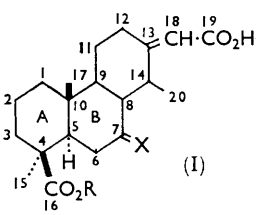
## 763. *The Configuration of Cassamic Acid.*

By G. T. Chapman, B. Jaques, David W. Mathieson, and (in part) V. P. Arya.

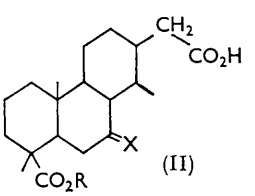
The correlation of cassamic acid with vouacapenic acid indicates a *trans*-A/B ring junction and a 4β-methoxycarbonyl group. Oxidative removal of the side-chain of cassamic acid and related compounds yields a series of ketones, and a suggested outline of their stability relations is given. The configuration of the asymmetric centres in cassamic acid is 4*S*, 5*R*, 8*S*, 9*S*, 10*R*.

Preliminary results on the constitution of the alkaloids cassamine and erythrophlamine have already been published;[1] the present paper reports certain aspects of the configuration of cassamic acid and the corresponding alcohol.

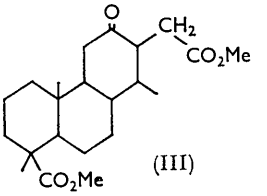
Hydrolysis of the total alkaloids from *Erythropleum guineese* barks gives a mixture of diterpene acids which are separated by partition chromatography on silica gel into three main crystalline fractions: (*a*) cassamic acid, (I; X = O, R = Me), m. p. 218—219°, $[\alpha]_D^{22}$ −70° (*c* 1 in $CHCl_3$), (*b*) the corresponding 7-hydroxy-acid (I; X = H,OH, R = Me), m. p. 246—247°, $[\alpha]_D^{22}$ −50° (*c* 1 in MeOH), and (*c*) dehydrocassamic acid, m. p. 191—192°, $[\alpha]_D^{22}$ +40° (*c* 1 in EtOH). Of these, the first two are discussed below.




(I)




(II)

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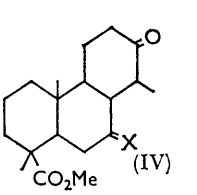
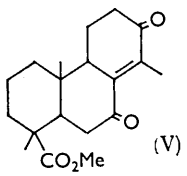



(IV)

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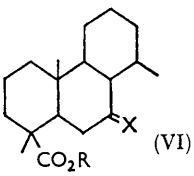
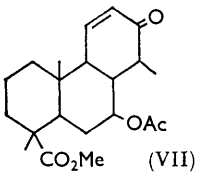
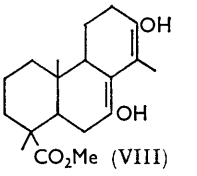



(VI)




(VII)




(VIII)

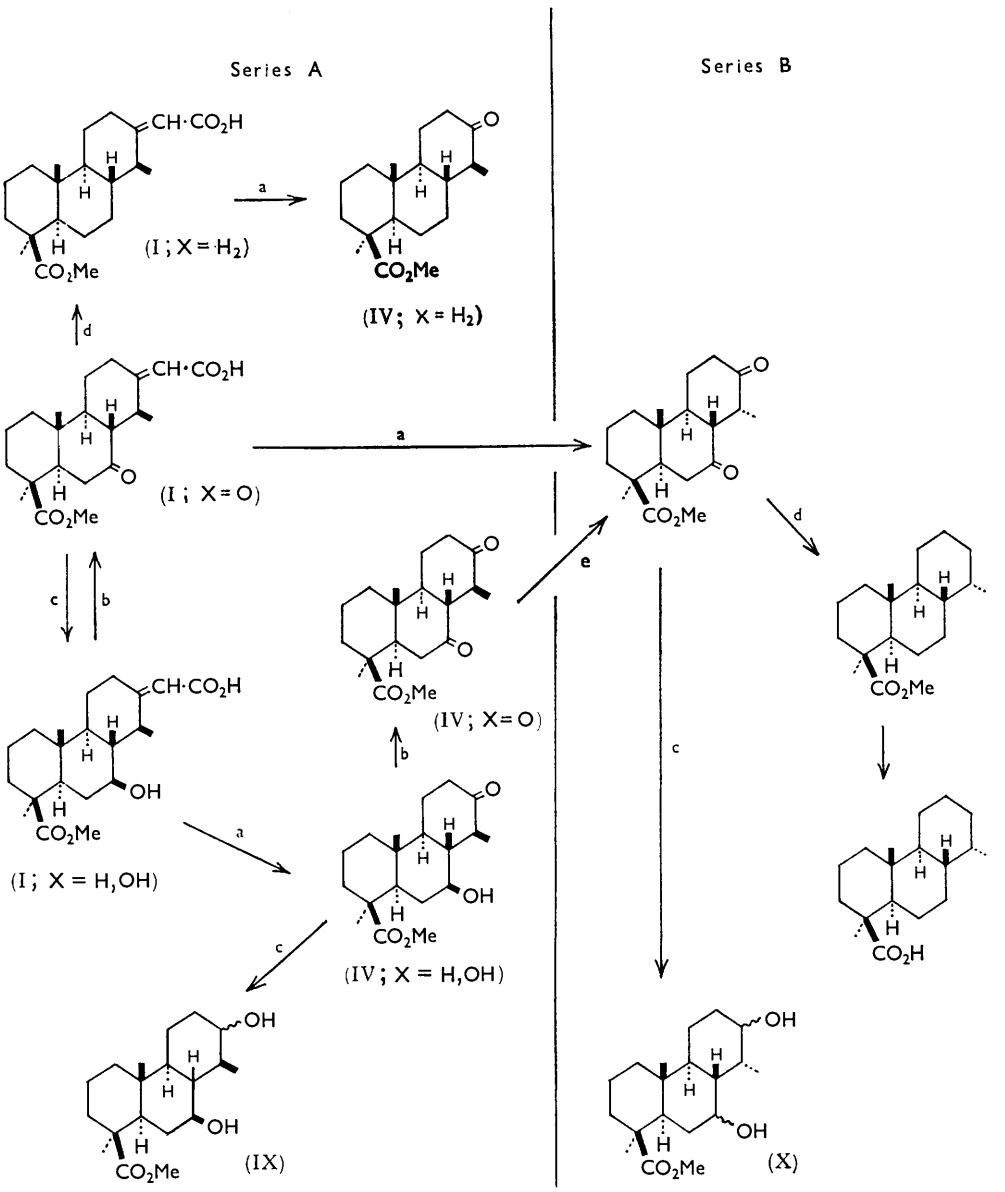
The molecular formulæ and functional groups[2] are confirmed by derivatives enumerated in the Experimental section. Details of the carbon skeleton and the position of the two carboxylic acid groups (one present as methyl ester) were obtained as follows.

