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SOME KETONES FROM *ACRADENIA FRANKLINII*

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Abstract—Four ketones, of which two had not previously been recorded in Nature, have been isolated from leaves and bark of *Acradenia franklinii*. The three simpler ones proved to be methylxanthoxylin, I (R = Me), a homologue of a naturally occurring phloroglucinol derivative, and the chromenes O-methylalloevodionol[1] (II) and O-methylevodionol[1] (III). For the fourth, the name franklinone and the pyrano-chromene structure IV are proposed. The biogenesis of these and related compounds is discussed.

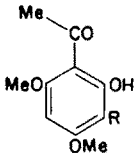
Acradenia franklinii (Kippist) grows in the rain-forest areas of the west coast of Tasmania as an endemic shrub or small tree. It was initially examined in the course of a survey for alkaloids of Australian rutaceous plants, from certain species of which a group of acridone alkaloids had been isolated.[2] No alkaloids could be detected in bark or leaf samples of the plant, but chromatography of an extract on alumina yielded two crystalline substances, A, m.p. 128°, and B, m.p. 108°. The small quantities available were sufficient to show that both were ketones, formed derivatives with Girard's reagent, and were steam volatile. A larger quantity of plant material was accordingly collected and steam-distilled. However, extraction of the essential oil with Girard's reagent gave a low recovery of the ketones, and better yields were obtained by fractional distillation, countercurrent distribution, or chromatography of the oil on alumina. In the course of the isolation of ketones A and B, two further ketones C, m.p. 143°, and D, m.p. 78–79°, were obtained.

The simplest of these compounds, (C) $C_{11}H_{14}O_4$, was very pale yellow and had two methoxyls, two C-methyl groups, and one carbonyl, which apparently was present as a methyl ketone since the compound gave an iodoform reaction. It also gave a ferric chloride test and dissolved in alkali, so that the remaining oxygen was presumably present in a phenolic group. Thus all the oxygen and carbon atoms could be accounted for assuming a benzene nucleus with a methyl, a hydroxy and a methylketo substituent, and two methoxyls. The ultra-violet spectrum agreed with this, and moreover indicated that the carbonyl was *ortho* to the phenolic group; the infrared-spectrum also gave strong evidence of "conjugate chelation."

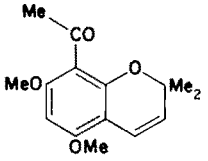
Possible structures for C could be written with either a pyrogallol or a phloroglucinol arrangement of the oxy substituents, but the latter would seem more likely since a side-chain in natural pyrogallols usually occurs at the 5 rather than the 4 position. Of the two positions remaining for the nuclear methyl group the one *para* to the hydroxyl can be eliminated since C gives a test with Gibb's reagent; thus a likely structure for C is I (R = Me). A substance with this structure does not seem to have

[1] T. G. H. Jones and S. E. Wright, *Pap. Dept. Chem. Univ. Q'ld.* 1, No. 27 (1946); M. D. Sutherland, *Ibid.* No. 35 (1949).
[2] J. R. Price, in Manske and Holmes, *The Alkaloids* Vol. II, p. 333. Academic Press, New York (1952).

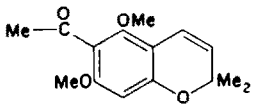
been found previously in Nature, although the homologous substance lacking the nuclear methyl group, xanthoxylin, I (R = H), does occur naturally.[3] However, the compound I (R = Me) has been prepared synthetically,[4] and the recorded properties, except for lack of colour, agreed well with those of compound C. A comparison sample, synthesized by one of the methods previously described,[4] proved identical with C in colour, m.p., mixed m.p. and infra-red spectrum.



