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Studies on the Chemistry of Lichens

XI.* Structure of Picrolichenic Acid **

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Picrolichenic acid, $C_{25}H_{30}O_7$, a bitter compound from *Pertusaria amara* (Ach.) Nyl., has been shown to contain a carboxyl group, a lactone ring, a phenolic hydroxyl group, a methoxyl group and two *n*-amyl groups. It reacts with piperidine forming a piperidide $C_{30}H_{41}O_7N$. Mild alkaline hydrolysis followed by acidification causes decarboxylation with formation of a monocarboxylic acid (A), $C_{24}H_{32}O_6$. On decarboxylation and demethylation acid (A) affords a phenol (C), $C_{12}H_4(C_5H_{11})_2(OH)_4$, identified as 2,2′-di-*n*-amyl-4,6,4′,6′-tetrahydroxydiphenyl (XII) by dehydration to 3,7-dihydroxy-1,9-di-*n*-amyldibenzofuran (XIV), methylated and oxidised to the known 3,7-dimethoxydibenzofuran-1,9-dicarboxylic acid. These results are in harmony with a structure (XXIII) for picrolichenic acid which is further supported by infra-red and ultra-violet absorption spectra.

The crustose lichen *Pertusaria amara* (Ach.) Nyl. is widely spread in Europe, occurring on the bark of broadleaf trees such as oak and beech. It has an intense, bitter taste similar to that of quinine. This attracted early chemical investigation, and a paper by Alms on "Picrolichenin" from *Variolaria amara* Ach., a synonym of *P. amara*, appeared in 1832 in the first volume of *Annalen der Pharmacie* [1]. According to Alms, picrolichenin showed promising results in the treatment of malaria.

Zopf [2,3] obtained the bitter principle which he called "Pikrolicheninsäure", in a state of reasonable purity (m.p. 178°, decomp.) and suggested the empirical composition $C_{17}H_{20}O_5$.

For the present investigation some hundred grams of *P. amara* were collected from beech trees in Blekinge, Southern Sweden. The powdery lichen was extracted with large volumes of cold ether and a concentrated solution was left in the refrigerator to crystallise. The crude acid, isolated in 5—7 % yield from the dry lichen, was purified by treatment with aluminium oxide and

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crystallisation from benzene or aqueous acetic acid. When pure, the acid forms colourless prisms, m.p. about 180° with decomposition. It is optically inactive and contains carbon, hydrogen and oxygen only. The analytical values for picrolichenic acid and a number of its derivatives and degradation products indicate the empirical composition $C_{25}H_{30}O_7$, including a carboxyl group, a methoxyl group and two C-methyl groups.

Picrolichenic acid is readily soluble in most common solvents except benzene and light petroleum. It dissolves slowly with the evolution of gas in aqueous sodium bicarbonate to give a colourless solution from which it can be recovered unchanged on acidification [3]. The solution in alkali turns brownish red when exposed to the air [1].

The acid gives an intense violet colour with ferric chloride in ethanol [2] but no coloration with 2,6-dichloroquinone-monochloroimide (Gibbs' reagent[4]), *bis*-diazotised benzidine [5] or bleaching powder [6]. However, after short treatment with cold aqueous alkali it gave a dark red colour with the benzidine reagent and a red colour with bleaching powder. This resembles the behaviour of certain easily hydrolysed depsides and depsidones. Phenolic groups were also liberated very rapidly when paper chromatographic spots of the acid were exposed to ammonia vapour.

On heating to the melting point the acid decomposed with the evolution of a gas containing carbon dioxide. A crystalline decomposition product, m. p. 153—155°, was isolated but this has not yet been subjected to thorough studies.

Short treatment of picrolichenic acid with diazomethane in the cold furnished methyl picrolichenate, m. p. 102—103,5° which was soluble in cold 0.05 N sodium hydroxide solution and gave a brownish ferric chloride reaction. Prolonged methylation with diazomethane yielded neutral methyl O-methylpicrolichenate $C_{23}H_{25}O_3(OCH_3)_2COOCH_3$, m. p. 80—82°.

Picrolichenic acid reacted in the cold with piperidine yielding a piperidide which gave a violet ferric test and was obtained in two interconvertible forms, m. p. 169—172° and 187—190° (decomp.) respectively. The piperidide titrated as a monobasic acid and gave analytical values which agreed with the composition $C_{30}H_{41}O_7N$ and thus contained all the atoms of the reacting components. On methylation with diazomethane a dimethyl derivative was formed which as shown by its low solubility in alkali and by its colour reactions contained a phenolic hydroxyl group.

Because of the sensitivity of picrolichenic acid to alkali and amines, tests for carbonyl functions were carried out with the piperidide instead of the acid itself. No positive results were obtained with carbonyl reagents under ordinary conditions.

On oxidation with permanganate picrolichenic acid afforded about 1.5 moles of volatile acids. The main component was *n*-caproic acid as indicated by paper chromatography and confirmed by the identity of the purified *p*-bromophenacyl ester with an authentic sample of *n*-caproic acid *p*-bromophenacyl ester. Paper chromatography also revealed the presence of small amounts of lower fatty acids but no spots corresponding to acids with more than six carbon atoms were observed.

These results indicate the presence in picrolichenic acid of a free carboxyl group, a lactone group, a phenolic hydroxyl group *ortho* to a carboxyl function,

a methoxyl group and two *n*-pentyl chains. Assuming the presence of two six-membered carbocyclic rings, all the carbon atoms and six of the seven oxygen atoms are accounted for.

The presence of *n*-pentyl chains in picrolichenic acid points to a relationship with the orcinol-homologue, olivetol, a fairly widespread unit in lichen acids. The empirical composition, $C_{25}H_{30}O_7$, agrees with that of a dehydrogenation product of a monomethylated depside $C_{25}H_{32}O_7$ derived from two molecules of olivetol carboxylic acid. A depside of this type, perlatolinic acid (II, R = *n*-C_5H_{11}) has been isolated from a *Parmelia*-species by Asahina and Fuzikawa [7] and picrolichenic acid might be a related depsidone such as (IV). This possibility could be ruled out by the following observations.

Picrolichenic acid after treatment with cold N sodium hydroxide solution and then acidification gave a gum which rapidly expanded to a spongy mass due to the evolution of carbon dioxide. The purified crystalline product (A) gave a violet ferric test and was found to be a monocarboxylic acid containing a methoxyl group, $C_{22}H_{28}O_3(OCH_3)COOH$ (= $C_{25}H_{30}O_7 + H_2O—CO_2$).

The acid (A) melted at about 145° with decomposition, losing one mole of carbon dioxide and forming an oily phenol (B) which was characterised by paper chromatography. It was very sensitive towards oxygen in alkaline solution and rapidly developed a brown-red colour.

