Tetrahedron, 1957, Vol. 1, pp. 177–185. Pergamon Press Ltd., London

THE STRUCTURE OF DENDROLASIN

A. QUILICO, F. PIOZZI, and M. PAVAN
Istituto di Chimica Generale del Politecnico, Centro di Chimica Industriale del C.N.R. Milano, Italia

(*Received* 7 *March* 1957)

Abstract—The chemical and i.r. spectrographic study of *dendrolasin*, the odorous substance $C_{15}H_{22}O$ isolated from the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr., indicates that it possesses a β-substituted furan structure containing a sesquiterpenoid skeleton formed by head to tail union of three isoprene units. Dendrolasin is, most probably, β-(4:8-*dimethylnona*-3:7-*dienyl*) *furan* (I). Catalytic hydrogenation affords, depending on the conditions, a tetrahydroderivative which is still a furan, and an octahydroderivative which is a tetrahydrofuran. Permanganate oxidation of dendrolasin yields acetone and succinic acid; on ozonolysis, besides these two products, levulinic aldehyde is also formed.

THE odorous substance which we isolated from the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr. was designated as *dendrolasin*. As previously described in a short paper,[1] this product is contained in the mandibular glands secretion of the insect. It can be isolated in a fairly pure state by fractionation under reduced pressure of the oil obtained by steam distillation of a light petroleum extract of the ant, from which the solvent had been previously removed. 8–10 kg of insect yield 60–70 ml of oil containing about 75 per cent of dendrolasin.

Dendrolasin, $C_{15}H_{22}O$, is a colourless oil with a lemon-grass odour, b.p. 148°–150°/16 mm, n_D^{20} 1·486, d_4^{20} 0·9108. It is optically inactive, exhibits a neutral character and is not dissolved by dilute alkalis or acids. It polymerises on long keeping into a viscous oil. Strong mineral acids, particularly nitric and sulphuric acids, transform dendrolasin into resinous products. It is readily attacked by bromine in the presence of water giving a nearly colourless resin.

Dendrolasin is indifferent towards hydrazine hydrate, *p*-nitrophenylhydrazine, semicarbazide hydrochloride and phenyl *iso*cyanate. It does not condense with maleic anhydride in hot toluene solution. With mercuric chloride or acetate it affords white solid compounds which could not be isolated in the pure state.

Dendrolasin gives the following characteristic reactions:

(a) Its solution in glacial acetic acid becomes orange-red colour when treated with a drop of conc. sulphuric acid.

(b) Acetic anhydride dissolves dendrolasin giving a dirty violet solution which turns rapidly black.

(c) A pine shaving, moistened with conc. HCl, acquires a dirty blue-green colour in contact with dendrolasin.

(d) With vanillin in HCl-ethanol solution at room temperature, it gives a fine fuchsia-red colour, which becomes very intense on heating, and turns finally to olive brown. A similar reaction is shown on heating with Ehrlich's reagent.

The inactivity of dendrolasin towards reagents for the carbonyl group and to phenyl *iso*cyanate, indicates that it is not an aldehyde, ketone or alcohol. On the other hand, the above described colour reactions, its stability towards alkalis and sensitivity to acids, and its capacity to give complexes with mercuric salts, pointed to a

[1] A. Quilico, F. Piozzi, and M. Pavan *Ric. Sci.* **26**, 177 (1956); M. Pavan *Ibid.* **26**, 144 (1956).

furan derivative. Taking into account the empirical formula, two double bonds should be present in side chains.

The *i.r. spectrum* (Fig. 1, No. 1) of dendrolasin strongly supports this hypothesis. No band which could be attributed to a CO or OH group is present, whereas many bands, most of them very intense, can be assigned to a furanoid system. Such are the