I

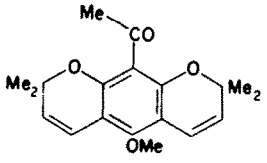


II

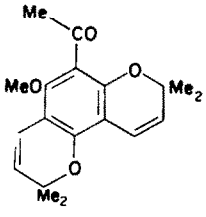


III

Compound B, $C_{15}H_{18}O_4$, had two methoxyls and one carbonyl, which also appeared to be in a methyl ketone group. A Kuhn–Roth determination gave about 1·5 C-methyl groups. The remaining oxygen was inert and presumably in an ether linkage. From its reaction with bromine and its uptake on hydrogenation, B had one double bond, and from the foregoing data would appear to have two rings of which one is aromatic. The evidence pointed to a chromene type of structure, which was supported by the orange-red colour given with concentrated sulphuric acid, and by the ultra-violet spectrum. The compound was finally found to be identical with O-methylalloevodionol, isolated previously from a Queensland rutaceous plant[1] and shown to have structure II. Compound D, of which only a very small amount was obtained, proved



IV



V

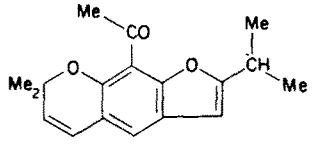
identical with the isomeric chromene O-methylevodionol (III) which occurs in a related Queensland plant.[1]

The remaining substance A, $C_{19}H_{22}O_4$, had one methoxyl, and one carbonyl which likewise appeared to be in a C-acetyl group. Kuhn–Roth determination gave rather over two C-methyl groups. A gave a dibromide, and on catalytic hydrogenation added on two moles of hydrogen. This evidence pointed to a structure with two double bonds and three rings, one of which is aromatic. There are two inert oxygens, which presumably are in ring ether links. Like the chromenes, compound A gave a bright cherry-red colour with concentrated sulphuric acid. A structure such as IV or V with an extra pyran ring fused to a chromene nucleus, would be consistent with these data, and also with the ultra-violet and infra-red spectra. In the latter there are two peaks in the 1300 cm^{-1} region corresponding to *gem* dimethyls, and also two peaks at 1632 and 1643 cm^{-1} respectively, which indicate two different olefinic bonds. This might be taken as

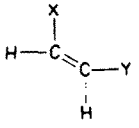
[3] W. Karrer, *Konstitution and Vorkommen der organischen Pflanzenstoffe* p. 181. Birkhaüser, Basel (1958).
[4] F. H. Curd and A. Robertson, *J. Chem. Soc.* 437 (1933).

favouring the unsymmetrical structure V rather than IV; however, structure IV is not completely symmetrical either, since the carbonyl group will tend to align itself in the plane of the aromatic ring. The data would be consistent with either of these structures or with one such as VI with one or even two furan rings.

A coumarone structure is, however, excluded by the NMR spectrum*, shown diagrammatically in Table 1. The spectrum consists of seven sharp peaks only, of which two prominent ones of equal intensity at 6·3 and 7·6 (τ scale) can be ascribed to the methoxyl and acetyl hydrogens respectively.

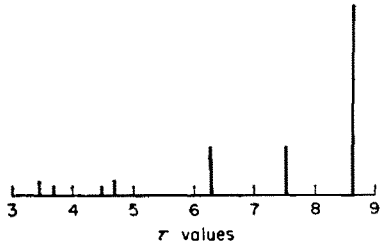


VI



VII

TABLE 1. NMR SPECTRUM OF FRANKLINONE (DIAGRAMMATIC)