Hydrogenation of cassamic acid saturated the 13,18-double bond and Wolff–Kishner reduction then gave cassane-16,19-dioic acid (II; X = $H_2$, R = H) resulted. This was also synthesised from vouacapenic acid through the dimethyl keto-ester (III);[3] the carbonyl group was removed by hydrogenolysis of the thioketal, and vigorous hydrolysis then yielded the identical diacid (II; X = $H_2$, R = H). By this result the absolute configuration at positions 4, 5, and 10 is also demonstrated: rings A and B are thus *trans*-fused, and the 4-methoxycarbonyl group is *cis* with respect to the 10β-methyl group.

Ozonolysis of cassamic acid (I; X = O, R = Me) gave oxalic acid, as expected, from the exocyclic unsaturated side-chain at C-13. The main fragment, a diketone (IV; X = O) showed only weak absorption at 280 mμ, characteristic of isolated ketone groups. Bromination of the diketone, followed by dehydrobromination, yielded, however, an enedione (V), $\lambda_{max.}$ 265 mμ (ε 12,600), easily reconverted into the dione (IV; X = O) by zinc in acetic acid.[4] Such transformations place the ketone group of cassamic acid at position 7.

[1] Mathieson, Jaques, Chapman, Arya, and Engel, *Experientia*, 1960, **9**, 404.
[2] Engel, Tondeur, and Ruzicka, *Helv. Chim. Acta*, 1950, **69**, 396.
[3] King, King, and Uprichard, *J.*, 1958, 3428.
[4] Turner, Herzog, Morin, and Riebel, *Tetrahedron Letters*, 1959, No. 2, 7.

Further, since cassamic acid (I; R = Me, X = O) and the corresponding hydroxy-acid (I; X = H,OH, R = Me) are easily interconvertible with sodium borohydride or chromic anhydride–pyridine, formula (I; X = H,OH, R = Me) represents also the acid (*b*) mentioned above.

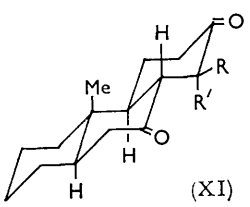



Reagents: (a) $O_3$. (b) $CrO_3$–pyridine. (c) $NaBH_4$. (d) Clemmensen reduction. (e) Alumina.

Cassamic acid and its congenors give rise to a series of ketones between which some interesting stability relations obtain. These ketones may be grouped into two series which can be defined on the basis of the stereochemistry of the 20-methyl group. Thus oxidative removal of the side chain from 7-deoxocassamic acid (I; X = $H_2$, R = Me) yields the 13-monoketone (IV; X = $H_2$) (series A). From the hydroxy-acid (I; X =

