535. *The Constitution of Piceatannol.*

By JILL CUNNINGHAM, E. HASLAM, and R. D. HAWORTH.

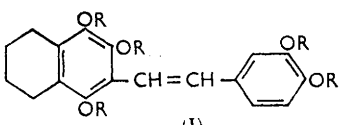
Previous work leading to the structure (I; R = H) for piceatannol, a crystalline aglucone of spruce bark, is reviewed.

A number of derivatives of 5,6,7,8-tetrahydronaphthalene-1,2,4-triol have been synthesised but differed from piceatannol, and the nuclear magnetic resonance spectrum of the latter indicated that the tetralin structure was incorrect. Oxidation of piceatannol acetate by potassium permanganate gave protocatechuic acid or aldehyde and 3,5-dihydroxybenzoic acid which suggested that piceatannol was stilbene-3,3′,4,5′-tetraol (XII; R = H). This identity has been confirmed by a comparison of the phenols and their derivatives and by synthesis of piceatannol from 3,5-dihydroxyphenylacetic acid and protocatechualdehyde.

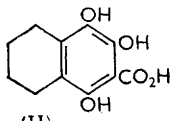
THE isolation of crystalline components from the inner bark of the spruce was first reported by Grassmann *et al.*[1a,b] and the properties and structures of these and other constituents of the bark have been discussed in a series of papers [1] from their Institute. Ethyl acetate, ethanol, or water extracts of the bark contain, in addition to much non-tannin material, a complex mixture of glucosides and aglucones which were partially separated by chromatography on cellulose–silica gel or polyamide columns. The glucosides were best hydrolysed enzymically by an extract of *Aspergillus oryzae*, and the main aglucones isolated were quercetin, 5,6,7,8-tetrahydronaphthalene-1,2,4,-triol (III; R = H), and piceatannol [supposedly (I; R = H)] and its dihydro-derivative. The structure (I; R = H) for

[1] (*a*) Grassmann, *Colloquimsber. Inst. Gerbereichemie techn. Hochschule, Darmstadt*, 1948, **3**, 59; (*b*) Grassmann, Deffner, Schuster, and Pauckner, *Chem. Ber.*, 1956, **89**, 2523; (*c*) Grassmann, Endres, Pauckner, and Mathes, *ibid.*, 1957, **90**, 1125; (*d*) Endres, *Das Leder*, 1957, **8**, 222; (*e*) Grassmann, Endres, Brockhaus, and Merkle, *Chem. Ber.*, 1957, **90**, 2416; (*f*) Grassmann, Endres, and Pauckner, *ibid.*, 1958, **91**, 134; (*g*) Endres, Grassmann, and Mathes, *ibid.*, p. 141; (*h*) Endres, *ibid.*, p. 636; (*i*) Grassmann, *Das Leder*, 1958, **9**, 193; (*j*) Endres, Stadler, and von der Crone, *ibid.*, 1960, **11**, 1; (*k*) Grassmann and Endres, *ibid.*, 1959, **10**, 237; (*l*) Endres and Leppmeier, *Chem. Ber.*, 1961, **94**, 419; (*m*) Endres and Merkle, *ibid.*, p. 431; (*n*) Endres, Merkle, and Bauriedel, *ibid.*, p. 438.

piceatannol was consistent with the analytical evidence which was in agreement with $C_{18}H_{16-18}O_5$, with the formation of a penta-acetate $C_{28}H_{28}O_{10}$,[1f] and with the ultraviolet spectroscopic similarity of piceatannol with 3,3′-dimethoxystilbene-4,4′-diol.[1e] The stilbene characteristics were, however, no longer present in dihydropiceatannol, obtained from natural sources or by catalytic hydrogenation of piceatannol.[1g] Strong support was obtained from oxidation of the penta-acetate which with potassium permanganate gave, after hydrolysis, protocatechuic acid and a phenolic carboxylic acid, $C_{11}H_{12}O_5$ (II). This acid lost carbon dioxide readily and yielded 5,6,7,8-tetrahydronaphthalene-1,2,4-triol[1f] (III; R = H) which had been isolated from spruce bark.[1n] This phenol gave a triacetyl derivative which was claimed to be identical with a synthetic specimen,[1n] and nitric acid oxidation of piceatannol, the phenol or the phenolic carboxylic acid was stated to give adipic acid.[1f]



(I)



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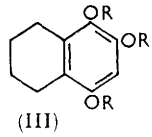


(III)

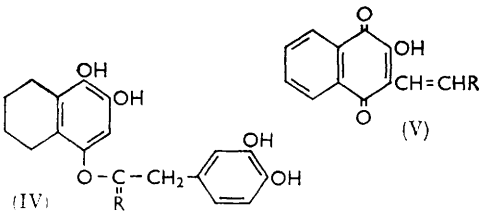
The structure (I; R = H) for piceatannol aroused interest as the first recorded instance of a naturally occurring stilbene containing a tetralin residue, and as it was difficult to suggest a simple biogenetic pathway for this structure confirmation was sought by the synthesis of the natural product or a closely related compound. The triacetate (III; R = Ac) which was selected as a starting material was prepared by the three-stage process involving (*a*) high-pressure hydrogenation of 1,4-naphthaquinone to 5,6,7,8-tetrahydronaphthalene-1,4-diol,[2] (*b*) oxidation by potassium bromate to 5,6,7,8-tetrahydro-1,4-naphthaquinone,[3] and (*c*) Thiele acetylation of the quinone.[4] 5,6,7,8-Tetrahydronaphthalene-1,2,4-triol (III; R = H) was prepared by hydrolysis of the acetate (III; R = Ac) with alcoholic hydrochloric acid in an inert atmosphere and the trimethyl ether was prepared directly from the triacetate by the action of dimethyl sulphate and alkali; preliminary attempts to prepare the ether by the action of ethereal diazomethane on the triol yielded 5,6,7,8-tetrahydro-2-methoxy-1,4-naphthaquinone, which was also obtained by the action of diazomethane on 5,6,7,8-tetrahydro-2-hydroxy-1,4-naphthaquinone.[4]

