564. *Structure and Some Reactions of Acoric Acid.*

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Acoric acid is shown to have structure (I) by its reactions and by partial synthesis from acorone (XXVI).

The acidic fraction from extracts of the roots of *Acorus calamus* L. shows some anti-epileptic activity, and this led to an examination of its constituents. The main component is a crystalline acid, $C_{15}H_{24}O_4$, named acoric acid, the structure of which has been examined. Attempted dehydrogenation gave no useful results, and it was therefore necessary to attack the structure by examination of the active groups, their inter-relations, and the spectra of various derivatives.

Active Groups.—That acoric acid contains a carboxyl group is shown by its solubility in potassium hydrogen carbonate, by $\nu_{max.}$ (in Nujol) 3500—2400 and 1725 cm.$^{-1}$, and by formation of a methyl ester [$\nu_{max.}$ (in CS_2) 1738 cm.$^{-1}$] on reaction with diazomethane. The other two oxygen atoms are present as carbonyl groups [$\nu_{max.}$ (in Nujol) 1702 and 1690 cm.$^{-1}$ in the acid, and $\nu_{max.}$ (in CS_2) 1715 and 1700 cm.$^{-1}$ in the ester]. The first band in each case corresponds to a carbonyl group of normal reactivity, and the second to an extremely inactive one which was detected by a band at 1695 cm.$^{-1}$ in the mono-oximes of acoric acid and methyl acorate, and by the reactions described below. Tetranitromethane gave no colour, and attempted hydrogenation with a palladium catalyst failed entirely. In the presence of platinum in acetic acid, acoric acid absorbed two mol. of hydrogen, to give an acid, $C_{15}H_{26}O_3$, containing neither a carbonyl nor a hydroxyl group, as shown by the infrared spectra of the acid and its methyl ester. The third oxygen must be present in an ether link as in (II). There is, therefore, no evidence of the presence of an ethylenic link in acoric acid and it must be monocarbocyclic.

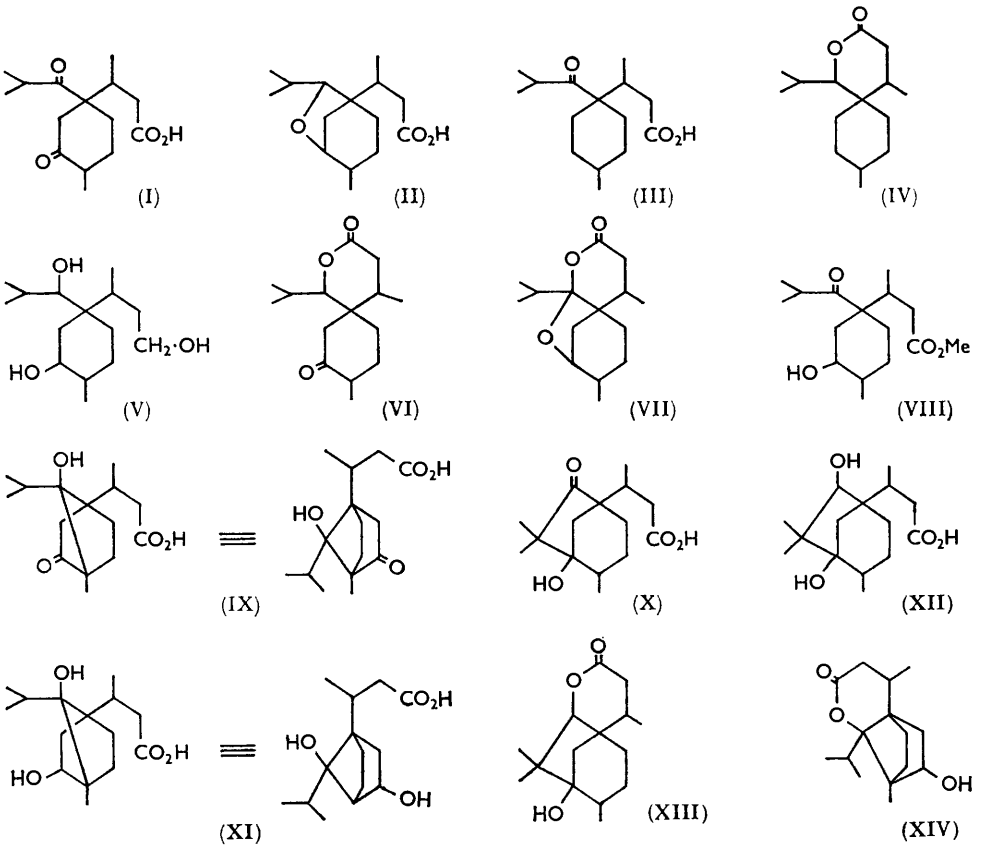
Reduction of acoric acid monosemicarbazone by the Wolff–Kishner method led to a monoketo-acid (III), $\nu_{max.}$ (in CS_2) 1700 cm.$^{-1}$, which still contained the unreactive carbonyl group, as shown by the spectrum of its methyl ester [$\nu_{max.}$ (in CS_2) 1735 and 1696 cm.$^{-1}$]. Reduction of the acid (III) with lithium and ethanol in liquid ammonia produced a lactone (IV), $\nu_{max.}$ (in CS_2) 1747 cm.$^{-1}$.

