704. *The Chemistry of Fungi. Part XLII.*[1] *The Absolute Configuration of Citrinin.*

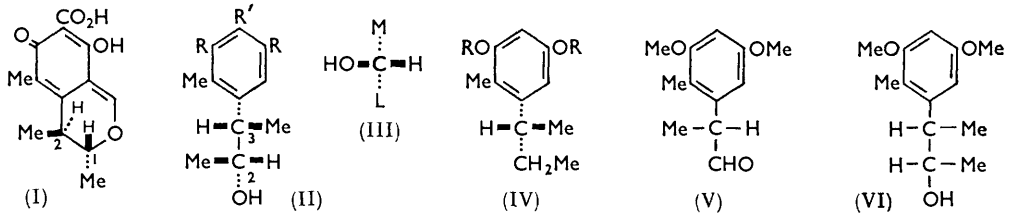
By P. P. Mehta and W. B. Whalley.

The absolute stereochemistry of citrinin has been defined as (I).

The structure of (—)-citrinin, a metabolite of various fungi, including *Penicillium citrinum* Thom,[2] has been established as (I) (without stereochemical implications) by degradation and by synthesis.[3-5] The action of alkali on (—)-citrinin furnishes the lævorotatory alcohol (II; R = OH, R′ = H without stereochemical assignment), designated as phenol A,[2,3] from which (—)-citrinin is readily regenerated.[4] Treatment of phenol A with acid gives the corresponding (±)-butanol, phenol B.[2,3] Since the second theoretically

[1] Part XLI, *J.*, 1963, 3641.
[2] Hetherington and Raistrick, *Phil. Trans.*, 1931, **220**, *B*, 269.
[3] Brown, Cartwright, Robertson, and Whalley, *J.*, 1949, 859, 867.
[4] Cartwright, Robertson, and Whalley, *J.*, 1949, 1563.
[5] Johnson, Robertson, and Whalley, *J.*, 1950, 2971.

possible racemate of phenol A is either absent or is formed in only very minor amounts,[2-4] it follows from the work of Cram[6] on the stereochemical transformations of (+)- and (−)-*threo*-, and (+)- and (−)-*erythro*-3-phenylbutan-2-ol that phenols A and B have the *threo*-configuration (cf. II).[7,8] Further, (−)-citrinin has the same *threo*-configuration (cf. I) since the interconversion of (−)-citrinin and phenol A does not appear to involve any stereochemical changes at C-2 and C-3 of formula (II).[7]



The absolute configuration of (−)-citrinin and hence of the cognate derivatives has now been defined by the application of the Prelog atrolactic acid method.[9] The phenylglyoxylate of the di-*O*-methyl ether of phenol A was treated with methylmagnesium iodide. Hydrolysis of the resultant ester gave atrolactic acid of $[\alpha]_D$ −14° (after two crystallisations from benzene), corresponding to a 37% excess of the (−)-isomer. This shows that phenol A is represented by the Fisher projection (III) in which M is the methyl and L is the ·CHMeAr group, attached to C-2 of the butanol (II; R = OMe, R′ = H). Consequently phenol A and (−)-citrinin have the absolute configurations (II; R = OH, R′ = H) and (I), respectively, in agreement with earlier suggestions.[8] In terms of the Cahn, Ingold, and Prelog nomenclature,[10] (−)-citrinin has the (1*R*,2*S*)- and phenol A the (2*R*,3*S*)-configuration.

	[*M*]		[*M*]
(−)-Citrinin (I)	−82·5°		
(−)-Phenol A (II; R = OH, R′ = H)	−72·0°	(−)-3-Phenylbutan-2-ol[6]	−45·0°
(−)-2-(3,5-Dimethoxy-2-methylphenyl)-butane (IV; R = Me)	−52·0°	(−)-2-Phenylbutane[6]	−29·5°

The correspondence (cf. Table) between the molecular rotations of (−)-citrinin, phenol A, (−)-2-(3,5-dimethoxy-2-methylphenyl)butane (IV; R = Me), (−)-*threo*-3-phenylbutan-2-ol, and the derived (−)-*threo*-2-phenylbutane is in agreement with these configurational assignments in the (−)-citrinin series.

