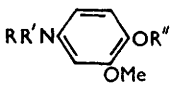
34. *The Chemotherapy of Schistosomiasis. Part V.*[1] *Cholesteryl and Choloyl Derivatives of 4-Amino-2-methoxyphenyl Ethers.*

By M. Davis.

Some of the 4-aminoguaiacyl ethers reported earlier [1] have been combined with cholesterol or cholic acid in various ways. None of the products was of value against *Schistosoma mansoni* infections.

Schistosomicidal activity has been found for many alkyl and substituted alkyl ethers of the general formula (I),[1] and the combination of these compounds with a steroid molecule seemed attractive as the product might be absorbed better and excreted more slowly. The detoxifying power of cholesterol is well known,[2] and several derivatives incorporating aminoguaiacyl and cholesteryl groups were therefore prepared. Bile acid conjugates are largely reabsorbed and returned to the liver *via* the portal circulation. Adult schistosomes reside in the mesenteric and portal veins, and it seemed possible that administration of a bile acid amide of a schistosomicidal amine would be a means of bringing the drug into contact with the parasite.

Since many compounds of formula (I) are highly active when R'' is a phenoxyalkyl group, the analogous 2-cholesteryloxyethyl ether (Ia) was prepared from cholesteryl



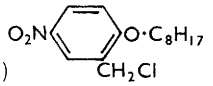
(I)

(a); R = R' = H, R'' = $[CH_2]_2$·O·Cholesteryl
(b); R = R' = H, R'' = $[CH_2]_5$·S·Cholesteryl
(c); R = R' = Me, R'' = $[CH_2]_5$·S·Cholesteryl
(d); R = H, R' = Cholesteryl, R'' = n-C_8H_{17}
(e); R = R' = H, R'' = $[CH_2]_5$·NH·Choloyl
Cholesteryl = cholest-5-en-3β-yl
Choloyl = 3α,7α,12α-trihydroxycholanoyl

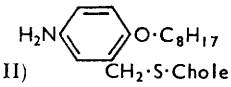
2-hydroxyethyl ether toluene-*p*-sulphonate by reaction with potassium 2-methoxy-4-nitrophenoxide and subsequent reduction of the nitro-group. Cholesteryl 2-hydroxyethyl ether was readily obtained from cholesteryl toluene-*p*-sulphonate and ethylene glycol in dioxan,[3] but omission of the solvent led to the formation of 1,2-dicholesteryloxyethane. Treatment of cholesteryl toluene-*p*-sulphonate with 2-chloroethanol unexpectedly gave a sparingly soluble hydrocarbon which appeared to be Chopin's bicholestatriene (compound

[1] Part IV. Collins and Davis, *J.*, 1961, 1863.
[2] Fieser and Fieser, "Steroids," Reinhold Publishing Corporation, New York, 1959, p. 29.
[3] Julia, Neuville, and Davis, *Bull. Soc. chim. France*, 1960, 297.

280).[4] Bi-steroids are frequently formed from cholesterol and acidic reagents, especially in the Liebermann–Burchard and the Salkowski reactions with sulphuric acid and chloroform.[4,5]



(II)



(III)

Arylthioalkyl ethers of 4-aminoguaiacol show high schistosomicidal activity and a cholesterylthiopentyl analogue (Ib) was obtained by condensation of nitroguaiacyloxypentyl bromide [1] with thiocholesterol,[6] followed by reduction. Treatment with methyl iodide afforded the bismethiodide of the tertiary base (Ic).

The chloromethyl derivative (II) was available from concurrent work [7] and was similarly condensed with thiocholesterol, forming the sulphide, which was reduced to the amine (III). Methylation with methyl iodide–sodium carbonate caused degradation to cholesteryldimethylsulphonium iodide.[8]

N-Substitution of 3-methoxy-4-n-octyloxyaniline [1] was readily effected with cholesteryl toluene-*p*-sulphonate to give the secondary amine (Id).[9]

Alkyl ethers of 4-aminoguaiacol containing an amide linkage in the chain are in many instances active and well tolerated,[1] and the 5-cholmidopentyl ether (Ie) was therefore synthesised. Triformylcholyl chloride was condensed with 5-(2-methoxy-4-nitrophenoxy)-pentylamine,[10] the formyl groups were hydrolysed, and the nitro-group was hydrogenated. Cholamides were similarly prepared from the known schistosomicide 1-(3-chloro-4-methylphenyl)piperazine [11] and from 3-chloro-4-methylaniline.

