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CHEMICAL INVESTIGATION OF INDIAN LICHENS—XXVI*

CONSTITUTION OF VICANICIN FROM *TELOSCHISTES FLAVICANS*†

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Abstract—A new chlorodepsidone has been isolated from the lichen *Teloschistes flavicans* and named 'vicanicin'. Based on analytical evidence and spectral studies as well as degradation reactions, it is shown to be 2,4-dichloro-3-hydroxy-7-methoxy-1,5,8-trimethyldepsidone (VII).

ZOPF[1] first examined the lichen *Teloschistes flavicans* and reported the isolation of physcion (4,5-dihydroxy-7-methoxy-2-methylanthraquinone) and a colourless substance, m.p. 240–245°. An Indian sample of this lichen was studied by Seshadri and Subramanian[2] and found to contain physcion, teloschistin (4,5-dihydroxy-2-hydroxymethyl-7-methoxyanthraquinone) and also a colourless component, m.p. 245–250°. A sample of the same lichen, collected in 1955, however contained fallacinal (2-formyl-4,5-dihydroxy-7-methoxyanthraquinone) instead of teloschistin.[3] Thus there was variation in the composition of the anthraquinone pigments but the colourless substance originally designated *A* seems to have been the same in all the samples of the lichen. This colourless substance was originally isolated in small amount (about 0·1 per cent) from the petroleum ether extract of the lichen as an alkali-insoluble portion. Since the yield of the colourless substance was low after the alkali treatment, other methods for its isolation in improved yields were explored. Using column chromatography with magnesium carbonate the colourless component could be isolated pure and in better yields (about 1 per cent). The anthraquinone pigments were firmly held and the colourless substance came through. This component has been found to be a new substance and hence given the name 'vicanicin' based on the species name of the lichen and omitting the first syllable in view of the compound being colourless.

Vicanicin crystallized from benzene as colourless stout needles, m.p. 248–250°. It had the molecular formula $C_{17}H_{14}O_5Cl_2$ with one methoxyl (Zeisel) and three C-methyl (Kuhn-Roth) groups. The crystalline solid did not dissolve in aqueous sodium hydroxide but a fine suspension of it, obtained by dilution of an ethanolic solution with water, dissolved easily and the solution turned pink on long standing. It did not give any prominant colour with either alcoholic ferric chloride or concentrated sulphuric acid.

* Part XXV, K. Aghoramurthy, K. G. Sarma and T. R. Seshadri, *J. Sci. Industr. Res., India* **20B**, 166 (1961).

† A preliminary communication was published in *Tetrahedron Letters* No. 10, 1 (1959).

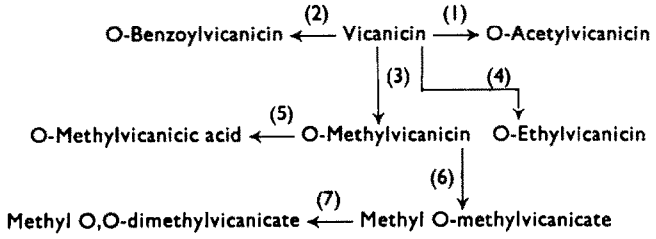
[1] W. Zopf, *Liebig's Ann.* **340**, 300 (1905).

[2] T. R. Seshadri and S. S. Subramanian, *Proc. Indian Acad. Sci.* **30A**, 67 (1949).

[3] T. R. Rajagopalan and T. R. Seshadri, *Proc. Indian Acad. Sci.* **49A**, 1 (1959).

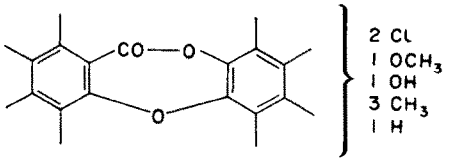
Vicanicin contained a free hydroxyl group since (i) it formed a monoacetate, $C_{19}H_{16}O_6Cl_2$, m.p. 213–214°, by acetylation with acetic anhydride alone or with acetic anhydride and concentrated sulphuric acid and (ii) it gave a monobenzoate, $C_{24}H_{18}O_6Cl_2$, m.p. 190–191°, with benzoyl chloride and pyridine. The free hydroxyl group was phenolic in nature since it underwent easy methylation and ethylation with the appropriate alkyl iodide and potassium carbonate yielding a monomethyl ether (O-methylvicanicin), $C_{18}H_{16}O_5Cl_2$, m.p. 193–194°, and a monoethyl ether (O-ethylvicanicin), $C_{19}H_{18}O_5Cl_2$, m.p. 185–186°.

