*Anal.* Calcd. for $C_{14}H_7O(OCH_3)_3$: C, 71.8; H, 5.64; OMe, 32.8. Found: C, 71.5; H, 5.82; OMe, 32.4.

**Ozonolysis of 2-(2′,4′-Dimethoxyphenyl)-6-methoxybenzofuran (Fig. 2, II).**—A Welsbach ozonizer was used. Ozonization of 25 mg. dissolved in methanol was carried out by passing 0.0865 mmole of $O_3$ at 0° through the solution for 50 minutes. A few drops of hydrogen peroxide and water were added to the methanol and the solution left overnight to decompose the ozonide to the acid. The decomposition of the ozonide was not complete to the acid, however, and a number of other products were seen when the material was observed on the chromatostrips. The amounts of the products present were insufficient to be isolated, so identification was made by comparison with known synthetic compounds. Synthetic 2,4-dimethoxybenzoic acid and 2-hydroxy-4-methoxybenzoic acid were prepared as described in an earlier publication.[12]

**Synthetic 4-Methoxy-2-(2′,4′-dimethoxybenzoyl)-benzoic Acid (Fig. 2, III).**—To 2.6 g. of 2,4-dimethoxybenzoic acid was added 20 ml. of thionyl chloride and the mixture allowed to stand at room temperature for 24 hours. The excess thionyl chloride was removed from the acid chloride *in vacuo* and 1.5 g. of 2-hydroxy-4-methoxybenzoic acid, dissolved in 10 ml. of benzene containing 8 ml. of dimethylaniline, were added with agitation. After 3 hours, the benzene and aniline were removed under reduced pressure. The reddish colored oil failed to crystallize. The expected benzoyl ester appeared as a separate purple spot near the origin when migrated on chromatostrips in a solvent system of a mixture of acetone and petroleum ether (1:3).

In order to isolate the compound, the crude mixture was subjected to a 200-tube Craig countercurrent distribution. The solvent system consisting of acetone, ether, petroleum ether, and water (42:15:22:21) was employed. The ester appeared pure in tubes 90–102 and crystallized from methanol and water into white needles (200 mg.), m.p. 151°. Hydrolysis with 10% methanolic potassium hydroxide solution for 15 minutes on the steam-bath gave 2-hydroxy-4-methoxybenzoic acid and 2,4-dimethoxybenzoic acid exclusively.

*Anal.* Calcd. for $C_{14}H_7O_4(OCH_3)_3$: C, 61.5; H, 4.82; OMe, 28.1. Found: C, 61.6; H, 4.89; OMe, 28.1. The compound was relatively unstable, and decomposed into its two component acids when dissolved in methanol and allowed to stand at room temperature.

**Identification of 4-Methoxy-2-(2′,4′-dimethoxybenzoyl)-benzoic Acid (Fig. 2, III) as One of the Ozonolysis Products.**—Following decomposition of the ozonide with hydrogen peroxide, the methanol was evaporated and the oil obtained dissolved in 5% sodium bicarbonate solution. Extractions with ether were made at *p*H 8 to 9, *p*H 7.0 and *p*H 4.0. The ether extract at *p*H 7.0 contained two prominent spots when migrated on a silicic acid strip in acetone and petroleum ether (1:3). The lower spot appeared identical to the synthetic benzoyl ester and was scraped off the glass strip, eluted with methanol and the solution concentrated. Migration in two other solvent systems assured purity as well as identity with the synthetic product. The two additional systems employed were ethyl acetate and petroleum ether (3:1) and ether and petroleum ether (7:3). Ultraviolet absorption spectra made from the synthetic compound isolated on silicic acid as well as the pure ozonolysis product isolated similarly were also identical. The absorption maxima were at 253 and 290 mμ and minima at 233 and 278 mμ.

Hydrolysis with 0.1 *N* methanolic potassium hydroxide solution of the synthetic and ozonolysis products resulted in formation of 2,4-dimethoxy- and 2-hydroxy-4-methoxybenzoic acid in both cases.

**Identification of 2,4-Dimethoxybenzoic Acid (Fig. 2, IV) and 2-Hydroxy-4-methoxybenzoic Acid (Fig. 2, V) as Two of the Other Ozonolysis Products.**—The ether extract at *p*H 4.0 contained mostly a material that corresponded to 2,4-dimethoxybenzoic acid. The $R_f$'s of the ozonolysis product was identical with that of the synthetic 2,4-dimethoxybenzoic acid when migrated in the three solvent systems employed for identification of 4-methoxy-2-(2′,4′-dimethoxybenzoyl)-benzoic acid. The ultraviolet absorption spectra were also identical. The absorption maxima were at 253 and 287 mμ and the minima at 233 and 272 mμ.

The extract at *p*H 7 contained the 2-hydroxy-4-methoxybenzoic acid. The latter appeared as a blue fluorescent spot on a chromatostrip when viewed under a 2540 Å. ultraviolet light, while the 2,4-dimethoxybenzoic acid showed as a brown absorption area. The $R_f$'s of the ozonolysis product was identical with that of synthetic 2-hydroxy-4-methoxybenzoic acid when migrated in the three solvent systems described above. The ultraviolet absorption spectra were also identical. The absorption maxima were at 250 and 293 mμ and the minima at 233 and 271 mμ.

