Steroidal Acetoxy, Haloepoxides and Their Reactions

Panayotis Catsoulacos

Laboratory of Pharmaceutical Chemistry,
University of Patras,
Patras, Greece

Received July 22, 1985

J. Heterocyclic Chem., **23**, 321 (1986).

Contents.

Introduction.

The details of the formation of steroidal acetoxyepoxides and haloepoxides from enol-acetates and halo-ene have long intrigued the organic chemist.

This interest is due to the effort to develop applicable methods for the preparation of ketols or bromohydrines as metabolites of hormones and potentially useful intermediates in the synthesis of glycols, haloketones, aminoketones and aminoalcohols.

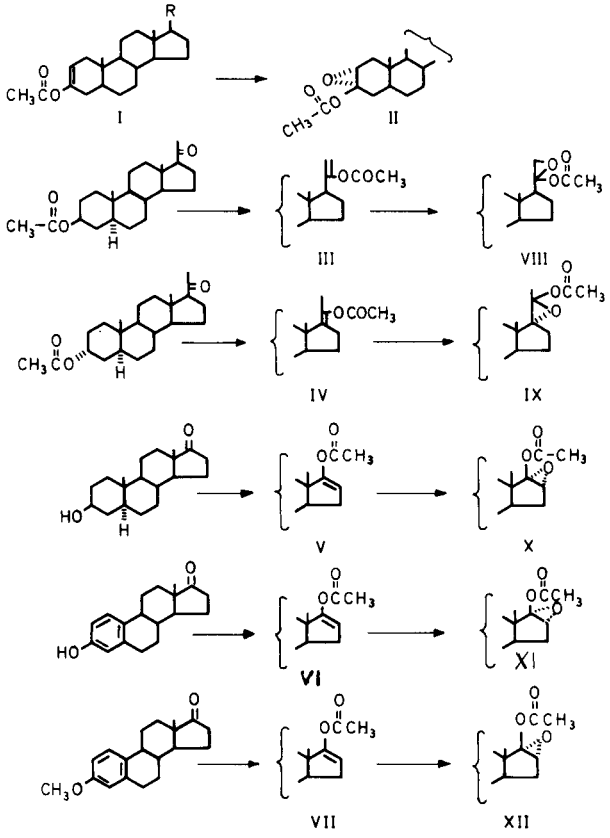
One cannot exclude the possibility that these compounds will prove useful in the fight against various forms of cancer of a hormone-dependent type. They may also prove interesting as antihormonal preparations capable of reaction with the same receptor systems as steroids and behave as antagonists to them.

For this reason and because of the well defined stereochemistry in such a system it has been chosen as a substrate steroidal acetoxyepoxides of A and D-ring and haloepoxides.

Formation of Acetoxy- and Haloepoxides.

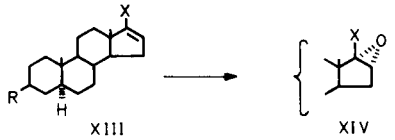
I. Formation of Acetoxyepoxides.

Cholestanone enol acetate (I) on treatment with perbenzoic acid gave, in good yield, 2α,3α-oxido-3β-acetoxycholestane (II) [1], mp 133-135°, $[\alpha]_D$ +16.5°. The α-orientation of the epoxide follows, by analogy, occurring from the unhindered back side of the molecule.



Upon treatment of 3β-hydroxyallopregnane-20-one, 3α-hydroxypregnan-20-one, 3β-hydroxy-5α-androstan-17-one, 3-hydroxy-estra-1,3,5(10)-trien-17-one with isopropenyl acetate, in the presence of catalytic amounts of sulfuric acid, the enol acetates III [2], IV [3], V [4], VI [4], VII [5] were obtained, which with perbenzoic acid at room temperature were readily converted to the corresponding epoxy acetates VIII [6], IX [7], X [4], XII [5].

Formation of Haloepoxides.



