Structure of Orchinol, Loroglossol, and Hircinol

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The proposed structures of orchinol and loroglossol (9,10-dihydro-2,4-dimethoxy-5- and 7-phenanthrol, respectively) are confirmed by syntheses, and hircinol is shown to be 9,10-dihydro-4-methoxyphenanthrene-2,5-diol.

UNDER the influence of certain morbific agents, defensive substances are produced in the corms of Orchidaceae. Hardegger and his co-workers have isolated orchinol [1,2] from infected *Orchis militaris*, and loroglossol [2] from infected *Loroglossum hircinum*, and Urech *et al.*[3] have found orchinol, loroglossol, and hircinol in the latter, again only after infection. The structures suggested for orchinol and (in particular) for loroglossol have not been rigorously established and no structure has yet been suggested for hircinol.

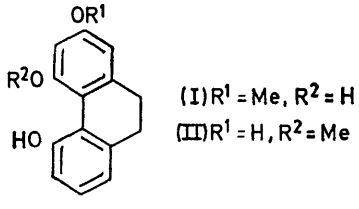
Orchinol has been shown [2] to be a 9,10-dihydro-2,4-dimethoxyphenanthrol on the basis of dehydroxylation and dehydrogenation of orchinol to the known 2,4-dimethoxyphenanthrene. An argument based on ring C–H out-of-plane deformation frequencies in the i.r. spectrum of orchinol, and the non-identity of didehydro-orchinol with synthetic 2,4-dimethoxy-6-phenanthrol indicated that orchinol might be 9,10-dihydro-2,4-dimethoxy-7-phenanthrol.[2] We now confirm this structure following a synthesis of 2,4-dimethoxy-7-phenanthryl acetate, which we have found to be identical with *O*-acetyl-didehydro-orchinol. A Perkin condensation of 3,5-dimethoxyphenylacetic acid and 3-hydroxybenzaldehyde gave α-(3,5-dimethoxyphenyl)-3-hydroxycinnamic acid, which on acetylation and decarboxylation, followed by irradiation, gave 2,4-dimethoxy-7-phenanthryl acetate as the only isolable product.[4] The structure of this compound was confirmed by its n.m.r. spectrum; the only other possible product from the photochemical cyclisation is 2,4-dimethoxy-5-phenanthryl acetate (sterically the less favourable product [4]), which would not exhibit the characteristic low-field H-5 signal (n.m.r.) shown by the isolated product. Attempts to reduce catalytically *O*-acetyl-didehydro-orchinol resulted in indiscriminate reduction of the aromatic rings.

Hardegger *et al.*[2] showed that loroglossol was isomeric with, and possessed spectral characteristics very similar to, orchinol, and they concluded from biogenetic considerations [5] that loroglossol was 9,10-dihydro-2,4-dimethoxy-5-phenanthrol. We now confirm this structure: an unambiguous synthesis of 9,10-dihydro-2,4-dimethoxy-5-phenanthryl, acetate *via* the Pschorr route,[6] gives a product identical with *O*-acetyl-loroglossol. A Perkin condensation of 3,5-dimethoxyphenylacetic acid and 3-hydroxy-2-nitrobenzaldehyde gave α-(3,5-dimethoxyphenyl)-3-hydroxy-2-nitrocinnamic acid, which was selectively reduced to the amino-acid. Diazotization and intramolecular coupling gave the phenanthrene-10-carboxylic acid which on acetylation, decarboxylation,

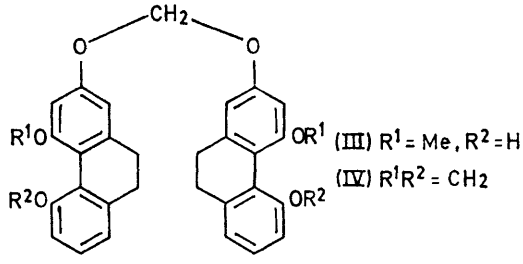
[1] A. Boller, H. Corrodi, E. Gaumann, E. Hardegger, H. Kern, and N. Winterhalter-Wild, *Helv. Chim. Acta*, 1957, **40**, 1062.
[2] E. Hardegger, M. Schellenbaum, and H. Corrodi, *Helv. Chim. Acta*, 1963, **46**, 1171.
[3] J. Urech, B. Fechtig, J. Nüesch, and E. Vischer, *Helv. Chim. Acta*, 1963, **46**, 2758.
[4] R. M. Letcher, L. R. M. Nhamo, and I. T. Gumiro, *J.C.S. Perkin I*, 1972, 206.
[5] E. Hardegger, N. Rigassi, J. Seres, Ch. Egli, P. Müller, and K. O. Fitzi, *Helv. Chim. Acta*, 1963, **46**, 2543.
[6] R. M. Letcher and L. R. M. Nhamo, *J. Chem. Soc.*, (*C*) 1971, 3070.

