Triterpenoids. Part XVIII. The Constitutions of Phyllanthol and* cyclo*Artenol.*

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A method for the location of *cyclo*propane rings has been developed and applied to give a final solution for the constitutions of the *cyclo*propane triterpenoids phyllanthol and *cyclo*artenol. The method consists in opening the *cyclo*propane ring with, respectively, hydrogen chloride and deuterium chloride, and comparing the intensities of the C–H bending maxima in the infra-red absorption spectra of the two products. In this way the degree of substitution of the carbon atom to which the proton (deuteron) attaches itself may be determined. The direction of *cyclo*propane fission in steroid and terpenoid derivatives appears to be in accordance with the Markownikoff rule.

The isolation of two *cyclo*propane triterpenoids, phyllanthol (Alberman and Kipping, *J.*, 1951, 2296; Barton and de Mayo, *J.*, 1953, 2178) and *cyclo*artenol (Barton, *J.*, 1951, 1444; Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673), has been reported. In both cases the structural problem has been reduced to the location of the *cyclo*propane ring. Thus the possible formulæ (Barton and de Mayo, *loc. cit.*) for phyllanthol, which affords α-amyrin (I; R = OH, R′ = Me) on acid-catalysed isomerisation, are (II—V; R = OH) and, conceivably, (VI; R = OH).

Now the opening of a *cyclo*propane ring by deuterium chloride (cf. Barton and de Mayo, *loc. cit.*) must afford one of the groupings $-CH_2D$, $\succ$CHD, or $\succcurlyeq$CD. Methyl and methylene groups show infra-red absorption in the C–H bending region between 1300 and 1500 cm.$^{-1}$ (see R. N. Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; R. N. Jones, Cole, and Nolin, *ibid.*, p. 5662; Nolin and R. N. Jones, *ibid.*, 1953, **75**, 5626; Sheppard and Simpson, *Quart. Reviews*, 1953, **7**, 19) and therefore, if the infra-red spectra of *cyclo*propane compounds opened respectively with hydrogen chloride and deuterium chloride were compared, there would be observed a diminution in the intensity of the CH_3 peak at 1380 cm.$^{-1}$ or of the CH_2 peak near 1450 cm.$^{-1}$ depending on whether the grouping $-CH_2D$ or $\succ$CHD were produced. If the grouping $\succcurlyeq$CD were formed there would be no change in the intensities of

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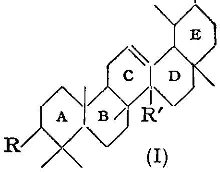
* Part XVII, *J.*, 1954, 903.

the peaks at 1380 and 1450 cm.$^{-1}$. Thus a general method for the location of *cyclo*propane rings would become available.

In order to examine the feasibility of the procedure the fission of 3 : 5-*cyclo*cholestane (VII) to give (with hydrogen chloride) 3-methyl-A-norcholest-3(5)-ene (VIII; R = Me) (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582; Shoppee and Summers, *J.*, 1952, 2528) and (with deuterium chloride) the 3-deuteromethyl analogue (VIII; R = CH_2D) was investigated. As shown by the data summarised in the Table the reduction in intensity of the 1380 cm.$^{-1}$ band in the deutero-derivative was proportional to the change in the number of methyl groups contributing to this maximum.* Some reduction in the strength of the ring-methylene peak near 1450 cm.$^{-1}$ was also produced. This must be due to the



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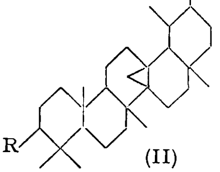

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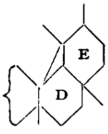

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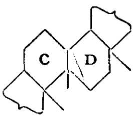

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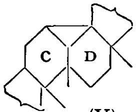

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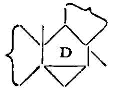

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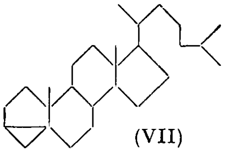
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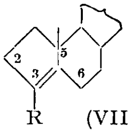