XIIIa R = H, x = Br
XIIIb = $OCOCH_3$, x = Br
XIIIc = $OCOCH_3$, x = Cl

XIVa x = Br
XIVb x = Cl

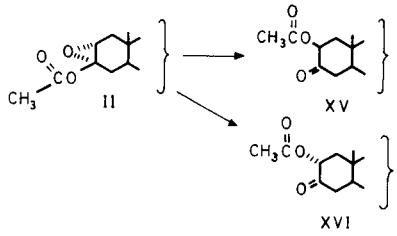
Haloepoxides XIV [8] were readily prepared by peracid oxidation of 17-bromo- or 17-chloro-16-androstene XIII, which was in turn obtained from 5α-androstan-17-one hydrazone and 3β-hydroxy-5α-androstan-17-one hydrazone as outlined by Mori and Tsuneda [9].

The assignment of the α-configuration for epoxides XIV is based on the well-known approach of reagents from the α side of steroid nucleus and has its analogy in the formation of other 16α,17α-oxido compounds on epoxidation of steroid 16-enes [4,10].

All the haloepoxides showed four peaks in the ir spectrum between 850 and 750 cm^{-1} characteristic for the haloepoxides.

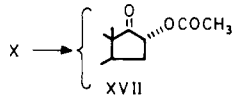
Isomerization of Acetoxy- and Haloepoxides.

I. 2α,3α-Oxido-3β-acetoxycholestane (II).



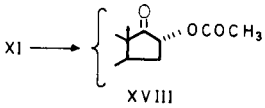
The 2α,3α-oxido-3β-acetoxychloestane (II) was rearranged by heating to 160° for five minutes to 2β-acetoxycholestan-3-one (XV), mp 145-146°, $[\alpha]_D^{25}$ +16.5° [1]. Acid converts the epoxy acetate (II) directly to the equatorial acetoxy ketone, 2α-acetoxycholestan-3-one (XVI), mp 124-125°, $[\alpha]_D$ +51.55 [11].

II. 16α,17α-Oxidoandrostan-3β,17β-diol Diacetate (X).



Leeds, Fukushima and Gallagher [4] obtained, 3β,16α-diacetoxyandrostan-17-one (XVII) from 16α,17α-oxidoandrostan-3β-17β-diol diacetate (X), with subsequent rearrangement of the D ring epoxyacetate by chromatography upon silica gel, by heating above its melting point or subjected to acid hydrolysis followed by reacetylation. The rearrangement of the product occurred with the opening of the oxide ring and migration of the 17-acetoxy group to yield the acetoxy ketone, mp 184-185°, $[\alpha]_D^{23}$ +57.1°.

III. 16α,17α-Oxido-$\Delta^{1,3,5}$-estratriene-3,17β-diole Diacetate (XI).



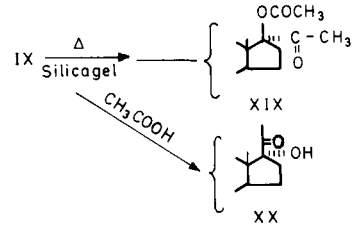
The method for synthesising compounds potentially useful intermediates in the synthesis of D rings glycols of estrone, consist by chromatography or acid catalysis rearrangement of 16α,17α-oxido-$\Delta^{1,3,5}$-estratriene-3,17-diole diacetate (XI) producing 3,16α-diacetoxy-$\Delta^{1,3,5}$-estratrien-17-one (XVIII), mp 179-180°, $[\alpha]_D^{28}$ +122 (4).

IV. 3-Methoxy-16α,17α-oxido-13α-estra-1,3,5(10)-trien-17β-ol Acetate (XII).

When 3-methoxy-16α,17α-oxido-13α-estra-1,3,5(10)-trien-17β-ol acetate (XII) was treated with sulfuric acid and then acetylated, the 16α-acetoxy-17-ketone (3-OCH_3, XVIII) was obtained, mp 135-136°, $[\alpha]_D^{22}$ −142.9(5).