Reduction of acoric acid with lithium aluminium hydride produced the expected triol (V) which yielded a diacetyl ester with acetic anhydride in pyridine. The free hydroxyl group in the ester [$\nu_{max.}$ (in CS_2) 3500 cm.$^{-1}$] must be that derived from the unreactive carbonyl group since oxidation with chromic acid gave a ketone [$\nu_{max.}$ 1695 cm.$^{-1}$]. This unreactivity is a further indication of the sterically hindered nature of the original carbonyl group. Oxidation of the triol with chromic acid in acetone regenerated some acoric acid, and produced also a keto-lactone (VI) [$\nu_{max.}$ (in CS_2) 1741 and 1713 cm.$^{-1}$] which must have arisen by lactonisation of the carboxyl group with the unreactive hydroxyl group.

Inter-relations of the Active Groups.—The lactone (IV) and the keto-lactone (VI) both contain what is almost certainly a six-membered lactone ring, from its spontaneous formation and infrared absorption. This defines the δ-relationship of the unreactive carbonyl group to the carboxyl group.

Another neutral compound, $C_{15}H_{24}O_3$, containing a six-membered lactone ring [$\nu_{max.}$ (in Nujol) 1718 cm.$^{-1}$] was obtained by borohydride reduction of acoric acid. It is assigned structure (VII) for the following reasons. Borohydride reduced only the reactive carbonyl group in methyl acorate since the product (VIII) has $\nu_{max.}$ (in CCl_4) 3450, 1735, and 1683 cm.$^{-1}$. Presumably, similar reduction occurred with acoric acid, but the product shows no absorption near 3400 or 1690 cm.$^{-1}$, and shows a pattern of strong bands near 940 cm.$^{-1}$ usually associated with a ketal grouping. Furthermore, the lactone (VII) was also obtained in good yield by alkaline hydrolysis of the ester (VIII), and, conversely, reaction of the lactone (VII) with sodium methoxide gave a substantial proportion of the ester (VIII). Such facile ketal formation requires the original carbonyl groups to be 1,4 or, less

likely, 1,5 to each other. The lactone (VII), on reduction with lithium aluminium hydride or with hydrogen and platinum in acetic acid, produced, respectively, the same triol (V) and the same acid (II) as were obtained from acoric acid itself.



The 1,4-relationship of the two carbonyl groups was confirmed by carrying out several cyclisations by means of aldol condensation. Acoric acid was refluxed with 5N-aqueous potassium hydroxide to convert it into a hydroxy-keto-acid, $C_{15}H_{24}O_4$, m. p. 163—165°, $\nu_{max.}$ (in Nujol) 3500—2400, 3420, 1725, and 1700 cm.$^{-1}$, containing a carbonyl group in a five-membered ring since its methyl ester ($\nu_{max.}$ 3630 cm.$^{-1}$) shows only one carbonyl peak, at 1735 cm.$^{-1}$. With N-aqueous potassium hydroxide solution, acoric acid was converted into a mixture containing unchanged material, the above acid, and, as the major component, an isomeric hydroxy-keto-acid, m. p. 191—194°, $\nu_{max.}$ (in Nujol) 3500—2400, 3350, 1723, and 1712 cm.$^{-1}$. This acid also contained a carbonyl group in a five-membered ring, since its methyl ester [$\nu_{max.}$ (in CCl_4) 3620 cm.$^{-1}$] also has only one band in the carbonyl region, at 1738 cm.$^{-1}$. The latter acid (IX) was readily converted into the isomer (X), m. p. 163—165°, by the action of 5N-potassium hydroxide solution, showing (X) to be the thermodynamically stable isomer, and (IX) the kinetically favoured one. It seems clear that the kinetically favoured reaction should be nucleophilic attack of the enol from the more reactive carbonyl on the less reactive carbonyl, to give acid (IX). The stable isomer must, therefore, be (X); the cyclisations are presumably reversible.

Both (IX) and (X) were reduced by the action of lithium and ethanol in liquid ammonia to the two isomeric dihydroxy-acids, (XI), m. p. 156—158°, and (XII), m. p. 234—238°, respectively. These were stable to refluxing hydrochloric acid in acetone, but reacted in presence of toluene-*p*-sulphonic acid in benzene to give isomeric neutral products, $C_{15}H_{24}O_3$,

m. p. 216—217°, [$\nu_{max.}$ (in Nujol) 3475, 1720, 1710sh cm.$^{-1}$], and m. p. 150—151°, [$\nu_{max.}$ (in CS_2) 3620, 1752, 1740sh cm.$^{-1}$], respectively. The latter is almost certainly the hydroxy-lactone (XIII) since it is stable to chromic acid and is reconverted into (XII) by alkaline hydrolysis. For steric reasons the carboxyl group of the acid (XI) cannot cyclise on to the secondary hydroxyl, and of the alternative lactone (XIV) is not formed, since the lactonic product is stable to chromic acid; moreover the hydroxy-keto-acid (IX) failed to give a lactone on similar treatment. Probably some rearrangement occurs, but since the structure of the product is not critical for the present work it was not investigated further.

The relationship of the reactive carbonyl to the carboxyl group was deduced from the action of sodium methoxide on methyl acorate. The product was an enolic β-diketone (XV), giving a typical ferric chloride test, the infrared absorption of which [$\nu_{max.}$ (in CCl_4) 1742, 1697, 1672, and 1615 cm.$^{-1}$] indicated that it probably contained a carbonyl group in a five-membered ring (1742 cm.$^{-1}$). A crystalline copper salt was obtained, the infrared absorption of which [$\nu_{max.}$ (in Nujol) 1687, 1595, and 1500 cm.$^{-1}$] showed that the unreactive carbonyl, which gives a band in its usual position (1687 cm.$^{-1}$) cannot be involved in the β-diketone system. The formation of an enolic β-diketone system shows that there must be a methylene next to the reactive carbonyl and that the carboxyl group is on the end of a side-chain and can cyclise to produce a *cis*-enol, which cannot therefore be part of a bridged ring.

