852. *Studies in Relation to Biosynthesis. Part XXIII.*[1] *The Formation of Aromatic Compounds from β-Polyketones.*

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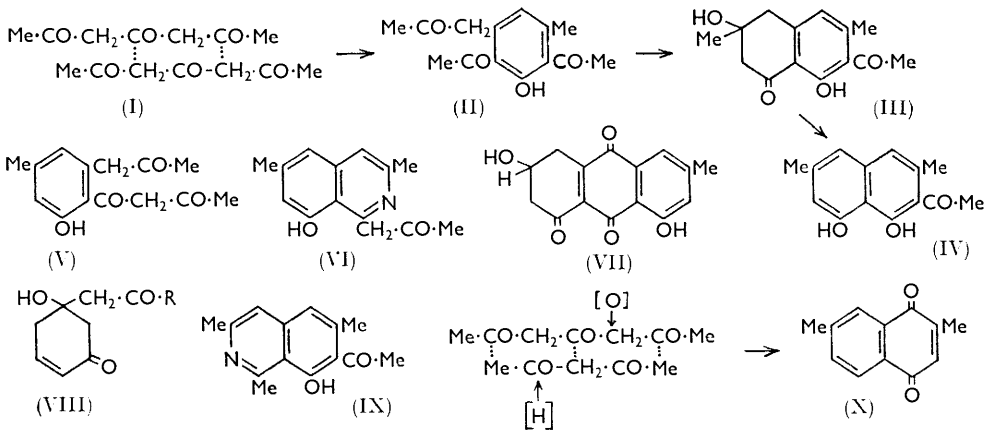
Intermolecular condensation of heptane-2,4,6-trione leads successively to compounds (II), (III), and (IV). 8-Phenyloct-7-ene-2,4,6-trione (XI; R = H) and its dihydro-derivative (XVI) have been synthesised. The latter can be cyclised to dihydropinosylvin (XVII).

Linear β-polyketones and analogous compounds, although not extensively investigated, have been shown to undergo condensation to more complex structures, some of which are related in type to substances found in Nature. The ease of some of these reactions led Collie[2] in 1907 to suggest that such compounds might be intermediates in some biosynthetic processes, and might be derived from acetic acid. Collie's views appear to have been ignored until the hypothesis was re-stated[3] on different grounds in 1953, since when the origins of a number of natural products from acetic acid units (presumably acetyl coenzyme-A) have been demonstrated by isotopic experiments.[4] No information is yet available to show whether β-polyketones are in fact intermediates. The hypothesis is attractive, however, and in order to assist eventual biochemical studies we have examined some aspects of the chemistry of such compounds.

[1] Part XXII, Birch and Kocor, *J.*, 1960, 866.
[2] Collie, *J.*, 1907, **91**, 1806.
[3] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360.
[4] See earlier papers in this series.

Two molecules of heptane-2,4,6-trione (I written in triketo-form for convenience) condense under weakly alkaline conditions [2,5] to form a yellow compound $C_{14}H_{14}O_3$, assigned [5] the structure (IV) without the rigorous proof which has since been provided.[6] In addition to the naphthalene (IV), Collie [2,5] obtained a substance (A), $C_{14}H_{16}O_4$, m. p. 137—138°, readily converted into compound (IV) by heat or by acid or alkaline conditions; for this he provisionally suggested structure (V). This formula we considered *a priori* to be unlikely because it involved reaction of a carbonyl group with the anion from –COMe in preference to the more readily formed anion from $-CO\cdot CH_2\cdot CO-$. Later,[7] he and Wilsmore obtained by a slightly modified procedure another similar substance (B), $C_{14}H_{16}O_4$, m. p. 108—109°, also readily convertible into compound (IV). Collie appears not to have distinguished clearly between (A) and (B) and in Beilstein's " Handbuch " [8] they are treated as identical. The action of ammonia on compound (B) gave a substance, $C_{14}H_{15}O_2N$, which was formulated as (VI).



The substances (A) and (B) were prepared by Collie's procedures from the barium salt of heptane-2,4,6-trione, the former by using just sufficient hydrochloric acid to dissolve the salt (resulting pH 7—8), the latter by dissolving it in aqueous acetic acid (resulting pH 6). They were found not to be identical. Examination of spectra led to the conclusion that compound (A) has structure (III) and that (B) has structure (II).