Substitution of 5,6,7,8-tetrahydronaphthalene-1,2,4-triol (III; R = H) or its trimethyl ether in the 3-position proved difficult and reaction of the ether with 3,4-dimethoxyphenylacetyl chloride in presence of aluminium chloride gave no ketonic product. An attempted Hoesch reaction between the triol and 3,4-dimethoxyphenylacetonitrile gave, instead of the expected ketimine hydrochloride, an imidoate hydrochloride, probably (IV; R = NH,HCl), which was hydrolysed by cold water to the ester (IV; R = O) and by aqueous acid to the starting triol and 3,4-dimethoxyphenylacetic acid. The structure assigned to this ester (IV; R = O) is preferred to isomers involving one of the other phenolic groups as the infrared spectrum shows the presence of a single carbonyl stretching frequency (1741 cm.$^{-1}$), whilst isomeric structures should exhibit two carbonyl stretching frequencies characteristic of *O*-phenolic depsides.[5] Similar formation of imidoate hydrochlorides has been observed when phenol and α-naphthol react with phenylacetonitrile and acetonitrile, respectively.[6]

Whilst investigating the synthesis of lapachol, Hooker[7] studied the reaction between

[2] Cardini, *Gazzetta*, 1952, **82**, 155.
[3] Grinev, Terent'ev, and Terent'ev, *Zhur. obschei Khim.*, 1956, **26**, 560; *Chem. Zentr.*, 1958, **129**, 1280.
[4] Skita and Rohrmann, *Ber.*, 1930, **63**, 1481.
[5] Biggins, Cairns, Eglinton, Haslam, and Haworth, *J.*, 1963, 1750.
[6] Houben, *Ber.*, 1926, **59**, 2878.
[7] Hooker, *J. Amer. Chem. Soc.*, 1936, **58**, 1163.

2-hydroxy-1,4-naphthaquinone and a variety of aldehydes, to give 2-alkenyl-3-hydroxy-1,4-naphthaquinones (V). Catalytic hydrogenation of these quinones gave the corresponding alkylnaphthalenetriols which were unstable and were oxidised to the alkylhydroxynaphthaquinones (VI) during attempted isolation. It was hoped to adapt the


(IV)

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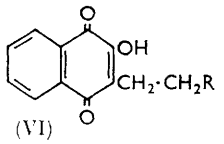
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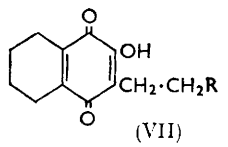
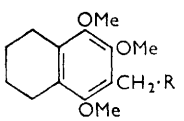

(VII)

former reaction to the synthesis of piceatannol; but n-heptaldehyde, which Hooker had used in the formation of the quinone (V; R = C_5H_{11}), did not react with 5,6,7,8-tetrahydro-2-hydroxy-1,4-naphthaquinone. It was discovered, however, that the condensation products (V; R = C_5H_{11}) and (V; R = Ph) of 2-hydroxy-1,4-naphthaquinone with n-heptaldehyde and phenylacetaldehyde, respectively, when subjected to high-pressure hydrogenation gave, perhaps rather unexpectedly, compounds whose analysis, infrared and ultraviolet spectra, and chemical properties were consistent with the structures (VII; R = C_5H_{11} and R = Ph, respectively), but the corresponding triols could not be isolated because of their ready atmospheric oxidation.

On the basis of these hydrogenation experiments it was hoped that a dihydropiceatannol dimethyl ether might be prepared by a Hooker condensation between 2-hydroxy-1,4-naphthaquinone and 3,4-dimethoxyphenylacetaldehyde followed by reduction. However, in the acidic reaction conditions the aldehyde preferentially underwent self-condensation to give 6-(3,4-dimethoxyphenyl)-2,3-dimethoxynaphthalene;[8] analogous condensation has been observed in the conversion of 3,4-methylenedioxyphenylacetaldehyde into 2,3-methylenedioxy-6-(3,4-methylenedioxyphenyl)naphthalene.[9]

Chloromethylation of the trimethyl ether (III; R = Me) proved a successful method of substitution in position 3, and the chloromethyl derivative (VIII; R = Cl) was converted into the nitrile (VIII; R = CN) and thence into the acid (VIII; R = CO_2H). This acid condensed readily with veratrole in the presence of polyphosphoric acid, yielding the ketone (IX) which was reduced by lithium aluminium hydride to an oily secondary alcohol. The alcohol was not isolated, but dehydration of the crude product with potassium hydrogen sulphate gave the crystalline 2-(3,4-dimethoxystyryl)-5,6,7,8-tetrahydro-1,3,4-trimethoxynaphthalene (I; R = Me), which on cleavage with potassium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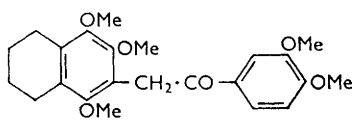

