## 409. *The Structure of Nyctanthic Acid.*

By G. H. Whitham.

Nyctanthic acid has been shown to be the ring-opened acid (IV) related to β-amyrin; its partial synthesis from β-amyrin is described.*

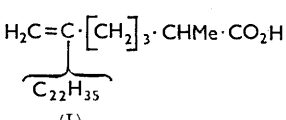
Nyctanthic acid is one of the constituents of the seeds of the Indian shrub *Nyctanthes arbor-tristis*. Previous work,[2] which favoured the empirical formula $C_{30}H_{48}O_2$, showed that the oxygen atoms were present in a carboxyl group and that there were two double bonds, thus indicating a tetracyclic structure. One of the double bonds was a methylene group which could be readily hydrogenated to give a dihydro-series of compounds; the other double bond was trisubstituted and inert to hydrogenation and monoperphthalic acid. A skeleton of the lanostane type was assumed by analogy with other tetracyclic triterpene acids, and the information was summarised by the tentative partial structure (I). The residual nucleus was tetracyclic and contained the trisubstituted double bond.

On biogenetic grounds [3] this structure possessed two weaknesses. First, all known naturally occurring triterpenes with the lanostane type of skeleton are oxygenated at $C_{(3)}$

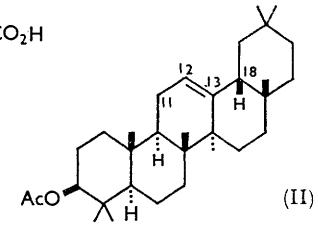
* A preliminary account of this work has appeared.[1]

[1] Whitham, *Proc. Chem. Soc.*, 1959, 271.
[2] Turnbull, Vasistha, Wilson, and Woodger, *J.*, 1957, 569.
[3] Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.

and secondly the possession of a methylene group at what would be $C_{(20)}$–$C_{(21)}$ in a compound containing a nuclear double bond would require the intrusion of some special effect. Thus dammardienol,[4] in which there is a $C_{(20)}$–$C_{(21)}$ double bond, has no nuclear double bond.




(I)

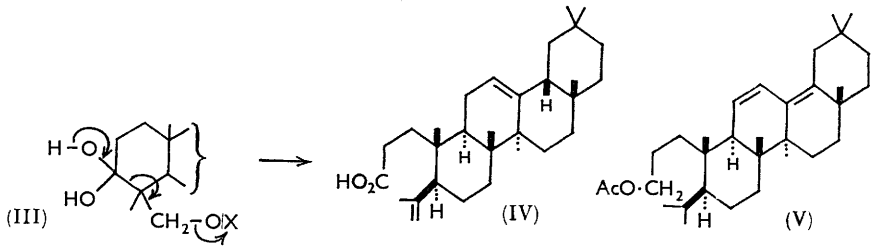



(II)

Further information was therefore sought concerning the environment of the nuclear trisubstituted double bond in nyctanthic acid. Oxidation with selenium dioxide in acetic acid was studied since the " inert " double bond in the various classes of triterpenes reacts characteristically with this reagent.[5] A suitable substrate was dihydronyctanthinyl acetate [2] in which the methylene group had been removed by hydrogenation and the carboxyl group converted into a primary acetate by consecutive reduction with lithium aluminium hydride and acetylation. This acetate was heated under reflux with selenium dioxide in acetic acid, and a crystalline product was isolated in good yield. The ultraviolet spectrum of the latter ($\lambda_{max.}$ 243, 251, and 260 mμ; ε 24,600, 28,700, and 18,800 respectively) showed it to be a diene. Furthermore this absorption pattern is characteristic of an oleana-11,13(18)-diene [6] and quite different from that of a lanosta-7,9(11)-diene. The reaction thus parallels the conversion of β-amyrin acetate (II) into 3β-acetoxyoleana-11,13(18)-diene under the same conditions [7] and indicates that the environment of the trisubstituted double bond in nyctanthic acid is similar to that in β-amyrin. Similarity to α-amyrin was discounted since α-amyrin acetate is unaffected by selenium dioxide under the same reaction conditions.[7]

Molecular-rotation differences reinforce the above conclusion; a large negative change in rotation accompanies the dehydrogenation of dihydronyctanthinyl acetate ($\Delta[M]_D$ −682°) and this is in close agreement with the corresponding value in the case of β-amyrin acetate ($\Delta[M]_D$ −697°).