and catalytic reduction gave 9,10-dihydro-2,4-dimethoxy-5-phenanthryl acetate. We have found *O*-acetylloroglossol to be inert to dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[6] and loroglossol itself inert to methylation with methyl iodide and anhydrous potassium carbonate; this undoubtedly results from the steric effects within the 9,10-dihydro-4,5-disubstituted phenanthrene system.

Hircinol [$C_{14}H_9(OH)_2OMe$] was shown spectroscopically by Urech *et al.*[3] to be a 9,10-dihydrophenanthrene, with a substitution pattern different from that of orchinol. Since the n.m.r. spectrum (see Table) of hircinol shows no low-field signals, and since di-*O*-acetylhircinol resists dehydrogenation, a 9,10-dihydro-4,5-disubstituted phenanthrene structure is suggested. Furthermore, methylation of hircinol with methyl iodide and anhydrous potassium carbonate gave only loroglossol, showing that hircinol has either structure (I)



or (II). Deuteriation[6] of hircinol, followed by acetylation gave a tetradeuteriated species (mass spectrometry) exhibiting only one aromatic proton in the n.m.r. spectrum, in accordance with hircinol being either compound (I) or (II). Compound (I), and not (II), should give a 4,5-methylenedioxy-derivative with di-iodomethane; in fact hircinol gave a product, which lacked the characteristic methylenedioxy-signal in its n.m.r. spectrum which favours structure (II). The product actually obtained was that from two moles of hircinol and one mole of di-iodomethane, the methylenedioxydiphenanthrene derivative (III), which could be acetylated. Of the two hydroxy-groups, the 5-OH is known to be inert to methylation under mild conditions, and consequently it is unlikely to react under the methylenation conditions used by us. To prove that a 9,10-dihydrophenanthrene-4,5-diol will react with di-iodomethane to produce a seven-membered ring, we demethylated loroglossol with boron tribromide. The resulting 9,10-dihydrophenanthrene-2,4,5-triol with di-iodomethane gave the methylenedioxybis-(4,5-methylenedioxyphenanthrene) (IV). Both compounds (III) and (IV) possess the characteristic methylene singlet at about τ 4·3 in their n.m.r. spectra. This is also exhibited by the diphenoxy-methylene derivatives which we have



prepared from *o*- and *p*-cresol[7] in the same way. Consequently hircinol is 9,10-dihydro-4-methoxyphenanthrene-2,5-diol.

Assignments of chemical shifts [τ (intensity)] in the ^{1}H n.m.r. spectra of substituted 9,10-dihydrophenanthrenes †

Substituents	6- and 8-, and 5- or 7-H			1- and 3-H	OMe	9- and 10-H	OAc or OH
7-Hydroxy-2,4-dimethoxy- (Orchinol)	1·95 (1H, 5-H) (d, *J* 10)	3·38 (1H) (dd, *J* 10, 3)	3·41 (1H) (d, *J* 3)	3·63 (2H)	6·20 (6H)	7·31 (4H)	4·88 (1H) *
7-Acetoxy-2,4-dimethoxy-	1·88 (1H, 5-H) (d, *J* 10)	3·16 (1H) (dd, *J* 10, 2)	3·19 (1H) (d, *J* 2)	3·70 (2H)	6·24 (3H) 6·28 (3H)	7·31 (4H)	7·79 (3H)
5-Hydroxy-2,4-dimethoxy- (Loroglossol)		2·9—3·4 (3H)		3·53 (2H)	6·14 (3H) 6·23 (3H)	7·35 (4H)	2·20 (1H) *
5-Acetoxy-2,4-dimethoxy-		3·0 (3H)		3·63 (2H)	6·28 (3H) 6·35 (3H)	7·40 (4H)	7·86 (3H)
2,5-Dihydroxy-4-methoxy- (Hircinol)		2·9—3·4 (3H)		3·61 (2H)	6·17 (3H)	7·38 (4H)	2·07 (1H) * 4·35 (1H)
2,5-Diacetoxy-4-methoxy-	2·85 (1H, 7-H)	2·92 (2H)		3·43 (1H) (d, *J* 2) 3·36 (1H) (d, *J* 2)	6·28 (3H)	7·32 (4H)	7·70 (3H) 7·80 (3H)
[1,3,6,8-$^2H_4$]-2,5-Diacetoxy-4-methoxy-	2·85 (1H, 7-H)				6·28 (3H)	7·32 (4H)	7·70 (3H) 7·80 (3H)

