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Cortical Steroids: Configurations at C_{20} relative to C_{17}

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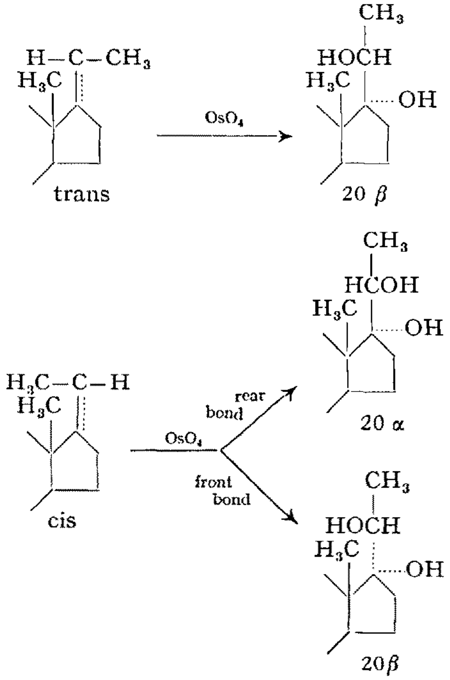
The elucidation of the complex chemistry and stereochemistry of the twenty-eight substances isolated from adrenal cortical extracts and the development of partial syntheses that render the active compounds available for use in medicine is one of the most brilliant and significant achievements of modern science. The existence of hormonal principles in adrenal glandular extracts was discovered in investigations conducted in the United States by Rogoff and Stewart, and by Swingle and Pfiffner, and Americans can also be proud of the very extensive contributions to the chemistry of the cortical steroids made by Kendall, by Wintersteiner and Pfiffner; by Kuizenga and Cartland; by Gallagher, Sarett, and others. However, chemists of all nations can join in praise of the work done in Switzerland, particularly by Reichstein and his able associates, whose masterly contributions to all phases of the problem–isolation, proof of structure, and partial synthesis–have played the leading role in the rapid advancement of the field. Furthermore, the now classical method of Ruzicka for the degradation of the sterol side chain paved the way for most of the initial methods of synthesis, and Meystre and Miescher's remarkable new methods for the degradation of the bile acid side chain have enormously enhanced the efficiency of synthesis. Distinguished research on the problem of structure was done in Switzerland during the war by the English chemist Shoppee, and related contributions of importance to steroid chemistry have been made by Plattner and by Prelog.

The present contribution to a stereochemical detail of the problem is presented in this place as a tribute to Swiss science. Our suggestions are the outcome of work on a revision of the monograph *Chemistry of Natural Products Related to Phenanthrene*. It has been evident from this study that configurational assignments and nomenclature are at the point of another, possibly final, revision. For this reason, and because our proposals of specific configurations at C_{20} require a new convention, we shall present first a general scheme of convention and nomenclature based upon a selection of those systems in current use that seem best adaptable to general application and that, with minor modifications, permit greater simplification and systematization of nomenclature.

Proposed Conventions and Nomenclature

(1) Configurations at nuclear centers of asymmetry relative to the molecule as a whole are designated β if the orientation of the hydrogen atom or a substituent corresponds to that of the two angular methyl groups and the side chain (written above the plane of the ring system; full line), α if the reverse (below the plane; dotted line). The Greek letters are written without parentheses. A purely arbitrary trivial index is written with quotation marks.

(2) The configuration at C_{20} relative to that at C_{17} and the whole ring system is designated α or β according to the following convention for projection formulation:



The projection is best derived from an actual model; carbon atom 21 is swung to the furthest back position, whether the side chain is attached to the front or back of the molecule, and therefore appears in the projection

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in the top position. A given side chain of 20α- or 20β-orientation should make the same contribution to the rotatory power of the molecule as a whole whether attached to the front or the back side of C_{17}.

(3) Arbitrary, non-relative configurations in the side chain are designated a and b. Bergmann and Low[1] established that cholesterol, ergosterol, and stigmasterol correspond in configuration at C_{20} and that ergosterol and stigmasterol correspond in configuration at C_{24}. In reversal of the proposal of these investigators but with the gracious approval of Dr. Bergmann, we propose to describe cholesterol and the bile acids as compounds of 20b-orientation, and ergosterol and stigmasterol as 20b-,24b-compounds. Thus campesterol can be described as 24a-methylcholesterol. The substance arbitrarily named pregnane-3α,20α-diol by Marker[2] according to the present proposal could be called pregnane-3α,20a-diol. The arbitrary, non-relative designations provisionally applied in one series imply no correspondence to those in another.

(4) Where a substance can be regarded as derived from either of two natural or typical compounds, the choice should be guided by the consideration of practical chemical relationship.

Examples. The products of the Oppenauer oxidation of cholesterol and of the dehydrohalogenation of cholestene hydrochloride are called cholestenone and Δ^4-cholestene, not coprostenone and coprostene as suggested by Rosenheim and King[3], and adopted in the Elsevier Encyclopedia. The two oxides of cholesterol are described adequately by their trivial names; thus cholesterol β-oxide is preferred to 5β,6β-oxidocoprostane[4]. The classical name coprosterol violates the spirit of the principle and can be replaced by coprostanol.

(5) A substance differing from a natural or typical steroid in the configuration at an asymmetric center other than C_5 but similarly involving the orientation of a carbon-carbon or carbon-hydrogen linkage is ordinarily described as an iso compound.

Examples. 17-Isoallopregnane, 17-iso-R diacetate, 5-isoandrosterone (instead of the cumbersome 3α-hydroxyetiocholanone-17), 8-isoestradiol (not 8-epiestradiol), 8-isoestrone (not 8-epiestrone), 14-isoequilin (isoequilin-A), *d*-14-isoequilenin (*d*-isoequilenin), 17-isoetioallocholanic acid, 14-iso-17-isoetioallocholanic acid.

Exceptions. Where convenient descriptive trivial names are available, these are preferred: lumisterol, lumiestrone.

(6) The configuration at C_5 in most instances is indicated by classical names: cholestane, allocholanic acid, allopregnane, androstane; coprostane, cholanic acid, pregnane, etiocholane or 5-isoandrostane. The prefix allo is reserved for indication of the configuration at C_5. The name allocholesterol is discarded and replaced by Δ^4-cholestenol-3β.

(7) The configuration of the carbon skeleton should be indicated by the basic name and not merely implied by the orientation of hydroxyl groups.

Example. The compound listed by Salamon and Reichstein[1] as allopregnanetriol-3β,17β,20β is actually a 17-isoallopregnanetriol and should, we think, be so named.

(8) A substance differing from a natural or typical steroid with respect to the steric orientation of a hydroxyl group is ordinarily described as an epi compound.

Examples. Epicholestanol, epitestosterone, 11-epicorticosterone, epiestradiol (the natural hormone can now be called estradiol-17β), 16-epiestriol (not isoestriol-A), 17-epiestriol, 17-epitestosterone, 12-epietiodesoxycholic acid, epiandrosterone (for isoandrosterone), dehydroepiandrosterone (for dehydroisoandrosterone).

The suggested names epiandrosterone, dehydroepiandrosterone, and 5-isoandrosterone are departures from names currently used for three urinary steroids, one of which is also the starting point for many important syntheses. The old names, which would obstruct the systematization suggested, seem to us less descriptive and less convenient than those proposed. Another argument in favor of a change is that there is still no agreement on the name of the unsaturated substance isolated fourteen years ago by Butenandt. The name dehydroandrosterone was originally assigned in ignorance of the fact that the substance is the dehydro derivative of the epimer of androsterone, but the German school never accepted the revision to dehydroisoandrosterone suggested in the first edition of the monograph by one of us. Many workers elsewhere have accepted the suggestion, but others have preferred the third name dehydro-t-androsterone introduced by Ruzicka. We hope that the present suggestion will prove to be an acceptable compromise.

