Steroids and Walden Inversion. Part XXIV. The Methylation of 3-Hydroxy-steroids.*

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Methylation of coprostan-3α-ol with potassium–methyl iodide gives 3α-methoxycoprostane, identical with the product obtained from *epi*cholesteryl methyl ether by hydrogenation with platinum in the presence of hydrobromic, perchloric, or sulphuric acid. Similar methylation of coprostan-3β-ol does not cause inversion at $C_{(3)}$ and affords 3β-methoxycoprostane; partial epimerisation was observed only with a prolonged reaction time. In our hands, methylation of cholestan-3α-ol did not cause inversion at $C_{(3)}$ and furnished 3α-methoxycholestane in contrast to the observation by Beynon, Heilbron, and Spring (*J.*, 1937, 406).

DURING their investigation of the structure of *i*-cholesteryl methyl ether (6β-methoxy-3 : 5-*cyclo*cholestane), Beynon, Heilbron, and Spring (*J.*, 1937, 406; ref. *a*) found that methylation of either of the epimeric cholestan-3-ols with potassium and methyl iodide in boiling benzene gave 3β-methoxycholestane, previously prepared by Wagner-Jauregg and Werner (*Z. physiol. Chem.*, 1932, **213**, 119; ref. *b*). It seemed probable that epimerisation of the axial 3α-hydroxyl group to the more thermodynamically stable equatorial 3β-hydroxyl group under the influence of alkoxide ions had taken place before methylation in their experiments.

We have examined the methylation of the epimeric coprostan-3-ols in which the stereo-electronic relations are inverted as compared with the cholestan-3-ols. Methylation of coprostan-3α-ol (I; OH, equatorial) with potassium and methyl iodide in boiling benzene

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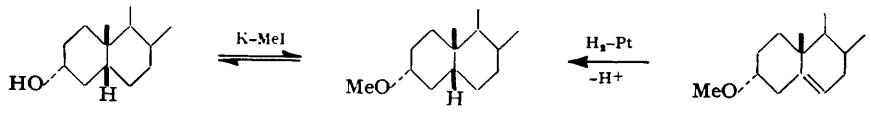
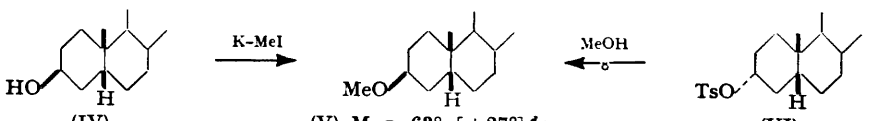
gave 3α-methoxycoprostane (II), identical with that obtained from *epi*cholesteryl methyl ether (III) by catalytic hydrogenation with platinum in the presence of hydrobromic, perchloric, or sulphuric acid (Lewis and Shoppee, *J.*, 1955, 1365, ref. *c*), and demethylated to coprostan-3α-ol (I).



(I) (II) M. p. 88°, [+36°][c]; m. p. 88°, [+32°] (III)

Values in square brackets are $[\alpha]_D$.

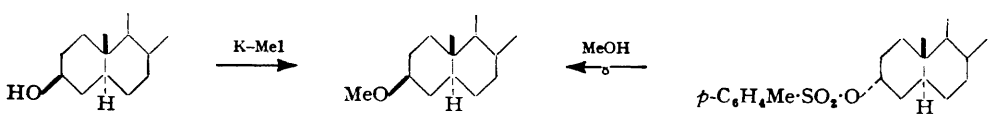
Coprostan-3β-ol (IV; HO, axial) by methylation under similar conditions gave 3β-methoxycoprostane (V), previously prepared by reductive methylation of coprostan-3-one (Babcock and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5472; ref. *d*) and by methanolysis of 3α-toluene-*p*-sulphonyloxycoprostane (VI) (Evans and Shoppee, *J.*, 1953, 540; ref. *e*).



(IV) (V) M. p. 63°, [+27°][d]; m. p. 64/79°,* [+23°][e]; m. p. 78°, [+28°] (VI)

* This designates double m. p.