The Structure of Acoric Acid.—Further conclusions required a closer examination of structures adjacent to the active groups by chemical and spectral methods. Degradation of the lactone (VII) revealed the presence of the unit (XVI). Formylation of (VII) unexpectedly yielded the acid (XVII), showing none of the expected properties of a formyl ketone or ester. Its structure is supported by the ultraviolet absorption [$\lambda_{max.}$ 237 mμ (ε 11,000)], which is almost identical with that of loganic acid containing a similar chromophore,[1] by its infrared spectrum [$\nu_{max.}$ (in Nujol) 3500—2400, 1657, and 1625 cm.$^{-1}$] and that of its methyl ester [$\nu_{max.}$ (in CCl_4) 1703 and 1627 cm.$^{-1}$], and by its proton magnetic resonance (p.m.r.) spectrum, in which a single vinylic proton, H_d, appears at τ 2·61 (J = 1·5 c./sec.). Also present are resonances due to H_a as a doublet at τ 6·02 (J = 6·8 c./sec.), to H_c as a quintuplet at τ 7·60 (J = 6·7 c./sec.), and to H_b as a diffuse quartet at τ 7·82. There is, threfore, a methylene group adjacent to the original carboxyl of acoric acid. Ozonolysis of the acid (XVII) led ultimately to the nor-lactone (XVIII), which contains a γ-lactone ($\nu_{max.}$ 1774 cm.$^{-1}$), confirming the δ-relationship of the unreactive carbonyl and the carboxyl group. The nor-lactone also shows a pattern of ketal bands near 930 cm.$^{-1}$. The p.m.r. spectrum of (XVIII) shows the same doublet at τ 5·86 (J = 6·7 c./sec.) (H_a) and quintuplet at τ 7·60 (J = 6·7 c./sec.) (H_c) as (XVII), but the diffuse quartet at τ 7·80 is replaced by a sharp quartet at τ 7·39 (J = 7·0 c./sec.) (H_b), indicating that the carbon atom β to the carboxyl in (XVIII) carries no proton. The diffuseness of the quartet at τ 7·80 in (XVII) must be due to long-range coupling of H_b to H_d.

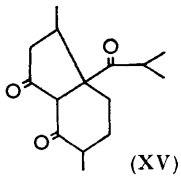
The quintuplet at τ 7·60 present in the spectra of (XVII) and (XVIII) is exactly the same shape as that in acoric acid at τ 6·82 and the monoketo-acid (III) at τ 6·83, and must be due to a grouping CH·CHMe adjacent to the unreactive carbonyl group. Thus, the grouping (XIX) must be present in acoric acid.

It has been demonstrated above that the reactive carbonyl group is ε to the carboxyl group, and in a 1,4-relationship to the unreactive carbonyl. It must, therefore, be as in (XXIV), and, since the β-diketone (XV) is enolic, the carbon atom marked with an asterisk must be present as a methylene group. The carbon on the other side of the reactive carbonyl was shown by several methods to carry a hydrogen atom and a methyl group.

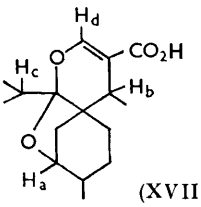
Acoric acid was oxidised by oxygen in the presence of potassium t-butoxide to a diketo-diacid (XX) which produced iodoform in good yield on reaction with hypoiodite. The dimethyl ester of (XX) had $\nu_{max.}$ (in CCl_4) 1740 (ester), 1719 (methyl ketone), and 1701 cm.$^{-1}$

[1] Birch and Grimshaw, *J.*, 1961, 1407.

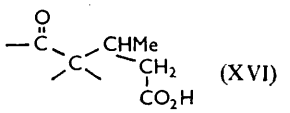
(isopropyl ketone), and the mono-oxime of the ester had no absorption at 1715 cm.$^{-1}$. The monoketo-acid (III) could not be oxidised by similar treatment, so the fission occurred adjacent to the reactive carbonyl, to yield a methyl ketone and a carboxyl group. The same acid (XX) was obtained by ozonolysis of the enol acetate (XXI) [$\nu_{max.}$ (in CCl_4) 1737 and 1698 cm.$^{-1}$], prepared by the action on methyl acorate of acetic anhydride in the presence of a trace of toluene-*p*-sulphonic acid. The p.m.r. spectra of this enol acetate, and of the enol acetate (XXII) (see below), indicated the presence of an allylic methyl group (τ 8·50), thus confirming the conclusion about the substitution of the carbon atom marked with a dagger.



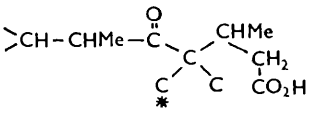
(XV)



(XVII)



(XVI)



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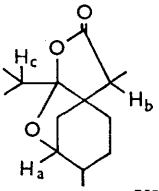
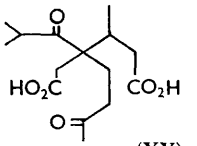
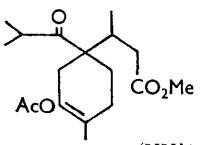


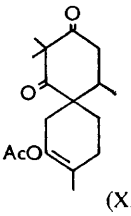
(XVIII)



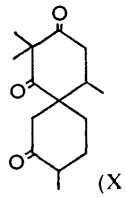
(XX)



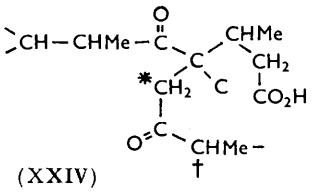
(XXI)