(9) Where the basic name indicates the orientation of one of two groups at C_{17}, an index defining the orientation of the other group is unnecessary. However, the inclusion of the second index may be desirable in instances where an index has recently been reversed, for emphasis, or in order to avoid the implication that the orientation of one of several hydroxyl groups is unknown.

Examples. 17α-Hydroxyprogesterone (natural), 17-β-hydroxy-17-isoprogesterone (synthetic series), 17α-ethinyltestosterone (OH in testosterone is β-oriented), 17α-vinyltestosterone (the trivial name is both more convenient and more informative than 17-iso-$\Delta^{4,20}$-pregnandiene-17β-ol-3-one), estradiol-17β, cholestane-3β,5α,6β-triol.

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[1] W. Bergmann and E. M. Low, J. org. Chem. *12*, 67 (1947).

[2] R. E. Marker and co-workers, J. Am. chem. Soc. *59*, 2291 (1937).

[3] O. Rosenhein and H. King, Chemistry and Industry *53*, 91 (1934).

[4] V. Prelog and E. Tagmann, Helv. chim. acta *27*, 1867 (1944). – Pl. A. Plattner and W. Lang, ib. *27*, 1872 (1944).

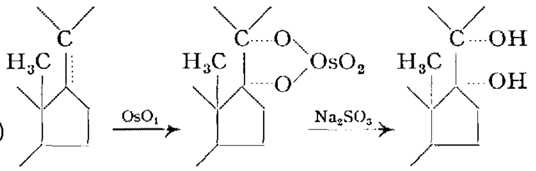
[1] I. Salamon and T. Reichstein, Helv. chim. acta *30*, 1929 (1947).

(10) The position of a double bond, or of a pair of formerly unsaturated carbon atoms, is indicated by a number that locates the first atom of the pair. The number of the second atom is also given if it is not the next higher number. Alternate methods of writing the numbers are given in the examples.

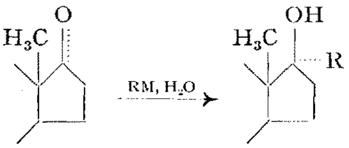
Examples. $\Delta^{7,14}$-Cholestadiene, or cholestadiene-(7, 14); $\Delta^{7,9(11)}$-cholestadiene, or cholestadiene-(7,9:11); $\Delta^{8(14)}$-cholestenol-3β, or cholestene-(8:14)-ol-3β; 22-dihydroergosterol; 5-dihydroergosterol ("α"-dihydroergosterol); 7-dehydrocholesterol; 6-dehydroestrone (Δ^{6}-isoequilin); 9-dehydrocorticosterone; 9-dehydroprogesterone.

Steric Hindrance at C_{17}

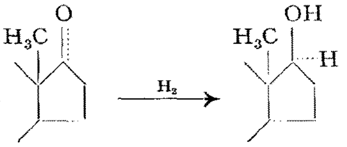
Since the deductions to be presented in the next section are based in part upon a consideration of probable hindrance effects in the determination of the steric direction of synthetic reactions, a review of known instances of such control is in order[1]. Two types of steric hindrance effects associated with position 17 are discernible. One type influences the direction of opening of a double bond extending from position 17. Hydroxylation of a 17-ethylene with osmium tetroxide (a) proceeds in most recorded instances by a path schematically described as the opening of the rear bond (dotted line). The reactions of 17-ketosteroids with Grignard reagents and with potassium acetylide (b) also proceed chiefly by rear-bond attack, and the same is true of reduction (c). The course of these reactions would seem to indicate that more space is available for attack by reagents at the back side of the molecule than at the front side.

(a)


(usual product)

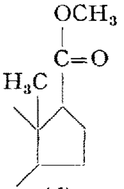
(b)


(chief product)

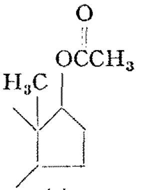
(c)


(chief product)

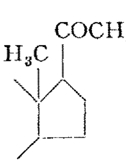
A second set of facts appears to be at variance with the first: β-oriented etio esters (d) and 17β-acetoxy compounds (e) are more easily hydrolyzed than the 17α-epimers; 17β-aceto compounds such as progesterone or pregnanolone (f), and also desoxycorticosterone acetate, are thermodynamically more stable than the 17α-isomers and predominate in equilibrium mixtures; in a (natural) 17α-hydroxy-20-ketone (g) the hydroxyl group is not acylable but the carbonyl group possesses normal reactivity, whereas in a (synthetic) 17β-hydroxy-20-ketone (h) the hydroxyl group is acylable and the carbonyl group in the rear position is scarcely available for reaction. These observations all point to a greater hindrance at the back side of the molecule than at the front.



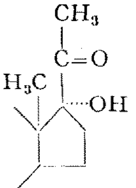
(d)



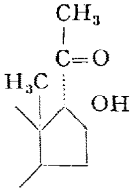
(e)



(f)



(g)



(h)

The two sets of observations refer to phenomena of different types. The opening of a 17-double bond involves an attack at carbon atom 17, and from an inspection of Stuart models we see some rationalization in the observed preference for attack from the rear. The front side of C_{17} is probably nearly the same distance from the angular methyl carbon as the rear side is from carbon atom 12, but the vibrating methyl group can dominate more space than the restricted 12-methylene group and so exert a short-range or bond-hindrance effect. The phenomena of the second type are concerned with groups of functional parts of groups occupying space remote from the immediate environment of C_{17}. The hydrolysis of the esters (d) and (e) proceeds through initial attack of the carbonyl groups, and the acetylation of (h) by severance of the oxygen-hydrogen bond; the isomerization of 17-isoprogesterone to progesterone (f) doubtless involves enolization, but the position of equilibrium must be concerned with the space available for the whole acetyl group in the alternate α- and β-orientations. Thus it seems to be an empirical fact that whereas the back side of the molecule offers better opportunity for attack at the 17-carbon atom, the front side has more space available for the accommodation of a substituent group. We see no explanation of the group-hindrance effect but present the two sets of correlations in evidence of the regularity of the operation of specific hindrance fac-

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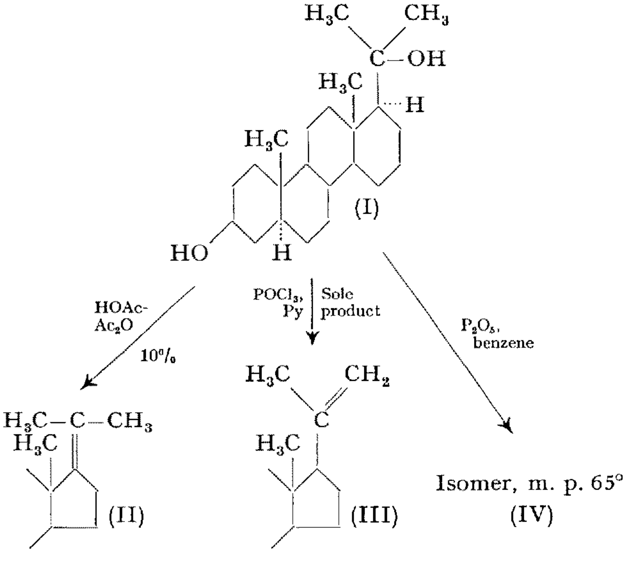
[1] For references, see the reviews by T. Reichstein and C. W. Shoppee, Vitamins and Hormones *1*, 345 (1943). – C. W. Shoppee, Ann. Repts. chem. Soc. *43*, 200 (1946).

