691. *A Proof of the Constitution of Cassanic Acid based on its Derivation from Vouacapenic Acid.*

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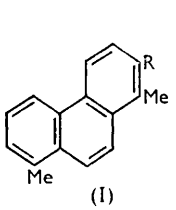
The structure attributed [1] to cassanic acid, namely, that of a perhydro-1 : 8 : 8 : 13-tetramethyl-2-phenanthrylacetic acid, has been confirmed by a partial synthesis of the acid from methyl vouacapenate.[2]

The suggested *trans*-arrangement of the A/C ring junction in vinhaticoic acid,[3] and therefore in vouacapenic acid, has been confirmed by oxidation of methyl tetradehydrovinhaticoate to a dimethyl*cyclo*hexanetricarboxylic acid of known configuration.[4]

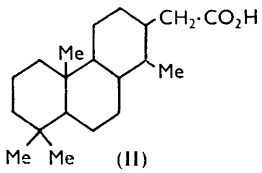
AMONG the well-defined class of *Erythrophleum* alkaloids,[5] which are of interest for their cardiac activity, the most extensively investigated is cassaine, $(C_{19}H_{29}O_2)\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2$, an ester of cassaic acid, $(C_{19}H_{29}O_2)\cdot CO_2H$. Cassaic acid is an αβ-unsaturated monocarboxylic acid, the presence of a hydroxyl and of a carbonyl group accounting for the remaining oxygen atoms.[5,6] Reduction of the ethylenic

[1] Humber and Taylor, *J.*, 1955, 1044.
[2] King, Godson, and King, *J.*, 1955, 1117.
[3] King and King, *J.*, 1953, 4158.
[4] Barton and Schmeidler, *J.*, 1948, 1197; 1949, S 232.
[5] G. Dalma, " The Alkaloids," edited by Manske and Holmes, Academic Press. New York, Vol. IV, p. 265.
[6] Woodward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399.

bond and removal of the alcoholic and carbonyl functions affords cassanic acid, $C_{19}H_{33}\cdot CO_2H$, and, by dehydrogenation of this acid, 1 : 2 : 8-trimethylphenanthrene ($C_{17}H_{16}$) (I; R = Me) is obtained.[7] An attempt to locate the carboxyl group by reaction with methylmagnesium iodide and dehydrogenation of the product gave a C_{20} alkylphenanthrene,[8] and in accord with the suggestion [1] that the carbonyl group in cassaic acid is extranuclear, the C_{20} hydrocarbon was identified by synthesis as 2-*iso*butyl-1 : 8-dimethylphenanthrene (I; R = $CH_2\cdot CHMe_2$). As a result of this evidence it was concluded that cassanic acid is a perhydrophenanthrylacetic acid (II).



(I)



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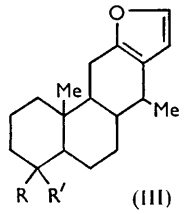

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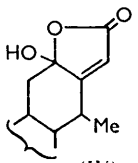
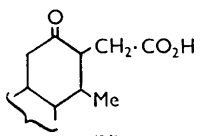
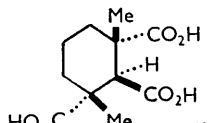


(IV)



(V)



(VI)

Although cassanic acid is thus assigned to the tricyclic diterpene series, it will be seen that structure (II) does not entirely conform to the isoprene rule because of the methyl group at position 1. In this respect it resembles the epimeric esters methyl vouacapenate and methyl vinhaticoate (III; R = Me, R′ = CO_2Me, and *vice versa*).[2,3] To see if the skeletal similarity extended also to stereochemical details, a partial synthesis of the acid (II) from one or other of the esters (III) was investigated. Perphthalic acid converted methyl vouacapenate into a hydroxylated lactone (IV; R = Me, R′ = CO_2Me), but catalytic hydrogenation of this failed, as with menthofuran.[6] Reduction under modified Clemmensen conditions [9] gave the neutral crystalline ester of acid (V), containing an isolated carbonyl group, further characterised as 2 : 4-dinitrophenylhydrazone and oxime. The acid then obtained by hydrolysis was more readily prepared by zinc–acetic acid reduction of the lactone, and related acids were similarly derived from methyl vinhaticoate and vouacapenol (III; R = Me, R′ = $CH_2\cdot OH$). These reactions, applied to vouacapenane (vinhaticane) (III; (R = R′ = Me) gave the keto-acid necessary for our synthesis.