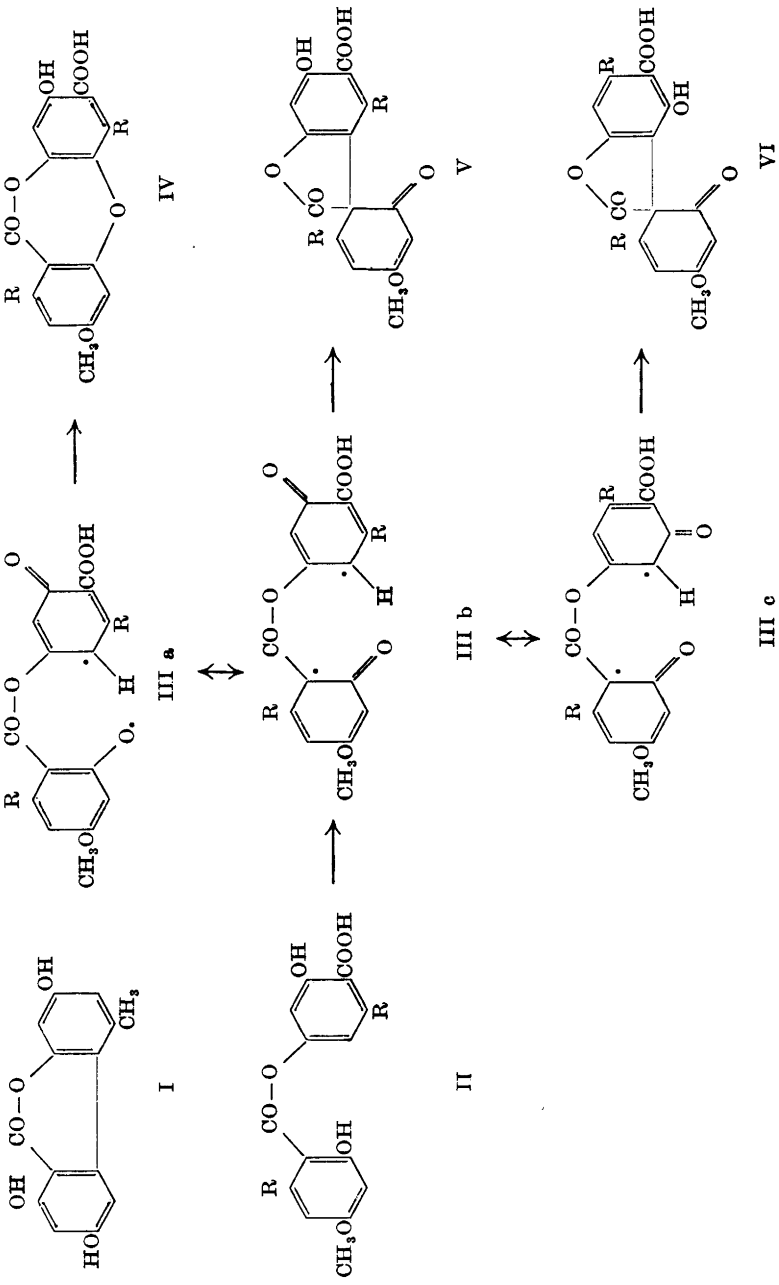
On simultaneous decarboxylation and demethylation with hydrobromic acid, the acid (A) furnished a phenol m. p. 180—181°, identical with a phenol (C), $C_{22}H_{30}O_4$, obtained directly from picrolichenic acid under similar conditions. Like phenol (B) it gave no colour with ferric chloride.

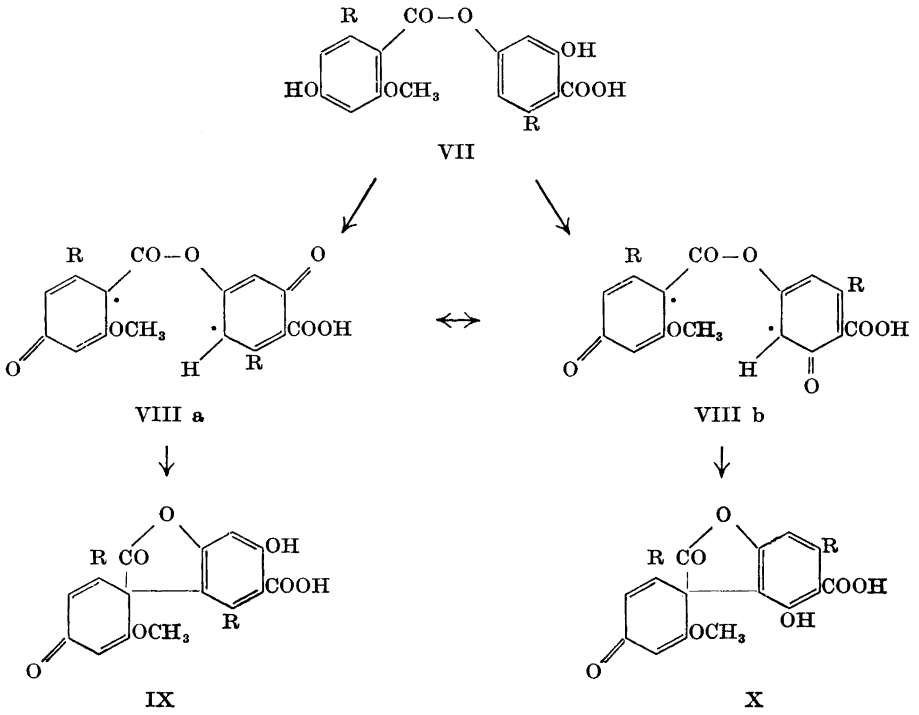
On methylation the phenols (B) and (C) afforded the same tetramethyl ether $C_{12}H_4(C_5H_{11})_2(OCH_3)_4$, m. p. 34.5—35.5°, which on bromination furnished di-, tri- and tetrabromoderivatives. The composition of the tetramethyl ether and its bromination products clearly shows that the phenol (C) and its monomethyl ether (B) are diphenyl derivatives. The U.V. spectrum of the tetramethyl ether was very similar to that of 2,2′-dimethyl-4,6,4′,6′-tetramethoxydiphenyl, the tetramethyl ether of a symmetrical diorcinol.

The acid (A) which gives a violet ferric test is obviously a carboxy derivative of phenol (B) with the carboxyl group in the *ortho*-position to a free hydroxyl group. The very facile decarboxylation of the acid indicates that there is also a free hydroxyl group in the *para*-position to the carboxyl group.

The above results indicate that picrolichenic acid contains two six-membered rings joined by a carbon-carbon bond as well as by an ester linkage. This brings to mind compounds of the ellagic acid and alternariol [8] (I) type. Such compounds, however, in contrast to picrolichenic acid do not lose carbon dioxide on acidification after alkaline hydrolysis. Moreover, structures of this type cannot be derived from orcinol derivatives.

It has been suggested [9,10] that depsidones are formed in Nature by dehydrogenation of depsides such as (II) with a mesomeric diradical (IIIa ⟷ IIIb ⟷ IIIc) as an intermediate. Coupling oxygen-carbon (IIIa → IV) would yield a depsidone. Coupling carbon-carbon (IIIb → V; IIIc → VI), however, would yield products of a structural type so far not encountered in lichens, γ-lactones containing a 2,4-*cyclo*hexadien-1-one structure (V, VI).

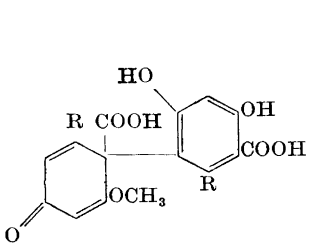




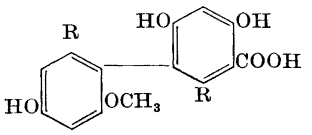
A depside precursor (VII) in which the phenolic hydroxyl group *ortho* to the ester group is methylated (or protected in some other way) would yield a diradical (VIIIa, VIIIb) which could stabilise by carbon-carbon coupling with the formation of γ-lactones (IX, X) containing a 2,5-*cyclo*hexadien-1-one structure [11].

The properties expected for γ-lactones of these types are compatible with the known chemical behaviour of picrolichenic acid. Alkaline hydrolysis of for example a lactone (IX) would yield a dicarboxylic acid (IX a) which, being a vinylogue of a β-keto-acid, should be easily decarboxylated and aromatised to a monocarboxylic acid (IX b) with a diphenyl structure. On the other hand, the dienone structure would be expected to be retained if the lactone ring opens on aminolysis to form an amide. This is exactly what was observed when picrolichenic acid was treated with piperidine. On this basis (V), (VI), (IX) and (X) (R = n-C_5H_{11}) would appear to be plausible structures for picrolichenic acid and a structure like (XI) for the piperidide.

