60. *The Structure of Dehydrocassamic Acid.*

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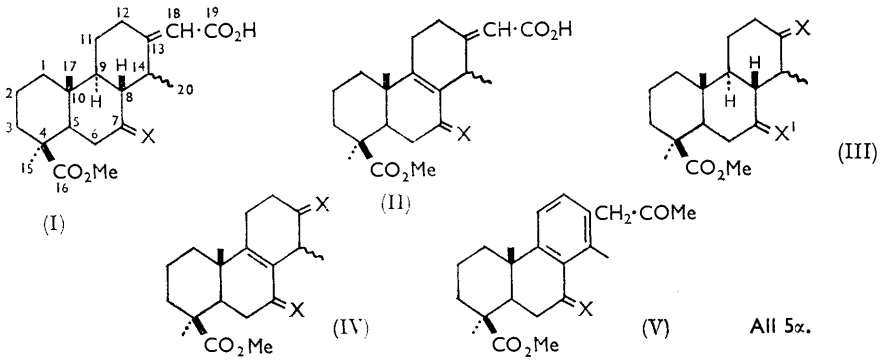
The structure of dehydrocassamic acid is shown to be (II; X = O).

Dehydrocassamic acid, the third diterpene acid whose isolation from *Erythrophleum guineense* bark was recently described,[1] has the structure (II; X = O). Carbon skeleton and functional groups (apart from the double bond) were defined by Clemmensen reduction, which yielded 7-deoxycassamic acid (I; X = H_2) (cf. ref. 2). Treatment of dehydrocassamic acid with sodium borohydride, moreover, reduced both the double bond and the carbonyl group, furnishing compound (I; X = H, OH) (cf. ref. 3). Similarly, the ozonolysis product (IV; X = O) yielded (III; X = X^1 = H, OH), oxidised with chromic anhydride to the dione (III; X = X^1 = O) (series B) previously obtained [1] from cassamic acid. The ultraviolet spectrum of dehydrocassamic acid shows one main band at 221 mμ characteristic of all members of this series and due to the αβ-unsaturated acid. In addition, a shoulder at 244 mμ is associated with an αβ-unsaturated ketone. The band due to this alone is seen more clearly at 247 mμ, in the spectrum of the ozonolysis product (IV; X = O) whilst the 2,4-dinitrophenylhydrazone of dehydrocassamic acid absorbs at 388 mμ, confirming the presence of an αβ-unsaturated ketone.



Of the two possible positions for the double bond, 5,6 or 8,9, molecular-rotation differences suggest the latter. ΔE for dehydrocassamic acid is +398,[4] compared with −298 for a 5,6-double bond and +96 for an 8,9-double bond in the steroid 5α-series.[4] The nuclear magnetic resonance spectrum allows a clear choice. Dehydrocassamic acid (II; X = O) shows but a single olefinic proton at 4·1 τ, assigned to the hydrogen on C-18: the ozonolysis product (IV; X = O) shows no signal at all in this region. Structure (II; X = O) is therefore to be preferred.

Confirmation of this was obtained on refluxing dehydrocassamic acid with 70% aqueous alkali, which yielded a dibasic acid isolated as its dimethyl ester (V; X = O). Absorption at 255 mμ (ε 8860) is consistent with an aryl ketone [5] as are the infrared bands at 1745, 1730 (ester C:O groups), and 1690 $cm.^{-1}$ (alkyl aryl ketone). Wolff–Kishner reduction of the ketone group yielded a diacid isolated as the diester (V; X = H_2), showing simple benzenoid absorption at 265—267 mμ (ε 500); two peaks, at 1740 and 1710 $cm.^{-1}$, may be attributed to the two ester groupings. The nuclear magnetic resonance spectra of these

[1] Chapman, Jaques, Mathieson, and (in part) Arya, *J.*, 1963, 4010.
[2] Burton and Shoppee, *J.*, 1939, 567.
[3] Albrecht and Tamm, *Helv. Chim. Acta*, 1957, **40**, 2217.
[4] Barton and Klyne, *Chem. and Ind.*, 1948, 755.
[5] Fried and Klingsberg, *J. Amer. Chem. Soc.*, 1953, **75**, 4929.

compounds confirm their aromatic character with the appearance of two aromatic protons (C-11 and C-12) at low field values. The 10- and 14-methyl groups also show the expected downfield shifts. For these and for other members of this series the proton resonance data are recorded in the Table.