In this series Clemmensen reduction was ineffective, and Huang-Minlon reduction gave a mixture, as, for example, with methyl 3 : 16-dioxoeburico-7 : 9(11)-dien-21-oate.[10] The methyl ester of (V; R = R′ = Me) failed to give a ketal with ethanethiol, but a crystalline product was obtained with ethanedithiol and was readily converted by Raney nickel into the required compound (II). Identity with methyl cassanate was confirmed by comparison of the infrared absorption spectra which were virtually indistinguishable. We thank Dr. B. Engels, Eidgenossische Technische Hochschule, Zürich, for generous samples of methyl cassanate. The properties of the derived dimethylcarbinol also and of the acid were similar to those recorded for the dimethylcarbinol from methyl cassanate and for cassanic acid, but direct comparison was not practicable.

The relationship of the *Erythrophleum* alkaloids to the group of diterpenes represented by vouacapenic and vinhaticoic acids is therefore firmly established and embraces the

[7] Ruzicka, Dalma, and Scott, *Helv. Chim. Acta*, 1940, **23**, 757.
[8] Ruzicka, Engel, Ronco, and Berse, *ibid.*, 1945, **28**, 1038.
[9] Fieser, Fry, and Jones, *J. Amer. Chem. Soc.*, 1939, **61**, 1852.
[10] Bowers, Halsall, and Sayers, *J.*, 1954, 3070.

whole hydrophenanthrene nucleus. However, little is definitely known of the absolute configuration of this ring-system, and although there is substantial evidence by analogy, no rigid proof of the A/C ring fusion has so far been advanced. Attempts to oxidise methyl vinhaticoate, for example, to the dimethyl*cyclo*hexanetricarboxylic acid (VI) obtained from abietic acid have so far been unsuccessful. This work has been renewed since starting the present investigation, but with methyl tetradehydrovinhaticoate, and it has been found that vigorous oxidation with nitric acid does in fact give the C_{11} triacid on which the stereo-structure of the abietic A/C ring junction is based. Identity of the product with the known acid was established by mixed m. p. and infrared absorption measurement. The *trans*-configuration of the A/C ring in vinhaticoic, vouacapenic, and cassanic acid and its precursors is thus determined.

Experimental

Light petroleum was of b. p. 60—80°. Optical rotations were determined for the D line in $CHCl_3$ solution at room temperature.

Perhydro-8β-methoxycarbonyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = Me, R′ = CO_2Me).—(*a*) The permonophthalic acid oxidation product of methyl vouacapenate [2] (1·5 g.) in methanol (60 c.c.) and benzene (60 c.c.) was added to amalgamated zinc turnings (15 g.). Hydrochloric acid (30 c.c. conc. + 8 c.c. water) was added and the mixture boiled for 7 hr., a further 10 c.c. of concentrated hydrochloric acid having been added after 4 hr. The mixture was cooled, the benzene layer collected, and the aqueous layer exhausted with ether. The combined extracts were evaporated, to give a gum (1·3 g.) which crystallised from aqueous methanol in needles (0·95 g.), m. p. 116—120°, raised to 119—120° by crystallisation from light petroleum, of the *methyl ester*, [α] +10° (*c* 1·1) (Found: C, 69·5; H, 8·8. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1%). The derived 2 : 4-*dinitrophenylhydrazone* formed golden-yellow needles (from methanol–ethyl acetate), m. p. 234—236° (Found: C, 60·1; H, 7·1; N, 10·1; OMe, 10·9. $C_{28}H_{38}O_8N_4$ requires C, 60·2; H, 6·9; N, 10·1; 2OMe, 11·1%). The *oxime*, prepared in pyridine, crystallised from aqueous methanol in rods, m. p. 107—108° (Found: N, 3·6. $C_{22}H_{35}O_5N$ requires N, 3·6%). The above ester with 10% ethanolic sodium hydroxide (reflux) for 1 hr. gave the corresponding *acid* (see below) (Found: C, 69·3; H, 8·8. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%).