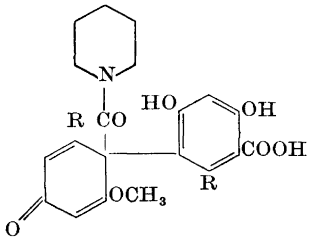
Two alternative structures would then be possible for the phenolic degradation product, (C): 2,2′-di-n-amyl-4,6,4′,6′-tetrahydroxydiphenyl (XII) and 2,4′-di-n-amyl-4,6,2′,6′-tetrahydroxydiphenyl (XIII). Tetrahydroxydiphenyls of this type undergo acid catalysed cyclisation to dibenzofuran derivatives. (XII) and (XIII) would yield homologues of 3,7- and 1,7-dihydroxydibenzofuran respectively and it would be possible to distinguish between these iso-



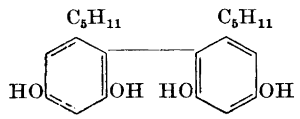
IX a



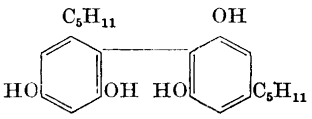
IX b



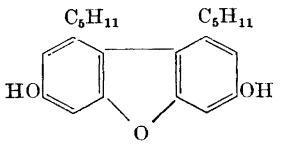
XI



XII



XIII



XIV

mers by their behaviour with Gibbs' reagent [4]. The 1,7-dihydroxy-derivative, containing a methine group in the *para*-position to a hydroxyl group, should give a blue colour with this reagent while the 3,7-derivative should give only a greyish colour [12].

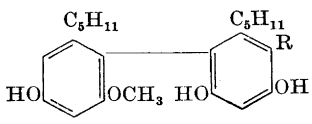
When treated with zinc chloride for a few minutes at 240—250°, phenol (C) gave a phenol (D), $C_{12}H_4O(C_5H_{11})_2(OH)_2$, m. p. 124—125°, which on methylation gave a dimethyl ether. Phenol (D) gave a greyish colour with Gibbs' reagent and the solution in alkali exhibited an intense bluish fluorescence in ultra-violet light. The U.V. spectrum of the dimethyl ether was very similar to that of 3,7-dimethoxy-1,9-dimethyldibenzofuran which was synthesised essentially by a method described by Shibata [13]. This indicates strongly that phenol (D) is 3,7-dihydroxy-1,9-di-*n*-amyldibenzofuran (XIV).

The structure (XIV) of phenol (D) was definitely settled by oxidation of its dimethyl ether with permanganate. The crude oxidation product was, paper chromatographically, identical with 3,7-dimethoxydibenzofuran-1,9-dicarboxylic acid [13] and on methylation afforded a dimethyl ester $C_{18}H_{16}O_7$, m. p. 191—193.5°, identical with 3,7-dimethoxy-1,9-dicarbomethoxydibenzofuran [13].

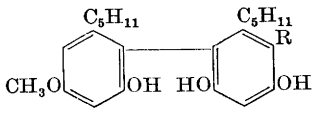
Accordingly phenol (C) is 2,2′-di-*n*-amyl-4,6,4′,6′-tetrahydroxydiphenyl (XII), a structure which is also supported by the U.V. spectrum of its tetramethyl ether. Lower homologues show very similar properties and give oily tetramethyl ethers [13].

It follows that two structures, (XV) and (XVI), are possible for phenol (B), the monomethyl ether of (C). Two alternative structures, (XVII) and (XVIII), remain for the monocarboxylic acid (A) in view of its violet ferric reaction and easy decarboxylation. These alternatives are also biogenetically plausible, being related to orsellinic acid.

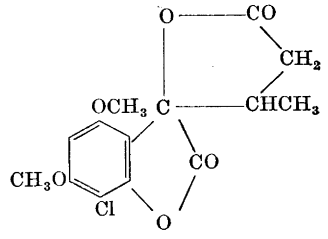
It may thus be concluded that the structures (V) and (IX) (R = n-C_5H_{11}) for picrolichenic acid are in accordance with observed facts while the alternatives (VI) and (X) are ruled out.



XV : R=H
XVII : R=COOH



XVI : R=H
XVIII : R=COOH



XIX

Additional evidence in favour of a dienone-γ-lactone structure is provided by the infra-red spectra of picrolichenic acid and its derivatives (Figs. 1—4).

Picrolichenic acid (Fig. 1), methyl picrolichenate (Fig. 2) and methyl O-methylpicrolichenate (Fig. 3) all show strong absorption at 1 820—1 825 cm^{-1} but the piperidide (Fig. 4) shows no absorption in this region. Aliphatic β,γ-unsaturated γ-lactones are known [14] to absorb at about 1 800 cm^{-1} but picrolichenic acid should be compared with β,γ-unsaturated γ-lactones in which the double bond forms part of an aromatic ring. Two recent examples are 4,6-diacetoxy-7-acetyl-3,5-dimethylcoumaran-2-one (1 822, 1 780 and 1 698 cm^{-1} in the carbonyl region; $CHCl_3$-solution) [15] and the spirane γ-lactone (XIX) (1 815 and 1 795 cm^{-1}) [16]. The 1 820 cm^{-1} band of picrolichenic acid and its methyl derivatives is therefore strong support for the presence of a γ-lactone carbonyl group.

The two remaining carbonyl functions of picrolichenic acid give rise to a single band at 1 665—1 670 cm^{-1}. Methyl O-methylpicrolichenate (Fig. 3), however, shows two strong bands at 1 725—1 730 cm^{-1} and 1 665—1 670 cm^{-1} which may be ascribed to the carboxymethyl group and the dienone carbonyl group, respectively [14]. As is shown by examples from steroid chemistry [17], cross conjugated as well as linear conjugated dienones absorb strongly in a narrow region at 1 660—1 670 cm^{-1}.

Methyl picrolichenate, containing a hydroxyl group in the *ortho*-position to a carboxymethyl group, would be expected to show an ester band in the frequency range characteristic for chelated aromatic esters (1 670—1 690 cm^{-1}) [14]. Hence, the strong band at 1 665—1 670 cm^{-1} shown by the methyl ester (Fig. 2) may be due to an ester band overlapping a dienone carbonyl band. The unexpected medium intensity band at 1 725 cm^{-1} shown by this compound may indicate that chelation is weak. It should perhaps be mentioned that substituents such as methyl or bromine in the *ortho*-position to the carboxyl group of salicylic acid have recently been regarded as the cause of a decrease in the strength of chelation between the hydroxyl and the carboxyl group [18].

The infra-red spectrum of the piperidide of picrolichenic acid (Fig. 4) shows a broad absorption in the 1 650—1 725 cm^{-1} region with a maximum at 1 690—1 700 cm^{-1}, indicating overlapping of the carbonyl bands.

Picrolichenic acid and its piperidide show broad absorption in the 2 500—2 800 cm^{-1} region, indicating strongly hydrogen bonded hydroxyl groups [14]. These compounds as well as methyl picrolichenate also show a broad hydroxyl band at about 3 450 cm^{-1}. Methyl O-methylpicrolichenate has no hydroxyl absorption.

