[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORP.]

The Stereoselective Electrochemical Reduction of Nonconjugated Steroidal Ketones and α-Ketols[1]

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Electrochemical reduction of a number of nonconjugated steroidal nuclear ketones at a stirred mercury cathode afforded the equatorial epimeric alcohol with a high degree of stereospecificity and in good yield comparable to reduction with sodium in alcohol. With α-hydroxy or acetoxy ketols, the hydroxyl function was reductively cleaved and the ketone reduced to an alcohol. Reduction of the $C_{17,20}$ ketols produced mixtures of normal and iso side-chain products in the same ratio as acid or basic equilibration of C_{17}-H, C_{20} keto steroids. Stereospecific reduction did not occur for the C_{20} side-chain ketones but approximately 70% of the C_{20}-β epimer was formed. The stereochemistry of electrolytic reduction of steroidal ketones is compared with chemical methods.

Although a number of investigations have been conducted on the polarographic reductions of steroidal ketones at the dropping mercury electrode,[2] only conjugated or activated derivatives[3] have been reduced. Recently the preparative reduction of several conjugated steroidal ketones at a stirred mercury pool cathode and at controlled potentials have been described.[4] A few saturated nonsteroidal ketones have been polarographically reduced,[5] while at controlled potentials, other aliphatic ketones have been shown to yield secondary alcohols and pinacols depending on the conditions.[6]

Little information is available concerning the stereochemistry of cathodic reductions of ketonic carbonyls although the stereochemistry of a number of carbon-carbon multiple bond electrolytic reductions have been described.[7]

In the case of ketonic substances the activated carbonyl in α-methyldesoxybenzoin was reduced to give exclusively *erythro*-1,2-diphenylpropan-1-ol.[8] The reduction of 2-methylcyclohexanone has been reported to give *cis*- or *trans*- or mixtures of 2-methylcyclohexanol depending on the cathode while 2,6-dimethylcyclohexanone yielded *trans*-2,6-dimethylcyclohexanol with a mercury or lead cathode.[9]

Polarographic studies recently completed in these laboratories[10] have shown a two-electron reduction for saturated steroidal ketones and a four- or six-electron reduction for α-hydroxy or dihydroxy ketols, respectively. Thus, the gross reaction suggested the formation of secondary alcoholic products in both cases as well as the reduction of the α-hydroxy function when present. It was not known, however, whether any consistent stereochemical pattern was followed for different substances or the degree of selectivity of individual reductions. The present work describes the structural and stereochemical characterization of the products obtained from the reductions of steroidal nonconjugated ketones and α-hydroxy ketols.

RESULTS

The results of the electrochemical reduction of eight saturated steroidal ketones and nine *alpha* ketols having keto groups in the steroid nucleus at positions 3, 6, 11, 12, 17, and in the side chain at 20 are summarized in Tables I and II. The nuclear ketones gave stereospecific products while the reduction of the C_{20} ketones, either with pregnenolone or the six α-ketols, resulted in mixtures of the C_{20} isomeric alcohols. The yields were generally 90% or greater. Complete reduction was shown by the lack of carbonyl bands in the infrared spectra of all the products with the exception of the stepwise

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(2)(a) H. Adkins and F. W. Cox, *J. Am. Chem. Soc.*, 60, 1151 (1938); (b) J. Eisenbrand and H. Picher, *Z. physiol. Chem.*, 260, 83 (1939); (c) J. K. Wolfe, E. B. Hershberg, and L. F. Fieser, *J. Biol. Chem.*, 136, 653 (1940); (d) G. Sartori and E. Bianchi, *Gazz. chim. Ital.*, 74, 8 (1944); (e) P. Zuman, J. Tengl, and M. Brezina, *Coll. Czechoslov. Chem. Communs.*, 19, 46 (1954); (f) C. Ricciuti, C. O. Willits, M. E. Wall, and M. M. Krider, *J. Am. Chem. Soc.*, 74, 4461 (1952); (g) P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, 78, 5032 (1956).

(3) V. Prelog and B. Hafliger, *Helv. Chim. Acta*, 32, 2088 (1949).

(4) P. Bladon, J. W. Cornforth, and R. H. Jaeger, *J. Chem. Soc.*, 863 (1958); H. Lund, *Acta Chem. Scand.*, 11, 283 (1957).

(5)(a) M. B. Neiman and Z. V. Markina, *Chem. Abstr.*, 43, 4183 (1949); (b) R. M. Powers and R. A. Day, Jr., *J. Org. Chem.*, 24, 722 (1959); (c) M. von Stackelberg and W. Stracke, *Z. Electrochem.*, 53, 118 (1949).

