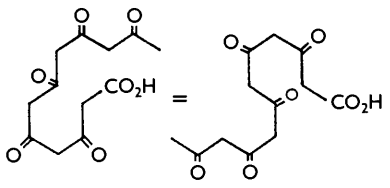
794. *Oxidative Pairing of Phenolic Radicals. Part II.* The Synthesis of Picrolichenic Acid.*

By T. A. Davidson and A. I. Scott.

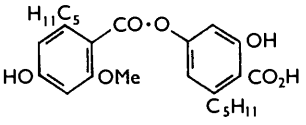
The synthesis of the bitter principle of *Pertusaria amara*, picrolichenic acid (I), has been accomplished by a method which probably parallels the biogenesis of this and related lichen substances, namely the intramolecular oxidation of depside precursors by a one-electron oxidising agent.

The bitter acidic principle of the crustose lichen, *Pertusaria amara* (Ach.) Nyl., was first described in the treatment of malaria by Alms in 1832.[1] In 1900 Zopf [2] attributed the formula $C_{17}H_{20}O_5$ to the purified acid, and named the compound picrolichenic acid. Wachtmeister recently [3] corrected the formula to $C_{25}H_{30}O_7$ and suggested expression (I) for the acid.

The most probable biogenetic pathway leading to the rather unusual spiro-lactone part involves the condensation of a poly-β-ketone chain [4] of 6 acetate units (as II) and self-esterification and reduction to the depside (III) (cf. griseofulvin). The unusual methylation pattern of (III) [a] prevents the operation of the biogenetically acceptable C–O coupling [5] involved in the depside-depsidone transformation (IV ⟶ V). Instead the diradical (IIIa) leads by C–C coupling to the acid (I). This mechanism was suggested



(II)



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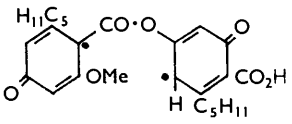
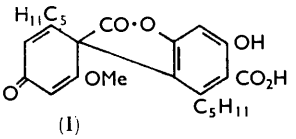
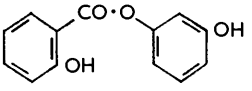


(IIIa)



(I)



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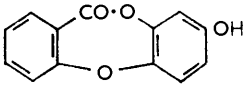


(V)

by Wachtmeister and formed a useful basis for his degradative work. We therefore considered that a rational synthesis of picrolichenic acid by such a radical-pairing reaction would offer considerable support for this biogenetic hypothesis, and, at the same time, provide confirmation, albeit indirectly, of the depside–depsidone relationship.

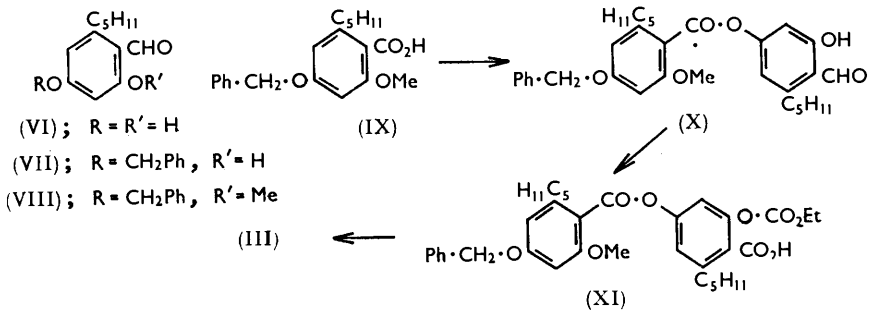
We chose as starting material the aldehyde (VI), which can be used for construction of both components of the required depside system, by modification of Asahina's general synthetic method.[6] To this end, monobenzylation of the aldehyde gave the 4-benzyl

* Part I, preceding paper; for preliminary communication see Davidson and Scott, *Proc. Chem. Soc.*, 1960, 390.

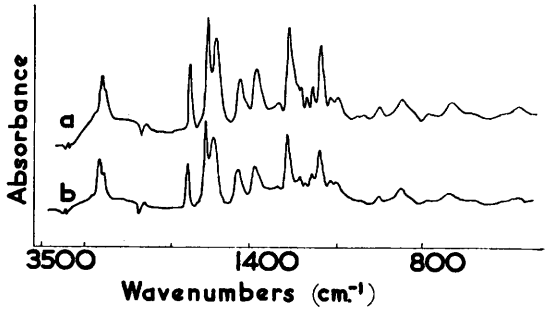
[a] Methylation of hydroxyl in the *ortho*-position to the depside linkage has, in fact, been observed in the tridepside, umbilicaric acid (ref. 10).

