941. *Steroids and Walden Inversion. Part XXXIV.* Solvolysis of Cholesteryl Toluene-*p*-sulphonate with Thiophenoxide Ions.*

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Cholesteryl toluene-*p*-sulphonate, on treatment with sodium thiophenoxide in boiling ethanol under nitrogen, affords 3 : 5-*cyclo*cholest-6-ene (8%), 6β-phenylthio-3 : 5-*cyclo*cholestane (32%), and 3α-phenylthiocholest-5-ene (13%), but 3β-phenylthiocholest-5-ene could not be detected. The structures of the last three compounds were proved by unambiguous partial syntheses.

The reaction mechanisms responsible for the formation of the above products are discussed. The experimental observations provide further evidence of the high nucleophilic power of the thiophenoxide ion, and of the abnormally great reactivity of this ion in processes involving attack on covalently bound hydrogen.

In Part XXIII [1] of this series it was established that replacement reactions at $C_{(3)}$ in 3β-substituted Δ^5-steroids under appropriate conditions can lead to 3α-substituted Δ^5-steroids. It was also suggested that the important factors influencing the course of the reaction are the reactivity of the nucleophil and the dielectric constant of the medium. Thus replacement reactions with weakly nucleophilic reagents,[2] *e.g.*, ethoxide, methoxide, and acetate ions, proceed by a unimolecular heterolysis (S_N1) leading to retention of configuration, a result dependent on the intervention of the π-electrons of the 5 : 6-double bond in the intermediate transition state. However, with more powerful nucleophils, *e.g.* ammonia, benzylamine, this reaction pattern is accompanied by a bimolecular substitution (S_N2) with inversion of configuration at $C_{(3)}$ in which the π-electrons of the 5 : 6-double bond do not participate. In order to obtain further information concerning the effect of nucleophilic reactivity on the reaction path, the reaction of cholesteryl toluene-*p*-sulphonate with the thiophenoxide ion has been studied.

The selection of this reagent followed from its very great reactivity demonstrated in replacement reactions at carbon atoms in both aliphatic and aromatic systems. de la Mare and Vernon [3] have shown that in the reaction of thiophenoxide ion with 3 : 3-dichloroprop-1-ene bimolecular displacement (S_N2 and S_N2') proceeds 240 times faster than in the corresponding reaction with ethoxide ion. Quayle and Royals,[4] by comparing the reactivities of phenoxide ion and thiophenoxide ion with *n*-butyl bromide, have provided evidence that the latter nucleophil is about 1000 times the more powerful. Furthermore, Bunnet and Davis [5] have found that the reaction of thiophenoxide ion with 1-chloro-2 : 4-dinitrobenzene was immeasurably fast at 0° and that the reactivity of the thiophenoxide ion was 580 times greater than that of methoxide ion under identical conditions; they have established the following comparative scale of nucleophilic activity: thiophenoxide ion $\gg$ piperidine $>$ methoxide $>$ phenoxide $\gg$ hydroxide. In comparison with its extreme nucleophilic power, the thiophenoxide ion has only a small tendency to attack a proton and is therefore unlikely to cause prototropic changes or elimination reactions.

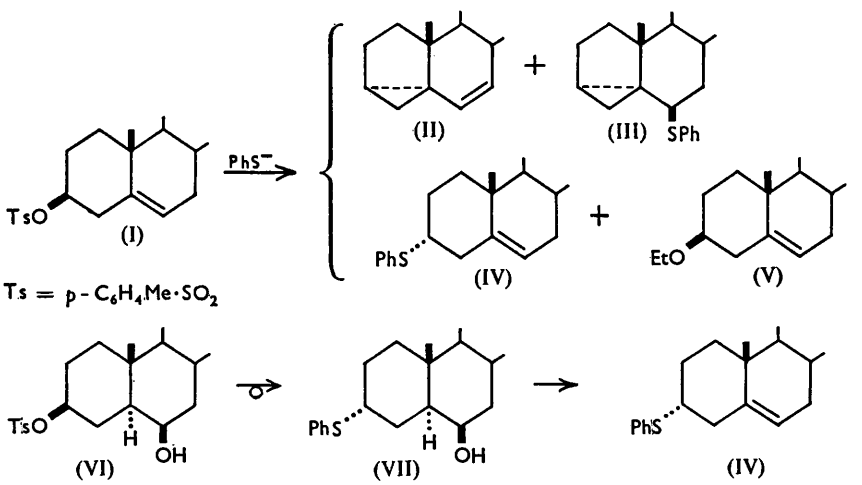
* Part XXXIII, *J.*, 1956, 2492.

