353. *Steroids and Walden Inversion. Part XI.* Acetolysis of the Coprostanyl Halides.*

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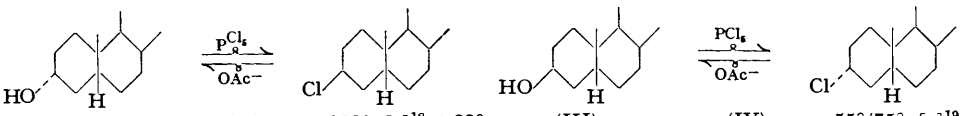
3α- and 3β-Chlorocoprostane have been prepared from coprostanol and *epi*coprostanol, respectively, but only the 3β-bromo-epimeride could be obtained in a state of purity. Acetolysis of the 3α-chloride gave coprost-2-ene and coprostanol, unaccompanied by *epi*coprostanol; conversely, acetolysis of the 3β-chloride or 3β-bromide gave coprost-2-ene and *epi*coprostanol, unaccompanied by coprostanol Absence of racemisation shows that these substitutions take place with inversion of configuration by the bimolecular mechanism S_N2.

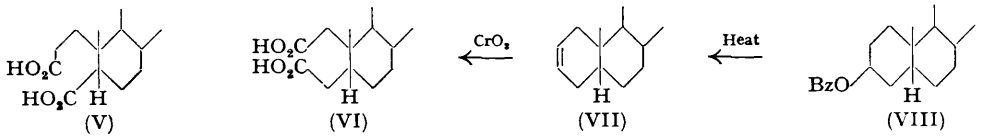
Differences in molecular geometry lead to differences in steric compression which can influence reaction rates and equilibria and so can modify the course of a reaction. Since a previous investigation (Shoppee, *J.*, 1946, 1138) has dealt with the stereochemical course of substitution at $C_{(3)}$ in the cholestane series, it seemed of interest to investigate the parallel problem in the coprostane series.

Treatment of *epi*coprostanol (I) with phosphorus pentachloride in chloroform in the presence of calcium carbonate at 0—25° gave an 80% yield of 3β-chlorocoprostane (II); use of phosphorus pentabromide similarly furnished 3β-bromocoprostane, but thionyl chloride afforded only unsaturated oils.



(I) (II) m. p. 123°, $[\alpha]_D^{18}$ +23° (III) (IV) m. p. 55°/75°, $[\alpha]_D^{19}$ +31°

Similar treatment of coprostanol (III) with phosphorus pentachloride gave 3α-chlorocoprostane (IV) in 40% yield, accompanied by unsaturated hydrocarbon(s). Isolation of the chloride could be achieved only after oxidative destruction of the unsaturated material, whereby an acid, m. p. 202° (dimethyl ester, m. p. 72°), regarded as 2 : 3-*seco*-coprostane-2 : 3-dioic acid (VI) because it differed from the known 3 : 4-*seco*coprostane-3 : 4-dioic acid (V), m. p. 245° (dimethyl ester, m. p. 61°), was obtained. This suggests that the accompanying hydrocarbon consisted essentially of coprost-2-ene. Use of thionyl chloride gave as the sole crystalline product coprost-2-ene (VII), which appeared to be identical with a specimen obtained from coprostanyl benzoate (VIII) by pyrolysis and gave a mixture of the 2β : 3α- and 2α : 3β-dibromides, which could not be separated satisfactorily.



(V) (VI) (VII) (VIII)

Coprostanol (III) and phosphorus pentabromide gave a mixture of bromo- and dibromocoprostanes. 3α-Bromocoprostane could not be obtained free from the dibromo-compound; a small amount of the latter was however isolated in a pure state, and is regarded provisionally as 3α : 4β-dibromocoprostane (both Br equatorial) because it exhibited some resistance to debromination whereby a hydrocarbon, m. p. 48°, was produced, which depressed the m. p. (48°) of coprost-2-ene and may be coprost-3-ene. The formation from a monohydric alcohol of a dibromo-compound is probably due to addition of bromine, formed by dissociation of phosphorus pentabromide in chloroform (cf. Shoppee and Summers, *J.*, 1952, 1786), to an intermediate olefin.

The two chlorides (II) and (IV) are stable to hot pyridine; 3β-chlorocoprostane (II) with hot collidine yields coprost-2-ene, whilst this hydrocarbon is obtained from both chlorides by treatment with hot quinoline.

* Part IX, *J.*, 1953, 241; Part X, *J.*, in the press.