Nuclear magnetic resonance spectral data (τ values) of dehydrocassamic acid and related compounds.

Compound	4-Me	10-Me	14-Me	CO_2Me	Olefinic or aromatic protons	Other groups
(I; X = H_2)	8·82	9·38	9·03; 8·92	6·37	4·32	−1·17 *
(I; X = H, OH) (dimethyl ester)	8·8	9·37	8·97; 8·84	6·37, 6·32	4·27	
(I; X = O)	8·82	9·18	8·97; 8·82	6·33	4·24	−0·67 *
(II; X = O)	8·77	9·05	8·88; 8·77	6·32	4·12	−0·75 *
(III; X = X^1 = H_2) †	8·77	9·25	9·2; 9·1	—	—	−1·13 *
(III; X = O, X^1 = H_2)	8·78	9·35	9·03; 8·93	6·37	—	
(III; X = X^1 = O)(Series B)	8·79	9·08	9·0; 8·9	6·31	—	
(IV; X = X^1 = O)	8·77	8·97	8·87; 8·77	6·3	—	
(V; X = H_2)	8·72	8·94	7·85	6·35	2·89, 2·91	6·38 ‡
(V; X = O)	8·72	8·89	7·45	6·29, 6·27	2·65	6·29 ‡

In compounds (I)—(IV) the position of both peaks of the 14-methyl doublet ($J \simeq 7$ c./sec.) is given.

* Carboxylic acid proton. † Examined as the 4-carboxylic acid. ‡ CH_2 between aromatic ring and CO_2Me group, τ value calculated by Schoolery's Rules (cf. Jackmann, "Applications of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry," Pergamon, London, 1959, p. 60) is 6·22.

In this group of compounds the position of the 4-methyl signal is almost constant. The 10-methyl group appears more subject to structural change. Thus, from the value 9·25 τ for (III; X = X^1 = H_2) the introduction of a trigonal carbon at C-13 produces a shift to higher fields of about 6—7 c./sec.; when, in addition, a carbonyl group is introduced at C-7, a shift to lower field of 12—16 c./sec. is observed.

Comparison of (I; X = O) with (II; X = O) and of (III; X = X^1 = O) with (IV; X = O) indicates that the 8,9-double bond causes a downfield shift of about 7 c./sec. in the 10-methyl resonance. Dreiding models confirm that this methyl group lies to the side of the double bond in the deshielding zone. In contrast, a 7,8-double bond allows the analogous 10-methyl group of steroids to take up a position approximately above the plane of the bond (shielding zone) with a consequent shift of about 6 c./sec. to higher field values.[6]

For the aromatic compounds (V; X = O and H_2) the shift of this 10-methyl resonance to even lower field is as expected from its position to the side and slightly above the plane of the aromatic ring. From the isoshielding diagram of Johnson and Bovey [7] its position is one for which negative shielding would be expected.

The 14-methyl resonance likewise moves to lower field as ring C becomes aromatic. Whereas this signal is split into a doublet ($J \simeq 7$ c./sec.) in the alicyclic compounds (I) to (IV), it collapses to a single peak in both the aromatic compounds examined.

The aromatisation with alkali (or on heating) probably proceeds by way of the "allo-compounds" [8] when the resulting dihydrobenzenoid structure suffers dehydrogenation. This is possible only if the original double bond is in the 8,9- rather than the 5,6-position.