Sulphides derived from antimony trichloride and long-chain aliphatic thiols have some utility in the treatment of *S. mansoni* infections,[12] and the reaction of antimony trichloride with thiocholesterol was therefore investigated. Only two of the chlorine atoms were replaced, giving the chloroantimony bis-sulphide $ClSb(S{\cdot}Cholesteryl)_2$.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°, unless otherwise specified.

Cholest-5-en-3β-yl 2-Hydroxyethyl Ether.—A solution of cholesteryl toluene-*p*-sulphonate (45 g.) in dioxan (600 ml.) and ethylene glycol (300 ml.) was refluxed for 2 hr., concentrated under reduced pressure to remove dioxan, diluted with water, and extracted with ether. The washed and dried extract was concentrated, and diluted with light petroleum to give the ether (86%), m. p. 93—105°, pure enough for conversion into the toluene-*p*-sulphonate. The latter, prepared (86%) by using toluene-*p*-sulphonyl chloride in pyridine, had m. p. 110—112° (lit.,[3] m. p. 111—112°).

1,2-*Di*(*cholest-5-en-3β-yloxy*)*ethane*.—A mixture of cholesteryl toluene-*p*-sulphonate (3 g.) and ethylene glycol (20 ml.) was heated at 100° for 6½ hr., diluted with water, cooled and filtered. The solid product (0·98 g., m. p. 165—182°) was crystallised twice from dioxan giving the *ether*, m. p. 189—191°, $[\alpha]_D^{26}$ −54° in chloroform (Found: C, 83·7; H, 11·3. $C_{56}H_{94}O_2$ requires C, 84·1; H, 11·9%).

Reaction of Cholesteryl Toluene-p-*sulphonate with 2-Chloroethanol.*—A mixture of cholesteryl

[4] Chopin, *Bull. Soc. chim. France*, 1956, 258; cf. ref. 2, pp. 31, 163; Dulou, Chopin, and Raoul, *Bull. Soc. chim., France*, 1951, 616.
[5] Cook, "Cholesterol," Academic Press, New York, 1958, pp. 87, 129.
[6] King, Dodson, and Subluskey, *J. Amer. Chem. Soc.*, 1948, **70**, 1176; Strating and Backer, *Rec. Trav. chim.*, 1950, **69**, 904.
[7] Collins, unpublished work.
[8] Jones, Smith, and Webb, *Nature*, 1948, **162**, 857; Blau and Stuckwisch, *J. Org. Chem.*, 1960, **25**, 1611.
[9] Cf. Müller and Batyka, *Ber.*, 1941, **74**, 705.
[10] May and Baker Ltd., B.P. 809,023.
[11] Farbwerke Hoechst A.G., Belgian Patent 539,950.
[12] Schubert, *Amer. J. Trop. Med. Hyg.*, 1950, **30**, 525; Kagan and Chang-Ling Lee, *J. Infectious Diseases*, 1952, **91**, 224; Clemence and Leffler, *J. Amer. Chem. Soc.*, 1948, **70**, 2439.

toluene-*p*-sulphonate (1 g.) and 2-chloroethanol (6 ml.) was heated at 100° for 7 hr. Solvent was removed *in vacuo* from the thick paste formed and the residue was triturated with ethanol and filtered. The pale yellow hydrocarbon (0·62 g., 91%) was crystallised from light petroleum (b. p. 100—120°) and had m. p. 265—280° (open capillary) (Found: C, 88·1; H, 12·3. Calc. for $C_{54}H_{88}$: C, 88·0; H, 12·0%), $\lambda_{max.}$ (in chloroform) 274, 282, and 292 mμ, $E^{1\%}_{1\,cm.}$ (282) = 401. Dulou *et al.*[4] give $\lambda_{max.}$ ($CHCl_3$) 272, 280, and 293 mμ, $E^{1\%}_{1\,cm.}$ (280) = 419.

