279. *Steroids. Part XII.* Some Examples of the Favorski Reaction.*

By D. E. Evans, A. C. de Paulet, C. W. Shoppee, and F. Winternitz.

2α-Bromocholestan-3-one undergoes the Favorski reaction to give methyl A-norcholestane-2α-carboxylate accompanied by methyl A-norcholestane-3α-carboxylate, whose structures are proved by Wieland–Barbier degradation respectively to A-norcholestan-2- and -3-one; the latter undergoes inversion to give A-norcoprostan-3-one.

4β-Bromocoprostan-3-one, similarly, by the Favorski reaction yields approximately equal amounts of methyl A-norcoprostane-2β- and -3β-carboxylate, whose structures are proved by Wieland–Barbier degradation to A-norcoprostan-2- and -3-one respectively.

The mechanism of the Favorski reaction is briefly discussed and the configurations of the above four esters are deduced.

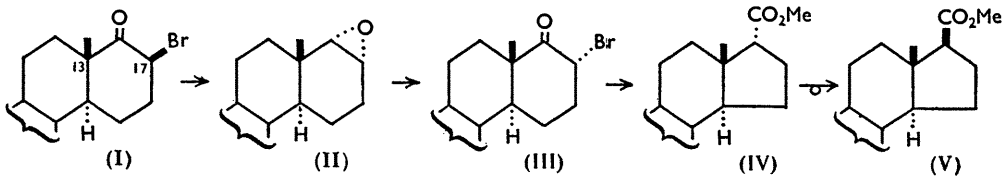
One of us and Prins [1] examined the reaction with methoxide ions of the bromo-ketones derived from D-homoandrostan-17*a*-one. Partial separation of the epimeric bromo-ketones was achieved on a small scale, but the work was complicated by the necessity of

* Part XI, *J.*, 1957, 93.

[1] Shoppee and Prins, *J.*, 1946, 494.

using the mixed epimerides, probably present in approximately equal amounts,[2] for the reaction. The main product isolated was the 17α : 17aα-epoxide (II) derived from the 17β-bromo-ketone [I; Br(axial)], whilst the rearranged ester (V), formed *via* the 17-*iso*-ester (IV) from the 17α-bromo-ketone [III; Br(equatorial)], was produced only in traces.

It appeared that the $C_{(13)}$-angular methyl group might be a factor in the situation, and it was therefore of interest to apply the Favorski reaction to the bromo-ketones derived from cholestan-3-one and coprostan-3-one, which yield respectively only the 2α-epimeride and the 4β-epimeride.[3]



After our work had started we learned from Dr. Winternitz of a parallel investigation at the University of Montpellier; by arrangement we abandoned the application of the Favorski reaction to 2α-bromocholestan-3-one, which had made considerable progress in France,[4] and confined ourselves to the application of the reaction to 4β-bromocoprostan-3-one. The results in both series are now published jointly.

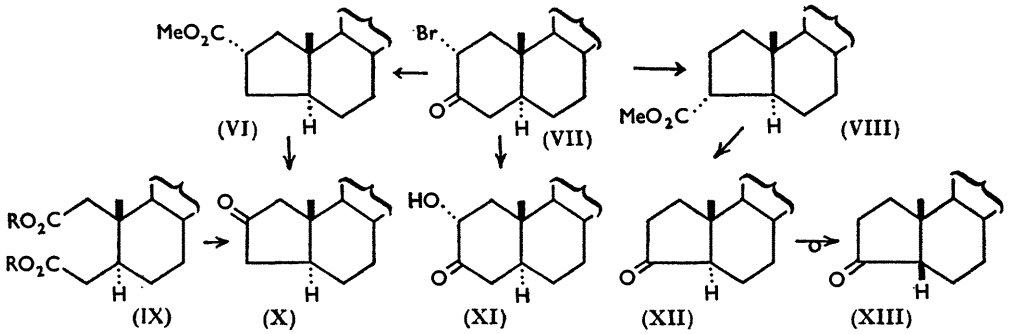
2α-Bromocholestan-3-one (VII) by treatment with sodium methoxide in methanol–ether at 15° affords a mixture of neutral and acidic products. The neutral fraction contains substantial amounts of cholestan-3-one (20—25%), 2α-hydroxycholestan-3-one (XI), and its transformation products (which are being examined by Dr. Winternitz); attention has been directed to the lability of this hydroxy-ketone in alkaline conditions,[5] which was not evident from previous work.[6] The acid fraction, after esterification with diazomethane, affords methyl A-norcholestane-2α-carboxylate (VI) (~25%), accompanied by a relatively small quantity of methyl A-norcholestane-3α-carboxylate (VIII), and dimethyl 2 : 3-*seco*cholestane-2 : 3-dioate (IX; R = Me). When the reaction is carried out in anhydrous ethanol at 15° and the product subjected to alkaline hydrolysis, the acidic fraction is larger, and after re-esterification readily affords the Favorski esters (VI) and (VIII) in approximately equal quantity, together with the dimethyl ester (IX; R = Me).