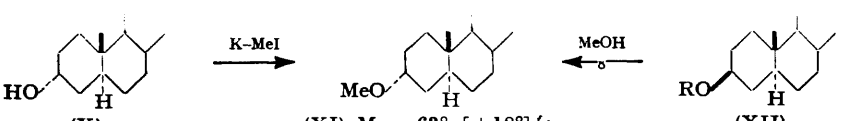
Since the expected inversion of coprostan-3β-ol (IV) to coprostan-3α-ol (I) did not occur, methylation of the epimeric cholestan-3-ols with potassium–methyl iodide was re-investigated. Cholestan-3β-ol (VII; OH, equatorial) gave 3β-methoxycholestane (VIII) recently obtained by methanolysis of 3α-toluene-*p*-sulphonyloxycholestane (IX) (Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937; ref. *f*); contrary to the observation by Beynon, Heilbron, and Spring (*loc. cit.*), cholestan-3α-ol (X; OH, axial) gave 3α-methoxycholestane



(VII) (VIII) M. p. 81°, [+20°][a,f]; m. p. 83°, [+20°][b,d]; m. p. 83°, [+20°] (IX)

(XI), identical with the compound obtained by methanolysis of 3β-toluene-*p*-sulphonyloxycholestane (XII; R = *p*-$C_6H_4Me{\cdot}SO_2$) (Nace, *loc. cit.*), or of cholestan-3β-yl methyl sulphate (XII; R = $MeO{\cdot}SO_2$) (McKenna and Norymberski, *Chem. and Ind.*, 1954, 961; ref. *g*).

Attempts were made to repeat the conversion (X ⟶ VIII) observed by Beynon, Heilbron, and Spring. In view of the evidence adduced by Ashner and Doering (*J. Amer. Chem. Soc.*, 1949, **71**, 838) that the epimerisation of secondary alcohols involves an

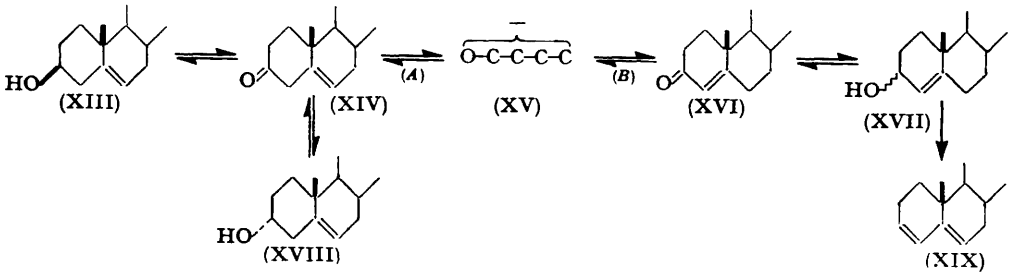


(X) (XI) M. p. 63°, [+18°][f]; m. p. 64°, [+23°][g]; m. p. 63°, [+21°] (XII)

oxidation–reduction analogous to that operating in Oppenauer oxidation and Meerwein–Ponndorf reduction, additions of (i) 5% of cholestan-3-one, (ii) methanol, and (iii) 5% of cholestan-3-one and methanol, to the methylations were made, but resulted in production only of the 3α-methyl ether (XI). Formation of the 3β-methyl ether (VIII) would have afforded a readily identifiable molecular compound, m. p. 74°. Similarly, coprostan-3β-ol

(IV), under the same conditions, gave only the 3β-methyl ether (V). Partial epimerisation of coprostan-3β-ol was obtained by extending the time of reaction with potassium in the presence of methanol from 1 to 3 hr.; reaction with methyl iodide then gave a product, m. p. 68°, $[\alpha]_D$ +29·5°, which appeared to be identical with a molecular compound artificially prepared from the two epimerides. Under similar conditions, cholestan-3α-ol (X) did not undergo epimerisation, but it is likely that prolonged reaction in the presence of alkoxide ions can cause some degree of epimerisation.