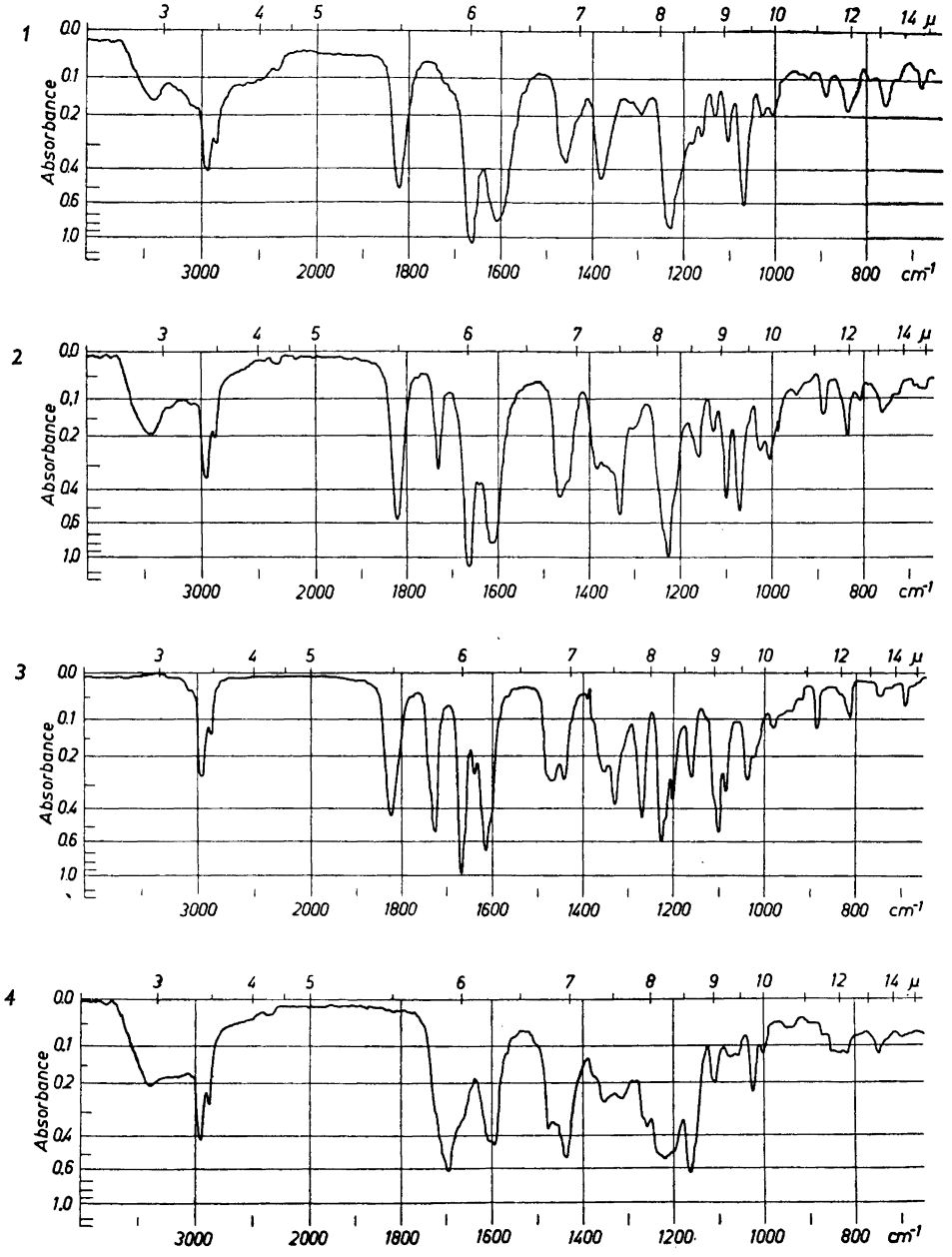


Fig. 1—4. Infra-red absorption spectra (in potassium bromide) of picrolichenic acid (XXIII) (Fig. 1), methyl picrolichenate (XXIV) (Fig. 2), methyl O-methylpicrolichenate (XXV) (Fig. 3) and picrolichenic acid piperidide (XI, R = n-C_5H_{11}) (Fig. 4).

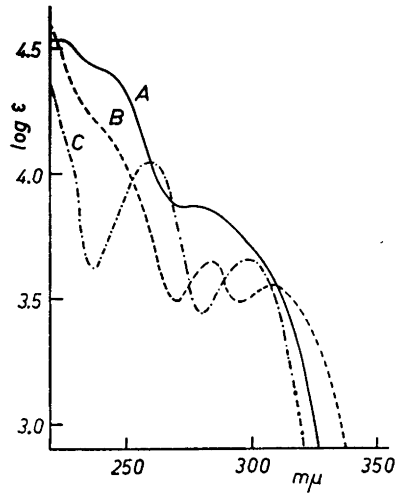


Fig. 5. Ultra-violet absorption spectra (in ethanol) of picrolichenic acid (XXIII) (A ————), picrolichenic acid piperidide (XI, R = *n*-C_5H_{11}) (B - - -) and orsellinic acid (C —.—.—.—).

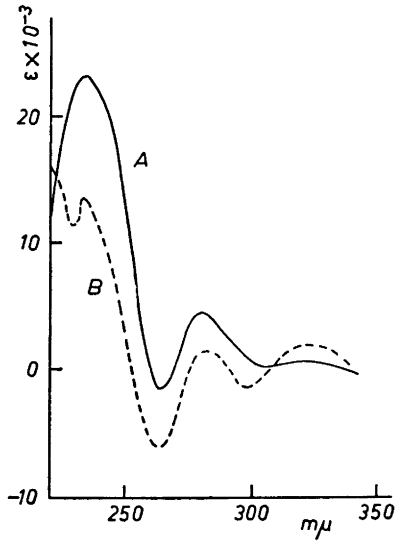


Fig. 6. Difference curves; A: Picrolichenic acid — orsellinic acid; B: Picrolichenic acid piperidide — orsellinic acid

While the main skeleton of picrolichenic acid as in (V) or (IX) (R = *n*-C_5H_{11}) appears well established, the choice between the two alternatives remains. From a biological point of view the structure (IX) derived from (VII) appears far more likely than (V). The widespread occurrence of depsidones in lichens indicates that the dehydrogenation of depsides such as (II) usually proceeds with oxygen-carbon coupling. In the case of depsides methylated as in (VII), however, oxygen-carbon coupling cannot occur and only carbon-carbon coupling is possible. A few depsides of this type are known, one example being umbilicaric acid[19], a tridepside derived from orsellinic acid.

The stability of the piperidide of picrolichenic acid may also be taken as an indication of the correctness of the structure (IX) for the acid. A piperidide derived from (V) would be expected to undergo ready *cyclo*-acetalisation and aromatisation to a dibenzofuran.

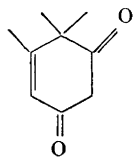
However, a final choice between the alternatives (V) and (IX) requires a knowledge of the exact position of the methoxyl group in phenol (B), the monomethyl ether of (XII). A strong indication in favour of structure (XV) for this phenol — and hence structure (IX) for picrolichenic acid — is its great sensitivity to oxygen in alkaline solution. Similar easy oxidation is characteristic of for example 2,4,2′,4′-tetrahydroxydiphenyl but not of 2,4,2′,6′-tetrahydroxydiphenyl which possesses only one hydroxyl group in a 4-position.

Since no direct conjugation exists between the two moieties of picrolichenic acid, information about the structure of the *cyclo*hexadienone part could be

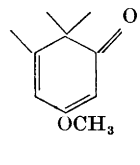
obtained by subtracting the U.V. spectrum of the aromatic part from the spectrum of the acid itself. The difference curves obtained by subtracting the U.V. curve for orsellinic acid (Fig. 5:C) — used as a model for the aromatic part of the molecule — from the curves for picrolichenic acid (Fig. 5:A) and picrolichenic acid piperidide (Fig. 5:B) are shown in Fig. 6. The two curves, of course, give only a rough idea of the spectral type of the methoxy *cyclo*hexadienone chromophore of picrolichenic acid.

2,4- and 2,5-*cyclo*hexadien-1-ones differ considerably in spectral properties, the former absorbing at a longer wavelength in the U.V. region. Wessely and Sinwel [20] report unspecific absorption in the short U.V. region for 4-methyl-4-hydroxy-2,5-*cyclo*hexadien-1-one, 2,4,6-trimethyl-4-hydroxy-2,5-*cyclo*hexadien-1-one and their acetates whereas 6-methyl-6-acetoxy-2,4-*cyclo*hexadien-1-one and related compounds which are linear conjugated showed well-defined maxima in the 290—310 mμ region (log ε 3.6—3.7).

