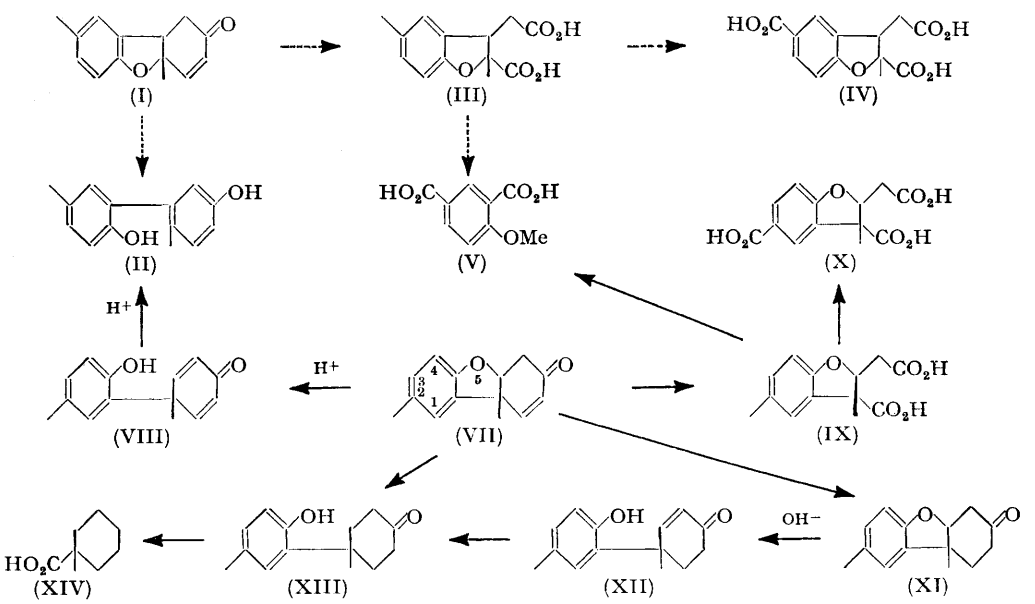
108. *The Synthesis of Usnic Acid.*

By D. H. R. Barton, A. M. Deflorin, and O. E. Edwards.

The constitution of the neutral crystalline dimer obtained by oxidation of *p*-cresol has been determined. The biogenetic significance of this compound has been illustrated by a simple two-step synthesis of (±)-usnic acid. The more important features of this work have already been summarised in preliminary form.[1]

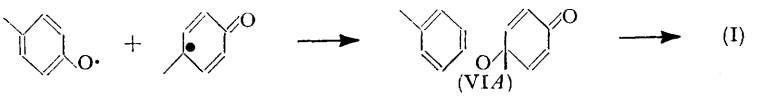
The oxidation of phenols has received much attention.[2] Our interest in this subject was first stimulated by a disbelief in the structure (I) advanced by Pummerer, Puttfarcken, and Schopflocher [3] for the neutral crystalline dimer, m. p. 124°, obtained by oxidation of *p*-cresol by one-electron-transfer oxidising agents.[4] Although the constitution (I) appears to have been generally accepted, it is based on ambiguous evidence. Pummerer, Puttfarcken, and Schopflocher [3] showed that, on treatment with acid, the dimer gave 2 : 5′-dihydroxy-5 : 2′-dimethyldiphenyl ("2 : 3′-dicresol") (II). Westerfeld and Lowe [5] oxidised the compound with potassium permanganate to a dicarboxylic acid $C_{13}H_{14}O_5$, formulated as (III), which was further transformed by the same reagent into a tricarboxylic acid, $C_{13}H_{12}O_7$, regarded as (IV). Fusion of the acid $C_{13}H_{14}O_5$ with potassium hydroxide, methylation, and further permanganate oxidation gave 4-methoxy*iso*phthalic acid (V).