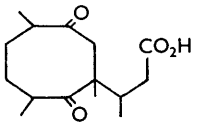
(XXII)



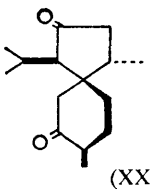
(XXIII)



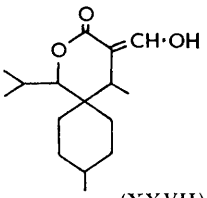
(XXIV)



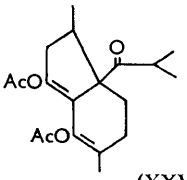
(XXV)



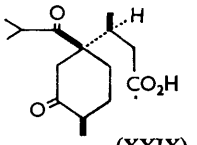
(XXVI)



(XXVII)



(XXVIII)



(XXIX)

The enol acetate (XXII), prepared from acoric acid by the method used for the ester, had $\nu_{max.}$ (in CS_2) 1750, 1721, and 1695 cm.$^{-1}$. It is neutral, as is its acid hydrolysate (XXIII) [$\nu_{max.}$ (in CCl_4) 1718 and 1693 cm.$^{-1}$], and both compounds contain two quaternary methyl groups, as shown by their p.m.r. spectra. The structure (XIX) can therefore be expanded to (XXIV).

No decision could be reached about the possible quaternary nature of methyl groups in other compounds because of the complexity of the methyl region of the p.m.r. spectra, although four methyl groups are undoubtedly present. The spectra of the enol acetates (XXI) and (XXII) rule out the possibility of any ethyl group being present, and there is a strong indication, from the lactone (XVIII) in particular, that the simple derivatives of acoric acid do not contain a quaternary methyl group.

With these further restrictions only two probable structures for acoric acid remain: (I) and (XXV). It was immediately clear that (I) should be obtainable from acorone (XXVI), a known [2] constituent of *Acorus calamus*, by oxidation with oxygen in the presence of potassium t-butoxide, if the cyclohexanone group could be protected. The mixture of acorone and its stereoisomer, isoacorone, obtained from acorone bis-semicarbazone [3] by the standard method,[4] yielded, with 1·1 mol. of hydroxylamine, a gum, in which the absorption at $\nu_{max.}$ 1710 cm.$^{-1}$, due to the cyclohexanone group, had disappeared. Oxidation of this gave, in 35% overall yield, acoric acid oxime, identified by infrared spectrum and mixed m. p. Hydrolysis of the oxime with oxalic acid yielded acoric acid itself.

Stereochemistry.—The absolute configuration of acorone has recently [5] been shown to be as in (XXVI). There is no possibility of inversion of the quaternary centre during conversion into acoric acid, but the centre next to the ring-carbonyl might have been epimerised. The methyl group here must be equatorial, however, since acoric acid is the more stable isomer, showing no tendency to epimerise in a number of reactions involving acid or base. Assuming that the more bulky acid side-chain occupies an equatorial position in a chair ring, acoric acid has the absolute configuration shown in (XXIX).

Biogenesis.—The proportion of acoric acid varies considerably from one sample of root to another. It is questionable whether it is a genuine biosynthetic product or an autoxidation product, but in either case it is clearly derived by oxidative fission of the five-membered ring of acorone in a manner similar to that described above.

Experimental

Ultraviolet spectra were measured for ethanol solutions. Light petroleum had b. p. 40—60°. M. p.s are uncorrected.

Isolation of Acoric Acid.—Ground root of *Acorus calamus* L. (10 kg.) was extracted with ether (percolations total *ca.* 40 l.) for 12 hr., the extract evaporated to 2 l., extracted with 10% potassium hydrogen carbonate solution (3 × 500 ml.), and the aqueous extract carefully acidified with 10N-hydrochloric acid. Re-extraction into ether (3 × 300 ml.), evaporation of almost all the solvent, and addition of carbon tetrachloride (50 ml.) to the residue (*ca.* 50 ml.) gave crude acoric acid (8·4 g.). Several further crops (total 3·2 g.) were obtained from the mother-liquors. Two crystallisations from ether–light petroleum gave pure *acoric acid* (9·7 g.), m. p. 166—168°, $[\alpha]_D^{25}$ +27° (*c* 1·0 in $CHCl_3$), p*K* 5·65 (Found: C, 67·1; H, 9·1%; Equiv. 269. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%; *M* 268), $\lambda_{max.}$ 290 mμ (ε 45) and $\nu_{max.}$ (in Nujol) 3500—2400, 1725, 1702, and 1690 cm.$^{-1}$.

Acoric acid yielded a *monosemicarbazone*, prisms, m. p. 229—233° (decomp.) (from aqueous methanol) (Found: C, 59·4; H, 8·4; N, 13·6. $C_{16}H_{27}N_3O_4$ requires C, 59·1; H, 8·4; N, 12·9%), and a *mono-oxime*, prisms, m. p. 205—207° (decomp.) (from aqueous methanol) (Found: C, 63·4; H, 8·6. $C_{15}H_{25}NO_4$ requires C, 63·6; H, 8·9%).

Reaction of acoric acid with ethereal diazomethane or with N-methanolic hydrochloric acid yielded *methyl acorate* as a colourless oil, b. p. 150°/0·1 mm., $\nu_{max.}$ (in CS_2) 1738, 1715, and 1700 cm.$^{-1}$ (Found: C, 67·7; H, 9·2. $C_{16}H_{26}O_4$ requires C, 68·0; H, 9·3%). Methyl acorate gave a *mono-oxime*, needles, m. p. 110—111° (from aqueous methanol) (Found: C, 64·3; H, 9·5; N, 5·3. $C_{16}H_{27}NO_4$ requires C, 64·6; H, 9·1; N, 4·7%). This compound was also obtained by treatment of the mono-oxime of acoric acid with ethereal diazomethane.

