Stereospecificity in the Perkin–Oglialoro Reaction. The Stereochemical Configurations of Some Substituted α-Phenylcinnamic Acids.

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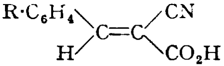
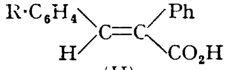
The Perkin–Oglialoro reaction is found to give with various aromatic aldehydes the corresponding α-phenylcinnamic acids, of *trans*-configuration (with respect to aryl and carboxyl groups as in cinnamic acid). Salicylaldehyde is an exception and nitro-aldehydes give rise to some *cis*-acid. Configurations allotted previously to these acids have been confirmed in some cases, and revised in others, and some new acids have been examined. Factors affecting the stereochemical course of the reaction are discussed.

Baker and Howes (*J.*, 1953, 119) showed that condensation of salicylaldehyde or its methyl ether with cyanoacetic acid or its ester gives only the isomers (I; R = *o*-Me or *o*-OH) with the *trans*-configuration (with respect to aryl and carboxyl groups). This agrees with what would be expected on steric grounds, for in these products the bulkiest groups are at a distance. It is surprising, therefore, to find that in the rather similar aldehyde condensation, namely Oglialoro's modification (*Gazzetta*, 1878, **8**, 429) of the Perkin reaction, the main and usually the only product has *cis*-arrangement of the bulkiest groups. Oglialoro's modification consists merely in using sodium phenylacetate in place of acetate in the Perkin reaction. The product of the condensation of various aryl aldehydes with phenylacetic anhydride under these conditions is the *trans*-acid (II; R = H, *o*-, *m*-, or *p*-NO_2, OH, or OMe) in all cases except from salicylaldehyde, though when R = H or NO_2 small amounts of the *cis*-isomers (III) are also formed. In the *trans*-isomer (II) the bulkiest groups (Ph being assumed to be bulkier than CO_2H) are *cis* with respect to one another, which must involve a measure of steric compression greater than in the *cis*-isomer (III). Apparently therefore the relative stability of the possible products is not the determining factor in the stereochemical course of this reaction. Before pursuing this, however, it is essential to be sure of the configurations of the products. These have been established for the new acids and confirmed for those of doubtful structure as follows.



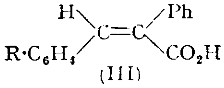
$\begin{matrix}R\cdot C_6H_4 & & CN\\ & C{=}C & \\ H & & CO_2H\end{matrix}$

(I)



$\begin{matrix}R\cdot C_6H_4 & & Ph\\ & C{=}C & \\ H & & CO_2H\end{matrix}$

(II)

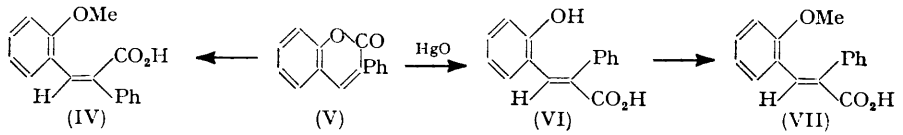


$\begin{matrix}H & & Ph\\ & C{=}C & \\ R\cdot C_6H_4 & & CO_2H\end{matrix}$

(III)

ortho-*Acids.*—*cis*-*o*-Methoxy-α-phenylcinnamic acid (IV), m. p. 131·5°, has been prepared for the first time by the methylation of 3-phenylcoumarin (V), and its configuration is thus established. The *trans*-acid (VII), m. p. 184°, was obtained from 3-phenylcoumarin by isomerisation with yellow mercuric oxide (see Sen and Chakravarti, *J. Indian Chem. Soc.*, 1929, **6**, 852), followed by methylation of the (new) *trans*-*o*-hydroxy-α-phenylcinnamic acid (VI) first formed. Compound (VII) does not depress the m. p. of a sample prepared by Funk and Kostanecki's method (*Ber.*, 1905, **38**, 939). They held it to be the *cis*-acid.

meta-*Acids.*—The configurations of *cis*- and *trans*-*m*-amino-α-phenylcinnamic acids have now been definitely established by diazotisation and reduction to the corresponding deaminated acids (II and III; $R = H$) of known configuration (Stoermer and Prigge, *Annalen*, 1915, **409**, 13). The structures of the *m*-amino-acids determine those of the *m*-nitro-acids from which they were prepared and of the *m*-hydroxy-acids into which they were converted.