By a Wieland–Barbier degradation with phenylmagnesium bromide the Favorski ester (VI) gives A-norcholestan-2-one (X), identical with a specimen prepared by pyrolysis of 2 : 3-*seco*cholestane-2 : 3-dioic acid [7] (IX; R = H). The isomeric Favorski ester (VIII), by similar degradation, yields initially the unknown A-norcholestan-3-one (XII), which however undergoes inversion under the experimental conditions to A-norcoprostan-3-one [8] (XIII).

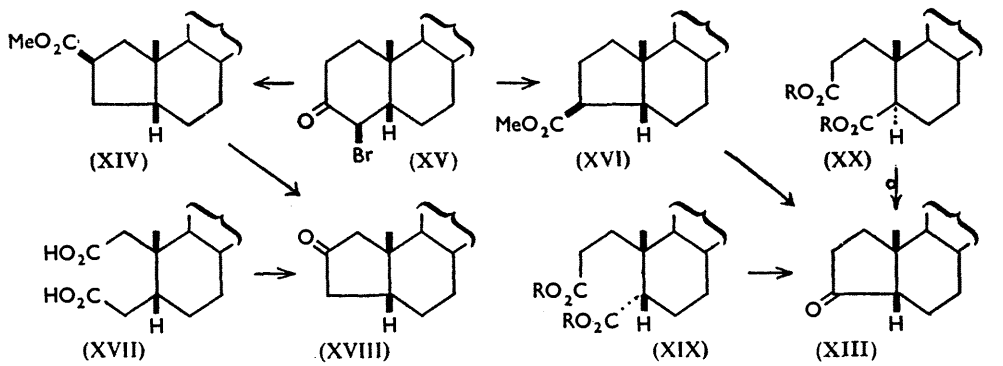
Some of the foregoing results were recorded in a preliminary communication by Winternitz and de Paulet [4] in 1954, which was unfortunately overlooked by Smith and Nace.[9] Smith and Nace obtained the Favorski ester (VI) in a state of purity, but were unable completely to separate the isomeric ester (VIII); they degraded the ester (VI) to A-norcholestan-2-one (X), and from an enriched sample of the ester (VIII) obtained a

[2] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.
[3] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828; Fieser and Etorre, *ibid.*, 1953, **75**, 1700; Beereboom, Djerassi, Ginsburg, and Fieser, *ibid.*, p. 3500; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837; Cookson, *J.*, 1954, 282; Alt and Barton, *J.*, 1953, 4284.
[4] Winternitz and de Paulet, *Bull. Soc. chim. France*, 1954, 288.
[5] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 727.
[6] Ruzicka, Plattner, and Aeschbacher, *ibid.*, 1938, **21**, 866; Inhoffen and Huang-Minlon, *Ber.*, 1937, **70**, 1695; 1938, **71**, 1720.
[7] Windaus and Dalmer, *Ber.*, 1919, **52**, 162.
[8] Windaus, *ibid.*, p. 170.
[9] Smith and Nace, *J. Amer. Chem. Soc.*, 1954, **76**, 6119.

ketone, m. p. 73—74°, which they described as the unknown A-norcholestan-3-one (XII), but which is clearly A-norcoprostan-3-one (XIII) (our product had m. p. 74°).



4β-Bromocoprostan-3-one (XV) with sodium methoxide in methanol–ether at 15° yielded a neutral fraction containing coprostan-3-one (20%), methyl A-norcoprostane-2β-carboxylate (XIV) (~24%) and methyl A-norcoprostane-3β-carboxylate (XVI) (~24%); the acidic fraction (after esterification) gave a small amount of the Favorski ester (XVI) together with dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate (XIX; R = Me). When the reaction was performed in anhydrous methanol at 15° little or no acidic material was formed,[10] and the yield of Favorski esters (XIV + XVI) increased to 60%; in 98% methanol at 15° it was only 18%.