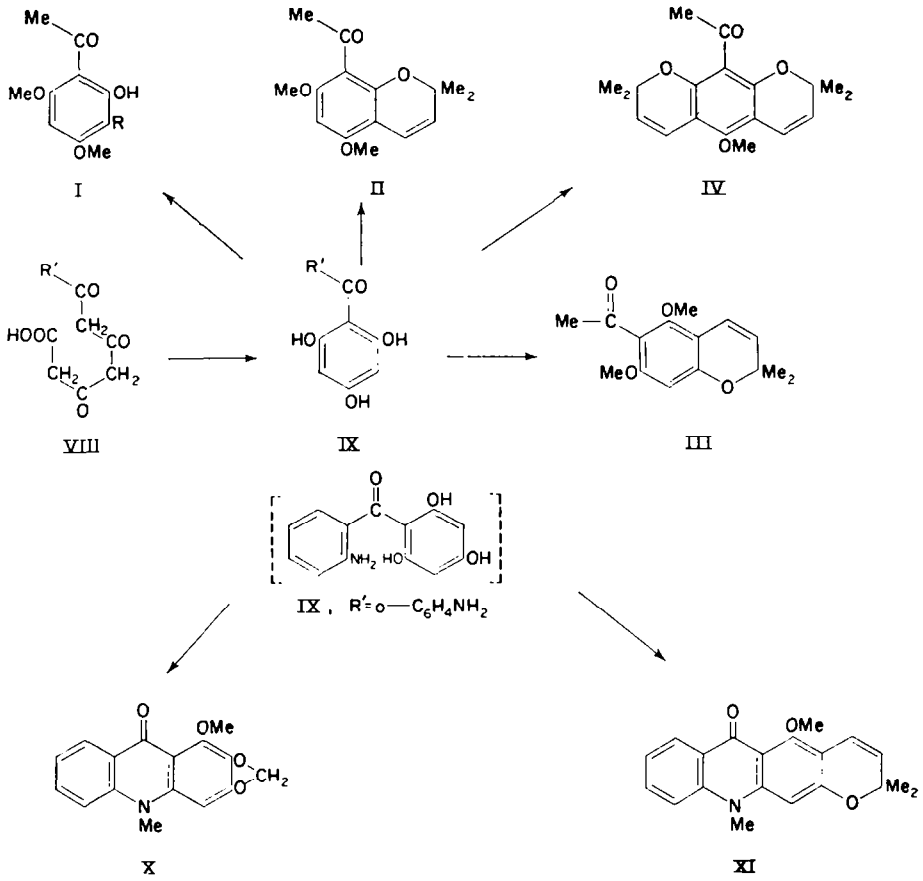


At one end of the spectrum, at 8·7, there is a very strong peak of about four times the intensity of the others, due to the two pairs of *gem* dimethyls. Any structure with an isopropyl group such as VI can be ruled out since it would show spin-spin splitting of the *gem* dimethyl peaks. The remaining peaks are much smaller and consist of two pairs of doublets between 3·6 and 4·7. This is the expected pattern for the group VII (X and Y are atoms to which no hydrogen is attached) and the fact that only one set of four sharp peaks is obtained indicates that the values for the hydrogens involved in the two unsaturated bonds must lie exactly on top of one another. This favours structure IV, in which under the conditions of the determination, the acetyl group could alternately assume each possible conformation in the plane of the ring, so that the spectrum obtained would be that of a completely symmetrical compound. We therefore put forward tentatively structure IV for compound A, for which we propose the name franklinone.

The formation of the three ketones in the plant is well accounted for by the polyacetate theory of biogenesis,[5] in which a chain formed from acetate units, VIII, cyclizes to give an acylphloroglucinol (IX). This yields methylxanthoxylin, I(R = Me) on methylation, in the course of which a nuclear methyl group is introduced; it is of

* The spectrum was obtained using a Varian Associates V-4300B spectrometer and 12″ electromagnet, at 40 Mc/s, with flux stabilization and sample spinning. The chemical shifts are quoted in parts per million on the silicon tetramethyl (τ) scale.

[5] A. J. Birch, *Fortschritte Chem. Org. Naturstoffe* **14**. 186 (1957).



interest to note that methylation of phloracetophenone, IX (R′ = Me), with methyl iodide gives I in good yield.[4] Substitution of a nuclear prenyl group instead of the methyl would lead to O-methylalloevodionol (II) or O-methylevodionol (III). Introduction of a second prenyl group would lead to the formation of franklinone (IV). The acridone types of alkaloid[2] evoxanthine (X) and acronycin, (XI) found in related plants are presumably formed similarly from precursors with a terminal anthranilate instead of an acetate residue[5] (XIII and IX; R′ = *o*-$C_6H_4NH_2$).