Experimental

Dehydrocassamic acid (II; X = O) was isolated as previously described,[1] m. p. 191—192°, $[\alpha]_D$ +40° (*c* 1 in EtOH), $\lambda_{max.}$ (EtOH) 220 mμ (log ε 4·1), $\lambda_{infl.}$ 244 mμ (log ε 4·0), $\nu_{max.}$ (KBr) 1717 (ester C:O), 1682 (unsaturated acid C:O), 1674 (unsaturated ketone C:O), 1616 (C:C), and 1150 cm.$^{-1}$ (C·O·C of ester) (Found: C, 69·8; H, 7·9; O, 21·9; OMe, 9·3%; active hydrogen, 1 equivalent. Calc. for $C_{21}H_{28}O_5$: C, 70·0; H, 7·8; O, 22·2; OMe, 8·6%). The methyl ester was a gum; p-*phenylphenacyl ester*, needles, m. p. 102—105° (from ethanol) (Found: C, 73·7;

[6] Shoolery and Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.
[7] Johnson and Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.
[8] Ruzicka and Dalma, *Helv. Chim. Acta*, 1939, **22**, 1516.

H, 6·9. $C_{35}H_{38}O_6,C_2H_5OH$ requires C, 74·0; H, 7·4%); *2,4-dinitrophenylhydrazone*, needles, m. p. 170—172° (from ethanol), $\lambda_{max.}$ 388 mμ (log ε 4·3) (Found: C, 60·7; H, 6·2; N, 9·6. $C_{27}H_{32}N_4O_8$ requires: C, 60·0; H, 6·0; N, 10·4%); *methyl ester 2,4-dinitrophenylhydrazone*, m. p. 213—214° (from ether), $\lambda_{max.}$ 391—393 mμ (log ε 4·3) (Found: C, 60·0; H, 6·4; N, 9·6. $C_{28}H_{34}N_4O_8$ requires C, 60·6; H, 6·2; N, 10·1%).

16-Methyl Hydrogen 7-Hydroxycassane-16,19-dioate (I; X = H, OH).—Dehydrocassamic acid (500 mg.) in methanol (5 ml.) was neutralised with potassium hydroxide solution and set aside for 18 hr. at 22° with sodium borohydride (500 mg.) in water (10 ml.). Working up in the usual manner yielded the ester (I; X = H, OH), m. p. and mixed m. p. 230—232° (from methanol). The infrared spectrum of the methyl ester of the product was identical with that of dimethyl 7-hydroxycassane-16,19-dioate.

7-Deoxycassamic Acid (I, X = H_2).—Dehydrocassamic acid (500 mg.), in toluene (20 ml.) and ethanol (6 ml.), was reduced by the Clemmensen method as previously described.[1] Chromatography of the product on silica gel [1] (20 g.) gave (I; X = H_2) (400 mg.), m. p. and mixed m. p. 133—135°.

Oxidative Removal of the 13-Side-chain.—(*a*) Dehydrocassamic acid (5 g.) in dry chloroform (100 ml.) was treated with ozone until the solution was deep blue. The solvent was removed and the residue treated with glacial acetic acid (50 ml.) containing zinc dust (5 g.) for 30 min. A neutral colourless gum (3·5 g.) was obtained which gave *methyl 7,13-dioxo-18,19-dinorcass-8-en-16-oate* (IV; X = O), m. p. 143 (from ether), $[\alpha]_D^{20}$ +270° (*c*, 1 in EtOH), $\lambda_{max.}$ 243 mμ (log ε 4·0), $\nu_{max.}$ (CCl_4) 1713 (ester and saturated ketone C:O), 1663 (unsaturated ketone C:O), 1608 (C:C), 1153 cm.$^{-1}$ (C·O·C of ester) (Found: C, 71·8; H, 8·4; O, 19·8. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2; O, 20·1%).