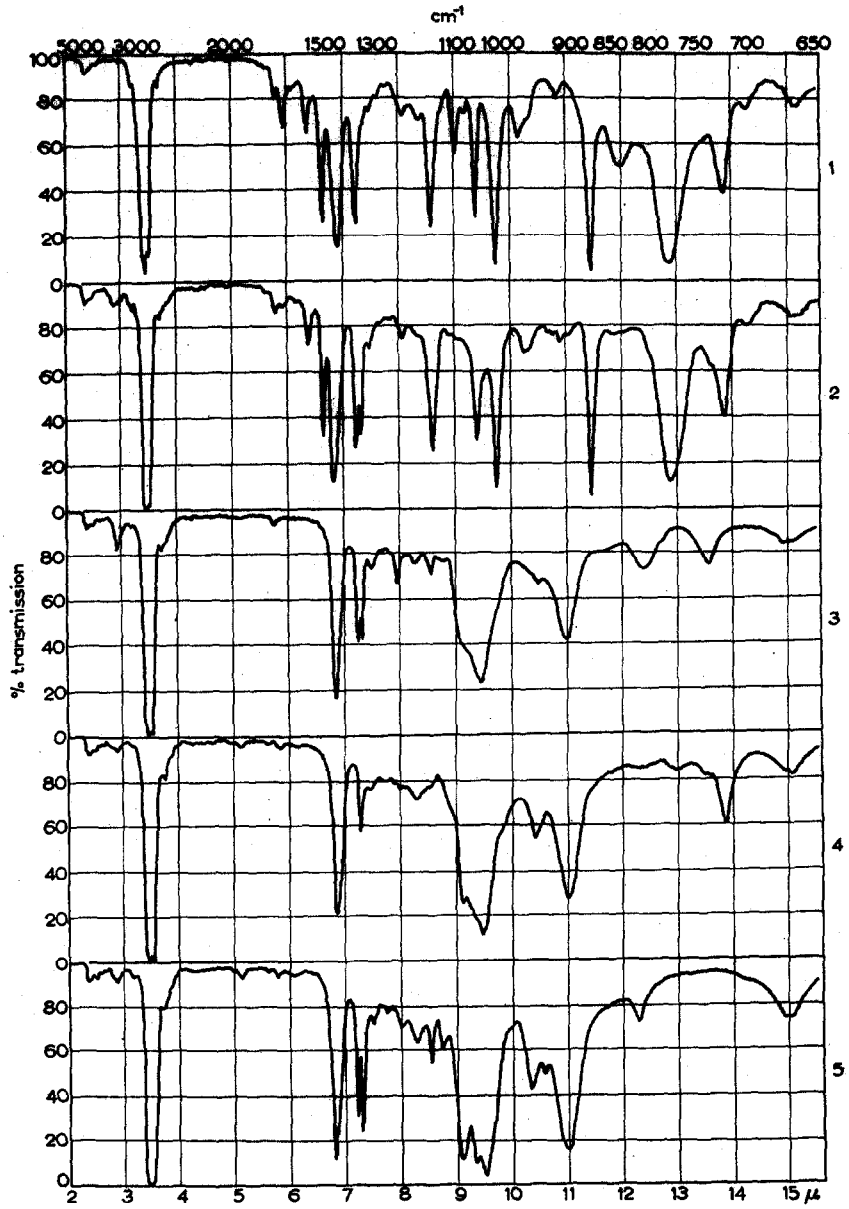


FIG. 1.—i.r. Spectra.

1. Dendrolasin; liquid 0·025 mm
2. Tetrahydroden drolasin; liquid 0·026 mm
3. Perhydrodendrolasin; liquid 0·022 mm
4. β-*n* Heptyltetrahydrofuran; liquid 0·025 mm
5. β-i-Butyltetrahydrofuran; liquid 0·024 mm

bands at 1565; 1504; 1164; 1065; 1028; 874 and 779 cm^{-1}.* The two bands at 1679 and 834 cm^{-1} are probably due to aliphatic double bonds of the type —CH=C<.

Scanty information on the structure of dendrolasin is obtained from its *u.v. spectrum* in ethanol solution (Fig. 2a). It shows a practically continuous absorption between 220 and 350 mμ, with some inflections and no peak. It is generally similar to the spectra of some terpenic alcohols such as geraniol and farnesol (Fig. 2c),[2]

Catalytic hydrogenation of dendrolasin at the ordinary pressure and temperature, both in acetic acid solution over PtO_2 and in ethanol in the presence of Raney nickel or Pd—C, yields an octahydroderivative; $C_{15}H_{30}O$.