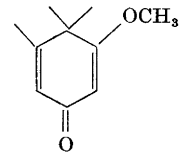
Jeger, Rüegg and Ruzicka [21] studied a system with a more direct bearing upon the present problem. A pyrolysis product of α-amyrin containing the partial structure (XX) afforded two isomeric monomethyl ethers, one of which showed a very broad maximum at 330 mμ (log ε about 3.8) and was alloted the linear conjugated formula (XXI). The isomer which showed maxima at 250 and 278 mμ (log ε 4.2 and 3.7, respectively) was given the cross-conjugated partial structure (XXII).



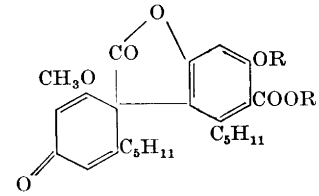
XX



XXI



XXII

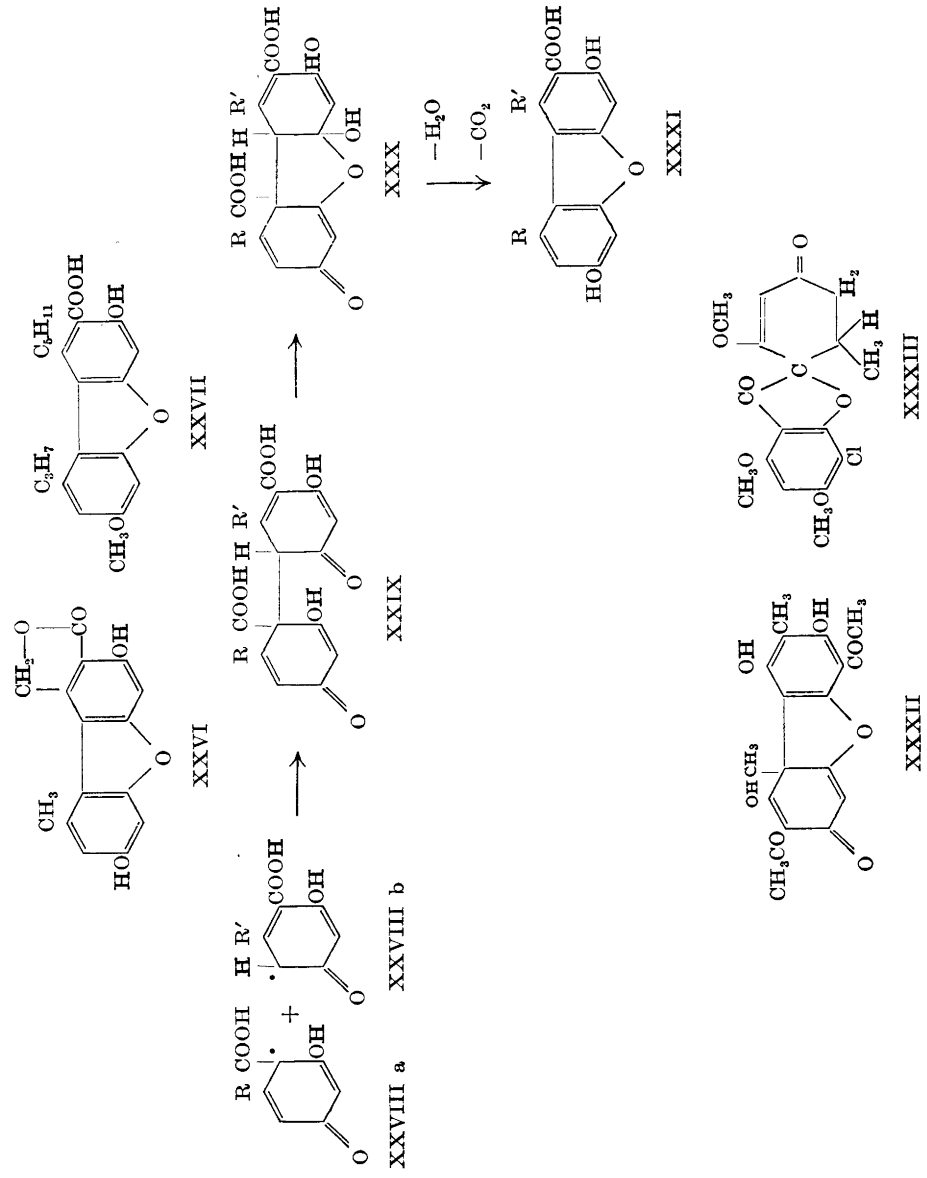


XXIII : R=R'=H
XXIV : R=H, R'=CH_3
XXV : R=R'=CH_3

One of the two difference curves mentioned above (Fig. 6) shows a distinct maximum at about 325 mμ, but this maximum is less intense (log ε 3.25) and much narrower than the broad maximum of the compound containing the structure (XXI). Both curves, however, show maxima near 235 mμ (log ε 4.4; 4.1) and 280 mμ (log ε 3.8; 3.15) corresponding roughly to the two maxima of the cross-conjugated compound (XXII) which again supports the structure (IX) for picrolichenic acid.

The chemical and physical evidence so far discussed appears to be in harmony with a structure (XXIII) (IX, R = *n*-C_5H_{11}) for picrolichenic acid. The structure of the piperidide $C_{30}H_{41}O_7N$ would then be (XI) (R = *n*-C_5H_{11}) and that of the monocarboxylic acid (A), (XVII).

There is, however, one observation which could be taken as evidence against structure (XXIII); the lack of optical activity in the compound. Several explanations could be offered to explain this inactivity, but a successful resolution of picrolichenic acid would constitute a valuable confirmation of the



structure. Work is in progress in this direction, and attempts are also being made to obtain a more direct proof of the position of the methoxyl group in phenol (B) and to elucidate the structure of the thermal decomposition product of picrolichenic acid.

The lichen acids strepsilin [22] (XXVI) and didymic acid [13] (XXVII) are dibenzofurans which unlike most depsides and depsidones contain only one carboxyl group. It appears reasonable to suggest that their biosynthesis has proceeded essentially along the same lines as picrolichenic acid (XXVIII a, b → XXXI) but that, owing to the presence of a free hydroxyl group in the *ortho*-position to the carbon-carbon linkage between the two nuclei of the radical coupling product (XXIX), a *cyclo*acetalisation to (XXX) has taken place followed by elimination of water and carbon dioxide with formation of (XXXI).

Essentially the same scheme has recently been proposed by Barton and Cohen [9]. However, the above scheme differs in details which are also of importance for an understanding of the structure of related dibenzofurans such as porphyrilic acid [12]. A full discussion of these questions will be presented elsewhere.

The unique structure (XXIII) of picrolichenic acid combines features of the depsidones and of usnic acid (XXXII) [23-25] and it may also be compared with the fungal metabolite griseofulvin [26] (XXXIII) which contains a similar spirane structure. These compounds like the dibenzofurans contain a heterocyclic ring system and it is obvious that the theory of oxidative coupling of phenols provides a common basis for a rational interpretation of their possible biosynthesis from simple phenolic progenitors.

EXPERIMENTAL

Unless otherwise stated the melting points were determined on the Kofler-Block. Whatman No. 1 paper was used for paper chromatography. The U.V. spectra were measured with a Beckman spectrophotometer, model DU. The infra-red spectra were recorded with a Perkin-Elmer double beam spectrophotometer, model 21, using the potassium bromide technique.

Isolation of picrolichenic acid (XXIII). The powdery lichen material (250 g) was extracted with cold ether (2 500 ml) in several portions and the combined extracts were concentrated to 30 ml. On standing in the refrigerator, the solution deposited a crystallisate which was collected and washed with cold ether (yield, 11.0 g). The mother liquor on evaporation in air and treatment with benzene/light petroleum (2:1) gave a second crop (6 g), contaminated by resinous material. The resulting mother liquor was not further investigated.

The first fraction (11.0 g) was dissolved in hot benzene (50 ml) and the insoluble residue was filtered off. The solution deposited a yellowish crystallisate of crude picrolichenic acid (7.4 g); a second crop (2.3 g) was obtained from the mother liquor. The fraction 6.0 g gave crude picrolichenic acid (3.0 g) on treatment with ice-cold ether and crystallisation from benzene.