[1] Alms, *Ann. Pharm.*, 1832, **1**, 61.
[2] Zopf, *Annalen*, 1900, **313**, 335; 1902, **321**, 38.
[3] Erdtman and Wachtmeister, *Chem. and Ind.*, 1957, 1042; Wachtmeister, *Acta Chem. Scand.*, 1958, **12**, 147.
[4] Birch, " Fortschritte der Chemie Organischer Naturstoffe," 1957, **14**, 186.
[5] Barton and Cohen, " Festschrift Artur Stoll," Birkhäuser, Basle, 1957, p. 117.
[6] Asahina and Shibata, " The Chemistry of Lichen Substances," Japan Society for Promotion of Science, Tokyo, 1954; Asahina and Hashimoto, *J. Pharm. Soc. Japan*, 1938, **58**, 221.

ether (VII) which with dimethyl sulphate in alkaline solution afforded the methyl ether (VIII). Oxidation to the protected carboxylic acid (IX) was effected with neutral potassium permanganate; condensation [7] of the corresponding acid chloride with the original aldehyde (VI) than gave the depside (X) in 85% yield. Ethoxycarbonylation of the free phenolic group and oxidation with potassium permanganate now afforded the protected depside (XI), which was successively hydrogenolysed to remove the benzyl group and briefly treated with alkali to hydrolyse the *O*-ethoxycarbonyl grouping. The resultant depside, dihydropicrolichenic acid (III), showed the expected light absorptions.



Selection of a suitable reagent for the ultimate and biogenetically informative oxidation step proved to be crucial. Thus the acid (III) was recovered unchanged from a number of oxidising systems including ferric, ceric, and vanadic salts, lead dioxide, and electro-oxidation at a platinum electrode (see Experimental). The use of manganese was now investigated, as previous experience in the benzophenone series had indicated that good yields of coupled products could be obtained by taking advantage of the high potential of the one-electron oxidising power of manganese compounds.[8] When a solution of



Picrolichenic acid: (a) natural; (b) synthetic (as potassium chloride discs) (curve a has been displaced vertically).

dihydropicrolichenic acid (III) in benzene containing fifteen equivalents of manganese dioxide was subjected to spectroscopic control, the intensity of the carbonyl band at 1750 cm.$^{-1}$ (depside) decreased at a rate parallel to the corresponding increase in the intensity of the 1655 cm.$^{-1}$ band, and a new band appeared at 1820 cm.$^{-1}$, the position expected for the spiro-lactone chromophore. Increasing the molar ratio of reagent or the temperature of the reaction led to rapid deterioration of the required spectrum, a single broad band at 1700—1720 cm.$^{-1}$ representing the only carbonyl function. When the solution resulting from six successive treatments under these conditions was rapidly chromatographed over

[7] Asahina and Yosioka, *Ber.*, 1937, **70**, 1827; Fuzikawa, *J. Pharm. Soc. Japan*, 1936, **56**, 25.
[8] Charlot, "Tables of Constants and Numerical Data," Vol. 8, Oxido-Reduction Potentials, Pergamon, Oxford, p. 17.

silica gel there resulted a 15—25% yield of a fraction,[b] m. p. 178° (with evolution of gas), undepressed on admixture with authentic picrolichenic acid (m. p. 178°), which showed spectra in chloroform solution at 1820 (spirolactone), 1670 (bonded CO_2H and dienone), and 1607 (aromatic) cm.$^{-1}$ and $\lambda_{max.}$ 245, 270—277 mμ (ε 24,000, 7800), corresponding exactly with the data for the natural acid. The infrared spectra (in potassium chloride) of the natural and synthetic acids were, moreover, identical (Fig.).

The structure of picrolichenic acid is thus confirmed and the postulated biogenesis is supported in some measure by this synthesis. Resolutions with the natural (racemic) acid are now in progress.

Experimental

For general directions see Part I (preceding paper).