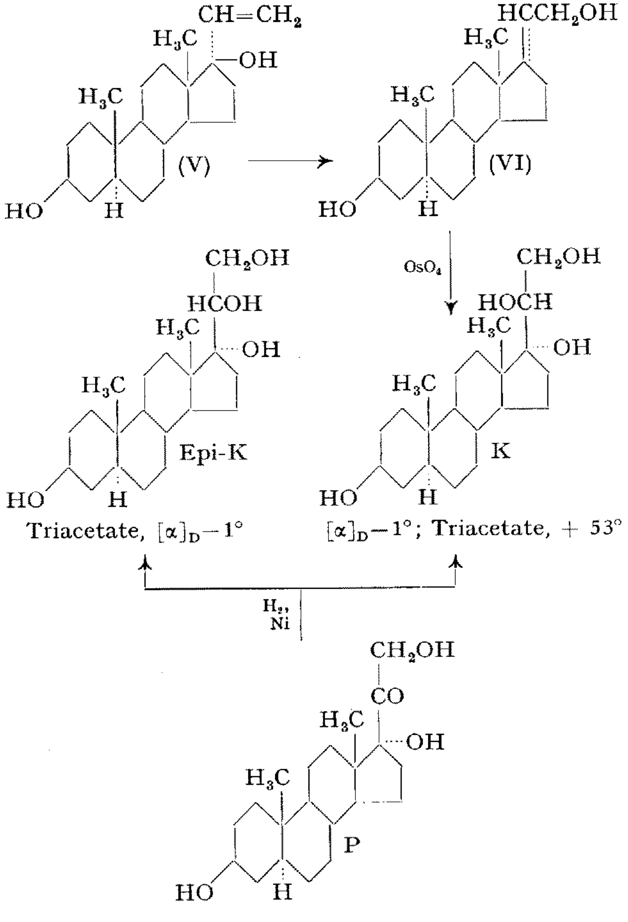
tors; incidentally the correlations strengthen the case for the 17β-orientation of estradiol and testosterone[1].

Configuration at C_{20}

Most of the syntheses of 20-hydroxy compounds proceed by osmium tetroxide hydroxylation of a 17-ethylene obtained either by a dehydration reaction or by allylic rearrangement of a 17-vinylcarbinol. The hydroxylation proceeds by cis addition through a cyclic intermediate, and the experimentally determined orientation of the side chain shows whether the front or rear bond has opened. Hence the configuration at C_{20} relative to C_{17} would follow from a knowledge of the configuration of the 17-ethylene. Although no direct evidence is available, we feel that reasonable inferences can be made. Inspection of models shows that there is an enormous difference in the spatial characteristics of cis and trans 17-pregnenes; the trans structure presents no unusual features, but the cis structure is very strongly hindered, for the methyl group facing the ring system is closely crowded by both the angular methyl group and the 12-methylene group. Evidence is at hand that a substance of so hindered a character is not easily formed. BUTENANDT[2] dehydrated 20-methylallopregnane-3β, 20-diol (I) with acetic acid and acetic anhydride and isolated the 17-ethylene II in about 10% yield along with traces of two isomers, and he has reported similar results in other instances[3] by the same method or by high-vacuum sublimation. KOECHLIN and REICHSTEIN[4] reinvestigated the dehydration of I under various conditions and in no case obtained more than a trace of II. Refluxing with acetic acid gave chiefly (85%) the 20-ethylene III, and III was the sole product of dehydration with phosphorus oxychloride in pyridine and the only substance isolated by high-vacuum sublimation. Dehydration with phosphorus pentoxide in benzene gave chiefly a third, unidentified isomer. Since the structure of the carbinol I permits trans elimination of the tertiary hydroxyl with the tertiary hydrogen at C_{17}, the preponderance of other reactions is a clear demonstration of resistance to the formation of a 17-ethylene with a methyl group cis to the ring system. In one instance[1], even a diphenylcarbinol of structure analogous to I was found to afford on dehydration no material convertible to a 17-ketone by ozonization.



If the 17-ethylene II is formed with difficulty, the same must be true of a cis 17-pregnene. We therefore assume that dehydration reactions that can proceed by normal trans elimination to give either a cis or trans 17-pregnene will yield a preponderant amount of the trans isomer. The allylic rearrangements of 17α-vinyl-17-hydroxy compounds that have been reported all seem to afford a single, sterically pure 17-ethylene. Since the ionic resonance hybrid should be free to give rise to the more stable of the two possible final products, it is probable that these invariably are trans 17-ethylenes.



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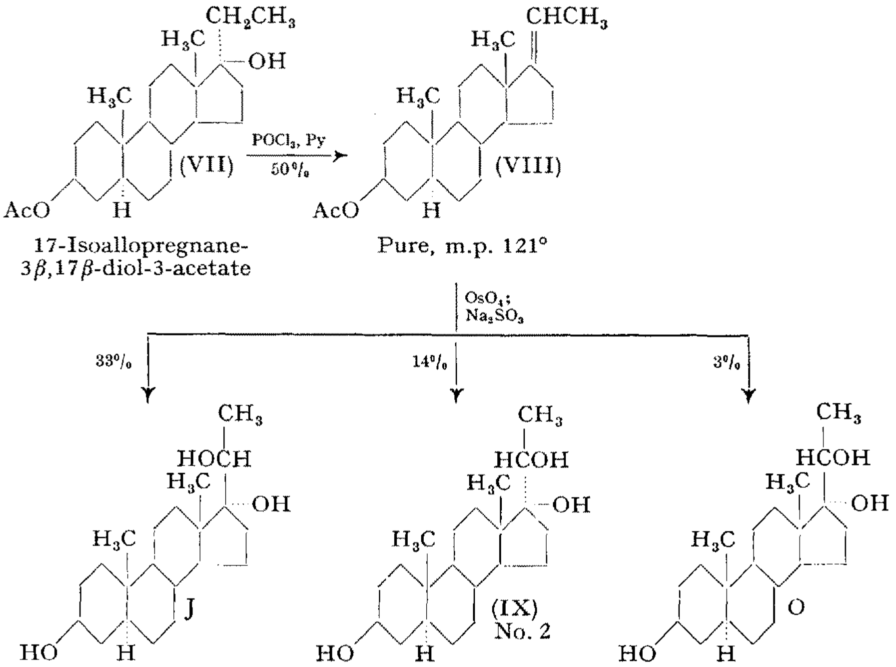
[1] M. W. GOLDBERG, J. SICÉ, H. ROBERT, and PL. A. PLATTNER, Helv. chim. acta *30*, 1441 (1947).

[2] A. BUTENANDT and H. COBLER, Z. physiol. Chem. *234*, 218 (1935).

[3] A. BUTENANDT and G. MÜLLER, Ber. Dtsch. chem. Ges. *71*, 191 (1938).

[4] B. KOECHLIN and T. REICHSTEIN, Helv. chim. acta *27*, 549 (1944).

[1] B. KOECHLIN and T. REICHSTEIN, Helv. chim. acta *27*, 549 (1944).