(6)(a) M. J. Allen, *Organic Electrode Processes*, Reinhold Publishing Corp., New York, 1958, p. 61; (b) G. W. Mansell, *Diss. Abs.*, XX, 2041 (1959).

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(8) L. Mandell, R. M. Powers, and R. A. Day, Jr., *J. Am. Chem. Soc.*, 80, 5284 (1958).

(9) P. Anziani, A. Anbry, and R. Cornubert, *Compt. rend.*, 225, 878 (1947).

(10) P. Kabasakalian and J. McGlotten, *Anal. Chem.*, 31, 1091 (1959).

TABLE I

ELECTROCHEMICAL REDUCTION OF SATURATED KETONES

Starting Material	Product	Yield, %	M.P., °			Optical Rotation, °		
			Crude	Pure	Lit.	Crude	Literature Equatorial	Literature Axial
I-Androstane-17β-ol-3-one	II-Androstane-3β,17β-diol	100	154–155	166–167	168[a] 164[b]	+11.6 (C_2H_5OH)	+4[b] +10.7[c]	+12.6[d]
III-Etiocholane-17β-ol-3-one	IV-Etiocholane-3α,17β-diol	95	229–233	234–236	235–236[e]	+25.1 (C_2H_5OH)	+25[e]	—
V-Δ⁵-Pregnene-17α,21-diol-3,11,20-trione-3,20-bisdioxolane	VI-Δ⁵-Pregnene-11α,17α,21-triol-3,20-bisdioxolane	90	283–285	288–292	299–301[f]	−33.5 (Py)	−31[f]	−52.9[f]
VII-Pregnane-3α,20β-diol-12-one	VIII-Pregnane-3α,12β,20β-triol	89	227–229	228–230	228–229[g]	+29.0 (DMF)	+25.1[g]	+32[h]
IX-22a,5-allospirostane-3β-ol-12-one acetate (Hecogenin acetate)	X-22a,5-allospirostane-3β,12β-diol (β Rockogenin)	91	200–203	212–214	218.5–220[i]	−63.3 ($CHCl_3$)	−63.7[i]	−34.4[i]
XI-Estrone	XII-17β-Estradiol	96	162–166	172–175	176–178[j]	+79 (C_2H_5OH)	+81[j]	+53.8[j]
XIII-Androstane-3α-ol-17-one	XIV-Androstane-3α,17β-diol	93	218–222	222–224	221[d]	+16.2 (C_2H_5OH)	+12.6[d]	—
XV-Pregnenolone	XVI and XVII-Mixture of Δ⁵-Pregnene-3β,20α and β-diols	92	185–193		211° (20β)[k] 183–184 (20α)	−70.9 ($CHCl_3$)	−53.5[k] (20α)	−64.3[k] (20β) −76.9[k] (20β)

[a] L. Ruzicka, M. W. Goldberg, and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935). [b] A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.*, **68**, 2097 (1935). [c] Optical rotation found for androstane-3β,17β-diol prepared from androstane-3β-ol-17-one by reduction with sodium in propanol. See reference 11. [d] A. Butenandt and K. Tscherning, *Z. physiol. Chem.*, 237 (1935). [e] L. Ruzicka, M. W. Goldberg, and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937). [f] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953). [g] Prepared from pregnane-3α,20β-diol-12-one by reduction with sodium in alcohol. There is a difference of 4° in the specific rotation of VIII obtained electrochemically and by sodium reduction. However, the latter material was recrystallized from ethyl acetate and contained 0.5 mole of this solvent (see experimental section). The specific rotation after correction for the solvate is +28.4° (DMF). [h] We wish to thank Mrs. O. Gnoj who prepared this material as well as the starting material, VII, for the reduction. [i] B. Whitman, O. Wintersteiner, and E. Schwenk, *J. Biol. Chem.*, **118**, 789 (1937). [j] R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951). [k] See ref. 15. [l] R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **74**, 2693 (1952).

reduction of androstane-3β,16α-diol-17-one diacetate.

Saturated ketones. Androstane-17β-ol-3-one (I) gave the 3β equatorial isomer, androstane-3β,-17β-diol (II). The melting point, infrared spectrum and specific rotation agreed well with authentic material.[11]

Acetylation of II prepared by electrochemical reduction gave a crude diacetate whose melting point, 125–126°, specific rotation −1.1° (acetone), and infrared spectrum were in good agreement with authentic androstane-3β,17β-diol diacetate,[12] m.p. 125–127°, $[\alpha]_D$ −2° (acetone) but not with androstane-3α,17β-diol diacetate,[13] m.p. 159–160°, $[\alpha]_D$ +12.5°. Paper chromatography of crude II as well as the residue from a recrystallization gave only a single spot with the same R_f as authentic II.