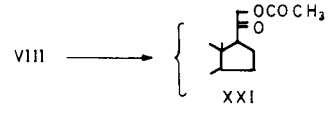
The stereochemistry of the acetoxy group at C-16 was tentatively assigned to be α, because of the splitting pattern of 16-proton signal: δ 1.12 (3H, s, 18-CH_3), 2.08 (3H, s, 16α-$OCOCH_3$), 3.72 (3H, s, 3-OCH_3), 5.06 (1H, t, J = 9 cps, 16β-H).

V. 17α,20β-Oxidoallopregnane-3β,20α-diol Diacetate (IX).



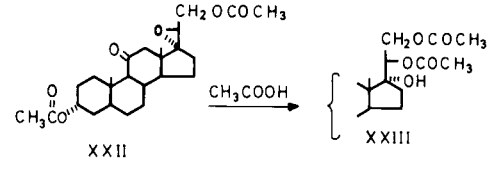
When 17α,20β-oxidoallopregnane-3β,20-diol diacetate (IX) was allowed to remain upon a column of silica gel, the product obtained proved to be 3β,17β-diacetoxyallopregnan-20-one (XIX) mp 227-229°. By treatment of the same epoxide with glacial acetic acid, then the 3β-acetoxy-17α-hydroxyallopregnan-20-one (XX) was obtained, mp 188-190° [6].

VI. 20,21-Oxidoallopregnane-3β,20β-diol Diacetate (VIII).



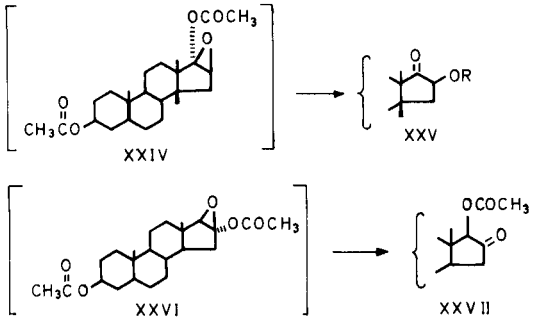
When Δ^{20}-allopregnene-3β,20β-diol diacetate (IV) was treated with perbenzoic acid the crude epoxide VIII was obtained and chromatographed on silica gel to give 3β,21-diacetoxyallopregnan-20-one (XXI), mp 150-151°.

VII. 17α,20β-Oxidopregnan-11-one-3α,21-diol Diacetate (XXII).



When 3α,21-diacetoxy-17,20-β-oxidopregnan-11-one (XXII) was heated under reflux in acetic acid for 24 hours, the 17α-hydroxy-3α,20,21-triacetoxypregnan-11-one (XXIII) was obtained [6], mp 212-214°.

VIII. 16β,17β-Oxido-5α,14β-androstane-3β,17α-diol Diacetate (XXIV) and 16β,17β-oxido-5α,14β-androstane-3β,16α-diol Diacetate (XXVI).

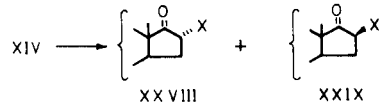


β-Epoxide diacetates XXIV, XXVI of the 14β-series were obtained from 3β,17-diacetoxy-5α,14β-androst-16-ene, and 3β,16-diacetoxy-5α,14β-androst-16-ene.

Nambara and Fishman [12], in their study on the formation of the C-16, 17 D ring ketols of 14β-steroids, have used β-epoxide XXIV as the substrate, which was not obtained crystalline, and under mild mineral acid treatment followed by reacetylation ketol diacetate XXV was obtained, mp 144 -146°.

The same authors have succeeded to rearrange non crystalline epoxide XXVI to ketol 16-oxo-5α,14β-androstane-3β,17β-diol diacetate (XXVII) under acidic conditions.