(*b*) The lactone (IV) (2·7 g.) from methyl vouacapenate, and zinc turnings (11 g.), were heated under reflux in acetic acid (80 c.c.) for 7 hr. The solution was then poured into water and extracted with ether. The product crystallised from aqueous methanol to give the acid as needles, m. p. 152—154° (1·8 g.). Further purification from light petroleum gave needles, m. p. 155—156°, [α] +7° (*c* 2·1) (Found: C, 69·1; H, 8·9%). Diazomethane afforded the ester identical with that prepared by method (*a*). The acid gave a 2 : 4-*dinitrophenylhydrazone*, golden needles, m. p. 235—236° (Found: C, 59·4; H, 6·7; N, 10·4. $C_{27}H_{36}O_8N_4$ requires C, 59·6; H, 6·7; N, 10·3%).

Perhydro-8α-methoxycarbonyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = CO_2Me, R′ = Me).—The oxidation product (2·7 g.) of methyl vinhaticoate [3] was reduced as in (*b*) above. The crude product was initially purified through the insoluble sodium salt formed with aqueous sodium hydrogen carbonate and then crystallised from light petroleum–ethyl acetate, to give the *acid* (1·2 g.) in long flat prisms, m. p. 156—157°, [α] −9° (*c* 2·3) (Found: C, 69·4; H, 8·8%). The 2 : 4-*dinitrophenylhydrazone* was golden needles (from methanol–chloroform), m. p. 245—246° (decomp.) (Found: C, 59·3; H, 6·6%). Diazomethane yielded the *methyl ester*, rods (from aqueous methanol), m. p. 133—134° (Found: C, 69·9; H, 9·0; OMe, 15·3. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1; 2OMe, 16·4%). The ester *dinitrophenylhydrazone* formed golden needles (from methanol), m. p. 205—206° (Found: C, 60·0; H, 6·8%), and the *ester-oxime* separated from aqueous methanol as rods, m. p. 134—135° (Found: N, 4·0%).

Perhydro-8β-hydroxymethyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = Me, R′ = CH_2·OH).—The peracid oxidation product (2 g.) from vouacapenol,[2] reduced as above, afforded the 8β-*acetoxymethyl compound* (1·7 g.) as laths (from aqueous methanol), m. p. 175—177°, changed by recrystallisation from light petroleum–ethyl acetate to rods, m. p. 179—180° (Found: C, 69·5; H, 8·9; Ac, 11·4. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1; 1Ac, 11·4%). The acetate gave a 2 : 4-*dinitrophenylhydrazone* as yellow needles (from methanol–chloroform),

m. p. 243—245° (decomp.) (Found: C, 60·2; H, 7·0; N, 10·4. $C_{28}H_{38}O_8N_4$ requires C, 60·3; H, 7·0; N, 10·0%). The *acetate methyl ester* formed with diazomethane crystallised from aqueous methanol as needles, m. p. 76—77° (Found: C, 70·3; H, 9·4; OMe, 7·1. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·3; 1OMe, 7·9%).

Hydrolysis of the above acetate with aqueous-methanolic 10% potassium hydroxide on the steam-bath for 1 hr. gave the derived *hydroxy-acid* as rods (from aqueous methanol), m. p. 212—213° (Found: C, 71·6; H, 9·7. $C_{20}H_{32}O_4$ requires 71·4; H, 9·6%). Diazomethane formed the *methyl ester*, rods (from aqueous methanol), m. p. 149—150° (Found: C, 72·0; H, 9·7; OMe, 9·1. $C_{21}H_{34}O_4$ requires C, 71·9; H, 9·8; 1OMe, 8·9%).