Vicanicin gave evidence for the presence of a lactone ring. By the action of 2 N sodium hydroxide in dioxan solution followed by acidification, O-methylvicanicin formed a hydroxy acid (O-methylvicanicic acid), $C_{18}H_{18}O_6Cl_2$, m.p. 217–218°, by the opening of the lactone ring. On the other hand, when refluxed with absolute methanolic sodium methoxide, a methyl ester (methyl O-methylvicanicate), $C_{19}H_{20}O_6Cl_2$, m.p. 155–156°, was formed by methanolysis of the lactone ring. This substance still contained a hydroxyl group which could be methylated to a neutral methyl ether-ester, $C_{20}H_{22}O_6Cl_2$, m.p. 97–98°. These transformations of vicanicin and its derivatives are summarized in the following scheme:



Reagents: (1) Ac_2O–H_2SO_4; (2) C_6H_5COCl–Pyridine;
(3) CH_3I–K_2CO_3; (4) C_2H_5I–K_2CO_3;
(5) 2 N–NaOH; (6) CH_3ONa–CH_3OH; (7) $(CH_3)_2SO_4$–K_2CO_3.

Of the five oxygen atoms of vicanicin, four could be accounted for as part of a methoxyl, a hydroxyl and a lactone. The fifth oxygen being inert could be placed in a diphenyl ether linkage. All these considerations suggested the possibility of vicanicin being a chlorodepsidone of partial formula I.



The above possibility of a chlorodepsidone structure was supported by spectral studies. The ultra-violet absorption spectrum of vicanicin was similar to those of diploicin,[4] nidulin[5] and nornidulin.[5] The comparative U.V. spectral data are given

[4] P. A. Spillane, J. Keane and T. J. Nolan, *Sci. Proc. Roy. Dublin Soc.* **21**, 333 (1936).

TABLE 1. U.V. SPECTRA OF VICANICIN AND OTHER CHLORODEPSIDONES

Compound	Absorption: λ_{max} (log ε)
Vicanicin	270 mμ (3·94), 324 mμ (inflexion) (2·48)
Diploicin	270 mμ (3·79), 325 mμ (inflexion) (3·04)
Nidulin	267 mμ (3·95), 323 mμ (inflexion) (3·08)
Nornidulin	266 mμ (3·91), 323 mμ (inflexion) (2·87)

in Table 1. These have been considered by Dean *et al.*[5] to be associated with ring A.

The infra-red spectra of vicanicin and diploicin were also similar (Figs 1 and 2). These data led to the possibility of the partial structure (I) of vicanicin to be developed

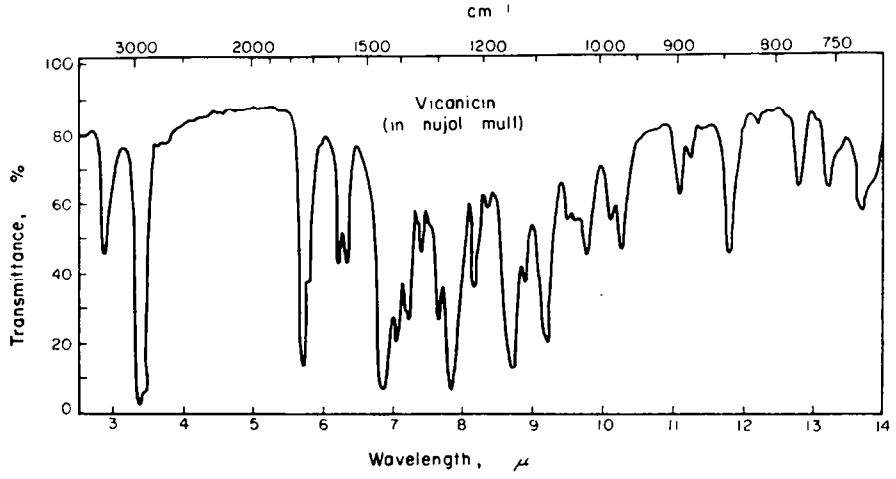


FIG. 1.