H,OH, R = Me), the hydroxy-ketone (IV; X = H,OH) (series A) results and this on oxidation with chromic anhydride–pyridine yields a diketone (IV; X = O) (series A). This diketone is easily converted in presence of alumina or of mineral acids into a more stable dione (series B) in almost quantitative fashion. It is the same dione of series B which is obtained directly from cassamic acid (I; X = O, R = Me) as described above. Of these three compounds (IV; X = $H_2$, H,OH, or O), only the last-mentioned is easily converted into a compound of series B. It seems unlikely that a change of B/C ring junction is involved, since methyl cassamate is stable on alumina under conditions where the diketone (IV; X = O) is completely epimerised. Esters of cassamic acid, moreover, are readily hydrolysed to cassamic acid with either acid or alkali. Because of this stability, in the reaction sequence Clemmensen reduction, then ozonolysis, to give the ester (IV; X = $H_2$), it may reasonably be assumed that the B/C ring stereochemistry of cassamic acid is preserved in this product. Optical rotatory dispersion measurements on (IV, X = $H_2$), in conjunction with the relation to vouacapenic acid, are consistent with a *trans-anti-trans*-assignment with a 17β-methyl group. The positive sign of the Cotton effect agrees with that predicted on the basis of the octant rule:[5] the shape of the curve and its amplitude ($10^{-2}\alpha$ = 78°) are almost identical with that of 4α-methyl cholestan-3-one.[6] This *trans-anti-trans*-assignment is also supported by the optical rotatory dispersion curve for 13,18-dihydrocassamic acid, which is similar to that for 5α-cholestan-7-one. The stereochemistry at C-8 and C-9 is now additionally defined, and the absolute configuration is confirmed.

Although conformational changes in ring C cannot be ruled out, we suggest that the stability relationships in the series of ketones described above can be interpreted at present on the basis of epimerisation of the 20-methyl group, and the suggested relations are contained in the Chart. Experiments on this and related aspects are at present in hand. Analogy may be drawn between rings B and C of the tricyclic ketones (IV; X = $H_2$ or H,OH), and rings A and B of the 4-methylcholestan-3-ones.[7] In this way preferential enolisation towards C-12 would provide an explanation for the failure of the 20-methyl group to epimerise. The direction of enolisation was suggested by bromination and dehydrobromination of the acetoxy-ketone (IV; X = H,OAc), where the αβ-unsaturated ketone (VII) resulted. The spectral characteristics ($\lambda_{max.}$ 230 mμ) are as expected for the 11-dehydro-13-ketone as opposed to the alternative 8(14)-dehydro-isomer (254 mμ). In the case of the diketone (IV; X = O) the dienolic form (VIII) involving C-8 and C-14 would be stabilised by conjugation and would lead to epimerisation of the 20-methyl group. One anomaly remains, namely, that ozonolysis of cassamic acid itself produces a dione of series B. This is probably due to epimerisation under the influence of oxalic acid, concomitantly produced during the ozonolysis; indeed, if the diketone of series A is refluxed with 0·1% oxalic acid in methanol, conversion into that of series B results. In the case of the ketone (IV; X = $H_2$) the rotatory dispersion curve showed but little change under ketalising conditions, an observation consistent with an equatorial 20β-methyl group.[8]



(XI)

The stereochemistry of the diketones of series A and B may best be appreciated from a projection (XI) along a plane drawn through C-7, C-13, and C-14. Thus the methyl group in series A is to be found in the " endo "-position (R) with respect to the 1,4-dione system and is subject to considerable interaction with both oxygen atoms in consequence. In series B the " *exo* "-position (R′) leads to relief of this interaction despite the axial position now taken up by the 20-methyl group.

[5] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, p. 178.
[6] Djerassi, Halpern, Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.
[7] Beton, Halsall, Jones, and Philips, *J.*, 1957, 753.
[8] Ruzicka, Dalma, and Scott, *Helv. Chim. Acta*, 1941, **24**, 63.

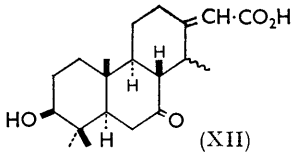
With regard to the 7-hydroxyl group of the acids (I; X = H,OH, R = Me) and (IV; X = H,OH), the configuration is most simply decided from molecular rotational differences and is assigned 7β (equatorial).

By the same token the molecular rotation contribution of the hydroxyl group in the 7-hydroxy-acid (+119°) indicates a β-configuration.

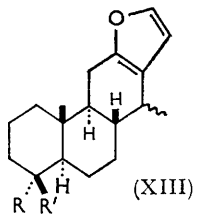
| | X = | H,OH | H,OAc | $\Delta_1$ |
|---|---|---|---|---|
| (II; R = Me) ..... | | +28° | +59° | +44° |
| (VI) ..... | | +154 | +224 | +70 |
| (IV) ..... | | +87 | +131 | +44 |
| 7-Substituted 5α-cholestane ..... | 7α | −47 | −135 | −88 |
| | 7β | +111 | +146 | +35 |

* Value derived from the 20-oic acid.

Apart from the side-chain and the 20-methyl group, the absolute configuration of this group of compounds would then be as shown in the Chart [formulæ (I)]. The interconversions previously described [1] also mean that formula (XII) represents cassaic acid. Formulæ for vinhaticoic acid (XIII; R = $CO_2H$, R′ = Me), vouacapenic acid (XIII; R = Me, R′ = $CO_2H$), and voucapenol (XIII; R = Me, R′ = $CH_2$·OH) likewise follow.