IX. 17β-Bromo-16α,17α-oxidoandrostane-3β-ol-acetate (XIVa) and 17β-Chloro-16α,17α-oxidoandrostane-3β-ol Acetate (XIVb).



XXVIIIa = Br XXIXa = Br
XXVIIIb = Cl XXIXb = Cl

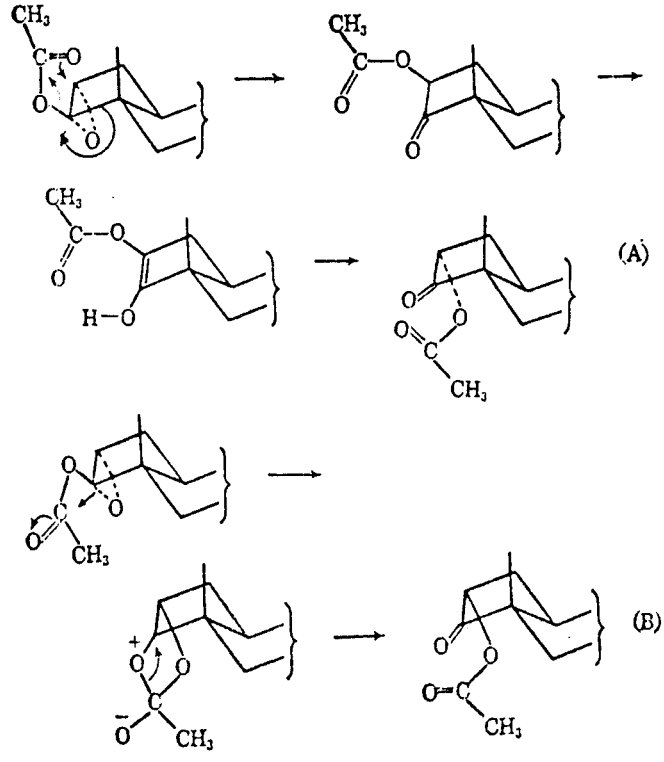
Mamlok and Jackes obtained 16-chloro-5α-androstan-17-one from 17β-chloro-16α,17α-oxido-5α-androstane, by heating it above its melting point [13].

We have studied the thermal rearrangement of 3β-acetoxy-17β-bromo-16α,17α-oxido-5α-androstane (XIVa) at 160° in one minute and we have obtained 3β-acetoxy-16α-bromo-5α-androstan-17-one (XXVIIIa) and its 16β-isomer XXIXa in 26% and 66% yield respectively. Similar results have been obtained when 3β-acetoxy-17β-chloro-16α,17α-oxido-5α-androstane (XIVb) was heated at 210° during 10 minutes [14] to give 16α-chloroketone XXVIIIb and 16β-chloroketone XXIXb.

Mechanism of the Rearrangement of Enol-Ester Epoxides and α-Haloepoxides.

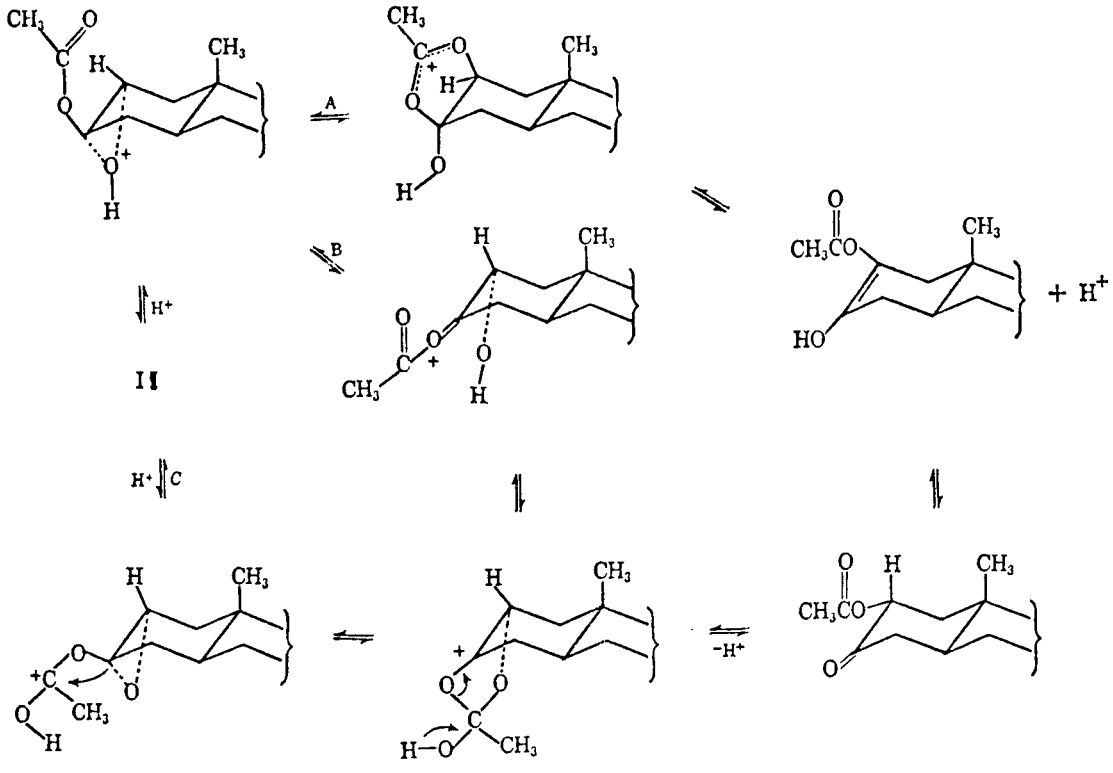
I. Mechanism of Rearrangement of Enol-Ester Epoxides.