[1] Shoppee, Pierce, Richards, Stephenson, and Summers, *J.*, 1955, 694.
[2] Shoppee and Westcott, *J.*, 1955, 1891.
[3] de la Mare and Vernon, *J.*, 1952, 3331.
[4] Quayle and Royals, *J. Amer. Chem. Soc.*, 1942, **64**, 226.
[5] Bunnet and Davis, *ibid.*, 1954, **76**, 3011.

Consequently it is reasonable to expect that in its reaction with 3β-substituted Δ^5-steroids, unimolecular heterolysis will be very largely superseded by bimolecular substitution, giving an increased yield of 3α-substituted Δ^5-steroid.

Previous attempts to prepare thiocholesterol derivatives by solvolysis of cholesteryl toluene-*p*-sulphonate (I) have not in general been successful. Thus this ester failed to react with boiling propane-1-thiol [6] or with ethanethiol in acetone or dioxan.[7] Treatment with thiophenol at 50° yielded a compound tentatively regarded as 3 : 5-diphenylthiocholestane, m. p. 186°, although the specific rotation, $[\alpha]_D$ −127°, appears to exclude this formulation. On the other hand, treatment of 3β-chlorocholest-5-en-7-one in acetic–hydrochloric acid with ethanethiol gave 3β-ethylthiocholest-5-en-7-one in excellent yield.[8] It is improbable that this product results directly by replacement of the chlorine atom by the mercaptan since normally inversion occurs, *e.g.*, in the acetolysis of 3β-chlorocholest-5-en-7-one;[9] it most probably arises by 1 : 4-addition of ethanethiol to the intermediate cholesta-3 : 5-dien-7-one produced by dehydrohalogenation (cf. Ralls, Dodson, and Riegel [8]).

Extended treatment of cholesteryl toluene-*p*-sulphonate (I) with sodium thiophenoxide in boiling ethanol under nitrogen gave a complex mixture, which by repeated chromatography was separated into 3 : 5-*cyclo*cholest-6-ene,[10] m. p. 72°, $[\alpha]_D$ −43° (II) (8%),



6β-phenylthio-3 : 5-*cyclo*cholestane, $[\alpha]_D$ +34° (III) (32%), 3α-phenylthiocholest-5-ene, double m. p. 102° and 114°, $[\alpha]_D$ −43° (IV) (13%), 3β-ethoxycholest-5-ene (V) (3·5%), and diphenyl disulphide, m. p. 61° (13·5%). No detectable amount of 3β-phenylthiocholest-5-ene (IX) was formed.

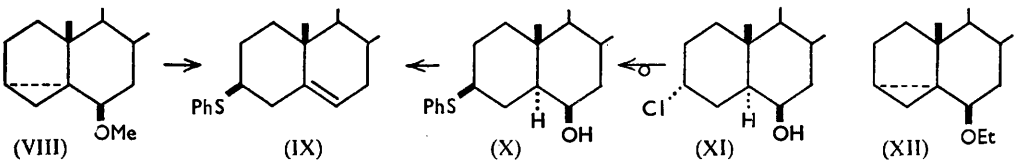
The structure of the sulphide (IV) was proved by the following partial synthesis. 6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate [11] (VI) with sodium thiophenoxide in boiling ethanol furnished, with inversion of configuration, 3α-phenylthiocholestan-6β-ol (VII), smoothly dehydrated by phosphorus oxychloride–pyridine at 15° to 3α-phenylthiocholest-5-ene (IV).

Cleavage of 6β-phenylthio-3 : 5-*cyclo*cholestane (III) with thiophenol in benzene containing sulphuric acid gave 3β-phenylthiocholest-5-ene, m. p. 72—74°, $[\alpha]_D$ −39° (IX), identical with the product obtained by rearrangement of 6β-methoxy-3 : 5-*cyclo*cholestane (VIII) in the same medium. Alternatively this sulphide (IX) was obtained by treatment of

[6] McKennis, *J. Amer. Chem. Soc.*, 1948, **70**, 675.
[7] J. C. Colbert, Ph.D. Thesis, Northwestern University, 1946, p. 51.
[8] Ralls, Dodson, and Riegel, *J. Amer. Chem. Soc.*, 1949, **71**, 3320.
[9] Shoppee, *J.*, 1946, 1149; cf. Marker, *J. Amer. Chem. Soc.*, 1937, **59**, 619.
[10] Riegel, Hager, and Zenitz, *J. Amer. Chem. Soc.*, 1946, **68**, 2562.
[11] Shoppee and Stephenson, *J.*, 1954, 2230.