17-Isoallopregnane-3β,17β-diol-3-acetate

Pure, m.p. 121°

$[\alpha]_D - 8°$
Diacetate, $[\alpha]_D + 25°$

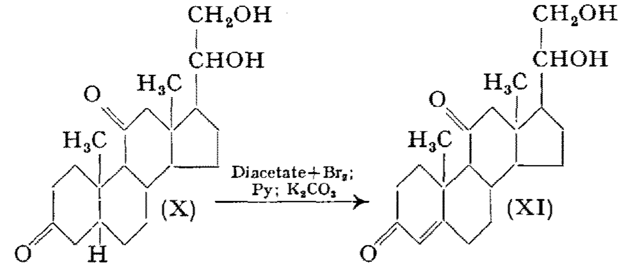
17-Isoallopregnane-3β,17β,20α-triol
m.p. 212°, $[\alpha]_D - 19°$

$[\alpha]_D - 13°$
Diacetate, $[\alpha]_D - 30°$

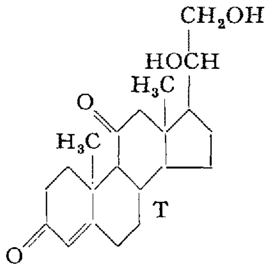
In Serini's[1] partial synthesis of Substance K the allylic rearrangement of V should afford the trans ethylene VI and hence K probably has the 20β-configuration as shown. Substance K, as the triacetate, is distinctly more dextrorotatory than the 20α-epimer prepared[2], with K, by the hydrogenation of P (as triacetate).

Substances J and O, along with a third isomer of the unnatural series, were synthesized by Reich, Sutter, and Reichstein[3] by the hydroxylation of the ethylene VIII resulting from the dehydration of the carbinol VII. This ethylene when fully purified melted at 120—121·5°, but the preparation hydroxylated melted over the range 114—117° and evidently contained both geometrical isomers. Now J and O are known to be C_{20}-epimers with the 17-hydroxyl group in the α-orientation, and therefore they arise by rear-bond opening of the two ethylenes. Since J is formed in ten times as high yield as O, it must have come from the predominating trans ethylene and therefore can be assigned the 20β-configuration. Substance O, then, belongs to the 20α-series and is formed from the cis ethylene in the mixture. The third isomer (IX) was recognized as having an α-side chain by its non-identity with J or O. The configuration shown is based upon evidence to be cited below; the orientation would indicate that the substance arises by front-bond hydroxylation of the trans ethylene.

J-Diacetate and O-diacetate differ in specific rotation by 55°; the difference is of the same magnitude and in the same direction as that between K-triacetate and epi-K triacetate (54°). Thus reasoning based upon two independent syntheses employing different types of reactions both lead to the conclusion that a 20β-hydroxysteroid in an acetylated condition is significantly more dextrorotatory than the 20α-epimer.



	(X) M.p.	(X) $[\alpha]_D$		(XI) M.p.	(XI) $[\alpha]_D$
Diols	A 183°	+68·5°	Diols	A 195°	+176·5°
	B 168°	+61·5°		B 224·5°	+176°
Diacetates	A 181°	+45°	Diacetates	A 154·5°	+133°
	B 175°	+74°		B 208°	+170°



Diol; m.p. 210° (crude)
Diacetate, m.p. 213°

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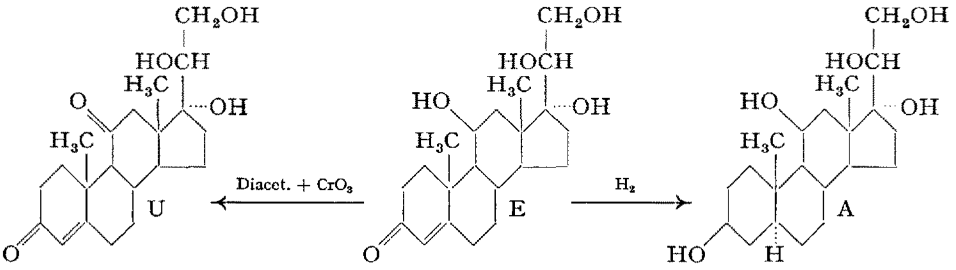
[1] A. Serini, W. Logemann, and W. Hildebrand, Ber. Dtsch. chem. Ges. 72, 391 (1939).

[2] T. Reichstein and G. Gätzi, Helv. chim. acta 21, 1185 (1938).

[3] H. Reich, M. Sutter, and T. Reichstein, Helv. chim. acta 23, 170 (1940).

Sarett[1], in the course of his synthesis of 11-dehydrocorticosterone, reported and characterized two C_{20}-epimers of the formula X; these were derived from a mixture evidently containing the cis and trans 17-ethylenes. Each epimer, XA and XB, was converted through the 4-bromo diacetate into the unsaturated derivative, XIA and XIB. The two pairs of diols have nearly the same specific rotation, but both diacetates of the B-series are significantly more dextrorotatory than their epimers and hence must belong to the *20β*-series. Reichstein's substance T is known from the course of its oxidation[2] to have the structure XI, and it corresponds in melting point and in that of the diacetate reasonably well with XIB and not at all with XIA. Therefore, substance T can be assigned the *20β*-configuration.

In Sarett's first synthesis[3] of 17α-hydroxy-11-dehydrocorticosterone an intermediate 17,20,21-triol proved to be identical with substance U. Since the synthesis proceeded through the allylic rearrangement of a 17α-vinyl-17-hydroxy compound similar to VI above, followed by osmium tetroxide hydroxylation, U like K must belong to the *20β*-series. Two other cortical steroids have been correlated with U by Reichstein and v. Euw[4], who oxidized E-diacetate to a substance identical with U diacetate and hydrogenated E to a substance identical with A; E and A therefore also are *20β*-compounds.



Diacetate, $[\alpha]_D + 178°$ Diacetate, $[\alpha]_D + 163°$ Triacetate, $[\alpha]_D + 74°$

Configurations can thus be assigned to all seven of the known cortical steroids that are asymmetric at C_{20}. Evidence derived from sources that in some instances are completely independent of each other indicate that six of the substances isolated from the adrenal cortex belong to the same stereochemical series (*20β*); the seventh, substance O, is the 20-epimer of J.

Several pairs of C_{20}-epimers of the unnatural series of α-oriented side chain have been prepared synthetically. One pair comprises the 17-isoallopregnanetriol represented above by formula IX and the 20-epimer synthesized by Prins and Reichstein[5]. A recent paper by Salamon and Reichstein[1] summarizes the properties and references to the preparation of this pair of $17\beta,20\text{-}(OH)_2$ compounds and of three pairs of interrelated $17\beta,20,21\text{-}(OH)_5$ compounds differing only in the nature of the ring substitution: saturated 3β-ols, Δ^5-unsaturated 3β-ols, and Δ^4-3-ketones. These will be identified by the serial numbers listed in Table I. Salamon and Reichstein sought to relate the two series by the conversion of the epimeric 20,21-oxides derived from 17α-vinylandrostane-3β-17β-diol into 17,20-diols by hydrogenation and into 17,20,21-triols by hydrolysis. The hydrogenation of one oxide proceeded in part in the desired direction and gave a product identical with Compound No. 1. Alkaline hydrolysis of the same oxide afforded the tetrol No. 3, and this could be reconverted into the original oxide through the 3-benzoate-21-tosylate. Although these results seem to indicate that No. 1 and No. 3 have the same configuration at C_{20}, for example as in formulas XII and XIV, certain other observations made in the course of the research render this conclusion subject to uncertainty. The hydrogenation product XII (No. 1) was accom-

Table I

C_{20}-Epimers of the 17-Isopregnane Series

No.	Salamon and Reichstein, Table p. 1935: «Neue Bezeichnung»	$[\alpha]_D$	
		Free	Acetate
1	Allo-pregnan-triol-(3β,17β,20β)	− 9 Al	− 11 Chf
2	Allo-pregnan-triol-(3β,17β,20α)	− 17 Al	− 18 An
3	Allo-pregnan-tetrol-(3β,17β,20β,21)	0 Al	− 32 An
4	Allo-pregnan-tetrol-(3β,17β,20α,21)	0 Al	0 An
5	Pregnen-(5)-tetrol-(3β,17β,20β,21)	− 73 Di	− 88·5 Di
6	Pregnen-(5)-tetrol-(3β,17β,20α,21)		− 44 An
7	Pregnen-(4)-triol-(17β,20β,21)-on-(3)		+ 22 An
8	Pregnen-(4)-triol-(17β,20α,21)-on-(3)	+ 66 Di	+ 44 Di

Al = Alcohol, Chf = Chloroform, An = Acetone, Di = Dioxane

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[1] L. H. Sarett, J. biol. Chem. *162*, 601 (1946); J. Am. chem. Soc. *68*, 2478 (1946).