The action of methylmagnesium iodide on (±)-α-(3,5-dimethoxy-2-methylphenyl)-propionaldehyde (V) furnishes a mixture of (±)-*threo*- and (±)-*erythro*-3-(3,5-dimethoxy-2-methylphenyl)butan-2-ol (II; R = OMe, R′ = H without stereochemical assignment) in which the diastereoisomer corresponding to phenol B is the minor constituent.[5] General principles[9] predict that the major component of the product from this reaction has the *erythro*-configuration (VI) and that the minor product has the *threo*-configuration. This result is in accord with the above deductions concerning the relative configuration of phenol B [and hence of phenol A and of (−)-citrinin].

The definition of (−)-citrinin as (I) establishes the absolute configuration of its various derivatives, *e.g.*, (+)-citrinin;[5] (−)-3-(3,5-dimethoxy-2,4-dimethylphenyl)butan-2-ol, derived by *C*-methylation of citrinin methyl ester, is represented by (II; R = OMe, R′ = Me).

Independent confirmation for these stereochemical assignments could not be obtained. Reduction of the toluene-*p*-sulphonate of the alcohol (II; R = OMe, R′ = H) gave the

[6] Cram, *J. Amer. Chem. Soc.*, 1949, **71**, 3863; 1952, **74**, 2129, 2152.
[7] Cram, *J. Amer. Chem. Soc.*, 1950, **72**, 1001.
[8] Whalley, " Progress in Organic Chemistry," ed. Cook, Butterworths Scientific Publns., London, 1956, Vol. IV, p. 78.
[9] Prelog, *Helv. Chim. Acta*, 1953, **36**, 308; Prelog and Meier, *ibid.*, p. 320; cf. " Progress in Stereochemistry," ed. Klyne, Butterworths Scientific Publns., London, 1954, Vol. I, p. 198.
[10] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

(−)-2-(3,5-dimethoxy-2-methylphenyl)butane (IV; R = Me). But attempts to synthesise this butane by interaction of 3,5-dimethoxyphenylmagnesium bromide with the toluene-*p*-sulphonates of (+)- and (−)-butan-2-ol (cf. Kenyon and Pickard [11]) failed, since 1-bromo-3,5-dimethoxybenzene could not be converted into a Grignard reagent. In addition, efforts to isolate an optically active α-methylbutyric acid by ozonolysis of (−)-2-(3,5-dihydroxy-2-methylphenyl)butane (IV; R = H) were unsuccessful.

Experimental

Phenylglyoxylate of (−)-3-(3,5-*Dimethoxy*-2-*methylphenyl*)*butan*-2-*ol*.—A solution of phenylglyoxylyl chloride (5 ml.) in benzene (8 ml.) was added to (−)-3-(3,5-dimethoxy-2-methylphenyl)butan-2-ol (2·5 g.) in pyridine (5 ml.). Next day the mixture was diluted with water and, after isolation with ether, the *phenylglyoxylate* (2·4 g.), b. p. 174°/0·6 mm., was obtained (Found: C, 71·9; H, 6·8. $C_{21}H_{24}O_5$ requires C, 70·7; H, 6·8%).