* Signal removed on shaking with D_2O. † Unless indicated to the contrary all signals are singlets and have the appropriate intensities; *J* in Hz.

EXPERIMENTAL

Details of general techniques, reactions, and physical measurements are described in references 4 and 6.

2,4-*Dimethoxy*-7-*phenanthryl Acetate*.—A mixture of 3,5-dimethoxyphenylacetic acid (3 g), 3-hydroxybenzaldehyde (1 8 g), acetic anhydride (3 ml), and triethylamine (1 ml) was heated overnight at 90°. The solution was evaporated under reduced pressure to leave a gum, which was warmed with dilute ammonia solution and charcoal. The solution was filtered, acidified with dilute hydrochloric acid, and

[7] M. Arnhold, *Annalen*, 1887, 192.

extracted with ethyl acetate. Evaporation of the solvent and crystallisation of the product (2·5 g) gave laths of *α-(3,5-dimethoxyphenyl)-3-hydroxycinnamic acid*, m.p. 190—193°, $\nu_{max.}$ 3400—2500br, 1675, and 1600 cm^{-1} (Found: C, 67·5; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). This product was acetylated, and decarboxylated (copper chromite–quinoline) to give the stilbene, which was purified by t.l.c.[4] The pure material (1·0 g), $\lambda_{max.}$ 230 (log ε 4·29) and 295 nm (4·11), was irradiated in ethanol (1 l) (containing 0·005% iodine) for 6 h with a Hanovia medium-pressure mercury arc submerged in the solution in quartz apparatus (the reaction was monitored by u.v. spectroscopy [4]) to give the *acetate* (0·34 g), m.p. 154—156°, $\nu_{max.}$ 1745, 1620, 1580, and 1535 cm^{-1}, $\lambda_{max.}$ 258 (log ε 4·86) and 279sh nm (4·31), τ 0·54 (1H, d, *J* 10 Hz, H-5), 2·44 (2H, s, H-9 and H-10), 2·48 (1H, d, *J* 3 Hz, H-8), 2·73 (1H, dd, *J* 10 and 3 Hz, H-6), 3·18 (1H, d, *J* 3 Hz, H-1 or H-3), 3·29 (1H, d, *J* 3 Hz, H-3 or H-1), 6·00 (3H, s, OMe), 6·13 (3H, s, OMe), and 7·69 (3H, s, OAc), *m/e* 296, 254 (base peak), and 239 (Found: C, 72·6; H, 5·6. $C_{18}H_{16}O_4$ requires C, 72·95; H, 5·45%). This compound was identical (mixed m.p., and i.r. and n.m.r. spectra) with *O*-acetyl-didehydro-orchinol prepared from orchinol in the usual way.[6] Hydrolysis of the synthetic compound gave 2,4-dimethoxy-7-phenanthrol, m.p. 168—170° (lit.,[2] 168—170°), τ 0·63 (1H, d, *J* 11 Hz), 2·48 (2H, s), 2·7—3·0 (2H, m), 3·17 (1H, d, *J* 2 Hz), 3·28 (1H, d, *J* 2 Hz), 5·2br (1H, s, disappears with D_2O), 5·93 (3H, s), and 6·19 (3H, s).

