447. *Triterpenoids. Part XIII.* Phyllanthol, the First Hexacarbocyclic Triterpenoid.*

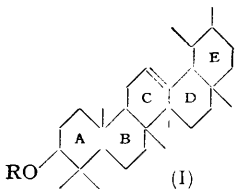
By D. H. R. Barton and P. de Mayo.

Phyllanthol (Alberman and Kipping, *J.*, 1951, 2296) has been characterised as a hexacarbocyclic secondary alcohol containing one *cyclo*propane ring. It is closely related to α-amyrin, for with acidic reagents the *cyclo*propane ring is opened to give the α-amyrin double bond. By the application of a new method for the location of *cyclo*propane rings it has been shown that phyllanthol is not 10 : 12- or 11 : 13-*cyclo*-α-amyranol. Some alternative possibilities are discussed.

The triterpenoid alcohol phyllanthol, $C_{30}H_{50}O$, was isolated by Alberman and Kipping (*J.*, 1951, 2296) from the root bark of *Phyllanthus engleri* (Pax.). Through the courtesy of Drs. Kipping and Alberman and the good offices of Sir John Simonsen, F.R.S., it has been possible to investigate it further.

Phyllanthol was characterised as a secondary alcohol by chromic acid oxidation to the corresponding ketone. The presence of a *cyclo*propane ring was established by the following evidence. (i) Phyllanthyl acetate gave only a weak colour with tetranitromethane, of an intensity comparable with that given by 3 : 5-*cyclo*cholestane. (ii) Phyllanthyl acetate was not attacked by hot perhydrol–acetic acid or by ozone. These are oxidation conditions to which even the very hindered double bond of α-amyrin acetate is susceptible (cf. McLean, Silverstone, and Spring, *J.*, 1951, **935**, and references there cited). (iii) Phyllanthyl acetate showed no double-bond absorption in the far ultra-violet (cf. Bladon, Henbest, and Woods, *J.*, 1952, 2737; Halsall, *Chem. and Ind.*, 1951, 867). On these bases phyllanthol must have six, not five, rings; as such it is the first hexacarbocyclic triterpenoid. The only other known *cyclo*propane compounds of the triterpenoid series are *cyclo*artenone and its derivatives (Barton, *J.*, 1951, 1444; Bentley, Henry, Irvine, and Spring, *Chem. and Ind.*, 1953, 217).

Phyllanthol was shown to be closely related to α-amyrin by the following experiments. (*a*) Wolff–Kishner reduction of phyllanthone afforded phyllanthane which was smoothly converted into α-amyrene by refluxing hydrochloric–acetic acid. (*b*) Similar treatment of phyllanthyl acetate gave α-amyrin acetate in good yield, further identified by hydrolysis to α-amyrin and by conversion of the latter into α-amyrin benzoate. (*c*) Treatment of phyllanthyl acetate in chloroform with hydrogen chloride gas also furnished α-amyrin acetate.



(I)

(II)

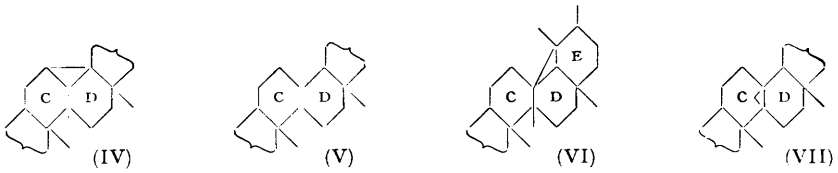
(III)

The simplest interpretation of these results is that phyllanthol is a *cyclo*propane derivative of α-amyranol with one apex of the *cyclo*propane ring terminating at $C_{(12)}$ or $C_{(13)}$. On the basis of the α-amyrin formula (I; R = H) (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075), there are then six possible representations for phyllanthol (II)—(VII). On biogenetic grounds (II) seemed to deserve prior consideration.

The precise location of a *cyclo*propane ring in an organic structure is not easily determined. However, if the *cyclo*propane ring were opened with deuterium chloride, the

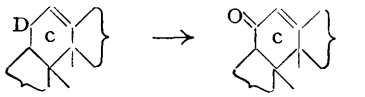
* Part XII, *J.*, 1953, 1842.

position of the deuterium atom thus introduced would reveal one point of attachment of the ring. Our development of this new method for the location of *cyclo*propane rings was made possible by the generous co-operation of Dr. T. F. Gallagher and Dr. D. K. Fukushima (of the Sloan-Kettering Institute, New York) in the carrying out of precision deuterium micro-analyses (cf. Fukushima and Gallagher, *J. Biol. Chem.*, in the press).