The acid was purified by passing a benzene solution through a small column of alumina to adsorb some of the coloured impurities. The analytical samples crystallised (I) from benzene as prisms, m. p. 184—187° (decomp.) or (II) from aqueous acetic acid as prisms, m. p. 187—190° (decomp.) (m.p:s uncorrected, measured in a capillary tube; rate of temperature increase, 4°/min). The samples were dried *in vacuo* at 120°.

The acid, dissolved in aqueous acetone, titrated sharply with bromothymol blue as indicator. (Found: I. C 68.3; 68.6; H 6.74; 6.70; OCH_3 6.91; $C-CH_3$ 4.0; 4.0; equiv. wt. 443. II. C 67.9; H 7.15. $C_{25}H_{30}O_7$ requires C 67.9; H 6.83; OCH_3 7.01; $(C-CH_3)_2$ 6.8; equiv. wt. (as a monobasic acid) 442.5.)

The acid in ethanol ($c = 5$) or chloroform ($c = 5$) showed $[\alpha]_D^{20} \pm 0$ as measured in a 1 dm tube.

U.V. spectrum (in ethanol): Fig. 5 A; I.R. spectrum, Fig. 1.

Picrolichenic acid (0.01 % in ethanol) gave a violet colour with ferric chloride. The acid gave no colour with bleaching powder in aqueous methanol but gave a red colour when treated with bleaching powder and aqueous alkali. It gave no colour with *bis*-diazotised benzidine when tested on neutral filter paper but an intense red colour with this reagent after pretreatment with 0.1 N sodium hydroxide solution for a few minutes. As shown by spot tests on filter paper, phenolic groups were also liberated by exposure of the acid for a few seconds to ammonia vapour. Picrolichenic acid gave no colour with Gibbs' reagent when tested in a borate buffer (pH 9.0).

Thermal decomposition of picrolichenic acid. The acid (200 mg) in a test tube was heated for a few minutes in a salt bath to 210°; a gas containing carbon dioxide was evolved. The residue when distilled in high vacuum gave a yellowish, viscous oil which crystallised as prisms, m. p. 153—155° from 90 % acetic acid. The compound gave a yellowish-brown colour with *bis*-diazotised benzidine but no colour with ferric chloride.

Methyl picrolichenate (XXIV). An excess of ethereal diazomethane was added to an ice-cold solution of picrolichenic acid in ether, followed after one minute by a drop of acetic acid. Evaporation afforded the ester as an oil, which crystallised from methanol as needles, m. p. 102—103.5°. (Found: C 68.1; H 7.16; OCH_3 13.8. $C_{26}H_{32}O_7$ requires C 68.4; H 7.06; $(OCH_3)_2$ 13.6.) $[\alpha]_D^{20} \pm 0$ (ethanol, $c = 1$). I.R. spectrum, Fig. 2.

The ester was soluble in cold 0.05 N sodium hydroxide solution and gave a brownish ferric test.

Methyl O-methylpicrolichenate (XXV). Picrolichenic acid (150 mg) was treated overnight with an excess of ethereal diazomethane containing methanol. The methyl derivative (90 mg) crystallised from a solution of the oily reaction product in light petroleum (b.p. 40—60°; 70 ml) and was finally obtained from hexane as needles, m. p. 80—82°. (Found: C 68.4; H 7.21; OCH_3 20.0. $C_{27}H_{34}O_7$ requires C 68.9; H 7.28; $(OCH_3)_3$ 19.8.) I.R. spectrum, Fig. 3.

The compound was insoluble in 0.1 N sodium hydroxide solution in the cold and gave no colour with phenol reagents.

Piperidide of picrolichenic acid (XI, R = n-C_5H_{11}). The acid (720 mg) in dry piperidine (10 ml) was set aside at room temperature in an atmosphere of nitrogen. After a few days, the solution was poured with stirring into 2 N hydrochloric acid (500 ml) containing ice. The crude piperidide (800 mg) separated as a brownish precipitate which crystallised from benzene as prisms m.p. 168—172° (I); a second form (II) was obtained as prisms, m. p. 187—190° (decomp.) from 80 % acetic acid. A benzene solution of the higher melting form gave the lower melting form on seeding with it.

The piperidide in aqueous acetone titrated sharply as a monobasic acid (bromothymol blue). (Found: (I) N 2.58; OCH_3 6.29; equiv. wt 527. (II) C 68.8; H 8.09; N 2.76. $C_{30}H_{41}O_7N$ requires C 68.3; H 7.80; N 2.66; OCH_3 5.88; equiv. wt. 527.6.) $[\alpha]_D^{20} \pm 0$ (c 5.0, ethanol or chloroform.) U.V. spectrum (in ethanol), Fig. 5 B; I.R. spectrum, Fig. 4.

Colour reactions: Ferric chloride-ethanol, violet; *bis*-diazotised benzidine, yellowish brown; bleaching powder, no colour.

Prolonged methylation of the piperidide with ethereal diazomethane in the presence of methanol gave a dimethyl derivative which crystallised from methanol as prisms, m.p. 163—165°. (Found: N 2.62; OCH_3 17.0. $C_{32}H_{45}O_7N$ requires N 2.52; $(OCH_3)_3$ 16.8.) The compound gave no colour with ferric chloride but gave a yellowish-brown colour with *bis*-diazotised benzidine when tested on buffered paper (Na_3PO_4). It was slightly soluble in 1 N sodium hydroxide solution.

Permanganate oxidation of picrolichenic acid. A 1 % aqueous solution of potassium permanganate (200 ml) was added dropwise with stirring to a solution of picrolichenic acid (192 mg, 0.435 mmole) in 0.05 N sodium hydroxide solution (50 ml). After 2 h at 20°, the temperature was kept at 45° for 30 min to complete the oxidation. Excess permanganate was destroyed, the solution was acidified with sulphuric acid and the manganese sludge was dissolved by passing sulphur dioxide through the solution. The solution was extracted with ether (600 ml) and the ether phase was shaken with 1 N sodium hydroxide solution (50 ml). The alkaline solution was acidified with sulphuric acid, saturated with

sodium sulphate and steam distilled. The distillate (250 ml) contained 0.64 mmole of volatile acids, as estimated by titration.

A sample of the distillate was extracted with ether and the ether phase was analysed by chromatography using paper impregnated with dimethyl sulphoxide and a mobile phase of ether-light petroleum (b.p. 65—75°) 1:1 [27]. A reference sample containing the normal saturated acids with 2, 3, 4, 5, 6 and 8 carbon atoms was run on the same chromatogram. The spots were detected by spraying the paper with a mixed indicator solution as recommended by Duncan and Porteous [28]. The main component of the ether extract appeared as a spot with the same R_F-value as *n*-caproic acid. Faint spots of the lower fatty acids were also observed but no spots corresponding to acids with more than six carbon atoms.

The main part of the distillate, neutralised with standard alkali, was evaporated to dryness and the *p*-bromophenacylester prepared in the usual way. The crude ester (102 mg, m. p. 55—63°) on crystallisation from aqueous methanol yielded blades (50 mg), m. p. 68.5—69.5, undepressed on admixture with an authentic sample of *p*-bromophenacyl caproate, m. p. 71—72°.

Alkaline hydrolysis of picrolichenic acid. The acid (2.7 g) in 1 N sodium hydroxide solution (50 ml) was left for 40 min at 20° in a nitrogen atmosphere. The reddish solution poured into 1 N hydrochloric acid (100 ml) gave the hydrolysis product as a voluminous precipitate which changed to a gum and rapidly expanded to a spongy mass due to the evolution of gas. The product was taken up in ether and the ether solution was washed, dried and evaporated *in vacuo*. The oily residue (2.1 g) was dissolved in benzene (30 ml) and the solution was filtered through a small column of alkali-free alumina. The monocarboxylic acid (A) (XVII) separated from the filtrate as needles (1.2 g) and was recrystallised from benzene. To avoid decarboxylation which was noticeable even below the melting point of the acid the analytical sample, m. p. 145—148° (decomp.) was dried *in vacuo* at 100° for only a short time. (Found: C 68.9; H 7.55; OCH_3 7.52; equiv. wt. 419. $C_{24}H_{32}O_6$ requires C 69.2; H 7.75; OCH_3 7.45; equiv. wt. 416.5.) U.V. absorption (in ethanol): λ_{max} 264 mμ (log ε 4.06); 306 mμ (3.67). λ_{min} 254 mμ (4.01); 294 mμ (3.61).