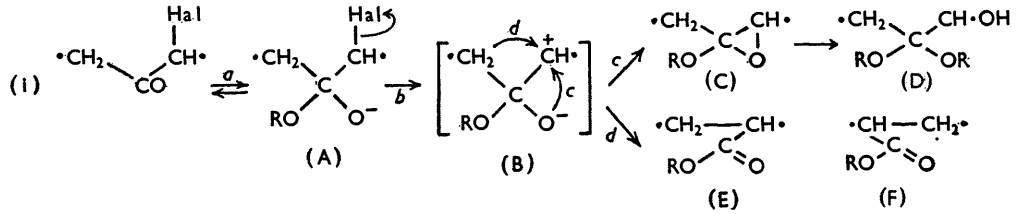
Wieland–Barbier degradation (phenylmagnesium bromide) of the Favorski ester (XIV) furnished A-norcoprostan-2-one (XVIII), identical with a specimen obtained [11] by pyrolysis of 2 : 3-*seco*coprostane-2 : 3-dioic acid (XVII). Similar degradation of the isomeric ester (XVI) gave A-norcoprostan-3-one (XIII), originally obtained by Windaus [8] by distillation with acetic anhydride of 3 : 4-*seco*coprostane-3 : 4-dioic acid (XIX) or 3 : 4-*seco*cholestane-3 : 4-dioic acid [12] (XX).

The above degradations establish the positions of the methoxycarbonyl groups in the rearranged products (VI), (VIII), (XIV), and (XVI); it seems of interest to examine the mechanism of the Favorski reaction with a view to the elucidation of the configurations of the four esters.

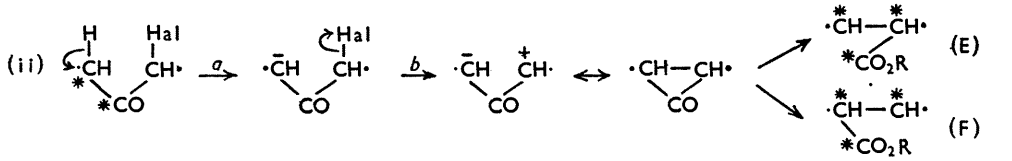
We have previously [1] interpreted the Favorski reaction as a pinacolic change (i) involving the reversible addition (*a*) of an alkoxide ion, with subsequent separation of a halide ion as the rate-determining step and leading to two competing reaction paths, as shown. Path *bc* gives cyclic dimerides of the intermediate (B) and the hydroxy-ketal (D), whilst

[10] Loftfield and Schaad, *J. Amer. Chem. Soc.*, 1954, **76**, 35.
[11] Windaus and Mielke, *Annalen*, 1938, **536**, 116.
[12] Shoppee and Summers, *J.*, 1953, 2528.

path *bd* affords the rearranged ester (E). The Favorski reaction with ω-chloromethyl *cyclo*hexyl ketone, however, follows path *bc* only in part and also furnishes, not the rearranged ester (as E), but the isomeric rearranged ester (as F); [10,13] similarly, α-chlorobenzyl methyl ketone gives, not methyl α-phenylpropionate (as E), but methyl β-phenylpropionate (as F).[14] The production of esters of type (F) cannot be explained by the pinacolic mechanism.



An alternative mechanism (ii) for the rearrangement was proposed by Loftfield,[15] after his discovery that 2-chloro[1 : 6-^{14}C]*cyclo*hexanone yields a *cyclo*pentanecarboxylic ester (E≡F) in which the isotope has become equally distributed among the positions (*) corresponding to *both* α-carbon atoms of the chloro-ketone. Extraction of a proton by an



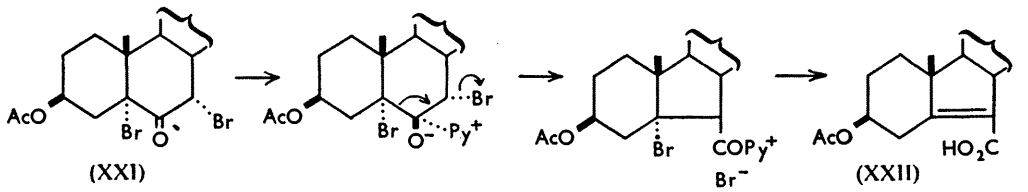
alkoxide ion is now the rate-determining step (*a*), and leads to a mesomeric carbanion which loses a halide ion (*b*) to give a dipolar ion * (cf. Aston and Newkirk [16]), which is one of the resonance structures of a *cyclo*propanone. Burr and Dewar [17] have shown by calculations based on molecular-orbital theory that such a *cyclo*propanone intermediate should be relatively stable and by reaction with alkoxide ions could afford both the isomeric esters (E) and (F). It is clear that this mechanism cannot apply to the conversion of the bromo-ketone (III) into the ester (V) because of the presence of the $C_{(13)}$-angular methyl group, or to the transformation of the 5α : 7α-dibromo-ketone (XXI) (cf. Corey [3] and Cookson [3]) into the unsaturated B-noracid [18] (XXII), which presumably occurs by a pinacolic process, as shown.