**Acknowledgment.**—The authors gratefully acknowledge the assistance of L. M. White and G. Secor for all the elemental analyses; G. F. Bailey and E. Gong for ultraviolet absorption spectra; T. R. Govindachari and K. Nagarajan, Presidency College, Madras, India, for helpful suggestions and a sample of wedelolactone; T. R. Seshadri, University of Delhi, India, for a sample of dalbergin; and J. H. Simpson, Torry Research Station, Aberdeen, Scotland, for a sample of 7,2′,4′-trihydroxyflavone, all of which were used for comparison purposes.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

# Transmission of Electrical Effects Through Homoallylic Systems. I. The Synthesis and Physical Properties of a Series of 6-Arylcholesterols and of 6-Arylcholesteryl *p*-Toluenesulfonate Esters

BY RICHARD A. SNEEN

RECEIVED DECEMBER 16, 1957

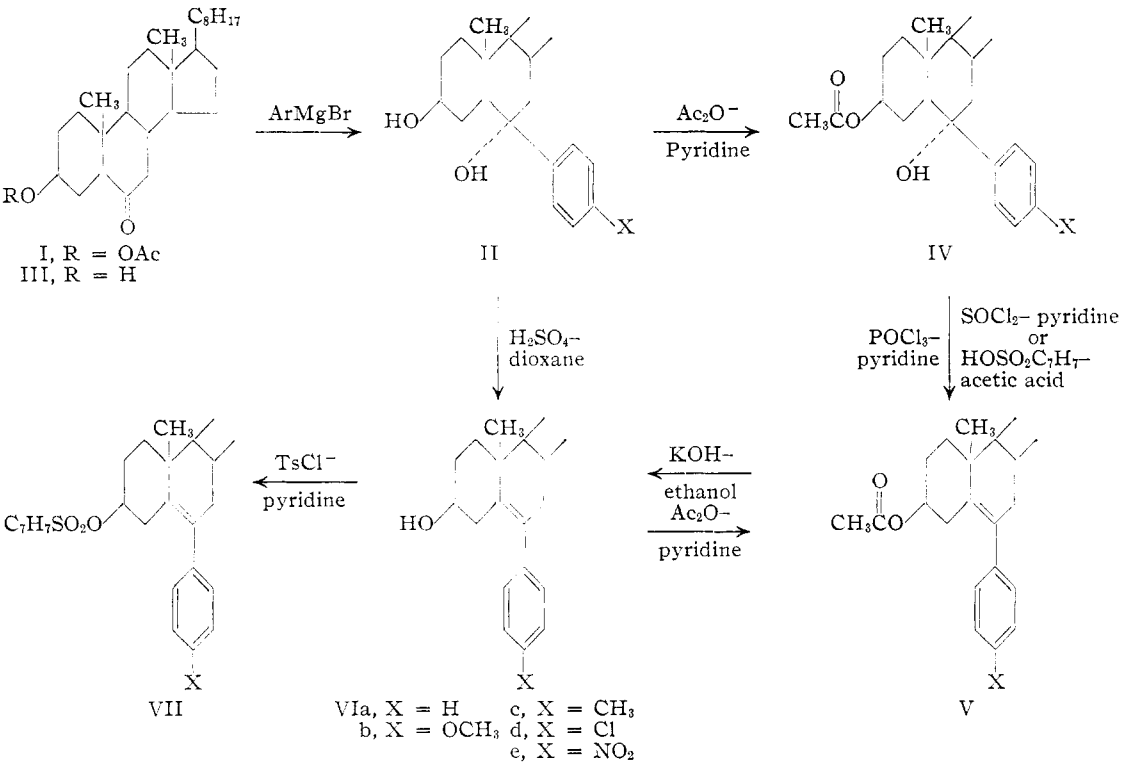
The syntheses of 6-phenyl-, 6-*p*-anisyl-, 6-*p*-tolyl-, 6-*p*-chlorophenyl- and 6-*p*-nitrophenylcholesterol, and of the corresponding *p*-toluenesulfonate esters have been accomplished by the synthetic scheme outlined below.

As part of a study designed to assess the relative stabilizing effects of various substituents on the transition states of unimolecular solvolyses of homoallylic systems, the synthesis of a series of five 6-arylcholesterols was undertaken. This communication reports the successful synthesis of 6-phenyl-, 6-*p*-anisyl-, 6-*p*-tolyl-, 6-*p*-chlorophenyl- and 6-*p*-nitrophenylcholesterol. A kinetic study of the solvolyses of the *p*-toluenesulfonate esters of these substituted cholesterols is reported in a subsequent publication.[1]

The synthesis of all of the arylcholesterols began with the readily available cholestan-3β-ol-6-one acetate[2] (I). This keto acetate, when treated with

(1) R. A. Sneen, THIS JOURNAL, **80**, 3977 (1958).

(2) B. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).




a twofold excess of the appropriate Grignard reagent (molar ratio, 6:1) furnished, in excellent yields, 6β-phenyl-, 6β-*p*-anisyl- and 6β-*p*-tolylcholestan-3β,6α-diol (IIa, b, c). A similar attempt to form the *p*-chlorophenyldiol from this keto acetate resulted in a difficultly-purified mixture, apparently containing significant amounts of a *p*-chlorophenyl adduct of the acetate moiety. This difficulty was circumvented by the prior hydrolysis of the keto acetate to cholestan-3β-ol-6-one (III)[2] and treatment of this keto alcohol with *p*-chlorophenylmagnesium bromide to form 6β-*p*-chlorophenylcholestan-3β,6α-diol (IId).

Monoacetylation of these diols furnished, in each case, the corresponding 3-monoacetate (IVa-d). Nitration of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa) with fuming nitric acid and acetic acid–acetic anhydride at 0° furnished, in 41% yield, the fifth member of the series, 6β-*p*-nitrophenylcholestan-3β,6α-diol monoacetate (IVe).