(IX)

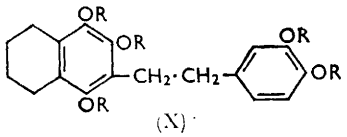
permanganate yielded veratric acid, thereby establishing the position of condensation of the acid (VIII; R = CO_2H) with veratrole. As piceatannol methyl ether had not been described, demethylation of the synthetic stilbene derivative (I; R = Me) was attempted, but experiments with hydrogen bromide–acetic acid, pyridine hydrochloride, or aluminium chloride–benzene were unsuccessful. Hydrogenation of this derivative (I; R = Me) gave 2-(3,4-dimethoxyphenethyl)-5,6,7,8-tetrahydro-1,3,4-trimethoxynaphthalene (X; R = Me), but demethylation of this gave the orange quinone (XI), whose infrared spectrum showed absorption at 1641 and 1626 cm.$^{-1}$, and whose ultraviolet spectrum was very

[8] Bailey, Robinson, and Staunton, *J.*, 1950, 2277.
[9] Erdtman and Robinson, *J.*, **1933**, 1530.

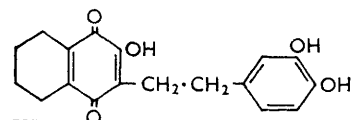
similar to those of the quinones (V; R = C_5H_{11} and Ph). Catalytic hydrogenation of this quinone (XI) in methanol yielded smoothly a colourless solution which became orange again on exposure to air and from which the quinone (XI) was recovered.

Although the acetyl derivative (X; R = Ac) was prepared by reduction of the quinone (XI) and subsequent acetylation in an inert atmosphere, attempts to isolate the pentaol (X; R = H) failed because of the ready oxidation of compounds of this type, prepared by Hooker [7] and also during this investigation. Grassmann and his colleagues,[1a,b,c,g] on the other hand, were able to isolate piceatannol and its dihydro-derivative without apparent difficulty. However, they mention [1i] the conversion of these substances in air and in the presence of acids into red or yellow quinone-like products which, unlike our products, could not be isolated as they were readily converted into amorphous polymeric forms resembling phlobaphenes.

An exchange of specimens of some of our synthetic products and some of Dr. Endres's piceatannol derivatives led to unsatisfactory and inconclusive results, and consequently we isolated piceatannol from spruce bark as described by Grassmann and his co-workers [1b,c] and reinvestigated its properties.



(X)



(XI)

The nuclear magnetic resonance results (Table 1) for a number of tetralin derivatives recorded at 60 Mc./sec. with tetramethylsilane as internal standard (τ 10) showed characteristic peaks at τ 7·4 and τ 8·3 which are attributed to the α- and β-methylene-hydrogen atoms of the tetralin structures. However, these peaks were absent from the spectrum of piceatannol acetate and it was concluded that the natural product could not have the tetralin structure (I; R = H). This conclusion was supported by oxidation experiments on piceatannol acetate. After its treatment with potassium permanganate in acetone–tetrahydrofuran in conditions which Grassmann *et al.*[1f] claimed gave protocatechuic acid and the acid (II), we detected by paper chromatography four phenols giving positive reactions with Gibbs's reagent. The two main products were isolated and identified as protocatechualdehyde and 3,5-dihydroxybenzoic acid, but the other two (minor) phenols have not been identified. When potassium permanganate was used in

TABLE 1.

Nuclear magnetic resonance data (τ values).

		Proton assignment					
	Solvent	α-CH_2	β-CH_2	CH_2·CH_2	Arom. and vinyl	OMe	CO·CH_3
5,6,7,8-Tetrahydro-2-methoxy-1,4-naphthaquinone	H·CO·NMe_2	7·47	8·37	—	—	6·33	—
(III; R = Me)	CCl_4	7·4	8·29	—	3·77	6·18, 6·24, 6·29	—
(III; R = Ac)	$CHCl_3$	7·42	8·26	—	3·1	—	7·71
(X; R = Me)	CCl_4	7·38	8·30	7·29	3·33	6·27, 6·28, 6·39	
(X; R = Ac)	$CHCl_3$	7·45	8·37	7·28		—	7·71
(I; R = Me)	CCl_4	7·33	8·27	—	2·5—3·4	6·15, 6·21, 6·38	—
Piceatannol acetate	$CHCl_3$	—	—	—	2·9—3·1	—	7·70

aqueous acetone, only protocatechuic and 3,5-dihydroxybenzoic acid were identified (both were isolated by chromatography on a polyamide column).

It was then concluded that piceatannol was stilbene-3,3',4,5'-tetraol (XII; R = H) which King, King, Godson, and Manning [10] recently isolated from the heartwood of

[10] King, King, Godson, and Manning, *J.*, 1956, 4477.

