4. G. E. ARTH, G. I. POOS, and L. H. SARETT. J. Am. Chem. Soc. **77**, 3834 (1955).
5. P. LASZLO and P. VON R. SCHLEYER. J. Am. Chem. Soc. **86**, 1171 (1964).

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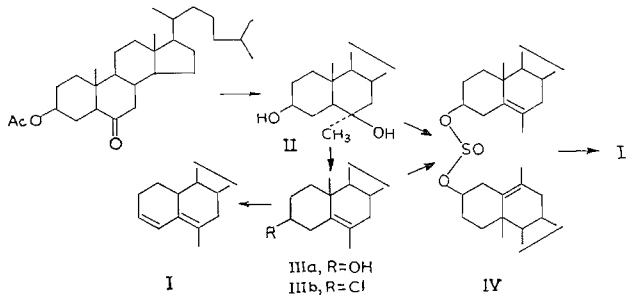
SYNTHESIS OF 6-METHYLCHOLESTA-3,5-DIENE; SOLVOLYSIS OF 6-METHYLCHOLESTERYL IODIDE[1]

GEORGE JUST AND EDWARD LEE-RUFF[2]

In connection with a study of the photolysis of substituted cholesta-3,5-dienes, we required a sample of 6-methylcholesteryl ethyl ether and adequate amounts of 6-methylcholesta-3,5-diene (I). The latter compound had been obtained by Bauslaugh (1) in an unsatisfactory yield.

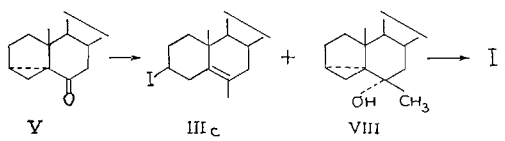
We therefore investigated an alternate pathway. 6α-Methylcholestan-3β,6β-diol (II) (2), obtained as outlined in Reaction Scheme 1, was submitted to various dehydrating agents. Treatment of II with 10% ethanolic hydrochloric acid gave 6-methylcholesterol (III*a*) (2) and 6-methylcholesteryl chloride (III*b*) (3) in 67 and 20% yields, respectively.



REACTION SCHEME 1.

Reaction of 6-methylcholesterol with thionyl chloride gave di(6-methylcholesteryl) sulfite (IV). The same product was obtained by reacting diol II with thionyl chloride. Its structure was proven by hydrolysis to III*a*. Pyrolysis of sulfite IV gave 6-methylcholesterol (III*a*) and diene I. Pyrolysis of 6-methylcholesterol with anhydrous copper sulfate gave a 1:1 mixture of the desired diene I and di(6-methylcholesteryl) ether.

The most convenient sequence proved to be that depicted in Reaction Scheme 2.



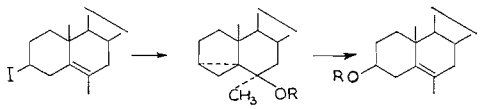
REACTION SCHEME 2.

[1]*We thank the National Research Council of Canada for financial support.*
[2]*Holder of a National Research Council of Canada bursary, 1964–1965, and studentship, 1965–1966.*

Reaction of 3α,5-cyclo-5α-cholestan-6-one (V) with methylmagnesium iodide gave 6β-methyl-3α,5-cyclo-5α-cholestan-6α-ol (VIII) (4) in a 75% yield. The minor product of this reaction was 6-methylcholesteryl iodide (III*c*). The assignment of the stereochemistry of alcohol VIII at C-6 was based on arguments similar to those used to explain the stereochemistry of the lithium aluminium hydride reduction of V (5). The formation of 6-methylcholesteryl iodide is easily rationalized, since the reaction medium contained iodide ions and a Lewis acid. Dehydration and rearrangement of the cyclopropyl carbinol was achieved by stirring alcohol VIII in dry benzene with phosphorus pentoxide. The desired 6-methylcholesta-3,5-diene (I) was obtained in over 90% yield.

*6-Methylcholesteryl Ethyl Ether; a Study of the Solvolysis of 6-Methylcholesteryl Iodide (III*c*)*

One of the by-products obtained above was 6-methylcholesteryl iodide (III*c*). Since a sample of 6-methylcholesteryl ethyl ether (VII*a*) was required for comparison purposes, we solvolyzed iodide IIIc in ethanol. The major product obtained was cycloether VI*a*, accompanied by small amounts of VII*a*. Cycloether VI*a* was not stable under the solvolysis conditions and was slowly transformed to VII*a*. When cycloether VI*a* was treated with acidified ethanol at room temperature, it was quantitatively converted into ether VII*a*. The methanolysis and hydrolysis of iodide III*c* proceeded in a similar fashion.