Two possible mechanisms were proposed to rationalize the conversion of the α-acetoxy ketone. One (A) assumes that the acetate migrated with inversion to give the β-acetoxyl or hydroxyl group, which then rearranges to the more stable α-configuration under mild enolizing conditions. An alternative mechanism (B) without inversion involves opening the epoxide ring to an ionic intermediate which gives the α-acetoxy ketone [4].



Williamson and co-workers [11] have shown the rearrangement to be intramolecular, involving acetate migration with retention of configuration. The thermal and acid-catalyzed rearrangements of enol-ester epoxides are shown to proceed under quite different mechanisms. They have shown that the 3β-acetoxy-2α,3α-oxidocholestane (II) will rearrange in acid to 2α-acetoxy-cholestan-3-one (XVI) a thousand times faster than 2β-acetoxycholestan-3-one (XV).

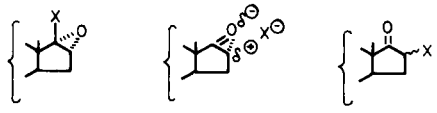
The same authors have concluded that a variety of mechanisms can be proposed for the acid-catalyzed rearrangement that differ primarily in the order of bond breaking and bond making.



II. Mechanism of Rearrangement of Haloepoxides.

The thermal rearrangement of 17β-bromo epoxide occurs more rapidly without the solvent than when it was pyrolyzed in the presence of protic solvents.

The thermal rearrangement of XIVa in the presence of sodium acetate does not lead to the formation of acetoxyketones with the incorporation of the acetate. This conforms to the observations of McDonald and Schwab [15] an ionic mechanism B.



B

Table I

Pyrolysis of 3β-Acetoxy-17β-bromo-16α,17α-oxido-5α-androstane, in Different Solvents

Solvents	T °C	Time	Yield %
Acetic acid	110	30 minutes	57
Acetic acid/ sodium acetate	110	1 hour	58
Acetic acid/ sodium acetate	25	12 hours	No reaction
Camphor	150	1 hour	No reaction
Diglyme	150	4 hours	65
Tetramethyl, 2,2,6,6-piperidine	160	2 hours	65

A detailed study of thermal rearrangement in polar solvents and particularly in protic solvents, the 17β-bromo-16α,17α-epoxide XIVa rearranged slower (Table I) [14].

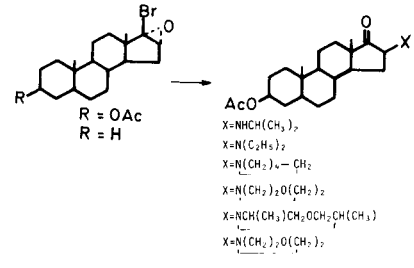
Table II

Melting Points and IR Spectra of 16-Chloro-17-ketones and 16-bromo-17-ketones

Compound No	Mp °C	C=O, Stretching vibrations (cm^{-1})
16α-Br XXVIIIa	166-167	1750, 1725
16β-Br XXIXa	147-148	1750, 1730
16α-Cl XXVIIIb	198-199	1750, 1725
17β-Cl XXIXb	127-128	1750, 1735

Reaction of Bromoepoxides and Acetoxyepoxides with Aliphatic amines.