The most notable features of the foregoing substitution reactions are the ease of substitution of *epi*coprostanol (I —→ II) and the absence here of coprost-2-ene, and the relative difficulty* of substitution of coprostanol (III —→ IV) with production of much coprost-2-ene. These observations are consistent with the equatorial character of the 3α-hydroxyl group in *epi*coprostanol as opposed to the polar nature of the 3β-hydroxyl group in coprostanol. Thus lesser steric compression in *epi*coprostanol and greater steric compression in coprostanol affect the formation of the ester–halide complex $RO{\cdot}PCl_4$; whilst the non-planarity of the four centres [3α-oxygen atom, $C_{(3)}$, $C_{(2)}$, and the 2-hydrogen atom (α or β)] in (I) is to be contrasted with the uniplanar arrangement of the four centres [3β-oxygen atom, $C_{(3)}$, $C_{(2)}$, and the 2α(or 4α)-hydrogen atom in (II)], which facilitates the ionic elimination reaction (*E*2) leading to coprost-2-ene. An alternative, and equally probable, path involving the 4α-hydrogen atom leads to coprost-3-ene.

Whereas the epimeric cholestanyl chlorides were found to undergo acetolysis only slowly at 180°, the epimeric coprostanyl chlorides react fairly rapidly with 3M-potassium acetate in acetic acid at 130°. Acetolysis of 3β-chlorocoprostane (II) afforded material which, after alkaline hydrolysis, was resolved into coprost-2-ene and pure *epi*coprostanol (I); absence of coprostanol (III) was proved by exhaustive chromatographic analysis and by use of digitonin. Conversely, acetolysis of 3α-chlorocoprostane (IV) gave a product which, after alkaline hydrolysis, was separated chromatographically into coprost-2-ene and coprostanol (III), unaccompanied by any detectable amount of *epi*coprostanol (I).

The production of only a *single* epimeric acetate in each case shows that a bimolecular acetolysis (S_N2) proceeding with inversion of configuration is solely responsible for the substitution process. Since secondary alkyl halides in non-aqueous media and in the absence of effective basic reagents can afford olefins by the unimolecular elimination mechanism (*E*1), the formation of coprost-2-ene (or coprost-3-ene) in the presence of the weakly basic acetate anion as a result of the expulsion of a proton from an intermediate coprostanyl cation is not unexpected. The slow halogen ionisation stage of mechanism *E*1 would also be the initial stage of a unimolecular acetolysis (S_N1) involving racemisation, but it is clear from the singular formation of the acetates of the epimers (I) and (III) that such unimolecular acetolysis does not occur.

Some kinetic observations have been made on the acetolysis of 3β-bromocoprostane at 94·8° in the presence of sodium acetate. The halide undergoes simultaneous substitution and elimination reactions; the former involves the acetate anion and must be of first order with respect to both halide and acetate, whilst the latter, owing to the ineffectiveness of the acetate anion as a base, should be of first order with respect to the halide and of zero order to acetate. If the initial concentrations of halide and acetate ion are a and b respectively, and the amount x of halide reacting in time t to give stanyl acetate is x_S and to give coprost-2-ene is x_E so that $x = x_S + x_E$, then

$$S\mathrm{d}x/\mathrm{d}t = k[S_N2](a-x)(b-x) \text{ and } E\mathrm{d}x/\mathrm{d}t = k[E1](a-x) \quad . \quad . \quad . \quad . \quad (1)$$

Owing to the extreme weakness of hydrogen chloride in dry acetic acid (Davies, Meecham, and Shoppee, to be published shortly), it was necessary to use 3β-bromocoprostane in order to determine residual acetate anion to obtain a measure of the total halide reacting. The concentration of acetate anion was determined by titration with a standard solution of perchloric acid in dry acetic acid, whilst that of coprost-2-ene was estimated colorimetrically by the Liebermann reaction. Owing to the necessity of using the less accessible 3β-bromocoprostane, the number of runs was restricted; it was also unfortunate that the concentration of acetate anion was large (5 : 1) compared with the total amount of halide reacting, so that (1) reduces to :

$$S\mathrm{d}x/\mathrm{d}t = k[S_N\psi1](a-x) \text{ and } E\mathrm{d}x/\mathrm{d}t = k[E1](a-x)$$

whence

$$k[S_N\psi1] + k[E1] = \frac{1}{t}\ln\frac{a}{a-x} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

* The difficulty cannot be purely " spatial " because two bromine atoms can be attached to $C_{(3)}$, *e.g.*, coprostan-3-one with phosphorus pentabromide gives 3 : 3-dibromocoprostane, m. p. 134°, $[\alpha]_D$ +12°.