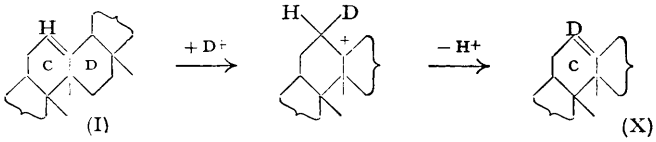


(IV) (V) (VI) (VII)

If phyllanthyl acetate had formula (II), treatment with deuterium chloride would give 11-deutero-α-amyrin acetate (VIII) which on chromic acid oxidation would afford the undeuterated 11-keto-α-amyrin acetate (IX). As expected, phyllanthyl acetate gave in this way a deuterated α-amyrin acetate having 2·65 atoms % excess of deuterium (theor. 1·9). Oxidation, however, afforded an 11-keto-α-amyrin acetate with the deuterium content (2·65 atom %) unchanged (theor. 2·0). Phyllanthol cannot, therefore, have formula (II).

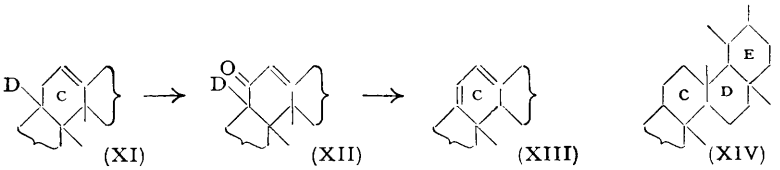
(VIII)  (IX)

The introduction of more than the theoretical amount of deuterium deserves brief comment. There are two reasonable explanations. (*a*) The acetate residue could have been deuterated through the ester enol. (*b*) The vinyl hydrogen at $C_{(12)}$ in α-amyrin acetate could be replaced by D^+ by the mechanism indicated * to give 12-deutero-α-amyrin acetate (X). That (*b*) was probably the correct explanation was demonstrated as follows. Alkaline hydrolysis of the deuterated (2·65 atom %) α-amyrin acetate followed by re-acetylation afforded a deuterated α-amyrin acetate with unchanged deuterium content.



(I) (X)

Another formula (III) for phyllanthol, which would appear reasonable on biogenetic grounds, has been excluded in the following way. On the basis of (III), deuteration of phyllanthyl acetate would afford 10-deutero-α-amyrin acetate (XI), which on oxidation would furnish 10-deutero-11-keto-α-amyrin acetate (XII) transformable by lithium



(XI) (XII) (XIII) (XIV)

aluminium hydride reduction followed by dehydration and re-acetylation into a deuterium-free α-amyra-10 : 12-dienyl acetate (XIII) (Spring *et al.*, *J.*, 1937, 249; 1938, 1233; 1939, 1075). A repetition of the treatment of phyllanthyl acetate with deuterium chloride

* This possibility was pointed out to us by Dr. D. K. Fukushima, to whom we express our best thanks.

gave a deuterated α-amyrin acetate (2·55 atom %), in agreement with the first experiment. Conversion into the acetate (XIII) afforded a compound in which all the deuterium had been retained. We have not so far been able to pursue our investigations further owing to the difficulty of obtaining additional supplies of phyllanthol.

Further discussion of the other possible formulæ is not justified at present. We point out, however, that there remain for consideration formulæ such as (XIV) * which represent simple modifications of the ordinary α-amyrin carbon skeleton.

Experimental

For general experimental details see Part VII (*J.*, 1952, 2339). $[\alpha]_D$ are in $CHCl_3$.

Phyllanthol.—The crude alcohol (7·5 g.) was acetylated and chromatographed over alumina. Elution with benzene and crystallisation from chloroform–methanol afforded phyllanthyl acetate (2·5 g.), m. p. 262—264°, $[\alpha]_D$ +48° (*c*, 1·02), in good agreement with the constants recorded by Alberman and Kipping (*loc. cit.*). Phyllanthyl acetate was recovered unchanged (m. p. and mixed m. p.) after (*a*) treatment in acetic acid with perhydrol on the steam-bath for 1 hr., (*b*) treatment in chloroform with ozone for 30 min. at room temperature. It showed no significant absorption in the ultra-violet between 200 and 225 mμ.

