17.02. Found: C, 58.91; H, 6.69; O, 16.92; Br, 17.03.

The following 6β,19-epoxides were prepared in the same way: 5α-bromo-6β,19-epoxyandrostan-3β-ol-17-one acetate (IIIb, R′ = Ac, X = Br, Y = H_2; 29%), m.p. (from methanol) 177–178°, [α]D +36° (*c* 0.72). *Anal.* Calcd. for $C_{21}H_{29}O_4Br$: C, 59.30; H, 6.85; O, 15.05; Br, 18.80. Found: C, 58.85; H, 7.20; O, 14.75; Br, 18.75.

(32) Compare J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

5α-Bromo-6β,19-epoxypregnan-3β-ol-20-one acetate (IIId, R′ = Ac, X = Br, Y = H_2; 42%), m.p. (from methanol) 154–157°, $[\alpha]_D$ +56° (*c* 0.63). *Anal.* Calcd. for $C_{23}H_{33}O_4Br$: C, 60.92; H, 7.34; O, 14.11; Br, 17.62. Found: C, 61.07; H, 7.04; O, 14.21; Br, 18.15.

Preparation of 19-Hydroxysteroids.—The following example is illustrative. The diacetate IIIc (R′ = Ac, X = Cl, Y = H_2; 1.10 g.) in methanol (110 ml.) and methanolic sodium hydroxide (5.5 ml., 0.5 *N*) was kept at room temperature for 2 hr. Dilution with saturated aqueous sodium chloride, extraction into methylene dichloride, and chromatography over alumina eluting with ether and with ether–methanol mixtures gave 5α-chloro-6β,19-epoxyandrostane-3β,17β-diol 17-acetate (IIIc, R′ = H, X = Cl, Y = H_2; 680 mg.), m.p. (from acetone–hexane) 183–186°, $[\alpha]_D$ +6° (*c* 0.85).

Anal. Calcd. for $C_{21}H_{31}O_4Cl$: C, 65.86; H, 8.16; O, 16.71; Cl, 9.26. Found: C, 65.79; H, 8.09; O, 17.00; Cl, 9.27.

The following compounds were obtained by essentially the same procedure: 5α-bromo-6β,19-epoxypregnan-20-one (IIId, R′ = H, X = Br, Y = H_2; 68%), m.p. (from acetone–hexane) 186–187°, $[\alpha]_D$ +57° (*c* 0.89). *Anal.* Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59; O, 11.67; Br, 19.43. Found: C, 61.88; H, 7.60; O, 11.48; Br, 18.87.

5α-Chloro-6β,19-epoxypregnan-20-one (IIId, R′ = H, X = Cl, Y = H_2), m.p. (from methanol) 191–193°; $[\alpha]_D$ +58° (*c* 0.67), +62° (*c* 0.58). *Anal.* Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.55; H, 8.84; Cl, 9.65.

5α-Chloro-3β,17α-dihydroxy-6β,19-epoxypregnan-20-one 17-acetate, m.p. (from methylene dichloride–hexane) 225–255°, $[\alpha]_D$ −17° (*c* 0.94). *Anal.* Calcd. for $C_{23}H_{33}O_5Cl$: C, 65.00; H, 7.83; O, 18.82; Cl, 8.34. Found: C, 64.86; H, 7.73; O, 18.74; Cl, 9.03.

The acetate IIIc (R′ = H, X = Cl, Y = H_2; see above; 50 mg.) in acetone (50 ml.) was treated with slight excess of chromium trioxide in acetone[11] for 2 min. at room temperature. Dilution with water and filtration gave crude ketone IVd (X = Cl, Y = H_2). This was refluxed with pyridine (20 ml.) for 2 hr., water added, and the product extracted into methylene dichloride. Crystallization from chloroform–methanol gave the conjugated ketone Vc (Y = H_2; 325 mg.), m.p. 157–159°, $[\alpha]_D$ −96° (*c* 1.00), λ_{max} 237 mμ (ε 13,000).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19; O, 18.58. Found: C, 73.34; H, 8.18; O, 18.62.

The following compounds were obtained by essentially the same procedure: 6β,19-oxidoprogesterone (Vd, Y = H_2; 62%), m.p. (from methanol) 142–145°, $[\alpha]_D$ −23° (*c* 1.74), λ_{max} 239 mμ (ε 12,400). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14.61. Found: C, 76.97; H, 8.61; O, 14.24.