(VIII)

Compound	Infra-red frequencies (cm.$^{-1}$) and, in parentheses, apparent molecular extinction coefficients					No. of CH_3 groups contributing to 1380 cm.$^{-1}$ max.	Intensity per CH_3 at 1380 cm.$^{-1}$ or equiv.
	CH_2 (" aliphatic ")	CH_2 (" ring ")	CH_3 (*gem*)	CH_3	CH_3 (*gem*)		
3-Methyl-A-norcholest-3(5)-ene (VIII; R = CH_3)	1470 (125)	1446 (108)	—	1380 (100)	1368 (100)	5	20
3-Deuteromethyl-A-norcholest-3(5)-ene (VIII; R = CH_2D)	1470 (117)	1446 (88)	—	1380 (82)	1368 (92)	4	20
α-Amyrene (I; R = H; R′ = CH_3)	—	1460 (152)	1386 (104)	1380 (138)	1370 (73)	6	23
27-Deutero-α-amyrene (I; R = H, R′ = CH_2D)	—	1460 (152)	1388 (108)	1382 (117)	1370 (69)	5	23
Lanost-9(11)-ene (IX; R = H, R′ = CH_3)	1466 (159)	1448 (91)	1386 (96)	1372 (161)	1364 (122)	5	32
19-Deuterolanostenes (IX; R = H, R′ = CH_2D; 7 : 8- and 8 : 9-ene isomers)	1466 (159)	1448 (93)	1386 (93)	1372 (129)	1364 (123)	4	32
Lanostane (XVI; R = CH_3)	1468 (167)	1450 (105)	— —	1386 (138)	1368 (112)	6	23
19-Deuterolanostane (XVI; R = CH_2D)	1468 (167)	1450 (107)	— —	1386 (120)	1368 (112)	5	24
3 : 5-*cyclo*Cholestane (VII)	1470 (138)	1446 (91)	— —	1380 (90)	1368 (70)	4	22
Phyllanthane (II; R = H)	—	1454 (148)	1386 (84)	1382 (120)	1368 (68)	5	24
*cyclo*Artane (X; R = H)	1468 (153)	1453 (123)	1380 (123)	1375 (116)	1364 (110)	4	29

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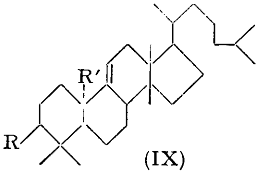
* The intensity values summarised in the Table are reported in apparent molecular extinction coefficients calculated as defined in the Experimental section. The corresponding data given in a previous Part of this series (Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571; see also *idem, Chem. and Ind.*, 1952, 426) were expressed in a purely arbitrary manner. Since, both in these papers and in the present article, relative values only are concerned, the form in which the intensity data are presented is of no significance.

(not unexpected) further deuteration (at $C_{(6)}$ and possibly at $C_{(2)}$) of (VIII; $R = CH_2D$) after the fission of the *cyclo*propane ring.

*cyclo*Propane fission of phyllanthane with deuterium chloride produced a deuteromethyl group, as shown by the infra-red results summarised in the Table. Since only (II; R = H) could afford such a grouping the constitution of phyllanthol must be (II; R = OH). This conclusion is confirmed by the intensity data for phyllanthane itself (see Table), which clearly has one less methyl group than α-amyrene (cf. the similar data for 3 : 5-*cyclo*cholestane also summarised in the Table).