The average values found from (2) are $k[S_N\psi 1] = 0{\cdot}0023$ hr.$^{-1}$ and $k[E1] = 0{\cdot}0071$ hr.$^{-1}$, and the results show that both the substitution and elimination reactions are of the first order with respect to the bromide.

The situation disclosed in the coprostane series is in striking contrast to that in the cholestane series :

	Chloride (%) involved in elimination reaction *E*1	Chloride (%) involved in substitution reactions	3α-Ol (%) isolated arising by S_N2	3α-Ol (%) isolated arising by S_N1	3β-Ol (%) isolated arising by S_N2	3β-Ol (%) isolated arising by S_N1
3α-Chlorocoprostane	77, 82	22, 17	—	0	100	0
3β-Chlorocoprostane	79, 81	17, 19	100	0	—	0
3α-Chlorocholestane	77	23	—	12	76	12
3β-Chlorocholestane	74	26	70	15	—	15

The results suggest that the stability of the coprostanyl cation is less than that of the cholestanyl cation. Either its life is too short to permit reaction with an external acetate anion and it acquires stability by internal expulsion of a proton, or the rate of reaction with an acetate anion may be so slow relative to the internal depolarisation process that the former is completely excluded. The apparent instability of the coprostan-3-yl cation, compared with the cholestan-3-yl cation, may be a reflexion of the L-shaped character of the coprostane molecule, which leads to repulsions between the polar $C_{(2)}$–H_α and $C_{(3)}$–H_α bonds and the polar $C_{(7)}$–H_α and $C_{(9)}$–H_α bonds comparable in magnitude with these between the $C_{(1)}$–H and $C_{(4)}$–H bonds in the boat conformation of the *cyclo*hexane molecule.

Experimental

For general and experimental directions see *J.*, 1953, 243, 540. Phosphorus pentachloride and pentabromide were sublimed at 40—60°/0·02 mm. For halogenations pure dry chloroform (free from ethanol) was used. Rotations were determined in chloroform.

Coprostan-3α-ol was prepared by hydrogenation of coprostan-3-one (5·5 g.) in methanol–ether (1 : 1) with platinum oxide (cf. Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407). The product, m. p. 100—102°, was purified by chromatography on aluminium oxide; elution with ether–benzene (1 : 24) gave coprostan-3α-ol (3·1 g.), m. p. 116—117° [acetate, m. p. 87—89°, $[\alpha]_D^{18}$ +42° (*c* 1·42)], and further elution with ether–benzene (1 : 24 and 1 : 9) gave coprostan-3β-ol (700 mg.), m. p. 99—101°.

3β-*Chlorocoprostane*.—Coprostan-3α-ol (1·9 g.; dried at 100°/0·1 mm.), dissolved in chloroform (110 c.c.) containing dry calcium carbonate (3 g.) in suspension, was treated with phosphorus pentachloride (4·5 g., freshly sublimed) added during 1·5 hr. at 0° with shaking. The mixture was shaken for a further 0·5 hr. at 0°, then for 2 hr. at 25°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The crystalline product (2·04 g.) gave no colour with tetranitromethane–chloroform, and recrystallisation from acetone gave 3β-*chlorocoprostane* (1·5 g.) as plates, m. p. 122—123°, $[\alpha]_D^{18}$ +22·5° ± 1° (*c* 1·85) [Found (after drying at 90°/0·01 mm. for 2 hr.) : C, 79·7; H, 11·6; Cl, 8·6. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·65; Cl, 8·7%]. The material in the mother-liquor by chromatography on aluminium oxide and elution of the column with pentane gave crystals (230 mg.), which recrystallised from acetone in plates (160 mg.), m. p. 119—121°. The yield was 80%; use of pyridine for calcium carbonate decreased the yield to 40%.

3β-*Bromocoprostane*.—Coprostan-3α-ol (1·6 g.; dried at 100°/0·1 mm.) in chloroform (65 c.c.) containing a suspension of dry calcium carbonate (5 g.) was treated with phosphorus pentabromide (5·6 g.; freshly sublimed) added during 0·5 hr. at −4° with shaking. The mixture was shaken for a further 0·5 hr. at −4°, 0·25 hr. at 0°, and 3·5 hr. at 20°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The orange crystalline product (1·42 g.) was dissolved in pentane and filtered through a column of aluminium oxide (10 g.); the product, crystallised from acetone, gave 3β-*bromocoprostane* (835 mg.) as plates, m. p. 112·5—113·5°, $[\alpha]_D^{20}$ +18° ± 1·5° (*c* 1·24) [Found (after drying at 80°/0·05 mm. for 5 hr.) : C, 71·6; H, 10·3. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·55%]. The mother-liquors yielded a further quantity (136 mg.), m. p. 111·5—113·5°, giving a faint positive reaction in the Liebermann–Burchard test.