3α-chlorocholestan-6β-ol [12] (XI) with sodium thiophenoxide in ethanol, followed by dehydration of the intermediate 3β-phenylthiocholestan-6β-ol (X) with phosphorus oxychloride–pyridine at 15°.

It is evident from these experiments that solvolysis of cholesteryl toluene-*p*-sulphonate in the presence of thiophenoxide ions involves a bimolecular substitution (S_N2) with



inversion of configuration at $C_{(3)}$, to give 3α-phenylthiocholest-5-ene (IV), accompanied by a unimolecular heterolysis (S_N1) leading to 6β-phenylthio-3 : 5-*cyclo*cholestane (III) and 3 : 5-*cyclo*cholest-6-ene (II). The formation of the sulphide (IV) is consistent with the high nucleophilic power of the thiophenoxide ion.

The production of 3 : 5-*cyclo*cholestan-6β-yl sulphide (III) rather than of the 3β-Δ^5-isomeride (IX) appears to be explicable by the high nucleophilic power of the thiophenoxide ion in terms of its rate of attack on carbon; there is evidence to support the view that the equilibria involved in the 3 : 5-*cyclo*steroid rearrangement are subject to kinetic control,[13, 14, 15] so that the mesomeric cation is attacked relatively much more rapidly at $C_{(6)}$ to give (III) than at $C_{(3)}$ to yield (IX). It also seems that of the two possible elimination reactions available to the mesomeric cation, *viz.*, the formation of cholesta-3 : 5-diene and of 3 : 5-*cyclo*cholest-6-ene (II), that leading to the latter is again relatively much more rapid; the formation of (II) constitutes a case, additional to those recently reported by de la Mare and Vernon [16] and Eliel and Ro,[17] in which abnormally great reactivity of the thiophenoxide ion appears as a characteristic of rate processes involving attack on covalently bound hydrogen.

The small amount (3·5%) of 3β-ethoxycholest-5-ene (V) appears to be a primary reaction product; it does not arise by rearrangement [13] of 6β-ethoxy-3 : 5-*cyclo*cholestane (XII), since under the experimental conditions we find that 6β-ethoxy-3 : 5-*cyclo*cholestane (XII) does not rearrange to 3β-ethoxycholest-5-ene (V). We are unable satisfactorily to account for the formation of the ether (V), and we are examining the production and properties of the ethyl ethers (V) and (XII).

Experimental

$[\alpha]_D$ are measured in chloroform.

Solutions of sodium thiophenoxide were prepared by adding the theoretical quantity of thiophenol to sodium dissolved in ethanol.

3β-*Phenylthiocholest-5-ene*.—(i) 6β-Methoxy-3 : 5-*cyclo*cholestane (2 g.) in benzene (50 c.c.) containing concentrated sulphuric acid (4 drops) was refluxed with thiophenol (3 c.c.) for 18 hr. After several washings with 2N-potassium hydroxide the benzene solution on evaporation yielded an oil, $[\alpha]_D$ −23·5° (*c* 1·4) (2·1 g.), which was chromatographed on aluminium oxide (30 g.). Elution with pentane (6 × 30 c.c.) furnished an oil which by crystallisation from acetone gave 3β-*phenylthiocholest-5-ene* as plates, m. p. 72—74°, $[\alpha]_D$ −39° (*c* 1·1) (1·5 g.) [Found (after drying at 18°/0·03 mm. for 12 hr.): C, 82·4; H, 10·7. $C_{33}H_{50}S$ requires C, 82·8; H, 10·5%].