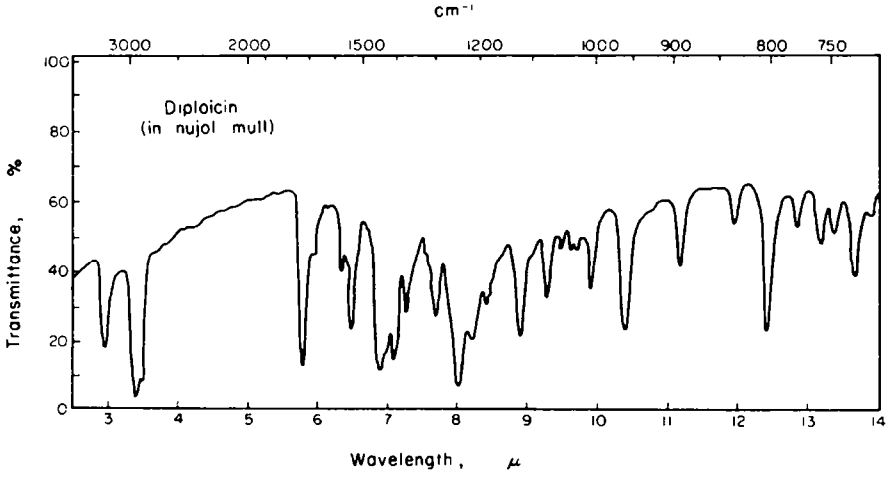


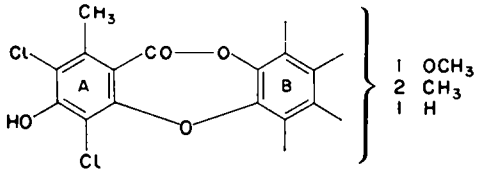
FIG. 2.

[5] F. M. Dean, J. C. Roberts and A. Robertson, *J. Chem. Soc.* 1432 (1954).

into the formula (II) indicating the common structure of the left half of all the four compounds, diploicin, nidulin, nornidulin and vicanicin.

The close similarity of vicanicin to nidulin and diploicin was further supported by the behaviour of these three substances towards alkali. All of them appeared to be insoluble in the crystalline form[4,5] but did dissolve when in the form of a fine suspension as mentioned earlier.

Two methods have been used in the past for the degradation of chlorodepsidones into smaller units: (i) Perchlorination of the methyl ester of the hydroxy acid obtained from the depsidone or from its methyl ether, followed by treatment with stannous chloride and hydrolysis with methanolic potash.[6] (ii) Oxidation of the methyl ester, obtained from the methylated depsidone, with concentrated nitric acid



II

in acetic acid[5] or in propionic acid.[7] The success of the first method seems to depend upon the easy fission of the diphenyl ether with alkali when both the halves are fully chlorinated. The need for preliminary chlorination and stannous chloride reduction carried out by Nolan *et al.*[6] in the case of diploicin derivative is not clear; if we take the analogy of methyl orsellinate under this treatment, diploicin derivative should undergo no change as it is already fully chlorinated. In this method of fission, only the left half of the molecule was isolated and characterized. In the second method, the reaction involved is one of oxidative dealkylation for which analogies are known, e.g., oxidation of 1,2,3,5-tetramethoxybenzene to 2,6-dimethoxy-*p*-benzoquinone.[8,9]

For the degradation of vicanicin, the second method, viz., treatment with nitric acid was used. Methyl O-methylvicanicate (III), obtained from O-methylvicanicin (IV) by methanolysis, gave by this treatment methyl 3,5-dichloroeverninate[10] (V), m.p. 77–78°. During this oxidation, a small quantity of an orange-red quinone could also be isolated as a sodium bicarbonate-soluble fraction. It gave a characteristic purple colour (λ_{max} 532 mμ) in alkaline buffer solution (pH 10·4) and was identified as 2-hydroxy-3,6-dimethyl-*p*-benzoquinone[11] (VI) (λ_{max} 530 mμ in buffer solution, pH 10·4). Spectral comparison with an authentic sample of this benzoquinone was also made and the identity established. The alternative possible structures, viz., 2-hydroxy-5,6-dimethyl-*p*-benzoquinone[11] and 2-hydroxy-3,5-dimethyl-*p*-benzoquinone[12] were also considered and ruled out for the following reasons: (i) The *ortho*-xyloquinone derivative was reported[11] to absorb at 490 mμ in buffer solution

[6] T. J. Nolan, J. Algar, E. P. McCann, W. A. Manahan and N. Nolan, *Sci. Proc. Roy. Dublin Soc.* **24**, 319 (1948).