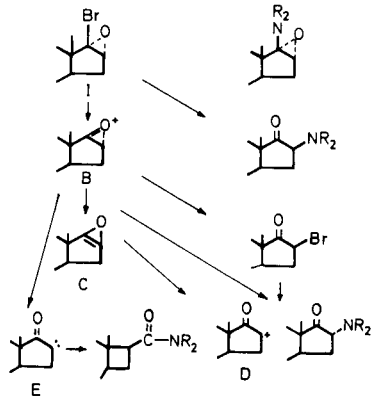
I. 17β-Bromo- or 17β-acetoxy-16α,17α-oxidoandrostane with Amines.



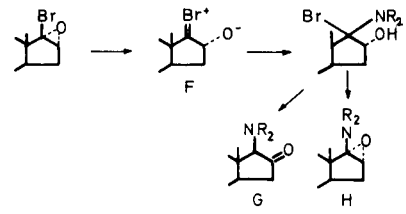
It has been shown that 17β-bromo-16α,17α-oxidoandrostan reacts readily at room temperature with primary or secondary amines to give amino ketones.

Two pathways appear most reasonable for the transformation of 17β-bromo-16α,17α-oxidoandrostane to the corresponding 16β-amino-17-ketone. One involves ionization of haloepoxides to B in analogy to the known behavior of α-haloethers except that intermediate B, as well as the derivable C and D, is expected to be rather unstable. Conversion of B to an α-keto carbene **G** is feasible but this carbene is known to undergo ring contraction to a D-nor steroid system. The other plausible pathway for the conversion of bromo-epoxide to amino ketone is a concerted process with ring opening by amine at C-16 proceeding more or less simultaneously with the expulsion of bromine ion. The following facts speak against an ionization of bromo ketone to amino ketone. Bromo epoxide remains unaffected by silver nitrate indicating that the formation of bromine ion is not a facile process. Also, sodium iodide reacts with bromo epoxide in acetone leading to the corresponding iodo ketone. Consistent with both pathways is the fact that acetoxy epoxide reacts much more slowly with amines than does bromo epoxide (For instance, while brom epoxide is converted to amino ketone by morpholine in 25 minutes at 25°, acetoxy epoxide X remains unchanged on contact with morpholine for 24 hours at 25°).

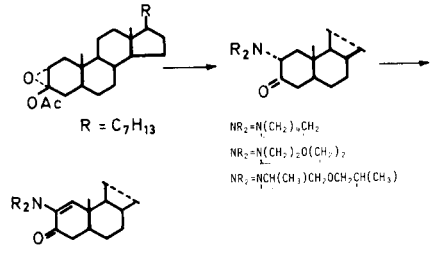
A concerted process with attack by the amine from the β side at C-16 would also be stereochemically consistent with the formation of a 16β-amino-17-ketone. In addition, 17β-acetoxy-16α,17α-oxidoandrostan-3β-ol acetate (X) reacted with morpholine to yield 16β-morpholino-17-ketone.



It is noteworthy that, among the pathways available to the bromoepoxide in its reaction with amines, ring opening leading to intermediate **F** is apparently not involved here since none of biological products **G** and **H** of such an intermediate was observed.



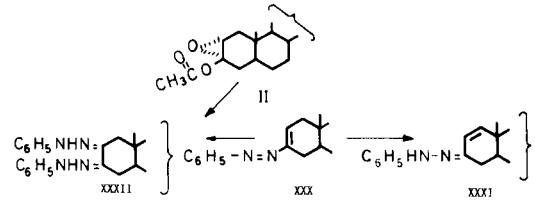
II. 3β-Acetoxy-2α,3α-oxidocholestane with Amines.



