toluenesulfonyl chloride was allowed to stand overnight at room temperature. The colorless solution was poured on ice and water and the oily precipitate was extracted with ether. The ethereal solution was washed with water, 5% hydrochloric acid, water, 2% sodium bicarbonate solution and dried over sodium sulfate. The solution was concentrated to dryness *in vacuo* and the oily residue dissolved in 25 ml. of benzene. The benzene solution was concentrated to 15 ml. and 15 ml. of dry ether and 6 ml. of a 1.6 *M* lithium aluminum hydride solution in ether added. The mixture was refluxed overnight, treated with a few drops of ethyl acetate and 15 ml. of 6 *N* hydrochloric acid. The aqueous layer was separated, washed twice with ether and the washings combined with the benzene–ether layer. The benzene–ether solution was washed with 10% sodium bicarbonate solution and water and dried over sodium sulfate. The solution was concentrated to dryness *in vacuo* and the residue was crystallized from ether–ethanol to yield 0.14 g. of cholestane (VI), white plates, m.p. 75–77°, negative tetranitromethane test. Chromatography on neutral alumina afforded 0.13 g. of plates, m.p. 79.5–80°, $[\alpha]^{20}D$ +25°, from the fraction eluted with hexane. This material was identical with an authentic sample of cholestane.

The mother liquor from the lithium aluminum hydride reduction was chromatographed on neutral alumina. The fraction eluted with hexane yielded a colorless semi-solid residue which gave a strong positive test with tetranitromethane. The oily crystals were dissolved in 10 ml. of dioxane and shaken under hydrogen in a stainless steel bomb for 24 hours at 150° and 1500 p.s.i. in the presence of 2 ml. of Raney nickel in ethanol. An additional 0.025 g. of VI, m.p. 80–82°, was obtained from this reaction.

5-Cholestene-3β,26-diol-16-one (III).—The mother liquor from the Clemmensen reduction of kryptogenin described above was concentrated to dryness *in vacuo* and the residue chromatographed on benzene-washed alumina to give 2.0 g. of non-crystalline material from the fractions eluted with benzene–chloroform 9:1 and 6:1. This material could not be crystallized and was discarded. From the fraction eluted with benzene–chloroform 1:1 was obtained 0.3 g. of **5-cholestene-3β,26-diol-16-one** as white plates, m.p. 170–171°, $[\alpha]^{20}D$ −156°, $\nu_{max}^{CHCl_3}$ 3623 cm.$^{-1}$ and 3448 cm.$^{-1}$ (hydroxyl), 1736 cm.$^{-1}$ (carbonyl on a five-membered ring).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.84; H, 10.65. Found: C, 77.96; H, 10.78.

The **diacetate** was crystallized from methanol; m.p. 114–116°, $[\alpha]^{20}D$ −118°.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.56; H, 9.43.

The **oxime** was crystallized from methanol; m.p. 193–196°, $[\alpha]^{20}D$ −73° (EtOH).

Anal. Calcd. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51; N, 3.25. Found: C, 75.25; H, 10.75; N, 3.24.

When 0.1 g. of III, 0.01 g. of Adams catalyst and 25 ml. of acetic acid was shaken with hydrogen at room temperature and pressure for two hours, 0.08 g. of **tetrahydrotigogenin (IX)** was obtained (from ethyl acetate), m.p. 199–200°, identical with an authentic sample.

Treatment of III with sodium borohydride in aqueous methanol, as described above for the reduction of the mixture of II and III, yielded tetrahydrodiosgenin (IV) in 80% yield.

When III was subjected to Wolff–Kishner reduction, as described above for the preparation of II, an 85% yield of 5-cholestene-3β,26-diol (II) was obtained.

5-Cholestene-3β,16β-diol (X).—Tetrahydrodiosgenin (IV) (0.3 g.) was tosylated and reduced in exactly the same manner as described above for the preparation of VII from V. The resulting crystalline residue was chromatographed on benzene–chloroform (7:1) washed alumina. The fraction eluted with benzene–chloroform 6:1 was crystallized from dilute methanol to yield 0.08 g. (27.7%) of analytically pure, white needles of **X**, m.p. 176.5–178°, $[\alpha]^{20}D$ −33°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.38; H, 11.39.

Further elution with benzene–chloroform (3:1 and 1:1) yielded 0.17 g. of starting material after crystallization of the combined fractions from dilute methanol.

The **diacetate** of X was obtained as colorless plates from methanol; m.p. 174–176°.

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.23; H, 10.39.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

Reactions of B-Norcholesterol

BY WILLIAM G. DAUBEN AND GERHARD J. FONKEN

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The preparation of B-norcholesterol and the intermediates used in its preparation, as reported earlier by Sorm and Dykova, was investigated and the structures unequivocally established. Various transformations of this modified sterol involving oxidation, reduction and *i*-ether formation were studied. The results obtained showed that in this nucleus with a 5-membered B-ring, the *trans–anti–trans* arrangement is the stable configuration. The rate of acetolysis of the tosylate was found to be approximately half that of the cholesterol derivative. Comparison of molecular rotational differences in this series with those of the cholesterol series is given.

In recent years, it has become increasingly evident that, by modification of the natural steroid hormones, it is possible either to increase or decrease certain physiological properties of this series of compounds. Such modifications as expansion of ring D to a six-membered ring,[1] contraction of ring A to a five-membered ring,[2] removal of the angular methyl group at C_{10}[3] or C_{13},[4] introduction of different functional groups, such as double bonds,[5–8] methyl groups[9] or fluorine atoms,[9,10] into the nucleus are examples of the types of structural changes which have been studied. To date, no investigation has been reported which has studied how critical the sizes of rings B and C in the

(1) *Cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., pp. 328, 377.

(2) B. B. Smith and H. R. Nace, THIS JOURNAL, **76**, 6119 (1954).

(3) L. Miramontes, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3540 (1951); A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954).

(4) W. S. Johnson, H. Lemaire and R. Pappo, *ibid.*, **75**, 4866 (1953).

(5) Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **32**, 1978 (1949).

(6) R. F. Hirshmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, THIS JOURNAL, **77**, 3167 (1955).

(7) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955).

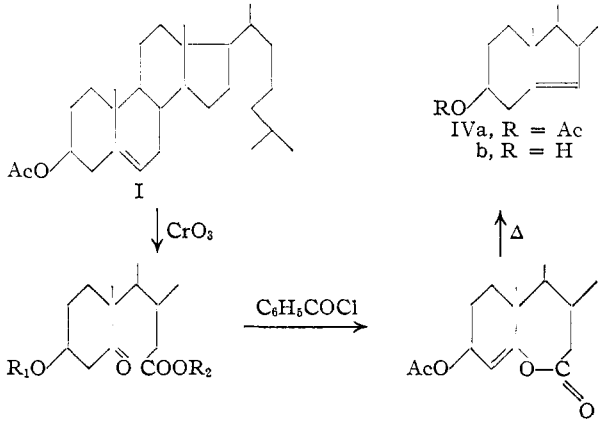
(8) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(9) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955).

(10) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953); **76**, 1455 (1954).

steroid hormones are to biological activity. In order to obtain information in this regard, it would be of interest to find a type of nucleus which is closely related to the various hormones with regard to the presence of functional groups so that the standard chemical transformations could be performed.