Etiocholane-17β-ol-3-one (III) yielded the 3α equatorial isomer, etiocholane-3α,17β-diol (IV), with physical properties in good agreement with authentic IV. No data are available in the literature for the 3β isomer. Paper chromatography of the crude diol and of the mother liquors from a recrystallization showed only a single spot.

Δ⁵-Pregnene-17α,21-diol,3,11,20-trione 3,20-bisdioxolane (V), with a single reducible ketone group at C_{11}, also yielded the stable equatorial isomer, Δ⁵-pregnene-11α,17α,21-triol-3,20-dione-bisdioxolane (VI). The melting point, specific rotation, and infrared spectrum matched that of VI prepared by sodium reduction of V.[14] Paper chromatographic analysis showed a single spot with the same R_f as the authentic 11α isomer. None of the con-

(11) Initially the stereochemical purity was in doubt as the observed rotation +11.6 (ethanol) agreed with the literature data for the 3α isomer, +12.6 (ethanol), m.p. 221° [A. Butenandt and K. Tscherning, *Z. physiol. Chem.*, 234 (1935)] rather than with the 3β isomer, +4° (ethanol), [A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.*, 68, 2097 (1935)]. However, reduction of androstane-3β-ol-17-one with sodium in alcohol gave a product identical in all respects with the material obtained by electrochemical reduction of I and which had a rotation of +10.7° (ethanol).

(12) D. K. Patel, V. Petrov, R. Royer, and I. A. Stuart-Webb, *J. Chem. Soc.*, 161 (1952).

(13) See footnote *d*, Table I.

(14) See footnote *f*, Table I.

TABLE II

ELECTROCHEMICAL REDUCTION OF *Alpha* KETOLS

Starting Material	Product	Yield, %	M.P., ° Crude	M.P., ° Literature	Optical Rotation, ° Crude	Optical Rotation, ° Literature Equatorial	Optical Rotation, ° Literature Axial
XVIII-Δ^5Pregnene-3β,21-diol-20-one	XVI and XVII-mixture of Δ^5-pregnene-3β,20α and β diols	93	180–197	See Table I, reduction products of Pregnenolone (XV)	−70.2	See Table I, reduction products of Pregnenolone (XV)	
XIX-Δ^5-Pregnene-3β,17α-diol-20-one	XVI and XVII plus some C_{17} iso side chain C_{20} diols	82	175–190	" "	−72.3	"	"
XX-Δ^5-Pregnene-3β,17α,21-triol-20-one	Same as from XIX	94	182–198	" "	−64.4	"	"
XXI-Δ^5-Pregnene,3β,-17α,21-triol-20-one 3,21-diacetate	Same as from XIX	96	177–191	" "	−69.7	"	"
XXII-Δ^5-Pregnene-3β,17α,21-triol-20-one triacetate	Same as from XIX	90	176–188	" "	−68.0	"	"
XXIII-17-Isoallopregnane-3β,17β-diol-20-one diacetate	XXIV and XXV-mixture of allopregnane-3β,20α and β diols, plus some C_{17} iso side chain C_{20} diols	98	171–175	218–219 (20α)[a] 194–195 (20β)[b]	+4	+23[a] (20α)	+2.9[b] (20β)
XXVI-Androstane-3β,16α-diol-17-one diacetate	II-Androstane-3β,17β-diol	95	158–169	168[c]	+10.1 (C_2H_5OH)	+10.7[d] (C_2H_5OH)	−10[e] ($CHCl_3$)
	XXVII-Androstane-3β-ol-17-one	98	159–168	175–176[f]	58.8 (C_2H_5OH)	+10.7[d] (17β-ol)	+95[f] (17-one)
XXVIII-Cholestane-3β,5α-diol-6-one	XXIX-Cholestane-3β,6α diol	93	190–209	216–217[g]	+29.5 ($CHCl_3$)	+38[g]	+13[g]
XXX-22a,5-allo-spirostane-3β,12β-diol-11-one diacetate	XXXI-22a,5-allospirostane-3β,11α-diol	97	215–220	217–218[h]	−69.5 ($CHCl_3$)	−69[h]	−49[h]

[a] W. Klyne and D. H. R. Barton, *J. Am. Chem. Soc.*, **71**, 1500 (1949). [b] W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950). [c] See Table I, footnote (a). [d] See Table I, footnote (c). [e] A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5500 (1958). [f] D. H. R. Barton, *J. Chem. Soc.*, 1116 (1946). [g] P. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944). [h] C. Djerassi, E. Batres, M. Valasco, and G. Rosenkranz, *J. Am. Chem. Soc.* **74**, 1712 (1952).

siderably faster migrating 11β axial isomer was observed.