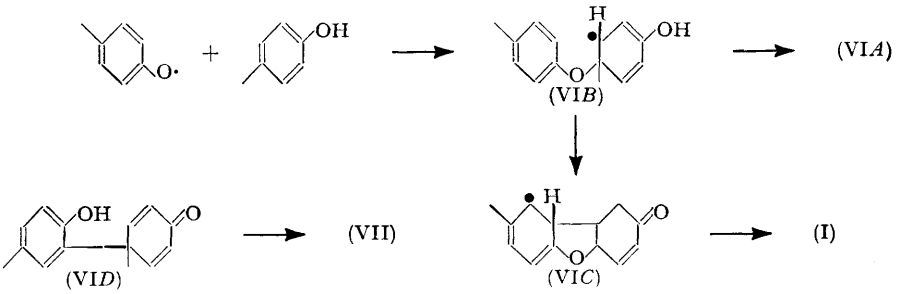
Now oxidative dimerisations of phenols of the type under discussion can be regarded as *either* the pairing of radicals *or* the substitution of one radical into a neutral phenol molecule

[1] Barton, Deflorin, and Edwards, *Chem. and Ind.*, 1955, 1039.
[2] For leading references see, for example, (*a*) Erdtman, *Annalen*, 1933, **503**, 283; *Svensk kem. Tidskr.*, 1934, **46**, 226; Haworth, *J.*, 1942, 455; (*b*) Critchlow, Haworth, and Pauson, *J.*, 1951, 1318; Waters and Wickham-Jones, *J.*, 1952, 2420; Witkop and Goodwin, *Experientia*, 1952, **8**, 377; Pummerer, Schmidutz, and Seifert, *Chem. Ber.*, 1952, **85**, 535; Freudenberg and Schraube, *ibid.*, 1955, **88**, 16; C. D. Cook, Nash, and Flanagan, *J. Amer. Chem. Soc.*, 1955, **77**, 1783; Harington, *J.*, 1944, 193; Pitt-Rivers, *Biochem. J.*, 1948, **43**, 223.
[3] Pummerer, Puttfarcken, and Schopflocher, *Ber.*, 1925, **58**, 1808.
[4] For leading references see : Pummerer, Melamed, and Puttfarcken, *Ber.*, 1922, **55**, 3116; Bowden and Reece, *J.*, 1950, 2249; Cosgrove and Waters, *J.*, 1951, 1726; Cavill, Cole, Gilham, and McHugh, *J.*, 1954, 2785.
[5] Westerfeld and Lowe, *J. Biol. Chem.*, 1942, **145**, 463.

followed by further oxidation. Pummerer *et al.*,[2,3] Schöpf,[6] and others [7] have regarded the formation of the dimer (I) as proceeding through an intermediate (VI*A*). It seemed to us, however, that the change from (VI*A*) to (I) was improbable. A second scheme for the formation of structure (I) involves radical substitution using radicals (VI*B*) and (VI*C*) as intermediates. In so far as radical (VI*B*) is the same type of hemiquinone radical that is encountered in the oxidation of quinols and catechols, it seemed to us that its probable



fate would be oxidation to (VI*A*) rather than cyclisation to (VI*C*). On these grounds we were encouraged to search for an alternative scheme for the dimerisation. If C–C coupling, either by pairing or by substitution, is the first step in the reaction, the first non-radical



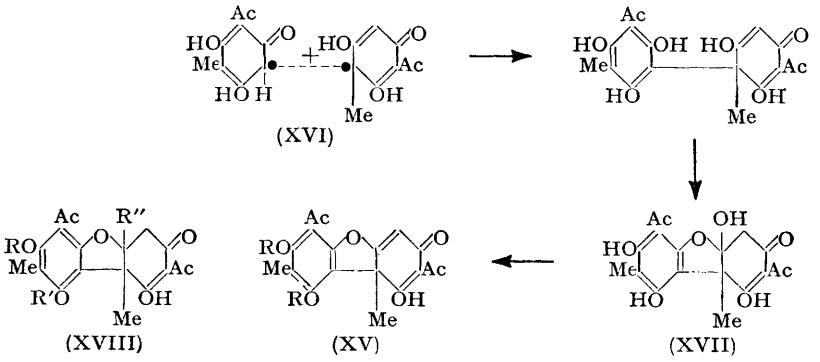
product would be (VI*D*). β-Addition of the phenolic hydroxyl to the enone system would then afford the product (VII). Such a scheme would avoid the theoretical difficulties referred to above.