Hydrogenation of Acoric Acid.—(*a*) Acoric acid (250 mg.) was shaken with 10% palladium–carbon (50 mg.) in methanol (25 ml.) under hydrogen for 4 hr. No uptake was observed. 10N-Hydrochloric acid (2 ml.) was added and the mixture was shaken under hydrogen for 4 hr. Again no uptake occurred, and acoric acid was recovered from the solution.

(*b*) Acoric acid (200 mg.) and Adams catalyst (150 mg.) were shaken under hydrogen in

[2] Sýkora, Herout, Pliva, and Šorm, *Chem. and Ind.*, 1956, 1231.
[3] Šorm and Herout, *Coll. Czech. Chem. Comm.*, 1948, **13**, 202.
[4] Šorm and Herout, *Coll. Czech. Chem. Comm.*, 1949, **14**, 753.
[5] Vrkoč, Herout, and Šorm, XIXth International Congress of Pure and Applied Chemistry, London, 1963, Abstracts A, p. 320.

glacial acetic acid (15 ml.). Uptake ceased after 2 mol. of hydrogen had been absorbed. The mixture was filtered and the acetic acid evaporated, to give the *acid* (II) as plates (165 mg.), m. p. 181—182° from ether–light petroleum, $\nu_{max.}$ (in Nujol) 3500—2400 and 1715 cm.$^{-1}$ (Found: C, 70·7; H, 10·1. $C_{15}H_{26}O_3$ requires C, 70·8; H, 10·3%).

Hydride Reductions of Acoric Acid.—(*a*) Acoric acid (500 mg.) was refluxed for 3·5 hr. with lithium aluminium hydride (500 mg.) in dry tetrahydrofuran (10 ml.) and dry ether (50 ml.), and left overnight at room temperature. Working up in the standard manner gave a gummy solid (485 mg.) which yielded the triol (V) as a *benzene solvate*, needles, m. p. 156—157° (from benzene), $\nu_{max.}$ (in Nujol) 3300 cm.$^{-1}$ [Found: C, 73·7; H, 11·4; active H (by acetylation), 1·32. $C_{15}H_{30}O_3$,0·67C_6H_6 requires C, 73·5; H, 11·0; active H, 1·9%]. Sublimation of the solvate at 150°/0·1 mm. yielded the pure *triol*, m. p. 158—160° (Found: C, 69·4; H, 11·8. $C_{15}H_{30}O_3$ requires C, 69·7; H, 11·7%).

(*b*) Acoric acid (200 mg.) was refluxed with potassium borohydride (200 mg.) in methanol (20 ml.) for 2 hr. The mixture was diluted with water, acidified with 2N-sulphuric acid, and left at room temperature for 30 min. The crystalline precipitate was extracted with ether, and the extract washed with aqueous sodium carbonate solution, dried, and evaporated to a crystalline residue (185 mg.) which gave the *lactone* (VII) as needles, m. p. 126° (from ether–light petroleum), $\nu_{max.}$ (in Nujol) 1718 cm.$^{-1}$, and a pattern of peaks about 940 cm.$^{-1}$ (Found: C, 71·4; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

The Monoketonic Acid (III).—Acoric acid semicarbazone (700 mg.), potassium hydroxide (1 g.), and diethylene glycol (5 ml.) were heated at 150° for 20 min., and then at 200° for 2 hr. The cooled mixture was diluted with water (20 ml.), washed with ether, and acidified with 2N-hydrochloric acid. The crude product (370 mg.) was an oil, $\nu_{max.}$ (in CS_2) 3500—2400 and 1700 cm.$^{-1}$. Treatment with diazomethane gave a *methyl ester* which was chromatographed on neutral alumina in light petroleum, to give a colourless oil, $\nu_{max.}$ (in CS_2) 1735 and 1696 cm.$^{-1}$ (Found: C, 71·3; H, 10·7. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%).

The acid (III) (150 mg.) was dissolved in liquid ammonia (25 ml.) and ethanol (1 ml.), and lithium added in thin slices to keep the solution blue for 1 hr. The ammonia was evaporated and the residue was taken up into 2N-sulphuric acid and left for 30 min. The product was extracted into ether, and the extract washed with aqueous potassium hydrogen carbonate and evaporated, to give the *lactone* (IV) as a colourless oil (135 mg.), $\nu_{max.}$ (in CS_2) 1740 cm.$^{-1}$ (Found: C, 74·6; H, 10·7. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%).

Reactions of the Triol (V).—(*a*) The triol (100 mg.) was treated overnight at room temperature with acetic anhydride (0·5 ml.) and pyridine (0·5 ml.). The mixture was diluted with water, extracted with ether, and the extract dried and evaporated, to give the oily *diacetate*, $\nu_{max.}$ (in CS_2) 3475 and 1730 cm.$^{-1}$ (Found: C, 66·9; H, 10·2; OAc, 22·9. $C_{19}H_{34}O_5$ requires C, 66·6; H, 10·0; 2OAc, 24·6%). Oxidation of the ester (55 mg.) with chromic acid in acetone (3 ml.) gave, after dilution with water and ether extraction, another oil (53 mg.), $\nu_{max.}$ (in CS_2) 1734 and 1695 cm.$^{-1}$.