EXPERIMENTAL

Preliminary examination of Acradenia franklinii

Milled leaves (3·3 kg) were extracted with warm ethanol, and after removal of the solvent *in vacuo*, the extract was treated successively with hot water, hot aqueous hydrochloric acid (2%), aqueous sodium hydroxide (10%) and water. The aqueous and acid washings gave no tests for alkaloids. The residual extract was further treated with carbon tetrachloride, and the solution chromatographed on alumina. The oil obtained on evaporation of the eluate was redissolved in pet ether (60–80°) and rechromatographed on alumina. Evaporation of the eluate gave compound A (2·3 g). Further eluation with benzene–carbon tetrachloride (1:1) gave compound B (0·22 g).

Essential oil of Acradenia franklinii

Leaves and terminal branchlets (220 kg) collected at Corinna, W. Tasmania, were steam-distilled, the total yield of oil being 0·67%. Another batch collected at Lake Macquarie yielded 0·72% oil.

Isolation of ketones from essential oil

(a) *By extraction with Girard's reagent.* Acradenia oil (100 g) was refluxed with Girard's reagent P (15 g) in ethanolic acetic acid (400 ml of 10%) during 2 hr. The solution was cooled in a freezing mixture and poured into a solution of sodium carbonate (700 ml of 4%) containing crushed ice (3·5 kg). The mixture was extracted thoroughly with ether. The ethereal solution, dried with sodium sulphate, was evaporated. The residue (10·4 g) was dissolved in benzene and chromatographed on an alumina column. Elution with benzene gave compound A (0·69 g), which after recrystallization from pet ether (60–80°) had m.p. 127°. Elution with benzene–chloroform (1:1) gave compound B (0·08 g), m.p. 103–106°.

(b) *By fractional distillation.* Acradenia oil (584 g) was distilled through a short column at 1·0 mm press. From the fraction boiling between 100 and 130°, compound C (0·36 g) crystallized, which after recrystallization from pet ether (60–80°) had m.p. 143°.

(c) *By countercurrent distribution.* Acradenia oil (30 g) was submitted to a 50 cycle distribution between pet ether (40–60°) and aqueous methanol (90%) in a Craig machine. From fractions 20–40, compound A (0·8 g) separated, m.p. 120–128°.

(d) *By chromatography.* Acradenia oil in pet ether (20·2 g; 100 ml) was chromatographed on alumina. Elution with pet ether yielded a considerable liquid terpene fraction. Benzene removed compound A (0·4 g), m.p. 127°, and compound D (12 g), m.p. 78–79°. Elution with benzene–chloroform (1:1) gave compound B (0·1 g), m.p. 105°, with benzene–chloroform (1:3) compound C (20 mg), m.p. 142·5°. In other experiments the yield of compound A on chromatography was 2·7%, but little or no compound C or D was obtained.

Compound C (*methylxanthoxylin*). After recrystallization from pet ether (60–80°) compound C formed pale yellow needles, m.p. 143°. (Found: C, 62·9; H, 6·6; O, 30·0; MeO, 29·5; MeC, 12·8; M.W. (Rast) 215; Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7; O, 30·4; 2MeO, 29·5; 2MeC, 12·9%; M.W. 210), UV λ max 290 mμ (log ϵ 4·3). Compound C gave a 2,4-*dinitrophenylhydrazone* which crystallized from ethyl acetate in bright red needles, m.p. 275°. (Found: C, 52·2; H, 4·9; N, 14·3. $C_{17}H_{18}O_7N_4$ requires: C, 52·3; H, 4·6; N, 14·4%). C was insoluble in water but dissolved in dilute aqueous alkali. It gave an iodoform test, a purple brown test with ethanolic ferric chloride which was unaltered by addition of water, and a positive test with Gibb's reagent. I.R. max. *inter alia* 1629 and 1598 cm^{-1} (conjugated chelated carbonyl, hydroxy virtually absent). C was identical (mixed m.p. and I.R. spectrum) with a sample of 2-hydroxy-4,6-dimethoxy-3-methylacetophenone, synthesized as described by Curd and Robertson[4] by methylation of phloracetophenone with methyl iodide and potassium carbonate.