β-Amyrin, however, is pentacyclic whereas nyctanthic acid is tetracyclic. An acceptable structure could be biogenetically derived by ring-opening of a suitable β-amyrin derivative to give the functional groups of nyctanthic acid. Naturally occurring oleanane derivatives oxygenated at $C_{(23)}$ or $C_{(24)}$ are well known so that an attractive biogenetic sequence leading from a 3-oxo-precursor to the desired type of compound could be as in



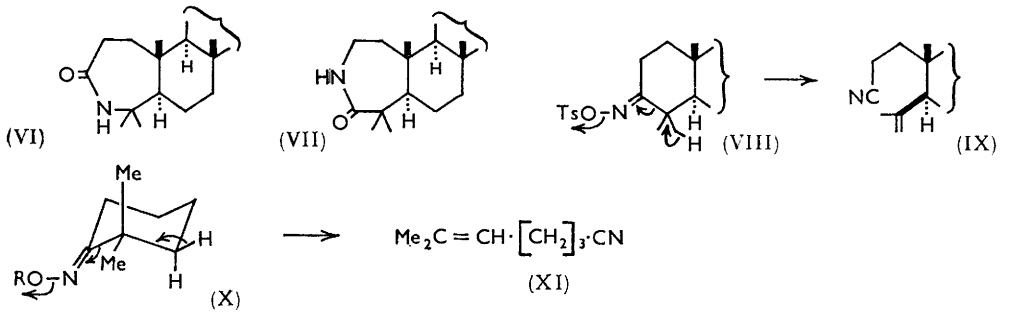

(III) (IV) (V)

(III ⟶ IV), where $OX^-$ is a suitable leaving group. Formula (IV) possesses all the features necessary to explain the known reactions of nyctanthic acid and on this basis the diene acetate obtained above would be formulated as (V).

[4] Mills, *J.*, 1956, 2196.
[5] Simonsen and Ross, " The Terpenes," Cambridge University Press, 1957, Vol. IV and V.
[6] Barton and Brooks, *J.*, 1951, 257.
[7] Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767.

Some support for structure (IV) was given by the infrared spectra of a number of derivatives of nyctanthic and dihydronyctanthic acid. Suitable compounds of the dihydro-series exhibited a distinct band of medium intensity at *ca.* 1165 cm.$^{-1}$ which was absent from the spectra of the corresponding non-hydrogenated compounds. A band in this region has been attributed to the isopropyl group.[8]

Confirmation of structure (IV) for nyctanthic acid was obtained by partial synthesis as follows. β-Amyrin was converted into the corresponding ketoxime [9] and the latter was treated with toluene-*p*-sulphonyl chloride in dry pyridine. Two compounds were isolated by chromatography of the product. One, which preponderated, had the formula $C_{30}H_{49}ON$; its infrared spectrum had a strong band at 1665 cm.$^{-1}$ (amide). The lactam structure (VI) was assigned to this since hydrolysis occurred with 18% potassium hydroxide in n-butanol under reflux [highly hindered amides, such as the alternative formulation (VII), should not be affected under these conditions [10]]. It is thus the expected product of Beckmann rearrangement resulting from the oxime toluenesulphonate with the toluenesulphonyloxy-group in the less-hindered position *anti* to the gem-dimethyl group. The other product, $C_{30}H_{47}N$, showed infrared bands at 2240 (–C≡N) and 3050, 1635, and 899 cm.$^{-1}$ (>C=CH$_2$) and was thus the abnormal Beckmann product (IX) derived from the oxime toluenesulphonate (VIII ⟶ IX). The unhindered nature of the nitrile group was demonstrated by relatively mild alkaline hydrolysis to an unsaturated acid to which constitution (IV) must be assigned since the hydrogen atom at $C_{(5)}$ has not been involved in the transformations. The identity of acid (IV) with nyctanthic acid was demonstrated by melting point and infrared data, further confirmed by a comparison of the methyl esters.