The structure (VII) provides in every way a satisfactory formulation for the dimer, m. p. 124°, of *p*-cresol. Thus by dienone–phenol rearrangement (see VIII) the formation of (II) would be unexceptional. The $C_{13}H_{14}O_5$ acid (see above) becomes (IX), a formula which explains equally as well as (III) the formation of a tricarboxylic acid [now formulated as (X)] and of (V). The correctness of formulation (VII) was confirmed as follows. Hydrogenation of the dimer in ethyl acetate over palladised calcium carbonate gave a dihydro-derivative (XI). This showed the ultraviolet absorption spectrum of an aromatic ether and gave infrared maxima (in CS_2 solution) at 1722 (*cyclo*hexanone), 1210 (aromatic ether), and 862 and 807 cm.$^{-1}$ (1 : 2 : 4-trisubstituted benzene) consistent with its formulation. The ketone (XI) resisted further hydrogenation in neutral medium, but readily took up a second mol. of hydrogen in ethanolic sodium ethoxide over palladised charcoal [hydrogenation of (XII)] to give the keto-phenol (XIII). This showed an infrared maximum at 1712 cm.$^{-1}$ (*cyclo*hexanone; CS_2 solution); it also gave bands at 3300 (phenolic OH), 3100, 1614, 1520, 890, 822 (1 : 2 : 4-trisubstituted benzene), and 1688 (*cyclo*hexanone) cm.$^{-1}$ (all in Nujol). The keto-phenol was conveniently obtained in one step by the similar hydrogenation of the dimer (VII). Wolff–Kishner reduction of the keto-phenol (XIII) and oxidation of the product with potassium permanganate gave 1-methyl*cyclo*hexane-1-carboxylic acid (XIV).

In agreement with others,[2a] we believe that the oxidative pairing (or equivalent substitution process) of phenolic radicals is of some biogenetic importance. We illustrate the particular significance of the dimer (VII) in biogenetic concepts by a simple synthesis of (±)-usnic acid (XV; R = H).[8] Oxidation of methylphloracetophenone [see (XVI)]

[6] Schöpf, *Naturwiss.*, 1952, **39**, 241.
[7] See Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, 1954, p. 394 *et seq.*
[8] Curd and Robertson, *J.*, 1937, 894; see also: (*a*) Schöpf and Ross, *Annalen*, 1941, **546**, 1; (*b*) Barton and Bruun, *J.*, 1953, **603**; (*c*) Asahina and Shibata, "The Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Tokyo, Japan, 1954.

with potassium ferricyanide, as in the formation of (VII), gave as main crystalline product (15%) the expected dimer (XVII). Acetylation of this with acetic anhydride containing a trace of sulphuric acid gave a reasonable yield of (±)-usnic acid diacetate (XV; R = Ac),



further characterised by hydrolysis to (±)-usnic acid. Alternatively the dimer (XVII) was dissolved in concentrated sulphuric acid to give (±)-usnic acid (XV; R = H) directly in a two-step synthesis. The resolution of (±)-usnic acid has already been reported.[9]

Compounds analogous to (XVII) have been obtained by Takahashi.[10] Thus addition of methanol under acidic conditions to (±)-usnic acid diacetate gave (±)-usnic acid *iso*-methoxide monoacetate (XVIII; R = H, R′ = Ac, R″ = OMe), which we have hydrolysed to (±)-usnic acid "*iso*methoxide" (XVIII; R = R′ = H; R″ = OMe). It would be expected that the ultraviolet absorption spectra of dihydrousnic acid (XVIII; R = R′ = R″ = H),[11] of the dimer (XVII), and of the "*iso*methoxide" (XVIII; R = R′ = H, R″ = OMe) would be superimposable. This is indeed the case, although our spectral data are not in agreement with those recorded by Takahashi.[10]

The revised structure (VII) for the *p*-cresol dimer has a direct bearing [6, 7] on the biogenesis of morphine alkaloids [12] which we are currently exploring.