Both mechanisms for the Favorski rearrangement lead to the same stereochemical result. In the pinacolic mechanism (i), attack of the electron pair constituting the bond broken, synchronously with the departure of the halogen atom, leads to a linear transition state with *formal* inversion of configuration, but no actual change of orientation

* Professor Dewar (personal communication) has pointed out that in his intermediate [his formula [17] (IV)] all the electrons have their spins paired, and that his formula (IV) must not be taken to represent a diradical with two unpaired electrons with opposed spins. Since this paper was written, another example has been reported by Engel [19]; 3α-acetoxy-17α-bromopregnane-11 : 20-dione affords methyl 3α-acetoxy-17β-methyl-11-oxo-17-*iso*etianate together with the 17α-methyl isomer. The structures of these products have been established by Wendler, Graber, and Hazen,[20] who explain the formation of the second compound by triad cationotropy involving a mobile bromonium ion; it appears however that the Loftfield *cyclo*propanone mechanism (ii) is adequate also for this case.

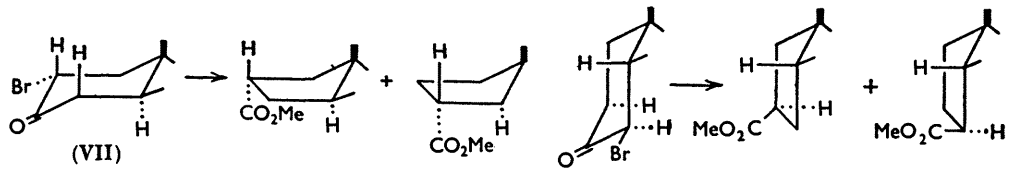
[13] Mousseron, Jacquier, and Fontaine, *Compt. rend.*, 1951, **232**, 1562.
[14] MacPhee and Klingsby, *J. Amer. Chem. Soc.*, 1944, **66**, 1132.
[15] Loftfield, *J. Amer. Chem. Soc.*, 1950, **72**, 632; 1951, **73**, 4707.
[16] Aston and Newkirk, *ibid.*, *p.* 3900.
[17] Burr and Dewar, *J.*, 1954, 1201.
[18] Woodward and Clifford, *J. Amer. Chem. Soc.*, 1941, **63**, 1123, 2727.
[19] Engel, *ibid.*, 1955, **77**, 1064.
[20] Wendler, Graber, and Hazen, *Chem. and Ind.*, 1956, 847.

if the appropriate hydrogen atom finally remains above the plane of the ring upon which it is situated; the bromo-ketone (III) possessing an equatorial 17-bromine atom with α-configuration furnishes an α-oriented carboxyl group (IV).



(XXI) (XXII)

In the Loftfield mechanism (ii) the most energetically probable structure for an intermediate *bicyclo*[3 : 1 : 0]hexanone is that in which the bridge involves two distorted " axial " bonds; models suggest that the two " equatorial " C–H bonds at the bridgeheads are approximately collinear. Breakage of either of the bonds adjacent to the carbonyl



(VII) (XV)

group leads in the case of a 3-ketone of the A/B-*trans*-series (VII) to an α-oriented carboxyl group, and in the case of a 3-ketone of the A/B-*cis*-series (XV) to a β-oriented carboxyl group.

Experimental

$[\alpha]_D$ are in $CHCl_3$. Microanalyses marked * were carried out in the microanalytical laboratory of the Université de Montpellier under the direction of Dr. F. Winternitz.

2α-Bromocholestan-3-one (VII) was prepared as described by Butenandt and Wolff,[21] and had m. p. 166—167°, $[\alpha]_D$ +44·5°. Numerous experiments on the reaction with sodium methoxide were carried out, of which the following are typical.