Vouacapoua macropetala. The analytical figures reported by Grassmann *et al.*,[1b] which we have confirmed, for piceatannol and its acetate are in good agreement with the formula $C_{12}H_{12}O_4$ and its tetra-acetate (XII; R = Ac), respectively, and comparison of piceatannol and its derivatives with samples of the stilbene and its derivatives kindly supplied by Dr. T. J. King conclusively established the identity, as shown in Table 2.

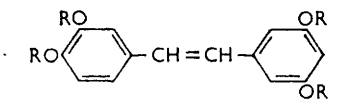
TABLE 2.

M. p. comparison of piceatannol and its derivatives.

	Ref. 1*b*, *f*	Ref. 10	Present work	Mixture	M. p.
Piceatannol (from spruce bark)	(a) 216°		229°	a + b	229°
,, (synthetic)	(b)		229	a + c	229
Stilbene-3,3′,4,5′-tetraol (T. J. K)	(c)	229°		b + c	229
Piceatannol acetate (spruce bark)	(d) 124		114; 125 *	d + e	114; 125
,, ,, (synthetic)	(e)		115; 125	d + f	114; 125
3,3′,4,5′-Tetra-acetoxystilbene (T. J. K.)...	(f)	114—115	64—66	e + f	115; 125
Piceatannol Me ether (spruce bark)	(g) amorph.			g + h	67—69
3,3′,4,5′-Tetramethoxystilbene (T. J. K.)	(h)	68—69			
Trinitrobenzene adduct of piceatannol methyl ether (spruce bark)	(i) —		116		
Trinitrobenzene adduct of 3,3′,4,5′-tetramethoxystilbene (T. J. K.)	(j)	109—110	116—117		
Piceatannol benzoate (spruce bark)	(k)		153—154		
3,3′,4,5′-Tetrabenzoyloxystilbene (T. J. K.)	(l)	123—124 †			

* Piceatannol acetate has a double m. p. † Dr. T. J. King informs us that other workers have drawn attention to the low m. p. reported for this specimen.

Although King *et al.*[10] synthesised, in poor yield, 3,3′,4,5′-tetramethoxystilbene (XII; R = Me) from 3,5-dimethoxybenzaldehyde and sodium 3,4-dimethoxyphenyl acetate, they did not prepare the phenol (XII; R = H) (piceatannol). We have now prepared this phenol from 3,5-dihydroxyphenylacetic acid and 3,4-dihydroxybenzaldehyde, which reacted under the conditions of the Perkin reaction. The amorphous acidic condensation



(XII)

product was decarboxylated by copper in boiling quinoline, and after removal by alkaline hydrolysis of any acetyl groups and absorption on Perlon powder a small yield of piceatannol (XII; R = H) was obtained and shown by mixed m. p. and by comparison of the tetra-acetate to be identical with the product from spruce bark.

The claims of Grassmann, Endres, and Pauckner[1f] to have isolated the acid (II), the phenol (III; R = H), and adipic acid by oxidation of piceatannol are difficult to explain on the basis of the stilbenetetraol structure (XII; R = H), but it is tentatively suggested that the adipic acid might have arisen from the Perlon columns which were used in the purification of the nitric acid oxidation products.

Nevertheless the revised structure (XII; R = H) for piceatannol containing resorcinol and pyrocatechol nuclei may be used to explain the formation of phlobaphenes when piceatannol is treated with acid. Polymerisation may occur by oxidation in a manner similar to that suggested by Hathway and Seakins[11] for catechin polymerisation, or by acid catalysis which probably involves protonation of the stilbene double bond followed by attack of the resultant electrophile on a resorcinol nucleus; the latter process is analogous in certain respects to the mode of acid-catalysed polymerisation of catechin put forward by Freudenberg *et al.*[12]

[11] Hathway and Seakins, *J.*, 1957, 1562; *Biochem. J.*, 1957, **67**, 239.
[12] Freudenberg, Stocker, and Porter, *Chem. Ber.*, 1957, **90**, 957.

Experimental

Alumina refers to Peter Spence's grade H.

Paper Chromatography.—Whatman No. 2 paper was used and chromatograms were developed at 20° ± 3°. Substances were chromatographed in two dimensions with solvent systems composed of (*a*) 6% acetic acid and (*b*) butan-2-ol–acetic acid–water (14 : 1 : 5). *o*-Dihydric phenols were revealed with a spray composed of ferric chloride and potassium ferricyanide.[13] Phenols with a free *para*-position were detected by spraying with a 0·1% methanolic solution of 2,6-dibromobenzoquinone 4-chloroimide (Gibbs's reagent) followed by sodium hydrogen carbonate solution.

5,6,7,8-*Tetrahydronaphthalene*-1,2,4-*triol* (III; R = H) *and its Trimethyl Ether.*—The triacetate (III; R = Ac) (6·1 g.), 36% hydrochloric acid (5 c.c.), and ethanol (30 c.c.) were refluxed in an atmosphere of nitrogen until a sample gave a clear solution in water (½ hr.). The solution was cooled, water (75 c.c.) added, and the product extracted with ether (3 × 25 c.c.). The extract was washed with brine until acid-free, dried, and evaporated in an atmosphere of nitrogen. Crystallisation of the residue from benzene gave the product as needles (1·85 g.), m. p. 140—141° (*in vacuo*, sealed tube) [lit.,[1n] m. p. 135° (decomp.)] (Found: C, 66·5; H, 6·9. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%).