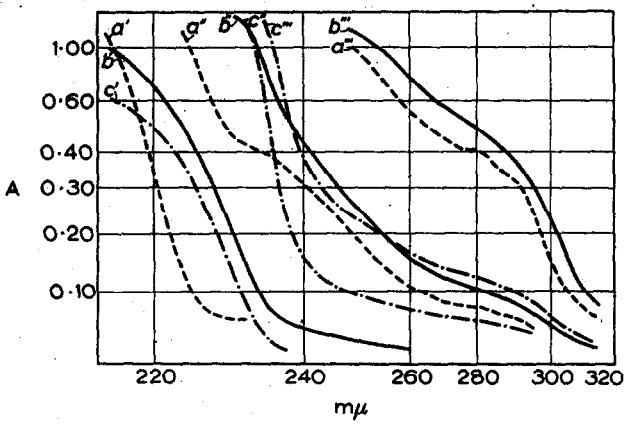


FIG. 2.—u.v. Spectra.

Farnesol	*a'* 56·76 mg/l.	*a''* 567·6 mg/l.	a''' 2838 mg/l.
Dendrolasin	*b'* 32·48 mg/l.	*b''* 324·8 mg/l.	*b'''* 1624 mg/l.
Tetrahydrodendrolasin	*c'* 33·32 mg/l.	*c''* 646·4 mg/l.	*c'''* 1616 mg/l.

Perhydrodendrolasin thus obtained is an odourless liquid b.p. 155°/15 mm, n_D^{20} 1·4478, which does not give the pine shaving reaction and the red colour with vanillin. Its *i.r. spectrum* (Fig. 1, No. 3)† is characterised by the total disappearance of the bands belonging to the furan system and the occurrence, at about 1060 and 910 cm^{-1}, of two broad bands which can be assigned to the saturated tetrahydrofuran ring. The presence at 1383 and 1364 cm^{-1} of the *iso*propyl group bands, associated with the absence of those at 1679 and 834 cm^{-1} belonging to the —CH=C< group, indicates that an *iso*propylidene group (C)=C$(CH_3)_2$ is contained in dendrolasin.

If dendrolasin is actually a furan derivative containing two double bonds in side chains, we might expect that from its hydrogenation is suitable conditions, a saturated furan $C_{15}H_{26}O$, could be obtained.

The determination of the appropriate experimental conditions to achieve this result has been very laborious, because of the difficulty of arresting the process at the required

* Most of these bands appear to be shifted from the position they normally occupy in α-substituted furans which, in addition to the fundamental member of the series, are practically the only furan derivatives of which i.r. spectra data are available. This fact, in union with the aspect of the u.v. spectrum of dendrolasin and some peculiarities in its chemical behaviour, led us to the conviction that we were dealing with a β-derivative.

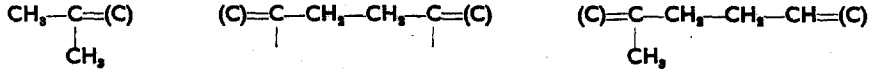
† Sample prepared in ethanol solution over Raney nickel. The i.r. spectra of specimens obtained with PtO_2 in acetic acid show weak bands assignable to OH and CH_3COO groups, indicating that hydrogenolysis of the tetrahydrofuran ring, followed by esterification, has partially occurred.

[2] Y. R. Naves and P. Ardizio *Helv. Chim. Acta* 31, 1240 (1948); F. Bader *Ibid.* 34, 1632 (1951).

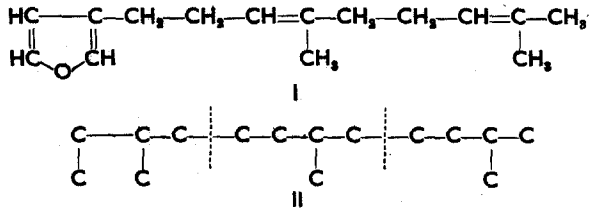
stage. Eventually we succeeded by the use of a mixture of Pd—C and Pd—$BaSO_4$ as the catalyst.

Tetrahydro-dendrolasin is a colourless liquid, b.p. 160°/15 mm, n_D^{20} 1·4855. Its *i.r. spectrum* (Fig. 1, No. 2) is closely similar to that of dendrolasin. The bands at 1565; 1504; 1163; 1065; 1027; 874 and 778 cm^{-1} are due to the furan ring; the bands at 1383 and 1366 cm^{-1}, to the *iso*propyl group. The colour reactions with vanillin and the pine shaving test are practically the same as with dendrolasin.