Peracid Oxidation of Vouacapenane.—Vouacapenane [2] (10 g.) in carbon tetrachloride (125 c.c.) was treated with an ethereal solution of monoperphthalic acid (18·6 g.) during 140 hr. After having been washed successively with aqueous potassium iodide, sodium thiosulphate, and water the organic layer was evaporated to a yellow gum. This was treated with boiling water (3 × 500 c.c.) and then crystallised from aqueous methanol to give pale yellow prisms (7·5 g.), m. p. 216—218° (decomp.). The pure *lactone* (IV; R = R′ = Me) was finally obtained by further crystallisation as plates, m. p. 218—220° (decomp.) (Found: C, 75·6; H, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The lactone was characterised as the *anhydro-derivative*; obtained after 10 min. at 220—230°, this separated from aqueous methanol as short rods, m. p. 167—168° (Found: C, 79·9; H, 9·3. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%).

Perhydro-1 : 8 : 8 : 13-*tetramethyl*-3-*oxo*-2-*phenanthrylacetic Acid* (V; R = R′ = Me).—Reduction of the above lactone (4·3 g.) as previously described afforded an acetic acid solution which was evaporated to *ca.* 70 c.c. and diluted with water (20 c.c.). After 1 hr. at 0° the crystalline *keto-acid* (3·1 g.) was collected. It crystallised from aqueous methanol in hexagonal plates, m. p. 214—216° (Found: C, 74·5; H, 9·9. $C_{20}H_{32}O_3$ requires C, 74·9; H, 10·0%). The *methyl ester* (prepared with diazomethane) crystallised from aqueous methanol in rectangular plates, m. p. 94—95° (Found: C, 75·7; H, 9·9; OMe, 8·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·2; 1OMe, 9·3%).

Methyl Cassanate.—The above methyl ester (0·8 g.) in a mixture of ethanedithiol (6 c.c.) and ether (15 c.c.) was treated with a slow stream of hydrogen chloride for 25 min. After 15 hr. at 0° a solution of sodium carbonate was added to the mixture and the product was collected into chloroform. The solution was washed with sodium hydroxide and water, then evaporated to give the *thioketal* as colourless needles (0·74 g.; 74%), m. p. 209—211°, raised by crystallisation from ethanol–chloroform to 211—212° (Found: C, 67·7; H, 9·2; S, 15·3. $C_{23}H_{36}O_2S_2$ requires C, 67·6; H, 8·9; S, 15·7%).

The above ketal (0·7 g.) and Raney nickel (*ca.* 10 g.) were heated under reflux in ethanol for 2½ hr. Removal of the nickel and evaporation of the solvent afforded an oil which crystallised from aqueous methanol, to give the ester as plates, m. p. 48—49°, [α] +9° (*c* 1·0) (Found: C, 78·7; H, 11·4; OMe, 9·6. Calc. for $C_{21}H_{36}O_2$: C, 78·7; H, 11·3; 1OMe, 9·7%). The mixed m. p. with methyl cassanate (m. p. 44—45°, [α] +4° ± 2°) was 47—48°.

The synthetic methyl cassanate was converted with methylmagnesium iodide into the derived dimethylcarbinol which crystallised from light petroleum as needles, m. p. 134—135° (lit., 132—133°) (Found: C, 82·6; H, 12·7. Calc. for $C_{22}H_{40}O$: C, 82·4; H, 12·6%).

Hydrolysis of the ester afforded cassanic acid which sublimed at 130°/0·05 mm., to give slender prisms, m. p. 220—221°, [α] +4·7° (*c* 0·5) (lit., m. p. 224°, [α] +3° ± 2°) (Found: C, 78·4; H, 11·0. Calc. for $C_{20}H_{34}O_2$: C, 78·4; H, 11·2%).

Nitric Acid Oxidation of Methyl Tetradehydrovinhaticoate.—Methyl tetradehydrovinhaticoate [3] (2·3 g.) was gradually added to concentrated nitric acid (20 c.c.) at 70—80°, fuming nitric acid (5 c.c.) was then added, and the mixture was boiled for 15 hr. Evaporation of the solution then gave a yellow gum which crystallised from nitric acid. Further crystallisation from acetone afforded flat rectangular prisms (50 mg., 3%), m. p. 218—220° (decomp.), undepressed on being mixed with the tricarboxylic acid (VI) similarly prepared from abietic acid (Found: C, 54·4; H, 6·7. Calc. for $C_{11}H_{16}O_6$: C, 54·1; H, 6·6%).

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