In 1948, Sorm and Dykova[11] reported the preparation of B-norcholesterol (IV) by an interesting sequence of reactions. They found that when cholesteryl acetate (I) was oxidized in the usual fashion with chromium trioxide in acetic acid, in addition to the isolation of 7-ketocholesteryl acetate, the keto-acid IIa, 3-acetoxy-5-oxo-5,6-secocholestane-6-oic acid, resulting from the fission of the double bond between carbons 5 and 6 could be isolated in crystalline form. When this keto-acid IIa was allowed to react with benzoyl chloride in pyridine, it was transformed into a neutral com-

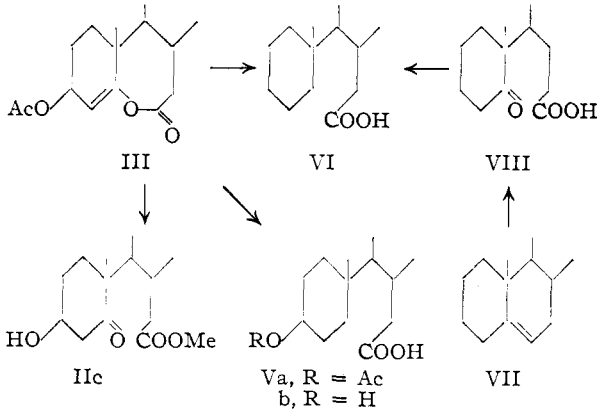


pound formulated as the enolic seven-membered lactone III, 3-acetoxy-5-hydroxy-5,6-secocholes-4-ene-6-oic acid 5,6-lactone. This enol lactone, upon being heated to its melting point, was reported to lose carbon dioxide and form B-norcholesteryl acetate (IVa). These workers called attention to the interesting transformation to a seven-membered enol lactone and the unique formation of the olefin with loss of carbon dioxide and offered the following evidence in support of their assigned structures. First, with regard to the lactone, it was found that the compound lacked a titratable carboxyl and failed to react with diazomethane, its ultraviolet spectrum resembled vinyl acetate (CH_2=CH–O–$COCH_3$) and not ethyl acrylate (CH_2=CH–COOEt) and the ester acetate of keto-acid IIb failed to form the lactone. Second, with regard to B-norcholesteryl acetate, the compound could be hydrolyzed to an alcohol which, in turn, could be oxidized to an unsaturated ketone, the alcohol formed a monoepoxide and it also could be hydrogenated to a dihydro derivative. These series of reactions clearly established the nature of the functional groups present in the products III and IV but did not unequivocally establish their structures.

(11) F. Sorm, *Collection Czechslov. Chem. Communs.*, **12**, 437 (1947); F. Sorm and H. Dykova, *ibid.*, **13**, 407 (1948).

In view of these interesting transformations performed in arriving at B-norcholesterol, the chemistry of II, III and IV was examined, in detail, so that one could both evaluate the synthetic sequence and establish the structures of the compounds. Attention was first directed toward the acetoxy-keto-acid IIa. As was reported by Sorm and Dykova,[11] it was prepared in 24% yield by the oxidation of cholesteryl acetate (I). The infrared spectrum of the acid was complex in the carbonyl region of 5.7–6.0 μ since the carboxyl band overlapped that of the acetate and the six-ring ketone. The material upon hydrolysis of the acetyl group followed by esterification of the carboxyl group with diazomethane yielded a crystalline ester IIc, the infrared spectrum of which clearly displayed bands characteristic of the hydroxyl, six-ring ketone and carbomethoxy groups. Establishment of the carbon skeleton of the keto-acid as well as the lactone III, which was prepared as described by Sorm and Dykova,[11] was achieved by conversion of the lactone to a compound of established structure and by methanolysis of the lactone III back to the methyl ester of keto-acid IIc.

Degradation of the lactone III to a compound possessing a readily established structure appeared to be possible by many routes, but since the des-hydroxy-des-keto acid VI, 5,6-seco-cholestane-6-oic acid, could be prepared readily in a straightforward manner, this latter compound appeared to be the best reference material. The presence of both an enolic lactone and an allylic ester in III

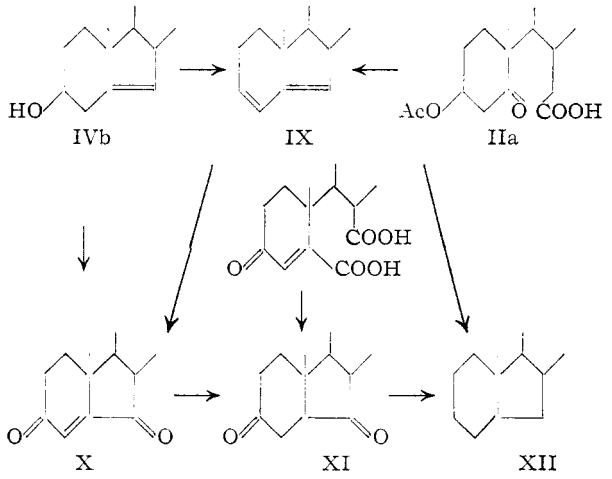


suggested that it should be possible to make this conversion by a one-step hydrogenation since it is well established that both such groupings undergo hydrogenolysis.[12] When the lactone III was hydrogenated in acetic acid over platinum, however, only hydrogenolysis of the enol lactone occurred and the acetoxy acid V, 3-acetoxy-5,6-secocholestane-6-oic acid, was obtained. Quite surprisingly, when the reaction was conducted in ethanol in the presence of palladium-on-strontium carbonate, hydrogenolysis of both groupings took place and the desired acid, VI, was isolated. It was found to be identical with the acid prepared from Δ^5-cholestene (VII) by ozonolysis to the keto-acid

(12) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **87**, 601 (1930); **93**, 139 (1931); W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941); H. Adkins and R. L. Shriner, Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, Chapt. 9, p. 820.

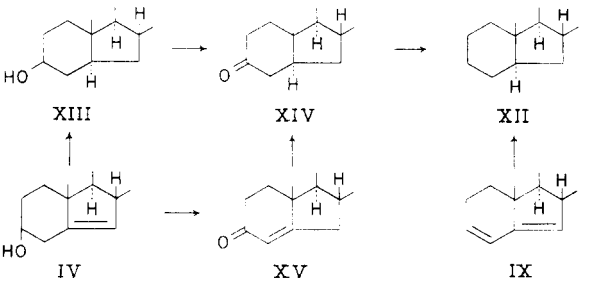
VIII which, in turn, was reduced by a Wolff–Kishner reaction. This degradative reaction sequence not only showed the carbon skeleton but clearly established the exact nature of the functional groups in lactone III to be as postulated by Sorm and Dykova.[11]

With regard to the structure of B-norcholesterol IVb, the main features to be established were the carbon skeleton and the interrelationship between the hydroxyl group and the double bond. The carbon skeleton was determined by preparation of