6β,19-Epoxy-17α-hydroxypregn-4-ene-3,20-dione acetate (50%), m.p. (from ethyl acetate–ether) 230–236°, $[\alpha]_D$ −117° (*c* 0.61), λ_{max} 237 mμ (ε 14,000). *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.44; H, 8.02; O, 20.46.

The crude ketone IVc (X = Cl, Y = H_2) from the oxidation of the alcohol IIIc (R′ = H, X = Cl, Y = H_2; 1.00 g.) in acetic acid (100 ml.) was heated under reflux with zinc dust (16 g.) as in the examples already given. Working up in the usual way and crystallization from chloroform–methanol gave 19-hydroxytestosterone acetate (VIc, R′ = CH_2OH; 45%), m.p. 165–170°, $[\alpha]_D$ +69° (*c* 0.80).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 73.09; H, 8.73; O, 18.41.

The following compounds were prepared by the same procedure: 19-hydroxyprogesterone (VId, R′ = CH_2OH; 50%), m.p. (from acetone–hexane) 165–168°, $[\alpha]_D$ +170° (*c* 0.53), λ_{max} 244 mμ (ε 14,000). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 14.53. Found: C, 76.56; H, 8.98; O, 14.81.

17α,19-Dihydroxypregn-4-ene-3,20-dione 17-acetate, m.p. (from methylene dichloride–ether) 243–245°, $[\alpha]_D$ +66° (*c* 0.94), λ_{max} 241 mμ (ε 16,300). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.37; H, 8.43; O, 20.38.

Miscellaneous Oxidations with Mercuric Oxide and Iodine.—The acetoxy alcohol XIII (R = R′ = H; 376 mg.) in dry carbon tetrachloride (50 ml.) was refluxed with finely divided mercuric oxide (3.0 g.) and iodine (3.0 g.) for 3 hr. with irradiation. After filtration and washing with 10% aqueous sodium thiosulfate the solvent was removed *in vacuo* and the residue chromatographed over alumina. Elution with benzene gave the oxide XIV (X = H_2; 60 mg.) identical with material already described above.

11α-Hydroxyprogesterone (XVII; 1.0 g.) in dry carbon tetrachloride (300 ml.) containing finely divided mercuric oxide (2.0 g.) and iodine (2.2 g.) was photolyzed as above for 2.5 hr. After filtration and washing with 10% aqueous sodium thiosulfate the solvent was removed *in vacuo*. The product in 5% methanolic potassium acetate (100 ml.) was refluxed for 2 hr. Crystallization from methanol gave 11α-hydroxypregna-1,4-diene-3,20-dione[33] (XVIIa; 640 mg.), m.p. 221–227°, $[\alpha]_D$ +107° (*c* 1.00). The identity of the product was confirmed by oxidation to pregna-1,4-diene-3,11,20-trione.

Cyclopentanol (1.0 g.) in dry carbon tetrachloride (100 ml.) was refluxed with finely divided mercuric oxide (7.8 g.) and iodine (8.0 g.) under irradiation for 20 min. After filtration and washing with 10% aqueous sodium thiosulfate, the solvent was removed *in vacuo* to furnish δ-iodovaleraldehyde. The derived 2,4-dinitrophenylhydrazone had m.p. 127–218°, λ_{max} 358 mμ (ε 21,600).

Anal. Calcd. for $C_{11}H_{13}O_4N_4I$: C, 33.69; H, 3.34; O, 16.32; N, 14.29; I, 32.36. Found: C, 33.84; H, 3.32; O, 16.40; N, 14.16; I, 32.60.

Reactions Using the *tert*-Butyl Hypochlorite–Iodine Reagent.—3β-Acetoxycholestan-6β-ol (IIa, R′ = Ac, R″ = X = H, Y = H_2; 500 mg.), iodine (2.0 g.), and *tert*-butyl hypochlorite (redistilled; 0.5 ml.) in benzene (100 ml.) was photolyzed[3] at room temperature for 45 min. The benzene solution was washed with 10% aqueous sodium thiosulfate and with water. Removal of the benzene *in vacuo* and crystallization of the product from methanol afforded 6β,19-oxidocholestanyl acetate (IIIa, R′ = Ac, X = H, Y = H_2; 415 mg.) identical with an authentic specimen.