Several synthetic methods were employed in the conversion of these diol monoacetates to the corresponding 6-arylcholesteryl acetates. The action of phosphorus oxychloride in pyridine on 6β-phenyl-, 6β-*p*-tolyl- and 6β-*p*-chlorophenylcholestan-3β,6α-diol monoacetate effected dehydration in excellent yields to give their respective arylcholesteryl acetates (Va,c,d). The dehydrating action of *p*-toluenesulfonic acid in refluxing acetic acid effected the elimination of water from 6β-*p*-tolyl- and 6β-*p*-anisylcholestan-3β,6α-diol monoacetate. Resort was had to the thionyl chloride–pyridine system in the synthesis of 6β-*p*-nitrophenylcholesteryl acetate (Ve). Phenylcholesterol (VIa) could be obtained directly from 6β-phenylcholestan-3β,6α-diol by the action of sulfuric acid in boiling dioxane, but both yields and purity of this product were inferior to those obtained by the route outlined above.

The arylcholesteryl acetates were smoothly saponified by ethanolic potassium hydroxide to furnish the desired 6-arylcholesterols (VIa-e). The preparation of the *p*-toluenesulfonate esters of these alcohols VIIa-e was accomplished with *p*-toluenesulfonyl chloride in pyridine.

In Table I are compiled molecular rotation data for several of the series of compounds prepared during the course of this work. It is interesting to note the general similarities between the molecular rotation values within any one series of compounds. Thus the 6β-arylcholestan-3β,6α-diol monoacetates exhibit molecular rotation values ranging from +7 ± 4° for the *p*-chlorophenyl compound to +21 ± 4° for the phenyl compound.[3] This internal consistency has been used as a criterion for the stereochemical and geometric identity of all of the members of a particular series. Except in the case of 6-*p*-nitrophenylcholesterol, the ultraviolet spectra of the arylcholesterols show similar conformities (see Table II). Since, in general, the aryl compounds within each series showed similar relationships, the arguments to be presented for the assigned stereochemistry and geometry of specific compounds in the discussion which follows can be justifiably extended to apply to all of the *p*-substituted aryl derivatives within that series.

One difficulty which arises in attempting to assign stereochemistry to $C_6$ of the arylcholestandiols is the well-known flexibility of the cyclo-

(3) Only in the case of the 6-arylcholesteryl *p*-toluenesulfonates are the observed molecular rotations sufficiently different to justify an analysis of the rotations as a function of the *p*-aryl substituent. The order of increasing levorotation can be seen to be Ar = *p*-chlorophenyl < phenyl < *p*-anisyl < *p*-tolyl.

TABLE I

MOLECULAR ROTATION VALUES IN CHLOROFORM

| Compound, R = | Molecular rotation[a] |
|---|---|
| 6β-R-Cholestan-3β,6α-diol | |
| *p*-Tolyl | + 61 |
| *p*-Anisyl | + 54 |
| Phenyl | + 50 |
| *p*-Chlorophenyl | + 48 |
| 6β-R-Cholestan-3β,6α-diol monoacetate | |
| *p*-Tolyl | + 15 |
| *p*-Anisyl | + 12 |
| Phenyl | + 21 |
| *p*-Chlorophenyl | + 7 |
| *p*-Nitrophenyl | + 19 |
| 6-R-Cholesterol | |
| *p*-Tolyl | −219 |
| *p*-Anisyl | −214 |
| Phenyl | −203 |
| *p*-Chlorophenyl | −198 (−195) |
| *p*-Nitrophenyl | −195 |
| 6-R-Cholesteryl *p*-toluenesulfonate | |
| *p*-Tolyl | −160 (−160)[b] |
| *p*-Anisyl | −126 |
| Phenyl | −71 |
| *p*-Chlorophenyl | −37 |

[a] Limits of accuracy ±5°. [b] Determined in 9:1 dioxane–water.

TABLE II

ULTRAVIOLET SPECTRAL CHARACTERISTICS OF SOME 6-ARYLCHOLESTEROLS AND STYRENES

| Compound | λmax, mμ | ε | log ε |
|---|---|---|---|
| 6-*p*-Tolylcholesterol | 235 | 17100 | 4.23 |
| 6-*p*-Anisylcholesterol | 232 | 24200 | 4.38 |
| 6-Phenylcholesterol | 234 | 18700 | 4.27 |
| 6-*p*-Chlorophenylcholesterol | 241 | 16500 | 4.22 |
| 6-*p*-Nitrophenylcholesterol[a] | 270–300 | 16400 | 4.21 |
| Styrene[b] | 245 | 14100 | 4.15 |
| *p*-Nitrostyrene[c] | 291 | 18000 | 4.25 |

[a] No well-defined absorption maximum. [b] A. C. Cope and M. Burg, THIS JOURNAL, **74**, 168 (1952). [c] Saburo Nagakura, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **75**, 822 (1954).

hexane ring. Models indicate that substitution of a bulky aryl group at the 6β (axial) position should result in severe steric interference with the angular methyl group at $C_{10}$. It is conceivable that the steroidal B ring might find it energetically advantageous to pass over into a boat conformation. However, since a molecule with 6α-aryl-6β-hydroxy stereochemistry would most certainly *not* assume a boat conformation, the arguments presented can reasonably be used as evidence *against* this latter stereochemistry and thus, indirectly, *for* the assigned stereochemistry (6β-aryl-6α-ol).