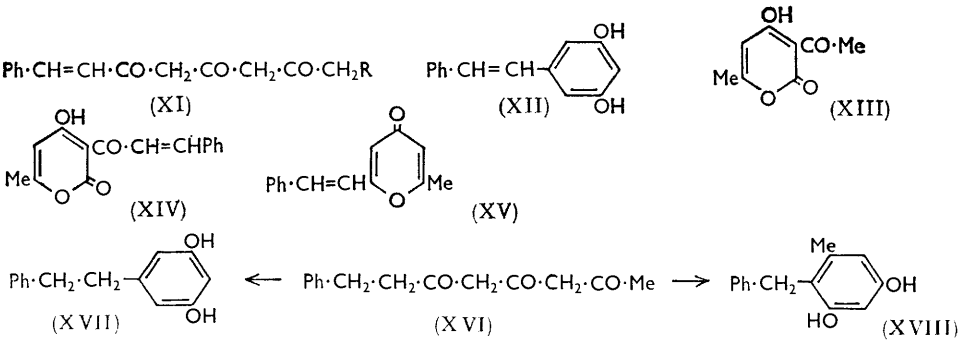
The ultraviolet spectra of the two compounds are similar: (A) $\lambda_{max.}$ 242, 264, and 336 mμ (log ε 4·22, 4·04, and 3·71); (B) $\lambda_{max.}$ 238·5, $264_{infl.}$, and 338 mμ (log ε 4·18, 3·93, and 3·58). These values are compatible with the structure of substituted diacylphenols [9] in which steric hindrance to conjugation [10] has lowered considerably the intensity of the maxima, and also the wavelengths. The infrared spectra (in Nujol) are quite distinct: (A) $\nu_{max.}$ 3479 (free OH), 1691 (aromatic C=O), and 1624 cm.$^{-1}$ (H-bonded aromatic C=O or aromatic C=C); (B) no maximum above 3000 cm.$^{-1}$ (no free OH), 1706 (aliphatic C=O), 1675 (aromatic C=O), and 1619 cm.$^{-1}$ (H-bonded aromatic C=O or aromatic C=C). Substance (A) (III) was less stable than (B) (II) and was converted into the naphthalene (IV) even by prolonged heating during recrystallisation. Natural compounds containing similar hydroxycyclohexenone structures, *e.g.*, (VII) [11] and (VIII; R·CO = oleoyl),[12] are readily aromatised by dehydration.

[5] Collie, *J.*, 1893, **63**, 122, 329.
[6] Dr. P. Maitland, personal communication.
[7] Collie and Wilsmore, *J.*, 1896, **69**, 293.
[8] Beilstein, " Handbuch der Organischen Chemie," Vol. I, p. 810.
[9] Burawoy and Chamberlain, *J.*, 1952, 2314.
[10] Braude and Sondheimer, *J.*, 1955, 3754.
[11] Shibata, Murakami, and Kitazawa, *Proc. Japan Acad.*, 1956, **32**, 356.
[12] Dalton and Lamberton, *Austral. J. Chem.*, 1958, **11**, 46.

Compounds (II) and (III) both reacted with ammonia, to give the same substance, $C_{14}H_{15}O_2N$, described by Collie. The absence of infrared carbonyl absorption above 1625 cm.$^{-1}$ makes Collie's formula (VI) extremely unlikely, and the substance is probably the isoquinoline (IX).

It is notable that the use of the sodium salt of heptane-2,4,6-trione gave only traces of compound (IV) instead of the 30% yield obtained from the barium salt. Collie and Wilsmore [7] observed that the barium salt, $Ba[Ba(C_7H_8O_3)_2]$, could be neutralised and dissolved by the addition of acid equivalent to only one atom of barium. The remaining atom probably covalently binds the bistrione complex and facilitates intermolecular condensation.

Chimaphilline [13] (X) from *Ericaceae* species is an example of a natural product which could arise by intermolecular condensation of this type between β-polyketones or polyketo-acids, although other biosynthetic routes can be visualised.