Action of Thionyl Chloride.—A solution of coprostan-3α-ol (100 mg.) in ether (5 c.c.) was slowly added to purified thionyl chloride (5 c.c.) in ether (5 c.c) containing dry calcium carbonate (300 mg.) with stirring. After 24 hr. at 20°, the product was isolated in the usual way as an

oil giving a yellow colour with tetranitromethane–chloroform. Chromatography and attempted crystallisation failed to give crystalline material.

Coprostan-3β-ol.—This was prepared by hydrogenation of coprostan-3-one (8·3 g.) in acetic acid containing hydrogen bromide with 10% by wt. of platinum oxide; the reduction product was separated chromatographically into coprostane (14%), coprostan-3α-ol (23%), and coprostan-3β-ol (57%), which crystallised from methanol in needles, m. p. 100—101° [acetate, m. p. 91°, $[\alpha]_D^{18}$ +14·5° ± 1° (*c* 1·37)] (cf. Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407).

3α-Chlorocoprostane.—Coprostan-3β-ol (3 g.; dried at 40°/0·01 mm.), in chloroform (175 c.c.) containing dry calcium carbonate (4·4 g.) in suspension, was treated with phosphorus pentachloride (7·2 g.; freshly sublimed) added during 1·5 hr. at 0° with shaking. The mixture was shaken for a further 1·5 hr. at 0°, then for 19 hr. at 25°, poured into ice-water, and extracted with ether. The extract, after working up in the usual way, gave a neutral oil (3·25 g.), which was chromatographed in pentane on a column of aluminium oxide (90 g.) prepared in pentane. Elution with pentane (300 c.c.) gave a colourless oil (2·2 g.); further elution with benzene (3 × 300 c.c.) gave crystalline fractions (350, 250, and 200 mg.), which by recrystallisation from methanol yielded coprostan-3β-ol (600 mg.), m. p. 101—102°. The foregoing oil was suspended in acetic acid and stirred with a 2% solution of chromium trioxide in 98% acetic acid at 60° for 0·5 hr.; after removal of acetic acid under reduced pressure, the reaction mixture was poured into 2N-sodium carbonate and extracted with chloroform–ether. Evaporation of the dried extract gave material (2·05 g.) which was treated with pentane (200 c.c.); after filtration from an insoluble solid, the pentane solution was passed through a column of aluminium oxide (50 g.) prepared in pentane, and evaporated. The residue (1·2 g.) was crystallised from acetone–methanol (2 : 1), to give *3α-chlorocoprostane* (730 mg.), m. p. 74—75°, $[\alpha]_D^{19}$ +31° ± 1° (*c* 1·46) [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 79·95; H, 11·65; Cl, 9·0. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·65; Cl, 8·7%]; a further quantity (210 mg.), m. p. 72—75°, was obtained from the mother-liquor. Elution of the column with benzene (2 × 200 c.c.) and with ether–benzene (1 : 1; 200 c.c.) gave fractions (350, 100, and 50 mg.), which were united and rechromatographed on aluminium oxide (20 g.). Elution of this column with benzene–pentane (1 : 49) gave crystalline material (45 mg.), recrystallised from acetone–methanol to give an unidentified *substance* (20 mg.), m. p. 70—71° [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 84·0; H, 11·9. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%]; elution with benzene–pentane (1 : 1) gave needles (228 mg.), recrystallised from aqueous acetone to give cholest-4-en-3-one, m. p. 79—80°, mixed m. p. 78—80° (characterised as the red 2 : 4-dinitrophenylhydrazone, m. p. 233°), the origin of which is obscure. The solid (260 mg.) insoluble in pentane was recrystallised from aqueous acetic acid, to give 2 : 3-*seco*coprostane-2 : 3-dioic acid, m. p. 201—202°, unchanged by recrystallisation and characterised by treatment with ethereal diazomethane as the *dimethyl* ester, m. p. 72°, after purification by chromatography (elution with benzene–pentane, 1 : 9) and crystallisation from methanol [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 75·1; H, 10·9. $C_{29}H_{50}O_4$ requires C, 75·25; H, 10·9%].