In connection with the mechanism of epimerisation suggested by Ashner and Doering, it is relevant that Heilbron, Barnett, Jones, and Verrill (*J.*, 1940, 1390) were able partially to convert cholesterol (XIII) and lumisterol [10α-ergosterol] into *epi*cholesterol (XVIII) and *epi*lumisterol, respectively, by treatment with aluminium *iso*propoxide in boiling xylene. The intermediate here must be the βγ-unsaturated ketone cholest-5-en-3-one (XIV); equilibrium with the corresponding αβ-unsaturated ketone cholest-4-en-3-one (XVI) is rapidly established in the presence of acidic or alkaline catalysts (Butenandt and



Schmidt-Thomé, *Ber.*, 1936, **69**, 882; Shoppee and Summers, *J.*, 1950, 687; Birch, *ibid.*, p. 2325; cf. Fieser and Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728), and is greatly in favour of this. As has been pointed out by Birch, if protonation of the mesomeric anion (XV) is irreversible, then kinetic control (*A*) will lead to a high proportion of the unconjugated ketone (XIV), giving by reduction cholesterol and *epi*cholesterol; but if protonation of the mesomeric anion (XV) is reversible then thermodynamic control (*B*) will lead to the conjugated ketone (XVI), giving by reduction the epimeric cholest-4-en-3-ols (XVII) (Schoenheimer and Evans, *J. Amer. Chem. Soc.*, 1936, **58**, 182), which are readily dehydrated to cholesta-2 : 4-diene, which in turn is converted by heat into cholesta-3 : 5-diene (XIX). The 5% yield of *epi*cholesterol obtained by Heilbron, Barnett, Jones, and Verrill is thus due partly to the preferential production of cholesterol (XIII; OH, equatorial) and partly to thermodynamic as opposed to kinetic control of the equilibria in which the mesomeric anion (XV) is involved.

The infra-red absorption spectra of the methyl ethers (II, V, VIII, and XI) show that the C–OMe stretching vibration appears at slightly lower frequencies when the methoxyl group has the axial conformation [(V), $\nu_{max.}$ 1095 cm.$^{-1}$ in CS_2; (XI), $\nu_{max.}$ 1086 cm.$^{-1}$ in CS_2] than when it has the equatorial conformation [(II, VIII), $\nu_{max.}$ 1100 cm.$^{-1}$ in CS_2], which recalls the similar small difference in frequency observed between conformational pairs of 3-hydroxy-steroids by Cole, Jones, and Dobriner (*ibid.*, 1952, **74**, 5571). These infra-red spectra, *inter alia*, will be discussed in detail by Dr. J. E. Page in a forthcoming paper.

Experimental

For general details see *J.*, 1955, 694. Specific rotations were determined in $CHCl_3$; infra-red absorption spectra were measured in CS_2 on a Perkin–Elmer double-beam instrument.

3α-Methoxycoprostane from Coprostan-3-α-ol.—Coprostan-3α-ol (m. p. 116°; 850 mg.) was dissolved in benzene (40 c.c.), potassium (450 mg.) added, the solution heated to 70°, and the metal emulsified by vigorous agitation. After 1 hour's refluxing, methyl iodide (15 c.c.) was added and heating continued for 3 hr., potassium iodide being gradually precipitated. The solution was cooled to 0°, methanol added, and solvents removed in a vacuum. The residue was extracted with pentane, the pentane extracts were filtered through a column of aluminium

oxide, and the filtrate was evaporated to yield 3α-methoxycoprostane (470 mg.), m. p. 88°, $[\alpha]_D$ +32° (*c*, 1·3) [Found (after drying at 50°/0·01 mm. for 2 hr.) : C, 83·6; H, 12·5%]. This gave no m. p. depression on admixture with a specimen prepared from *epi*cholesteryl methyl ether by hydrogenation with platinum in the presence of hydrobromic acid (Lewis and Shoppee, *J.*, 1955, 1365, and the infra-red absorption spectra were identical. Demethylation with hot 48% hydrobromic acid and acetic acid for 1·5 hr. (cf. Stoermer, *Ber.*, 1908, **41**, 323) gave an oil, which was chromatographed on aluminium oxide; after elution with pentane, use of benzene–pentane (1 : 9) gave an oil, which crystallised and proved to be 3α-methoxycoprostane, m. p. 86—88°. Elution with ether–benzene (1 : 9) gave crystalline material, which by recrystallisation from methanol furnished coprostan-3α-ol, m. p. and mixed m. p. 110—114°.