A somewhat naive approach to the problem of assigning stereochemistry at $C_6$ of the arylcholestandiols would perhaps suggest that the rather large incoming aryl residue would approach from the less-hindered alpha or under side to form the 6α-aryl-3β,6β-diol. However, when one considers that the carbonyl oxygen is undoubtedly coördinated with some magnesium species in the transition state,[4] it becomes problematic whether α-attack would produce a more stable transition state. Actually, a β-orientation has been tentatively assigned to the aryl substituent in these adducts. This stereochemistry is supported by two pieces of evidence, one chemical and one physical. The chemical evidence derives from an attempt to dehydrate 6β-phenyl-3β,6α-cholestandiol monoacetate (IVa) with 8% hydrochloric acid in refluxing ethanol. The hydroxyl group remained intact, the only chemical change being hydrolysis of the ester group to furnish 6β-phenylcholestan-3β,6α-diol (IIa). The reluctance of a tertiary alcohol, labilized by a phenyl group, to dehydrate under these conditions would be surprising indeed if the alcohol function occupied an axial orientation in which *trans*-coplanar elimination would be possible. On this basis, then, the aryl substituent would seem to occupy an axial orientation.

The physical evidence for the suggested stereochemistry is perhaps more convincing. It is based on an analysis of molecular rotational data as a function of molecular geometry by a method recently developed by J. H. Brewster.[5] Assembled in Table III are some of the pertinent data used in this analysis together with the molecular rotation values predicted by the method. Some representative compounds of known stereochemistry are included to show the limits of discrimination of this type of analysis. The observed disagreement between the experimentally determined rotation of our 6-phenylcholestan-3β,6-diol with the predicted value for 6α-phenylcholestan-3β,6α-diol (equatorial phenyl) argues strongly against this stereochemistry.[6]

The $C_5$–$C_6$ assignment of unsaturation in the arylcholesterols and their esters was made on the basis of the following pieces of evidence: 1, the ultraviolet spectra of the arylcholesterols (see Table II) reveal that the double bond is conjugated with the aryl rings and, therefore, that it must be located at either $C_5$–$C_6$ or $C_6$–$C_7$; 2, a tentative assignment of unsaturation to the $C_5$–$C_6$ position can be made on the basis of the molecular rotation data[7] assembled in Table IV; 3, corroboration of the formulation of our 6-phenylcholestenol as 6-phenylcholesterol is found in the rate data for the solvolysis of the derived *p*-toluenesulfonate esters

(4) H. L. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

(5) In principle this method of analysis is based on the assignment of empirical parameters to interactions between various substituents. Positive or negative contributions to the total molecular rotation are attributed to various "skew" interactions according to whether substituents lie in a clockwise or counterclockwise relationship when drawn according to the Newman convention. The author wishes to thank Professor Brewster for making the details of this method known to him prior to its publication.

(6) On the other hand, the agreement with the value predicted for 6β-phenylcholestan-3β,6α-diol with a chair-formed B ring would seem to favor not only this stereochemistry but also this conformation.

(7) In interpreting these data it has been assumed that, since the phenyl group would not be directly bonded to an asymmetric carbon atom in either isomer, the effect of introducing a 6-phenyl group into an unsubstituted cholestenol would be simply to intensify any effect which the double bond exerts on the molecular rotation. Since for both possible cholestenols the effect of the double bond is seen to be an increase in levorotation (*cf.* cholestanol), the molecular rotation of either 6-arylcholestenol should be more levorotatory than its hydrogen analog. Experimentally, the molecular rotation of our 6-phenylcholestenol is somewhat more levorotatory than that of cholesterol but considerably more dextrorotatory than that of $\Delta^4$-cholestenol.

TABLE III

| Compound | Molecular rotation Obsd. | Calcd. |
|---|---|---|
| Cholestanol[a] | + 93 | ... |
| Cholestan-3β,6β-diol[a] | + 57 | + 48 |
| Cholestan-3β,6α-diol[a] | +154 | +138 |
| 6α-Phenylcholestan-3β,6β-diol | | +138 to +168[b] |
| | | +147 to +177[c] |
| 6β-Phenylcholestan-3β,6α-diol | + 50 | + 18 to + 48[b] |
| | | + 34 to + 64[d] |

[a] L. F. Fieser and Mary Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 216. [b] Cholestanol used as a basis for calculation. [c] Cholestan-3β,6β-diol used as a basis for calculation. [d] Cholestan-3β,6α-diol used as a basis for calculation.

TABLE IV

| Compound | Molecular rotation | $\Delta M_D$[c] |
|---|---|---|
| Cholestanol[a] | + 89 | ... |
| Cholesterol[a] | −154 | +243 |
| Δ⁶-Cholesten-3β-ol[b] | −359 | +448 |
| 6-Phenylcholesterol | −203 | +291 |

[a] L. F. Fieser and Mary Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 216. [b] D. H. R. Barton and W. J. Rosenfelder, *Nature*, **164**, 316 (1949). [c] $\Delta M_D$ = $M_D$ cholestanol − $M_D$ compound.

reported separately.[1] The observed kinetic results are consistent with a Δ⁵-formulation but would be very difficult to rationalize in terms of Δ⁶-unsaturation; 4, the internal consistencies noted in the physical and chemical properties of the 6-arylcholestenols and of the 6-methylcholestenol described in a separate communication[8] provide strong support for a similar assignment of unsaturation in these two series of compounds and, in particular, for a Δ⁵-assignment; and 5, careful scrutiny of the nuclear magnetic resonance spectrum of our 6-phenylcholestenol reveals the absence of any absorption due to vinyl hydrogen[9] even though such absorption is quite apparent in the spectra of cholesterol and of its *p*-toluenesulfonate ester.