A solution of this glyoxylate (2·5 g.) in benzene (5 ml.) and ether (20 ml.) was added during 30 min. to a stirred solution of methylmagnesium iodide, prepared from methyl iodide (4·0 g.), magnesium (0·67 g.), and ether (50 ml.). The mixture was heated under reflux for 5 hr., acidified with dilute acetic acid, and extracted with ether. The residue remaining on removal of the ether was dissolved in methanol (25 ml.) containing potassium hydroxide (2·5 g.), and the mixture was refluxed for 6 hr. Isolated in the usual manner, the acidic fraction furnished atrolactic acid which separated from benzene in needles (0·9 g.), m. p. 86—88°, $[\alpha]_D^{24}$ −14° (*c* 4·0 in EtOH), corresponding to a 37% excess of the (−)-isomer (Found: C, 61·5; H, 6·3. Calc. for $C_9H_{10}O_3,0{\cdot}5H_2O$: C, 61·7; H, 6·3%).

(−)-2-(3,5-*Dihydroxy*-2-*methylphenyl*)*butane* (IV; R = H).—Prepared by the interaction of (−)-3-(3,5-dimethoxy-2-methylphenyl)butan-2-ol (4 g.) in pyridine (12 ml.) containing toluene-*p*-sulphonyl chloride (3·5 g.) during 24 hr. at room temperature, the *toluene*-p-*sulphonate* formed prisms (5·2 g.), m. p. 72°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 63·1; H, 7·0; S, 8·3. $C_{20}H_{26}O_5S$ requires C, 63·4; H, 6·9; S, 8·4%), $[\alpha]_D^{24}$ −59·8° (*c* 2·0 in EtOH).

This ester (5 g.) in ether (75 ml.) was added during 1 hr. to a refluxing slurry of lithium aluminium hydride (3·6 g.) in ether (200 ml.). The mixture was refluxed for 2 hr., and 24 hr. later the product was isolated in the usual manner and distilled, to furnish a colourless oil (2·5 g.), b. p. 76—78°/0·08 mm., $[\alpha]_D^{17}$ −23·8° (*c* 5·0 in EtOH). A solution of this product (2·0 g.) in acetic acid (3 ml.) containing 2,4-dinitrobenzenesulphonyl chloride (1·2 g.) was kept at room temperature for 24 hr., then the crystalline olefin adduct and the excess of reagent were collected. The filtrate was diluted with water and extracted with light petroleum (b. p. 40—60°). The washed, dried extract was percolated through a short column of alumina and distilled, to give (−)-2-(3,5-dimethoxy-2-methylphenyl)butane (1·1 g.), b. p. 77°/0·07 mm. [Found: C, 74·9; H, 9·6; OMe, 30·1. $C_{11}H_{14}(OMe)_2$ requires C, 75·9; H, 9·7; OMe, 29·8%], $[\alpha]_D^{20}$ −25·1° (*c* 5·0 in EtOH).

A solution of this butane (5·5 g.) in hydriodic acid (25 ml.) (*d* 1·7) containing acetic acid (from 25 ml. of anhydride) was refluxed for 2 hr. After isolation in the usual manner (−)-2-(3,5-*dihydroxy*-2-*methylphenyl*)*butane* was obtained as a viscous oil (2·6 g.), b. p. 137—139°/0·25 mm. (Found: C, 73·4; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 9·0%).

The (−)-*di*-p-*nitrobenzoate* formed yellow needles, m. p. 165°, from alcohol (Found: C, 62·9; H, 4·7; N, 5·9. $C_{25}H_{22}N_2O_8$ requires C, 62·8; H, 4·6; N, 5·9%), $[\alpha]_D^{20}$ −8·2° (*c* 4·0 in acetone). The infrared spectrum was identical with that of the corresponding (±)-di-*p*-nitrobenzoate.[3]

Remethylation of the phenol by the methyl iodide–potassium carbonate method in boiling acetone furnished a quantitative yield of the parent di-*O*-methyl ether, b. p. 77°/0·08 mm., $[\alpha]_D^{17}$ −22·6° (*c* 5·0 in EtOH).

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Robert Robinson Laboratories, The University, Liverpool.
The School of Pharmacy, The University, London. [*Received, January* 23*rd*, 1963].

[11] Kenyon and Pickard, *J.*, 1911, **99**, 45; 1913, **103**, 1923.