9,10-Dihydro-2,4-dimethoxy-5-phenanthryl Acetate.—A Perkin condensation of 3-hydroxy-2-nitrobenzaldehyde [5] (0·9 g) (prepared by preparative t.l.c. separation of the three nitration products of 3-hydroxybenzaldehyde) and 3,5-dimethoxyphenylacetic acid (1 g) using the method described above, gave a gum (1·5 g), presumably α-(3,5-dimethoxyphenyl)-3-hydroxy-2-nitrocinnamic acid, which was reduced with ammoniacal iron(II) sulphate [6] to the aminocinnamic acid (0·8 g). Cyclisation [6] to the phenanthrene-10-carboxylic acid (0·3 g), followed by acetylation and decarboxylation [6] gave 2,4-dimethoxy-5-phenanthryl acetate as a gum (0·15 g), τ 2·3—2·75 (5H, m), 3·22 (1H, d, *J* 2 Hz), 3·40 (1H, d, *J* 2 Hz), 6·12 (3H, s), 6·20 (3H, s), and 7·70 (3H, s). Reduction of this product with Adams catalyst in glacial acetic acid under hydrogen (30 lb in^{-2}) with shaking at ambient temperature for 48 h followed by t.l.c. purification gave the *dihydro-acetate* (0·1 g), m.p. 108—110° (from ethanol), identical (mixed m.p. and i.r. and n.m.r. spectra) with a sample of *O*-acetyl-loroglossol prepared from loroglossol.

2,2′-Methylenedioxybis-(9,10-dihydro-4,5-methylenedioxyphenanthrene) (IV).—A mixture of 9,10-dihydro-2,4-dimethoxy-5-phenanthryl acetate (60 mg) and boron tribromide (0·5 ml) was refluxed in dry benzene (10 ml) for 15 min, and cooled, methanol (5 ml) was added, and the solution was evaporated under reduced pressure to a gum, presumably containing 9,10-dihydrophenanthrene-2,4,5-triol. This product was refluxed in dry acetone (20 ml) with anhydrous potassium carbonate (0·1 g) and di-iodomethane (1 ml) for 48 h. The solution was filtered and evaporated to dryness, and the residue was purified by t.l.c. (chloroform) to give the *product* (IV) (30 mg), m.p. 148—153° (methanol–chloroform), $\nu_{max.}$ 2920, 1615, 1570, and 1480 cm^{-1}, $\lambda_{max.}$ 275sh (log ε 4·39), 283 (4·40), 293sh (4·18), and 309 nm (4·16), τ 3·0—3·4 (10H, m), 4·32 (2H, s), 4·58 (4H, s), and 7·18 (8H, s), *m/e* 492, 253 (base peak), and 239 (Found: C, 72·45; H, 5·1. $C_{31}H_{24}O_6,H_2O$ requires C, 72·6; H, 5·5%).

2,2′-Methylenedioxybis-(9,10-dihydro-4-methoxy-5-phenanthrol) (III).—Following the procedure above, hircinol was treated with di-iodomethane to give almost quantitatively, the *product* (III), m.p. 128—130° (chloroform–light petroleum), $\nu_{max.}$ 1608 and 1570 cm^{-1}, $\lambda_{max.}$ 268sh (log ε 4·37), 273 (4·39), and 300 nm (4·15), τ 2·28 (2H, s, disappears with D_2O), 2·9—3·4 (10H, m), 4·32 (2H, s), 6·13 (6H, s), and 7·33 (8H, s), *m/e* 496, 255, and 241 (base peak) (Found: C, 73·7; H, 6·0. $C_{31}H_{28}O_6,0·5H_2O$ requires C, 73·7; H, 5·8%). Acetylation yielded a gum, τ 2·85 (2H, s), 2·92 (4H, s), 3·32 (2H, d, *J* 2 Hz), 3·42 (2H, d, *J* 2 Hz), 4·28 (2H, s), 6·28 (6H, s), 7·32 (8H, s), and 7·82 (6H, s).

Methylation [6] of hircinol gave only one product, m.p. 98—99°, identical (mixed m.p. and i.r. and n.m.r. spectra) with a sample of loroglossol.

Dehydrogenation of di-*O*-acetylhircinol [m.p. 127—128° (lit.,[3] 126·5—127·5°), prepared from hircinol] was attempted using the following methods: (*a*) refluxing with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene, and also in xylene; (*b*) heating an intimate mixture of di-*O*-acetylhircinol, 30% Pd–C, and sulphur in an oil-bath at 300° for 10 min; (*c*) refluxing with 30% Pd–C and sulphur in naphthalene for 12 h. In all cases only unchanged hircinol was recovered.

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[5] P. Friedländer and O. Schenck, *Ber.*, 1914, **47**, 3040.