4-Benzyloxy-2-hydroxy-6-pentylbenzaldehyde (VII).—2,4-Dihydroxy-6-pentylbenzaldehyde (5 g.) and benzyl chloride (5 c.c.) were heated under reflux for 4 hr. in aqueous ethanol (25%; 25 c.c.) containing potassium hydroxide (1·6 g.). Removal of the ethanol under reduced pressure followed by acidification and recovery in ether gave an oil which on chromatography over silica gel (100 g.) and elution with light petroleum–benzene (9 : 1; 1600 c.c.) gave the *monobenzyl derivative* (3·9 g.; 55%), b. p. 190°/0·5 mm., $n_D^{18°}$ 1·5852; ν (film) 1640 cm.$^{-1}$ (bonded CHO) (Found: C, 76·65; H, 7·45. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·45%). The compound gives a red colour with 2% ethanolic ferric chloride solution.

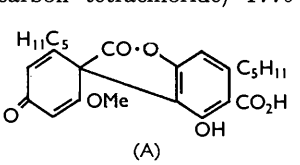
4-Benzyloxy-2-methoxy-6-pentylbenzaldehyde (VIII).—The monobenzyl-aldehyde (3·9 g.), dimethyl sulphate (1·5 c.c.), and potassium carbonate (12 g.) were stirred under reflux in dry acetone (100 c.c.) for 16 hr., addition of dimethyl sulphate and potassium carbonate having been made in four portions during the first 2 hr. Filtration of the cooled solution, evaporation, and isolation in ether gave the *benzyl methyl ether* (VIII) (3·6 g.; 88%) as plates (from methanol), m. p. 51—52°; ν (Nujol) 1680 cm.$^{-1}$ (aromatic CHO) (Found: C, 76·95; H, 7·85. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·75%).

4-Benzyloxy-2-methoxy-6-pentylbenzoic Acid (IX).—To a stirred solution of 4-benzyloxy-2-methoxy-6-pentylbenzaldehyde (1·8 g.) in acetone (500 c.c.) was added potassium permanganate (7 g.) in water (100 c.c.) during 2 hr. at 45°, then the mixture was stirred (at this temperature) for 6 hr. Sulphur dioxide was passed through the cooled solution, and the acetone removed. Separation into an acidic and a neutral fraction and isolation of the acid in ether gave an oil. Chromatography of this on silica gel (15 g.) and elution with benzene–ether (19 : 1; 250 c.c.) afforded the required *acid* (700 mg.; 37%) as needles (from light petroleum), m. p. 62—63°; ν (Nujol) 1700 cm.$^{-1}$ (CO_2H) (Found: C, 73·35; H, 7·45. $C_{20}H_{24}O_4$ requires C, 73·15; H, 7·35%).

4-Formyl-3-hydroxy-5-pentylphenyl 4-Benzyloxy-2-methoxy-6-pentylbenzoate (X).—4-Benzyloxy-2-methoxy-6-pentylbenzoyl chloride [prepared from the above acid (5 g.) by the oxalyl chloride–benzene method] was dissolved in anhydrous ether (500 c.c.) containing 2,4-dihydroxy-6-pentylbenzaldehyde (3·3 g.). The solution was cooled to 0° and pyridine (20 c.c.) added. After 16 hr. at room temperature the solution was acidified and the acidic fraction isolated as an oil, which after chromatography on silica gel and elution with light petroleum–benzene (2 : 3; 2 l.) gave the required ester as a viscous oil (6·8 g.; 85%); this had $\nu_{max.}$ (film) 1750 (depside C=O) and 1640 (bonded CHO) cm.$^{-1}$ and gave a red ferric colour. The *2,4-dinitrophenylhydrazone* had m. p. 152—153° (from ethanol–ethyl acetate) (Found: C, 65·65; H, 6·0; N, 8·15. $C_{38}H_{42}N_4O_9$ requires C, 65·3; H, 6·05; N, 8·0%).

4-Carboxy-3-ethoxycarbonyloxy-5-pentylphenyl 4-Benzyloxy-2-methoxy-6-pentylbenzoate (XI).—The foregoing aldehyde was converted into the *O*-ethoxycarbonyl derivative (ethyl chloroformate–pyridine at −20° for 2 hr.). Oxidation of this with potassium permanganate, the conditions described above being used, gave the required *O-ethoxycarbonyl-acid* (XI) (45%) as prisms (from benzene–petroleum), m. p. 107—109°; $\nu_{max.}$ (in carbon tetrachloride) 1770

[b] Coupling might have occurred with the position "*ortho-*" to the hydroxyl group in ring B leading to the isomeric acid (A), but no evidence was obtained of its presence.