B-norcholesta-3,5-diene (IX) from the alcohol IVb on heating with boric acid.[13] Since this same diene also is formed by pyrolysis of the keto-acid II, the basic structure of IX must be assigned to the B-nor series. The previous workers[11] have oxidized B-norcholesterol by the Oppenauer procedure to an α,β-unsaturated ketone which could not be obtained crystalline and was only characterized in the form of a solid semicarbazone. In the present work, this ketone (XV) was obtained as a pure crystalline solid. The material had an ultraviolet spectrum identical with that of cholestenone but such an α,β-unsaturated ketone could arise from either an α,β- or β,γ-unsaturated alcohol. That the latter is, indeed, the case was shown by the fact that the B-norcholesterol was stable toward oxidation by manganese dioxide under conditions which rapidly converted cholest-4-en-3-ol to cholestenone.[14] When the alcohol IVb was oxidized with potassium dichromate, the enedione X was formed. Also, the diene IX upon oxidation with chromium trioxide yielded the same compound. The preparation of the same enedione from these two compounds further established the β,γ-relationship between the hydroxyl group and the olefinic linkage in IVb. When the enedione X was reduced with zinc and acetic acid, the known saturated dione XI[15] was formed. Fieser has reported that reduction of the diketone XI under Wolff–Kishner conditions gives rise to the saturated hydrocarbon XII and the identical hydrocarbon was obtained by hydrogenation of diene IX in acetic acid over platinum. Thus, the structure IVb assigned by Sorm and Dykova to B-norcholesterol is correct.

The transformations performed with B-norcholesterol not only clearly established the basic structure of the compound but also yielded information in regard to the stereochemistry of the compound prepared. Since in all of the reactions reported carbon atoms 3, 9 and 10 were not affected, these three centers must have the same configuration they possessed in cholesterol, *i.e.*, 3β, 9α and 10β. The configuration at carbon 8 can be assigned as β on the basis of the following evidence. The formation of the diene IX by the pyrolysis of the keto-acid II should not affect the configuration of C_8 which existed in the original cholesterol. Hydrogenation of the diene IX then should yield a hydrocarbon XII in which C_8 is β. This same hydrocarbon was prepared by the hydrogenation of B-norcholesterol to the saturated alcohol XIII which, in turn, was oxidized to the saturated ketone XIV and then reduced by the Wolff–Kishner reaction. In this last sequence of reactions, C_8 remains unchanged and since this center possesses a



β-configuration in XII, the same configuration must be assigned to that carbon in B-norcholesterol IV, the saturated alcohol XIII and the saturated ketone XIV.

The configuration of C_5 in the saturated series is most interesting, since here, as in the C/D ring juncture, one has a five-membered ring fused to a six-membered ring. Previously, Fieser[15] has assigned an A/B *cis* configuration to the saturated hydrocarbon XII, prepared by Wolff–Kishner reduction of the diketone XI. Under such reaction conditions, the more thermodynamically stable isomer should be formed and the *cis* assignment evidently was based on the assumption that in the hydrindane series, the *cis* is the more stable arrangement. Such an assumption is open to question for the thermodynamically stable configuration of either a simple or a complex hydrindane derivative varies, unpredictably, with small changes in structure.[16] On the basis of the present work, however, it has been possible to arrive at a stereochemical assignment which does not depend upon an assumed thermodynamically stable arrangement. As pointed out above, the configuration of the backbone carbon atoms in B-norcholesterol are the same as those in cholesterol, *i.e.*, *anti–trans–anti*. It is reasonable to assume that the steric course of hydrogenation of the Δ^5-bond in acid solution will be the same in both compounds. If such be the case, a C_5–β configuration (A/B *trans*) must be as-

(13) W. Brandenberg and A. Galat, THIS JOURNAL, **72**, 3275 (1950).

(14) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953).

(15) L. F. Fieser, *ibid.*, **75**, 4386 (1953).

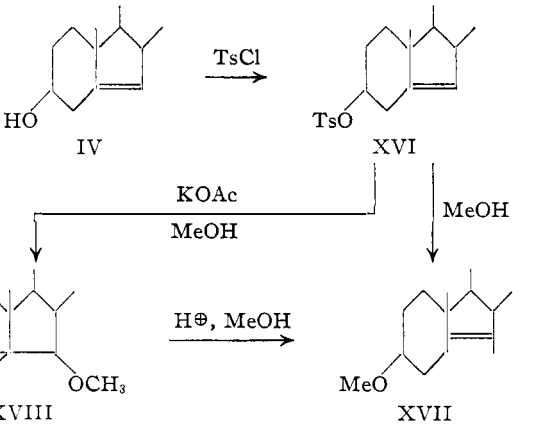
(16) E. L. Eliel and C. Pillar, *ibid.*, **77**, 3600 (1955).

signed to the A/B ring juncture of B-norcholestanol XIII since the hydrogenation of cholesterol yields cholestanol (A/B *trans*).[17] Since the conversion of this saturated alcohol to the ketone XIV and, in turn, to the parent hydrocarbon XII which is identical to that prepared by Fieser,[15] would not affect the A/B ring configuration, the *trans*, and not the *cis* as assumed by Fieser,[15] must be assigned to the entire saturated series. In accordance with this assignment, 3,5-B-norcholestadiene (IX) was hydrogenated in high yield to the same B-norcholestane XII and, again in analogy with the cholesterol series, 3,5-cholestadiene yields mainly (80%) of cholestane upon hydrogenation under acid conditions.[18]

Further evidence for this *trans* A/B ring juncture in the B-norcholestanol XIII was obtained by examination of the infrared spectrum of the acetate ester of the sterol. It has been shown by various investigators[19] that the acetate of a 3-hydroxyl of a sterol shows a single strong band in the 1200–1300 cm.$^{-1}$ region when the group is equatorial and two or three strong bands when the group is axial. The hydroxyl group of B-norcholestanol must have a β-configuration, based on the method of synthesis, and as such would be equatorial if the A/B configuration is *trans* and axial if the juncture is *cis*. The infrared spectrum of the acetate of XIII showed a single strong band at 1242 cm.$^{-1}$, as compared to a value of 1243 cm.$^{-1}$ for cholestanyl acetate, which indicated the equatorial nature of the C_3-hydroxyl group and the A/B *trans* configuration for the rings. In the 1000–1100 cm.$^{-1}$ region, it has been shown that two strong bands appear for 3-hydroxyl sterols and when the group is *trans* to the C_5–H, the bands appear at 1040 and 1075 cm.$^{-1}$, respectively, while when the group is *cis* to the C_5–H, the bands shift to 1000 and 1040 cm.$^{-1}$, respectively.[20] B-Norcholestanol displayed bands at 1040 and 1076 cm.$^{-1}$, respectively, characteristic of a hydroxyl group which is *trans* to the C_5–H, a result consistent with that arrived at on the basis of the acetate spectrum. Additional support for the assignment of an equatorial configuration of the C_3-hydroxyl group in XIII, and an A/B *trans* configuration, stems from the results obtained when B-norcholestanone XIV was reduced with lithium aluminum hydride. Barton[21] has called attention to the fact that reduction of unhindered cyclic ketones with this reagent always forms, predominantly, the equatorial isomer. As to be expected, XIV yielded B-norcholestanol as the major product.