1-(*Cholest-5-en-3β-yloxy*)-2-(*2-methoxy-4-nitrophenoxy*)*ethane*.—A mixture of cholesteryl 2-hydroxyethyl ether toluene-*p*-sulphonate (15 g.), potassium 2-methoxy-4-nitrophenoxide (6·4 g.), and 2-ethoxyethanol (100 ml.) was stirred and refluxed for 20 hr., diluted with water until incipient crystallisation, cooled and filtered. The solid was washed with aqueous sodium hydroxide and water, and crystallised successively from acetone–ethanol and ether, giving the *ether* (82%), m. p. 125—127° (Found: C, 74·4; H, 9·6; N, 2·4. $C_{36}H_{55}NO_5$ requires C, 74·3; H, 9·5; N, 2·4%).

1-(*Cholest-5-en-3β-ylthio*)-5-(*2-methoxy-4-nitrophenoxy*)*pentane*.—Ethanolic solutions of sodium (0·86 g. in 50 ml.) and of 5-(2-methoxy-4-nitrophenoxy)pentyl bromide [1] (12 g. in 50 ml.) were added to a suspension of thiocholesterol (15 g.) in hot ethanol (150 ml.), and the mixture was refluxed for 4 hr., concentrated *in vacuo*, diluted with water, and extracted with ether. The washed and dried ether solution was concentrated, and diluted with light petroleum, giving the *nitro-compound* (82%), m. p. 71—73° (Found: C, 73·1; H, 9·4; S, 5·0. $C_{39}H_{61}NO_4S$ requires C, 73·2; H, 9·6; S, 5·0%), which turned yellow on exposure to light. Similarly obtained from 5-nitro-2-n-octyloxybenzyl chloride (kindly supplied by Dr. R. F. Collins) [7] was *cholest-5-en-3β-yl 5-nitro-2-n-octyloxybenzyl sulphide* (89%), m. p. 71—74° (from acetone) (Found: C, 75·7; H, 10·45; S, 4·9. $C_{42}H_{67}NO_3S$ requires C, 75·7; H, 10·1; S, 4·8%).

1-(4-*Amino-2-methoxyphenoxy*)-2-(*cholest-5-en-3β-yloxy*)*ethane*.—The corresponding nitro-compound (19·55 g.) and ethanol (500 ml.) were added to fused sodium sulphide nonahydrate (60 g.) and the stirred mixture was refluxed for 22 hr., concentrated *in vacuo*, diluted with water, and extracted with ether. The washed and dried ether extract was concentrated and diluted with light petroleum, giving the *amine* (74%), double m. p. 65°, 132° (Found: C, 78·1; H, 10·1; N, 2·7. $C_{36}H_{57}NO_3$ requires C, 78·3; H, 10·4; N, 2·5%). Treatment with methyl iodide–sodium carbonate in boiling ethanol afforded 1-(*cholest-5-en-3β-yloxy*)-2-(*4-dimethylamino-2-methoxyphenoxy*)*ethane methiodide*, m. p. 169—171° (from ethanol) (Found: I, 18·1. $C_{39}H_{64}INO_3$ requires I, 17·6%).