(XII)




(XIII)

## Experimental

Values for $[\alpha]_D$ are quoted for ethanol solutions unless otherwise stated. Infrared spectra were run on a Perkin-Elmer model 137 spectrophotometer, for the purchase of which we are indebted to the Department of Scientific and Industrial Research. The bark of *Erythrophleum guineense* from the Congo was obtained through the kindness of l'Institut National pour l'Étude Agronomique du Congo Belge (INEAC).

The mixed alkaloids from the ground bark were extracted as previously described. Hydrolysis with 2N-hydrochloric acid furnished a mixture of diterpene acids, chromatography of which was carried out as follows: Silica gel (200 g.) was triturated portionwise with methanol (100 ml.), and the resulting mixture allowed to dry in the air to a free-flowing powder. This was then packed in benzene into a column (12″ × 2½″). The crude acids (15 g.) in benzene (2 l.) were applied to the column. Elution with benzene (3·5 l.) yielded cassamic acid (3·9 g.), crystallising from ethyl acetate in needles, m. p. 218—219°, $[\alpha]_D^{22}$ −70° (*c* 1 in $CHCl_3$). Elution with benzene containing 2—5% of ether (6 l.) yielded dehydrocassamic acid (4 g.), crystallising from ethyl acetate; this acid had m. p. 189—190°, $[\alpha]_D^{22}$ +40°. Elution with 1 : 9 ether–benzene (2·5 l.) yielded the 7-hydroxy-analogue of cassamic acid (2·2 g.), crystallising from methanol in needles, m. p. 227—228°, $[\alpha]_D^{22}$ −58° (*c* 1 in MeOH). This was contaminated with ketonic material which was most easily removed as follows. The acid (250 mg.) in methanol (5 ml.) containing 5% aqueous potassium hydroxide (1 ml.) was treated for 24 hr. at room temperature with sodium borohydride (100 mg.) in 50% aqueous methanol (10 ml.). The solution was made acid with dilute hydrochloric acid, and the precipitate (240 mg.) was collected. Crystallisation from methanol gave the hydroxy-acid (I; X = H,OH, R = Me) in prisms, m. p. 246—247°, $[\alpha]_D^{22}$ −50° (*c* 1 in MeOH), $\lambda_{max.}$ 222 mμ (log ε 4·18), $\nu_{max.}$ (KBr) 3460 (OH), 1736 (ester CO), 1701 (acid CO), 1647 (conj. C=C), and 1153 cm.$^{-1}$ (C–O–C of ester) (Found: 68·5; H, 8·8; O, 22·4; OMe, 8·7. Calc. for $C_{21}H_{32}O_5$: C, 69·2; H, 8·9; O, 22·0; OMe, 8·5%). The *methyl ester acetate* crystallised from ether in plates, m. p. 151—153°, $[\alpha]_D^{22}$ −59°, $\nu_{max.}$ (in $CCl_4$) 1727 (ester CO), 1650 (C=C conj. with ester), 1156 (C–O–C of ester), 1233 cm.$^{-1}$ (OAc) (Found: C, 68·3; H, 8·6. $C_{24}H_{36}O_6$ requires C, 68·5; H, 8·6%).

*Oxidation of the Hydroxy-acid* (I; X = H,OH, R = Me).—To chromic anhydride (1 g.) in dry pyridine (10 ml.), the hydroxy-acid (1 g.) in pyridine (5 ml.) was added. After 24 hr. the mixture was poured into ice–water, acidified, and extracted with ether. The crystalline residue (870 mg.) from the extract was separated into two components on a column of silica gel (20 g.) containing methanol. Benzene (400 ml.), 1 : 49 ether–benzene (200 mg.), then 1 : 9 ether–benzene (400 ml.) eluted cassamic acid (740 mg.), m. p. 213—214° (from ethyl acetate), $[\alpha]_D^{22}$ −70° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 1736 (ester CO), 1723 (ketone), 1692 (acid CO), 1655 (conj. C=C), and 1155 $cm.^{-1}$ (C–O–C of ester) (Found: C, 69·4; H, 8·1; O, 22·6. Calc. for $C_{21}H_{30}O_5$: C, 69·6; H, 8·3; O, 22·1%).

7-*Deoxocassamic acid* (I; X = $H_2$, R = Me).—Cassamic acid (3 g.) in toluene (50 ml.) and ethanol (15 ml.) was reduced for 24 hr. by amalgamated zinc (30 g.) in refluxing concentrated hydrochloric aid (50 ml.) and water (20 ml.), further additions of acid (15 ml.) being made after 8 and 16 hr. Isolation of the product by ether-extraction gave a crude product (3 g.) separated on silica gel (30 g.) in methanol. 1 : 1 Benzene–light petroleum (b. p. 40—60°) (300 ml.) yielded 7-deoxocassamic acid (2 g.), crystallising from ether–light petroleum in needles, m. p. 137—139°, $[\alpha]_D^{20}$ −60°, $\lambda_{max.}$ 221 mμ (log ε 4·0), $\nu_{max.}$ (in $CCl_4$) 1730 (ester CO), 1695 (acid CO), 1645 (conj. C=C), and 1152 $cm.^{-1}$ (C–O–C ester) (Found: C, 72·7; H, 9·5; O, 17·3. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3; O, 18·4%). Ether (200 ml.) eluted unchanged cassamic acid (900 mg.) from the column.