The *cis*-hydroxy-acid is new. The *trans*-acid has m. p. 187° which differs considerably from the various values in the literature. The *m*-methoxy-α-phenylcinnamic acids were prepared from the hydroxy-acids: the *cis*-acid is new and the configuration previously assigned to the *trans*-acid is found to be correct (Funk and Kostanecki, *loc. cit.*; Kon and Spickett, *J.*, 1949, 2724).

para-*Acids.*—Condensation of *p*-nitrobenzaldehyde with phenylacetic acid gave *cis*- and *trans*-*p*-nitro-α-phenylcinnamic acids in the ratio of about 1 : 4 (see Bakunin, *Gazzetta*, 1895, **25**, 137), from which the two amino-acids (new) were obtained on reduction. Their configurations have been established similarly to those of the *m*-amino-acids. Surprisingly the *cis*-nitro-acid, m. p. 143°, on reduction gives about equal quantities of *cis*- and *trans*-amino-acid, thus indicating that some stereomutation occurs during reduction. By a diazo-reaction the *cis*-amino-acid gives a nitro-acid of m. p. 127°, which depresses the m. p. of the *trans*-nitro-acid but not that of the *cis*-isomer; this is assumed to be a modification of the *cis*-acid similar to those of *allo*cinnamic acid; on reduction it gives only the *trans*-amino-acid. The *cis*-*p*-amino-acid shows, therefore, a marked stereolability.

Of the *p*-hydroxy-α-phenylcinnamic acids only the *trans*-form had previously been prepared (Zincke and Geibel, *Annalen*, 1906, **349**, 110) by Perkin–Oglialoro condensation of *p*-hydroxybenzaldehyde. Both isomers have now been obtained by diazotisation of the respective *p*-amino-acids and decomposition of the diazonium salts. The *cis*- and the *trans*-α-hydroxy-acids have the same m. p. and give no depression on admixture; conversion of one into the other, probably *cis* into *trans*, takes place on heating and is complete before the m. p. is reached. This resembles the conversion of *cis*- into *trans*-*p*-methoxystilbene by heat noted by Kon and Spickett (*loc. cit.*). That the two compounds are different is proved by methylation to *cis*- and *trans*-methoxy-acids of widely different m. p. Owing to the transformation it is impossible to say from the m. p. alone which isomer Zincke and Geibel (*loc. cit.*) prepared. The *p*-hydroxy-acid obtained from *p*-hydroxybenzaldehyde by their method, namely condensation, must be *trans* as it is found to give a methoxy-acid, which does not depress the m. p. of the *trans*-*p*-methoxy-acid prepared from the *trans*-*p*-hydroxy-acid derived from the *trans*-nitro-acid. Both the *trans*- (Oglialoro, *Jahresber. Fortsch. Chem.*, 1879, 731) and the *cis*-*p*-methoxy-acid (Stoermer and Prigge, *Annalen*, 1915, **409**, 20) were previously obtained respectively by condensation from *p*-anisaldehyde and by ultraviolet irradiation of the *trans*-isomer.

Discussion.—Apart from the *o*-nitro- and the *o*-amino-acid already fully substantiated, all the *cis*- and *trans*-aryl-α-phenylcinnamic acids *ortho*-, *meta*-, and *para*-substituted with the groups under consideration have thus been examined (insofar as they can exist as free acids), and their stereochemical configurations have been settled. It is seen from the Table that most, but not all, of the *trans*- melt higher than the corresponding *cis*-isomers. This property cannot, therefore, be used safely for allocation of configuration. Fractional precipitation used in separations shows that the *cis*-acids are the stronger in the nitro-series and probably throughout. The main, and usually the sole, products of the Perkin–Oglialoro condensation are now proved to have the *trans*-configuration.

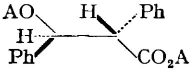
When benzaldehyde and phenylacetic anhydride condense, the initial product can have either the $(\pm)$-configuration (VIII*a*; A = acyl) or the isomeric $(\pm)$-form (IX*a*). No free hydroxyl groups are to be expected in the presence of acid anhydride at high temperatures. If the sterically effective bulk of the groups is assumed to be in the order

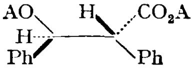
Ph > OA > H and Ph > CO_2A > H the configuration (VIII*a*) involves less steric compression than the alternative (IX*a*) and is consequently likely to be formed in preference. Once formed, the intermediate loses HOA by elimination. This takes place most readily (Barton, *J.*, 1953, 1029) when the four centres concerned lie in one plane, as in the alternative conformations (VIII*b*) and (IX*b*). Elimination from (VIII*b*) will clearly lead to *trans*- and from (IX*b*) to *cis*-α-phenylcinnamic acid. The formation of the *trans*-acids in practice, therefore, indicates that steric factors in the intermediate state are the determining factor. The formation of 3-phenylcoumarin, the lactone of the *cis*-acid, when salicylaldehyde is condensed is an exception: it has been shown (Crawford and Shaw, *J.*, 1953, 3435) to be due to interaction between groups OA in the ring and CO_2A before the elimination stage. Another exception, namely, the formation of small amounts of *cis*-nitro-acids, is more difficult to account for. Taylor and Hobson (*J.*, 1936, 181) have suggested that the stability of *cis*-*o*-nitrostilbene is due to the attraction between one phenyl group and the nitro-group attached to the other. Such an attraction in these condensations would overcome to some extent the steric repulsion between the bulky aryl groups resulting in the formation of some intermediate corresponding to (IX). The formation of *cis*-acids is being studied at present.