Methyl A-*Norcholestane-2α- and -3α-carboxylate* (VI, VIII).—(*a*) 2α-Bromocholestan-3-one (10 g.), in dry ether (500 c.c.), was added slowly with stirring and cooling to a cold solution of sodium (12·3 g.) in anhydrous methanol (150 c.c.). Precipitation of sodium bromide was immediate, and the mixture was set aside at 15° for 24 hr.; subsequent titration (Charpentier–Volhard) of an aliquot part gave 100% of ionic bromine. The mixture was poured into water, neutralised with 2N-sulphuric (or -acetic) acid, and extracted with ether. One-half of the product (4·3 g.) was esterified with ethereal diazomethane and chromatographed on neutralised aluminium oxide in light petroleum (b. p. 40—60°); elution with light petroleum gave material (1·85 g.) which was submitted to triangular fractional crystallisation from methanol, to yield as the more insoluble product *methyl* A-*norcholestane-2α-carboxylate* (VI), m. p. 94—95°, $[\alpha]_D$ +29° (*c* 3·0) (Found : * C, 80·3; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). Fraction B2, m. p. 65—68°, and mother-liquors 1 and 2 were united and rechromatographed, to give by elution with light petroleum (20 c.c. eluates) fractions : C1, oil (20 mg.); C2, crystals (300 mg.); C3, m. p. 44—45° (35 mg.); C4, C5, oils (5 mg., 12 mg.); and use of benzene–light petroleum (1 : 4) gave fractions : C6, m. p. 125—126° (200 mg.); C7, m. p. 125° (90 mg.); C8, C9, crystals (28 mg., 16 mg.). Triangular fractional crystallisation from methanol of C2 yielded finally the ester (VI), m. p. 90—91° (50 mg.), and *methyl* A-*norcholestane-3α-carboxylate*, m. p. 45—46°, $[\alpha]_D$ 0° ± 1° (*c* 1·35) (35 mg.), identical with C3 (Found : * C, 80·3; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). Fractions C6—9 consisted of cholestan-3-one (Found : * C, 83·85; H,

[21] Butenandt and Wolff, *Ber.*, 1935, **68**, 2093.

12·0. Calc. for $C_{27}H_{46}O$: C, 83·9; H, 12·0%) detected by a spot test,† and characterised as the 2 : 4-dinitrophenylhydrazone,[22] m. p. 227—229°, and the semicarbazone,[23] m. p. 236—238°.

The other half (4·3 g.) of the reaction product was hydrolysed with N-methanolic potassium hydroxide on the steam-bath for 2 hr., to yield a neutral (1·87 g.) and an acidic fraction (2·0 g.). The latter was converted by methanolic hydrogen chloride into a crude methyl ester, which by triangular fractional crystallisation furnished the ester (VI) (400 mg.), m. p. 95° (Found : * C, 80·4; H, 11·6%); chromatography of the mother-liquors failed to give the ester (VIII), although a little must have been present.

In another experiment, the 2α-bromo-ketone (6 g.) gave a neutral (3·25 g.) and an acidic fraction (1·57 g.), which yielded similar results.

(*b*) 2α-Bromocholestan-3-one (6·0 g.) was added to a cooled solution of sodium (4·5 g.) in *dry* ethanol (225 c.c.), and the mixture stirred with exclusion of moisture at 15° for 15 hr. After addition of water (30 c.c.), the solution was heated on a steam-bath for 2 hr. to yield, after working up, a neutral (3·8 g.) and an acidic frqction, which by the Fischer–Speier method yielded a crude methyl ester (2 g.). Triangular fractional crystallisation of this from methanol–ether easily afforded the ester (VI), m. p. 94—95° (800 mg.); the last crystalline fraction and the mother-liquor (1·2 g.), by chromatography and elution with light petroleum (20 c.c. eluates), gave fractions : D1, oil (9 mg.); D2, m. p. 59—60° (510 mg.); D3, m. p. 56—60° (140 mg.); D4, D5, m. p. 44—46° (65 mg., 25 mg.), and by use of benzene–light petroleum (1 : 9) D6—9, m. p. 125—126° (20, 135, 80, and 60 mg.). Fractions D2—5, by fractional crystallisation from methanol, readily gave the ester (VIII), m. p. 45° (700 mg.), in a state of considerable purity since the m. p. remained unchanged by further crystallisation. Fractions D6—9 consisted of cholestan-3-one.