Important information about the number and the structure of the side chains has been supplied by the permanganate oxidation and ozonolysis of dendrolasin. Aqueous $KMnO_4$ attacks dendrolasin, slowly in the cold and more rapidly at 100°, giving *acetone* and *succinic acid*. On ozonolysis in ethyl acetate solution several products are formed; among them *acetone* (in the form of its dimeric peroxide), *levulinic aldehyde* and *succinic acid* have been isolated and identified. The formation of these substances indicates that the following structural units must be present in dendrolasin:



Taking these typical degradation products into account as well as the i.r. spectra data and the colour reactions and the very probable presence of a furan nucleus, also a general similarity to the terpenoid substances, it appears likely that dendrolasin possesses a terpenoid structure. This could be formed by the union of three isoprene units,[3]* one of them oxygenated and involved in the formation of the furan ring. Among the different structures which could be assigned to dendrolasin on this basis formula (I), derived from the head to tail union of three isoprene units as shown in (II), is the most probable:

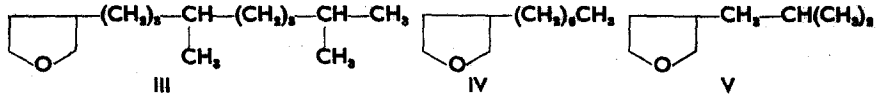


I

II

A *β-(4:8-dimethylnona-3:7-dienyl) furan* structure such as (I) would account for the lack of optical activity of dendrolasin, for its colour reactions,[4]† for the formation of acetone, levulinic aldehyde and succinic acid on ozonolysis, and would be consistent with the i.r. and u.v. spectra of this substance.

Attempts to synthesise dendrolasin and its hydroderivatives are in progress. Meanwhile indirect evidence for the structure (I) is provided by the results of i.r. spectra studies of some synthetic models of perhydrodendrolasin (III):‡



III IV V

* Or senecioic acid units.

† According to Reichstein *et al.*, α or β-monosubstituted furans give a bluish green colour in the pine shaving test, whereas with disubstituted furans the colour is violet-red.

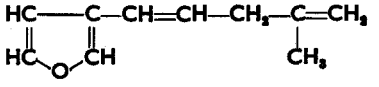
‡ The preparation of these substances and of other β-substituted tetrahydrofurans will be described in a subsequent paper.

[3] R. Robinson *The Structural Relations of Natural Products* p. 15. Oxford (1955).

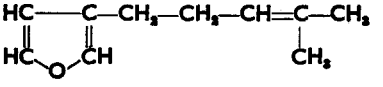
[4] Reichstein *et al.*, *Helv. Chim. Acta* **15**, 1110 (1932); *Ibid.* **16**, 28 and 37 (1933).

The i.r. spectrum of *β-n*-heptyltetrahydrofuran (IV) (Fig. 1, No. 4), shows at about 1060 and 910 cm^{-1} the characteristic bands due to the hydrogenated furan ring which are present in the i.r. spectrum of perhydrodendrolasin. Naturally, in spectrum No. 4 the bands of the *iso*propyl group are absent, whereas the band at 723 cm^{-1} belongs to the long saturated chain $(—CH_2—)_6$. In *β-isobutyltetrahydrofuran* (V) i.r. spectrum (Fig. 1, No. 5) the broad band at about 1060 cm^{-1} appears resolved into a group of bands; absorption due to the *iso*butyl group is evident in the 1365–1390 cm^{-1} region.

Further support to formula (I) is given by the occurrence in nature of two *β*-monosubstituted furan derivatives of unequivocal isopentanoid structure, which closely resembles dendrolasin both in their physical and chemical properties. Both *α-clausenane* (VI)[5] and *perillene* (VII)[6] are formed by head-to-tail linking of two isoprene units:*

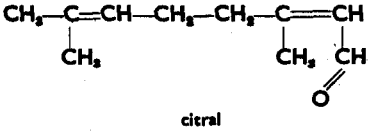


VI

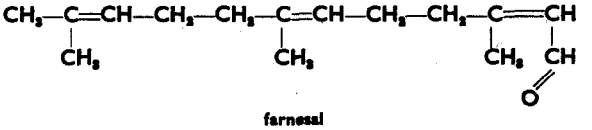


VII

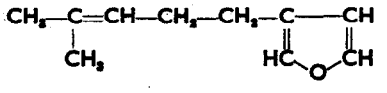
Particularly striking is the similarity between dendrolasin and perillene; both show the same colour reactions and behave in the same way towards catalytic hydrogenation and ozonolysis. It is interesting to notice that the evident structural relations existing between citral (or geraniol) and perillene in the C_{10} series, would find a corresponding relationship in the C_{15} series between farnesal (or farnesol) and dendrolasin, as shown by the scheme:



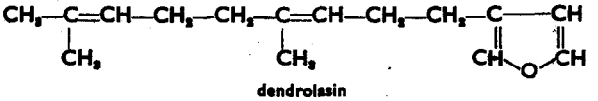
citral



farnesal



perillene



dendrolasin

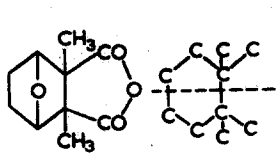
* Other furans occurring in nature and containing the isoprene skeleton are: *β*-furoic acid, from the roots of *Evonimus atropurpureus* and *Phaseolus multiflorus; β-iso*amyl furyl ketone, from the essential oil of *Perilla frutescens*, and *α-iso*valeroyl-*β*-methyl furan from the roots of *Elshozia cristata.*

[5] B. S. Rao and K. S. Subramanian *Proc. Indian Acad. Sci.* **1A**, 189 (1934); *Ibid.* **2A**, 574 (1935); *Ibid:* **3A**, (1936). B. S. Rao *J. Sci. Ind. Res. India* **7**, N. 1 B, 11 (1948) (From the essential oil of leaves of *Clausena willdenovii*).

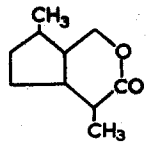
[6] H. Hondo and Yamaguchi *J. Pharm. Soc. Japan* **39**, 263 (1919); H. Kondo and H. Suzuki *Ber. Dtsch. Chem. Ges.* **69**, 2459 (1936); H. Suzuki *J. Pharm. Soc. Japan* **56**, 841 (1936); Goto *Ibid.* **57**, 77 (1937) (Isolated from the essential oil of *Perilla citriodora* Mak.).

This would suggest, from a purely formal point of view, a possible derivation of furan terpenes and sesquiterpenes from the corresponding acyclic members.

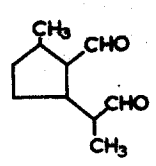
So far as the authors know, dendrolasin represents the first furan derivative ever found in the animal kingdom. It is worth noticing that structures which can be dissected into isoprene units do exist in other natural products occurring in insects. Such are: *cantharidin* $C_{10}H_{12}O_4$ (VIII), which contains a carbon atom skeleton corresponding to the tail-to-tail union of two isoprene residues*; *iridomyrmecin* $C_{10}H_{16}O_2$ (IX)[7] its epimer iso-*iridomyrmecin*,[8] and *iridodial* $C_{10}H_{16}O_2$ (X)[9] all the three with the head-to-tail structure:



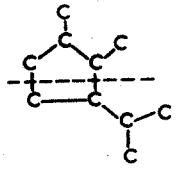
VIII



IX



X



The isoprene rules, which have been so helpful for the interpretation of the molecular architecture of many plant products, may also be a useful guide in the still scarcely investigated field of insect chemistry.

EXPERIMENTAL

Isolation of dendrolasin (I)

The brown oily residue obtained, after removal of the solvent, from the light petroleum ether extract of the insect,[10]† was steam distilled until no oily droplets were noticeable in the condenser. The aqueous distillate was extracted with ether; distillation of the solvent left a pale yellow oil which, fractionated under reduced pressure, yielded about 75 per cent of its weight of practically pure dendrolasin, b.p. 148–150°/16 mm. Dendrolasin is a colourless liquid, with a pleasant smell of lemon grass, almost insoluble in water, optically inactive. n_D^{20} 1·4860, d_4^{23} 0·9108 (Found: C, 82·43 82·51; H, 10·31 10·35. Calc. for $C_{15}H_{22}O$: C, 82·51; H, 10·16 per cent).

The product is stable towards alkalis and readily converted into resinous products by concentrated mineral acids. Does not react with hydrazine, *p*-nitrophenylhydrazine, semicarbazide hydrochloride, phenylisocyanate and maleic anhydride. With aqueous mercuric acetate, in the presence of sodium acetate, it gives a white precipitate, insoluble in methanol and acetone, which on heating is decomposed at 205° without melting.

The colour reactions of dendrolasin and its i.r. and u.v. spectra have already been reported and discussed in the introduction to this paper.