Electrochemical reduction of pregnane-3α,20β-diol-12-one (VII) gave the 12β equatorial isomer, pregnane-3α,12β,20β-triol (VIII). The melting point and specific rotation of the crude product agreed well with VIII prepared by sodium reduction of VII. There was no mixed melting point depression between the two samples; a significant depression, however, resulted upon mixed melting with the axial isomer, pregnane-3α,12α,20β-triol. The two isomeric triols could not be separated by paper chromatography, although after spotting with antimony trichloride, VIII showed a violet spot with orange fluorescence while the 12α isomer showed an orange spot with green fluorescence.

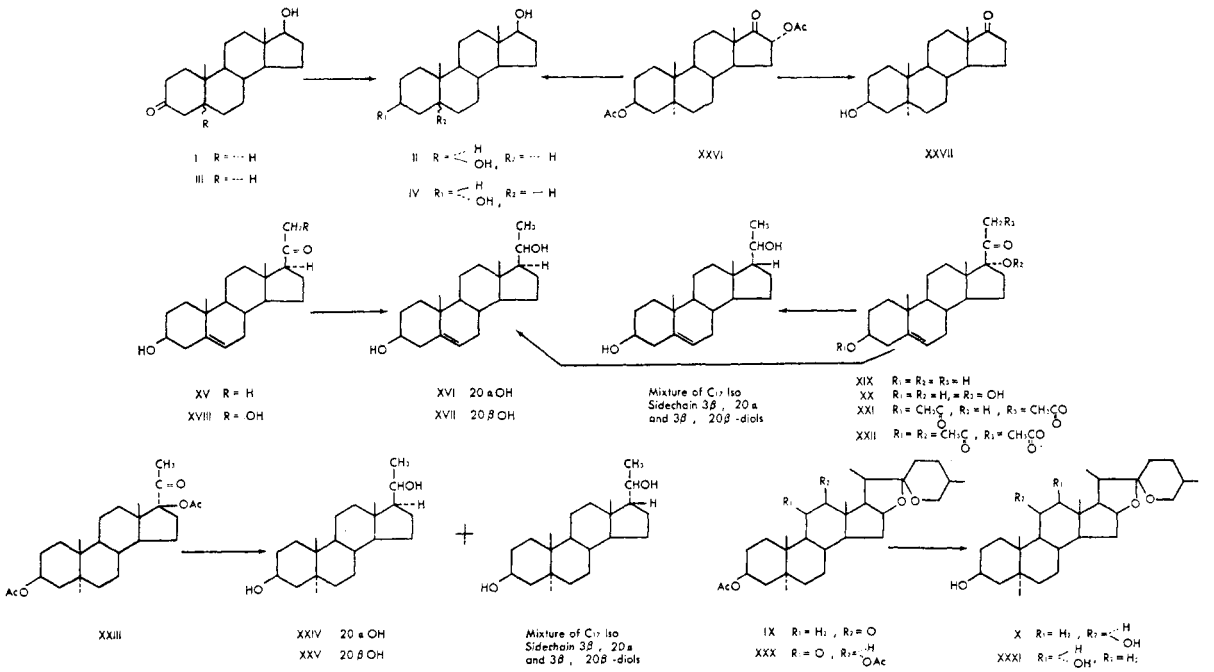
Hecogenin acetate (IX), a C_{12} keto sapogenin, upon reduction also yielded the C_{12} β equatorial alcohol, β-rockogenin (X). Optical rotation and paper chromatography indicated a single reduction product.

Reduction of estrone (XI) yielded β-estradiol (XII). Again, melting point, specific rotation and the infrared spectrum of crude (X) agreed well with the corresponding constants for authentic β-estradiol. Paper chromatography showed two spots for the crude product, a minor component (about 10%) and the major spot with the same R_f as β-estradiol. There was no evidence of the faster migrating α-estradiol when compared with reference compounds.

Similar reduction of androstane-3α-ol-17-one (XIII) afforded androstane-3α,17β-diol (XIV). Physical constants compared well with authentic material XIV. None of the slower migrating androstane-3β,17β-diol (II) was observed by paper chromatography.

The electrochemical reduction of XIII serves to demonstrate that the equatorial hydroxyl group is formed as a result of the electrochemical process and not merely to equilibration in the mildly alkaline reaction mixture since the axial 3α hydroxyl group of the starting material was not converted in any measurable quantity to the equatorial 3β epimer.

Reduction of pregnenolone (XV) gave a mixture of Δ^5-pregnene-3β,20α- and β-diols (XVI and XVII). Comparison of the specific rotation of the



crude reduction product with that of authentic Δ^5-pregnene-3β,20α- and β-diols indicated a mixture of 26% α and 74% β C_{20} isomers.[15] The diol mixture was diacetylated and a similar polarimetric analysis was carried out using the data of Turner and Voitle for the two isomeric Δ^5-pregnene-3β,20 diacetates. By this method the crude diacetate mixture was estimated to contain 30% of the C_{20}-α and 70% of the β isomer.