The *para* orientation assigned to the nitro group in this series of compounds remains to be justified. The conditions of nitration (fuming nitric acid in acetic acid–acetic anhydride) are well known to give significant amounts of *ortho* nitration.[10] It was hoped that the considerable steric congestion at the point of attachment of the phenyl ring to the steroid nucleus would slow down the rate of *ortho* nitration relative to *para* nitration. This hope apparently was realized. Confirmation of the *para* orientation of the nitro group was given by the ultraviolet spectrum (Table II) of 6-nitrophenylcholesterol, in which no evidence of steric inhibition of resonance was noted,[11] and in the close parallelism observed between the molecular rotations of the various nitrophenyl derivatives and the other series of compounds. These molecular rotation data should be fairly sensitive criteria of structure, since a bulky *o*-nitro group would be expected to affect the populations of the various rotational conformations about the $C_6$–aryl bond and, thus, the observed molecular rotation.

(8) R. A. Sneen, THIS JOURNAL, **80**, 3982 (1958).

(9) L. H. Meyers, A. Saika and H. S. Gutowsky, *ibid.*, **75**, 4567 (1953).

(10) See, for example, C. K. Ingold and M. S. Smith, *J. Chem. Soc.*, 917 (1938).

(11) See, for example, the ultraviolet spectrum of *o*-methyl-α-methylstyrene, P. Ramart-Lucas, *Bull. soc. chim. France*, **17**, 264 (1950).

## Experimental

**6β-Phenylcholestan-3β,6α-diol (IIa).**—To a previously prepared solution of the phenyl Grignard reagent (prepared by the dropwise addition of a solution containing 21.0 g. (0.134 mole) of bromobenzene in 40 ml. of anhydrous ether to a stirred suspension of 3.240 g. (0.133 mole) of magnesium turnings in 10 ml. of ether) was added a solution containing 6.931 g. (0.0155 mole) of cholestan-3β-ol-6-one acetate (I)[2] in 50 ml. of anhydrous ether. The addition was carried out at such a rate as to maintain a gentle reflux. When the initially-formed white crust had dissolved, stirring was discontinued and the reaction mixture was heated under reflux overnight. (In later experiments it was found that this heating could be neglected with no diminution in yield.)

The excess Grignard reagent was decomposed by the dropwise addition of methanol, followed by aqueous methanol. The precipitated salts were dissolved by dropwise addition of 10% aqueous hydrochloric acid. The ethereal layer was separated, washed once with water, and ether was removed on a steam-plate to a volume of *ca.* 125 ml. The addition of methanol and the removal of more solvent on a steam-plate resulted in crystallization. Filtration yielded 6.562 g. (86.2%) of 6β-phenylcholestan-3β,6α-diol, m.p. 190–192°. The analytical sample was prepared by recrystallization from the same solvent, m.p. 193.4–193.9°, $[\alpha]^{30}D$ +10.0° (chloroform).

*Anal.* Calcd. for $C_{33}H_{52}O_2$: C, 82.44; H, 10.90. Found: C, 82.20; H, 10.79.

**6β-*p*-Anisyl-, 6β-*p*-Tolyl- and 6β-*p*-Chlorophenylcholestan-3β,6α-diol (IIb,c,d).**—The synthesis of the first two compounds from cholestan-3β-ol-6-one acetate (I)[2] was patterned after that described above for their phenyl analog IIa. The synthesis of 6β-*p*-chlorophenylcholestan-3β,6α-diol (IId) differed only in that a twofold excess of the Grignard reagent prepared from *p*-chlorobromobenzene was allowed to react with cholestan-3β-ol-6-one (III).[2] The percentage yields, melting points and specific rotations are summarized in Table V.

**6β-Phenylcholestan-3β,6α-diol Monoacetate (IVa).**—To a solution containing 12.850 g. (0.0258 mole) of 6β-phenylcholestan-3β,6α-diol (IIa) dissolved in 75 ml. of anhydrous pyridine was added 40 ml. of acetic anhydride. The reaction mixture was placed on a steam-plate. After 1.5 hours the solution was cooled to room temperature and poured into ice-water. The solid material thus formed was filtered, washed with fresh water and dissolved in ether. Crystallization was effected by the addition of ethanol and the removal of more solvent by boiling. The material obtained in this manner weighed, after drying, 10.498 g. and had m.p. 176–176.5°. A second crop could be obtained from the mother liquor by the addition of water to the boiling solution to incipient crystallization, yielding 2.063 g., m.p. 175.5–176°. Total yield of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa) was 12.561 g. (93.2%). The analytical sample was prepared by recrystallization from ethanol–water, m.p. 176.0–176.4°, $[\alpha]D$ +3.9° (chloroform).

*Anal.* Calcd. for $C_{35}H_{54}O_4$: C, 79.94; H, 10.93. Found: C, 80.24; H, 10.68.

**6β-*p*-Anisyl-, 6β-*p*-Tolyl- and 6β-*p*-Chlorophenylcholestan-3β,6α-diol Monoacetate (IVb,c,d).**—The syntheses of these compounds proceeded in a manner analogous to that already described for the corresponding phenyl compound (IVa). The various percentage yields, specific rotations, melting points and analytical data are entered in Table V.