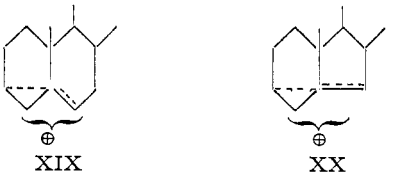
This A/B *trans* configuration must be the thermodynamically stable arrangement and further support for this fact is that when the unsaturated ketone XV is reduced with lithium and ammonia,[22] the same saturated ketone XIV is formed. It can be concluded, therefore, that the *trans–anti–trans* is the stable configuration of the backbone carbon atoms of rings A, B and C of the B-nor series.

Having unequivocally established the structure of B-norcholesterol, it was of interest to investigate the possibility of preparing an *i*-sterol (3,5-cyclo-B-norcholestan-6-ol), a system in which the cyclopropane ring would be attached to a five membered ring. It was found that a crystalline tosylate XVI was readily prepared and when it was allowed



to react with methanol, a normal ether XVII was formed. When the tosylate was allowed to react with methanol in the presence of potassium acetate, an isomeric ether was obtained to which the 3,5-cyclo-B-norcholestan-6-ol structure (XVIII) was assigned. This structural assignment is based on the fact that the isomeric ether XVIII is unstable to acid and is readily converted to the normal ether XVII or B-norcholesterol (IVb), the infrared spectrum shows a band at 3050 cm.$^{-1}$ which is characteristic of a methylene group in a cyclopropane[23] and the molecular rotational changes, which are discussed below, paralleled those in the cholesteryl series.

It was of further interest to obtain the rate of acetolysis of the tosylate XVI, for Winstein and Adams[24] have reported that the rate of acetolysis of cholesteryl tosylate is approximately 119 times faster than that of cyclohexyl tosylate. On the basis of such a result, they postulated an anchimeric assistance from the Δ^4-olefinic bond and the direct formation of the intermediate ion XIX. Since the geometrical placement of this unsaturated linkage



is different in cholesterol and B-norcholesterol, the extent of the π-overlap in the transition state would be expected to be different and the degree of anchimeric assistance should be affected. Employing the solvolysis conditions used by Winstein and Adams,[24] is was found that the rate of the B-

(17) R. Willstätter and E. W. Mayer, *Ber.*, **41**, 2199 (1908); "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, Coll. Vol. II, p. 191.

(18) H. E. Staveley and W. Bergmann, *J. Org. Chem.*, **1**, 567 (1937).

(19) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951); A. Fürst, H. H. Kuhn, R. Scotoni, Jr., and Hs. H. Günthard, *Helv. Chim. Acta*, **35**, 951 (1952).

(20) H. Rosenkrantz, A. T. Milhorat and M. Farber, *J. Biol. Chem.*, **195**, 509 (1952).

(21) D. H. R. Barton, *J. Chem. Soc.*, 1028 (1953).

(22) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954).

(23) A. R. H. Cole, *ibid.*, 3807 (1954).

(24) S. Winstein and R. Adams, THIS JOURNAL, **70**, 838 (1948).

norcholesteryl tosylate XVI is approximately half that of cholesteryl tosylate. Thus, in the B-norcholesteryl case, the overlap in the transition state still is quite significant. On the basis of the synthetic and kinetic results, the formation of intermediate XX is indicated.

A comparison of the optical rotations of the B-norcholesteryl series with those of the cholesteryl series show that, in all but two cases, the rotation of the B-nor compound is more negative and the molecular rotational differences are about constant. These values are summarized in Table I. Furthermore, the molecular rotational differences between that of B-norcholesterol and its derivatives are not only of the same sign but of the same order of magnitude as those found with cholesterol. These values are listed in Table II.

TABLE I

MOLECULAR ROTATIONAL DIFFERENCES BETWEEN B-NORCHOLESTEROL AND CHOLESTEROL COMPOUNDS

Compound	B Norcholesterol, M_D	Cholesterol, M_D	B-Norsteroid M_D − steroid M_D
Stanol	+ 60	+ 93	− 33
Stanone	+ 72	+158	− 86
Δ^5-Stenol	−335	−151	−184
Δ^5-Stenyl acetate	−373	−180	−193
Δ^5-Stenyl benzoate	−260	− 75	−195
Δ^5-Stenyl methyl ether	−380	−168	−212
3,5-Cyclo-6-methyl ether	+ 15	+208	−193
Stanyl-3,6-dione	−150	+ 7	−157
Δ^4-Stenone	− 32	−342	−374
$\Delta^{3,5}$-Diene	−435	−450	+ 15
Δ^4-Stenyl-3,6-dione	+641	−159	+800

TABLE II

MOLECULAR ROTATIONAL DIFFERENCES BETWEEN STEROID AND DERIVATIVE

	M_D ($CHCl_3$)			M_D steroid − M_D derivative	
	Δ^5-Stenol	Acetate	Benzoate	Δ Acetate	Δ Benzoate
B-Norcholesterol	−335	−373	−260	+38	−75
Cholesterol	−151	−180	− 75	+29	−76

	Δ^4-Enone	Stanol	Methyl ether	Δ Enone	Δ Stanol	Δ Methyl ether
B-Norcholesterol	− 32	+ 60	−380	−303	−395	+45
Cholesterol	+342	+ 93	−168	−493	−244	+17

	3,5-Cyclo-6-methyl ether	Δ3,5-Cyclo-6-methyl ether
B-Norcholesterol	+ 15	−350
Cholesterol	+208	−359

Experimental[25]

3-Acetoxy-5-oxo-5,6-secocholestane-6-oic Acid (II).—To a well-stirred mixture of 108 g. (0.232 mole) of cholesteryl acetate and 1200 ml. of glacial acetic acid, there was added over a period of 2 hours, a solution of 70 g. of chromium trioxide in 200 ml. of 50% glacial acetic acid. The reaction mixture was maintained at a temperature of 55°. Upon completion of the addition, the mixture was stirred for an additional 2 hours at 55°, the excess chromic acid was destroyed by the addition of 60 ml. of methanol, and then 800 ml. of acetic acid was removed by distillation under reduced pressure at a bath temperature of 40°. The remaining liquid was diluted with 50 ml. of water and allowed to stand for 12 hours. The crystalline 7-ketocholesteryl acetate which separated was removed by filtration and washed with 80% acetic acid, yield 33.3 g. (35%), m.p. 149–152°.

The filtrate was diluted with 140 ml. of 50% methanol–water and placed in the refrigerator for 3 days. The thick sheet of crystalline material which formed on the surface was removed by filtration and washed with 75% acetic acid, yield 32.5 g. The filtrate again was cooled overnight and an additional 8.7 g. of solid removed. The crops were combined and this material which was highly colored with chromium salts melted from 120–124°. Two recrystallizations from methanol yielded 27 g. (24%) of the keto-acid, m.p. 127–129°, $[\alpha]^{20}D$ +77.9° ($CHCl_3$), (lit.[11] m.p. 130°, $[\alpha]D$ +77.9°).

Anal. Calcd. for $C_{29}H_{48}O_5$ (476.67): C, 73.07; H, 10.15. Found: C, 73.31; H, 10.43.