Alkaline hydrolysis of the acetate gave phyllanthol, m. p. 227—228° (from chloroform–methanol), $[\alpha]_D$ +45° (*c*, 1·60) (Found: C, 84·0; H, 11·7. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

Phyllanthone.—Phyllanthol (170 mg.) in acetic acid (15 ml.) and " AnalaR " benzene (3 ml.) was treated with chromium trioxide (40 mg.) in the minimum of water, during 20 hr. at room temperature. The product was crystallised from methanol, to give *phyllanthone*, m. p. 164—165°, $[\alpha]_D$ +52° (*c*, 1·52) (Found: 83·3; H, 11·1. $C_{30}H_{48}O,\frac{1}{2}CH_3{\cdot}OH$ requires C, 83·2; H, 11·4%).

Phyllanthane.—The above-mentioned ketone (100 mg.) in ethanol (2·5 ml.) containing dissolved sodium (150 mg.) and 100% hydrazine hydrate (1 ml.) was heated in a sealed tube at 205° overnight. The product was chromatographed over alumina; elution with light petroleum and crystallisation from chloroform–methanol furnished phyllanthane, m. p. 166—167° (mixed m. p. with phyllanthone, 140—150°), $[\alpha]_D$ +46° (*c*, 1·65) (Found: C, 88·0; H, 12·25. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%).

Phyllanthane (20 mg.) in acetic acid (5 ml.) containing concentrated hydrochloric acid (0·5 ml.) was refluxed for 45 min. The product, on crystallisation form chloroform–methanol, was identified as α-amyrene by m. p., mixed m. p., and rotation {$[\alpha]_D$ +87° (*c*, 0·55)}.

Isomerisation of Phyllanthyl Acetate.—(i) The acetate (50 mg.) in chloroform (12 ml.) was treated with a stream of hydrogen chloride for 4 hr. After removal of the chloroform *in vacuo*, the product was crystallised from chloroform–methanol, to give α-amyrin acetate (20 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +73° (*c*, 1·58)}. The identity was confirmed by hydrolysis to α-amyrin, m. p. and mixed m. p. 180—183°, $[\alpha]_D$ +84° (*c*, 1·85), benzoylation of which afforded α-amyrin benzoate, m. p. and mixed m. p. 192—193°, $[\alpha]_D$ +91° (*c*, 1·61).

(ii) The acetate (50 mg.) in acetic acid (10 ml.) and concentrated hydrochloric acid (1·5 ml.) was refluxed for 30 min. The product, crystallised from chloroform–methanol, gave α-amyrin acetate (35 mg.), identified by m. p. and mixed m. p.

(iii) The acetate (150 mg.) in dry alcohol-free chloroform (5 ml.) and two drops of 99·65% deuterium oxide (Norsk Hydro) was stirred by a magnetic stirrer, and the containing flask evacuated. Gaseous deuterium chloride (prepared by addition of distilled phosphorus trichloride to 99·65% deuterium oxide) was then admitted, and the flask was re-evacuated and then filled once more with gaseous deuterium chloride. The system was then sealed and, after a further 15 min.' stirring, was left overnight at room temperature. Working up as described under (i) above gave *x*-deutero-α-amyrin acetate (115 mg.).

x-*Deutero*-11-*keto*-α-*amyrin Acetate.*—The deuterated α-amyrin acetate (55·2 mg.) in " AnalaR " acetic acid (4 ml.) was treated with chromium trioxide (28 mg.) in " AnalaR " acetic acid (1 ml.) at 85° during ¾ hr. After the addition heating was continued for ½ hr. at the end of which some of the chromium trioxide remained unconsumed. Crystallisation from chloroform–methanol gave *x*-deutero-11-keto-α-amyrin acetate (26 mg.), m. p. 270—272°.

* This was first suggested to us by Professor R. B. Woodward (Harvard) to whom we express our best thanks.

x-*Deutero*-α-*amyra*-10 : 12-*dienyl Acetate*.—*x*-Deutero-11-keto-α-amyrin acetate (300 mg.) in dry ether (80 ml.) and lithium aluminium hydride (300 mg.) in the same solvent (10 ml.) were refluxed for 30 min. After isolation the crude product was refluxed for 20 min. in acetic anhydride (11 ml.) containing toluene-*p*-sulphonic acid (20 mg.). Crystallisation from methanol gave *x*-deutero-α-amyra-10 : 12-dienyl acetate, m. p. 166—167°, $[\alpha]_D$ +335° (*c*, 2·15).

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