(*b*) The triol (120 mg.) was oxidised by chromic acid in acetone (4 ml.) in the usual way. Dilution of the mixture with water (10 ml.), and washing of the ether extract with aqueous potassium hydrogen carbonate, yielded a neutral fraction (75 mg.) which gave the *keto-lactone* (VI), prisms (40 mg.), m. p. 128—129° (from ether–light petroleum), $\nu_{max.}$ (in CS_2) 1740 and 1713 cm.$^{-1}$ (Found: C, 71·7; H, 10·1. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

The Hydroxy-keto-ester (VIII).—Methyl acorate (200 mg.) was refluxed with potassium borohydride (200 mg.) in methanol (10 ml.). Working up in the usual way gave the hydroxy-keto-ester (VIII) as a viscous oil (200 mg.), $\nu_{max.}$ (in CCl_4) 3450, 1735, and 1683 cm.$^{-1}$. The ester (80 mg.) was refluxed in methanol (3 ml.) with potassium hydroxide (50 mg.) for 1 hr. Dilution with water, acidification with 2N-hydrochloric acid, extraction with ether, and evaporation of the ether extract gave a solid product (80 mg.) which yielded the lactone (VII) (65 mg.) as needles, m. p. 125—126° (from ether–light petroleum), identified by infrared spectrum and mixed m. p.

The lactone (VII) (110 mg.) was refluxed in methanol (10 ml.) containing sodium (200 mg.) for 2 hr. The mixture was diluted with water and acidified as previously. Ether extraction and evaporation of the extract gave a viscous oil (105 mg.) whose infrared spectrum [$\nu_{max.}$ (in CCl_4) 3475, 1730, and 1686 cm.$^{-1}$] indicated it to be a mixture of the lactone (VII) and the hydroxy-keto-ester (VIII).

Aldol Reactions.—(*a*) Acoric acid (250 mg.) was refluxed with 5N-aqueous potassium

hydroxide (25 ml.) for 4 hr. After cooling, the mixture was acidified with 2N-sulphuric acid, saturated with sodium chloride, and extracted with ether. Evaporation of the extract gave a solid residue (230 mg.) which yielded the *acid* (X) as needles (155 mg.), m. p. 163—165° (from ether–light petroleum), $\nu_{max.}$ (in Nujol) 3500—2400, 3420, 1725, and 1700 cm.$^{-1}$ (Found: C, 67·2; H, 8·9. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%). Its methyl ester, prepared by the action of diazomethane, was an oil, $\nu_{max.}$ (in CCl_4) 3630 and 1735 cm.$^{-1}$.

(*b*) Acoric acid (250 mg.) was refluxed in N-aqueous potassium hydroxide (25 ml.) for 2 hr. Working up as in (*a*) yielded a gummy residue (235 mg.) which gave needles (145 mg.), m. p. 175—185° (from ether–light petroleum). After two crystallisations, the *acid* (IX) had m. p. 191—194, $\nu_{max.}$ 3500—2400, 3350, 1723, and 1712 cm.$^{-1}$ (Found: C, 67·0; H, 8·9. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%). Its oily methyl ester had $\nu_{max.}$ (in CCl_4) 3630 and 1738 cm.$^{-1}$. Seeding of the mother-liquors with the acid (X) yielded needles of the acid (50 mg.), m. p. 158—164°, identified by infrared spectrum and mixed m. p.

Further crystallisation by seeding with acoric acid produced prisms (25 mg.) m. p. 153—162°, shown by infrared spectroscopy to be impure acoric acid.

The acid (IX) (20 mg.) was recovered unchanged after being refluxed with toluene-*p*-sulphonic acid (10 mg.) in benzene for 3 hr.

The Dihydroxy-acids.—(*a*) The acid (X) (175 mg.), in liquid ammonia (25 ml.) and ethanol (1 ml.), was treated with lithium during 1 hr. The ammonia was evaporated and the residue taken up into water and acidified, to give a crystalline precipitate, m. p. 226—232°. Recrystallisation from aqueous methanol gave the *dihydroxy-acid* (XII) as small prisms (135 mg.), m. p. 234—238° (decomp.), $\nu_{max.}$ (in Nujol) 3500—2400, 3350, and 1722 cm.$^{-1}$ (Found: C, 65·7; H, 10·0. $C_{15}H_{26}O_4$ requires C, 66·6; H, 9·7%).

The acid (XII) (75 mg.) was refluxed in benzene (10 ml.) containing toluene-*p*-sulphonic acid (10 mg.) for 1 hr. The mixture was washed with potassium carbonate solution and evaporated, to give the *lactone* (XIII) as long needles (60 mg.), m. p. 150—151° (from ether–light petroleum), $\nu_{max.}$ (in CS_2) 3620, 1752, and 1740 cm.$^{-1}$ (Found: C, 71·1; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). Hydrolysis of the lactone (XIII) (30 mg.) with N-methanolic potassium hydroxide (5 ml.) yielded, after working up in the normal way, the dihydroxy-acid (XII) (25 mg.) identified by mixed m. p.

(*b*) The acid (IX) (150 mg.) was treated with lithium and ethanol in liquid ammonia as in (*a*). Ether extraction of the acidified residue and evaporation of the extract gave a gum (145 mg.) which crystallised as very fine needles from carbon tetrachloride containing a trace of ether. The *dihydroxy-acid* (XI) (125 mg.) had m. p. 156—158°, $\nu_{max.}$ (in Nujol) 3500—2400, 3500, 3425, 1720, and 1695sh cm.$^{-1}$ (Found: C, 66·4; H, 9·9. $C_{15}H_{26}O_4$ requires C, 66·6; H, 9·7%).

The acid (XI) (50 mg.) was treated with toluene-*p*-sulphonic acid as in (*a*). A *lactone* was obtained as prisms (40 mg.), m. p. 216—217° (subl.) (from ether–light petroleum), $\nu_{max.}$ (in Nujol) 3475, 1720, and 1710sh cm.$^{-1}$ (Found: C, 70·6; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The lactone (20 mg.) was recovered unchanged (infrared spectrum and mixed m. p. after treatment with chromic acid in acetone for 20 min.