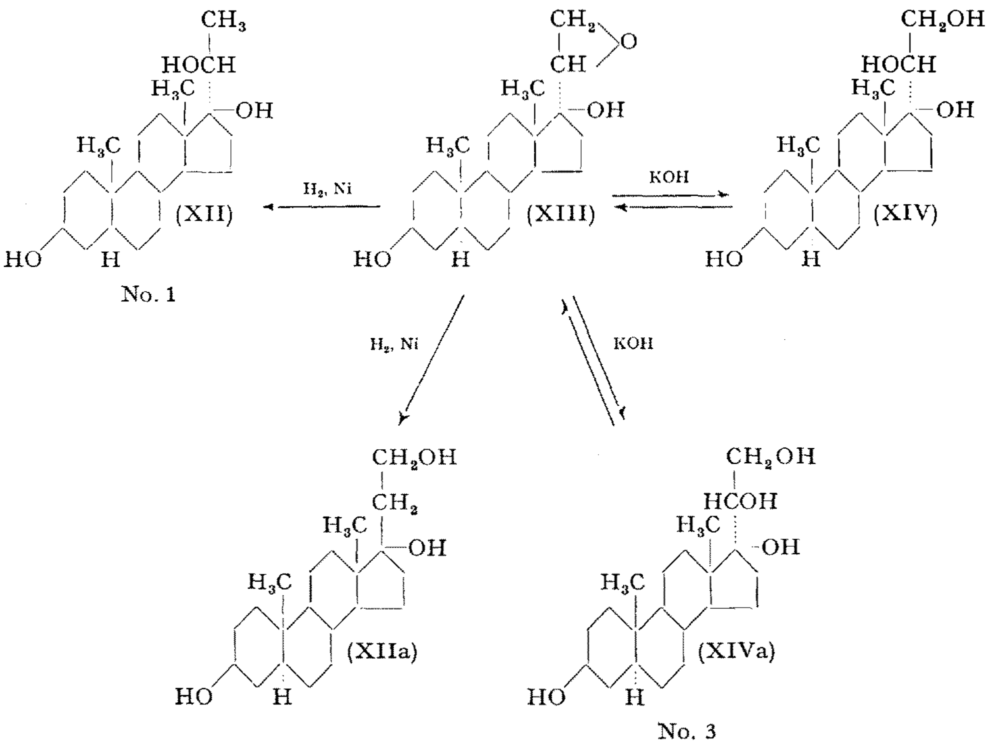
[2] T. Reichstein and J. v. Euw, Helv. chim. acta *22*, 1222 (1939).

[3] L. H. Sarett, J. biol. Chem. *162*, 601 (1946).

[4] T. Reichstein and J. v. Euw, Helv. chim. acta *24*, 247E (1941).

[5] D. A. Prins and T. Reichstein, Helv. chim. acta *23*, 1490 (1940).

[1] I. Salamon and T. Reichstein, Helv. chim. acta *30*, 1929 (1947).



panied by the isomer XIIa, which may have arisen by the opening of the oxide ring in an abnormal direction or, as suggested by SALAMON and REICHSTEIN, through an isomerization of the 20,21- to the 17,20-oxide. The hydrogenation of the epimeric oxide afforded the same abnormal product XIIa and an unidentified abnormal isomer, but none of the expected 17,20-dihydroxy compound. By analogy to the formation of XII and XIIa, the hydrolysis reactions might be expected to proceed either without or with inversion at C_{20}; in one case the evidence indicates that the hydrolysis may proceed through isomerization to the 17,20-oxide. The reconversion of the benzoate-tosylate of No. 3 to the original oxide seems to establish a configurational relationship, but reduction of the tosylate through the 21-iodide gave a product not identical with any of the known, probable products. The evidence from this work that the 3,17,20-triol No. 1 and the 3,17,20,21-tetrol No. 3 have the same configurations at C_{20} does not seem to us as secure as evidence pointing to the opposite conclusion derived from investigations of the Serini reaction: dehydration of a 17,20-diol to a 20-ketone. In examples of the reaction to be discussed in more detail below, Compound No. 8, which has been related through No. 6 to No. 4, the epimer of No. 3, has been shown to undergo the Serini reaction with inversion at C_{17}[1]; on the other hand, the 5-dehydro derivative of No. 2, the epimer of No. 1, reacts without inversion[2]. The two compounds 8 and 2 according to this evidence must belong to opposite stereochemical series, and hence the same must be true of Nos. 1 and 3. We tentatively assume, therefore, that No. 1 belongs to the series represented by Nos. 4, 6, and 8 and that the relationship of the oxide XII to the products derived from it still awaits clarification.

The 17,20,21-triols 4, 6, and 8 are all significantly more dextrorotatory than the epimers, and these substances together with No. 1 are therefore regarded as belonging to the 20β-series. Because of the vicinal effects to be expected where configurational and structural changes are made at adjacent centers, the most reliable means of comparison of members of the synthetic (17-iso) and natural series is with reference to the increment in molecular rotation of the free hydroxy compounds and their typical acetyl derivatives (last column of Table II). Figures representing comparisons in different solvents are inclosed in brackets; for acetone, alcohol, and dioxane the uncertainty due to solvent effect is estimated to be about ± 40 units in $[M]_D$. Some of the compounds listed are discussed in a later part of this article. In the natural series the effect of acetylation of the $17\alpha,20\beta,21$-triols K, A, E, and U is in the range of $[M]_D$ +240 to +410. The acetylation increments for the $20\beta,21$-diols T and XB and for the $17\alpha,20\beta$-diol J are in the range +110 to +130, and in each instance the increment for the 20α-epimer is of opposite sign and is 140 to 220 units more negative. In the 17-isoallopregnane series the acetylation increments for two $17\beta,20\beta,21$-triols are 0 and −40, and those for two $17\beta,20\alpha,21$-triols are −152 and −166. The magnitude of the difference and the close correspondence to that found in the natural series fully

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[1] A. SERINI, W. LOGEMANN, and W. HILDEBRAND, Ber. Dtsch. chem. Ges. 72, 391 (1939).

[2] A. BUTENANDT, J. SCHMIDT-THOMÉ, and H. PAUL, Ber. Dtsch. chem. Ges. 72, 1112 (1939).