Using similar conditions but reducing the reaction time after addition of phosphorus pentachloride to 0·5 hr. at 0° and 4 hr. at 15° gave a 23% yield of 3α-chlorocoprostane in a polymorphic *form*, needles (from acetone), m. p. 54—55°, solidification and remelting at 74—75° [Found (after drying at 30°/0·01 mm. for 2 hr.): C, 79·45; H, 11·6%]. Replacement of calcium carbonate by dry pyridine gave little or no chloro-compound; grinding coprostan-3β-ol with phosphorus pentachloride in a mortar gave 3α-chlorocoprostane in yields of 5—10%.

Attempted Preparation of 3α-Bromocoprostane.—Coprostan-3β-ol (1 g.; dried at 80°/0·05 mm.), in chloroform (60 c.c.) containing dry calcium carbonate (3·3 g.), was treated with phosphorus pentabromide (6·0 g.; freshly sublimed) added during 1 hr. at —8° with shaking. The mixture was then shaken for 0·25 hr. at —5°, 1 hr. at 0°, and 3·5 hr. at 15°, and poured into saturated sodium hydrogen carbonate solution, and the product extracted with ether. The resultant yellow oil was dissolved in pentane (50 c.c.) and filtered through a column of aluminium oxide (15 g.) prepared in pentane. The column was washed with pentane (2 × 50 c.c.), and the filtrate and washings were combined and evaporated to a colourless oil (1·06 g.; positive Beilstein test; weak Liebermann–Burchard test), which was dissolved in acetic acid and stirred with a 2% solution of chromium trioxide in 98% acetic acid at 60° for 0·5 hr. The reaction mixture was poured into water and worked up in the usual way, to give an oil, which was dissolved in pentane (50 c.c.) and filtered through a column of aluminium oxide (15 g.) prepared in pentane. The column was washed with pentane (50 c.c.), and filtrate and washings were united, to give an oil (955 mg.; faint Liebermann–Burchard test); further elution of the column with pentane (50 c.c.) gave a solid (45 mg.), which readily crystallised from acetone to give a

dibromocoprostane in plates, m. p. 97—98°, $[\alpha]_D^{19}$ −5° ± 1° (*c* 1·84) [Found (after drying at 70°/0·04 mm. for 5 hr.): C, 61·5; H, 8·5; Br, 29·85. $C_{27}H_{46}Br_2$ requires C, 61·15; H, 8·75; Br, 30·1%]; the dibromo-compound (20 mg.) was recovered unchanged after treatment with zinc dust (50 mg.) in boiling methanol (5 c.c.) for 0·75 hr., but debromination occurred after 6 hr. to give a hydrocarbon, m. p. 48° after recrystallisation from acetone. This material gave negative Rosenheim and Beilstein tests and depressed the m. p. of coprost-2-ene (48°) to 35°, but there was insufficient material for further identification. The oil (955 mg.) was re-oxidised and worked up as before to give an oil (917 mg.) which was dissolved in pentane (10 c.c.), filtered through a column of neutralised aluminium oxide (5 g.), and followed by pentane (100 c.c.). Evaporation of the combined filtrate and washing gave a colourless oil (900 mg.) which gradually crystallised. Repeated recrystallisation from acetone gave needles, m. p. 104—106°, which appeared to consist of an equimolecular *complex* of 3α-bromocoprostane and the above dibromide [Found (after drying at 20°/0·04 mm. for 18 hr.): C, 65·9; H, 9·45; Br, 23·6. $C_{27}H_{47}Br$,$C_{27}H_{46}Br_2$ requires C, 66·05; H, 9·55; Br, 24·4%]. The mother-liquors were united and evaporated; the residue was chromatographed on a long column (8·5 cm.) of aluminium oxide (10 g.) and eluted with pentane (6 × 5 c.c.), to give fractions weighing 0, 10, 156, 130, 10, and 2 mg. respectively. Fractions 3 and 4 crystallised when rubbed with acetone, and were united, and recrystallised from acetone, to give impure 3α-bromocoprostane (177 mg.), m. p. 80—84°, $[\alpha]_D^{19}$ +27·5° ± 1° (*c* 1·45) [Found (after drying at 70°/0·01 mm. for 3 hr.): C, 68·5; H, 9·9; Br, 21·5. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·5; Br, 17·7%].