**6β-*p*-Nitrophenylcholestan-3β,6α-diol monoacetate (IVc)** was prepared by nitration of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa). To a suspension containing 1.418 g. (2.71 mmoles) of the phenyldiol monoacetate (IVa) in 12 ml. of acetic acid and 12 ml. of acetic anhydride, cooled to 0° in an ice-bath and stirred magnetically, was added dropwise 13 ml. of a solution containing equal volumes of acetic acid, acetic anhydride and fuming nitric acid (previously prepared by the dropwise addition with cooling and stirring of fuming nitric acid to acetic acid–acetic anhydride). The addition required about 12 minutes at which time solution of the steroid had been effected. After an additional two

TABLE V

PHYSICAL PROPERTIES OF VARIOUS STEROIDS

| Compound | Prepn. method[a] | Yield, % | M.p., °C. | $[\alpha]_D$ (chloroform) | Carbon, % Found | Carbon, % Calcd. | H, % Found | H, % Calcd. |
|---|---|---|---|---|---|---|---|---|
| 6β-Phenylcholestan-3β,6α-diol (IIa) | A | 86.2 | 190–192 | +10.0 | 82.44 | | 10.90 | |
| | | | | | | 82.20 | | 10.79 |
| 6β-*p*-Anisylcholestan-3β,6α-diol (IIb) | A | 82.3 | 222–224 | +10.5 | | | | |
| 6β-*p*-Tolylcholestan-3β,6α-diol (IIc) | A | 78.4 | 221–223 | +12.3 | | | | |
| 6β-*p*-Chlorophenylcholestan-3β,6α-diol (IId) | A[b] | 79.4 | 209–213 | + 9.2 | | | | |
| 6β-Phenylcholestan-3β,6α-diol monoacetate (IVa) | B | 93.2 | 175.5–176 | + 3.9 | 79.94 | | 10.93 | |
| | | | | | | 80.24 | | 10.68 |
| 6β-*p*-Anisylcholestan-3β,6α-diol monoacetate (IVb) | B | 90.9 | 196–198 | + 2.2 | 78.21 | | 10.21 | |
| | | | | | | 78.22 | | 9.98 |
| 6β-*p*-Tolylcholestan-3β,6α-diol monoacetate (IVc) | B | 80.4 | 204 | + 2.8 | 80.54 | | 10.52 | |
| | | | | | | 80.43 | | 10.28 |
| 6β-*p*-Chlorophenylcholestan-3β,6α-diol monoacetate (IVd) | B | 78.5 | 198.5–200 | + 1.3 | 75.57 | | 9.42 | |
| | | | | | | 75.31 | | 9.70 |
| 6β-*p*-Nitrophenylcholestan-3β,6α-diol monoacetate (IVe) | C | 40.8 | >245 | + 3.4 | 74.04 | | 9.41 | |
| | | | | | | 74.25 | | 9.72 |
| 6-Phenylcholesteryl acetate (Va) | D | 84.0 | 153–153.5 | −69.4 | 83.28 | | 10.38 | |
| | E | ~70 | 148–150 | | | 83.02 | | 10.14 |
| 6-*p*-Anisylcholesteryl acetate (Vb) | F | 85.6 | 85–88 | | | | | |
| 6-*p*-Tolylcholesteryl acetate (Vc) | D | ~48 | 112–119 | | | | | |
| | F | 85.5 | 114–118 | | | | | |
| 6-*p*-Chlorophenylcholesteryl acetate (Vd) | D | 84.1 | 114.5–117.5 | | | | | |
| 6-*p*-Nitrophenylcholesteryl acetate (Ve) | G | 87.3 | 121–122 | | | | | |
| 6-Phenylcholesterol (VIa) | H | 89.6 | 165.5–166.5 | −43.9 | 85.65 | | 10.89 | |
| | | | | | | 85.36 | | 11.03 |
| 6-Phenylcholesterol (VIa) | J | 54.4 | 158 | | | | | |
| 6-*p*-Anisylcholesterol (VIb) | H | 92.1 | 171–173 | −43.4 | 82.87 | | 10.64 | |
| | | | | | | 82.60 | | 10.89 |
| 6-*p*-Tolylcholesterol (VIc) | H | 92.0 | 166–169 | −46.0 | 85.65 | | 10.99 | |
| | | | | | | 85.81 | | 11.29 |
| 6-*p*-Chlorophenylcholesterol (VId) | H | 95.5 | 182 | −39.8 | 79.72 | | 9.94 | |
| | | | | | | 79.91 | | 10.22 |
| 6-*p*-Nitrophenylcholesterol (VIe) | H | 81.4 | 158–159 | −38.4 | 78.06 | | 9.73 | |
| | | | | | | 78.01 | | 9.49 |
| 6-Phenylcholesteryl *p*-toluenesulfonate (VIIa) | K | 95 | 141–142 d. | −11.5 | 77.87 | | 9.15 | |
| | | | | | | 77.67 | | 9.44 |
| 6-*p*-Anisylcholesteryl *p*-toluenesulfonate (VIIb) | K | 54.0 | 147 d. | −19.5 | 76.11 | | 9.04 | |
| | | | | | | 76.38 | | 9.07 |
| 6-*p*-Tolylcholesteryl *p*-toluenesulfonate (VIIc) | K | 57.4 | 152.5 d. | −25.2 | 78.05 | | 9.27 | |
| | | | | | | 77.93 | | 9.55 |
| 6-*p*-Chlorophenylcholesteryl *p*-toluenesulfonate (VIId) | K | 80.0 | 163 d. | − 5.7 | 73.75 | | 8.51 | |
| | | | | | | 73.54 | | 8.67 |
| 6-*p*-Nitrophenylcholesteryl *p*-toluenesulfonate (VIIe) | K | 78.6 | 164 d. | | 72.58 | | 8.38 | |
| | | | | | | 73.27 | | 8.85 |