3β-*Methoxycoprostane.*—Coprostan-3β-ol (m. p. 100°; 1 g.) was heated with emulsified potassium (700 mg.) in benzene (50 c.c.) for 1 hr., methyl iodide (15 c.c.) was slowly added, and the mixture refluxed for 3 hr. The product was worked up as described above; elution from aluminium oxide with pentane gave 3β-methoxycoprostane (600 mg.), m. p. 78°, $[\alpha]_D$ +28·5° (*c*, 1·2), after crystallisation from acetone [Found (after drying at 50°/0·01 mm. for 2 hr.) : C, 83·2; H, 12·45. Calc. for $C_{28}H_{50}O$: C, 83·5; H, 12·5%], identical with a specimen obtained by methanolysis of 3α-toluene-*p*-sulphonyloxycoprostane (Evans and Shoppee, *loc. cit.*). Methylation in the same way of coprostan-3β-ol (256 mg.) in the presence of coprostan-3-one (9 mg.) gave 3β-methoxycoprostane (244 mg.), m. p. 77°, $[\alpha]_D$ +28° (*c*, 0·75); similarly, methylation of coprostan-3β-ol (113 mg.) in the presence of methanol (0·5 c.c.) gave 3β-methoxycoprostane, m. p. 77°; finally, similar methylation of coprostan-3β-ol (173 mg.) in the presence of coprostan-3-one (5 mg.) and methanol (0·5 c.c.) also gave 3β-methoxycoprostane, m. p. and mixed m. p. 77°.

Prolonged Methylation.—Coprostan-3β-ol (123 mg.) was heated with emulsified potassium in benzene (25 c.c.) containing methanol (0·3 c.c.) for 3 hr., and then refluxed with methyl iodide for a further 3 hr. The product (78 mg.), isolated in the usual way, crystallised by inoculation with either 3α- or 3β-methoxycoprostane; recrystallisation from acetone gave a 1 : 1 molecular compound, m. p. 68°, $[\alpha]_D$ +29·5° (*c*, 2·3), of the epimeric 3-methoxycoprostanes. The molecular compound was also prepared by mixing equal quantities of the epimeric 3-methoxycoprostanes, and on crystallisation from acetone formed plates, m. p. 68°, undepressed on on admixture with either component.

3α-*Methoxycholestane.*—Cholestan-3α-ol (m. p. 183—185°; 1 g.) [prepared by the method of Marker, Kamm, and Whitmore (*J. Amer. Chem. Soc.*, 1935, **57**, 2358)], by methylation with methyl iodide after treatment with emulsified potassium in boiling benzene for 1 hr., yielded 3α-methoxycholestane (650 mg.), m. p. 63°, $[\alpha]_D$ +21° (*c*, 0·6), after crystallisation from acetone, and identical with a specimen prepared by methanolysis of 3β-toluene-*p*-sulphonyloxycholestane (Nace, *loc. cit.*). Methylation in the same way of cholestan-3α-ol (84 mg.) in the presence of cholestan-3-one (8 mg.) gave a product (77 mg.) which by crystallisation from acetone furnished 3α-methoxycholestane, m. p. and mixed m. p. 62—63°; similarly, methylation of cholestan-3α-ol (73 mg.) in the presence of methanol (0·3 c.c.) gave 3α-methoxycholestane (44 mg.), m. p. 63°; finally, similar methylation of cholestan-3α-ol (50 mg.) in the presence of cholestan-3-one (3 mg.) and methanol (0·2 c.c.) gave 3α-methoxycholestane (35 mg.), m. p. and mixed m. p. 62—63°. In each case, the methyl ether was isolated by elution from aluminium oxide with pentane.

Prolonged Methylation.—Cholestan-3α-ol (73 mg.) was heated with emulsified potassium in benzene (15 c.c.) containing methanol (0·3 c.c.) for 3·5 hr., and then refluxed with methyl iodide for a further 3 hr. The product (44 mg.), isolated in the usual way, crystallised from acetone in plates, m. p. 63°, undepressed by admixture with a sample of 3α-methoxycholestane.

Molecular Compound of 3α- *and* 3β-*Methoxycholestane.*—Equal quantities of the epimeric 3-methoxycholestanes were mixed and the mixture crystallised from acetone to give a molecular compound, m. p. 74°.

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