*cyclo*Artanol, derived from *cyclo*artenol by saturation of the *iso*propylidene group in the side chain, affords a mixture of lanost-7-, -8-, and, mainly, -9(11)-enol (Bentley *et al.*, *loc. cit.*) on acid-catalysed isomerisation. The possible formulæ for *cyclo*artanol are (see Bentley *et al.*, *loc. cit.*) (X—XV; R = OH). Of these only (X; R = OH) would afford a deuteromethyl group based on a lanostane carbon skeleton on *cyclo*propane fission with deuterium chloride. That such a grouping was indeed produced was shown, first, by comparing the spectrum of the mixture of olefins [main component (IX; R = H, $R' = CH_2D$)] formed by treatment of *cyclo*artane with deuterium chloride with that of lanost-9(11)-ene (IX; R = H, $R' = CH_3$) (see Table). This conclusion was confirmed by consideration of the intensity of absorption at 1380 $cm.^{-1}$ of *cyclo*artane relative to that of lanost-9(11)-ene (IX; R = H, $R' = CH_3$) and, more securely, in the following way. *cyclo*Artanyl acetate was converted by deuterium chloride into a mixture of 7-, 8-, and 9(11)-olefins. Catalytic hydrogenation of the 9(11)-ethylenic linkage (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893) gave a mixture of deuterated lanostanyl acetate and (unhydrogenatable) lanost-7- and -8-enyl acetate. Treatment with peracetic acid and chromatography afforded pure deuterated lanostanyl acetate which, by hydrolysis, oxidation, and Wolff–Kishner reduction, gave deuterated lanostane (XVI; $R = CH_2D$). The infra-red spectrum of the latter compound, compared with that of lanostane (XVI; $R = CH_3$) (see Table), revealed beyond question the presence of a deuteromethyl group. The formula of *cyclo*artenol is thus [X; R = OH and with an ethylenic linkage at position 27(28)].



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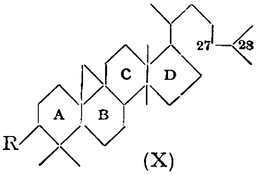

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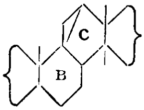

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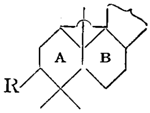

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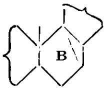

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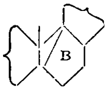

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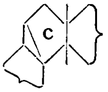

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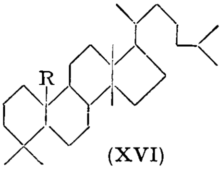

(XVI)

The same conclusion as to the formula of *cyclo*artenol has also been reached independently by Henry and Spring (*Chem. and Ind.*, 1954, 220) on the basis of exclusion evidence. We cordially thank Professor F. S. Spring, F.R.S., for his kindness in sending us a copy of his preliminary communication before its publication.

The constitutions (II; R =OH) and [X; R = OH; double bond at position 27(28)] for phyllanthol and *cyclo*artenol respectively are in agreement with Cole's observations *ibid.*, 1953, 946; also personal communication) that both compounds have an infra-red peak at 3042—3052 $cm.^{-1}$ which may be regarded as characteristic of the C–H stretching frequency of a methylene group within a *cyclo*propane ring.

With simple *cyclo*propane compounds acid-catalysed fission proceeds in accordance with the Markownikoff rule (see Raphael in Robinson and Rodd's " The Chemistry of Carbon Compounds," Elsevier Publ. Corpn., Amsterdam, 1953, Vol. IIA, p. 26). The question of the applicability of this concept to complex polycyclic sustems of the type discussed in the present paper is clearly of interest. The acid-catalysed isomerisations of 3 : 5-*cyclo*cholestane (VII), phyllanthol, and *cyclo*artanol are all in agreement with the rule. Of the other formulæ for phyllanthol, including those disproved by Barton and de Mayo (*loc. cit.*), only (III and IV; R = OH) might conceivably isomerise to α-amyrin with Markownikoff fission. Of the various possible formulæ for *cyclo*artanol (XII—XIV; R = OH), as well as the correct structure (X; R = OH), might all afford the observed product on Markownikoff fission.