[a] A, method described for preparation of 6β-phenylcholestan-3β,6α-diol (IIa); B, method described for preparation of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa); C, prepared by nitration of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa); D, prepared by dehydration of corresponding 6β-arylcholestan-3β,6α-diol monoacetate with phosphorus oxychloride as described for 6-phenylcholesteryl acetate (Va); E, prepared by acetylation of 6-phenylcholesterol (VIa); F, prepared by dehydration of corresponding 6β-arylcholestan-3β,6α-diol monoacetate with *p*-toluenesulfonic acid in acetic acid as described for 6-*p*-anisylcholesteryl acetate; G, prepared by dehydration of 6-*p*-nitrophenylcholestan-3β,6α-diol monoacetate (IVe) with thionyl chloride; H, prepared from the corresponding arylcholesteryl acetate as described for 6-phenylcholesterol (VIa); J, prepared by the sulfuric acid-catalyzed dehydration of 6β-phenylcholestan-3β,6α-diol (IIa); K, prepared from the corresponding arylcholesterol as described for 6-phenylcholesteryl *p*-toluenesulfonate (VIIa). [b] Synthesis began with cholestan-3β-ol-6-one (III).[2]

minutes of stirring, crystalline material separated. The reaction mixture was poured into ice-water. The white precipitated material was filtered off, washed well with fresh water, and taken up in ether. The ethereal solution was washed with fresh water and most of the solvent was removed on a steam-plate. The addition of ethanol followed by dropwise addition of water resulted in crystallization, yielding 629 mg. (40.8%), m.p. 245°, of 6β-*p*-nitrophenylcholestan-3β,6α-diol monoacetate. Purification was effected by repeated recrystallization from ether–ethanol $[\alpha]^{26}D$ +3.4° (chloroform).

*Anal.* Calcd. for $C_{35}H_{53}NO_6$: C, 74.04; H, 9.41. Found: C, 74.25; H, 9.72.

**6-Phenylcholesteryl Acetate (Va).**—To a solution containing 3.126 g. (0.00620 mole) of 6β-phenylcholestan-3β,6α-diol monoacetate (IVa) in 30 ml. of anhydrous pyridine (dried by distillation from barium oxide) was added 20 ml. of phosphorus oxychloride. The reaction mixture was allowed to stand at room temperature for 26 hours, was diluted with anhydrous ether, and the excess phosphorus oxychloride was decomposed by the dropwise addition of water. The water layer was removed and the ethereal layer washed

successively with fresh water, 10% sodium bicarbonate solution and again with fresh water. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and most of the solvent removed by boiling. Crystallization was effected by dilution with ethanol and subsequent dropwise addition of water to the boiling solution to incipient crystallization, yielding 2.535 g. (84.0%) of 6-phenylcholesteryl acetate (Va), m.p. 153.0–153.5°, $[\alpha]^{30}D$ −69.4° (chloroform).

An additional 183 mg. of ester was obtained from the mother liquor (total yield 89.9%). Repeated crystallization from the same solvent furnished the analytical sample, m.p. 153.0–153.5°.

*Anal.* Calcd. for $C_{35}H_{52}O_2$: C, 83.28; H, 10.38. Found: C, 83.02; H, 10.14.

**6-Phenylcholesteryl Acetate (Va).**—To a solution containing 45 mg. of 6-phenylcholesterol (VIa) (prepared by sulfuric acid-catalyzed dehydration of 6β-phenylcholestan-3β,6α-diol (IIa)) in 3 ml. of anhydrous pyridine was added 1.5 ml. of acetic anhydride. The reaction mixture was allowed to react on a steam-plate for 1.0 hour. On cooling, the solution was poured into water yielding an oil. This oil was dissolved in ether and the ethereal layer washed with fresh water. Most of the ether was removed on a steam-plate, methanol was added and the solubility of the product reduced with water until cloudy. On cooling, 37 mg. (70%) of 6-phenylcholesteryl acetate (Va), m.p. 144.5–148°, was obtained. Recrystallization from the same solvents gave 24 mg., m.p. 148.2–150°. A mixture melting point with authentic 6-phenylcholesteryl acetate, prepared by dehydration with phosphorus oxychloride, was undepressed.

**6-*p*-Anisylcholesteryl Acetate (Vb).**—A solution containing 1.941 g. (3.63 mmoles) of 6β-*p*-anisylcholestan-3β,6α-diol monoacetate (IVb) and 188 mg. of *p*-toluenesulfonic acid monohydrate in 200 ml. of glacial acetic acid was heated under reflux for 20 minutes, cooled to room temperature and diluted with water until cloudy; crystallization ensued. Two additional crops were obtained by further dilution of the mother liquor with water, yielding a total of 1.609 g. (85.6%) of 6-*p*-anisylcholesteryl acetate (Vb), m.p. 75–80°. This material was used without further purification in the succeeding synthetic step. The unpurified ester had m.p. 85–88°, $[\alpha]^{30}D$ −75.8° (chloroform).

**6-*p*-Tolylcholesteryl Acetate (Vc).**—The synthesis of this compound from 6β-*p*-tolylcholestan-3β,6α-diol monoacetate (IVc) was accomplished both by the action of phosphorus oxychloride–pyridine with techniques similar to those employed in the synthesis of 6-phenylcholesteryl acetate (Va) as well as with *p*-toluenesulfonic acid in acetic acid as described above for 6-*p*-anisylcholesteryl acetate (Vb). Pertinent physical constants are listed in Table V.

**6-*p*-Chlorophenylcholesteryl acetate (Vd)** was synthesized from 6β-*p*-chlorophenylcholestan-3β,6α-diol monoacetate (IVd) in a manner similar to that detailed above for 6-phenylcholesteryl acetate (Va); see Table V.