Quantitative paper chromatographic analysis of the mixture of XVI and XVII obtained from XV together with authentic reference samples indicated 36% of the slower migrating α-isomer and 64% of the faster moving β isomer. Only these two spots were observed.

Alpha ketols. Five hydroxy derivatives of pregnenolone, Δ^5-pregnene-3β,21-diol-20-one (XVIII), Δ^5-pregnene-3β,17α-diol-20-one (XIX), Δ^5-pregnene-3β,17α,21-triol-20-one (XX), Δ^5-pregnene-3β,-17α,21-triol-20-one 3,21-diacetate (XXI), and Δ^5-pregnene-3β,17α,21-triol-20-one triacetate (XXII), all possessing the additional alcoholic group(s) *alpha* to the C_{20} carbonyl, were electrochemically reduced. The $C_{21,20}$-α-ketol, Δ^5-pregnene-3β,21-diol-20-one (XVIII), gave a mixture of XVI and XVII that appeared to be identical with that obtained from pregnenolone as determined from rotation data of the crude diols and diacetates, paper chromatography and infrared spectrum. The other α-ketols in this group all containing a C_{17} α-hydroxyl function yielded the same diols but also some C_{17} *iso side chain isomers. Nevertheless the* physical properties of the latter mixtures differed little from those obtained from XV and XVIII. Paper chromatographic analysis showed two spots for each of the mixtures with the same R_f values corresponding to authentic XVI and XVII, indicating reduction of the C_{17} hydroxyl functions when present. Under the same conditions Δ^5-pregnene-3β,17α,20β-triol migrated more slowly than either components of the reduction mixture.

The infrared spectra showed the complete absence of any carbonyl absorption even for the reduction products of the C_3 acetylated reactants (XXI and XXII)[16] and were quite similar to that of Δ^5-pregnene-3β,20β-diol (XVII). However, the spectrum of XVII is also similar to the C_{20} α isomer (XVI) so that the relative amount of the isomers in the mixture could not be even approximately determined. Reduction of the C_{17} hydroxyl function was further demonstrated by the fact that the crude diacetates of XVI and XVII, prepared by mild acetylation of the reduction products of XIX, XX, XXI, and XXII, showed no infrared hydroxyl absorption.

(15) The specific rotation of Δ^5-pregnene-3β,20β-diol recorded in the literature ranges between $-64°$ and $-68°$. [R. B. Turner and C. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951); P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1927 (1949); W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950).] However, a number of measurements made on two different batches of authentic Δ^5-pregnene-3β,20β-diol resulted in an average value of $-76.9°$ (chloroform). It is this value and $-53.5°$ (chloroform) for Δ^5-pregnene-3β,20α-diol, reported by Turner and Voitle, that have been used to calculate the relative amounts of isomeric C_{20} Δ^5-pregnene-3β,20-diols formed after reduction of pregnenolone and α-hydroxypregnenolones.

(16) In a control experiment pregnenolone acetate was added to an electrolysis solution in which an equivalent amount of acetone had been previously reduced and allowed to stand under no potential for three hours at room temperature. Pregnenolone was isolated in good yield indicating that hydrolysis of the nonreducible acetate was not a direct result of the electrochemical reduction but to the action of base produced by the electrolysis process.

Unsuccessful attempts were made to oxidize directly the mixture of XVI and XVII obtained from XIX to C_{17} normal and isoprogesterone, from which the relative amounts of C_{17} isomers formed during electrochemical reduction could be estimated, but the yields were insufficient for quantitative measurements. After the C_5 double bond was catalytically reduced, however, mild chromic acid oxidation afforded a near quantitative yield of a mixture of C_{17} normal and isoallopregnane-3,-20-diones. No hydroxyl absorption was present in the infrared spectrum and a single spot with the same R_f as allopregnane-3,20-dione was observed on a paper chromatograph. Comparison of the specific rotation data obtained from the crude mixture with that from the authentic C_{17} epimers indicated 74% of the normal and 26% of the iso product.

The relative amounts of XVI and XVII obtained from reduction of the four $C_{17,20}$ α-ketols could not be directly determined due to the formation of some C_{17} isopregnenediols for which rotation data are not available. By analogy with pregnenolone (XV) and Δ^5-pregnene-3β,21-diol-20-one (XIX) it was estimated that approximately 30% of the C_{20} α and 70% of the C_{20} β isomers are formed.