(ii) A solution of 3α-chlorocholestan-6β-ol (1 g.) and sodium thiophenoxide (3 g.) in ethanol (50 c.c.) was boiled for 18 hr. After dilution with water the product was extracted with ether, the ethereal solution washed with 2N-potassium hydroxide solution, dried, and evaporated to yield an oil (1·1 g.) which was chromatographed on aluminium oxide (30 g.). Elution with

[12] Shoppee and Summers, *J.*, 1952, 1790.
[13] Winstein and Schlesinger, *J. Amer. Chem. Soc.*, 1948, **70**, 3528.
[14] Shoppee and Nes, *J.*, in the press.
[15] Shoppee and Williams, *J.*, 1956, 2488.
[16] de la Mare and Vernon, *J.*, 1956, 41.
[17] Eliel and Ro, *Chem. and Ind.*, 1956, 251.

pentane (350 c.c.) yielded oils (400 mg.) which gave a positive Beilstein test; elution with benzene–pentane and with benzene gave oils (500 mg.) giving a positive Lassaigne test for sulphur. A solution of the last in pyridine (5 c.c.) was treated at 0° with phosphorus oxychloride (0·5 c.c.) and left for 16 hr. Working up in the usual way gave an oil (350 mg.) which was chromatographed on aluminium oxide (20 g.). Elution with pentane gave, after crystallisation from acetone, 3β-phenylthiocholest-5-ene, m. p. and mixed m. p. 72—74°.

3α-*Phenylthiocholest-5-ene*.—6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (2·8 g.) in ethanol (100 c.c.) was refluxed with sodium thiophenoxide (10 g.), for 18 hr. Working up in the usual way gave an oil (3 g.) which was chromatographed on aluminium oxide (100 g.). Elution with pentane (900 c.c.) gave diphenyl disulphide, m. p. 54—56°; elution with pentane–ether gave an oil (2 g.) which by crystallisation from ethanol yielded 3α-*phenylthiocholestan*-6β-*ol*, m. p. 107—109°, $[\alpha]_D$ +27° (*c* 1·03) [Found (after drying at 18°/0·03 mm. for 12 hr.): C, 79·3; H, 10·6. $C_{33}H_{52}OS$ requires C, 79·8; H, 10·55%]. A solution of this sulphide (1·5 g.) in pyridine (10 c.c.) was treated at 0° with phosphorus oxychloride (2 c.c.). Working up in the usual way gave a solid (1·2 g.) which by crystallisation from acetone gave 3α-*phenylthiocholest-5-ene*, double m. p. 102° and 112°, $[\alpha]_D$ −42·8° (*c* 0·92) [Found (after drying at 18°/0·03 mm. for 12 hr.): C, 81·8; H, 10·1. $C_{33}H_{50}S,C_3H_6O$ requires C, 82·0; H, 10·3%].

Reaction of Sodium Thiophenoxide with Cholest-5-en-3β-yl Toluene-p-*sulphonate*.—(i) Cholest-5-en-3β-yl toluene-*p*-sulphonate (4·5 g.) and sodium thiophenoxide (10 g.) in ethanol (100 c.c.) were refluxed for 18 hr. Working up as described above gave a yellow oil (4·5 g.) which was chromatographed on aluminium oxide (200 g.). Elution with pentane (3 × 70; 2 × 70; 4 × 70 c.c.; and 16 × 70 c.c.) gave respectively fractions A1, m. p. 70—72° (from methanol), $[\alpha]_D$ −43° (*c* 1·2) (200 mg.); A2, an oil (300 mg.); A3, an oil (500 mg.); A4, m. p. 52—54° (from ethanol) (1·3 g.). Elution with ether–pentane (7 × 70 c.c.) gave fraction A5, a solid (1·1 g.), whilst elution with methanol and chloroform gave fraction A6, a brown oil (500 mg.). Fraction A1 consisted of pure 3 : 5-*cyclo*cholest-6-ene (mixed m. p.). Fraction A2 was rechromatographed on aluminium oxide (40 g.). Elution with pentane (1 × 50 c.c. and 5 × 50 c.c.) gave fractions B1, 3 : 5-*cyclo*cholest-6-ene, m. p. and mixed m. p. 70—72° (50 mg.), and B2, 6β-*phenylthio*-3 : 5-cyclo*cholestane*, an oil, $[\alpha]_D$ +34° (*c* 1·1) (250 mg.) [Found (after drying at 18°/0·03 mm. for 12 hr.): C, 82·9; H, 11·1. $C_{33}H_{50}S$ requires C, 82·8; H, 10·5%]. Fraction A3 was rechromatographed on aluminium oxide (50 g.). Elution with pentane (3 × 50 and 11 × 50 c.c.) gave fractions C1, 3 : 5-*cyclo*cholest-6-ene, m. p. 70—72° (50 mg.), and C2, 6β-phenylthio-3 : 5-*cyclo*cholestane, an oil, $[\alpha]_D$ +36° (*c* 0·78) (400 mg.). Fraction A4 consisted of pure diphenyl disulphide. Rechromatography of fraction A5 on aluminium oxide (40 g.) gave on elution with pentane (3 × 50 and 13 × 50 c.c.) fractions D1, an oil (50 mg.), and D2, 3α-phenylthiocholest-5-ene, m. p. 101° and 111° (1 g.). Fraction A6 was rechromatographed on deactivated aluminium oxide (20 g.). Elution with pentane (5 × 50 and 5 × 50 c.c.) gave fractions E1, an oil (150 mg.), and E2, a greasy solid (300 mg.) which after repeated recrystallisation from methanol gave cholesterol, m. p. 144—145°, $[\alpha]_D$ −41° (*c* 0·77).