Action of Thionyl Chloride.—A solution of coprostan-3β-ol (100 mg.) in ether (5 c.c.) was slowly added to purified thionyl chloride (5 c.c.) in ether (5 c.c.) containing a suspension of calcium carbonate (300 mg.). After 24 hr. at 20°, the reaction product was isolated in the usual way as an oil which was chromatographed on a column of aluminium oxide (8 g.) prepared in pentane. Elution with pentane (4 × 5 c.c.) gave fractions: 1, nil; 2, needles (10 mg.), m. p. 46—47° after crystallisation from acetone; 3, needles (20 mg.), m. p. 47—48° after crystallisation from acetone; 4, crystals (3 mg.); the material in fractions 2 and 3 consisted of coprost-2-ene, mixed m. p. 48°. Various modifications of temperature, medium ($CHCl_3$), and reaction time yielded oils from which in some cases coprost-2-ene could be isolated.

Coprost-2-ene. (*a*) 3α-Chlorocoprostane was refluxed for 6 hr. with quinoline; after removal of the base under reduced pressure, the product was dissolved in ether, washed successively with 2N-hydrochloric acid, water, 2N-sodium carbonate, and water, dried, and evaporated, to give *coprost-2-ene*, m. p. 47—48°, $[\alpha]_D^{22}$ +23° ± 1° (*c* 1·59) [Found (after drying at 35°/0·01 mm. for 4 hr.): C, 87·15; H, 12·9. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%].

(*b*) 3β-Chlorocoprostane by similar treatment with quinoline gave coprost-2-ene, m. p. 48°; a mixed m. p. with the specimen obtained as under (*a*) showed no depression.

(*c*) Coprostan-3α-yl benzoate (4·5 g.; m. p. 85—86°) was pyrolysed at 320°/10 mm. in an atmosphere of carbon dioxide and the product distilled at 0·01 mm.; the distillate was dissolved in ether and the solution washed with 2N-sodium carbonate, then with water, dried, and evaporated. Chromatography on a column of aluminium oxide (50 g.) prepared in pentane gave by elution with pentane coprost-2-ene (1·2 g.), m. p. 47—48°, after crystallisation from acetone. Further elution of the column with benzene–pentane mixtures gave oils (800 mg.), followed by unchanged coprostanyl-3α-yl benzoate (2 g.).

(*d*) Coprostan-3β-yl benzoate (1·6 g.; m. p. 124—125°) was pyrolysed similarly; chromatography of the reaction product gave by elution with pentane coprost-2-ene (520 mg.) in needles, m. p. 46—48°, $[\alpha]_D^{22}$ +24·5° ± 1° (*c* 1·52), after crystallisation from acetone.

Coprost-2-ene, by treatment in ether with an ethereal solution of 1 mol. of bromine at 20°, gave an oil which crystallised after some days; recrystallisation from acetone gave a product, m. p. 76—96°, regarded as a mixture of 2α : 3β- and 2β : 3α-dibromocoprostane [Found (after drying at 40°/0·01 mm. for 5 hr.): C, 61·3; H, 8·9. Calc. for $C_{27}H_{46}Br_2$: C, 61·15; H, 8·75%], which could not be separated by further crystallisation of the material available.

Action of Pyridine and s-*Collidine.*—3α-Chlorocoprostane was recovered unchanged as needles, m. p. 75—76°, mixed m. p. 74—76°, after 3 hr.' refluxing with pyridine or 6 hr.' with *s*-collidine. 3β-Chlorocoprostane was likewise recovered unaltered, m. p. 124°, mixed m. p. 123—124°, after similar treatment.

Acetolysis of 3α-*Chlorocoprostane.*—3α-Chlorocoprostane (250 mg.), freshly fused potassium acetate (2·5 g.), and anhydrous acetic acid (7 c.c.) were refluxed with exclusion of moisture for 6 hr. The cooled mixture was poured into water and extracted with ether, and the product hydrolysed by refluxing 4% methanolic potassium hydroxide for 3 hr. After addition of a little water and saturation with carbon dioxide, methanol was removed under reduced pressure