To examine further the stereochemical nature of the reduction, particularly at C_{17}, 17-isoallopregnane-3β,17β-diol-20-one diacetate (XXIII)[17] was reduced to yield a mixture of allopregnane-3β,20α and β-diols (XXIV and XXV) together with some C_{17} iso side-chain diols. Paper chromatographic analysis showed two spots of approximately equal intensity (XXIV and XXV). No unchanged starting material was present. Chromic acid oxidation of the mixture of XXIV and XXV quantitatively led to C_{17} normal and isoallopregnane-3,20-dione. Absence of hydroxyl absorption in the infrared spectrum of this material confirmed the reductive cleavage of the C_{17} acetate. The crude oxidation product although melting only slightly lower than authentic allopregnane-3,20-dione had a rotation of 35° lower than this material. Analysis of the rotation data indicated 80% of the normal and 20% of the isoallopregnane-3,-20-dione. Recrystallization of the mixture from ethanol afforded the pure normal isomer.

The reduction of androstane-3β,16α-diol-17-one diacetate (XXVI)[18] resulted in two different products depending on the experimental conditions. At the more negative potentials, androstane - 3β,-17β-diol (II) was formed. Paper chromatography, optical rotation and infrared spectroscopy data were all consistent with this single product. An attempt was made to reduce only the 16α-acetoxy group since two clearly separated half-waves were observed polarographically.[10] However, a mixture of II and the desired androstane-3β-ol-17-one (XXVII) was isolated. The presence of each of the two materials was confirmed by paper chromatography; the specific rotation indicated 57% of XXVII and 43% of II.

A second nuclear α-ketol, cholestane-3β,5α-diol-6-one (XXVIII)[19] was investigated to determine the stereochemistry of the A/B ring junction after reduction as well as at the C_6 position. The crude product showed properties similar to cholestane-3β,6α-diol, but the melting point and optical rotation were both lower than reported in the literature. Specific rotation data indicated 66% of the 6α isomer. Comparison of rotation data for cholestane-3β,6α- and β-diacetates with that from the crude diacetate indicated 92% of the 6α-isomer. Mild oxidation with chromic acid in acetic acid gave a near quantitative yield of cholestane-3,6-dione, 98%, m.p. 166–172°, $[\alpha]_D$ + 1.1° (chloroform).[20]

The electrolysis of 22a,5-allospirostane-3β,12β-diol-11-one diacetate (XXX), prepared by the method of Elks, *et al.*,[21] reductively cleaved the C_{12} hydroxyl function and afforded the C_{11} equatorial diol, 22a,5 - allospirostane - 3β,11α - diol (XXXI). Paper chromatography of the crude diol showed only a single spot, consistent with the formation of a single isomer. Chromic acid oxidation yielded 22a,5-allospirostane-3,11-dione.[22]

DISCUSSION

Electrochemical reduction of the steroidal nuclear ketones and α-hydroxy ketols at positions 3, 6, 11, 12, and 17 afforded the equatorial alcohol which has unequivocally been shown to be the thermodynamically more stable isomer.[23]

In particular, the observed electrolytic reductions stereochemically parallel the reduction of the analogous steroidal ketones with sodium in alcohol. It is this latter reaction upon which many of the conclusions on relative stability are based. This procedure affords that epimer or mixture of epimers of the same composition as is obtained by direct equilibration of an alcohol with sodium.[24]

(17) C. W. Shoppee, *Helv. Chim. Acta*, 26, 1013 (1943).

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

(19) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, 71, 3938 (1949).

(20) Cholestane-3,6-dione, m.p. 172°, $[\alpha]_D$ +4° (chloroform), D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948); Coprostane-3,6-dione, m.p. 175–179°, $[\alpha]_D$ −79° (chloroform), J. S. Moffatt, *J. Chem. Soc.*, 812 (1947).

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

(22) C. Djerassi, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.*, 76, 5533 (1954).

(23) See the excellent review articles by D. H. R. Barton, *Experientia*, 6, 316 (1950), *J. Chem. Soc.*, 1027 (1953), and W. Klyne, *Progress in Stereochemistry*, Chapter 2, p. 36, Academic Press Inc., 1954, for a summary of the data leading to these conclusions.

(24) G. Vavon, *Bull. soc. chim.*, 49, 937 (1931); W. Hückel, *Ann.*, 533, 1 (1937).

It is unfortunate that in general there is relatively little difference in the specific rotations of the authentic equatorial and axial epimeric reduction products (see Table I) so that rotation data alone are not a very sensitive means for product analysis. However, within the limits of the experimental data a single epimeric alcohol was formed for all the nuclear ketones except for cholestane-3β,5α-diol-6-one.