(A)

(-O·CO_2Et), 1750 (depside), and 1700 (CO_2H) cm.$^{-1}$ (Found: C, 69·1; H, 6·8. $C_{35}H_{42}O_9$ requires C, 69·3; H, 7·0%).

Dihydropicrolichenic Acid (III).—The acid (XI) (1·0 g.) was hydrogenolysed in ethanol (50 c.c.) over palladium–charcoal (10%; 200 mg.). After the consumption of 1 mole of hydrogen the solvent was removed and replaced by acetone (5 c.c.). When this solution was treated with sodium hydroxide solution (N; 10 c.c.) for 10 min. and the resulting acidic fraction isolated in ether, the required *acid* formed prisms (460 mg.; 65%), m. p. 117—118° (from benzene); $\lambda_{max.}$ 250 and 291 mμ (13.000 and 7600); $\nu_{max.}$ (potassium chloride disc) 3400 (OH), 1725 (depside C=O), 1650 (bonded CO_2H); $\nu_{max.}$ (in chloroform) 3300, 1750, and 1655 cm.$^{-1}$ (Found: C, 68·05; H, 7·1. $C_{25}H_{32}O_7$ requires C, 67·55; H, 7·25%).

Picrolichenic Acid (I).—Dihydropicrolichenic acid (30 mg.) was treated with manganese dioxide (J. Woolley Co.; 15 equivs.; 90 mg.) in benzene (30 c.c.) with stirring for 30 min. The manganese dioxide was removed by filtration and extracted with sodium carbonate solution, and the acidified solution extracted with ether. The combined benzene and ether extracts were evaporated to leave a gum, which had in its infrared spectrum (in chloroform) a new band at 1820 cm.$^{-1}$, while the intensity of the band at 1750 cm.$^{-1}$ had decreased in proportion to the increase in intensity of the 1660 cm.$^{-1}$ band. Five more treatments of the mixture under the same conditions (with spectroscopic control) gave a product with maximum intensity of the 1820 cm.$^{-1}$ band. Chromatography on a short column of silica gel (300 mg.) and elution with benzene–ether (49 : 1) gave a solid fraction (5–7 mg.; average of several experiments), which on crystallisation from ether–petroleum gave prisms, m. p. 178° (with evolution of carbon dioxide) which was identical in m. p., mixed m. p., and ultraviolet and infrared absorption with authentic picrolichenic acid; $\lambda_{max.}$ 245 and 270—277 mμ (ε 22,000 and 7800); $\nu_{max.}$ (potassium chloride disc) 1820 (spirolactone), 1670 cm.$^{-1}$ (bonded CO_2H and dienone superimposed) (see Fig.).

When the reaction was carried out at 50—60°, or in the presence of 40, 55, or 100 equivalents of manganese dioxide in benzene or chloroform solution, a new band in the infrared spectrum rapidly grew at 1700—1710 cm.$^{-1}$ and no crystalline product was isolable from such a mixture. This effect was also observed when picrolichenic acid (20 mg.) was treated for 24 hr. with manganese dioxide (200 mg.) in benzene (15 c.c.) at room temperature, or for 30 min. at 50°.

The following oxidising conditions led to quantitative recovery of dihydropicrolichenic acid from the reaction mixture.

Oxidant (moles)		Solvent	Time	Temp.
$K_3Fe(CN)_6$	(2)	Na_2CO_3–H_2O	1 hr.	0°
,,	(2)	,,	2 hr.	20
,,	(2)	,,	2 hr.	70
,,	(5)	,,	24 hr.	20
$FeCl_3$	(5)	EtOH–H_2O	14 hr.	20
,,	(5)	,,	14 days	20
PbO_2	(3)	Benzene	24 hr.	80 *
,,	(3)	Toluene	2 hr.	110 *
$Ce(SO_4)_2$	(3)	AcOH–H_2SO_4(aq.)	24 hr.	20
NH_4VO_3 [9]	(5)	,,	24 hr.	20
Dichlorodicyanobenzoquinone	(2)	Benzene	24 hr.	80

* 30% recovery of starting material; residue resinous.

Oxidation at a smooth platinum anode (3 × 2 cm.) in acetic acid–sulphuric acid mixtures at 110 v (D.C.) gave back dihydropicrolichenic acid in quantitative yield.

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Glasgow, W.2. [*Received, October 27th*, 1960.]

[9] Littler and Waters, *J.*, 1959, 3014.