A solution of potassium hydroxide (64 g.) in methanol (350 c.c.) was rapidly added to a boiling solution of this triacetate (15 g.) in methanol (75 c.c.) and dimethyl sulphate (75 c.c.). After 1 hour's boiling, the methanol was removed by distillation and sufficient water added to redissolve the potassium methyl sulphate. The solution was extracted with ether, and the extract washed with water, dried (Na_2SO_4), and evaporated to an oil which solidified on cooling. Recrystallisation from aqueous methanol gave the *trimethyl ether* (III; R = Me) as needles (10 g.), m. p. 55—56° (Found: C, 70·0; H, 7·9. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%).

5,6,7,8-*Tetrahydro*-2-*methoxy*-1,4-*naphthaquinone.*—The triacetate (III; R = Ac) (26 g.) was treated with ethanolic hydrochloric acid as above and the ethereal extract of the triol was left for 20 hr. after being mixed with an ethereal solution of diazomethane (from *N*-nitrosomethylurea, 40 g.). Removal of the ether and chromatography of the product on alumina with benzene as eluant gave a yellow solid which crystallised from methanol as prisms (7·4 g.), m. p. 172°, undepressed on admixture with 5,6,7,8-*tetrahydro*-2-*methoxy*-1,4-*naphthaquinone* prepared by methylation of 5,6,7,8-tetrahydro-2-hydroxy-1,4-naphthaquinone[4] (Found: C, 68·9; H, 6·4. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·25%).

Attempted Hoesch Reaction between the Triol (III; R = H) *and* 3,4-*Dimethoxyphenylacetonitrile.*—3,4-Dimethoxyphenylacetonitrile[14] was prepared from the oxime[15] of 3,4-dimethoxyphenylpyruvic acid.[16] 5,6,7,8-Tetrahydronaphthalene-1,2,4-triol (1·2 g.) and 3,4-dimethoxyphenylacetonitrile (1·2 g.) were dissolved in ether (10 c.c.), and dry hydrogen chloride was passed through the solution for 3 hr. at 0°. After 2 days at 0°, ether (30 c.c.) was added and the yellow solid (A) which separated was washed several times with ether, dissolved in water (75 c.c.), and left at room temperature overnight. The precipitate which separated was crystallised twice from benzene, to give a *mono*-3,4-*dimethoxyphenylacetate* (0·33 g.), m. p. 158°, $\nu_{max.}$ (KBr disc) 1741 cm.$^{-1}$, of 5,6,7,8-tetrahydronaphthalene-1,2,4-triol (Found: C, 66·7; H, 6·3. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%).

In another experiment the crude product (A) (2·6 g.) was refluxed for 1½ hr. with 2% aqueous sulphuric acid. The solution was filtered from traces of dark oil, saturated with sodium chloride, and extracted with ether. Evaporation of the ether gave a brown solid which was separated by fractional crystallisation from benzene into (*a*) white needles (0·31 g.), m. p. 140° (*in vacuo*, sealed tube) alone and on admixture with 5,6,7,8-tetrahydronaphthalene-1,2,4-triol, and (*b*) yellow prisms (0·33 g.), m. p. 98—99° alone and when mixed with 3,4-dimethoxyphenylacetic acid.

2-*Heptyl*-5,6,7,8-*tetrahydro*-3-*hydroxy*-1,4-*naphthaquinone* (VII; R = C_5H_{11}).—A solution of 2-hept-1′-enyl-3-hydroxy-1,4-naphthaquinone (V; R = C_5H_{11}) (4 g.) (prepared by condensation of n-heptaldehyde with 2-hydroxy-1,4-naphthaquinone[7]) in ethanol (100 c.c.) was hydrogenated in presence of Raney nickel (~5 g.) at 70°/100 atm. for 5 hr. Removal of the

[13] Kirby, Knowles, and White, *J. Soc. Leather Trades' Chemists*, 1953, **37**, 283.
[14] Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1127.
[15] Edwards, *J.*, 1926, **127**, 744.
[16] Perkin, Haworth, and Rankin, *J.*, 1924, **125**, 1693.

catalyst and solvent, and steam-distillation to remove secondary products (0·3 g.; oil), gave a brown residue which was dried and extracted with boiling light petroleum (b. p. 60—80°) for 1 hr. Removal of the petroleum gave a yellow oil which solidified at 0°; sublimation at 100°/0·01 mm. gave the *product* as needles (1·9 g.), m. p. 46° (Found: C, 73·7; H, 8·8. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·8%), $\nu_{max.}$ (KBr disc) 1656 and 1630 cm.$^{-1}$, $\lambda_{max.}$ (in 95% EtOH) 278 and 415 mμ (log ε 4·25 and 2·82, respectively).

5,6,7,8-*Tetrahydro*-2-*hydroxy*-3-*phenethyl*-1,4-*naphthaquinone* (VII; R = Ph).—A solution of 2-hydroxy-3-styryl-1,4-naphthaquinone (V; R = Ph) (4 g.) (prepared by condensation of phenylacetaldehyde with 2-hydroxy-1,4-naphthaquinone [7]) in ethanol (100 c.c.) was hydrogenated, and the product isolated as in the preceding experiment. Recrystallisation from aqueous methanol gave 5,6,7,8-*tetrahydro*-2-*hydroxy*-3-*phenethyl*-1,4-*naphthaquinone* as prisms (0·65 g.), m. p. 113° (Found: C, 76·1; H, 6·7. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%), $\nu_{max.}$ (in Nujol) at 1668, 1645, and 1626 cm.$^{-1}$, $\lambda_{max.}$ (in 95% EtOH) 275 and 413 mμ (log ε 4·17 and 2·77, respectively).