* In cantharidin the saturated C_4O ring is also present.

† This was obtained by extracting the insects with petroleum ether, after the insect had been mixed with kieselguhr and pressed at 300 atm.

[7] R. Fusco, R. Trave and A. Vercellone *Chim. et Industr.* **37**, 351 958 (1955) (From the ant *Iridomyrmex humilis* Mayr.).

[8] G. W. K. Cavill, D.L . Ford and H. D. Locksley *Australian Chem. J.* **9**, 288 (1956); *Chem. & Ind. (Rev).* 465 (1956) (From the ant *Iridomyrmex nitidus* Mayr.).

[9] Cavill *et al., loc. cit.*; R. Trave and M. Pavan *Chim. et Industr.* **38**, 1015 (1956) (From the ants *Iridomyrmex detectus* Sm., *I. conifer.* For. and *Tapinoma nigerrimum* Nyl.).

[10] M. Pavan *Ric. Sci.* **26**, 147 (1956).

Catalytic hydrogenation of dendrolasin to perhydrodendrolasin (III)

(a) *In acetic acid solution over PtO_2.* A solution of 3 g of dendrolasin in 100 ml of glacial acetic acid was shaken with hydrogen, at ordinary pressure and room temperature, in the presence of 30 mg of PtO_2. The absorption of H_2 ceased when 1300 N ml had been fixed, amounting to 4·23 mole per mole of substance. After removal of the catalyst, the solution was treated with an excess of dilute NaOH, and the oil thus separated was extracted with ether. The dried (Na_2SO_4) ethereal layer, gave after removal of the solvent, an oily residue which was fractioned twice at reduced pressure. The hydrogenated derivative is an odourless liquid, b.p. 155°/15 mm, n_D^{20} 1·4484, which does not give the pine shaving reaction, and only a very faint pink colour on heating with HCl-ethanol solution of vanillin. The analysis was in good agreement with the required for an octahydroderivative. (Found: C, 79·16 79·20; H, 13·23 13·19. Calc. for $C_{15}H_{30}O$: C, 79·57; H, 13·36 per cent).

The i.r. spectrum of the sample prepared above, indicated the presence of traces of hydroxylated and acetylated impurities, evidently formed by reductive cleavage of the tetrahydrofuran ring.

(b) *In ethanol over Raney nickel.* 1·6 g of dendrolasin dissolved in 100 ml of ethanol, were hydrogenated at room temperature in the presence of 0·5 g of W_5 Raney nickel.[11] After 3–4 hr 657 N ml of H_2 were absorbed (4·0 mole per mole of dendrolasin). Distillation of the solvent after removal of the catalyst gave a liquid residue which distilled *in vacuo* yielded an oil n_D^{20} 1·4478. Vanillin reaction was negative.

(c) *In ethanol over Pd—C.* A solution of 5 g of dendrolasin in 100 ml of ethanol was shaken with hydrogen at the ordinary conditions in the presence of 0·2 g of Pd—C (containing 10 per cent Pd). The absorption of hydrogen (rather slow) ceased completely when 1960 N ml of H_2 had been absorbed (3·83 mole per mole of substance). After removal of the catalyst and the solvent, the oily residue was distilled under reduced pressure. B.p. 155°–157°/16 mm; 186°–187°/46 mm; n_D^{20} 1·4490. Vanillin and pine shaving reaction were negative. For the i.r. spectrum (Fig. 1, No. 3), see the introduction.

Catalytic hydrogenation of dendrolasin to tetrahydrodendrolasin

A suspension of 0·2 g of Pd—C (10 per cent Pd) and 0·2 g of Pd—$BaSO_4$ (5 per cent Pd) in 5 ml of ethanol was left overnight, then added to a solution of 2 g of dendrolasin in 100 ml of ethanol. By shaking with hydrogen at room temperature a slow absorption occurred, which ceased when 410 N ml of H_2 had been absorbed (about 2 mole per mole of substance). After removal of the catalyst and of the solvent, the residue was fractioned at reduced pressure. B.p. 160°/5 mm; n_D^{20} 1·4585 (Found: C, 80·52; H, 11·67. The tetrahydroderivative $C_{15}H_{26}O$ requires: C, 80·02; H, 11·79 per cent).