In the same way 5α-chloro-3β,6β,17β-trihydroxyandrostane 3,17-diacetate gave the 6β,19-oxide IIIc (R′ = Ac, X = Cl, Y = H_2; 64%); 5α-bromo-3β,6β,17β-trihydroxyandrostane 3,17-diacetate afforded the 6β,19-oxide IIIc (R′ = Ac, X = Br, Y = H_2; 64%); and 5α-chloro-3β,6β,17α-trihydroxypregnan-20-one 3,17-diacetate yielded the corresponding 6β,19-oxide (70%).

Reaction Using *tert*-Butyl Hypobromite.—Potassium *tert*-butoxide (M.S.A. Research Corp., Callery, Pa.) suspended in benzene (25 ml.) containing bromine (0.28 ml.) was stirred for 5 min. (anhydrous conditions). 3β-Acetoxycholestan-6β-ol (250 mg.) was added and the solution left for 5 min. at room temperature in diffuse daylight. Excess of 5% aqueous potassium iodide was added and then the organic layer was washed with 10% aqueous sodium thiosulfate. Chromatography of the product over alumina (7 g.), eluting with benzene, gave the 6β,19-oxide IIIa (R′ = Ac, X = H, Y = H_2; 132 mg.). (When the reaction was repeated in the dark only starting material was recovered.)

The above experiment was repeated using 500 mg. of starting alcohol. Prior to chromatography, the crude product was treated with a slight excess of chromium trioxide in acetone for 3 min. Addition of water containing a little methanol, extraction into ether, and removal of the solvent gave, after chromatography over alumina (50 g.) eluting with benzene and with benzene–ether, the 6β,19-oxide IIIa (R′ = Ac, X = H, Y = H_2; 18 mg.), the 6β,19-lactone IIIa (R′ = Ac, X = H, Y = O; 10 mg.), 6-ketocholestanyl acetate (175 mg.), and the 5,19-cyclopropan-6-one (XVIII; 128 mg.) referred to above.

To potassium *tert*-butoxide (1.80 g.) in benzene (50 ml.) containing bromine (0.84 ml.) was added 11α-hydroxyprogesterone (XVII; 550 mg.) in 1:1 benzene–tetrahydrofuran (10 ml.). After working up as before (see above), the crude product was refluxed with 5% methanolic potassium acetate (20 ml.) for 15 min. Crystallization from acetone–hexane gave 11α-hydroxypregna-1,4-diene-3,20-dione (XVIIa; 211 mg.).

Reactions Using *tert*-Butyl Hypoiodite.—Potassium *tert*-butoxide (1.2 g.) in dry benzene (50 ml.) was stirred with iodine (7.65) under anhydrous conditions for 5 min. 3β-Acetoxycholestan-6β-ol (500 mg.) was added and the stirring continued for 2 min. After addition of excess of 10% aqueous sodium thiosulfate, the benzene layer was separated, dried (sodium sulfate), and evaporated. Crystallization from methylene dichloride–methanol gave 6-ketocholestanyl acetate (409 mg.).

Potassium *tert*-butoxide (600 mg.) in benzene (80 ml.) was stirred with iodine (4.3 g.) and the suspension filtered into the photolysis apparatus.[3] 6α-Methylcholestane-3β,6β-diol 3-acetate (250 mg.) was added and the solution irradiated under nitrogen. The crude product was treated with 5% methanolic potassium hydroxide at room temperature for 10 min. Crystallization from methylene dichloride–hexane then afforded the oxide XVI (120 mg.).

(33) H. Reimann, E. P. Oliveto, R. Neri, M. Eisler, and P. Perlman, *J. Am. Chem. Soc.*, **82**, 2308 (1960).

In the same way the tertiary alcohol XIII (R = R′ = H; 250 mg.) gave, after chromatography over alumina, the 18,20-lactone XIV (X = O; 41 mg.).

Potassium *tert*-butoxide (2.4 g.) in benzene (90 ml.) was stirred with iodine (7.6 g.) for 5 min. before addition of 11α-hydroxyprogesterone (XVII; 1.0 g.) in 1:1 benzene–tetrahydrofuran (10 ml.) under irradiation.[3] Working up and further processing as in prior oxidations of 11α-hydroxyprogesterone gave, on chromatography over alumina, the starting material (141 mg.) and 11α-hydroxypregna-1,4-diene-3,20-dione (240 mg.).