The methyl ester was prepared by allowing 1.32 g. (2.77 mmoles) of the acid to react with an excess of diazomethane in ether and the crude product was crystallized from methanol, yield 1.14 g. (84%), m.p. 79.2–80.6°, $[\alpha]^{22}D$ +64.7° ($CHCl_3$) (lit.[11] m.p. 80°).

Anal. Calcd. for $C_{30}H_{50}O_5$ (490.70): C, 73.43; H, 10.27. Found: C, 73.26; H, 10.10.

Methyl 3-Hydroxy-5-oxo-5,6-seco-cholestane-6-oate. (a) **From 3-Acetoxy Acid (II).**—A solution of 184 mg. (0.386 mmole) of the acetoxy acid in 20 ml. of anhydrous methanol containing 100 mg. of $NaHCO_3$ was shaken at room temperature for 27 hours. The solution was diluted with 100 ml. of water, acidified with acetic acid and extracted with ether. The ethereal solution was washed with water, dried, and the solvent removed. The residue was a colorless sirup which could not be crystallized and so it was methylated with an excess of diazomethane. The ester was recrystallized from petroleum ether (30–60°), m.p. 92.5–94.0°, yield 72 mg. (42%).

Anal. Calcd. for $C_{28}H_{48}O_4$ (448.66): C, 74.95; H, 10.78. Found: C, 74.61; H, 10.74.

(b) **From Enol Lactone III.**—A solution of 500 mg. (1.09 mmoles) of the enol lactone III in 100 ml. of absolute methanol containing 2.0 g. of $NaHCO_3$ was shaken for 30 hours, diluted with water and extracted with ether. The ethereal solution was washed with water, dried, and the solvent evaporated. The residue was recrystallized twice from petroleum ether (30–60°), m.p. 93.2–94.1°, yield 423 mg. (86%). When admixed with material from the above preparation, no depression was noted.

3-Acetoxy-5-hydroxy-5,6-seco-cholest-4-ene-6-oic Acid 5,6-Lactone (III).—A solution of 5.0 g. (0.011 mole) of keto-acid II, 4.4 g. of benzoyl chloride and 10 ml. of anhydrous pyridine was allowed to stand for three days at room temperature. After a short period the mixture had turned red-brown and at the end of the reaction the dark semi-solid mass was poured into 200 ml. of water and extracted with two 100-ml. portions of ether. The ethereal extracts were washed twice with equal portions of 5% NaOH, water, dried and the ether evaporated. The red sirupy residue was mixed with 10 ml. of methanol and a brown solid separated immediately. After standing for one hour, the solid was removed by filtration and washed with methanol. A second crop was obtained upon concentration of the filtrate. The combined product was recrystallized twice from methanol to give white needles, m.p. 124–125°, yield 2.8 g. (58%), $[\alpha]^{25}D$ +59.6° ($CHCl_3$) (lit.[11] m.p. 122°, $[\alpha]D$ +60°).

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 76.15; H, 10.17.

3-Norcholesteryl Acetate (IVa).—A test-tube containing 2.00 g. (4.35 mmoles) of enol lactone III was placed in an oil-bath at 150° and then the temperature of the bath slowly raised. After reaching 170°, the liquefied mass began to froth and the evolution of CO_2 was detected by passing the evolved gas through a freshly prepared $Ba(OH)_2$ solution. After 15 minutes, the frothing ceased and the evolution of CO_2 had dropped to a barely perceptible quantity. The melt was allowed to stand at 180° for an additional 15 minutes. Upon cooling to room temperature and trituration with 5 ml. of acetone, long white plates separated. The crystals were removed by filtration and washed with 70% acetone–water, yield 1.74 g. (94%), m.p. 77–79°.

(25) Analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California. All melting points are corrected.

After two recrystallizations from aqueous acetone, there was obtained 1.49 g. (80%) of B-norcholesteryl acetate, m.p. 78–79°, $[\alpha]^{25}D$ −86.9° ($CHCl_3$) [lit.[11] m.p. 78°, $[\alpha]^{20}D$ −89° ($CHCl_3$)].

Anal. Calcd. for $C_{28}H_{46}O_2$ (414.65): C, 81.10; H, 11.18. Found: C, 80.99; H, 10.97.

B-Norcholesterol (IVb).—A solution of B-norcholesteryl acetate (4.12 g., 9.95 mmoles) and KOH (4.0 g.) in 50 ml. of methanol was refluxed for 1 hour and upon dilution of the cooled solution with water, a voluminous white solid separated. The solid was filtered, washed with dilute MeOH and recrystallized from 15 ml. of MeOH to yield 3.36 g. (90.8%) of B-norcholesterol, m.p. 115.5–116.7°, $[\alpha]^{21}D$ −89.8° ($CHCl_3$) [lit.[11] m.p. 114°, $[\alpha]^{20}D$ −90° ($CHCl_3$)].

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.56; H, 11.63.

The benzoate was prepared as described by Sorm and Dykova,[11] m.p. 135.1–136.2°, $[\alpha]^{22}D$ −54.2 ($CHCl_3$) [lit.[11] m.p. 136°, $[\alpha]^{20}D$ −54° ($CHCl_3$)].

3-Hydroxy-5,6-secocholestane-6-oic Acid (V).—A solution of 0.239 g. (0.52 mmole) of enol lactone III in 25 ml. of glacial acetic acid was hydrogenated at atmospheric pressure over 47 mg. of prereduced PtO_2. The hydrogen uptake was very rapid, one molar equivalent being absorbed in 10 minutes and a second molar equivalent by the end of 30 minutes. Removal of the catalyst followed by evaporation of the solvent at reduced pressure left a clear, colorless sirup which could not be crystallized.

The sirup (0.215 g.) was saponified by heating for 2 hours with a 5% methanolic KOH solution. Upon dilution with water, the reaction mixture deposited 192 mg. of white needles which after 2 recrystallizations from ether–petroleum ether (30–60°), gave 176 mg. (81.5%) of product, m.p. 152.3–153.5°, $[\alpha]^{21}D$ +35.1° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{48}O_3$ (420.65): C, 77.09; H, 11.50. Found: C, 77.31; H, 11.23.

5,6-Secocholestane-6-oic Acid (VI). (a) From 3-Acetoxy-5-hydroxy-5,6-cholest-4-ene-6-oic Acid 5,6-Lactone (III).—A solution of 435 mg. (0.95 mmole) of enol lactone III in 30 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over 138 mg. of pre-reduced 10% Pd/$SrCO_3$ catalyst. The hydrogen uptake was slow and after 17 hours the reaction appeared to have stopped with an uptake of 2.68 moles. Removal of the catalyst and evaporation of the solvent left a colorless oil which crystallized from methanol, yield 308 mg., m.p. 111.5–112.5°. One additional recrystallization of the material from methanol yielded 287 mg. (74%) of small plates, m.p. 112.0–113.1°, $[\alpha]^{23}D$ +28.3° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{48}O_2$ (404.65): C, 80.14; H, 11.96. Found: C, 80.02; H, 11.58.