(*b*) Dehydrocassamic acid (360 mg.) was suspended in water and 0·1N-sodium hydroxide was added until the solution had pH 8. The volume was adjusted to 200 ml., sodium metaperiodate (1·68 g.) and potassium permanganate solution (0·01M; 80 ml.) were added, and the mixture was shaken vigorously (3 min.). Ether extraction of the acidified solution yielded a crude product, the neutral fraction of which was the diketo-ester (IV; X = O) (45%), m. p. 143°, obtained in (*a*). Further material was obtained by repeating the oxidation on the acid fraction of the crude product.

Methyl 7,13-Dioxo-18,19-dinorcassan-16-oate (III; X = X^1 = O).—(*a*) The diketo-ester (IV; X = O) (80 mg.) in glacial acetic acid (4 ml.) was refluxed (30 min.) with 60% aqueous hydrobromic acid (1 ml.). The product was chromatographed on alumina to yield the ester,[1] m. p. and mixed m. p. 149° (from light petroleum).

(*b*) Reduction of the ester (IV; X = O) with zinc and glacial acetic acid at 100° for 45 min., afforded the same product.

Methyl 7,13-Dihydroxy-18,19-dinorcassan-16-oate (III; X = X^1 = H, OH).—The diketo-ester (IV; X = O) (200 mg.) in 50% aqueous methanol (10 ml.) was treated for 18 hr. at 22° with sodium borohydride (200 mg.) in 50% aqueous methanol (10 ml.). The resulting dihydroxy-ester [1] had m. p. and mixed m. p. 186—187°. The diol (150 mg.) was oxidised with chromic anhydride in pyridine as previously described.[1] When the product was refluxed with hydrochloric acid–50% aqueous methanol the dione (III; X = X^1 = O) (60 mg.) resulted, identical with a sample obtained from cassamic acid.

Dimethyl 7-Oxocassa-8,11,13-triene-16,19-dioate (V; X = O).—Dehydrocassamic acid (1 g.) and 70% aqueous potassium hydroxide (30 ml.) were heated at 160° for 2½ hr. The acidic fraction of the product, a yellow gum (900 mg.), was methylated with diazomethane and chromatographed on alumina (Brockman grade III; 30 g.) to give the *triene* (116 mg.), needles, m. p. 154·5—155·5° (from ether–light petroleum), $\lambda_{max.}$ 215—223, 255, 305 mμ (log ε 4·3, 3·95, 3·32), $\nu_{max.}$ (KBr) 1745 (ester C:O), 1730 (ester C:O), 1690 cm.$^{-1}$ (ketone C:O) (Found: C, 71·6; H, 7·6. $C_{22}H_{28}O_5$ requires: C, 71·0; H, 7·6%).

Dimethyl Cassa-8,11,13-triene-16,19-dioate (V; X = H_2).—Sufficient anhydrous hydrazine was distilled into a flask containing the diester (V; X = O) (240 mg.) in redistilled diethylene glycol (20 ml.) and sodium (280 mg.). The mixture was gently refluxed at 170° for 6 hr. The hydrazine was distilled off, the temperature raised to 210°, and refluxing was maintained for a further 6 hr. The acidic fraction yielded *cassa-8,11,13-triene-16,19-dioic acid*, m. p. 285—286° (from methanol) (Found: C, 72·8; H, 7·9; O, 19·4. $C_{20}H_{26}O_4$ requires: C, 72·7; H, 7·9; O, 19·4). Methylation with diazomethane and chromatography on alumina yielded the *dimethyl ester*, needles, m. p. 155—156° (from ether–light petroleum), $[\alpha]_D^{22}$ +122° (*c* 1·15 in $CHCl_3$),

$\lambda_{max.}$ 265—267 mμ (log ε 2·7), $\nu_{max.}$ (KBr) 1740 (ester C:O), 1710 (ester C:O) (Found: C, 74·4; H, 8·9. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

Microanalyses were performed by Mr. G. Crouch and Miss M. Hartup of this School; n. m. r. spectra were recorded by Miss Lovenack on a Varian A60 spectrometer for deuterochloroform solutions, with tetramethylsilane as an internal standard.

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