IIIc VIa, R=Et VIb, R=Me VIc, R=H VIIa, R=Et VIIb, R=Me

REACTION SCHEME 3.

The structure of 6-methylcholesteryl ether was proven by comparison with the product obtained from the reaction of the potassium salt of III*a* with ethyl iodide. The assignments of the structures of the cyclo compounds VI*a*–VI*c* were based on the infrared and nuclear magnetic resonance spectra (which all showed cyclopropyl absorptions at 3 080 and 3 020 cm^{-1} (infrared) and 0.4–0.6 p.p.m. (nuclear magnetic resonance)) and the fact that acid treatment resulted in the formation of cholesteryl derivatives (VII*a*, VII*b*, and III*a*).

When 6-methylcholesteryl *p*-toluenesulfonate was solvolyzed under conditions identical with those used for the hydrolysis of 6-methylcholesteryl iodide, the same relative yield of 6α-methyl-3α,5-cyclo-5α-cholestan-6β-ol (VI*c*) was obtained. It is therefore apparent that the same homoallylic carbonium ion is involved in both the iodide and tosylate solvolyses, and the low yields of VI*c* reported by Davis *et al.* can be rationalized by the decomposition of VI*c* to 6-methylcholesterol (III*a*) under the reported reaction and work-up conditions (4). These results are therefore quite similar to those reported by Summers in the spirostane series (6).

EXPERIMENTAL

The general experimental details have been given in ref. 7. All preparative thin-layer chromatography (t.l.c.) separations were performed with glass plates (20 × 20 cm) covered with silica gel (½ mm, E. Merck A.G.).

Acid Dehydration of Diol II

A solution of 1.5 g of diol II in 50 ml of ethanol containing 5 ml of concentrated hydrochloric acid was refluxed for 3 h. The reaction mixture was diluted with 200 ml of ether, washed with 5% aqueous sodium bicarbonate and water, and dried with anhydrous magnesium sulfate. The residue, after evaporation,

crystallized from ether–hexane, giving 1.05 g of 6-methylcholesterol (III*a*), m.p. 131–135°. Recrystallization from hexane gave an analytic sample, m.p. 139–141°; the mixed melting point with an authentic sample showed no depression; ν 3 550 and 1 050 – 1 060 cm^{-1} (OH); δ 3.55 p.p.m. (1 H, multiplet, C_3—H), 2.90 p.p.m. (1 H, half of an AB quartet, C_4—H), 1.85 p.p.m. (1 H, singlet, exchangeable with D_2O, —OH), and 1.65 p.p.m. (3 H, singlet, C=C—CH_3). Crystallization of the mother liquor from ethanol–ether gave 300 mg of 6-methylcholesteryl chloride, m.p. 101–104°. Recrystallization from ethanol raised the m.p. to 105–106°; ν 847 cm^{-1} (C—Cl); δ 3.65 p.p.m. (1 H, multiplet, C_3—H), 3.0 p.p.m. (1 H, half of an AB quartet, C_4—H), and 1.62 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{28}H_{47}Cl$: C, 80.24; H, 11.21; Cl, 8.46. Found: C, 80.21; H, 11.21; Cl, 8.32.

Dehydration of Diol II with Thionyl Chloride – Pyridine

A solution of 200 mg of diol II in 15 ml of anhydrous pyridine was cooled to 0°, and 0.1 ml of thionyl chloride was added dropwise, with stirring. The reaction mixture was allowed to reach room temperature and the stirring was continued for an additional hour. The mixture was quenched with 20 ml of cold water, and the resulting white precipitate was filtered off, washed with water until neutral, and crystallized from ethanol–ether, giving 190 mg of di(6-methylcholesteryl) sulfite (IV), m.p. 191–192°; ν 1 200, 950, and 925 cm^{-1} (strong, sulfite); δ 4.25 p.p.m. (1 H, multiplet, C_3—H), 2.9 p.p.m. (1 H, half of an AB quartet, C_4—H), and 1.65 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{56}H_{94}SO_3$: C, 79.40; H, 11.17; S, 3.80. Found: C, 79.29; H, 10.95; S, 4.10.