Wieland–Barbier Degradation of Methyl A-*Norcholestane-2α-carboxylate.*—The ester (VI) (330 mg.), in pure benzene (30 c.c.), was added to phenylmagnesium bromide, prepared from magnesium (210 mg.) and bromobenzene (2·05 g.) in ether (20 c.c.) at 0° with stirring. After 3 hr. on the steam-bath the complex was decomposed with ice-cold saturated ammonium chloride solution and worked up to yield A-norcholestan-2α-yldiphenylmethanol, m. p. 184—186°. This was dehydrated by refluxing acetic anhydride (5 c.c.) in 2 hr. to 2-diphenylmethylene-A-norcholestane, m. p. 120°, $[\alpha]_D$ −143° (*c* 2·0), after chromatography and crystallisation from acetone–methanol. The olefin (470 mg.) in acetic acid (30 c.c.) was treated with chromium trioxide (300 mg.) in 70% acetic acid (1 c.c.) at 15°. (The olefin was oxidised by chromium trioxide only with difficulty, and in subsequent experiments ozonolysis was found more satisfactory.) The neutral product (300 mg.), isolated in the usual way, was chromatographed on aluminium oxide (3 g.) in light petroleum; elution with light petroleum (2 × 5 c.c.) gave fractions : E1, E2, oils (60, 28 mg.), which crystallised in the cold and consisted of benzophenone, m. p. 48°. Use of benzene–light petroleum (1 : 1) (5 × 5 c.c.) gave fractions E3—7, oils (total 140 mg.), whilst benzene gave fractions E7—10, oils (64 mg.). Fractions E3—7 were reabsorbed on aluminium oxide (6 g.), whereafter elution with light petroleum gave crystals (83 mg.), m. p. 78—95°; two recrystallisations from ether–methanol furnished A-norcholestan-2-one, m. p. and mixed m. p. 95—96°, $[\alpha]_D$ +142° (*c* 1·0), characterised as the semicarbazone, m. p. 230—232°, and 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166—167°.

Wieland–Barbier Degradation of Methyl A-*Norcholestane-3α-carboxylate.*—The ester was similarly treated with phenylmagnesium bromide to give, successively, A-*norcholestan-3α-yldiphenylmethanol*, m. p. 216—219° after crystallisation from light petroleum (Found : * C, 86·8; H, 10·4. $C_{39}H_{56}O$ requires C, 86·6; H, 10·4%), 3-*diphenylmethylene-A-norcholestane*, m. p. 143—144° after crystallisation from ethanol–ether–light petroleum (Found : * C, 89·7; H, 9·95. $C_{39}H_{54}$ requires C, 89·6; H, 10·4%), and by ozonolysis and reduction of the ozonide with zinc–acetic acid A-norcoprostan-3-one, m. p. and mixed m. p. 73°, $[\alpha]_D$ +104° (*c* 2·0), characterised as the semicarbazone, m. p. 268—270°, and 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159—160° (Found : * C, 69·4; H, 8·7. Calc. for $C_{32}H_{48}O_4N_4$: C, 69·5; H, 8·75%).

4β-*Bromocoprostan-3-one* (XVII).—Coprostan-3-one, prepared as described by Butenandt

† The product (several μg.) is dissolved in chloroform, and a drop deposited on Whatman chromatographic paper; the strip, after drying in a current of air, is sprayed with a freshly prepared methanolic-hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine. A yellow spot, not removed by a dilute acidic solution of sodium nitrite, indicates a ketone.

[22] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1007.
[23] Dorée and Petrow, *J.*, 1935, 1391.

and Wolff,[21] failed to crystallise from the reaction mixture which was therefore poured into saturated sodium hydrogen carbonate solution. The precipitated solid was filtered off and dried in the absence of light to furnish 4β-bromocoprostan-3-one, m. p. 106—108°, $[\alpha]_D$ +53° (*c* 0·6) (cf. lit.,[21] m. p. 111°).

Methyl A-*Norcoprostane*-2β- *and* -3β-*carboxylate* (XIV, XVI).—(*a*) 4β-Bromocoprostan-3-one (5 g.) in anhydrous ether (200 c.c.) was added dropwise to sodium methoxide in methanol [prepared from anhydrous methanol (300 c.c.) and sodium (6·2 g.)] at 15°; precipitation of sodium bromide occurred immediately and the solution was kept overnight at 15°. After acidification of the reaction mixture with 2N-sulphuric acid, extraction with ether gave an ethereal solution from which no acid was extracted by 2N-sodium hydroxide. Evaporation of the dry ethereal solution gave an opaque solid, which afforded a precipitate when triturated with ether. Collection of the sodium salt, acidification of its aqueous suspension, and extraction with ether in the usual manner furnished a yellow viscous oil which was esterified with ethereal diazomethane. Isolation of the methyl esters in the usual manner yielded an oil (1·39 g.). The ethereal mother-liquors from the filtration of the sodium salt were washed with water, dried, and evaporated, to afford an oil (2·87 g,).