6-(3,4-*Dimethylphenyl*)-2,3-*dimethoxynaphthalene*.—A solution of 3,4-dimethoxyphenylacetaldehyde [17] (2 c.c.) (prepared by oxidative cleavage of methyl eugenol glycol [18]), ethanol (4 c.c.), glacial acetic acid (5 c.c.), and concentrated hydrochloric acid (1 c.c.) was heated at 95°. Colourless crystals separated; after 1 hr. the mixture was poured into water (50 c.c.), and the product was collected and recrystallised from ethanol, giving 6-(3,4-dimethoxyphenyl)-2,3-dimethoxynaphthalene as thin plates (1·4 g.), m. p. 179° (lit.,[8] m. p. 179—180°) (Found: C, 73·5; H, 6·3. Calc. for $C_{20}H_{20}O_4$: C, 74·1; H, 6·2%).

2-*Chloromethyl*-5,6,7,8-*tetrahydro*-1,3,4-*trimethoxynaphthalene* (VIII; R = Cl).—A rapid stream of hydrogen chloride was passed into a solution of the ether (III; R = Me) (7·7 g.), 40% aqueous formaldehyde (25 c.c.), and concentrated hydrochloric acid (30 c.c.) for 3½ hr. The temperature rose initially but after 1 hr. the flask was immersed in a bath at 50—60°. The red-brown oil which separated from the cooled mixture was isolated with ether, washed with water and sodium hydrogen carbonate solution, dried (Na_2SO_4), recovered, dissolved in light petroleum (b. p. 60—80°) (30 c.c.), and passed down a column of alumina (500 g.) which removed coloured by-products; the *chloride* (VIII; R = Cl) was obtained as a colourless oil which crystallised and on recrystallisation from aqueous methanol gave prisms (5·85 g.), m. p. 51·5° (Found: C, 62·3; H, 7·2; Cl, 13·6. $C_{14}H_{19}ClO_3$ requires C, 62·1; H, 7·1; Cl, 13·1%).

5,6,7,8-*Tetrahydro*-1,3,4-*trimethoxy*-2-*naphthylacetonitrile* (VIII; R = CN).—The chloride (VIII; R = Cl) (2 g.) in acetone (25 c.c.) was added to sodium cyanide (1·5 g.) in water (10 c.c.), and the mixture was stirred for 2 hr. at 35—40°. The acetone was then removed and the *nitrile*, isolated as an oil with ether, crystallised in leaflets (1·6 g.) (from aqueous ethanol), m. p. 58° (Found: C, 68·8; H, 7·3; N, 5·7. $C_{15}H_{19}NO_3$ requires C, 69·0; H, 7·3; N, 5·4%), $\nu_{max.}$ (in KBr) 2271 cm.$^{-1}$.

5,6,7,8-*Tetrahydro*-1,3,4-*trimethoxy*-2-*naphthylacetic Acid* (VIII; R = CO_2H).—After the nitrile (VIII; R = CN) (0·5 g.) had been refluxed in ethanol (6 c.c.) and water (1 c.c.) containing potassium hydroxide (1 g.) for 6 hr., the ethanol was removed and the residue poured into water (20 c.c.). The small quantity of white solid, which was collected, was probably the amide as on further hydrolysis it gave the acid (VIII; R = CO_2H). Acidification of the filtrate yielded the *acid* (VIII; R = CO_2H) which separated from aqueous acetic acid in plates (0·22 g.), m. p. 135° (Found: C, 63·9; H, 7·35. $C_{15}H_{20}O_5$ requires C, 64·2; H, 7·2%), $\nu_{max.}$ (in KBr) 1708 cm.$^{-1}$.

3,4-*Dimethoxyphenyl* 5,6,7,8-*Tetrahydro*-1,3,4-*trimethoxy*-2-*naphthylmethyl Ketone* (IX).—Phosphorus pentoxide (30 g.) was added slowly to phosphoric acid (17 c.c.; *d* 1·75), and the resulting syrup stirred for ½ hr. at 95°. The preceding acid (VIII; R = CO_2H) (2·8 g.) and veratrole (1·5 g.) were added and, after being stirred at 95° for a further ½ hr., the mixture was poured into ice–water (200 c.c.). The oil which separated solidified, and crystallisation from methanol gave the *ketone* as plates (2·82 g.), m. p. 128° (Found: C, 68·7; H, 6·8. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·1%), $\nu_{max.}$ (in KBr) 1681 cm.$^{-1}$.