and the product extracted with ether. The resulting oil (238 mg.) was chromatographed on aluminium oxide (27 g.), prepared in pentane, 25-c.c. eluates being used. Elution with pentane [Fr. A 1—3] gave coprost-2-ene (175 mg.), m. p. 46°, after crystallisation from ether–methanol; benzene–pentane mixtures [Fr. A 10—12] and ether–benzene (1 : 24) [Fr. A 13] gave no significant amounts of material. Elution with ether–benzene (1 : 4) gave fractions A 14 (50 mg.; m. p. 101—102°) and A 15 (5 mg.; m. p. 101°), after crystallisation from methanol, consisting of pure coprostan-3β-ol, whilst use of ether–benzene (1 : 1) and ether yielded no material. The m. p. of fractions A 14 and A 15 were unaltered by recrystallisation from methanol [A 14 : mixed m. p. with coprostan-3β-ol, 100—101°; mixed m. p. with coprostan-3α-ol, 74—80°]; the total weight of material eluted from the column was 232 mg. A portion (28 mg.) of fraction A 14 was rechromatographed and by elution with ether–benzene (1 : 19) gave fractions: B 7 (1 mg.; m. p. 100—101°), B 8 (8 mg.; m. p. 100—101°), B 9 (8 mg.; m. p. 99—101°), B 10 (8 mg.; m. p. 100—101°), B 11 (0·2 mg.), all undepressed by admixture with coprostan-3β-ol and characterised by conversion into the acetate, m. p. 90°, mixed m. p. 90—91°.

In a second similar experiment 3α-chlorocoprostane (250 mg.) gave a hydrolysed product (236 mg.) resolved by chromatography on a slightly less active aluminium oxide into coprost-2-ene (187 mg.) eluted with pentane, oil (1 mg.) eluted with benzene–pentane, oil (1·5 mg.) eluted with benzene, and coprostan-3β-ol [Fr. C 12 (1 mg.; m. p. 100°); C 13 (18·5 mg.; m. p. 99—101°, mixed m. p. 100—101°), C 14 (18 mg.; m. p. 100—101°, mixed m. p. 100—101°), and C 15 (4 mg.; m. p. 100°)] eluted with ether–benzene (1 : 24) and characterised by conversion into coprostan-3β-yl acetate, m. p. 89—90°, mixed m. p. 89—91°. The total weight of material eluted from the column was 231 mg.

Acetolysis of 3β-*Chlorocoprostane*.—3β-Chlorocoprostane (250 mg.) was subjected to acetolysis under the same conditions as were used for the 3α-epimeride, and furnished a hydrolysed product (230 mg.), which was chromatographed on aluminium oxide (27 g.) prepared in pentane, 25-c.c. eluates being used. Elution with pentane (Fr. D 1—4] gave coprost-2-ene (179 mg.), m. p. 46°, after crystallisation from ether–methanol. Benzene–pentane (1 : 4 and 1 : 1) [Fr. D 5—9] gave oils (3·5 mg.); benzene [Fr. D 10—13] also gave oil (1·5 mg.). Elution with ether–benzene (1 : 1) gave Fr. D 14 (4 mg.; m. p. 110° after crystallisation from methanol), whilst use of ether gave Fr. D 15 and D 16 (which crystallised spontaneously and were united: 37 mg., m. p. 111°). The m. p. of fractions D 14 and D 15 + 16 were unchanged by recrystallisation from methanol (D 15 + 16: mixed m. p. with coprostan-3α-ol, 110—111°; mixed m. p. with coprostan-3β-ol, 81—84°), and neither gave a precipitate with digitonin in 90% methanol. The total weight of material eluted from the column was 225 mg.

In a repetition, 3β-chlorocoprostane (250 mg.) gave a hydrolysed product (235 mg.), resolved by chromatography on a slightly less active aluminium oxide into coprost-2-ene (185 mg.) eluted with pentane, oil (1 mg.) eluted with benzene–pentane (1 : 4 and 1 : 1), oil (0·5 mg.) eluted with benzene, and coprostan-3α-ol [Fr. E 11, nil; E 12 (4·5 mg.; m. p. 110—111°, mixed m. p. 110°); E 13 (24 mg.; m. p. 110°, mixed m. p. 110°); E 14 (14 mg.; m. p. 110—111° mixed m. p. 110—111°); E 15 (2 mg.; m. p. 110°, mixed m. p. 110—111°); E 16 (0·5 mg.)], eluted with ether–benzene (1 : 24), and characterised by conversion (Fr. E 13 and 14] into coprostan-3α-yl acetate, m. p. 87—88°, mixed m. p. 88°. The total weight of material eluted from the column was 231 mg.

Use of potassium acetate (250 mg.) in anhydrous propionic acid (b. p. 141°; 7 c.c.) for 4 hr. furnished coprost-2-ene and coprostan-3α-ol in essentially the same proportion (4 : 1). Use of potassium acetate in anhydrous formic acid (b. p. 100·5°) slowed down the reaction, and only 20% of 3β-chlorocoprostane was decomposed in 6 hr. as judged by estimation of chloride ion as silver chloride in the acetolysis product. Use of potassium acetate (400 mg.) in acetic acid–dioxan [3·2 c.c. (1 : 3·5), b. p. ~107°] for 24 hr. and chromatography led to recovery of 92% of the 3β-chlorocoprostane in the first three pentane eluates.