The Trione (XV).—Methyl acorate (225 mg.) was refluxed in methanol (15 ml.) containing dissolved sodium (100 mg.) for 1 hr. The solution was diluted with water, washed with ether, and acidified. The ether extract contained unchanged methyl acorate (35 mg.), identified by its infrared spectrum. The acidified mixture was extracted with ether and the extract washed with potassium hydrogen carbonate solution, dried, and evaporated, to give the trione (XV) as an oil (160 mg.), $\nu_{max.}$ (in CCl_4) 1742, 1697, 1675, and 1615 cm.$^{-1}$, $\lambda_{max.}$ (neutral) 281 mμ (ε 9000), $\lambda_{max.}$ (alkaline) 308 mμ (ε 19,000).

The trione (XV) (55 mg.) was warmed in methanol (2 ml.) with saturated aqueous cupric acetate (0·5 ml.) on a steam-bath for 5 min. Dilution of the dark green solution with water yielded, on cooling, the *cupric salt*, olive-green needles (55 mg.), m. p. 222—223° (decomp.), $\nu_{max.}$ (in Nujol) 1687, 1595, and 1500 cm.$^{-1}$ (Found: C, 64·1; H, 8·0. $C_{30}H_{42}CuO_6$ requires C, 64·1; H, 7·5%).

Formylation Reactions.—(*a*) The lactone (VII) (320 mg.) was treated overnight with sodium methoxide (500 mg.) in dry ethyl formate (5 ml.). The mixture was poured into ice-cold water, rapidly washed with ether, and acidified. The ether extract contained unchanged lactone (15 mg.). After 30 min. the crystalline precipitate which had formed in the acidified mixture was filtered off, to give the *acid* (XVII) as plates (280 mg.), m. p. 207—209° (from ether–light

petroleum), $\nu_{max.}$ (in Nujol) 3500—2400, 1657, and 1625 cm.$^{-1}$, $\lambda_{max.}$ 237 mμ (ε 11,000) (Found: C, 68·7; H, 8·5. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%).

Its methyl ester, an oil, made with ethereal diazomethane, had $\nu_{max.}$ (in CCl_4) 1703 and 1627 cm.$^{-1}$, $\lambda_{max.}$ 237 mμ (ε 11,000).

(*b*) The lactone (IV) (120 mg.) was formylated as in (*a*), to give a gum (125 mg.). The formyl lactone (XXVII) was totally insoluble in potassium hydrogen carbonate solution and had $\nu_{max.}$ (in CS_2) 1655 and 1613 cm.$^{-1}$, $\lambda_{max.}$ (neutral) 253 mμ (ε 9200), $\lambda_{max.}$ (alkaline) 287 mμ (ε 18,000). It gave a very intense violet colour with ferric chloride.

Ozonolysis of the Acid (XVII).—The acid (XVII) (110 mg.) was ozonised for 1 hr. at room temperature in ethyl acetate (10 ml.). Unreacted ozone was removed, and the solution was warmed and shaken with water (2 ml.) to decompose the ozonide. The ethyl acetate was evaporated and the aqueous residue warmed on a steam-bath for 30 min. with 2N-aqueous potassium hydroxide (10 ml.). After cooling, hydrogen peroxide (100 vol.; 3 ml.) was added to the solution and the mixture left overnight. After acidification, the mixture was left for 30 min. and then extracted with ether–light petroleum. The extract was washed with aqueous potassium carbonate, dried, and evaporated, to give a neutral fraction which yielded the *nor-lactone* (XVIII) as needles (38 mg.), m. p. 74—76° (from aqueous methanol), $\nu_{max.}$ (in CS_2) 1774 cm.$^{-1}$ and a pattern of bands near 930 cm.$^{-1}$ (Found: C, 70·2; H, 9·6. $C_{11}H_{22}O_3$ requires C, 70·6; H, 9·3%).

Enol-acetylation Reactions.—(*a*) Acoric acid (600 mg.) was left overnight with toluene-*p*-sulphonic acid (30 mg.) in acetic acid (3 ml.) and acetic anhydride (3 ml.). The mixture was concentrated under a vacuum, diluted with water, and extracted with ether, and the extract washed with potassium hydrogen carbonate solution and evaporated. The solid residue (580 mg.) gave the *enol acetate* (XXII) as needles, m. p. 112—113° (from ether–light petroleum), $\nu_{max.}$ (in CS_2) 1750, 1721, and 1695 cm.$^{-1}$ (Found: C, 69·6; H, 8·2. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·2%).

The enol acetate (XXII) (100 mg.) was refluxed in acetone (3 ml.) containing 10N-hydrochloric acid (0·3 ml.) for 1 hr. Dilution with water, ether extraction, and evaporation gave the *trione* (XXIII) (90 mg.) as needles, m. p. 98—99° (from light petroleum), $\nu_{max.}$ (in CS_2) 1718 and 1693 cm.$^{-1}$ (Found: C, 71·7; H, 8·6. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%).

(*b*) Methyl acorate (500 mg.) was acetylated and worked up as in (*a*), to give the enol acetate (XXI) as an oil (520 mg.), $\nu_{max.}$ (in CCl_4) 1737 and 1698 cm.$^{-1}$. Its p.m.r. spectrum, in particular three proton peaks, at τ 6·40 (methyl ester) and τ 7·91 (acetate), and a quintuplet at τ 6·80 (J = 6·8 c./sec.), was in good agreement with the expected structure. The enol acetate (XXI) (125 mg.) was refluxed with N-methanolic hydrochloric acid for 1 hr. Dilution with water, ether extraction, and evaporation gave methyl acorate (110 mg.), identified by its infrared spectrum.