Colour reactions: Ferric chloride, violet; *bis*-diazotised benzidine, red; bleaching powder, red-violet, changing to brown-red.

Decarboxylation of acid (A). A small sample of the acid in a test tube was heated in an oil bath for a few minutes to 150—160°; carbon dioxide was evolved. (Loss of weight, 10.5 %. Calculated for decarboxylation of a monocarboxylic acid $C_{24}H_{32}O_6$, 10.6 %). The decarboxylation product (B) (XV), obtained as a colourless oil by distillation *in vacuo*, did not crystallise. It gave a negative ferric test but otherwise gave colour reactions similar to those given by the acid (A). Paper chromatography, using the solvent system benzene-water, gave a single, somewhat elongated spot, $R_F = 0.4—0.5$. Phenol (B) in alkaline solution was rapidly oxidised in the air with the formation of a brown-red colour.

Methylation of phenol (B). The phenol (150 mg) in dry acetone (50 ml) was boiled under reflux for 8 h with potassium carbonate (5 g) and dimethyl sulphate (2.5 g). The oily reaction product, isolated in the usual way, was distilled under reduced pressure and crystallised on seeding with the tetramethyl ether of the phenol (C), described below. The crude methyl ether (m. p. 30—34°) on bromination in glacial acetic acid for 30 min afforded a dibromide which crystallised from acetic acid as prisms, m. p. 119—120°, undepressed on admixture with the dibromide of the tetramethyl ether of the phenol (C), described below. (Found: Br 29.1. $C_{26}H_{36}O_4Br_2$ requires Br 27.9.)

Demethylation and decarboxylation of acid (A). The acid (2 g) was boiled under reflux for 2 h with hydrobromic acid (20 ml, $d = 1.5$) and glacial acetic acid (25 ml) in an atmosphere of nitrogen. The reaction mixture when poured into water (300 ml) gave a voluminous, brownish precipitate which was collected, washed and dried (1.7 g). The crude phenol was dissolved in hot benzene (300 ml) and filtered through a small column of alkali-free alumina. The filtrate afforded a crystallisate (0.9 g), m. p. 175—178°. A second crop (0.5 g) was obtained from the mother liquor. Crystallisation from glacial acetic acid furnished the phenol as needles, m. p. 180—181°, undepressed on admixture with the phenol (C), obtained directly from picrolichenic acid as described below.

Degradation of picrolichenic acid with hydrobromic acid. Picrolichenic acid (5 g) was refluxed for 2.5 h with hydrobromic acid (20 ml, $d = 1.5$) and glacial acetic acid (25 ml)

in an atmosphere of nitrogen. The dark-brown reaction mixture was poured into water (500 ml) yielding a precipitate which was collected, washed and dried (4.0 g). Crystallisation from glacial acetic acid (30 ml) afforded the phenol (C) (XII) as greyish needles (1.1 g), m. p. 176–179°. The analytical sample, colourless needles from the same solvent, had m. p. 180–181°. (Found: C 73.0; H 8.61. $C_{32}H_{30}O_4$ requires C 73.7; H 8.44.)

Colour reactions: Ferric chloride, no colour; *bis*-diazotised benzidine, wine-red; bleaching powder, violet-red, changing to brown-red. Like phenol (B), the phenol (C) in alkaline solution was rapidly oxidised by air.

Paper chromatography, using the solvent system benzene-water, showed an elongated spot, $R_F = 0-0.2$ or higher, depending upon the amount of substance applied.

Methylation of phenol (C). The phenol (2.3 g) in dry acetone was boiled under reflux for 10 h with an excess of dimethyl sulphate and potassium carbonate. The tetramethyl ether was obtained as an oil which crystallised from methanol on cooling with liquid ammonia (yield, 1.9 g). After recrystallisation from methanol at −30° and distillation *in vacuo* it crystallised spontaneously, m. p. 34.5–35.5°. (Found: C 75.0; H 9.22; OCH_3 29.8; 30.2. $C_{36}H_{38}O_4$ requires C 75.3; H 9.24; $(OCH_3)_4$ 29.9.) U.V. absorption (in ethanol): λ_{max} 282 mμ (log ε 3.73); λ_{min} 261 mμ (3.34). λ = 220 mμ, log ε 4.35.

The tetramethyl ether was brominated in glacial acetic acid at room temperature. The first two moles of bromine were consumed rapidly and the excess of bromine was destroyed after 30 min by pouring the solution into water containing sulphur dioxide; the crude dibromide separated as an oil that crystallised rapidly. It was obtained from glacial acetic acid as prisms, m. p. 119.5–120.5°. (Found: Br 27.9. $C_{36}H_{36}O_4Br_2$ requires Br 27.9.)

A tribromide was obtained as the main product when the reaction time was extended to 24 h. Prisms, m. p. 106–107° from glacial acetic acid. (Found: C 47.9; H 5.63; Br 38.0; OCH_3 19.5. $C_{36}H_{35}O_4Br_3$ requires C 47.9; H 5.42; Br 36.8; $(OCH_3)_4$ 19.1.)

Prolonged bromination for 7 days gave a tetrabromide, which crystallised from glacial acetic acid as prisms, m. p. 97–98°. (Found: Br 44.0. $C_{36}H_{34}O_4Br_4$ requires Br 43.8.)

Dehydration of phenol (C). Zinc chloride (12 g) mixed with the phenol (C) (600 mg) in a test tube was heated in a salt bath to 240–250° and stirred continuously with a glass rod. The melt solidified after 4–5 min and was then cooled and extracted with water. The undissolved residue was collected, dried and dissolved in benzene (25 ml). Paper chromatography (solvent system, benzene-water) showed the main component as a spot, $R_F = 0.6-0.7$, characterised by a brownish-yellow colour with *bis*-diazotised benzidine and a greyish colour with Gibbs' reagent. A spot due to unreacted phenol (C) was also observed. The benzene solution was filtered through a small column of alkali-free alumina and the column was washed with further benzene. The absence of phenol (C) in the eluates was established by paper chromatography. Evaporation of the combined benzene solutions yielded the crude phenol (D) (XIV) (550 mg), m. p. 114–118°. It was recrystallised from benzene-light petroleum (40–60°) and showed m. p. 124–125° after sublimation *in vacuo*. (Found: C 77.3; H 8.16. $C_{32}H_{28}O_3$ requires C 77.6; H 8.29.)

The phenol (D) gave a green colour with bleaching powder but no colour with ferric chloride. An alkaline solution of the phenol showed an intense bluish fluorescence in ultra-violet light.

Methylation of phenol (D). The crude phenol (190 mg) was treated for two days with an excess of ethereal diazomethane containing methanol. Acetic acid was then added and the solution was shaken with 0.5 N sodium hydroxide solution, washed with water, dried and evaporated yielding an oil (200 mg) which crystallised on treatment with methanol. It was purified by chromatography on alumina. The material eluted by benzene was recrystallised from ethanol and from aqueous acetic acid to give the dimethylether of phenol (D) as needles, m. p. 72–73°. (Found: C 77.8; H 8.54; OCH_3 16.6. $C_{34}H_{32}O_3$ requires C 78.2; H 8.76; $(OCH_3)_2$ 16.8.) U.V. absorption (in ethanol): λ_{max} 229.5 mμ (log ε 4.37); 240.5 mμ (4.31); 255 mμ (4.07); 262 mμ (4.12); 300 mμ (shoulder, 4.24); 307 mμ (4.30). λ_{min} 238.5 mμ (4.30); 251 mμ (4.02); 257 mμ (4.06); 271 mμ (3.28).