Table II

Molecular Rotations of 20-Epimers $[M]_D = \frac{[\alpha]_D \cdot \text{Mol. weight}}{100}$

Type	Compound	$[M]_D$ [a]		$\Delta[M]_D$
		Free	Acetate	Acetylation
20β-Allopregnane Series				
$17\alpha,20,21\text{-(OH)}_3$	Substance K	− 4 Al	+ 258 An	(+ 262)
	Substance A	+ 87[b] An	+ 326 An	+ 239
	Substance E	+ 317 Al	+ 730 An	(+ 413)
	Substance U	+ 508[c] An	+ 800 An	+ 293
	Compound XIX	+ 220 Di	+ 541 Di	+ 321
$20\beta,21\text{-(OH)}_2$	Substance T	+ 610[c] An	+ 732[c] An	+ 122
	Compound XB	+ 214[c] An	+ 320[c] An	+ 116
$17\alpha,20\beta\text{-(OH)}_2$	Substance J	− 27 Al	+ 103 An	(+ 130)
	Compound XXIV	− 251[c] Al	− 140[c] Al	+ 111
20α-Allopregnane Series				
$17\alpha,20\alpha,21\text{-(OH)}_3$	Epi-K		− 5 An	
$20\alpha,21\text{-(OH)}_2$	Epi-T	+ 612 An	+ 594 An	− 18
	Compound XA	+ 239 An	+ 195 An	− 44
$17\alpha,20\alpha\text{-(OH)}_2$	Substance O	− 43 Al	− 132 An	(− 89)
20β-17-Isoallopregnane Series				
$17\beta,20\beta\text{-(OH)}_2$	No. 4 (3-ol)	0 Al	0 An	(± 0)
	No. 6 (Δ^5-3-ol)		− 210 An	
	No. 8 (XV, Δ^4-3-one)	+ 229 Di	+ 189 Di	− 40
$17\beta,20\beta\text{-(OH)}_2$	No. 1 (XII, 3-ol)	− 30 Al	− 46 Chf	(− 16)
20α-17-Isoallopregnane Series				
$17\beta,20\alpha,21\text{-(OH)}_3$	No. 3 (3-ol)	0 Al	− 153 An	(− 153)
	No. 5 (Δ^5-3-ol)	− 256 Di	− 422 Di	− 166
	No. 7 (Δ^4-3-one)		+ 96 An	
$17\beta,20\alpha\text{-(OH)}_2$	No. 2 (IX, 3-ol)	− 57 Al	− 76 An	(− 19)
	Compound XXV	− 341 Al	− 310 Al	+ 31

a Al = Alcohol, An = Acetone, Di = Dioxane, Chf = Chloroform. *b* Calculated from $[\alpha]_{5461}$; nineteen comparisons in this series indicate that $[\alpha]_D$ is 19% (av.) lower than $[\alpha]_{5461}$. *c* Synthetic.

substantiates the configurations assigned. Compounds 1 and 2 differ so little in rotation that comparisons of constants determined in different solvents are not significant; No. 1 does appear to be slightly less levorotatory than the epimer, as expected for a 20β-compound.

The useful synthetic reaction introduced by SERINI[1] is conducted by sublimation of a 17,20-diol 20-acetate from zinc dust; in an improved procedure accredited[2] to MIESCHER the acetate is refluxed in toluene with zinc dust. The free diol reacts in the same way but the yield is lower. In the example investigated by SERINI[1] the diacetate of the 17-isopregnenetriolene No. 8 (XV) was found to afford desoxycorticosterone acetate (XVI). The inversion at C_{17} that occurs in this instance is not associated with the fact that 20-ketones of the 17-iso series are labile with respect to the 17-normal epimers, for SHOPPEE and REICHSTEIN[1] found that Substance A triacetate (XVII) yields the labile, 17-iso ketone XVIII. In a third example of the reaction[2] the triol diacetate XIX used was the derivative of a triol[3] prepared from 17α-vinyltestosterone by allylic rearrangement followed by osmium tetroxide hydroxylation, and it therefore must belong to 20β-series. The transposition of the side chain from the front to the back side of the molecule is thus analogous to the result in the second example cited.

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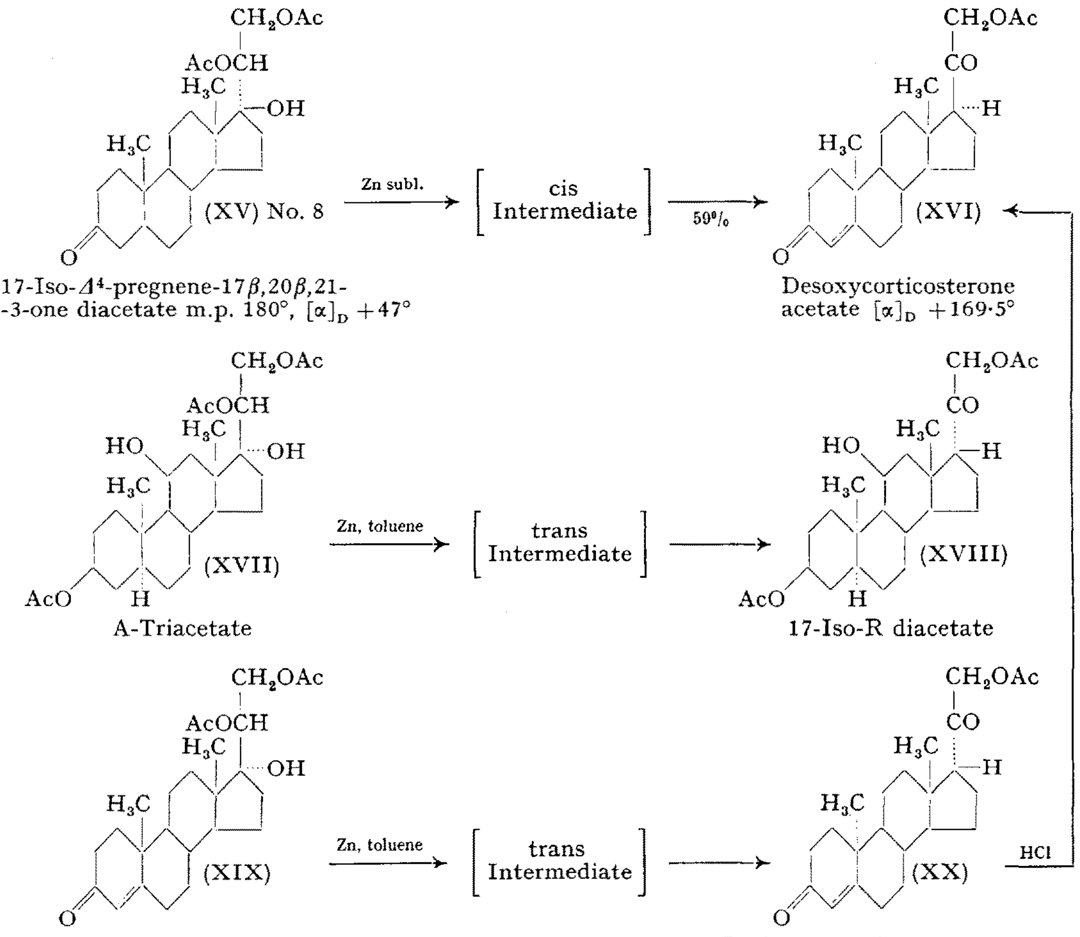
[1] A. SERINI, W. LOGEMANN, and W. HILDEBRAND, Ber. Dtsch. chem. Ges. *72*, 391 (1939).

[2] C. W. SHOPPEE and T. REICHSTEIN, Helv. chim. acta *23*, 729 1940).

[1] C. W. SHOPPEE and T. REICHSTEIN, Helv. chim. acta *23*, 729 (1940).