3β-Acetoxy-2α,3α-oxidocholestane on heating with piperidine, morpholine, or 2,6-dimethylmorpholine gave the corresponding aminoketones.

The morpholino ketone was very sensitive to air oxidation and became contaminated with its dehydro derivatives, 2-morpholino-1-cholesten-3-one.

Reaction of 2β-Acetoxy-2α,3α-oxidocholestane with Phenylhydrazine.

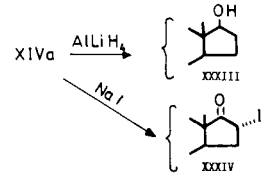


2β-Acetoxy-2α,3α-oxidocholestane(II) was exposed to phenylhydrazine-ethanol producing the yellow 3-phenylazocholest-2-ene (XXX) which isomerized to the colorless phenylhydrazone (XXXI). Epoxide II or azo compound XXX with excess of phenylhydrazine in acidic conditions osazone XXXII was obtained [16-17].

Reactions of 17β-Halo-16α,17α-oxido-5α-androstane.

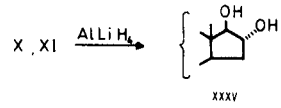
Reduction of 17β-bromo-16α,17α-epoxide or the 17β-chloro-16α,17-epoxide with lithium aluminum hydride produces the 5α-androstane-3β,17β-diol (XXXIII).

The haloepoxides XIVa or XXVIIIa react rapidly with sodium iodide in acetone to give iodoketone XXXIV [14].



Reduction of Acetoxyepoxides.

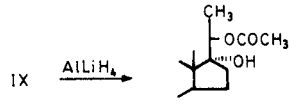
Estriol XXXV was obtained by direct reduction of the epoxyacetate XI using lithium aluminum hydride [4].



XXXV

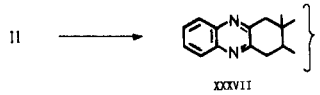
The same method was employed for the reduction of 16α,17α-oxidoandrostane-3β, 17β-diol diacetate for the preparation of 3β,16α,17β-driol [4].

Under the same reaction conditions as for the reduction of epoxides above, epoxide IX was reduced followed by acetylation produced allopregnane-3β,17α,20α-triol 3,20-diacetate [6].



XXXVI

Reaction of 3β-Acetoxy-2α,3α-oxidocholestane with *o*-phenylenediamine.



XXXVII

When epoxyacetate II was rected with *o*-phenylenediamine or substituted *o*-phenylenediamine, cholestano[2,3-*b*] quinoxaline (XXXVII) was obtained [18].

REFERENCES AND NOTES

[1] K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

[2] It. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 2810 (1952).

[3] C. Marshall, H. Kritchevsky, S. Lieberman and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

[4] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

[5] T. Nambara and T. Kudo, *Chem. Pharm. Bull.*, **20**, 2156 (1972).

[6] A. H. Solavay, W. J. Considine, D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2941 (1954).

[7] T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951).

[8] A Hassner and P. Catsoulacos, *J. Org. Chem.* **32**, 549 (1967).

[9] H. Mori and K. Tsuneda, *Chem. Pharm. Bull.*, **11**, 1413 (1963).

[10] J. Fajkos, *Collect. Czech. Chem. Commun.*, **20**, 312 (1955).

[11] K. I. Williamson, J. I. Coburn and M. F. Herr, *J. Org. Chem.*, **32**, 3934 (1967).

[12] T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962).

[13] L. Mamlok and J. Jacques, *Bull. Soc. Chim. France*, 484 (1960).

[14] P. Catsoulacos and A. Hassner, *Bull. Soc. Chim. France*, 717 (1973).

[15] R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **85**, 4004 (1963).

[16] A. Hassner and P. Catsoulacos, *Chem. Commun.*, 121 (1967).

[17] P. Catsoulacos, *Chim. Chronika*, **32A**, 49 (1967).

[18] P. Catsoulacos and N. Kyriakidis, *J. Heterocyclic Chem.*, **12**, 757 (1975).