Tetrahydrodendrolasin is a colourless, faintly scented oil, which gives the pine shaving reaction and a red colour with vanillin in HCl-ethanol solution. Concentrated sulphuric acid dissolves it with red-brown colour. The i.r. spectrum is reported in Fig. 1, No. 2.

The same tetrahydroderivative could be obtained also by hydrogenation over Willstaetter platinum, using a sparingly active sample of this catalyst.* 1·2 g of

* The catalyst had been prepared as described in *Houben Methoden der org. Chemie* 3d Ed. Vol. III. p. 312, and preserved for about 1 year before using.

[11] A. A. Pavlic and H. Adkins *J. Amer. Chem. Soc.* **68**, 1471 (1946).

dendrolasin shaken in ethanolic solution (100 ml) with 0·2 g of the catalyst, absorbed 260 N ml of H_2 (2·1 mole per mole of the substance), and gave a tetrahydroderivative with n_D^{20} 1·4595.

Oxidation of dendrolasin with potassium permanganate

To a suspension of 1 g of dendrolasin in 200 ml of water contained in a flask equipped with a dropping funnel and a reflux condenser and heated on the water-bath, were added drop wise under frequent shaking 75 ml of 2 per cent $KMnO_4$ solution. After 2 hr the reaction mixture was distilled, and the first 5 ml of distillate were collected in a solution of *p*-nitrophenylhydrazine in acetic acid. The abundant yellow precipitate thus formed was recrystallised twice from hexane. Yellow needles were obtained which melted at 149°·5 and showed no m.p. depression when mixed with an authentic specimen of *acetone* p-*nitrophenylhydrazone*.

The aqueous solution, after filtration from the MnO_2 and extraction with ether to remove the unchanged dendrolasin, was concentrated to small volume on the water-bath, acidified with sulphuric acid, and again extracted with ether. Removal of the solvent gave a white crystalline residue containing some *oxalic acid* which was dissolved in a small quantity of water. This solution was then treated with dilute H_2SO_4 and an amount of permanganate solution sufficient to destroy the oxalic acid. A new extraction with ether yielded a crystalline acid which, recrystallised from water, melted at 183°–184° and was identical with *succinic acid*. The identity has been confirmed by a mixed melting point test, and from the crystalline form of the sublimated acid.

Ozonolysis of dendrolasin

0·5 g of dendrolasin dissolved in 30 ml of pure ethyl acetate were submitted for 10 hr to a slow stream of ozonised oxygen. After remaining overnight the solvent was removed *in vacuo* at room temperature, and the resulting syrup refluxed for 2 hr with 50 ml of water. The solution was then distilled, and the first 4–5 ml of liquid were collected. On standing, white, square, tabular crystals were formed, which detonated when suddenly heated, and melted at 127°–131° (crude). The product is identical with cyclo-*diacetone peroxide*,* a sample of which we prepared by ozonolysis of geraniol.

The remaining solution was made slightly alkaline with dilute NaOH, then repeatedly extracted with ether. Evaporation of the solvent left a liquid (0·1–0·15 g) endowed with a strong aldehydic odour, which was treated with a boiling solution of 2:4-dinitrophenylhydrazine in methanol. The precipitate, collected and dried, was dissolved in hot nitrobenzene. The microcrystalline orange coloured product separated on cooling, washed with boiling ethanol to remove the last traces of nitrobenzene, melted at 235°. The substance is identical with *levulinic aldehyde* bis-2:4-*dinitrophenylhydrazone*, and showed no depression at the mixed melting point test with a pure synthetic specimen[12] (Found: N, 24·50. Calc. for $C_{17}H_{16}O_8N_8$: N, 24·34 per cent).

* The formation of this substance in ozonolysis of products containing $(C)=C(CH_3)_2$ groups has been reported by several authors.

[12] H. H. Strain *J. Amer. Chem. Soc.* **57**, 760 (1935).

The aqueous alkaline solution was again acidified with sulphuric acid and extracted with ether. The residue obtained after distillation of the solvent was dissolved in water, the solution evaporated to dryness, and the solid product pressed on a porous tile to remove oily impurities. Recrystallisation from water gave 0·2 g of an acid m.p. 187°, which was identical with *succinic acid.*

Acknowledgements—We thank Dr. E. Mantica for his assistance in the interpretation of the i.r. spectra, and Dr. F. Canal of the Farmitalia Laboratory for some of the analyses contained in this paper.