The assignment of infra-red absorption frequencies to the *gem*-dimethyl groupings of the compounds listed in the Table requires comment. These frequencies often appear as side maxima or shoulders on the main 1380 cm.$^{-1}$ band. The intensities reported for these maxima are therefore misleading in that there is a substantial contribution from ordinary methyl groups. The *gem*-dimethyl group in the side chain of 3 : 5-*cyclo*cholestane (VII) and its derivatives (VIII; R = CH_3 and CH_2D) shows one methyl group absorbing at 1368 cm.$^{-1}$ and the other contributing to the main peak at 1380 cm.$^{-1}$. α-Amyrene (I; R = H, R′ = CH_3) and its deutero-derivatives showed *gem*-dimethyl peaks at 1386 cm.$^{-1}$ as well as at 1370 cm.$^{-1}$. This resolution of the *gem*-dimethyl peaks was also noted in lanost-9(11)-ene (IX; R = H, R′ = CH_3) and its deuterated derivatives, but not in lanostane (XVI; R = CH_3) and 19-deuterolanostane (XVI; R = CH_2D). In the last two compounds two methyl groups of the two *gem*-dimethyl groupings must be contributing to the 1368 cm.$^{-1}$ peak whilst the other two methyl groups are not separated but contribute to a 1368 cm.$^{-1}$ maximum which represents also all the other methyl groups.

EXPERIMENTAL

For general experimental details see Part VII (*J.*, 1952, 2339). Rotations were determined in chloroform solution. The deuterium oxide used was 99·65—99·74% pure (Norsk Hydro).

Infra-red Spectroscopy.—The spectroscopic measurements were made with a Perkin–Elmer Model 21 double-beam spectrophotometer. Although an instrument fitted with a calcium fluoride prism is to be preferred for quantitative measurements in the C–H bending region (see R. N. Jones and Cole, *loc. cit.*), satisfactory resolution was achieved in the present investigation with a sodium chloride prism. The accuracy of the frequency measurements for sharp maxima was about ±3 at 1500 cm.$^{-1}$.

The samples were examined as about 0·05M-solutions in carbon tetrachloride in 0·8-mm. rock-salt cells; a matched cell containing the solvent was placed in the reference beam of the spectrophotometer to compensate for solvent absorption. The measurements were conducted over the spectral range 4000—650 cm.$^{-1}$.

The apparent molecular extinction coefficients listed in the Table were calculated from the relation $\varepsilon_a = \frac{1}{cl}\log_{10}\left(\frac{T_0}{T}\right)$, where T_0 and T are respectively the radiation (%) transmitted by the solvent and by the solution at the frequency of the absorption maximum, c is the solute concentration (moles l.$^{-1}$), and l is the thickness (cm.) of the cell (cf. R. N. Jones, Ramsay, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80). Duplicate determinations were run on nearly every sample. The reproducibility of the molecular extinction coefficients was well within 5%.

3-*Methyl*-A-*norcholest*-3(5)-*ene* (VIII; R = CH_3).—A solution of 3 : 5-*cyclo*cholestane, m. p. 79—80°, $[\alpha]_D$ +75° (*c*, 1·42) (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582) (109 mg.), in alcohol-free chloroform (3 ml.) to which 4 drops of water had been added, was saturated with hydrogen chloride and left at room temperature for 1 day. The product (102 mg.) was chromatographed over alumina. Elution with light petroleum (b. p. 40—60°) and crystallisation from chloroform–methanol gave 3-methyl-A-norcholest-3(5)-ene, m. p. 64—64·5°, $[\alpha]_D$ +53° (*c*, 1·99) (cf. Schmid and Kägi, *loc. cit.*; Shoppee and Summers, *J.*, 1952, 2528). The deuterium analogue (VIII; R = CH_2D), of the same m. p. and rotation {$[\alpha]_D$ +54° (*c*, 2·31)}, was prepared according to the analogous procedure of Barton and de Mayo (*loc. cit.*).

α-*Amyrene and Derivatives.*—α-Amyrene, kindly prepared by Mr. K. H. Overton, had m. p. 117—118°, $[\alpha]_D$ +93° (*c*, 2·08). Phyllanthane, m. p. 173—174°, $[\alpha]_D$ +43° (*c*, 1·91), was prepared from phyllanthol according to Barton and de Mayo's directions (*loc. cit.*). Fission of the *cyclo*propane ring of this hydrocarbon with deuterium chloride according to Barton and de Mayo's directions (*loc. cit.*) gave 27-deutero-α-amyrene (I; R = H, R′ = CH_2D), m. p. 118—119°, $[\alpha]_D$ +89° (*c*, 1·65).