Surprisingly the triterpene literature seems to have no previous example of the Beckmann rearrangement of a 3-ketoxine. However, the formation of an unsaturated nitrile from the oxime of a 2,2-disubstituted cyclic ketone has precedent.[11] The only point requiring comment is the formation of an isopropenyl rather than an isopropylidene group in nitrile (IX) since the abnormal Beckmann product from 2,2-dimethylcyclohexanone oxime [11a] (X; R = H) is the nitrile (XI) with the more highly substituted double bond. One explanation for this involves the stereoelectronic requirements for elimination, which would demand a preferred *trans*-orientation of the $C_{(3)}$–H bond [numbering as for oxime (X)] to the $C_{(2)}$–$C_{(1)}$ bond, which is the bond being broken. In the oxime (X; R = H) the equatorial hydrogen atom on $C_{(3)}$ satisfies these requirements. However, in β-amyrenone oxime only an axial 5α-hydrogen atom is available in the corresponding position so that *trans*-elimination of a proton from one of the methyl groups on $C_{(4)}$ is preferred, giving the less-substituted isopropenyl group.

[8] Sheppard and Simpson, *Quart. Rev.*, 1953, **7**, 19.
[9] Rollet, *Monatsh.*, 1922, **43**, 413.
[10] Heusser, Wohlfahrt, Müller, and Anliker, *Helv. Chim. Acta*, 1955, **38**, 1399.
[11] (*a*) Conley, Frainier, and Nowak, Abstracts Amer. Chem. Soc. Meeting, Sept. 1959, 7P; (*b*) Stevens, *J. Amer. Chem. Soc.*, 1959, **81**, 3593.

During preliminary work on nyctanthic acid the derived hydrocarbon 3,4-seco-olean-12-ene was readily prepared by the lithium aluminium hydride reduction of the dihydronyctanthinyl toluene-*p*-sulphonate.

After the appearance of the preliminary communication on this work the independent work of another group [12] was published also proposing structure (IV) for nyctanthic acid. Here dihydronyctanthic acid was obtained by photochemical cleavage of β-amyrenone. A further example of this biogenetic type, dammarenolic acid,[13] was also reported; it is the acid related to hydroxydammarenone-II [4] with ring A opened.

## Experimental

Rotations were determined in chloroform. Alumina for chromatography was B.D.H., deactivated and neutralised by addition of 5 c.c. of 10% acetic acid per 100 g. of alumina. Unless otherwise stated light petroleum refers to the fraction of b. p. 40—60°, and infrared spectra were determined in carbon tetrachloride.

3-*Acetoxy*-3,4-*seco*-*oleana*-11,13(18)-*diene*.—Dihydronyctanthinyl acetate [2] (78 mg.) was heated under reflux with selenium dioxide (80 mg.) in acetic acid during 2 hr. Selenium was filtered off and after dilution of the filtrate with water the product was isolated with ether as a gum (80 mg.). Adsorption on alumina (20 g.) followed by elution with light petroleum gave the *diene acetate* which crystallised from ethanol as fine needles (55 mg.), m. p. 133·5—135° (raised to 135—136° on recrystallisation from the same solvent), $[\alpha]_D$ −74° (*c* 1·6) (Found: C, 81·9; H, 11·2. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