Permanganate oxidation of the dimethyl ether of phenol (D). A solution of crude dimethyl ether (240 mg, m. p. 63–70°) in pyridine (75 ml, purified by treatment with selenium dioxide) [29] was boiled with stirring under reflux and a hot, 20 % aqueous solution of potassium permanganate was added in 5 ml portions until a total of 16 g had been added in 10 h. The solution was boiled for another 2 h, the manganese sludge was filtered

off and washed with pyridine and the combined filtrates were evaporated to dryness under reduced pressure. The residue was taken up in water and insoluble products removed from the alkaline solution by extraction with ether. For chromatography, a sample of the aqueous phase was acidified and extracted with ether. The presence in the ether phase of a number of acids was established using *n*-butanol-water and paper impregnated with trisodium phosphate [12,30]. The spots were visible in ultra-violet light. To effect complete oxidation, the main part of the aqueous phase was heated on a water bath and a 10 % permanganate solution (20 ml) was added dropwise with stirring over a 6 h period. The excess permanganate was destroyed and the manganese sludge was filtered off and washed with 0.1 N sodium hydroxide solution. The crude oxidation product (25 mg) separated from the concentrated filtrate on acidification with hydrochloric acid. The main component was chromatographically identical with 3,7-dimethoxydibenzofuran-1,9-dicarboxylic acid [13] synthesised as described below. The R_F-values on phosphate impregnated papers [12,30] were 0.05 (Na_3PO_4); 0.10 (Na_2HPO_4); 0.80 (NaH_2PO_4) (solvent system, *n*-butanol-water). The spots showed a very intense blue fluorescence in ultra-violet light.

The crude acid on methylation with diazomethane afforded a dimethyl ester, sparingly soluble in ethanol and crystallising from this solvent as needles (16 mg), m. p. 187—194°. The analytical sample, sublimed *in vacuo* and crystallised from ethanol, melted at 191—193.5° after slight sintering above 187°. The melting point was undepressed on admixture of 3,7-dimethoxy-1,9-dicarbomethoxydibenzofuran [13], m. p. 192—194°, described below. (Found: C 62.9; H 4.61. $C_{18}H_{16}O_7$ requires C 62.8; H 4.68.)

2-Iodo-3,5-dimethoxytoluene [31]. Iodine (84 g, 0.33 mole) and yellow mercuric oxide (66 g, 0.30 mole) was added in portions with stirring to orcinol dimethyl ether (45.8 g, 0.30 mole) and care was taken to keep the temperature below 50°. The solidified reaction mixture was extracted with ether (700 ml) and the ether solution was filtered and evaporated to dryness. The residue was dissolved in benzene (400 ml) and the solution was repeatedly extracted with a saturated aqueous solution of potassium iodide. The benzene solution was evaporated to dryness and the residue was distilled under reduced pressure to give 2-iodo-3,5-dimethoxytoluene (66 g, b.p. 155—170°/8 mm). It crystallised from ethanol as prisms, m. p. 84—85°. (Found: I 46.3. $C_9H_{11}O_2I$ requires I 45.6.)

The non-volatile residue from the distillation was crystallised from acetone to give (probably) 2,6-di-iodo-3,5-dimethoxytoluene as prisms, m. p. 203—204°. (Found: I 61.9. $C_9H_{10}O_2I_2$ requires I 62.8.)

The structure of the mono-iodide of orcinol dimethyl ether, not discussed in the available referate of the Japanese paper [31], follows clearly from its non-identity with 4-iodo-3,5-dimethoxytoluene [32], m. p. 96—97°.

2,2′-Dimethyl-4,6,4′,6′-tetramethoxydiphenyl [13]. 2-Iodo-3,5-dimethoxytoluene (20 g) was mixed with copper bronze (60 g) and heated in a salt bath to 200—210° for 15 min and then to 220—230° for a further 20 min. The reaction mixture was extracted with chloroform, the extract was evaporated to dryness and the residue was crystallised from ethanol (yield, 7.7 g). Distillation *in vacuo* and crystallisation from ethanol gave 2,2-dimethyl-4,6,4′,6′-tetramethoxydiphenyl as prisms, m. p. 106—107°. (Shibata [13] reports m.p. 103—104°.) U.V. absorption (in ethanol): λ_{max} 282 mμ (log ε 3.75); λ_{min} 261 mμ (3.36). λ = 220 mμ, log ε = 4.38.

Shibata [13] reports λ_{max} 282 mμ (3.7); 274 mμ (3.6); λ_{min} 262 mμ (3.4).

3,7-Dimethoxy-1,9-dimethyldibenzofuran [13]. 2,2′-Dimethyl-4,6,4′,6′-tetramethoxydiphenyl (2.5 g) was boiled under reflux for 24 h with hydrobromic acid (40 ml, d = 1.50) in an atmosphere of carbon dioxide. The material obtained from the solution on cooling was collected (1.8 g) and methylated with dimethyl sulphate and alkali to give 3,7-dimethoxy-1,9-dimethyldibenzofuran, which was distilled *in vacuo* and crystallised from ethanol as blades, m. p. 159—160°. (Shibata [13] reports m.p. 157°.) U.V. absorption (in ethanol): λ_{max} 226 mμ (4.46); 239 mμ (shoulder, 4.36); 257 mμ (shoulder, 4.10); 263 mμ (4.15) 299 mμ (4.26); 309 mμ (4.33). λ_{min} 250 mμ (4.00); 272 mμ (3.61); 302 mμ (4.25).

3,7-Dimethoxy-1,9-dicarbomethoxydibenzofuran [13]. 3,7-Dimethoxy-1,9-dimethyldibenzofuran (440 mg) in pyridine (25 ml) was boiled under reflux and a solution of potassium permanganate (5 g) in water (100 ml) was added dropwise with stirring over a period of 10 h after which the heating was continued for another 4 h. The solution was acidified

with sulphuric acid, the manganese sludge was dissolved and the crude oxidation product was collected (340 mg). It was dissolved in 5 % sodium carbonate solution and the solution was filtered and acidified with hydrochloric acid. The crude acid separated as a yellowish precipitate which was collected (220 mg). A sample was recrystallised from dioxan, yielding 3,7-dimethoxydibenzofuran-1,9-dicarboxylic acid as yellowish needles, m. p. about 300 (decomp.), characterised by paper chromatography as described above. (Shibata [13] reports m. p. 321—322° (decomp.)). The main part of the crude acid was methylated with diazomethane to give 3,7-dimethoxy-1,9-dicarbomethoxydibenzofuran, crystallised from ethanol as needles, m. p. 192—194° (Shibata [13] gives m. p. 188.5—189.5°). (Found: C 62.9; H 4.50; OCH_3 35.0. $C_{18}H_{16}O_7$ requires C 62.8; H 4.68; $(OCH_3)_4$ 36.0.)

Air oxidation of hydroxydiphenyls. 2,4,2′,6′-Tetramethoxydiphenyl [33] (20 mg) was boiled for 1.5 h with hydrobromic acid (d = 1.50; 0.5 ml) and glacial acetic acid (0.5 ml). The solution was evaporated to dryness *in vacuo*. The residue was shown by paper chromatography to contain only traces of 1,7-dihydroxydibenzofuran [33]. 2,4,2′,4′-Tetramethoxydiphenyl [34] was demethylated in the same way. Spots of 1 % solutions in acetone of the crude tetrahydroxydiphenyls and of the phenol (B) were applied to filter paper moistened with 1 N sodium hydroxide solution. The spots of phenol (B) and of 2,4,2′,4′-tetrahydroxydiphenyl turned brown-red within a few minutes but the spot for 2,4,2′,6′-tetrahydroxydiphenyl darkened only after about 30 min.

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