2-(3,4-*Dimethoxystyryl*)-5,6,7,8-*tetrahydro*-1,3,4-*trimethoxynaphthalene* (I; R = Me).—The ketone (IX) (3 g.) was extracted from the thimble of a Soxhlet apparatus on to lithium aluminium hydride (0·4 g.) in boiling ether (50 c.c.). After addition of water, the mixture was

[17] Kaufman, Eliel, and Rosenkranz, *Ciencia* (*Mexico*), 1946, **7**, 136; *Chem. Abs.*, 1947, **41**, 2398.
[18] Eliel, McBride, and Kaufmann, *J. Amer. Chem. Soc.*, 1953, **75**, 4293.

poured into ice–water (100 c.c.), and sufficient 10% sulphuric acid was added to decompose the complex. The aqueous layer was extracted with ether, the combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated and the residual oil (1·75 g.) was heated with potassium hydrogen sulphate (3 g.) at 160° for 3 hr. The cooled mixture was dissolved in ether (25 c.c.) and water (25 c.c.), the aqueous layer was extracted with further portions of ether, and the combined ether extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which solidified on trituration with cold light petroleum (b. p. 60—80°). Crystallisation from ethanol gave the *stilbene derivative* (I; R = Me) as prisms (1·35 g.), m. p. 81° (Found: C, 71·9; H, 7·5. $C_{23}H_{28}O_5$ requires C, 71·9; H, 7·4%), $\nu_{max.}$ (in Nujol) 1607, 1589, and 1519 cm.$^{-1}$.

A 5% solution of potassium permanganate in acetone was added to a boiling solution of 2-(3,4-dimethoxystyryl)-5,6,7,8-tetrahydro-1,3,4-trimethoxynaphthalene (I; R = Me) (0·2 g.) in acetone (10 c.c.) until a violet colour persisted. The excess of permanganate was destroyed with methanol; the acidic product separated from hot water in needles, m. p. 180°, alone and when mixed with veratric acid.

2-(3,4-*Dimethoxyphenethyl*)-5,6,7,8-*tetrahydro*-1,3,4-*trimethoxynaphthalene* (X; R = Me).—2-(3,4-Dimethoxystyryl)-5,6,7,8-tetrahydro-1,3,4-trimethoxynaphthalene (1·0 g.) in methanol (50 c.c.) was hydrogenated at 25°/1 atm. in the presence of 10% palladium–charcoal (0·1 g.) until the uptake of hydrogen was complete. Removal of the catalyst and solvent and crystallisation from methanol gave the *dihydro-derivative* as needles (0·85 g.), m. p. 51° (Found: C, 71·3 H, 7·5. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

2-(3,4-*Dihydroxyphenethyl*)-5,6,7,8-*tetrahydro*-3-*hydroxy*-1,4-*naphthaquinine* (XI).—2-(3,4-Dimethoxyphenethyl)-5,6,7,8-tetrahydro-1,3,4-trimethoxynaphthalene (0·1 g.) and pyridine hydrochloride (0·8 g.) were refluxed for ¼ hr., cooled, and diluted with water (20 c.c.). The *product*, isolated with ether (3 × 15 c.c.) and crystallised from aqueous methanol, was obtained as orange needles (0·07 g.), m. p. 198° (Found: C, 68·6; H, 6·0. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%), $\nu_{max.}$ (in Nujol) 1641 and 1626 cm.$^{-1}$, $\lambda_{max.}$ (in 95% EtOH) 279 and 410 mμ (log ε 4·14 and 2·75, respectively).

1,2,4-*Triacetoxy*-3-(3,4-*diacetoxyphenethyl*)-5,6,7,8-*tetrahydronaphthalene* (X; R = Ac).—The quinone (XI) (0·1 g.) in methanol (20 c.c.) was hydrogenated at 25°/1 atm. in the presence of 10% palladium–charcoal (0·05 g.) until uptake of hydrogen was complete. The catalyst and solvent were removed in an inert atmosphere, and pyridine (10 c.c., previously boiled under nitrogen) and acetic anhydride (5 c.c.) were added to the colourless residue. After being kept overnight at room temperature and at 80° for ¼ hr., the solution was evaporated to dryness. The residue was dissolved in ether, washed with dilute alkali and water, and dried. Removal of the solvent and crystallisation of the product from methanol gave the *acetyl derivative* as needles (0·05 g.), m. p. 117° (Found: C, 63·6; H, 5·7. $C_{28}H_{30}O_{10}$ requires C, 63·9; H, 5·7%).

Piceatannol (*Stilbene*-3,4,3′,5′-*tetraol*).—Extraction of spruce bark with ethyl acetate gave a mixture of glucosides which was hydrolysed enzymically and separated on a Perlon column according to the method of Grassmann and his co-workers.[1b,c] Crystallisation from water gave the product as plates, m. p. 229° (decomp.) in agreement with King, King, Godson, and Manning [10] (Grassmann *et al.*[1b] reported m. p. 216°) (Found: C, 68·75; H, 5·3. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 4·95%), R_F (*a*) 0·03, (*b*) 0·79, $\nu_{max.}$ (in Nujol) 1611 and 1522 cm.$^{-1}$. The tetra-acetate obtained with acetic anhydride–pyridine crystallised from methanol in needles (Found: C, 64·05; H, 4·95. Calc. for $C_{22}H_{20}O_8$: C, 64·0; H, 4·9%); its m. p. was 115° on rapid heating but if the temperature was maintained between 115° and 120° for 5 min. the sample resolidified and a second m. p. was observed at 127°; at normal heating rates, melting commenced at 115° but was usually incomplete until 125°. King *et al.*[10] reported m. p. 114° and Grassmann *et al.*[1f] m. p. 124°. The tetrabenzoate prepared with benzoyl chloride and pyridine crystallised from acetone–methanol as needles, m. p. 153—154° (King *et al.*[10] reported m. p. 123—124°) (Found: C, 75·8; H, 4·5. Calc. for $C_{42}H_{28}O_8$: C, 76·3; H, 4·25%) (cf. footnote to Table 2).