[2] C. W. SHOPPEE, Helv. chim. acta *23*, 925 (1940).

[3]. L. RUZICKA and P. MÜLLER, Helv. chim. acta *22*, 755 (1939). – W. LOGEMANN, Naturwiss. *27*, 196 (1939).



17-Iso-Δ^4-pregnene-17β,20β,21-triol-3-one diacetate m.p. 180°, $[\alpha]_D$ +47°

Desoxycorticosterone acetate $[\alpha]_D$ +169·5°

A-Triacetate

17-Iso-R diacetate

Δ^4-Pregnene-17α,20β,21-triol-3-one diacetate. Triol.: m.p. 190°, $[\alpha]_D$ +63°

17-Isodesoxycorticosterone acetate m.p. 137°, 174°; $[\alpha]_D$ −26°

One instance of the reaction in which inversion does not occur is in a series of experiments reported by Butenandt[1] and further clarified by Prins and Reichstein[2]. A crystalline and apparently homogeneous 17-ethylene XXIII prepared by the dehydration of the ethylcarbinol from dehydroepiandrosterone on hydroxylation afforded a separable mixture of two triols that were shown to contain the 17,20-glycol grouping by cleavage with lead tetracetate to XXI. Prins and Reichstein found that the triols are converted by hydrogenation into products identical with Substance J and the 17-isopregnanetriol No. 2 (IX), and hence the unsaturated triols are assigned the formulas XXIV and XXV. The nature of the isomers could also be deduced from the mode of their formation. The 17-ethylene prepared by dehydration would be expected to consist solely or largely of the trans isomer XXIII, and the chief product of hydroxylation should be the 17α,20β-diol XXIV resulting from rear-bond attack. The other isomer must arise from front bond hydroxylation of the trans ethylene, in analogy to the formation of Compound IX as a companion of Substances J and O, and therefore should be a 20α-compound of the 17-isoallopregnane series. The fact that the major reaction product XXIV is less levorotatory than the isomer XXV substantiates these deductions.

The diacetates of the isomers XXIV and XXV undergo the Serini reaction and, according to Butenandt, afford the same product, the 17-isopregnenolone XXVI. The reaction of the first isomer XXIV is analogous to the results in the second and third examples already cited, for again a 17α,20β-diol reacts with inversion at C_{17}. The 20α-isomer XXV of the 17-isoallopregnane series, however, reacts without transposition of the side chain from the original position. No evidence is available to reveal the mechanism if the Serini reaction. It may proceed through an enol acetate, a 17,20-oxide, or a cyclic ortho ester. An empirical correlation of the facts can be made on the assumption that the starting material undergoes trans elimination or cyclization to an intermediate that is designated cis or trans according to whether carbon atom 21 is toward the ring system or away from it. The results at hand indicate that a trans intermediate, whether derived from a 20α-compound of the 17-

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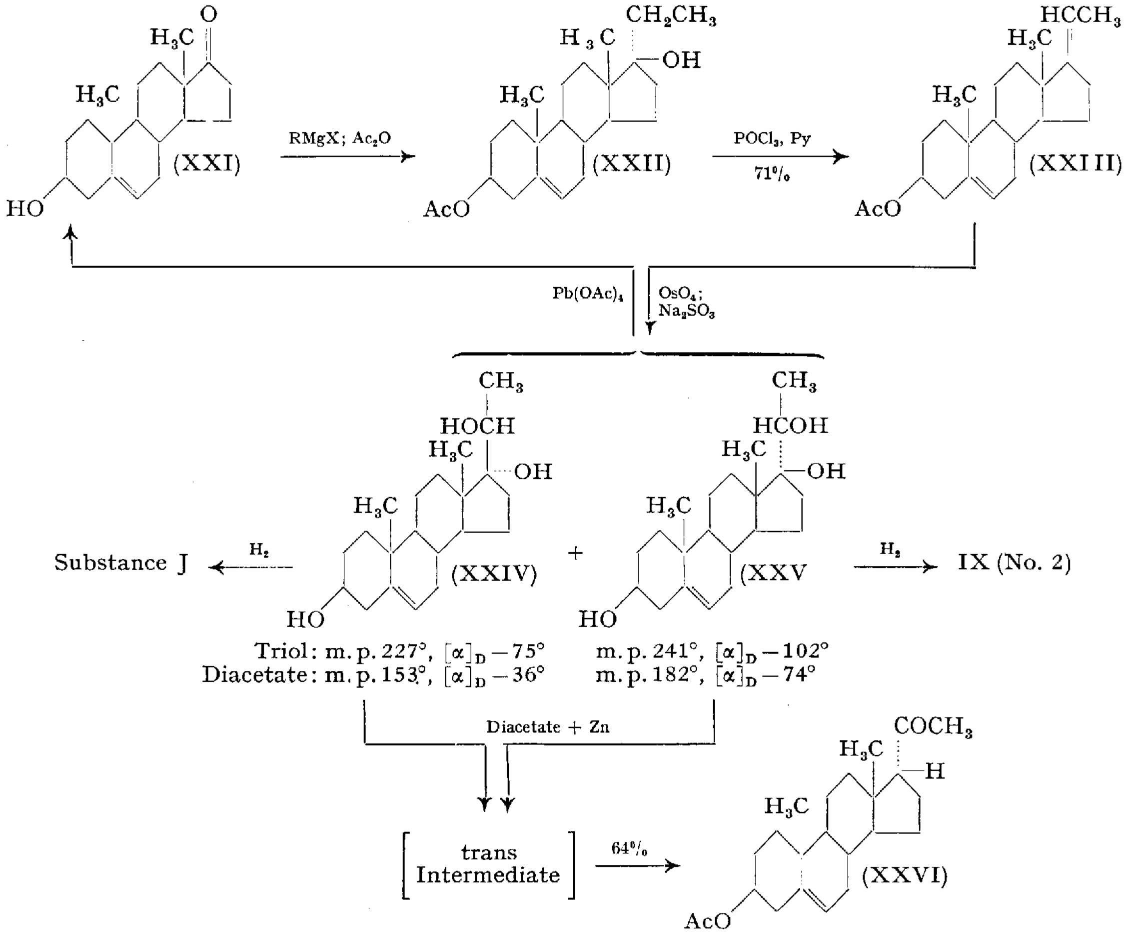
[1] A. Butenandt, J. Schmidt-Thomé, and H. Paul, Ber. Dtsch. chem. Ges. 72, 1112 (1939).

[2] D. A. Prins and T. Reichstein, Helv. chim. acta 23, 1490 (1940).



Triol: m.p. 227°, $[\alpha]_D -75°$
Diacetate: m.p. 153°, $[\alpha]_D -36°$

m.p. 241°, $[\alpha]_D -102°$
m.p. 182°, $[\alpha]_D -74°$

17-Iso-Δ^5-pregnene-3β-ol-20-one acetate
m.p. 171°, $[\alpha]_D$ −126°

normal series (XVII, XIX, XXIV) or from a 20α-compound of the 17-iso series (XXV), affords a final product with an α-oriented side chain; a cis intermediate derived in the one known instance from a 20β-17-iso compound (XV) yields a β-oriented 20-ketone. We would therefore predict, on the basis of the evidence cited, that a 20α-compound of the natural series would react through a cis intermediate without inversion at C_{17}; Substance O, for example, should yield allopregnane-3β-ol-20-one.

On the other hand, the present evidence concerning the Serini reaction may be faulty; the one reported instance of retention of configuration (XVIII) is not well documented and has not been confirmed.