*Cassane*-16,19-*dioic Acid* (II; X = $H_2$, R = H).—(*A*) *From cassamic acid.* Methyl cassamate (a gum; 640 mg.) was hydrogenated at Adams platinum oxide (130 mg.) in ethanol (50 ml.). Uptake of hydrogen (1 mol.) ceased after 30 min.; the residual *methyl* 13,18-*dihydrocassamate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 98—99°, $[\alpha]_D^{22}$ +48°, $\nu_{max.}$ 1742 (ester CO), 1715 (ketone), and 1151 $cm.^{-1}$ (C–O–C of ester) (Found: C, 69·7; H, 8·7. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1%).

Sufficient anhydrous hydrazine was distilled into diethylene glycol (35 ml.) containing methyl 13,18-dihydrocassamate (527 mg.) and sodium (500 mg.) to give a reflux temperature of 175°. After 12 hours' refluxing, hydrazine was distilled off so that the temperature rose to 205°; refluxing was then maintained for a further 10 hr. Acidic material was isolated in the usual manner to give *cassane*-16,19-*dioic acid* * (360 mg.) which crystallised from ethanol–ether in prisms, m. p. 260·5—261°, $[\alpha]_D^{22}$ +40°, $\nu_{max.}$ 1701 $cm.^{-1}$ (acid CO) (Found: C, 71·7; H, 9·6; O, 18·8%; equiv., 182. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6; O, 19·9%; equiv., 168). Treatment of this acid with diazomethane yielded the dimethyl ester as a gum whence saponification with 2N-sodium hydroxide gave 16-*methyl hydrogen cassane*-16,19-*dioate* (II; X = $H_2$, R = Me), m. p. 155°, $[\alpha]_D^{22}$ +53°, crystallising from ethyl acetate in prisms, $\nu_{max.}$ 1731 (ester CO), 1711 (acid CO), and 1151 $cm.^{-1}$ (ester) (Found: C, 71·0; H, 9·7; O, 18·4. $C_{21}H_{24}O_4$ requires C, 71·9; H, 9·8; O, 18·3%).

(*B*) *From vouacapenic acid.* We are indebted to Dr. T. J. King for a supply of vouacapenic acid. Dimethyl 12-oxocassane-16,19-dioate (III).[3] (1·7 g.) was added to ethanedithiol (10 ml.) in ether (15 ml.), and the solution was saturated with hydrogen chloride. After 16 hr. at 0°, ether (100 ml.) was added and the whole was extracted with 10% aqueous sodium hydroxide. The dried ether solution yielded a gum which was refluxed in ethanol (40 ml.) with Raney nickel (10 g.) for 6 hr. The nickel was filtered off and washed with ethanol. The bulked filtrates were evaporated and saponified with 2N-sodium hydroxide, to yield as acid fraction 16-methyl hydrogen cassane-16,19-dioate (550 mg.), m. p. 154° (from ethyl acetate) $[\alpha]_D^{22}$ +53°. The neutral fraction (175 mg.) in diethylene glycol (20 ml.) containing a few drops of hydrazine was refluxed for 15 hr. with sodium (500 mg.). Crystallisation of the acidic material from ethanol afforded cassane-16,19-dioic acid, m. p. 264°.

Specimens of the dicarboxylic acid (II; X = $H_2$, R = H) or of the 16-methyl ester from methods (*A*) and (*B*), above, gave no depression on admixture. The infrared spectra of the 16-monomethyl ester, and of the 16,19-dimethyl ester (a gum) prepared therefrom, were almost superimposable when run at 2% and 3% w/v solutions, respectively, in carbon tetrachloride.

*Oxidative Removal of C*-18 *and* C-19 *from the Hydroxy-acid* (I; X = H,OH, R = Me).—(*A*) The methyl ester (2·5 g.) of the hydroxy-acid in dry chloroform (200 ml.) was treated with ozone at −60° until the solution was deep blue (1½ hr.). The solvent was removed and the

* The nomenclature used for these compounds is based on the use of cassane for the parent hydrocarbon, $C_{20}H_{36}$. The systematic name for cassamic acid then becomes 16-methyl hydrogen 7-oxocass-13(18)-ene-16,19-dioate.