Experimental

Ultraviolet absorption spectra were taken in EtOH solution using the Unicam S.P. 500 Spectrophotometer. Infrared absorption spectra were kindly determined by Messrs. Glaxo Laboratories Ltd.

Hydrogenation of the Ketone (VII).—The ketone (Pummerer *et al.*[3]) (645 mg.) was hydrogenated in ethyl acetate over 1% palladised calcium carbonate (400 mg.). One mol. of hydrogen was consumed within 15 min.; there was no further uptake. After removal of the catalyst by filtration, the solvent was removed *in vacuo* and the residue recrystallised from light petroleum (b. p. 40—60°) to give 1 : 2 : 3 : 4 : 4*a* : 9*b* -*hexahydro*-8 : 9*b*-*dimethyl*-3-*oxodibenzofuran* (numbering : Ring Index No. 1719) (XI) (500 mg.), m. p. (prisms) 81—82°, $\lambda_{max.}$ 287 mμ (ε 3500) (Found : C, 77·65; H, 7·55. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·45%).

Preparation of the Keto-phenol (XIII).—(i) *From the ketone* (VII). The ketone (4·3 g.) in dry ethanol (150 ml.) containing dissolved sodium (4·6 g.) was hydrogenated over 10% palladised charcoal. Two mols. of hydrogen were rapidly consumed; there was no further uptake. The catalyst was removed by filtration and the alkaline solution diluted with 5% aqueous hydrochloric acid (500 ml.). Extraction with ether, removal of the ether *in vacuo*, and crystallisation of the residue from aqueous ethanol gave the (2-*hydroxy*-5-*methylphenyl*)-4-*methyl*-4-cyclo*hexanone* (XIII), m. p. 175—176° (Found : C, 77·3; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·05; H, 8·3%).

(ii) *From the dihydro-ketone* (XI). The dihydro-ketone (645 mg.) was hydrogenated in

[9] Dean, Halewood, Mongkolsuk, Robertson, and Whalley, *J.*, 1953, 1250.
[10] Takahashi, *Pharm. Bull.* (*Japan*), 1953, **1**, 36; for correct formulation see Asahina and Shibata, ref. 8*c*.
[11] For spectra see MacKenzie, *J. Amer. Chem. Soc.*, 1952, **74**, 4067; Barton and Bruun, ref. 8*b*.
[12] Robinson and Sugasawa, *J.*, 1931, 3163; 1932, 789; 1933, 280; 1936, 1079; (Sir) Robert Robinson, "The Structural Relations of Natural Products," Oxford University Press, 1955.

ethanolic sodium ethoxide as above. One mol. of hydrogen was rapidly absorbed. Crystallisation of the product as above gave the same keto-phenol (m. p. and mixed m. p.).

Conversion of the Keto-phenol (XIII) *into* 1-*Methylcyclohexane*-1-*carboxylic Acid* (XIV).—The keto-phenol (3·0 g.) was heated at 200° for 1 hr. with hydrazine hydrate (100%; 8 ml.) in diethylene glycol (300 ml.). Sodium (10 g.) in diethylene glycol (120 ml.) was then added and the solution refluxed for 6 hr. The cooled solution was diluted with aqueous 5% hydrochloric acid (500 ml.) and extracted with ether. Removal of the ether gave a gum (2·66 g.). This was filtered in benzene solution through silica gel (60 g.) to furnish a clear viscous oil (2·47 g.). The latter (2·40 g.) in "AnalaR" acetone (150 ml.) was stirred for 24 hr. at room temperature with powdered potassium permanganate (8·0 g.; added portionwise). Treatment with sulphur dioxide, addition of water, and extraction with ether gave a non-crystalline acid (1·76 g.). This was suspended in aqueous 0·87N-potassium hydroxide (20 ml.), and powdered potassium permanganate (2·1 g.) added with stirring during 2 hr. at room temperature. Additional potassium permanganate (200 mg.) was not consumed during a further 2 hours' stirring. After passage of sulphur dioxide and addition of dilute sulphuric acid, extraction with chloroform furnished an acid (1·0 g.). Extraction with light petroleum (b. p. 40—60°) gave a soluble acidic oil (665 mg.) and an insoluble residue. The light petroleum solution of the former was chromatographed over silica gel. Elution with benzene gave 1-methyl*cyclo*hexane-1-carboxylic acid (XIV) (312 mg.), identified by m. p., mixed m. p., and conversion into the *p*-bromophenacyl ester (m. p. and mixed m. p.) and *S*-benzylthiuronium salt (m. p. and mixed m. p.).