It was suggested [3] that the flavonoid constituents of pines could be correlated with the pinosylvin (XII) derivatives on the basis of a common origin from cinnamic acid and three acetate units through the intermediate (XI; R = CO_2H). Biogenetic considerations have aided considerably the synthesis of alkaloids, and their application to the synthesis of natural phenolic compounds is of interest. Collie [5] had observed the formation of orcinol, in poor yield, by intramolecular aldol cyclisation under strongly alkaline conditions of heptane-2,4,6-trione (I), and of the related 2,6-dimethyl-4-pyrone or dehydroacetic acid (XIII). We have synthesised 8-phenyloct-7-ene-2,4,6-trione (XI; R = H) which on cyclisation might be expected to yield pinosylvin itself. Condensation of benzaldehyde with dehydroacetic acid (XIII) in the presence of a Knoevenagel catalyst gave the benzylidene derivative (XIV) described also by Wiley *et al.*[14] This was hydrolysed and decarboxylated by acid to the pyrone (XV) which yielded the crystalline trione (XI; R = H) by way of its barium salt. However, paper chromatography [15] of the reaction mixtures obtained by treating this trione (XI; R = H) and compounds (XV) and (XIV) under a variety of alkaline conditions gave no indication of production of pinosylvin.

A closer analogy to Collie's conversion of the heptanetrione (I) into orcinol would be the cylisation of the trione (XVI) into dihydropinosylvin (XVII), of equal biosynthetic interest since this compound occurs with pinosylvin derivatives in pine heartwoods.[16] Attempted selective reduction of the benzylidene double bond in compounds (XI; R = H) and (XV) yielded mixtures from which only starting material could be isolated. However, the derivative (XIV) was readily hydrogenated catalytically [17] to the phenethyl ketone which was hydrolysed and decarboxylated to 2-methyl-6-phenethyl-4-pyrone. Comparison of the ultraviolet and infrared spectra of these compounds with those of

[13] Di Modica and Tira, *Gazzetta*, 1956, **86**, 234.
[14] Cf. Wiley, Jarboe, and Ellert, *J. Amer. Chem. Soc.*, 1955, **77**, 5102.
[15] Lindstedt, *Acta Chem. Scand.*, 1950, **4**, 448.
[16] Linstedt and Misiorny, *Acta Chem. Scand.*, 1951, **5**, 121.
[17] Walker, *J. Amer. Chem. Soc.*, 1956, **78**, 3201.

dehydroacetic acid and 2,6-dimethyl-4-pyrone, together with the production of β-phenylpropionic acid on alkaline hydrolysis, confirmed the assumption that reduction had occurred at the benzylidene double bond. Ring opening of the pyrone with barium hydroxide gave 8-phenyloctane-2,4,6-trione (XVI), a low-melting solid characterised as its crystalline di-enamine formed on condensation with pyrrolidine.

In basic conditions, ranging from hydrogen carbonate solution or tertiary organic bases to alkali fusion, both the β-triketone (XVI) and the corresponding pyrone cyclised to dihydropinosylvin (XVII), identified by paper-chromatography [15] (a spot R_F 0·11 coloured red by bisdiazotised benzidine spray). A second component (R_F 0·22, with a similar spray reaction) was invariably present, and under the milder conditions a further component (yellow spot, R_F 0·05) was detected. The former by-product (in agreement with its behaviour and similarity to dihydropinosylvin) almost certainly has structure (XVIII), produced by the alternative intramolecular aldol condensation of (XVI), while the latter is possibly a naphthalene derivative analogous to (IV).

Intramolecular cyclisation, competing with hydrolysis, appeared to be favoured under the more vigorous conditions. Alkali fusion of the pyrone [equivalent to (XVI) in these conditions] gave in 7% yield a mixture of phenols (XVII) and (XVIII) which was difficult to resolve. Bromination of the mixture yielded three substances separable by chromatography. Of these, one yielded dihydropinosylvin (XVII) on debromination [18] with Raney alloy and alkali; another yielded the isomer (XVIII); the third, a minor component, was not purified. The first bromo-derivative was identical (mixed m. p. and infrared spectrum) with a dibromo-derivative of authentic dihydropinosylvin. A polyketonic intermediate in the biogenesis of pinosylvin and its derivatives would probably retain the terminal carboxyl group, or a derivative thereof possibly with coenzyme-A, and cyclisation would be greatly assisted.

Experimental

Ultraviolet spectra were measured for EtOH solutions. Light petroleum refers to the fraction of b. p. 60—80°.