Dehydration of 6-Methylcholesterol (IIIa) with Thionyl Chloride – Pyridine

The same procedures as for the thionyl chloride dehydration of diol II were used for the dehydration of 100 mg of 6-methylcholesterol (III*a*). This yielded 90 mg of the diester sulfite IV, identical in all respects with the sample obtained above.

Acid Hydrolysis of Diester Sulfite IV

A solution containing 100 mg of IV in 20 ml of ethanol and 2 ml of concentrated hydrochloric acid was refluxed for 1 h. The reaction mixture was worked up in the usual manner, yielding 70 mg of 6-methylcholesterol (III*a*), identical in all respects with an authentic sample.

Pyrolysis of Diester Sulfite IV

A melting point tube containing 2 mg of IV was heated to 205°. The pyrolysate was dissolved in ether. Quantitative t.l.c. showed two stains, one having an R_f value identical with that of 6-methylcholesterol. The ultraviolet spectrum showed diene absorptions at 236, 242, and 249 mμ.

Pyrolysis of 6-Methylcholesterol (IIIa)

An intimate mixture of 500 mg of 6-methylcholesterol (III*a*) and 500 mg of anhydrous cupric sulfate was heated to 200° for 20 min. The residue was extracted with benzene and the extract chromatographed on silica gel. Hexane eluted 260 mg of 6-methylcholesta-3,5-diene, which was crystallized from an ethanol–ether mixture, m.p. 86–88°; ν 3 040 and 1 650 cm^{-1} (C=C—H); λ_{max}^{EtOH} 236 mμ (ϵ 18 220), 242 mμ (ϵ 19 800), and 249 mμ (ϵ 13 900); δ 6.42 p.p.m. (1 H, doublet, J = 10 c.p.s., C=C_4—H), 5.80 p.p.m. (1 H, broad signal, C=C_3—H), and 1.72 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 87.91; H, 12.28.

Hexane–benzene eluted 140 mg of di(6-methylcholesteryl) ether, which was crystallized from ether, m.p. 215–216°; ν 1 100 and 1 080 cm^{-1} (ether); δ 3.35 p.p.m. (1 H, multiplet, C_3—H), 2.87 p.p.m. (1 H, half of an AB quartet, C_4—H), and 1.65 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{56}H_{94}O$: C, 85.86; H, 12.10. Found: C, 85.86; H, 11.88.

6β-Methyl-3α,5-cyclo-5α-cholestan-6α-ol (VIII)

A solution of 5 g of 3α,5-cyclo-5α-cholestan-6-one (V) in 100 ml of ether was added dropwise to 120 ml of an ethereal solution of methylmagnesium iodide (3.2 g magnesium turnings, 8.8 ml methyl iodide). The solution was heated under reflux for 2 h. The excess reagent was destroyed by slowing adding 50 ml of 10% aqueous ammonium chloride. The ether layer was washed with water until neutral, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The oily residue was chromatographed on alumina (activity II–III, 140 g). Elution with hexane gave 6-methylcholesteryl iodide (III*c*) (1.1 g, 20%), m.p. 103–105°. Two crystallizations from ethanol–ether raised the melting point to 110–111°; δ 4.00 p.p.m. (1 H, broad signal, C_3—H), 2.95 p.p.m. (2 H, quartet, C_4—H), and 1.65 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{28}H_{47}I$: C, 65.88; H, 9.21; I, 24.81. Found: C, 65.93; H, 9.33; I, 24.94.

Elution with benzene–ether gave 3.7 g of 6β-methyl-3α,5-cyclo-5α-cholestan-6α-ol (VIII), identical in all respects with an authentic sample (4), m.p. 91–91.5°, $[\alpha]_D^{19}$ +38.2° (*c*, 0.87).

6-Methylcholesta-3,5-diene (I)

A solution of 3.5 g of 6β-methyl-3α,5-cyclo-5α-cholestan-6α-ol (VIII) in 100 ml of anhydrous benzene containing 3 g of phosphorus pentoxide was stirred for 3 h at room temperature. Ether extraction and crystallization from ethanol gave 3.2 g of 6-methylcholesta-3,5-diene (I), identical in all respects with the sample prepared above.