Oxidation of Piceatannol Acetate.—(i) The acetate (1 g.) in tetrahydrofuran (50 c.c.) was treated with 5% solution of potassium permanganate in acetone until a permanent pink colour was produced. The cleavage products were deacetylated and separated on a Perlon column by the method of Grassmann, Endres, and Pauckner.[1f] The compounds were eluted with water containing an increasing quantity of methanol and the eluant was collected in 15-c.c. fractions.

Fraction (*a*) had R_F (6% AcOH) 0·67 (the spot was violet in ultraviolet light after treatment with ammonia vapour) and gave a brown colour with Gibbs's reagent and a blue-green colour with ferric chloride; crystallisation from ethyl acetate gave needles, m. p. and mixed m. p. with 3,4-dihydroxybenzaldehyde 153°. Fraction (*b*) had R_F (6% AcOH) 0·53 (spot behaviour as above) and gave a violet colour with Gibbs's reagent; crystallisation from ethyl acetate–ligroin gave prisms, m. p. and mixed m. p. with 3,5-dihydroxybenzoic acid 230°.

(ii) The acetate (1 g.) in acetone (20 c.c.) was treated with saturated aqueous potassium permanganate until a permanent red colour was produced at room temperature. The products were deacetylated and adsorbed on a Perlon column as before. The acids were eluted successively with water (150 c.c.), 1 : 3 methanol–water (200 c.c.), and 1 : 1 methanol–water (200 c.c.). Fractions (15 c.c.) were examined by chromatography in solvent system (*b*) and spraying with Gibbs's reagent. Fractions 12 and 13 gave a grey colour with Gibbs's reagent; the product crystallised from water as prisms, m. p. alone and mixed with protocatechuic acid 197—198°. Fractions 14—19 contained a mixture of the two acids. Fractions 20—25 gave a violet colour with Gibbs's reagent; the product crystallised from ethyl acetate–ligroin (b. p. 60—80°) as prisms, m. p. alone and mixed with 3,5-dihydroxybenzoic acid 231°.

Piceatannol Methyl Ether.—Potassium hydroxide (5 g.) in methanol (30 c.c.) was added to a refluxing solution of piceatannol (0·5 g.) in methanol (10 c.c.) and dimethyl sulphate (5 c.c.), and the mixture was heated for 1 hr. The methanol was removed and the residue dissolved in water and extracted several times with ether. Removal of the solvent gave a yellow oil (0·6 g.) which was purified by chromatography on alumina in benzene. Crystallisation from aqueous methanol gave the product as needles, m. p. 64—66° (lit.,[10] m. p. 68—69°) (Found: C, 71·7; H, 6·8. Calc. for $C_{18}H_{20}O_4$: C, 72·0; H, 6·7%).

Stilbene-3,3′,4,5′-tetraol.—A mixture of sodium 3,5-dihydroxyphenylacetate [19] (5·8 g.), 3,4-dihydroxybenzaldehyde (4·2 g.), and acetic anhydride (30 c.c.) was heated at 175° for 8 hr., cooled, and poured into cold water (500 c.c.). The viscous brown oil which separated was washed with water and then dissolved in ethyl acetate (200 c.c.), and the solution was extracted with sodium hydrogen carbonate solution. Acidification of this extract gave 3,3′,4,5′-tetra-acetoxystilbene-α-carboxylic acid as a yellow amorphous solid (3·9 g.) which was heated with copper (4 g.) and quinoline (40 c.c.) at 200° for 1 hr. Ethyl acetate (150 c.c.) was added to the cooled mixture and, after filtration, the solution was washed several times with dilute hydrochloric acid, and then evaporated. The residue was hydrolysed with 0·2N-sodium hydroxide (100 c.c.) in an inert atmosphere for 2 hr. at 95°. After extraction with ether the aqueous layer was acidified with dilute sulphuric acid and extracted with ethyl acetate; removal of the solvent gave a brown oil which was dissolved in 1 : 1 methanol–water (20 c.c.) and adsorbed on a Perlon column (4·5 × 30 cm.). The column was eluted successively with 1 : 1 methanol–water (1000 c.c.), 3 : 1 methanol–water (500 c.c.), and methanol, the eluant being collected in 15-c c. fractions which were examined chromatographically in solvent system (*b*). Evaporation of fractions 115—150 and crystallisation of the residue from water gave the stilbenetetraol (0·09 g.) as leaflets, m. p. 229°, undepressed on admixture with piceatannol or the tetraol kindly supplied by Dr. T. J. King. The R_F values and infrared spectra were identical with those given above for piceatannol, and the tetra-acetate, prepared with acetic anhydride in pyridine, separated from methanol in needles showing the double m. p. reported above for piceatannol tetra-acetate.

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[19] Theilacker and Schmid, *Annalen*, 1950, **570**, 26.