The formation of cholestane-3,6-dione in quantitative yield after chromic acid oxidation of the crude diol is in good agreement with previous data on the relative stability of the *cis* and *trans* A/B ring fusion as coprostane-3,6-dione upon equilibration with hydrochloric acid in acetic acid has been shown to give cholestane-3,6-dione[25] while the lithium in ammonia reduction of both 5α-chlorocholestane and 5β,6α-dibromocoprostane yielded cholestane.[26] Prelog and Tagman[24] showed that chromic acid in acetic acid oxidation of coprostane-3β,6β-diol yielded coprostane-3,6-dione. Thus, cholestane-3,6-dione obtained in this work is a result of the formation of the *trans* A/B ring fusion during electrochemical reduction and not to isomerization during the oxidation.

Although the electrochemical reduction of C_{20} ketones led to approximately a 1 : 2 ratio of C_{20} α and β epimers in contrast to the highly stereoselective products obtained from nuclear ketones, the results are essentially consistent with those observed with reagents which give equatorial hydroxyl groups for nuclear ketones, *e.g.*, sodium in alcohol reduction of pregnane-3α-ol-20-one and allopregnane-3β-ol-20-one yielded approximately equal quantities of the C_{20} α and β isomers[27] while reduction of *i*-pregnenolone methyl ether with Raney nickel afforded 39% of the C_{20} α and 61% of the β isomers.[28] The estimation of the C_{20} diol isomeric ratio obtained from the $C_{17,20}$ ketols was further complicated by iso side-chain formation. Rotation data for the five such ketols indicated between a 1 : 2 and 1 : 1 ratio of C_{20} α and β isomers, but this is merely a very crude approximation as the analysis was based on a binary mixture.

The amounts of C_{17} normal and iso products arising from electrochemical reduction of such ketols as demonstrated by chromic acid oxidation of the reduction products from 17-isoallopregnane-3β,17β-diol-20-one diacetate (XXIII) and Δ^5-pregnene-3β,17α-diol-20-one (XIX) agreed well with the results obtained from acid or basic equilibration of C_{20} keto steroids.[29]

The novel electrochemical reduction of α-ketols has not been previously reported and offers a general means of cleaving the hydroxyl function in excellent yield. Treatment with zinc in acetic acid has also led to reductive cleavage of the hydroxyl function of α-ketols, as with the axial C_{11} β and C_{12} α-acetoxy $C_{11,12}$ ketols[30] and with $C_{16,17}$ ketols[31] but not with C_{11} or C_{12} equatorial acetoxy ketols of the same cholanic acid series,[29] nor with 3β,12α- or 3β,12β-diacetoxy-22a,5-allospirostane-11-one.[32] In closer analogy to the electrochemical reduction, the latter investigators[31] prepared in good yield 22a,5-allospirostane-3β-ol-11-one from 3β,12α-or 3β,12β-diacetoxy-22a,5-allospirostane-11-one with calcium or barium in ammonia. However, when the 3β,12β-diol was used instead of the diacetate, the 3β,11α,12β-triol was isolated as the major product. No such variations were observed in the electrochemical reductions of the α-hydroxy or acetoxy side chain ketols.

The equilibrium nature of the products obtained in this work indicates a mechanism in which reduction proceeds by direct electron transfer from the cathode with proton abstraction from the solvent.[33] This is consistent with the results obtained for the reduction of 2-methylcyclohexanone.[9] At high overvoltage cathodes such as mercury or lead the more stable *trans*-2-methylcyclohexanol was formed while at a low overvoltage cathode such as copper only the less stable *cis* isomer was isolated. Reduction is believed to take place at the cathode by hydrogen atoms or activated hydrogen molecules in the latter case. This is essentially the mechanism suggested for the reduction of cyclohexene-1,2-dicarboxylic acid at a number of different electrodes including stirred mercury from which only the thermodynamically less stable *cis*-cyclohexane-1,2-dicarboxylic acid was isolated.[7e]

EXPERIMENTAL[30]

Electrochemical reductions. The electrolyses were carried out using a potentiostat of the Lingane-Jones[34] type and the electrolysis cell was similar in design to that used by Pasternak.[35]

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(30) Melting points were taken on a capillary apparatus and were corrected. Infrared spectra were determined as Nujol mulls. Specific rotations were measured at 25° in the following solvents: chloroform, ethanol, dioxane (Di), pyridine (Py), acetone (Ac), and dimethylformamide (DMF).