The authentic specimen of 1-methyl*cyclo*hexyl-1-carboxylic acid was prepared [13] by carboxylation of the Grignard derivative of 1-methyl*cyclo*hexyl chloride.[14] It was converted into the p-*bromophenacyl ester*, m. p. 57·5—58·5° [from light petroleum (b. p. 40—60°)] (Found: C, 56·45; H, 5·7; Br, 22·7. $C_{16}H_{19}O_3Br$ requires C, 56·65; H, 5·65; Br, 23·55%), and the S-*benzylthiuronium salt* (from aqueous ethanol), m. p. 135—136° (139—140° after drying for 60 hr. at room temperature over phosphoric oxide *in vacuo*) (Found: C, 63·25; H, 7·85; N, 9·2. $C_{16}H_{24}O_2N_2S$ requires C, 62·3; H, 7·85; N, 9·1%); for characterisation (see above).

Oxidation of Methylphloracetophenone.—Anhydrous sodium carbonate (12·5 g.) in water (165 ml.) was deaerated with nitrogen (oxygen-free); methylphloracetophenone [15] (5·0 g.) was added and brought into solution by gentle warming. The solution was cooled to 0° and potassium ferricyanide (6·75 g., 1 mol.) in water (160 ml.) was added slowly under nitrogen (oxygen-free) during 30 min. with good stirring. After a further 30 minutes' stirring, the clear, red solution was acidified with 6N-sulphuric acid and extracted with ether. Removal of the ether after drying (Na_2SO_4) furnished a residue which was repeatedly digested with cold chloroform. The residue (2·1 g.), mainly starting material, was discarded. Removal of the chloroform gave a brown foam (2·8 g.). This was chromatographed in benzene over silica gel (75 g.). Elution with ether–benzene (2 : 98) (1800 ml.) gave traces of material which were not investigated further. Elution with ether–benzene (5 : 95) (1200 ml.) afforded the dimer, 2 : 6-*diacetyl*-3 : 4 : 4*a* : 9*b*-*tetrahydro*-1 : 4*a* : 7 : 9-*tetrahydroxy*-8 : 9*b*-*dimethyl*-3-*oxobenzofuran* (XVII) (395 mg. pure), prisms (from benzene), m. p. 192° (decomp.), $\lambda_{max.}$ 228, 284, and 329 mμ (ε 20,000, 24,800, and 3700 respectively), $\lambda_{min.}$ 252 and 327 mμ (ε 11,800 and 3600 respectively) (Found: C, 59·75; H, 5·0. $C_{18}H_{18}O_8$ requires C, 59·65; H, 5·0%). Elution with ether–benzene (1 : 9; 1 l.) gave back starting material (m. p., mixed m.p., and ultraviolet absorption spectrum) (100 mg.). Elution with ether–benzene (1 : 4; 1600 ml.) furnished only traces of material. Elution with ether–benzene (1 : 1; 2400 ml.) gave a compound, prisms (from dioxan or from acetone–ethyl acetate), m. p. 291—292° (decomp.), the nature of which was not investigated further.