residue refluxed for 30 min. with 50% aqueous methanol (60 ml.). The whole was extracted with ether, and the aqueous residues were reserved. The ether extract yielded a gum (1·4 g.). This was applied in 1 : 2 benzene–light petroleum (b. p. 40—60°) (60 ml.) to alumina (Brockmann, grade III) (40 g.). Elution with 1 : 1 benzene–light petroleum (800 ml.) yielded the keto-ester (IV; X = O) (152 mg.), crystallising from ether–light petroleum in needles, m. p. 147°, $[\alpha]_D^{22}$ 0°. Elution with 1 : 1 benzene–light petroleum (500 ml.), and then a 2 : 1 (300 ml.) and a 4 : 1 mixture (500 ml.) gave a compound *A* (213 mg.) (see below), crystallising from ether–light petroleum in prisms, m. p. 200—201°, $[\alpha]_D^{22}$ 0°. Elution with 4 : 1 (700 ml.) and then 2 : 3 benzene–ether (200 ml.), ether (400 ml.), and 3 : 1 ether–methanol (200 ml.) gave a hydroxy-ester (IV; X = H,OH) in two fractions (total 527 mg.), crystallising from ether in prisms, m. p. 174—175°, $[\alpha]_D^{22}$ +43°.

The aqueous residues, after extraction of the above crude products, were evaporated to 2 ml. under reduced pressure. On cooling, crystals separated which were dried at 80°, then sublimed. They had m. p. 188—189° alone or mixed with oxalic acid.

(*B*) An adaptation of an analytical estimation of double bonds [9] provided a convenient alternative. The hydroxy-acid (I; X = H,OH, R = Me) (620 mg.), suspended in acetone (5 ml.), was diluted to 50 ml. with water and sufficient potassium hydroxide was added to give pH 8. 2% Aqueous sodium metaperiodate (210 ml.) and 0·01M-potassium permanganate (40 ml.) were then added and the whole left overnight. After acidification, an ether extract was prepared and washed with aqueous sodium carbonate. The neutral fraction, thus resulting (345 mg.), was dissolved in benzene (40 ml.) and placed on alumina (30 g.). The main fraction finally removed from the column by ether was the hydroxy-ester (IV; X = H,OH) (295 mg.), m. p. 174—175°.

*Methyl* 7,13-*dioxo*-18,19-*dinorcassan*-16-*oate* series B (IV; X = O) (see above) had m. p. 147—148°, $[\alpha]_D^{22}$ 0°, $\lambda_{max.}$ 284 mμ (log ε 1·7), $\nu_{max.}$ (in $CCl_4$) 1709 (broad band, unresolved) (CO), 1147 (ester) (Found: C, 71·4; H, 8·7; O, 19·6. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8; O, 20·0%).

*Methyl* x-*hydroxy*-7,13-*dioxo*-18,19-*dinorcassan*-16-*oate*, compound *A* above, had m. p. 200—201°, $[\alpha]_D^{22}$ 0°, $\nu_{max.}$ (in $CCl_4$) 3546 (OH), 1715 (CO), 1152 $cm.^{-1}$ (ester) (Found: C, 67·6; H, 8·4; O, 23·4; OMe, 9·6 active H, 1. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4; O, 23·8; OMe, 9·2%.

*Methyl* 7-*hydroxy*-13-*oxo*-18,19-*dinorcassan*-16-*oate* (IV; X = H,OH) had m. p. 174—175°, $[\alpha]_D^{22}$ +43°, $\lambda_{max.}$ 290 mμ (log ε 1·54), $\nu_{max.}$ (in $CCl_4$) 3610, 3472 (OH), 1721 (ester CO), 1709 (ketone), 1155 $cm.^{-1}$ (ester) (Found: C, 70·8; H, 9·4; O, 19·9; OMe, 10·8. $C_{19}H_{30}O_4$ requires C, 70·8; H, 9·4; O, 19·9; OMe, 9·6%). The *acetate* crystallised from ether–light petroleum in prisms, m. p. 131—133°, $[\alpha]_D^{22}$ +48°, $\nu_{max.}$ (in $CCl_4$) 1734 (ester CO), 1720 (CO), and 1235 and 1155 $cm.^{-1}$ (esters) (Found: C, 69·9; H, 8·7. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%). The 2,4-*dinitrophenylhydrazone* crystallised from acetic acid in yellow plates, m. p. 149—150° (Found: N, 11·1. $C_{25}H_{36}N_4O_8$ requires N, 11·2%).

*Methyl* 13-*Oxo*-18,19-*dinorcassan*-16-*oate* (IV; X = $H_2$).—7-Deoxycassamic acid (390 mg.) in dry chloroform (35 ml.) was treated with ozone at −70° for 30 min. The solution was then shaken for 40 min. with zinc dust (2·5 g.) and acetic acid (25 ml.). Solvent was evaporated and the neutral residue (200 mg.) crystallised from ether in needles, m. p. 128—129°, $[\alpha]_D^{22}$ +14·5°, $\nu_{max.}$ (in $CCl_4$), 1728 (ester CO), 1717 (ketone), and 1152 $cm.^{-1}$ (ester) (Found: C, 74·1; H, 9·6. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

*Methyl* 7,13-*Dioxo*-18,19-*dinorcassan*-16-*oate* series A (IV; X = O).—The keto-alcohol (IV; X = H,OH) (260 mg.) in pyridine (5 ml.) was added to chromic anhydride (500 mg.) in pyridine (10 ml.). After 24 hr. at room temperature the mixture was worked up in the usual manner to give a neutral fraction, m. p. 127—129°, $[\alpha]_D^{22}$ 0°, when crystallised from ether–light petroleum. Mixed with its isomer (m. p. 147—148°) it had 100—104°. It had $\nu_{max.}$ (in $CCl_4$) 1712 (broad band) (CO) and 1152 $cm.^{-1}$ (ester) (Found: C, 71·2; H, 8·8; O, 19·9. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8; O, 20·0%).