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Small-Ring, Spiroalkyl Cations. Solvolysis Studies on Some 1-Halospiroalkanes

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1-Chlorospirohexane and 1-chlorospiro[2.4]heptane were synthesized by the addition of chlorocarbene to methylenecyclobutane and methylenecyclopentane, respectively. The corresponding bromides were prepared from the same alkenes by the addition of dibromocarbene followed by treatment with zinc and glacial acetic acid. The ethanolysis rate constant (50% aqueous ethanol, 95°) of 1-chlorospirohexane was 1.24 times that of cyclohexyl chloride and at least 1000 times greater than that of cyclopropyl chloride. 1-Chlorospiro[2.4]-heptane solvolyzed 1.98 times faster than cyclohexyl chloride. The implications of these rate measurements are discussed. The solvolysis rate of chlorospiropentane (50% aqueous ethanol, 200°) relative to cyclopropyl chloride was found to be 4–6.2. Tiglaldehyde was the only product isolated from the silver nitrate assisted hydrolysis (100°) of chlorospiropentane.

Introduction

Roberts and Chambers[3] noted that in acetic acid containing 1% acetic anhydride, cyclopropyl tosylate solvolyzed 2×10^{-5} times as fast as cyclohexyl tosylate and produced allyl acetate as the sole product.

The very low solvolytic reactivity of cyclopropyl derivatives was first explained by Brown[4] as a manifestation of excessive internal angle strain upon going to the assumed trigonal transition state.

Cromwell and Graff[5] have explained the low solvolytic reactivity of cyclopropyl halides by a large increase in the double bond character (and hence, bond energy) caused by overlap of the halogen p-orbitals with the "bent bonds" of the cyclopropane ring.

Although the difficulty of forming the cyclopropyl cation suggests that the transition state for its formation does not resemble the completely opened resonance stabilized allylic cation, there is evidence that cyclopropyl derivatives may undergo an assisted type of solvolysis faster than one might predict on the basis of simple angle strain arguments. Schleyer[6] has pointed out that although the bridging angle (C_1–C_7–C_4) of the norbornyl system is 98.3° as compared to the 60° internal angle of cyclopropane, the tosylate of the former solvolyzes about 100 times slower than that of the latter. The low reactivity in the norbornyl system has been attributed to angle strain alone, by comparison of its reactivity to corresponding adamantane derivatives.[6] A partially opened cyclopropyl cation involving extensive charge delocalization was proposed for the transition state resulting from heterolytic reactions of cyclopropyl derivatives leading to carbonium ion intermediates.

DePuy[7] has observed that *trans*-2-phenylcyclopropyl tosylate solvolyzed some 50 times faster than cyclopropyl tosylate at 100° (extrapolated rates), and Roberts and Snyder[8] have also observed a solvolytic rate increase upon introduction of a *cis*- or *trans*-2-methyl group on cyclopropyl bromide. Both of these observations are consistent with some degree of charge delocalization and thus more direct substituent participation in the transition state.

In the present study, solvolysis rate measurements have been made on spiropentyl chloride and several previously unknown strained spiroalkyl halides. These rate constants, together with a knowledge of the products of solvolysis, provide further insight relative to carbonium ion formation on three-membered rings.

Results and Discussion

Synthesis.—The 1-halospiroalkanes were prepared by carbene reactions. Because of the successful reported additions of chlorocarbene to alkenes to form the corresponding chlorocyclopropanes,[9,10] this method was applied to methylenecyclobutane (I). Chlorocarbene is normally generated by the addition of a simple alkyllithium reagent, *e.g.*, *n*-butyllithium, to a cold solution of methylene chloride in the presence of the alkene. *n*-Propyllithium was chosen for convenience because the coupling product, *n*-hexane, can be readily separated from the product chloride II. 1-Chlorospirohexane (II) was isolated in 19.5% of the theoretical yield and showed no sign of unsaturation in the infrared spectrum.

The structure of the compound was readily confirmed from the nuclear magnetic resonance (n.m.r.) spectrum. A quartet at τ 7.15 (area 1) was assigned to the proton on the chlorine-bearing carbon atom; a broad, slightly split peak at 7.90 (area 6) was assigned

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