[7] F. M. Dean, D. S. Deorha, A. D. T. Erni, D. W. Hughes and J. C. Roberts, *J. Chem. Soc.* 4829 (1960).

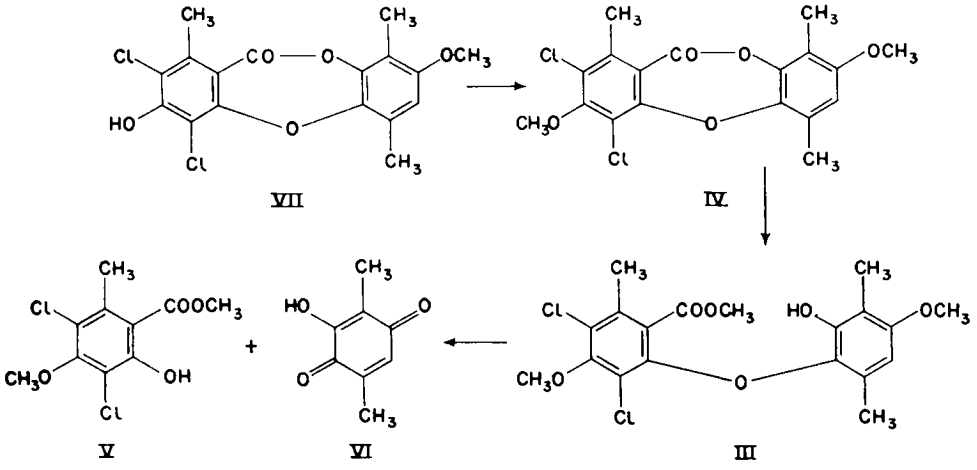
[8] G. S. K. Rao, K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **27A**, 245 (1948).

[9] T. R. Seshadri, *Rev. pure Appl. Chem., Australia* 186 (1951).

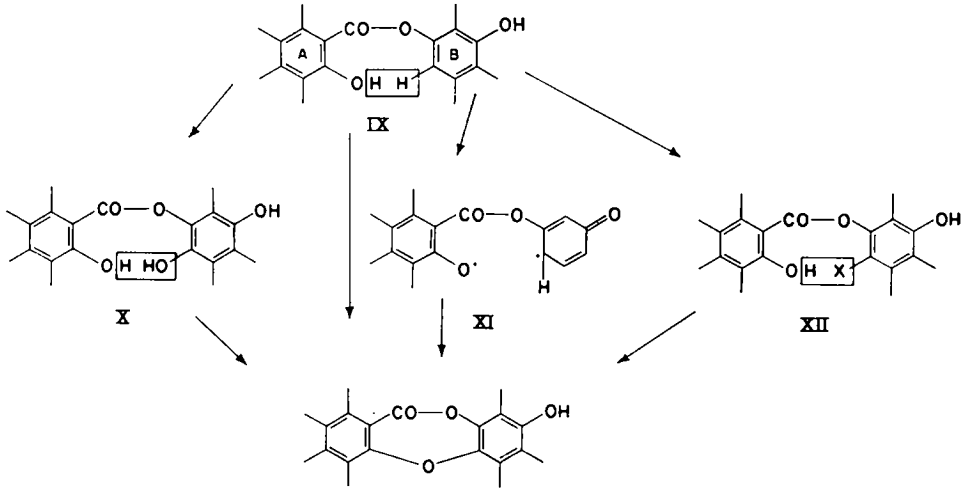
[10] T. J. Nolan and D. Murphy, *Sci. Proc. Roy. Dublin Soc.* **22**, 315 (1940).

[11] L. F. Fieser and M. I. Ardo, *J. Amer. Chem. Soc.* **78**, 776 (1956).