*Beckmann Rearrangement of* β-*Amyrenone Oxime*.—β-Amyrenone oxime (1·25 g.; prepared from β-amyrenone and hydroxylamine acetate in ethanol) was dissolved in dry pyridine (40 c.c.), and toluene-*p*-sulphonyl chloride (1·3 g.) was added. After 16 hr. at 25° a few drops of water were added and the mixture was set aside for ½ hr. After addition of dilute hydrochloric acid (1 : 1) the product was isolated with benzene as a semi-solid (1·23 g.) which was dissolved in the minimum of benzene and chromatographed on alumina (50 g.). Elution with benzene afforded 3-*cyano*-3,4-*seco*-*oleana*-4(23),12-*diene* (256 mg.), m. p. 212—214° after two recrystallisations from light petroleum (b. p. 60—80°), $[\alpha]_D$ +72° (*c* 1·9) (Found: C, 85·5; H, 11·0. $C_{30}H_{47}N$ requires C, 85·4; H, 11·2%). Further elution of the column with benzene–ether (1 : 1) gave 3b-*aza*-A-*homo*-*olean*-12-*en*-3-*one* (962 mg.), crystallising in plates (from ethanol), m. p. 280—282·5° after two recrystallisations, $[\alpha]_D$ +101° (*c* 1·8) (Found: C, 81·85; H, 10·9. $C_{30}H_{49}NO$ requires C, 81·9; H, 11·2%).

*Hydrolysis of* 3b-*Aza*-A-*homo*-*olean*-12-*en*-3-*one*.—The amide (100 mg.) was heated under reflux (in nitrogen) with 10 c.c. of 18% potassium hydroxide in n-butanol during 4 hr. The cooled solution was diluted with water and extracted with ether; on evaporation of the dried extract no starting material was recovered. Evaporation of the aqueous layer to small bulk, octan-2-ol being used as an anti-foam, followed by addition of concentrated hydrochloric acid until the pH was 5·6, precipitated the crude amino-acid which was not further investigated.

*Hydrolysis of* 3-*Cyano*-3,4-*seco*-*oleana*-4(23),12-*diene*.—The nitrile (50 mg.) was heated under reflux with 20% potassium hydroxide in ethanol (5 c.c.) until the smell of ammonia was no longer detectable (3 hr.). After dilution and acidification (because of insolubility of the potassium salt) the product was isolated with ether. The gummy residue crystallised on addition of ethanol; recrystallisation from the same solvent gave the acid as plates (39 mg.), m. p. 234—235·5°, $[\alpha]_D$ +81°. The melting point was undepressed on admixture with a recrystallised sample of nyctanthic acid, m. p. 234—235·5° (Turnbull, Vasistha, Wilson, and Woodger [2] record m. p. 222·5—223·5°, $[\alpha]_D$ +86°, for nyctanthic acid). The infrared spectra of the two acids were identical.

The acid obtained above (25 mg.) was esterified by using diazomethane. Crystallisation from methanol–ethyl acetate gave the methyl ester, m. p. 125—127° undepressed on admixture with a sample of methyl nyctanthate. The infrared spectra of the two esters (in carbon disulphide) were identical.

3,4-*Seco*-*olean*-12-*ene*.—Dihydronyctanthinol (35 mg.) was treated with toluene-*p*-sulphonyl chloride (250 mg.) in dry pyridine (2 c.c.), and the mixture set aside at 0° for 16 hr. After

[12] Arigoni, Barton, Bernasconi, Djerassi, Mills, and Wolff, *Proc. Chem. Soc.*, 1959, 306.
[13] Mills and Werner, *J.*, 1955, 3132.

addition of 3 drops of water and ½ hr. at 20°, dilute hydrochloric acid (1 : 1) was added and the product isolated with ether. Evaporation of the dried extract gave the crude toluenesulphonate as a gum (39 mg.). The infrared spectrum showed no hydroxyl band but possessed a strong doublet at 1180 and 1190 $cm.^{-1}$ (toluenesulphonate). This ester was dissolved in dry ether (15 c.c.), lithium aluminium hydride (100 mg.) added, and the mixture was heated under reflux during 1 hr. The gummy product was dissolved in light petroleum and filtered through alumina. The eluate afforded a gum (25 mg.) which was dissolved in methanol–ethyl acetate and set aside at 0°. The *hydrocarbon* crystallised as needles (16 mg.), m. p. 121·5—122·5°, $[\alpha]_D$ +102° (*c* 1·3) (Found: C, 87·5; H, 12·7. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

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