*Epimerisation.* (i) The diketone of series A (76 mg.) in 1 : 1 ether–light petroleum (10 ml.) was adsorbed on alumina (2 g.) and eluted with ether after 2 hr., to yield the isomer of series B (64 mg.), m. p. 147—147·5°, giving no depression on admixture with a sample obtained by ozonolyns of methyl cassamate.

(ii) The diketone of series A (95 mg.) in methanol (5 ml.) was refluxed with 1% aqueous

[9] Le Mieux and von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701, 1710, 1714; von Rudloff, *ibid.*, 1956, **34**, 1413; *J. Amer. Oil Chemists' Soc.*, 1956, **33**, 126.

hydrochloric acid (5 ml.) for 1 hr. The isomer (85 mg.) was extracted by ether from the resulting solution.

(iii) The diketone of series A (25 mg.) was refluxed for 1 hr. with a 0·1% solution of oxalic acid in 50% aqueous methanol (10 ml.). As before, the isomer of m. p. 146—147° resulted. When this experiment was repeated with methanol alone, the diketone of series A was recovered unchanged.

*Methyl* 7,13-*Dioxo*-8(14)-*dehydro*-18,19-*dinorcassan*-16-*oate* (V).—The diketone of series A (IV; X = O) (320 mg.) in acetic acid (10 ml.) was treated portionwise with bromine (160 mg.) in acetic acid (1·6 ml.). Water (200 ml.) was added and the whole extracted with ether. After being washed with 0·1N-sodium carbonate the ether yielded an amorphous bromo-compound (400 mg.). This was then refluxed for 45 min. with redistilled collidine (20 ml.), 0·1N-hydrochloric acid (200 ml.) was added, and the mixture extracted with ether. The resulting gum (200 mg.) was placed on an alumina column (grade I) in benzene (300 ml.); elution with 1 : 49 ether–benzene (500 ml.) yielded crystals (190 mg.), recrystallising from ether in prisms, m. p. 120°, $\lambda_{max.}$ 265 mμ (log ε 4·1), $\nu_{max.}$ 1735 (ester CO), 1685 (conj. CO), and 1155 cm.$^{-1}$ (ester C–O–C) (Found: C, 71·6; H, 8·0; O, 19·9. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2; O, 20·1%).

*Methyl* 7,13-*Dihydroxy*-18,19-*dinorcassan*-16-*oate* (X).—The diketone of series B (IV; X = O) (500 mg.) in methanol (20 ml.) was treated with sodium borohydride (100 mg.) in methanol (10 ml.). After 24 hr. at room temperature, working up in the usual manner gave the *diol* (X), crystallising from ether in needles, m. p. 110—112°, $\nu_{max.}$ (in $CCl_4$) 3540 (OH), 1727 (ester CO), 1150 cm.$^{-1}$ (ester C–O–C) (Found: C, 69·8; H, 10·0; O, 20·7. $C_{19}H_{32}O_4$ requires C, 70·3; H, 9·9; O, 19·7%).

This diol (200 mg.) in pyridine (5 ml.) was added to chromic anhydride (400 mg.) in pyridine (4 ml.) and set aside overnight at room temperature. Working-up in the usual manner gave the starting diketone, m. p. 147°.

*Methyl* 7,13-*Dihydroxy*-18,19-*dinorcassan*-16-*oate* (IX).—Methyl 7-hydroxy-13-oxo-18,19-dinorcassan-16-oate (50 mg.) in methanol (5 ml.) was reduced as described above, yielding the *diol* (IX) that, crystallised from aqueous methanol, had m. p. 185—186°, $\nu_{max.}$ (in $CCl_4$) 3600, 3400 (OH), 1730 (ester CO), and 1150 cm.$^{-1}$ (ester C–O–C) Found: C, 71·7; H, 9·8. $C_{19}H_{32}O_4$ requires C, 70·3; H, 9·9. Oxidation with chromic anhydride re-formed the diketone of series B.

*Methyl* 7-*Hydroxy*-18,19-*dinorcassan*-16-*oate* (VI; X = H,OH).—The alcohol (IV; X = H,OH) (580 mg.) was reduced under Clemmensen conditions as described above for 7-deoxocassamic acid. The crude product (550 mg.) was placed on an alumina column in 1 : 1 benzene–light petroleum. Elution with ether gave the required *compound* that crystallised from ether–light petroleum in needles, m. p. 129—129·5°, $[\alpha]_D^{22}$ +84°, $\nu_{max.}$ (in $CCl_4$) 3530 (OH), 1727 (ester CO), and 1150 cm.$^{-1}$ (ester C–O–C) (Found: C, 74·1; H, 10·4. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·5%).