The enol acetate (XXI) (325 mg.) was ozonised in ethyl acetate (10 ml.) for 1 hr. After removal of unused ozone, water was added to the solution, and the mixture was shaken and warmed for 15 min., and evaporated to dryness. 2N-Aqueous sodium hydroxide was added to the residue, and the mixture was boiled for 30 min. After acidification, the mixture, saturated with sodium chloride, was extracted with ether, and the extract evaporated, to yield the crude gummy diketo-diacid (XX) (340 mg.) which was partly purified by solution in ether, addition of light petroleum, and filtration. The acid thus obtained (295 mg.) had Equiv. 143. [Calc. for $C_{13}H_{22}O_2(CO_2H)_2$: Equiv., 150].

Esterification of the crude acid with ethereal diazomethane and chromatography on neutral alumina in light petroleum–ether gave a fraction (255 mg.), $\nu_{max.}$ (in CCl_4) 1740, 1719, and 1702 cm.$^{-1}$. The oxime obtained from this ester had $\nu_{max.}$ (in CS_2) 3625, 1740, and 1701, $\nu_{min.}$ 1715 cm.$^{-1}$, and, like the 2,4-dinitrophenylhydrazone of the ester, was oily. The diketo-diacid itself gave an oxime which failed to crystallise. The diacid (30 mg.) with iodine in aqueous alkaline potassium iodide, gave iodoform (23 mg.), m. p. 116—118°.

(*c*) Acoric acid (225 mg.) was refluxed with sodium acetate (1 g.) in acetic anhydride (7 ml.) for 4 hr. The cooled mixture was taken up into water (10 ml.) and ether (20 ml.), and the ether layer washed with potassium hydrogen carbonate solution and evaporated, eventually at 0·1 mm· to remove all the acetic anhydride. The product crystallised very slowly, and, after two crystallisations from light petroleum at 0°, the diacetate (XXVIII) (135 mg.) was obtained as needles, m. p. 82—88°, not improved by further recrystallisation, $\nu_{max.}$ (in CCl_4) 1756, 1703sh, and 1692 cm.$^{-1}$. It decomposed at room temperature within 3 days to a gum smelling strongly

of acetic anhydride; hence it could not be satisfactorily analysed. Its p.m.r. spectrum showed peaks at τ 7·85 and 7·86 (two acetoxy-groups) and was, as a whole, in accord with the postulated structure.

The diacetate (XXVIII) was refluxed with N-methanolic hydrochloric acid for 1 hr. Dilution with water, and ether extraction gave an oil (60 mg.), of which 35 mg. was soluble in potassium carbonate solution and was shown by infrared and ultraviolet spectra of itself and of its copper salt, m. p. 222—223°, to be the trione (XV). The infrared spectrum of the neutral fraction (25 mg.) was identical with that of methyl acorate.

Oxidation of Acoric Acid.—Acoric acid (250 mg.) was shaken under oxygen with N-potassium t-butoxide in t-butyl alcohol (10 ml.). After uptake of 1·1 mol. of oxygen in 3 min., absorption became relatively slow, and the reaction was stopped. The mixture was acidified with 2N-hydrochloric acid, saturated with sodium chloride, and extracted with ether. Evaporation of the extract gave the diketo-diacid (XX) as a gum (280 mg.), Equiv. 162. [Calc. for $C_{13}H_{22}O_2(CO_2H)_2$: Equiv., 150].

The acid closely resembled that derived from the enol acetate (XXI), above. The acid (45 mg.) yielded iodoform (35 mg.), m. p. 116—118°, on treatment with iodine in aqueous alkaline potassium iodide. Crystallisation of its oxime yielded a small amount (approx. 5%) of acoric acid oxime, m. p. 202—206°.

Acoric Acid Oxime from Acorone.—The neutral fraction of the extract of the root of *Acorus calamus* L. (above) (100 g.) was extracted with Girard reagent T in the usual way, to give a ketonic fraction (6·8 g.). After treatment of this with semicarbazide hydrochloride (5 g.) in pyridine (15 ml.) for 5 days, acorone bis-semicarbazone was obtained (750 mg.), m. p. 202—205° (from aqueous methanol) (lit.,[3] 205—207°). The bis-semicarbazone (570 mg.) was hydrolysed in the usual way, to yield an oil (335 mg.), $\nu_{max.}$ (film) 1735 and 1713 cm.$^{-1}$, presumably the 2 : 1 mixture of acorone and isoacorone similarly obtained by Šorm and Herout.[4] The oil (330 mg.) was refluxed in ethanol (5 ml.) with pyridine (1 ml.) and hydroxylamine hydrochloride (110 mg., 1·1 mole). On working up in the usual way, a gum was obtained (360 mg.), $\nu_{max.}$ (in CS_2) 3625, 3325, and 1740, with no absorption at 1715 cm.$^{-1}$. This material was treated with oxygen and N-potassium t-butoxide in t-butyl alcohol as for acoric acid, above. After uptake of 0·7 mol. in 10 min. absorption became slow and the reaction was stopped. After acidification with acetic acid and dilution with aqueous sodium chloride, the mixture was extracted with ether, to give a gum (200 mg.) which yielded acoric acid oxime (105 mg.), m. p. 203—206° (from aqueous methanol), identified by mixed m. p. and infrared spectrum. Hydrolysis of the oxime in the usual way produced acoric acid, also identified by mixed m. p. and infrared spectrum.

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