Configuration of Sterols and Bile Acids at C_{20}

Several pairs of 20-epimeric nor and bisnor bile acid derivatives of the normal and 20-iso series have been characterized with respect to optical rotation. If an acid or ester of either series is compared with a 20-hydroxypregnane in terms of Marker's[1] empirical rule for the prediction of configurational relationships on the assumption that the ring system attached to C_{20} has an ordinal number approximately the same as that of an isopropyl group, it is found that substitution of any of these acid or ester groups for the hydroxyl group is not attended with change in configurational series.

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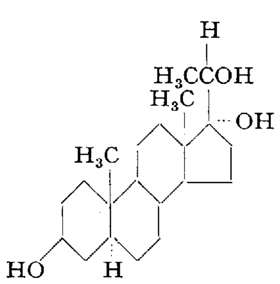
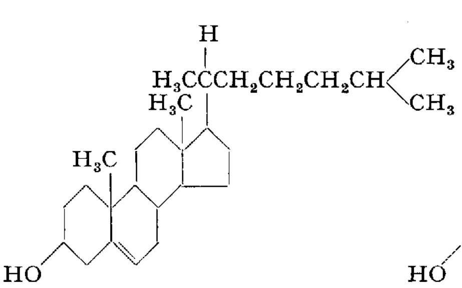
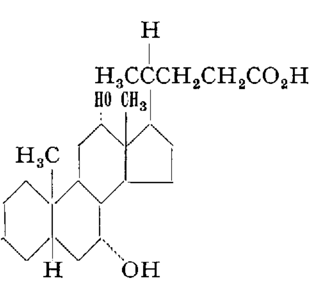
[1] R. E. Marker, J. Am. chem. Soc. *58*, 976 (1936).



Substance J



Cholesterol



Cholic Acid

Table III
3,12-Dihydroxybisnorcholanic Acids

Hydroxyl groups	Derivative	$[\alpha]_D$	
		Normal ser.	20-Iso ser.
$3\alpha,12\beta$	Methyl ester	+38°	+10°
$3\alpha,12\beta$	Methyl ester acetate	+59°	+20°
$3\alpha,12\alpha$	Methyl ester	+40°	+21°
$3\alpha,12\alpha$	Methyl ester acetate	+88°	+101°

Each of four known derivatives of 3β-hydroxynorcholanic acid is slightly more dextrorotatory than the corresponding 20-iso compound[1] (average increment in $[M]_D+14^0$). Three of four of the 3,12-dihydroxybisnorcholanic acid derivatives is more dextrorotatory than the 20-epimer[2] (see table); the one instance of reversal is of minor order. The comparisons as a whole thus indicate that these acidic groupings, and hence the terminal parts of the sterol and bile acid side chains, probably are in the β-orientation.

Note added to proof, July 31, 1948: Since this paper was submitted, Dr. C. W. SHOPPEE has kindly informed us that he has investigated the Serini reaction of Substance 0 diacetate with a result contrary to that predicted above and Dr. HUANG-MINLON in our laboratory has reinvestigated the Serini reaction of the diacetates of triols XXIV and XXV and found that, contrary to BUTENANDT's statement, both substances react with inversion. The apparent discrepancy in the evidence of the configurations of triols Nos. 1 and 2 therefore vanishes and the evidence of SALAMON and REICHSTEIN, coupled with the analysis of molecular rotation differences presented above establishes the configurations: No. 1, 20α; No. 2, 20β. Triol XXV should be formulated as the $3\beta,17\beta,20\beta$-triol; the other assignments of configuration remain valid.

Zusammenfassung

Sieben inaktive Begleit-Corticosteroide, die von REICHSTEIN und anderen aus der Nebennierenrinde isoliert worden sind, enthalten ein Asymmetriezentrum in C_{20}. Es sind bisher sind noch keine Schlußfolgerungen bezüglich der Konfiguration der natürlichen Substanzen in diesem Zentrum relativ zum Rest des Moleküls gezogen worden.

In der vorliegenden Abhandlung wird darauf hingewiesen, daß die Konfiguration an Hand der Betrachtung des Hinderniseffekts, welcher wahrscheinlich den sterischen Lauf der Reaktionen, die zur Partialsynthese der Verbindungen dieser Gruppe angewendet werden, reguliert, mit ziemlicher Sicherheit abgeleitet werden kann. Auf diese Weise sind die Konfigurationen aller sieben natürlichen Steroide festgesetzt und mit den Bezeichnungen der vorgeschlagenen Nomenklatur für die Beschreibung der Konfiguration in C_{20} relativ zu der in C_{17} unter Bezugnahme auf ein zyklisches Zwischenprodukt von festgesetzter geometrischer Orientierung ausgedrückt worden.

Die Konfiguration in C_{20} einiger synthetischer 20-Oxy-Verbindungen der 17-Isoallopregnan- und 17-Iso-Δ^5-pregnen-Reihe sind durch Vergleich mit den entsprechenden 17-Normal-Verbindungen mit Hilfe der Methode des Molekularrotationsunterschiedes nach BARTON abgeleitet worden. Im Falle zweier epimerischer 17-Isoallopregnan-3,β17β,20-triole sind die optischen Eigenschaften nicht entscheidend und zwei Serien von experimentellen Tatsachen scheinen sich zu widersprechen.

Experimentelles Beweismaterial, das erst nach der Fertigstellung dieser Abhandlung beigebracht worden war, zeigt, daß eine der Literaturangaben unrichtig ist, wie in der «Note added to proof» erwähnt worden ist.

In der Abhandlung ist eine Reihe von Vorschlägen für die Standardisierung der Nomenklatur der Steroide eingeschlossen.

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[1] PL. A. PLATTNER and J. PATAKI, Helv. chim. acta *26*, 1241 (1943).

[2] M. SORKIN and T. REICHSTEIN, Helv. chim. acta *27*, 1631 (1944); *28*, 875 (1945).

Warum sterben so wenig Menschen eines natürlichen Todes?[1]

Von R. RÖSSLE[2], Berlin

Dem natürlichen Tode steht der unnatürliche gegenüber. Dabei denken wir aber nicht an den gewaltsamen Tod durch Krieg, Verbrechen und Unfälle, sondern auch an den Tod durch Seuchen, ja durch Krankheiten überhaupt. Denn allzu leicht vergißt man, daß im Grunde der Tod durch ein Krebsleiden oder durch einen Schlaganfall kein natürlicher Tod ist.

Es wiederholt sich in dieser falschen Einstellung zur Frage der Todesursache die allgemeine Regel, daß man geneigt ist, eine pathologische Erscheinung nicht mehr als abnorm anzusehen, wenn sie zur Regel geworden ist. Über diese Verschiebungen des Normbegriffes ließe sich viel sagen. Im vorliegenden Zusammenhang soll nur festgelegt sein, daß der Tod an Krankheiten kein natürliches Sterben ist.

Der physiologische Tod ist die Folge des Erlöschens der Lebenskraft durch den Prozeß des Alterns, der uns in seinem Wesen noch durchaus rätselhaft ist, obwohl wir die im Körper durch das «Vergreisen» gesetzten anatomischen und funktionellen Auswirkungen einigermaßen kennen. Den geheimen Mechanismus des natürlichen Alterstodes kennen wir nicht, nur die in ihrer Seltenheit so großartige Erscheinung des «Hinüberschlafens», das der feinsinnige Maler der Biedermeier-

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[1] Nach einem Vortrag in der Naturforschenden Gesellschaft Basel.

[2] Pathologisches Institut der Universität Berlin.