The methyl esters (1·39 g.) obtained from the acidic fraction were chromatographed on neutral aluminium oxide (40 g.; reactivated at 180°/10 mm. for 2 hr.). Elution with pentane (3 × 130 c.c.) gave fractions A1—3, oils (559 mg.). Further elution with pentane (4 × 130 c.c.) yielded fractions A4—7, oils (409 mg.), which by crystallisation from methanol–ether gave needles of *methyl* A-*norcoprostane*-3β-*carboxylate* (XVI), m. p. 66—67° [Found (after drying at 40°/0·03 mm. for 10 hr.): C, 80·45; H, 11·2. $C_{28}H_{48}O_2$ requires C, 80·75; H, 11·5%]. Elution with benzene–pentane (1 : 9 and 1 : 4) gave fractions A8 and A9 as oils (294 mg.) which slowly crystallised and by recrystallisation from methanol–ether furnished dimethyl 3 : 4-*seco*-coprostane-3 : 4-dioate (XIX; R = Me), m. p. 60—61°.

Fractions A1—3 (559 mg.) were rechromatographed on neutral aluminium oxide (20 g.). Elution with pentane (10 × 20 c.c.) furnished oily fractions B1—10 (550 mg.), each fraction having $[\alpha]_D$ +46° ± 2°.

The neutral fraction (2·87 g.) was chromatographed on neutral aluminium oxide (81 g.). Elution with pentane (6 × 250 c.c.) furnished fractions C1—6 as oils (984 mg.). Elution with benzene–pentane (1 : 9; 3 × 250 c.c. and 1 : 1; 6 × 250 c.c.) afforded oily fractions C7—15 which by crystallisation from methanol–acetone gave coprostan-3-one, m. p. and mixed m. p. 61—62°. Elution with benzene, ether, and chloroform gave a yellow oil (480 mg.), which was not further examined.

Fractions C1—6 were rechromatographed on neutral aluminium oxide (60 g.). Elution with pentane (10 × 100 c.c.) gave D1—10 as mobile oils, which did not crystallise or solidify at −80°. Distillation of the oil at 170°/0·03 mm. afforded a mixture of methyl A-norcoprostane-2β- (XIV) and -3β-carboxylate (XVI), $[\alpha]_D$ +44° (*c* 1·1) (Found: C, 80·8; H, 11·5. Calc. for $C_{28}H_{48}O_2$: C, 80·75; H, 11·5%).

The yields were thus: Favorski esters 48%, dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate 3%, and coprostan-3-one 20%.

(*b*) 4β-Bromocoprostan-3-one (5 g.) in ether (200 c.c.) was added dropwise to a solution of sodium methoxide in methanol [prepared from anhydrous methanol (292 c.c.), water (8 c.c.), and sodium (6·2 g.)] at 15°; precipitation of sodium bromide occurred immediately and the solution was kept overnight at 15°, then worked up as in the previous experiment, to furnish the mixed Favorski esters (XIV, XVI) (833 mg., 17·5%), coprostan-3-one (897 mg., 18·7%), and dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate (134 mg., 2·8%).

(*c*) 4β-Bromocoprostan-3-one (4·2 g.) in anhydrous ether (120 c.c.) was added dropwise to a solution of sodium methoxide in methanol [prepared from methanol (150 c.c.) and sodium (5 g.)] at 15°; precipitation of sodium bromide occurred immediately and the solution was kept for 30 hr. at 15°. The ether was removed and after the addition of water (20 c.c.) the mixture was refluxed for 1 hr. Acidification with 2N-sulphuric acid and extraction with ether gave an ethereal solution which was washed with water, dried, and evaporated to a yellow oil (3·94 g.). The oil was esterified with ethereal diazomethane, and the product, isolated in the usual manner, treated with Girard's reagent T (200 mg.) in refluxing ethanol (90 c.c.) and acetic acid (10 c.c.) for 1 hr. The solution was diluted and extracted with ether, to give an ethereal solution which was washed with sodium hydrogen carbonate solution and water. Regeneration of the ketonic material from the aqueous layer by acid hydrolysis afforded coprostan-3-one, m. p. 61—62°

(700 mg.). Evaporation of the dry ethereal extracts furnished a yellow oil (3·22 g.) which was chromatographed on neutral aluminium oxide (90 g.). Elution with pentane gave as a colourless oil (1·1 g.), $[\alpha]_D$ +47° (*c* 0·86), a mixture of methyl A-norcoprostane-2β- and -3β-carboxylate. Elution with benzene–pentane (1 : 4) gave an oil (200 mg.), which by crystallisation from methanol–ether furnished dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate (XIX; R = Me), m. p. 60—61°. Elution with ether, chloroform, and methylene dichloride furnished a yellow oil (1 g.). The yields of product were thus : Favorski esters 28%, dimethyl-3 : 4-*seco*coprostane-3 : 4-dioate 5·2%, and coprostan-3-one 18·5%.