*Chromatographic Separation of Coprostan-*3α-*ol and* -3β-*ol*.—The epimerides (25 mg. each) were dissolved in pentane and chromatographed on aluminium oxide (3 g.) prepared in pentane, with 5-c.c. eluates No material was eluted with benzene or ether–benzene (1 : 49); use of ether–benzene (1 : 24) gave fractions: 1, 2 mg.; 2, 12 mg., m. p. and mixed m. p. with coprostan-3α-ol, 111°; 3, 9·5 mg., m. p. 111°, mixed m. p. with coprostan-3α-ol, 110—111°; 4, 6 mg., m. p. 90—100°, consisting of a mixture of the epimerides; 5, 15·5 mg., m. p. 101—102°, mixed m. p. with coprostan-3β-ol, 100—101°; 6, 1·5 mg., m. p. 100°; 7, 0·5 mg.; total 47 mg.

Acetolysis of 3β-*Bromocoprostane*.—Accurately weighed amounts of 3β-bromocoprostane (90·0 ± 0·1 mg.) with a standard solution (6·0 c.c.) of sodium acetate in anhydrous acetic acid (made by dissolution of sodium carbonate in acetic acid and standardisation against a 0·49N-

solution of perchloric acid in acetic acid with tropæolin as indicator) were introduced into a series of sealed ampoules and kept in a thermostat at 94·8°. At various times an ampoule was removed and cooled, and the contents were transferred into a graduated flask (10 c.c.) with chloroform. Aliquots of the chloroform solution were used as follows: (1) 2·0 c.c. were titrated against 0·49N-perchloric acid in anhydrous acetic acid (tropæolin), to determine the amount of acetate, whilst a similar titration on an aliquot of a similar run without 3β-bromocoprostane was made, the difference giving the amount of acetate used in the reaction, which is equivalent to the quantity of bromide decomposed; (2) 1·0 c.c. was pipetted on to anhydrous sodium carbonate (1·2 g.) in a glass mortar, and the mass freed from chloroform in a vacuum-desiccator, ground to a fine powder, and extracted (Soxhlet) with chloroform for 12 hr.; the extract was made up to 10 c.c. and the amount of coprost-2-ene in samples of this solution determined by use of the Liebermann–Burchard test. This was done by diluting the sample with chloroform to 10 c.c. and treating this with 9 : 1 acetic anhydride–concentrated sulphuric acid (2·0 c.c.); after 45 min. the intensity of colour was measured in a standard cell on a Spekker photometer and the amount of coprost-2-ene present read off from a calibration curve, previously prepared by using standard solutions of coprost-2-ene, with an error of ~3%. The results are tabulated.

Concn. of 3β-bromocoprostane, 0·0332 mole/l. Concn. of NaOAc, 0·1829 mole/l.

t (hr.)	10^4x	10^4x_S	10^4x_E	$k[S_N\psi 1] + k[E1]$ (hr.$^{-1}$)	$k[S_N\psi 1]$ (hr.$^{-1}$)	$k[E1]$ (hr.$^{-1}$)
26	0·575	0·126	0·389	0·0116	0·0028	0·0088
44	0·638	0·159	0·479	0·0092	0·0022	0·0070
90	1·00	0·255	0·746	0·0080	0·0020	0·0060
139	1·32	0·343	0·981	0·0081	0·0021	0·0060
190	1·67	0·379	1·290	0·0101	0·0023	0·0078
243	1·96	0·430	1·530	—	—	—

3 : 3-*Dibromocoprostane*.—Coprostan-3-one (100 mg.), in chloroform (15 c.c.), was treated with phosphorus pentabromide (600 mg.; freshly sublimed) during 20 min. at 0°. After 1 hr. at 0° and 12 hr. at 18°, working up in the usual way gave a solid which by recrystallisation from methanol gave needles of 3 : 3-*dibromocoprostane*, m. p. 134°, $[\alpha]_D^{18}$ +12° ± 1° (*c* 1·785) [Found (after drying at 90°/0·05 mm. for 2 hr.): C, 61·1; H, 8·7. $C_{27}H_{46}Br_2$ requires C, 61·15; H, 8·75%].

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