Lanostan-11-*one*.—This was prepared by an alternative method to that of McGhie, Pradhan, and Cavalla (*J.*, 1952, 3176). Potassium (300 mg.) in dry *tert.*-butanol (16 ml.) was heated with lanostane-3 : 7 : 11-trione (500 mg.) and anhydrous hydrazine (3 ml.) at 165° for 12 hr. The products from three such experiments (1·25 g. of trione used in all) were combined and chromatographed over alumina. Elution with light petroleum (b. p. 40—60°)–benzene(19 : 1) gave lanostan-11-one (276 mg., 22%). Recrystallised from chloroform–methanol this had m. p. 95—95·5°, $[\alpha]_D$ +59° (*c*, 2·04).

Lanostan-11β-*ol*.—A solution of lanostan-11-one (202 mg.) in sodium-dried ether (5 ml.) was added to a refluxing solution of lithium aluminium hydride (450 mg.) in the same solvent (10 ml.). Crystallisation of the product from chloroform–methanol afforded *lanostan*-11β-*ol*, m. p. 132—133°, $[\alpha]_D$ +52° (*c*, 2·45) (Found : C, 83·4; H, 12·4. $C_{30}H_{54}O$ requires C, 83·65; H, 12·65%). The alcohol (208 mg.) in anhydrous pyridine (10 ml.) and redistilled phosphorus oxychloride (1 ml.) with 1 drop of water was heated for 1 hr. on the steam-bath. Chromatography of the product over alumina, elution with light petroleum (b. p. 40—60°), and crystallisation from chlorofrom–methanol gave *lanost*-9(11)-*ene* (54 mg.), m. p. 86—87°, $[\alpha]_D$ +79° (*c*, 3·07) (Found : C, 87·6; H, 12·55. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

Other Derivatives of Lanostane.—*cyclo*Artane, m. p. 86—87°, $[\alpha]_D$ +54° (*c*, 2·23), was prepared according to Barton (*J.*, 1951, 1444). Treatment of *cyclo*artane (95 mg.) with deuterium chloride according to Barton and de Mayo's procedure (*loc. cit.*) gave a mixture of 19-deuterolanostenes (see Bentley, Henry, Irvine, and Spring, *loc. cit.*), m. p. 66—70°.

Similar treatment of *cyclo*artanyl acetate (377 mg.) (Barton, *loc. cit.*) gave a comparable mixture of isomers, m. p. 133—145° (cf. Bentley *et al.*, *loc. cit.*). This was hydrogenated in "AnalaR" acetic acid (50 ml.) over platinum oxide (200 mg.) at 80° until the $\varepsilon_{max.}$ at 203 mμ had decreased to 1200 [saturation of all 9(11)-olefinic material]. The product (354 mg.) in "AnalaR" acetic acid (25 ml.) and chloroform (5 ml.) was treated with 40% peracetic acid (2·5 ml.) and left overnight. Chromatography over alumina, elution with light petroleum (b. p. 40—60°)–benzene (3 : 1), and crystallisation from chloroform–methanol gave 19-deuterolanostanyl acetate, m. p. 147—151°, $[\alpha]_D$ +39° (*c*, 1·91). Hydrolysis, oxidation with chromic acid, and Wolff–Kishner reduction by standard procedures furnished 19-deuterolanostane, m. p. 97—98·5°, (from chloroform–methanol), $[\alpha]_D$ +33° (*c*, 1·84), which was saturated to tetranitromethane. An authentic specimen of lanostane, m. p. 97—98·5°, $[\alpha]_D$ +33° (*c*, 1·63), was prepared by Wolff–Kishner reduction of lanostan-3-one (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893).

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