(b) From Cholest-5-ene (VII).—A solution of 0.502 g. (1.37 mmoles) of cholest-5-ene in 50 ml. of ethyl acetate was ozonized by passing a stream of ozone (0.10 mmole/min.) through the solution for 20 minutes at a temperature of 0°. An aqueous solution of 3% H_2O_2 (10 ml.) was added to the reaction mixture and the solution stirred overnight at room temperature. After dilution with 500 ml. of water, the solution was extracted twice with 50-ml. portions of ether, the ethereal solution washed with water and then extracted with two 25-ml. portions of 5% NaOH solution. Acidification of the alkaline extract followed by extraction with ether and evaporation of the solvent at reduced pressure yielded 473 mg. of an oily keto acid. The entire acid fraction was refluxed with 1.5 g. of NaOH and 1.5 ml. of 85% hydrazine hydrate in 15 ml. of diethylene glycol for 1 hour. The excess hydrazine was distilled until an internal temperature of 190° was reached. The solution then was refluxed for an additional 6 hours. Upon cooling, the solution was diluted with 150 ml. of water, acidified with concd. HCl and extracted with two 50-ml. portions of ether. The ethereal extract was washed with water, dried and upon evaporation of the solvent a residue of 418 mg. of yellow oil was obtained. The oil was crystallized from methanol and 281 mg. of a solid acid was obtained, m.p. 109–112°. Two additional recrystallizations from methanol yielded 252 mg. (45.5%) of pure acid, m.p. 112.1–113.0°, no depression upon admixture with material prepared from enol lactone. The infrared spectra of the two samples were identical.

B-Norcholestadiene (IX). (a) From B-Norcholesterol (IVb).—A mixture of 372 mg. (1 mmole) of β-norcholesterol and 62 mg. of boric acid was heated in a side-armed test-tube at 300° for 2.5 hours. At the end of this period, a cold-finger condenser was inserted and the reaction mixture evacuated to 3 mm. pressure. The product rapidly distilled as a pale yellow semi-solid. Crystallization from ethanol (Norit) three times yielded 314 mg. (88.7%) of colorless needles, m.p. 75.1–76.0°, $[\alpha]^{23}D$ −119.2° ($CHCl_3$) [lit.[15] m.p. 73.5–74.5°, $[\alpha]D$ −117.5° ($CHCl_3$)].

(b) From 3-Acetoxy-5-oxo-5,6-secocholestane-6-oic Acid (II).—The keto acid II, 5.0 g. (10.5 mmoles), was heated to 350° and the product distilled at atmospheric pressure. The yellow distillate (3.1 g.) was recrystallized three times from methanol (Norit) to yield 2.3 g. (62%) of white needles, m.p. 75.0–76.0°, no depression upon admixture with product prepared above.

B-Norcholest-4-en-3-one (XV).—A solution of 500 mg. (1.34 mmoles) of B-norcholesterol in 50 ml. of anhydrous toluene containing 1.0 g. of aluminum isopropoxide and 2.0 g. of cyclohexanone was refluxed for 2 hours. The solution then was extracted with three 50-ml. portions of 5% H_2SO_4 and washed with water until neutral to litmus. The toluene solution was placed in a flask equipped for steam distillation and steam passed through until the distillate was practically free from organic material. The aqueous suspension of the ketone was extracted with ether, the ethereal extract washed with water and dried. Evaporation of the solvent at reduced pressure left a pale yellow oil residue which was crystallized from a 1:1 mixture of methanol–acetone to yield 429 mg. of pale yellow leaflets, m.p. 56–59°. Two further recrystallizations yielded 393 mg. (79%) of white crystals, m.p. 61.1–62.2°, $[\alpha]^{20}D$ +30.2° ($CHCl_3$), $\lambda_{max}^{heptane}$ 235 mμ (ε 14,900).

Anal. Calcd. for $C_{26}H_{42}O$ (370.60): C, 84.26; H, 11.42. Found: C, 84.18; H, 11.35.

B-Norcholest-4-en-3,6-dione (X). (a) From B-Norcholesterol (IVb).—A solution of 1.24 g. of $Na_2Cr_2O_7$ in 4 ml. of glacial acetic acid was cooled to 15° and added in one portion to a solution of 1.0 g. (2.69 mmoles) of B-norcholesterol in a mixture of 4 ml. of benzene and 4 ml. of acetic acid which had been pre-cooled to 10°. The temperature was maintained at 14–15° during the original exothermic reaction and then was placed in a refrigerator for a period of 13 hours. The brown solution was diluted with 50 ml. of water and extracted with two 50-ml. portions of ether. The ethereal extracts were washed with two 50-ml. portions of 5% Na_2CO_3 solution, twice with 50-ml. portions of water and then dried. Evaporation of the ether at reduced pressure left a yellow sirupy residue which crystallized from methanol as bright yellow needles, m.p. 103–109°, yield 413 mg. A further recrystallization yielded 389 mg. (37.6%), m.p. 116.1–117.2°, $[\alpha]^{21}D$ +167.3° ($CHCl_3$), $\lambda_{max}^{heptane}$ 243 mμ (ε 13,800).

Anal. Calcd. for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 81.31; H, 10.26.

(b) From B-Norcholestadiene (IX).—A solution of 1.80 g. of CrO_3 in 10 ml. of glacial acetic acid was added to a solution of 2.00 g. (5.65 mmoles) of B-norcholestadiene in 18 ml. of benzene and 2 ml. of acetic acid and the resulting mixture allowed to shake at room temperature for 7 hours. At the end of this period, the solution was poured into 100 ml. of water and extracted with ether. The organic extract was washed with 5% NaOH solution, water and dried. After evaporation of the solvent at reduced pressure, the remaining brown sirup was dissolved in 10 ml. of hot methanol, decolorized with Norit and allowed to crystallize, m.p. 113–116°, yield 0.79 g. Recrystallization of the yellow solid gave 0.63 g. (28.2%) of material melting from 116–117°, $[\alpha]^{25}D$ +167° ($CHCl_3$), $\lambda_{max}^{ethanol}$ 249 mμ (ε 11,240). This product did not depress the m.p. of the above prepared compound and the infrared spectra of the two samples were identical.

B-Norcholestan-3,6-dione (XI).—A mixture of 43 mg. (0.12 mmole) of B-norcholest-4-en-3,6-dione in 10 ml. of 90% acetic acid and 2.0 g. of powdered zinc was heated under reflux for 4 hours, diluted with water and extracted with two 50-ml. portions of ether. The ethereal extract was washed with $NaHCO_3$ solution until neutral, with water, and dried. The solvent was evaporated and the residual yellow sirup crystallized from methanol as colorless leaflets. The product was recrystallized from methanol, yield 29 mg.

(67.5%), m.p. 112.9–114.1°, $[\alpha]^{21}D$ −36.2° ($CHCl_3$) [lit.[15] m.p. 115–116°, $[\alpha]D$ −35.6° ($CHCl_3$)].

B-Norcholestane (XII). (a) From B-Norcholestadiene (IX).—A solution of 327 mg. (0.93 mmole) of B-norcholestadiene in 20 ml. of glacial acetic acid containing 83 mg. of PtO_2 was hydrogenated at atmospheric pressure and room temperature. The reaction was complete in about 40 minutes. The catalyst was filtered, the solvent evaporated and the product crystallized from methanol–ether (5:1) to yield 297 mg. of colorless plates, m.p. 44.6–45.9°. The compound was recrystallized twice from the same solvent mixture, yield 263 mg. (80.5%), m.p. 45.2–46.0°, $[\alpha]^{21}D$ +11.3° ($CHCl_3$) [lit.[15] m.p. 44–45°, $[\alpha]D$ +10° ($CHCl_3$)].