(pH 10·4). (ii) Since there was no record in the literature about the spectroscopic characteristics of the *meta*-xyloquinone derivative in alkaline buffer solution, it was prepared according to the method of Erdtman[12] and was found to absorb at 523 mμ in alkaline buffer solution (pH 10·4) while the quinone obtained by degradation of vicanicin had the absorption at 532 mμ. Further, in the infra-red spectrum there was difference between the *meta*-xyloquinone derivative and the degradation product. On the basis of the formation of the two products (V and VI) from methyl O-methyl-vicanicate (III), the structure (II) of vicanicin could be completed as shown in VII.



As already mentioned, the nitric acid method of degradation was earlier applied to nidulin by Dean *et al.*[5] They could isolate only the left half as methyl 3,5-dichloro-everninate. Our result reported in the preliminary communication that the right

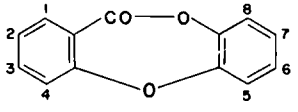


hand part could be obtained as a quinone has been supported by the more recent isolation of a similar quinone even from nidulin.[7]

[12] H. Erdtman, *Proc. Roy. Soc.* **143A**, 177 (1933).

This structure (VII) for vicanicin would also be in conformity with its possible formation from an orsellinic (C_8) unit and a C-methylorsellinic (derived C_8) unit. The biogenetic evolution of depsidones (VIII) was considered in an earlier paper[13] as based on depsides (IX) in two possible ways: (i) depsides first underwent *para*-nuclear hydroxylation (X) in the right half (B) followed by elimination of water; (ii) they underwent direct dehydrogenation. Barton and Cohen[14] as well as Erdtman and Wachtmeister[15] suggested that the dehydrogenation involved oxidative coupling through the diradical (XI) and the recent synthesis of the chlorodepsidone, diploicin, is based on this suggestion.[16] Another possible process seems to be particularly applicable to chlorodepsidones. It involves halogenation of the depside (IX) by a halogenating agent leading to XII and ring closure to the depsidone (VIII) by the elimination of hydrogen halide. Support has been provided for this scheme by recent experimental work in this laboratory. Essentially this will mean dehydrogenation by means of a halogenating agent and the depsidone ring closure may also take place in one direct stage. As a relevent analogy may be mentioned the biogenesis of thyroxine in which an iodinating agent not only iodinates tyrosine units but also forms the diphenyl ether linkage by an oxidative mechanism.

No attempt seems to have been made so far to number the positions in the depsidone skeleton. In view of the increasing number of depsidone derivatives occurring in Nature, the need for this has now come and we propose the following. Based on the analogy of numbering in xanthones, depsidones may be numbered starting with the free position *ortho* to the carbonyl as indicated in XIII. According to this, vicanicin (VII) would be 2,4-dichloro-3-hydroxy-7-methoxy-1,5,8-trimethyldepsidone.



XIII

EXPERIMENTAL

Isolation and purification of vicanicin

The following is a convenient method of isolation of *vicanicin* when small lots of the lichen are used.

The air-dried lichen (50 g), in coarse powder form, was extracted in a Soxhlet extractor till the liquid syphoning over was colourless. The deep orange-red extract was evaporated to dryness under red press and the residue (1·75 g) was dissolved in chloroform–benzene mixture (1:2; 120 ml) and chromatographed on a column of magnesium carbonate (B.D.H. Ltd., 'Heavy'). Three bands were obtained, viz., a top pink–red band A, a deep orange–red band B lower down and then a pale orange–yellow band C. The column was eluted with benzene (125 ml) when the lowest one (band C) came out first as a pale yellow solution. The bands A and B were mechanically pushed out of the column and separately studied.

Band A was acidified with ice-cold 2 N HCl and the precipitated colouring matter was extracted with chloroform. Evaporation of the chloroform solution and crystallization of the residue (0·47 g) from glacial acetic acid yielded dull orange plates and prisms, m.p. 229–230°. This was further purified by acetylation and deacetylation when pure teloschistin (m.p. 244–246°) was obtained.