*Methyl* 7-*Oxo*-18,19-*dinorcassan*-16-*oate* (VI; X = O, R = Me).—The hydroxy-compound (VI; X = H,OH) (110 mg.) in pyridine (4 ml.) was oxidised overnight at room temperature with chromic anhydride (200 mg.) in pyridine (2 ml.). The resulting ketone was a gum even after purification through the semicarbazone or by chromatography on alumina; it had $\nu_{max.}$ (in $CCl_4$) 1739 (ester CO), 1715 (ketone), and 1150 cm.$^{-1}$ (ester C–O–C).

*Methyl* 18,19-*Dinorcassan*-16-*oate* (VI; X = $H_2$).—(*a*) The diketone of series B (250 mg.) was reduced under modified Clemmensen conditions as detailed for 7-deoxocassamic acid, giving the required *compound*, m. p. 83—85°, $\nu_{max.}$ (in $CCl_4$) 1730 (ester CO) and 1154 cm.$^{-1}$ (ester C–O–C) (Found: C, 78·7; H, 10·8; O, 10·7. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4; O, 11·0%).

(*b*) The diketone of series B (360 mg.) in methanol (5 ml.) and ethanedithiol (2 ml.) were set aside for 4 hr. with 3 drops of a 45% solution of boron trifluoride in ether. 0·1N-Potassium hydroxide was added until the solution was alkaline: the thioketal (400 mg.) was then extracted with ether. Crystallisation from ethanol gave material of m. p. 163—164°. Desulphurisation in the usual manner gave the product (VI; X = $H_2$) (120 mg.; m. p. 83°) identical with the sample prepared by method (*a*).

18,19-*Dinorcassane*-16-*carboxylic Acid* (VI; X = $H_2$, R = H).—The diketone of series B (1 g.) in diethylene glycol (50 ml.) containing sodium (1 g.) and anhydrous hydrazine was reduced by the modified Wolff–Kischner method.[10] The crude product (840 mg.) in light petroleum (b. p.

[10] Barton, Ives, and Thomas, *J.*, 1955, 2056.

60—80°) (500 ml.) was placed on an alumina column (grade I). The fourth 100 ml. of eluate (light petroleum, b. p. 60—80°) gave a solid *acid* (430 mg.), crystallising from petroleum (b. p. 40°) in rosettes, m. p. 165°, $[\alpha]_D^{20}$ +31°, $\nu_{max.}$ 1705 cm.$^{-1}$ (acid CO) (Found: C, 77·6; H, 10·6; O, 11·9%; equiv., 272. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8; O, 11·5%; equiv., 278.

*Methyl 7-Acetoxy-11-dehydro-13-oxo-18,19-dinorcassan-16-oate* (VII).—Methyl 7-acetoxy-13-oxo-18,19-dinorcassan-16-oate (900 mg.) in acetic acid (50 ml.) was treated dropwise with 20 ml. of a solution of bromine (0·4 g.) and sodium acetate (anhyd., 0·5 g.) in acetic acid (50 ml.). The solvent was evaporated and the resulting gum in dimethylformamide (20 ml.) was refluxed for 4 hr. with lithium chloride (1·2 g.) and lithium carbonate (2 g.). After dilution with 10% sulphuric acid (100 ml.), ether-extraction gave a gum (760 mg.). Since an infrared spectrum indicated the presence of some free carboxylic acid, the gum was methylated with diazomethane and, dissolved in 2 : 1 ether–light petroleum (60 ml.), placed on an alumina column (grade I) (30 g.). The same solvent (50 ml.) removed a yellow gum, followed in the next 150 ml., by a crystalline fraction (330 mg.). This crystallised from ether–light petroleum in needles, m. p. 167—168°, $\lambda_{max.}$ 230 mμ (log ε 4·03), $\nu_{max.}$ (in $CCl_4$) 1739 (ester CO), 1688 (conj. CO), 1614vw (conj. C=C), and 1233 and 1160 cm.$^{-1}$ (ester C–O–C) (Found: C, 69·6; H, 8·3. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

*Methyl 7-Hydroxy-11-dehydro-13-oxo-18,19-dinorcassan-16-oate.*—The acetate (VII) (100 mg.) in ethanol (10 ml.) was refluxed for 1 hr. with 0·5N-sodium hydroxide (2·5 ml.). Ether-extraction yielded the required hydroxy-ketone, m. p. 183—185° (from ether), $\lambda_{max.}$ 227 mμ (log ε 3·8), $\nu_{max.}$ (in $CCl_4$) 3630, 3400 (OH), 1736 (ester CO), 1690 (conj. CO), 1157 cm.$^{-1}$ (ester C–O–C).

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