(ii) Cholest-5-en-3β-yl toluene-*p*-sulphonate (9 g.) and sodium thiophenoxide (24 g.) in ethanol (500 c.c.) were refluxed under nitrogen for 65 hr. The usual working up gave an oil (7·6 g.) which was chromatographed on aluminium oxide (200 g.). Elution with pentane (1 × 70; 1 × 70; 1 × 70; 4 × 70; 11 × 70 c.c.), and ether–pentane (1 : 9) (2 × 500 c.c.) and ether–pentane (1 : 1) (6 × 500 c.c.) gave the following oily fractions: Z1 (600 mg.); Z2 (1·26 g.); Z3, $[\alpha]_D$ +40° (*c* 0·72) (980 mg.); Z4 (1·2 g.); Z5 (800 mg.); Z6 (720 mg.); and Z7 (700 mg.). Fraction Z1 was rechromatographed on aluminium oxide (15 g.), and elution with pentane (3 × 15 and 6 × 15 c.c.) gave fractions Y1, 3 : 5-*cyclo*cholest-6-ene, m. p. 69—71° (300 mg.), and Y2, 6β-phenylthio-3 : 5-*cyclo*cholestane (250 mg.). Rechromatography of Z2 on aluminium oxide (60 g.) gave on elution with pentane (4 × 15 and 10 × 15 c.c.) fractions X1, 3 : 5-*cyclo*cholest-6-ene (300 mg.), and X2, 6β-phenylthio-3 : 5-*cyclo*cholestane, $[\alpha]_D$ +35° (*c* 1·2) (65 mg.). Fraction Z3 consisted of pure 6β-phenylthio-3 : 5-*cyclo*cholestane. Fraction Z4 on rechromatography on aluminium oxide (80 g.) gave on elution with pentane (4 × 70 and 10 × 70 c.c.) fractions W1, 6β-phenylthio-3 : 5-*cyclo*cholestane, $[\alpha]_D$ +35° (*c* 0·99) (500 mg.), and W2, diphenyl disulphide, m. p. 54—56° (600 mg.). Fraction Z5 on rechromatography on aluminium oxide (30 g.) gave on elution with pentane (2 × 70 and 7 × 70 c.c.) fraction V1, diphenyl disulphide, m. p. 54—56° (400 mg.), and V2, 3α-phenylthiocholest-5-ene, double m. p. 99° and 110° (100 mg.). Fraction Z6 on rechromatography on aluminium oxide (60 g.) gave on elution with pentane (2 × 70 and 10 × 70 c.c.), fraction V1, an oil (100 mg.), and V2, 3α-phenylthiocholest-5-ene, double m. p. 100° and 111° (580 mg.). Finally, fraction Z7 on rechromatography on aluminium oxide (40 g.) gave on elution with pentane (5 × 70 and

8 × 70 c.c.) fractions T1, 3α-phenylthiocholest-5-ene, double m. p. 99° and 110° (300 mg.), and T2, 3β-ethoxycholest-5-ene, m. p. and mixed m. p. 83—84° (250 mg.).

Rearrangement of 6β-*Phenylthio*-3 : 5-cyclo*cholestane to* 3β-*Phenylthiocholest*-5-*ene*.—6β-Phenylthio-3 : 5-*cyclo*cholestane (300 mg.) was refluxed for 18 hr. in dry benzene (50 c.c.) containing thiophenol (2 c.c.) and concentrated sulphuric acid (4 drops). Working up in the usual way gave a brown oil (500 mg.) which after several crystallisations from acetone gave 3β-phenylthiocholest-5-ene, m. p. 69—72°.

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