7-*Acetyl*-1,2,3,4-*tetrahydro*-3,8-*dihydroxy*-3,6-*dimethyl*-1-*oxonaphthalene* (III).—The barium salt of heptane-2,4,6-trione [5] (from 2,6-dimethylpyrone) (4 g.) was almost completely dissolved by careful addition of dilute hydrochloric acid. The lemon-yellow solution (pH 7—8) was filtered and left at 15°, the crystals which were deposited being collected daily for 3 days (1·2 g.). Crystallisation from benzene–light petroleum yielded the *ketone* (III) as almost colourless crystals, m. p. 137—137·5° (Found: C, 68·0; H, 6·5. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%), $\lambda_{max.}$ 242, 264, 336 mμ (log ε 4·22, 4·04, 3·71), $\nu_{max.}$ (in Nujol) 3479s, 1691s, 1624s cm.$^{-1}$.

The mother-liquors from crystallisation of ketone (III) gave bright yellow needles of 2-acetyl-1,8-dihydroxy-3,6-dimethylnaphthalene (IV), m. p. 180° (Found: C, 73·2; H, 6·2. Calc. for $C_{14}H_{14}O_3$: C, 73·1; H, 6·1%), $\lambda_{max.}$ 228, 261·5, 298, 306, 322, 340, 350 mμ (log ε 4·58, 4·34, 3·63, 3·64, 3·58, 3·66, 3·68), $\nu_{max.}$ (in Nujol) 1635s, 1600 (sh) cm.$^{-1}$.

3-*Acetonyl*-2,6-*diacetyl*-5-*methylphenol* (II).—To the barium salt [5] from dimethylpyrone (2 g.) was added 20% acetic acid (10 ml.), and the solution (pH 6) was filtered. After 4 days at 15°, the crystals were collected and recrystallised from benzene, to yield the *phenol* (II) (0·7 g.), m. p. 113° (Found: C, 67·7; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%), $\lambda_{max.}$ 238·5, 264 (infl.), 338 mμ (log ε 4·18, 3·93, 3·58), $\nu_{max.}$ (in Nujol) 1706s, 1675s, 1619s cm.$^{-1}$.

When the sodium salt of heptane-2,4,6-trione was neutralised to pH 7 and left for 10 days, a yellow precipitate (5 mg.), m. p. 174°, undepressed by admixture with phenol (IV), was obtained. 2,6-Dimethylpyrone was recovered from the solution.

7-*Acetyl*-8-*hydroxy*-1,3,6-*trimethylisoquinoline* (IX).—Substance (II) (0·4 g.) was treated with ammonia as described by Collie and Wilsmore.[7] The residue after evaporation of the ammonia was dissolved in 2N-hydrochloric acid and neutralised, to give the *isoquinoline* (IX) (0·33 g.), yellow needles, m. p. 167—168·5° (from ethanol) (Found: C, 70·2; H, 6·3; N, 5·9. $C_{14}H_{14}O_2N,0{\cdot}5H_2O$ requires C, 70·6; H, 6·2; N, 6·0%), $\lambda_{max.}$ 216·5, 225 (infl.), 265·5, 367 mμ

[18] Schwenk, Papa, Whitman, and Ginsberg, *J. Org. Chem.*, 1944, **9**, 1.

(log ε 4·47, 4·45, 4·52, 3·94), $\nu_{max.}$ (in Nujol) 3470 (sh), 3310m, broad, 1625s, 1602s cm.$^{-1}$. Similar treatment of compound (III) gave predominantly the naphthalene (IV), m. p. 176°, and some isoquinoline (IX), m. p. 164—165°, identified by mixed m. p.s and infrared spectra.

3-*Cinnamoyl*-4-*hydroxy*-6-*methyl*-2-*pyrone* (XIV).—Dehydroacetic acid (25·2 g., 0·15 mole), benzaldehyde (15·9 g., 0·15 mole), and piperidine (1·5 ml.) in anhydrous pyridine (120 ml.) were warmed at 45° for 45 min., then at 100° for 15 min. Removal of the solvent in a vacuum and recrystallisation of the residue from aqueous alcohol or benzene–light petroleum gave the pyrone (XIV) (26 g.), m. p. 130—132° (Found: C, 70·5; H, 4·7. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7%), $\lambda_{max.}$ 234, 355 mμ (log ε 3·98, 4·47), $\nu_{max.}$ (in CCl_4) 1733—1720s, 1640s, 1625s cm.$^{-1}$.