The best yield of the dimer (XVII) was obtained as follows. Methylphloracetophenone (2·36 g.) in water (150 ml.) containing anhydrous sodium carbonate (6·0 g.) was oxidised with potassium ferricyanide (6·5 g., 1·5 mol.) essentially as described above. Chromatography over silica gel (50 g.) and elution with ether–benzene (5 : 95; see above) gave pure dimer (XVII) (367 mg., 15%). No starting material was recovered.

(±)-*Usnic Acid.*—The dimer (XVII) (200 mg.) in acetic anhydride (2 ml.) containing concentrated sulphuric acid (0·5 ml. per 100 ml. of acetic anhydride) was heated at 40° (water-bath) for 30 min. After cooling to 0°, the solution was poured on ice (20 g.). Filtration gave crude (±)-usnic acid diacetate (115 mg.). Three recrystallisations from benzene–methanol afforded pure (±)-usnic acid diacetate (60 mg.), m. p. and mixed m. p. 205—207°. The identity

[13] Cf. Gutt, *Ber.*, 1907, **40**, 2069; Schuerch and Huntress, *J. Amer. Chem. Soc.*, 1949, **71**, 2233.
[14] Brown and Borkowski, *ibid.*, 1952, **74**, 1894.
[15] Curd and Robertson, *J.*, 1933, 437.

was confirmed by identical ultraviolet ($\lambda_{max.}$ 223 mμ, inflections at 243 and 307 mμ; ε 25,400, 17,700, and 8200 respectively) and infrared spectra ($CHCl_3$ solution) and by hydrolysis to (±)-usnic acid as follows. The synthetic diacetate (10 mg.) was added to ice-cold concentrated sulphuric acid, left for 5 min., and poured on ice. Extraction with chloroform and crystallisation from methanol gave pure (±)-usnic acid, identified by m. p. and mixed m. p. (195°) and ultraviolet absorption spectrum ($\lambda_{max.}$ 234 and 282 mμ; ε 32,900 and 24,300: $\lambda_{min.}$ 255 mμ; ε 12,700), identical with that of an authentic specimen.

A one-step conversion of the dimer (XVII) into (±)-usnic acid was secured as follows. The dimer (XVII) (364 mg.) was treated in three portions with concentrated sulphuric acid (3 ml. for each portion) at 0° for 5 min., the initial gummy mass being stirred with a rod until dissolved. The solutions were poured on ice and extracted with chloroform. Removal of the chloroform from the combined extracts and crystallisation ten times from ethanol gave pure (±)-usnic acid (8 mg.), identified by m. p., mixed m. p., and ultraviolet absorption spectrum (see above).

(±)-*Usnic Acid* "iso*Methoxide*."—The monoacetate (XVIII; R = H, R′ = Ac, R″ = OMe), m. p. 178°, of this compound was prepared according to Takahashi.[10] The monoacetate (96 mg.) was dissolved in concentrated sulphuric acid (1 ml.) at 0° and the solution poured on ice. Crystallisation from methanol gave (±)-*usnic acid* "iso*methoxide*" (XVIII; R = R′ = H, R″ = OMe) (56 mg.), m. p. 188—190°, $\lambda_{max.}$ 226 and 283 mμ (ε 19,800 and 24,900 respectively), $\lambda_{infl.}$ 330 mμ (ε 3400), $\lambda_{min.}$ 251 mμ (ε 11,700) (Found: C, 60·55; H, 5·6. $C_{19}H_{20}O_8$ requires C, 60·65; H, 5·35%).

The usnic acid used in this work was generously provided by Professor and Mrs. N. A. Sörensen and Dr. T. Bruun (Trondheim). We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial assistance. One of us (O. E. E.) is on leave of absence from the National Research Council, Ottawa; another (A. M. D.) is indebted to the Stiftung für Stipendien auf dem Gebiete der Chemie (Switzerland) for a Post-doctorate Fellowship. The initial experiments on the constitution of the dimer (VII) from *p*-cresol were kindly carried out by Dr. R. B. Kelly, now of Merck and Co., Montreal, Canada.

Birkbeck College, London, W.C.1.
The University, Glasgow, W.2.

[*Received, September 14th*, 1955.]