Anal. Calcd. for $C_{26}H_{46}$ (358.63): C, 87.07; H, 12.93. Found: C, 86.98; H, 13.00.

(b) From B-Norcholestanone (XIV).—A solution of 41 mg. (0.11 mmole) of B-norcholestanone, 1 g. of KOH, 1 ml. of 85% hydrazine hydrate in 5 ml. of diethylene glycol was refluxed for 2 hours. The excess hydrazine and water were removed by taking off the condenser and raising the bath temperature to 210°. The remaining solution then was refluxed for 4 hours, cooled to room temperature and diluted with water. The mixture was acidified with 5% HCl, the organic material extracted with ether, the ethereal solution dried and the solvent removed. The residual liquid was crystallized from methanol–ether (5:1) to yield 33 mg. of hydrocarbon. The material was recrystallized twice from the same solvent mixture, yield 22 mg. (56%), m.p. 45.0–45.9°, undepressed on admixture with B-norcholestadiene prepared above. The infrared spectra of both samples were identical.

B-Norcholestanol (XIII). (a) From B-Norcholesteryl Acetate (IVa).—A solution of 138 mg. (0.33 mmole) of B-norcholesteryl acetate in 10 ml. of glacial acetic acid containing 23 mg. of pre-reduced PtO_2 was hydrogenated at atmospheric pressure and room temperature. The reaction was complete in 35 minutes. Removal of the catalyst by filtration and evaporation of the solvent left a residue of 137 mg. of a clear oil which could not be crystallized. The oil was saponified by refluxing with 20 ml. of 5% methanolic KOH for 90 minutes. The mixture was diluted with water and extracted with two 20-ml. portions of ether. The ethereal extract was washed with water, dried and the solvent removed. The product was crystallized from methanol, yield 109 mg., m.p. 74–77°. One additional recrystallization from methanol yielded 96 mg. (77.5%) of colorless needles, m.p. 77.5–78.2°, $[\alpha]^{21}D$ −30.8° ($CHCl_3$).

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.06; H, 12.11.

The 3,5-dinitrobenzoate was prepared in the usual fashion from 54 mg. (1.41 mmoles) of B-norcholestanol and 67 mg. of 3,5-dinitrobenzoyl chloride in 3 ml. of pyridine. The product was crystallized from methanol, yield 39 mg. (48%), m.p. 139.3–140.6°.

Anal. Calcd. for $C_{33}H_{48}O_6N_2$ (568.73): C, 69.69; H, 8.51; N, 4.93. Found: C, 69.89; H, 8.41; N, 5.03.

(b) From B-Norcholestanone (XIV).—A solution of 34 mg. (0.092 mmole) of B-norcholestanone in 5 ml. of anhydrous ether was added dropwise to a slurry of 103 mg. of crushed $LiAlH_4$ in 10 ml. of anhydrous ether. The mixture was stirred at room temperature for 4 hours, the excess hydride decomposed with water and the ethereal layer separated. The ethereal solution was dried, and the solvent evaporated. The residue crystallized upon trituration with 2 ml. of cold methanol. The total solids were removed by filtration, yield 31 mg., m.p. 68–72°. The infrared spectrum of this crude material was essentially identical with that of pure stanol. The product was recrystallized three times from methanol, yield 22 mg. (65%), m.p. 77.0–77.9°, no depression upon admixture with stanol prepared by hydrogenation of B-norcholesteryl acetate, $[\alpha]^{20}D$ −31.2° ($CHCl_3$).

B-Norcholestanone (XIV). (a) From B-Norcholestanol (XIII).—A solution of 1.5 g. of $Na_2Cr_2O_7$ in 5 ml. of glacial acetic acid was added in one portion to a solution of 630 mg. (1.68 mmoles) of B-norcholestenol in 5 ml. of glacial acetic acid. The mixture was warmed on a steam-bath for 30 minutes (the mixture turned green within a few minutes of mixing), then diluted with water and extracted with three 30-ml. portions of ether. The combined ethereal extracts were washed with an equal volume of 5% Na_2CO_3 solution, twice with an equal volume of water and then dried. Evaporation of the solvent left a clear oily residue which was crystallized from methanol to yield 587 mg. of colorless needles, m.p. 59–62°. The product was recrystallized from methanol, yield 561 mg. (90%), m.p. 62.6–63.7°, $[\alpha]^{22}D$ −9.4° ($CHCl_3$).

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.69; H, 11.86.

(b) From B-Norcholestenone (XV).—A solution of 73 mg. (0.2 mmole) of B-norcholestenone in 5 ml. of anhydrous ether was added to 20 ml. of liquid NH_3 in a three-necked flask fitted with a sealed stirrer and a Dry Ice condenser. Over a period of 10 minutes, a total of 110 mg. of lithium was added in 10–20 mg. portions to the stirred solution. The blue solution was stirred for an additional 20 minutes and then the solvent removed by warming the flask on a steam-bath. The residual solid was decomposed with 50 ml. of saturated aqueous NH_4Cl solution, the organic material extracted with ether, the ethereal solution washed with water and dried.

Evaporation of the ether left a clear colorless oil which was obtained in a solid form from 10:1 methanol–ether, m.p. 54–57°. Several attempted crystallizations failed to yield a pure, crystalline product and so the total material was combined and chromatographed on 2 g. of Woelm neutral alumina. Elution with 40% benzene–60% petroleum ether (fractions 26–31) yielded 38 mg. of a material which crystallized readily from methanol. Two further recrystallizations yielded 34 mg. (46%) of needles, m.p. 62.7–63.5°, no depression on admixture with material prepared above, $[\alpha]^{19}D$ −9.8° ($CHCl_3$). The infrared spectra of the two samples were identical.

B-Norcholesteryl Tosylate (XVI).—A solution of 500 mg. (1.35 mmoles) of B-norcholesterol and 500 mg. of tosyl chloride in 5 ml. of anhydrous pyridine was allowed to stand at 25° for 24 hours. The mixture was poured into ice-water and extracted three times with ether. The ethereal solution was washed with 50 ml. of cold 2 *N* HCl, 50 ml. of cold $NaHCO_3$, 50 ml. of saturated NaCl solution and dried. Removal of the solvent at 30° and reduced pressure left a white solid residue which was recrystallized twice from anhydrous ether, m.p. 91.2–92.7°, yield 501 mg. (70%), $[\alpha]^{20}D$ −67.0° ($CHCl_3$).

Anal. Calcd. for $C_{33}H_{50}O_3S$ (526.80): C, 75.23; H, 9.57. Found: C, 75.12; H, 9.61.