2-*Methyl*-6-*styryl*-4-*pyrone* (XV).—The pyrone (XIV) (9·2 g.) in acetic acid (50 ml.) and concentrated hydrochloric acid (50 ml.) was heated at 105° for 2 hr. (no further gas evolution), then refluxed for 20 min. The crystalline pyrylium salt obtained on removal of the solvent under reduced pressure was diluted with water (20 ml.) and decomposed with cold sodium hydroxide solution (10%). Chloroform-extraction and decolorisation on alumina gave the *pyrone* (XV) (7·1 g.), m. p. 124—125° (from benzene–light petroleum) (Found: C, 79·1; H, 5·5. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%), $\lambda_{max.}$ 227, 233 (infl.), 317 mμ (log ε 4·26, 4·20, 4·49), $\nu_{max.}$ (in Nujol) 1664s, 1640 (sh), 1601s cm.$^{-1}$.

8-*Phenyloct*-7-*ene*-2,4,6-*trione* (XI).—To the pyrone (XV) (3·0 g.) in hot 1 : 1 v/v aqueous ethanol (40 ml.) was added a hot saturated aqueous solution of barium hydroxide (4·0 g.), and the mixture was warmed for 30 min. on the steam-bath. The filtered yellow barium salt was decomposed with dilute hydrochloric acid, and the product extracted with chloroform. Crystallisation from benzene–light petroleum afforded bright yellow needles of the *trione* (XI) (2·06 g.), m. p. 114—115°, giving a brown ferric test (Found: C, 73·2; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

4-*Hydroxy*-6-*methyl*-3-β-*phenylpropionyl*-2-*pyrone*.—The cinnamoylpyrone (XIV) (9 g.) in ethyl acetate (300 ml.) was hydrogenated over 5% palladium–charcoal (1·25 g.); 1·06 mol. were absorbed. Filtration and removal of the solvent under reduced pressure afforded 4-*hydroxy*-6-*methyl*-3-β-*phenylpropionyl*-2-*pyrone* (7·2 g.) which formed pale yellow crystals, m. p. 74·5—76°, from ethanol (Found: C, 70·1; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%) and had $\lambda_{max.}$ 222 (infl.), 309 mμ (log ε 4·12, 4·15), $\nu_{max.}$ (in CCl_4) 1735s, 1640s, 1610s cm.$^{-1}$. Dehydroacetic acid [14] has $\lambda_{max.}$ 225, 310 mμ (log ε 4·06, 4·08).

2-*Methyl*-6-*phenethyl*-4-*pyrone*.—4-Hydroxy-6-methyl-3-β-phenylpropionyl-2-pyrone (7·0 g.), acetic acid (35 ml.), and concentrated hydrochloric acid (28 ml.) were refluxed for 3 hr. Concentration of the resulting solution to dryness in a vacuum gave the pyrylium salt, which was decomposed with warm saturated aqueous potassium hydrogen carbonate. Chloroform extracted 2-*methyl*-6-*phenethyl*-4-*pyrone* (5·17 g., 89%); when crystallised from benzene–light petroleum and sublimed at 90°/10^{-2} mm., this had m. p. 76·5—77° (Found, on freshly sublimed sample: C, 78·6; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%), $\lambda_{max.}$ 248 mμ (log ε 4·27), $\nu_{max.}$ (in CS_2) 1673, 1634 cm.$^{-1}$. 2,6-Dimethyl-4-pyrone [19] has $\lambda_{max.}$ 248 mμ (log ε 4·13), $\nu_{max.}$ (in Nujol) 1672 cm.$^{-1}$.[20]

8-*Phenyloctane*-2,4,6-*trione* (XVI).—To 2-methyl-6-phenethyl-4-pyrone (500 mg.) in 1 : 1 v/v aqueous ethanol (10 ml.) was added barium hydroxide (900 mg.) in hot water (5 ml.), and the mixture was warmed for 15 min. on the steam-bath. The filtered barium salt was decomposed with dilute hydrochloric acid. Chloroform-extracts, after being washed with potassium hydrogen carbonate, yielded the *trione* (XVI) (230 mg.), an oil which crystallised below room temperature, gave a red ferric test, and had $\lambda_{max.}$ 253, 260 (infl.), 276, 317 mμ (log ε 3·83, 3·81, 3·76, 3·73), $\nu_{max.}$ (in CS_2) 1727, 1674 cm.$^{-1}$.