Similarly prepared, by using sodium sulphide in 2-ethoxyethanol at 100°, were 1-(4-*amino-2-methoxyphenoxy*)-5-(*cholest-5-en-3β-yl*)*thiopentane* (72%), m. p. 88—90° and 99—101° (Found: C, 77·2; H, 10·5; S, 5·3. $C_{39}H_{63}NO_2S$ requires C, 76·8; H, 10·4; S, 5·3%) [converted by methyl iodide–sodium carbonate into 1-(*cholest-5-en-3β-yl*)*thio*-5-(*4-dimethylamino-2-methoxyphenoxy*)*pentane bismethiodide* (93%), m. p. 175—177° (efferv.) (from ethanol) (Found: I, 26·15; S, 3·6. $C_{43}H_{73}I_2NO_2S$ requires I, 27·5; S, 3·5%], and 5-*amino-2-n-octyloxybenzyl cholest-5-en-3β-yl sulphide* (84%), amorphous, m. p. *ca.* 55—58° (Found: C, 79·1; H, 11·1; N, 2·25; S, 5·2. $C_{42}H_{69}NOS$ requires C, 79·3; H, 10·9; N, 2·2; S, 5·05%). The last compound on treatment with methyl iodide–sodium carbonate in ethanol was cleaved to cholesteryldimethylsulphonium iodide (75%), m. p. 163—165° (Found: I, 22·6; S, 5·75. Calc. for $C_{29}H_{51}IS$: I, 22·7; S, 5·7%), identical with an authentic specimen.[8]

N-(*Cholest-5-en-3β-yl*)-3-*methoxy-4-n-octyloxyaniline*.—A solution of cholesteryl toluene-*p*-sulphonate (35 g.), and 3-methoxy-4-n-octyloxyaniline [1] (35 g.) in toluene (70 ml.) was refluxed for 24 hr., then evaporated *in vacuo*. The residue was triturated with methanol and filtered, and the solid was recrystallised from ethanol, giving the *amine* (49%), m. p. 95—97° (Found: C, 81·1; H, 11·0; N, 2·3. $C_{42}H_{69}NO_2$ requires C, 81·4; H, 11·2; N, 2·3%).

1-(2-*Methoxy-4-nitrophenoxy*)-5-(*3α,7α,12α-trihydroxycholanamido*)*pentane*.—Dry pyridine (80 ml.) and 5-(2-methoxy-4-nitrophenoxy)pentylamine [10] (10·16 g.) were added to the acid chloride [13] prepared from triformylcholic acid [14] (19·7 g.), and the mixture was kept for 18 hr., diluted with water, and extracted with chloroform. The extract was washed with aqueous hydrochloric acid, aqueous sodium hydroxide, and water, and evaporated. The residue, which could not be crystallised, was hydrolysed by heating it at 100° for 15 min. with 10% ethanolic potassium hydroxide (100 ml.), diluting with water, and extracting with chloroform. The washed and dried extract was evaporated, and the residue was ground with ether and dried *in*

[13] Chaplin, Hey, and Honeyman, *J.*, 1959, 3194.
[14] Hughes, Smith, and Webber, *J.*, 1949, 3437.

vacuo, giving the amorphous amide (90% overall), which slowly softens above 86° (Found: C, 66·95; H, 8·8; N, 4·1. $C_{36}H_{56}N_2O_8$ requires C, 67·1; H, 8·75; N, 4·3%).

Similarly prepared were N-(3-*chloro*-4-*methylphenyl*)-3α,7α,12α-*trihydroxycholanamide* (90% overall from cholic acid), m. p. 268—271° (from aqueous dimethylformamide) (Found: C, 69·6; H, 8·7; Cl, 6·6; N, 2·8. $C_{31}H_{46}ClNO_4$ requires C, 70·0; H, 8·7; Cl, 6·7; N, 2·6%), and 4-(3-chloro-4-methylphenyl)-1-(3α,7α,12α-trihydroxycholanoyl)piperazine (88% from cholic acid), decomposing 171—183°, which was purified by conversion in tetrahydrofuran–ether into the *di*-p-*toluoyl*-D-*tartrate*. The amorphous salt was ground with ether, dried, and equilibrated in air; it decomposed at 187—212° (Found: C, 64·0; H, 7·3; Cl, 2·8; N, 2·5; H_2O, 4·6. $C_{35}H_{53}ClN_2O_4,C_{20}H_{18}O_8,2{\cdot}5H_2O$ requires C, 64·0; H, 7·4; Cl, 3·4; N, 2·7; H_2O, 4·4%).