Ethanolysis of 6-Methylcholesteryl Iodide (IIIc)

A solution of 300 mg of iodide IIIc in 50 ml of absolute ethanol containing 200 mg of potassium acetate was refluxed for 1 h. The mixture was diluted with 150 ml of ether, washed with water until neutral, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was chromatographed on two t.l.c. plates (hexane–benzene (1:1)), giving 188 mg of oily 6β-ethoxy-6α-methyl-3α,5-cyclo-5α-cholestane (VIa), ν 3 080 and 3 020 cm^{-1} (cyclopropane), 1 115 and 1 085 cm^{-1} (ether); δ 3.39 p.p.m. (2 H, two overlapping quartets, O—CHH′—CH_3) and 0.4–0.6 p.p.m. (multiplet, cyclopropyl protons).

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.03; H, 12.12.

6-Methylcholesteryl Ethyl Ether (VIIa)

From 6-Methylcholesterol (IIIa)

To a solution of 180 mg of 6-methylcholesterol (IIIa) in 50 ml of anhydrous benzene was added 200 mg of potassium chips. The mixture was refluxed for 3 h and cooled to room temperature, after which 1 ml of ethyl iodide was added. The mixture was refluxed for a further 24 h. After the solution was cooled, absolute ethanol was slowly added to destroy the excess potassium. The mixture was diluted with 100 ml ether, washed with water until neutral, dried over anhydrous magnesium sulfate, and evaporated. The residue (131 mg) was chromatographed on one t.l.c. plate (benzene), giving 52 mg of 6-methylcholesteryl ethyl ether (VIIa), m.p. 95–96°; ν 1 105 cm^{-1} (ether); δ 3.42 p.p.m. (2 H, quartet, O—CH_2—CH_3), 2.80 p.p.m. (1 H, multiplet, C_3—H), and 1.55 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.95; H, 12.10.

From Cycloether VIa

A solution of 100 mg of cycloether VIa in 25 ml of absolute ethanol containing 0.5 ml of 72% perchloric acid was stirred overnight. The resulting precipitate was filtered off, washed with water, and crystallized from ethanol–ether, giving 75 mg of 6-methylcholesteryl ethyl ether (VIIa), identical in all respects with the sample prepared above.

Methanolysis of 6-Methylcholesteryl Iodide (IIIc)

A solution of 300 mg of iodide IIIc in 50 ml of absolute methanol containing 200 mg of potassium acetate was stirred at room temperature for 24 h. The reaction mixture was worked up in the usual manner, giving 290 mg of an oil, which was chromatographed on two t.l.c. plates (hexane–benzene (1:1)), yielding 135 mg of oily 6β-methoxy-6α-methyl-3α,5-cyclo-5α-cholestane (VIb), ν 3 080 and 3 020 cm^{-1} (cyclopropane), 1 089 cm^{-1} (ether); δ 3.11 p.p.m. (3 H, singlet, O—CH_3) and 0.3–0.6 p.p.m. (multiplet, cyclopropyl protons).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.96; H, 12.06.

Acid Reaction of Cycloether VIb

The same procedures were followed as for the acid rearrangement of cycloether VIa (100 mg of VIb being used). This gave, after crystallization from methanol–ether, 65 mg of 6-methylcholesteryl methyl ether, m.p. 101–102°; ν 1 105 cm^{-1} (ether); δ 3.20 p.p.m. (3 H, singlet, O—CH_3), 2.75 p.p.m. (1 H, multiplet, C_3—H), and 1.57 p.p.m. (3 H, singlet, C=C—CH_3).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.00; H, 12.05.

Hydrolysis of 6-Methylcholesteryl Iodide (IIIc)

A solution of 200 mg of iodide IIIc in 25 ml of acetone containing 5 ml of water and 50 mg of potassium bicarbonate was stirred for 72 h. This was worked up in the usual manner to give 184 mg of an oily residue. Chromatography of this residue on two t.l.c. plates (benzene) yielded 147 mg of oily cycloalcohol VIc, ν 3 620, 1 105, and 1 020 cm^{-1} (alcohol), 3 080 and 3 020 cm^{-1} (cyclopropane); δ 0.2–0.5 p.p.m. (multiplet, cyclopropyl protons).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.06; H, 11.91.

Acid Rearrangement of Cycloalcohol VIc

A solution of 100 mg of cycloalcohol VIc in 50 ml of ether containing 1 ml of 72% perchloric acid was stirred overnight. The solution was diluted to 100 ml with ether, washed with 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure, giving 95 mg of 6-methylcholesterol (IIIa), identical in all respects with the sample prepared above.