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The anolyte, prepared by combining 40 ml. of denatured 3 A ethanol, 5 ml. of 1*M* tetrabutylammonium chloride, 3 ml. of 1*M* tetrabutylammonium hydroxide, and 2 ml. of water, was added to the porous alundum cup and allowed to stand in air until the cup became damp on the outside. The catholyte, 19 g. of tetrabutylammonium bromide in 200 ml. of denatured 3 A ethanol and 60 ml. of water, was added to the electrolysis cell together with sufficient mercury to cover the bottom to a depth of 1 cm. After deaerating for 30 min. with nitrogen the alundum cup with a carbon rod anode and the calomel cell were inserted and the stirrer started. The controlled potential was set at −2.6 v. (SCE) for all reductions except for a run at −2.1 v. (SCE) with androstane-3β,16α-diol-17-one diacetate in an attempt to reduce selectively the 16α-acetoxy group. The solution was electrolyzed at this potential until the current decreased to a constant value. The sample, from 0.5 to 1.0 g., was then added in 40 ml. of denatured 3 A ethanol and the electrolysis continued until the current returned to that of the blank.

The electrolyzed material was siphoned off, filtered through Celite, acidified with a little acetic acid, and diluted with water. The ethanol was removed and the volume reduced to about 100 ml. The solids were filtered, washed thoroughly with water, and dried under vacuum to constant weight.

Chemical transformations. All acetylations were carried out at room temperature for 20–24 hr., using a 40 to 50-fold excess of a solution containing one part acetic anhydride and two parts of dry pyridine. Cholestane-3β,6α-diol was oxidized to cholestane-3,6-dione with a 50% excess of chromic acid in 95% acetic acid at room temperature for 18 hr. The mixtures of allopregnane-3β-20-diols were treated in the same manner except for a reaction time of 6 hr. Reductions of ketosteroids with sodium in propanol were carried out as described by Antonucci, *et al.*[14]

Pregnane-3α,12β,20β-triol was prepared in this manner from pregnane-3α,20β-diol-12-one in 95% yield after one recrystallization from ethyl acetate, m.p. 227–229°. A second recrystallization did not change the melting point. The infrared spectrum and combustion analysis indicated that the triol was solvated with 0.5 mole of ethyl acetate.

Anal. Calcd. for $C_{21}H_{36}O_3 \cdot {}^1/_2C_4H_8O_2$: C, 72.59; H, 10.59. Found C, 72.69; H, 10.65.

Paper chromatography. Papergrams were run in toluene-propylene glycol and ligroin (b.p. 60–90°)–propylene glycol. Precut sheets of Whatman No. 1 paper were dipped in 50% propylene glycol–methanol and blotted to dryness. The solvent was allowed to descend 45 cm. (3–5 hr.) or the paper was serrated and run overnight (16 hr.). A saturated solution of antimony trichloride in chloroform was used for the detection of Δ^5,3β-alcohols and 10% phosphomolybdic acid in methanol for saturated alcohols. Quantitative measurements were made with a Photovolt densitometer, model 525, and areas were measured with an Ott compensating planimeter.

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The Lithium Aluminum Hydride Reduction of Some *N*-Substituted Succinimides[1]

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The reduction of a number of *N*-substituted succinimides with lithium aluminum hydride has been studied. In all but one case reduction to the *N*-substituted pyrrolidines occurs smoothly. *N*-Benzhydryl, *N*-*t*-butyl and *N*-phenylsuccinimides undergo ring opening to yield the respective amino alcohols in addition to the normal reduction product. *N*-Tritylsuccinimide gives only *N*-trityl-4-hydroxybutyramide. Several succininamic acids have been reduced to the respective amino alcohols.

It has been reported in the literature[2-5] that *N*-substituted succinimides and *N*-substituted glutarimides, when treated with lithium aluminum hydride (I) undergo reduction solely to the *N*-substituted pyrrolidines and *N*-substituted piperidines respectively. In the course of some other work, it became necessary to reduce *N*-tritylsuccinimide with I. This compound did not undergo reduction in the manner mentioned above. It was therefore of interest to investigate the reduction of a number of *N*-substituted succinimides.

EXPERIMENTAL[6]

N-Substituted succinimides. All the succinimides, except *N*-tritylsuccinimide, were prepared by heating mixtures of succinic anhydride and the corresponding amine for a period of 24 hr.

Isopropylsuccinimide, m.p. 64–65°, lit. m.p. 60°,[7] was obtained in 84% yield.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.86; N, 9.92. Found: C, 59.72; H, 7.75; N, 9.74.

T-Butylsuccinimide, m.p. 49–50°, was obtained in 25% yield. The major product in this reaction was a solid, m.p. 164–166°. No attempt was made to determine the structure

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(3)(a) V. C. Barry and D. Twomey, *Proc. Roy. Irish. Acad.*, **55B**, (1), 1 (1952); (b) C. V. Barry, M. L. Conalty, and D. Twomey, *Proc. Roy. Irish. Acad.*, **55B**, (4), 137 (1953).

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(6) All microanalyses were performed by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium in Max-Planck Institut für Kohlenforschung, Mülheim, Germany. Boiling points and melting points reported herein are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Spectrophotometer Model 137.

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