(*d*) 4β-Bromocoprostan-3-one (4·5 g.) was added to a vigorously stirred solution of sodium methoxide in methanol [prepared from anhydrous methanol (150 c.c.) and sodium (5 g.)] at 15°. Stirring was continued for 30 hr., and after the addition of water (20 c.c.) the solution was refluxed for 1 hr. The product (4·2 g.) isolated as in the previous experiment was esterified with ethereal diazomethane and the ketonic material was removed with Girard's reagent T. Regeneration of the ketone from the aqueous layer afforded an oil (480 mg.), which by crystallisation from methanol–acetone furnished coprostan-3-one, m. p. 60—61°.

The non-ketonic material (3·7 g.) was chromatographed on neutral aluminium oxide (120 g.). Elution with pentane gave, as a colourless oil E (2·57 g.), $[\alpha]_D$ +45° (*c*, 1·0), a mixture of methyl A-norcoprostan-2β- and 3β-carboxylate [Found (after drying at 100°/0·03 mm. for 3 hr.) : C, 80·6; H, 11·5. Calc. for $C_{28}H_{48}O_2$: C, 80·75; H, 11·5%]. Elution with benzene–pentane (1 : 4) furnished an oil (210 mg.), which by crystallisation from methanol–ether gave dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate (XIX; R = Me), m. p. 60—61°. Elution with ether and chloroform gave an unidentified oil (1·0 g.). The oil E (2·57 g.) was rechromatographed on neutral aluminium oxide (90 g.). Elution with pentane (10 × 100 c.c.) furnished a series of oily fractions, all having $[\alpha]_D$ +45° ± 2°. The yields of products were thus : Favorski esters 61%, dimethyl 3 : 4-*seco*coprostane-3 : 4-dioate 11%, and coprostan-3-one 5%.

2- *and* 3-*Diphenylmethylene*-A-*norcoprostane*.—The mixed esters (XIV, XVI) (1·8 g.) in anhydrous benzene (120 c.c.) were added to phenylmagnesium bromide in ether [prepared from bromobenzene (8·4 c.c.), magnesium (1·62 g.), and ether (120 c.c.)]. The solution was refluxed for 5 hr., cooled, poured into ice-cold saturated ammonium chloride solution, and extracted with ether. Steam-distillation of the benzene–ether layer removed diphenyl, and the residual oil, obtained in the usual manner, was refluxed with acetic acid (120 c.c.) and acetic anhydride (60 c.c.) for 3 hr. Removal of the solvent under reduced pressure afforded a yellow oil (1·7 g.) which was chromatographed on aluminium oxide (50 g.). Elution with pentane (3 × 150 c.c.) furnished a colourless oil (1·7 g.), $\lambda_{max.}$ 252 mμ (log ε 4·1 in EtOH).

A-*Norcoprostan*-3- *and* -2-*one*.—The above oil (1·0 g.) in ethyl acetate was treated with a stream of ozonised oxygen at −70° for 30 min. The solution was set aside at room temperature for 1 hr., and the solvent removed under reduced pressure. The residual oil was treated with zinc dust (10 g.) in refluxing acetic acid (200 c.c.) for 2 hr., and after removal of solvent at 10 mm. and then at 0·03 mm. the residue (820 mg.) was chromatographed on aluminium oxide (30 g.). Elution with benzene–pentane (1 : 9; 3 × 100 c.c.) furnished oily fractions F1—3 (220 mg.), and benzene–pentane (1 : 4) afforded an oily fraction F4 (250 mg.). Elution with benzene–pentane (1 : 1) gave an unidentified fraction F5, m. p. 182° (305 mg.). Fractions F1—3 were rechromatographed on aluminium oxide (8 g.); elution with benzene–pentane (1 : 9; 5 × 30 c.c.) furnished an oil (210 mg.), which by crystallisation from methanol gave A-norcoprostan-3-one (XIII), m. p. and mixed m. p. 73—74°, $[\alpha]_D$ +102° (*c* 1·2). Further elution with benzene–pentane (1 : 4) gave an oil (5 mg.). Fraction F4 was rechromatographed on aluminium oxide (8 g.); elution with benzene–pentane (1 : 9 and 1 : 4) gave a solid (215 mg.) which by recrystallisation from methanol–ether afforded A-norcoprostan-2-one (XVIII), m. p. 101—103°, $[\alpha]_D$ +46° (*c* 2·0).

Methyl A-norcoprostane-3β-carboxylate [from (*a*), p. 1457] was degraded as in the previous experiment, to furnish only A-norcoprostan-3-one (XIII), m. p. 73—74°.

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