The trione (70 mg.) and pyrrolidine (110 mg.) in ethanol (0·2 ml.) were warmed briefly on the steam-bath. Next morning, the *di-enamine* (88 mg., 86%) was collected and recrystallised from benzene–light petroleum as pale yellow crystals, m. p. 142—144° (Found: C, 78·1; H, 8·5; N, 8·0. $C_{22}H_{30}ON_2$ requires C, 78·1; H, 8·9; N, 8·3%), $\lambda_{max.}$ 304, 373 mμ (log ε 4·00, 4·67), $\nu_{max.}$ (in Nujol) 1533 cm.$^{-1}$.

Cyclisation of 8-*Phenyloctane*-2,4,6-*trione* (XVI).—2-Methyl-6-phenethyl-4-pyrone (1·0 g.) and powdered sodium hydroxide (5 g.) in a nickel crucible under nitrogen were heated rapidly to 250° (bath-temp.), maintained there for 15 min., and then at 360° for 30 min. An ether-extract prepared after cooling and acidification of the mixture was washed with potassium

[19] Gibbs, Johnson, and Hughes, *J. Amer. Chem. Soc.*, 1930, **52**, 4895.
[20] Bu'Lock and Smith, *J.*, 1960, 502.

hydrogen carbonate and 10% potassium hydroxide solution. The recovered phenolic fraction (248 mg.) was sublimed at 150°/10^{-2} mm., and the sublimate (147 mg.) decolorised on " Florisil." Chromatography on " Florisil " and elution with pentane–ether (9 : 1) gave two non-crystalline fractions: the first (15 mg.) on paper chromatography [15] and development with bisdiazotised benzidine gave a yellow spot, R_F 0·82; the second (9 mg.) a pale violet spot, R_F 0·30. Pentane–ether (3 : 1) eluted a mixture (70 mg.) of dihydropinosylvin (XVII) (red spot, R_F 0·11) and the phenol (XVIII) (red spot, R_F 0·22), which could not be resolved by chromatography on silica gel.

Bromination of the cyclisation mixture. To the mixture (32 mg.) of compounds (XVII) and (XVIII) in chloroform (1 ml.) bromine in chloroform was added dropwise until decolorisation ceased. The excess of bromine was destroyed with sodium hydrogen sulphite, and the recovered oil (54 mg.) chromatographed on " Florisil." Three fractions were obtained: (i) (12 mg.) eluted with pentane–ether (4 : 1), sublimed at 130°/0·1 mm. and from benzene–light petroleum formed colourless crystals, m. p. 100·5—102°, $\nu_{max.}$ (in CS_2) 3479 (phenolic OH), 1375 $cm.^{-1}$ (sh; CMe); (ii) (18 mg.) eluted with pentane–ether (1 : 3) and purified as for (i) gave colourless crystals, m. p. 145·5—147·5°, $\nu_{max.}$ (in CS_2) 3499 $cm.^{-1}$ (phenolic OH); and (iii) (9 mg.) eluted with ether containing methanol (1%), $\nu_{max.}$ (in CS_2) 3485 $cm.^{-1}$ (phenolic OH).

Similar bromination of authentic dihydropinosylvin gave two fractions. One, *dibromodihydropinosylvin*, m. p. 146·5—148°, was identical (mixed m. p. and infrared spectrum) with (ii) above (Found: C, 45·7; H, 3·5. $C_{14}H_{12}O_2Br_2$ requires C, 45·2; H, 3·2%). The second fraction corresponded to (iii) above.

Debrominations.[19] Fractions (i), (ii), and (iii) above (0·7 mg. severally) in 5% aqueous sodium hydroxide (1 ml.) were treated portionwise with Raney alloy (30 mg.) during 30 min., and then warmed on the steam-bath for 30 min. The ether extracts obtained after acidification were examined by paper chromatography.[15] Fraction (i) gave a spot (red, R_F 0·22) identical with that of compound (XVIII). Fractions (ii) and (iii) gave dihydropinosylvin (red spot, R_F 0·11) identical with authentic material, and a spot (yellow, R_F 0·22) which may be due to incompletely debrominated material.

We are indebted to the Royal Commission for the Exhibition of 1851 for an Overseas Scholarship (D. W. C.) and to Professor H. Erdtman for a sample of dihydropinosylvin.

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