Compound B (O-*methylalloevodionol*). After recrystallization from pet ether (60–80°), compound B formed white prisms, m.p. 108°, $[\alpha]_D$ ±0° (Found: C, 69.0; H, 6·9; MeO, 24·1; MeC, 14·9; M.W. (Rast) 244; Calc. for $C_{15}H_{18}O_4$: C, 68·7; H, 6·9; 2MeO, 23·7; MeC 10·3%; M.W. 262), UV λ max 277 mμ (log ϵ 4·2), inflexion 220 mμ (log ϵ 4·1). I.R. max *inter alia* 1706, 1638, 1609, 1587, 1383, 1367 cm^{-1}. Compound B gave a 2,4-*dinitrophenylhydrazone*, red prisms from ethyl acetate, m.p. 187° (dec). (Found; C, 56·7; H, 5·1; N, 11·7. $C_{21}H_{22}O_7N_4$ requires: C, 57·0; H, 5·0; N, 12·7%). It also gave a yellow benzylidene derivative, m.p. 165° recrystallized from methanol. With conc sulphuric acid, compound C gave a bright orange-red colour. It decolorized a bromine–carbon tetrachloride solution and gave a bluish-purple nitroprusside reaction. The iodoform reaction was negative. On hydrogenation, using Adams catalyst, one mole of hydrogen was absorbed to give a dihydro compound, m.p. 81°. Compound B was identical (m.p. and mixed m.p., I.R. spectrum, m.p. and mixed m.p. of benzylidene derivatives) with an authentic specimen of O-methylalloevodionol.

Compound D (O-*methylevodionol*). After recrystallization from pet ether (40–60°) compound D had m.p. 78–79°, undepressed on admixture with an authentic sample of O-methylevodionol. The I.R. spectra (max *inter alia* 1697, 1634, 1607, 1572, 1385, 1366 cm^{-1}) were identical.

Compound A (*franklinone*). After recrystallization from pet ether (60–80°), *franklinone* formed colourless needles, m.p. 128–129°, $[\alpha]_D$ ±0. UV λ max 339 mμ (log ϵ 3·5) 262 mμ (log ϵ 4·7), 252 mμ (log ϵ 4·7), 220 mμ (log ϵ 4·0), I.R. *inter alia* 1704, 1643, 1632, 1390, 1365 cm^{-1}. (Found: C, 72·8; H, 7·3; O, 19·9; MeO, 9·9; MeC, 10·8; M.W. (Rast) 312. $C_{19}H_{22}O_4$ requires: C, 72·6; H, 7·0; O, 20·4; MeO, 9·9; MeC, 4·8%; M.W. 314). Franklinone gave a *dinitrophenylhydrazone*, m.p.-183–184°. (Found: C, 60·8; H, 5·3; N, 11·3. $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·4; N, 11·3%). With bromine in carbon tetrachloride, franklinone yielded a dibromo derivative with evolution of hydrogen bromide, m.p. 143°. On hydrogenation of franklinone with Adams catalyst, two moles of hydrogen

were absorbed and the product, *tetrahydrofranklinone*, after recrystallization from pet ether had m.p. 143°, UV λ max 274 (log ϵ 3·6). (Found: C, 72·0; H, 8·2; O, 20·2. $C_{19}H_{26}O_4$ requires: C, 71·7; H, 8·2; O, 21·1%). Franklinone gives a bluish purple nitroprusside reaction, and a bright cherry red colour with conc sulphuric acid. The iodoform reaction and the ferric chloride test were negative. Franklinone was recovered unchanged after boiling with aqueous potassium hydroxide (25%) for an hour.

Acknowledgments—We wish to thank Professor H. N. Barber and Dr. W. D. Jackson for assistance in collecting and identifying the plant material. Gifts of O-methylevodionol and O-methylalloevodionol and their derivatives from Dr. M. D. Sutherland are gratefully acknowledged. We also wish to express our thanks to Dr. R. L. Werner, and to Dr. N. Sheppard for their valuable assistance with I.R. and N.M.R. spectra respectively, and to Mr. P. Smith who carried out some of the chromatographic experiments.