[13] T. R. Seshadri, *Proc. Indian Acad. Sci.* **20A**, 1 (1944).
[14] D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll* p. 117. Birkhauser, Basle (1957).
[15] H. Erdtman and C. A. Wachtmeister, *Festschrift Arthur Stoll* p. 144. Birkhauser, Basle (1957).
[16] C. J. Brown, D. E. Clark, W. D. Ollis and P. L. Veal, *Proc. Chem. Soc.* 393 (1960).

Band B was worked up by a similar procedure and yielded an orange residue which was crystallized and identified as physcion (0·42 g), m.p. 207–208°.

The pale yellow benzene solution mentioned above was evaporated to dryness under red press and the residue (0·65 g) was boiled with pet ether (b.p. 40–60°; 100 ml) to remove any fatty matter and filtered when it became almost colourless. On further crystallization from benzene *vicanicin* was obtained as stout needles, m.p. 248–250° (0·48 g). (Found: C, 55·8; H, 3·9; Cl, 18·9; OCH_3, 8·9; C-CH_3, 11·2; $C_{17}H_{14}O_5Cl_2$ requires: C, 55·3; H, 3·8; Cl, 19·2; 1 OCH_3, 8·4; 3 C-CH_3, 12·2%). λ_{max}^{MeOH} (log ε): 270 mμ (3·94) and 324 mμ (inflexion) (2·48). It was optically inactive. It was not readily soluble in cold NaOH aq but a fine suspension of the solid, obtained by pouring an ethanolic solution into water, dissolved in NaOH and the solution turned pink on long standing. It did not give any characteristic colour with either alcoholic ferric chloride or conc H_2SO_4.

When the lichen was extracted in larger quantities (1 kg), hot benzene was used and the benzene extract (15 l.) was fractionally concentrated and different fractions I to VI were obtained. Fractions I, II and VI contained mainly the anthraquinone pigments; fractions III and V were mixtures of the pigments and vicanicin and fraction IV was only vicanicin. The mixtures were separated by column chromatography.

Acetylation of vicanicin

Vicanicin (0·5 g) was acetylated by heating with acetic anhydride (10 ml) and conc sulphuric acid (5 drops) for 1 min and then kept at the laboratory temperature for 2 hr. On pouring onto crushed ice, the *acetate* separated as a colourless solid and it crystallized from glacial acetic acid as thick rectangular prisms, m.p. 213–214°. (Found: C, 55·7; H, 4·2; $C_{19}H_{16}O_6Cl_2$ requires: C, 55·5; H, 3·9%). The same acetate could be prepared by heating vicanicin with acetic anhydride alone for 1 hr.

Benzoylation of vicanicin

Vicanicin (0·2 g) was dissolved in pyridine (3 ml) and benzoyl chloride (3 ml) was added and the mixture heated on a boiling water bath for 1 hr and then poured into ice-cold water containing conc HCl (5 ml). An oily product separated which solidified on keeping in the refrigerator. The *benzoate* crystallized from benzene as colourless tablets, m.p. 190–191°. (Found: C, 60·7; H, 4·3; $C_{24}H_{18}O_6Cl_2$ requires: C, 60·9; H, 3·8%).

Methylation of vicanicin

(a) A solution of vicanicin (0·5 g) in dry acetone (50 ml) was heated with anhydrous potassium carbonate (5 g) and methyl iodide (5 ml) for 6 hr. The product was crystallized from benzene and O-*methylvicanicin* (IV) was obtained as colourless fine needles, m.p. 193–194°. (Found: C, 56·4; H, 5·0; OCH_3, 16·9; $C_{18}H_{16}O_5Cl_2$ requires: C, 56·4; H, 4·2; 2 OCH_3, 16·2%). Main I.R. bands (as nujol mull): 1739 (s), 1667 (w), 1550 (w), 1408 (m), 1316 (w), 1271 (s), 1220 (w), 1190 (w), 1156 (s), 1093 (s), 990 (m), 952 (m), 905 (w), 848 (w), 820 (w) and 787 (w) cm^{-1}.

(b) A solution of vicanicin (0·5 g) in dry benzene (100 ml) was heated with methyl iodide (5 ml) and dry silver oxide (3 g) for 6 hr. The product was isolated (long fine needles, m.p. 193–194°) and found to be the same as that obtained by method (a).