1-(4-*Amino*-2-*methoxyphenoxy*)-5-(3α,7α,12α-*trihydroxycholanamido*)*pentane*.—The amorphous nitro-compound (4·25 g.) was reduced over Raney nickel in ethanol at 22°/5 atm. The non-crystalline base was converted into the *di*-p-*toluoyl*-D-*tartrate* (3·8 g., 58%) in tetrahydrofuran–ether; the amorphous salt melted at 136—190° (Found: C, 66·8; H, 7·9; N, 3·0. $C_{36}H_{58}N_2O_6,C_{20}H_{18}O_8$ requires C, 67·2; H, 7·65; N, 2·8%). A specimen of the salt was reconverted into the amorphous *base* which, after purification from tetrahydrofuran–ether, melted with effervescence at 75—140° (Found: C, 69·4; H, 9·2; N, 4·4; H_2O, 1·0; regain in air, 1·6. $C_{36}H_{58}N_2O_6,0{\cdot}5H_2O$ requires C, 69·3; H, 9·5; N, 4·4; H_2O, 1·4%).

Reaction of Cholesteryl Chloride or Toluene-p-*sulphonate with Potassium* 2-*Methoxy*-4-*nitrophenoxide*.—(*a*) No reaction occurred when cholesteryl chloride was heated with the potassium salt in boiling dimethylformamide for 4·5 hr., or in the absence of a solvent at 200—210° for 8 hr. Heating in ethylene glycol at 200—210° for 8 hr. and chromatography of the product on alumina afforded cholestadiene, 1,2-dicholesteryloxyethane, m. p. 183—185° (not depressed by an authentic specimen) (Found: C, 83·7; H, 11·7%), and cholesteryl 2-hydroxyethyl ether, m. p. 99° and 110°, not depressed by an authentic specimen (Found: C, 81·2; H, 11·6%). (*b*) A similar experiment using cholesteryl toluene-*p*-sulphonate in boiling 2-ethoxyethanol for 2·5 hr. gave cholestadiene and the free phenol.

Reaction of Cholesteryl Toluene-p-*sulphonate with* 1-(4-*Dimethylamino*-2-*methoxyphenoxy*)-5-*phenylpentane*.—(*a*) When equivalent quantities of the two compounds were refluxed in ethanol for 6 hr., cholesteryl ethyl ether, m. p. 86—87° (Found: C, 84·8; H, 11·9. Calc. for $C_{29}H_{50}O$: C, 84·0; H, 12·2%), was formed. (*b*) When cholesteryl toluene-*p*-sulphonate was heated with excess of the amine at 100° for 29 hr. or at 130° for 3 hr. cholestadiene and the *amine toluene*-p-*sulphonate* (77%), m. p. 114—116° (from ethanol–ether) (Found: C, 66·3; H, 7·4; N, 2·6; S, 6·5. $C_{20}H_{27}NO_2,C_7H_8O_3S$ requires C, 66·8; H, 7·3; N, 2·9; S, 6·6%), were isolated.

Di(*cholest*-5-*en*-3β-*ylthio*)*chloroantimony*.—A solution of thiocholesterol (12·09 g.) in dry benzene (50 ml.) was added to one of antimony trichloride (2·28 g.) in dry benzene (50 ml.), and the mixture was refluxed for 6 hr. (guard tube), kept for 3 days, concentrated under reduced pressure, diluted with light petroleum, and filtered. After crystallisation from chloroform–ethanol, the product (m. p. 160—163°) was boiled with light petroleum (200 ml.), concentrated, cooled, and filtered. The *product* (7·55 g., 79%) had m. p. 171—173°) Found: C, 67·7; H, 9·2; S, 6·6; Sb, 12·3. $C_{54}H_{90}ClS_2Sb$ requires C, 67·5; H, 9·45; S, 6·7; Sb, 12·7%) and gave a Beilstein test for halogen.

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