Solvolysis of 6-Methylcholesteryl p-Toluenesulfonate

The tosylate of 6-methylcholesterol was prepared according to the procedures of Davis *et al.* (4). A solution of 200 mg of the tosylate (m.p. 128–133°) in 25 ml of acetone containing 5 ml of water and 50 mg of potassium bicarbonate was stirred for 72 h. The usual work-up gave 194 mg of an oily residue, which was chromatographed on two t.l.c. plates, yielding 63 mg of unreacted 6-methylcholesteryl *p*-toluenesulfonate and 90 mg of cycloalcohol VIc, identical in all respects with the sample prepared above.

1. G. Bauslaugh. Ph.D. Thesis, McGill University, Montreal, Quebec. 1965.
2. L. F. Fieser and J. Rigaudy. J. Am. Chem. Soc. **73**, 4660 (1951).
3. M. Shiota. Nippon Kagaku Zasshi, **77**, 778 (1956); Chem. Abstr. **52**, 417 (1958).
4. M. Davis, S. Julia, and G. H. R. Summers. Bull. Soc. Chim. France, 742 (1960).

5. G. JUST and K. ST. C. RICHARDSON. Can. J. Chem. **42**, 456 (1964).
6. G. H. R. SUMMERS. J. Chem. Soc. 1821 (1961).
7. N. D. HALL and G. JUST. Steroids, **6**, 111 (1965).

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A CONVENIENT METHOD FOR THE PREPARATION OF OPTICALLY ACTIVE BENZYL-α-*d* ALCOHOL

SAUL WOLFE AND ARVI RAUK

Optically active benzyl-α-*d* alcohol was synthesized some years ago and the levo enantiomer shown to have the *R* absolute configuration (I) by Streitwieser and his co-workers (1). Their method involved the preparation of benzaldehyde-*d* from benzonitrile (2), the reduction of (+)-camphor to (−)-isoborneol with lithium aluminium hydride (3), and then asymmetric reduction of the benzaldehyde-*d* with isobornyloxymagnesium bromide (4). (−)-Benzyl-α-*d* alcohol, $[\alpha]_D$ −0.715° (neat), was obtained after a lengthy isolation procedure. The optical purity of this material cannot be better than 45%, since Mosher and his co-workers have now found (5) that the optically active benzyl-α-*d* alcohol produced in the reduction of benzaldehyde-*d* with actively fermenting yeast has $[\alpha]_D^{24}$ 1.58° (neat). The same workers also obtained (+)-benzyl-α-*d* alcohol, $[\alpha]_D^{26}$ 0.32° (neat), in a 16% yield (average of two runs) from the reaction of benzaldehyde-α-*d* with the optically active Grignard reagent from (+)-1-chloro-2-methylbutane.

During another investigation, we recently had to prepare optically active benzyl-α-*d* alcohol. Since high optical purity was not essential for this study, an alternative to the Streitwieser procedure was worked out and forms the subject of this note. The new synthesis, which proceeds with 30% stereospecificity, has the advantage of providing the dextro alcohol in 1 day's working time, with all the reactions being performed in a single vessel. The deuterium source is sodium borodeuteride; from 0.5 g of this compound is obtained 1.1 g of (+)-benzyl-α-*d* alcohol. The actual reducing agent is (−)-diisopinocampheyldeuterioborane (II), prepared from (+)-α-pinene and deuterated diborane, the latter in turn prepared in tetrahydrofuran by the reduction of boron trifluoride with sodium borodeuteride.

Brown and his co-workers have shown (6, 7) that hydroboration of olefins with undeuterated II followed by the usual oxidative work-up (8) leads to optically active alcohols and (−)-isopinocampheol. The reduction of methyl ketones III to optically active secondary alcohols (11–30% excess of the *R* enantiomer, i.e. IV) was reported in a brief communication (9).[1] By analogy with this work, the reduction of benzaldehyde (VI) by II is expected to produce VII, i.e. *S*-(+)-benzyl-α-*d* alcohol.

No volatile compounds were obtained directly from the reaction of II with benzaldehyde, even after prolonged treatment with sodium hydroxide. Benzyl alcohol and isopinocampheol were readily obtained, however, when this alkaline mixture was treated with

[1]*Although it is not specifically stated in this communication that the reducing agent was (−)-diisopinocampheylborane and not the (+)-isomer V, we infer that the former was, in fact, used, since the preparation of V was not described until somewhat later (7).*