Ethylation of vicanicin

Vicanicin (0·5 g) was ethylated with ethyl iodide (5 ml) and anhydrous potassium carbonate (5 g) in dry acetone solution (50 ml). O-*Ethylvicanicin* crystallized from benzene as colourless needles, m.p. 185–186°. (Found: C, 57·3; H, 4·9; $C_{19}H_{18}O_5Cl_2$ requires: C, 57·4; H, 4·6%).

Opening of the lactone ring of O-*methylvicanicin*

A mixture of O-methylvicanicin (IV; 0·2 g), 2 N NaOH aq (20 ml) and dioxan (20 ml) was heated on a steam bath till the solution did not give any precipitate on dilution with water (about 2½ hr). Water (100 ml) was added and the solution acidified with dil H_2SO_4. The solid product crystallized from benzene–pet ether mixture as colourless rectangular prisms, m.p. 217–218° (Found: C, 53·8; H, 5·0; $C_{18}H_{16}O_6Cl_2$ requires: C, 53·9; H, 4·5%). It was soluble in aqueous sodium hydrogen carbonate. Main I.R. bands (as nujol mull): 3448 (s), 1739 (s), 1667 (w), 1575 (w), 1418 (m), 1351 (w), 1325 (w), 1307 (w), 1258 (s), 1235 (m), 1198 (w), 1170 (s), 1105 (s), 1081 (m), 1042 (m), 980 (s), 885 (s) and 826 (m) cm^{-1}.

Methanolysis of O-methylvicanicin

O-Methylvicanicin (IV; 0·5 g) was refluxed with boiling methanol (25 ml) containing sodium (0·25 g) for 2 hr and the solvent was evaporated under red press and acidified with ice-cold dil HCl. *Methyl O-methylvicanicate* (III) crystallized from methanol as colourless prisms, m.p. 155–156°. (Found: C, 55·4; H, 5·0; $C_{19}H_{20}O_6Cl_2$ requires: C, 55·0; H, 4·9%). It was insoluble in aqueous sodium hydrogen carbonate but soluble in aqueous sodium hydroxide.

Methylation of methyl O-methylvicanicate

Methyl O-methylvicanicate (III; 0·2 g) was methylated with dimethyl sulphate (0·5 ml) and anhydrous potassium carbonate (1 g) in dry acetone solution (25 ml). *Methyl O,O-dimethylvicanicate* crystallized from benzene–pet ether mixture as colourless small prisms, m.p. 97–98°. (Found: C, 55·4; H, 5·4; $C_{20}H_{22}O_6Cl_2$ requires: C, 56·0; H, 5·2%). It was insoluble in aqueous sodium hydroxide solution.

Nitric acid degradation of methyl O-methylvicanicate

Conc HNO_3 (0·5 ml) was added to a solution of methyl O-methylvicanicate (III) (0·4 g) in glacial acetic acid (10 ml) at room temp. The solution soon turned deep orange-red. After 15 min, the reaction mixture was diluted with water (100 ml) and extracted repeatedly with ether. The ethereal solution was extracted with portions of aqueous sodium hydrogen carbonate when the first two extracts were only brown in colour. The subsequent extracts were purple and the purple solution was quickly acidified with ice-cold dil HCl and the deep yellow solution extracted with pet ether (b.p. 40–60°). Slow evaporation of the petroleum ether solution left a small quantity of an orange-red substance which had the properties of a hydroxyquinone. It gave a purple colour in alkaline solution (pH 10·4) with absorption maximum at 532 mμ. It was identified as 2-hydroxy-3,6-dimethyl-*p*-benzoquinone[11] (VI) based on its visible spectrum in buffer solution and by comparison of its infra-red spectrum with that of an authentic sample of this quinone.

The ethereal solution, left after extraction with sodium hydrogen carbonate, was extracted with aqueous sodium hydroxide (3 × 25 ml) and the alkaline solution was acidified with ice-cold conc HCl. The separated solid crystallized from aqueous methanol as colourless fine needles, m.p. 77–78°. It gave a violet colour with alcoholic ferric chloride changing to brown with excess of the reagent. It was insoluble in aqueous sodium hydrogen carbonate but dissolved in NaOH. From these properties, it was identified as methyl 3,5-dichloroeverninate (V) and the identity was confirmed by comparison with an authentic sample prepared by chlorination of methyl everninate according to the method of Nolan and Murphy.[10]