B-Norcholesteryl Methyl Ether (XVII).—A solution of 423 mg. (0.81 mmole) of B-norcholesteryl tosylate in 50 ml. of anhydrous methanol was heated under reflux for 3 hours. The solution was concentrated to 10 ml. at reduced pressure, diluted with 50 ml. of water and extracted with three 20-ml. portions of ether. The ethereal extracts were washed with 50 ml. of 5% $NaHCO_3$, twice with 50 ml. of water and dried. Evaporation of the solvent at reduced pressure yielded a colorless sirup which was chromatographed on 15 g. of Woelm neutral alumina. Elution with 2% benzene in petroleum ether (fractions 7–14) gave crystalline material. Recrystallization from ether–methanol yielded 218 mg. (70%) of colorless rods, m.p. 53.9–54.2°, $[\alpha]^{22}D$ −97.8° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.59; H, 11.90.

When 100 mg. of the ether was heated at 90° with 100 mg. of *p*-toluenesulfonic acid in 2 ml. of water and 5 ml. of dioxane, 84 mg. of starting material was recovered.

3,5-Cyclo-B-norcholestan-6-ol Methyl Ether (B-Norcholesteryl *i*-Methyl Ether) (XVIII).—A solution of 387 mg. (0.74 mmole) of B-norcholesteryl tosylate and 1.14 g. of freshly fused anhydrous KOAc in 50 ml. of anhydrous methanol was refluxed for 9 hours. The solution was concentrated to about 10 ml. at reduced pressure and diluted with 100 ml. of water. The mixture was extracted with three 20-ml. portions of ether, the combined ethereal extract washed with 50 ml. of water and dried. Evaporation of the solvent at reduced pressure left a sirup which was chromatographed on 15 g. of Woelm neutral alumina. Elution with petroleum ether (fractions 2–11) yielded crystalline solid which was recrystallized twice from methanol, yield 186 mg. (63%), m.p. 57.2–58.3°, $[\alpha]^{22}D$ −1.6° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.78; H, 11.93.

A solution of 100 mg. (0.26 mmole) of the ether and 100 mg. of *p*-toluenesulfonic acid in 2 ml. of water and 5 ml. of dioxane was heated for 4 hours. The solution was diluted

with 50 ml. of water and extracted with three 20-ml. portions of ether. The extracts were washed with 50 ml. of 5% $NaHCO_3$, 50 ml. of water and dried. Removal of the solvent at reduced pressure left a crystalline residue which was recrystallized from methanol to yield 81 mg. (84.5%) of B-norcholesterol, m.p. 113.5–115.0°, $[\alpha]^{22}D$ −89.3° ($CHCl_3$).

A solution of 147 mg. (0.38 mmole) of the ether and 19 mg. of *p*-toluenesulfonic acid in 15 ml. of anhydrous methanol was refluxed for 4 hours and processed as above. Evaporation of the ether gave a pale-yellow oil which was crystallized from ether–methanol (1:1) to yield 138 mg. of B-norcholesteryl methyl ether, m.p. 51.8–53.2°. A further recrystallization yielded 91 mg. (62%) of material melting from 53.6–54.5° and which did not depress an authentic sample of B-norcholesteryl methyl ether. The infrared spectra of the samples were identical.

Rate Measurements. (a) **B-Norcholesteryl Tosylate.**—Due to the solubility of the tosylate, a solution of the material in anhydrous acetic acid was made directly. This solution was approximately 0.01 *M*. The solution was placed in a bath at 50 ± 0.05°, aliquots (10 ml.) were withdrawn at intervals and immediately cooled in an ice-bath. Titrations were conducted with 0.0554 *M* NaOAc in anhydrous acetic acid using brom phenol blue as the indicator. Infinity titer taken indicated an initial concentration of 0.0104 *M*. The results from two runs gave the following values for the rate constant: 4.44×10^{-3} min.$^{-1}$ ($\pm 0.07 \times 10^{-3}$) and 4.58×10^{-3} min.$^{-1}$ ($\pm 0.18 \times 10^{-3}$).

(b) **Cholesteryl Tosylate.**—The experiment was performed as described by Winstein and Adams.[24] A value for the rate constant of 7.9×10^{-3} min.$^{-1}$ was reported by these workers and in the present work a value of 7.75×10^{-3} min.$^{-1}$ was found.

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[CONTRIBUTION FROM CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. III. A Selective Rearrangement of Steroid Polyenes[1]

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A rearrangement of sterol 5,7-dienes to isomeric 6,8(14)-dienes in the presence of anhydrous sulfur dioxide and pyridine has been discovered and applied to the preparation of 6,8(14),9(11),22-ergostatetraenol acetate, a useful intermediate for corticosteroid synthesis.

In the course of exploratory research directed toward new routes for corticosteroid synthesis,[2] a sulfur dioxide catalyzed rearrangement of steroid 5,7-dienes has been discovered. The rearrangement was first encountered when it was observed that ergosterol acetate (I) in the presence of liquid sulfur dioxide and pyridine had reacted to form in 70% yield a product II isomeric with starting material. The ultraviolet absorption spectrum of II was most consistent with its formulation as a 6,8(14)-diene, but the physical constants were not identical to those subsequently reported by Barton and Bruun[3] for 6,8(14),22-ergostatrienol acetate prepared by another method. Hydrogenation studies, however, confirmed the correctness of this formulation. That the product II had not undergone skeletal change was readily demonstrated by catalytic hydrogenation over platinum in ethyl acetate solution to 8(14)-ergostenol acetate (III), identical to an authentic specimen prepared by the hydrogenation of ergosterol acetate in acidic solution.[4] Since the hydrogenation was carried out under conditions known to be unfavorable to the migration of nuclear double bonds,[5] the isolation of III suggested further that the product II was a double bond isomer of ergosterol in which one of the centers of unsaturation was at the 8(14)-position. Further hydrogenation data supporting the latter conclusion were obtained by catalytic hydrogenation of II over a mild and selective Raney nickel catalyst.[6,7] The product IV resulting from the absorption of one molar equivalent of hydrogen was a dienol acetate, shown to be identical to a sample of 8(14),22-ergostadienol acetate prepared by another procedure.[8] A further result of the hydrogenation experiments was the demonstration of the 5α (allo) configuration of the AB ring juncture, which subsequently proved to be the characteristic steric result of sulfur dioxide–pyridine rearrangement of 5,7-dienes.

Rearrangement of ergosterol with strong acid has been long known.[4,9] However, no rigorously pure substance with the 6,8(14)-structure II was isolated from the complex reaction mixtures by the early workers.[4,9a] Repetition of the preparation in this Laboratory was carried out in order to confirm the non-identity of II with the 8,14,22- and 7,14,22-isomerides, and in the course of the fractionation no product identical to II was isolated. Work with the classical acid rearrangement procedures clearly demonstrated the superior specificity of the sulfur dioxide method.

The product obtained when the sulfur dioxide–pyridine rearrangement was carried out using the 9(11)-dehydro analog of I (V) was shown by analysis to be a new isomer of dehydroergosterol acetate, which in analogy to the simpler case was formulated as the 6,8(14),9(11),22-tetraene (VI).

Consistent with the formulation of VI as a re-

(1) Presented before the Division of Organic Chemistry, 124th Meeting of the American Chemical Society, September, 1953.

(2) G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, THIS JOURNAL, **75**, 1514 (1953).

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