**6-*p*-Nitrophenylcholesteryl Acetate (Ve).**—6β-*p*-Nitrophenylcholestan-3β,6α-diol monoacetate (IVe) (738 mg.), dissolved in 8 ml. of anhydrous pyridine, was stirred magnetically with ice-bath cooling. To this solution was added dropwise 5 ml. of thionyl chloride. When the addition had been completed (about 5 minutes) the reaction mixture was diluted with a large quantity of anhydrous ether, and excess thionyl chloride was decomposed by the dropwise addition of water. This water layer was removed and the ethereal solution was washed with fresh water. Ether was removed almost to dryness by boiling and the solution was diluted with ethanol. Crystallization ensued with the dropwise addition of water, giving 624 mg. (87.3%), m.p. 121–122°, of 6-*p*-nitrophenylcholesteryl acetate. This material was used without further purification in the succeeding synthetic step.

**6-Phenylcholesterol (VIa).**—A solution prepared by dissolving 1.351 g. of 6-phenylcholesteryl acetate (Va) in 100 ml. of 95% ethanol containing 2.0 g. of potassium hydroxide was heated under reflux for 55 minutes. The hot basic solution was diluted with water to incipient crystallization. After cooling, the crystals were filtered off, washed with about 15 ml. of 50% ethanol, and dried, yielding 1.111 g. (89.6%) of 6-phenylcholesterol (VIa), m.p. 165.5–166.5°. Additional material could be obtained from the mother liquor. The analytical sample was prepared by repeated recrystallization from the same solvent, m.p. 165.5–166.5°, $[\alpha]^{30}D$ −43.9° (chloroform). The ultraviolet spectral data are included in Table II.

*Anal.* Calcd. for $C_{33}H_{50}O$: C, 85.65; H, 10.89. Found: C, 85.36; H, 11.03.

**6-Phenylcholesterol (VIa).**—A solution containing 153 mg. of 6β-phenylcholestan-3β,6α-diol (IIa) dissolved in 20 ml. of dioxane was heated under reflux with 5 ml. of 30% aqueous sulfuric acid for 3.75 hr. The reaction mixture was cooled to room temperature, poured into water and extracted with ether. The ethereal layer was washed successively with water, 10% sodium bicarbonate solution, and water. Most of the ether was boiled off, methanol was added and then water to crystallization. The crude 6-phenylcholesterol (VIa) obtained in this manner was recrystallized from ether–methanol–water, yielding 80 mg. (54.4%), m.p. 158°. A mixture melting point with 6-phenylcholesterol, prepared as described above, was undepressed.

**6-*p*-Anisyl-, 6-*p*-Tolyl-, 6-*p*-Chlorophenyl- and 6-*p*-Nitrophenylcholesterol (VIb,c,d,e).**—The synthesis of these compounds from the corresponding acetates (Vb,c,d,e) was carried out in a manner analogous to that previously described for 6-phenylcholesterol (VIa). The percentage yields, melting points, specific rotations and analytical data are recorded in Table V. The ultraviolet spectral data are found in Table II.

**6-Phenylcholesteryl *p*-Toluenesulfonate (VIIa).**—6-Phenylcholesterol (VIa) (1.111 g.) and *p*-toluenesulfonyl chloride (829 mg.) in 5.5 ml. of anhydrous pyridine were allowed to react at room temperature. After two days the reaction mixture was poured into ice-water. The solid material which separated out was filtered, washed with fresh water, and taken up in ether. The ethereal solution was washed with fresh water, dried over anhydrous potassium carbonate and filtered. The filtrate was concentrated almost to dryness at water-pump pressure. Acetone was added and more solvent was removed *in vacuo*. Finally the addition of 20 ml. of 50% aqueous acetone resulted in crystallization. Thorough drying of the gelatinous solid obtained in this manner yielded 1.073 g. (72.5%) of 6-phenylcholesteryl tosylate, m.p. 140°, with red discoloration occurring subsequent to melting. A second crop (333 mg.) was obtained by dilution of the mother liquor with water, m.p. 139° dec. Total yield of 6-phenylcholesteryl *p*-toluenesulfonate (VIa) was 95%.

The analytical sample was prepared by recrystallization of this crude ester from anhydrous acetone and cooling to −80°. The analytical sample (recovered in 82.0% yield) had m.p. 141–142.25° with subsequent decomposition, $[\alpha]^{30}D$ −11.5° (chloroform).

*Anal.* Calcd. for $C_{40}H_{56}SO_3$: C, 77.87; H, 9.15. Found: C, 77.67; H, 9.44.

**6-*p*-Anisyl-, 6-*p*-Tolyl-, 6-*p*-Chlorophenyl- and 6-*p*-Nitrophenylcholesteryl *p*-Toluenesulfonate (VIIb,c,d,e).**—The syntheses of these esters from the corresponding alcohols (VIb,c,d,e) was patterned after that described above for 6-phenylcholesteryl *p*-toluenesulfonate (VIIa). Table V contains the pertinent physical constants and analytical data.

**Attempted Dehydration of 6β-Phenylcholestan-3β,6α-diol Monoacetate (IVa).**—This compound (368 mg.) was dissolved in 50 ml. of a solution containing 8% by volume hydrochloric acid. This reaction mixture was heated under reflux for 40 minutes. The condenser was removed and solvent was removed by boiling to a total volume of about 25 ml. Crystallization was effected by the dropwise addition of water to this warm reaction mixture. The crystalline product was filtered and air-dried, m.p. 190–191.5°; a mixture melting point with authentic 6β-phenylcholestan-3β,6α-diol (IIa) was undepressed.

**Acknowledgments.**—This work was supported, in part, by a grant from the du Pont Co. The elemental analyses were performed by Mrs. C. S. Yeh. The nuclear magnetic spectra were run at the University of Illinois by Mr. Ben Shoulders.

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