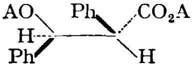
Melting points of aryl-α-phenylcinnamic acids.

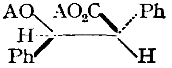
		NO_2	NH_2	OH	OMe	H
ortho	*cis*	147° *	—	—	131·5°	*cis* 137° *trans* 172
	trans	197 *	186°	195°	184	
meta	*cis*	196 †	190	134	86	
	trans	184 †	192	187	195	
para	*cis*	143 (127)	221	(222)	123	
	trans	217	213 (208)	223	192	

* Bakunin, *loc. cit.*; Pschorr, *Ber.*, 1896, **29**, 496; Stoermer and Prigge, *loc. cit.*
† Bakunin, *loc. cit.*


(VIII*a*)


(IX*a*)


(VIII*b*)


(IX*b*)

EXPERIMENTAL

trans-o-*Hydroxy-α-phenylcinnamic Acid.*—3-Phenylcoumarin (7·5 g.) in 6% sodium hydroxide solution (50 ml.) was refluxed for 4 hr. with yellow mercuric oxide (20 g.) and water (400 ml.). Addition of dilute acetic acid precipitated a mercury compound which was filtered off and boiled for 30 min. with concentrated hydrochloric acid (3 ml.), water (300 ml.), and alcohol (50 ml.). The solution, filtered cold and boiled to remove alcohol, deposited *trans*-*o*-hydroxy-α-phenylcinnamic acid (0·5 g.), colourless needles (from benzene), m. p. 195° (Found: C, 75·8; H, 5·3. $C_{15}H_{12}O_3$ requires C, 75·1; H, 5·0%).

trans-o-*Methoxy-α-phenylcinnamic Acid.*—*Method A.* The foregoing hydroxy-acid (0·2 g.) with methyl sulphate and potassium hydroxide gave the methoxy-acid (0·15 g.), cream plates (from benzene), m. p. 184°. *Method B.* Perkin–Oglialoro condensation of *o*-methoxybenzaldehyde (9 g.) gave the methoxy-acid (2 g.), colourless needles (from alcohol), m. p. 183° undepressed by the previous product. This *trans*-acid was readily converted into 3-phenylcoumarin by 20 minutes' refluxing with pyridine hydrochloride.

cis-o-*Methoxy-α-phenylcinnamic Acid.*—3-Phenylcoumarin (3·1 g.) in water (40 ml.) containing potassium hydroxide (6 g.) was refluxed for 1 hr. with methyl sulphate (6·2 ml.) and then for another 2 hr. after the addition of 50% potassium hydroxide solution (10 ml.). When the product was poured on ice and hydrochloric acid and suitably extracted, the cis-*acid* (1·1 g.)

was obtained; it formed colourless prisms, m. p. 131·5°, from benzene (Found: C, 76·0; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

Configuration of the Isomeric m-*Nitro- and* m-*Amino-α-phenylcinnamic Acids*.—The nitro-acids were prepared according to Bakunin (*loc. cit.*) from *m*-nitrobenzaldehyde (16 g.) (yields: acid of m. p. 184°, 7 g.; acid of m. p. 196°, 3·5 g.). The acid of m. p. 184° was reduced with ferrous sulphate and ammonia to the amino-acid, m. p. 192°, in 57% yield. This (3 g.) on diazotisation and reduction with hypophosphorous acid gave *trans*-α-phenylcinnamic acid (1·1 g.), m. p. 167—168°, not depressed on admixture with a genuine sample of m. p. 171°. The second nitro-acid on reduction gave a 40% yield of the amino-acid, m. p. 190—191°, which (1·5 g.) in turn gave *cis*-α-phenylcinnamic acid (0·55 g.), m. p. 133° alone or mixed with a genuine sample of m. p. 135°.

trans-m-*Hydroxy-α-phenylcinnamic Acid*.—*Method A*. Perkin–Oglialoro condensation of *m*-hydroxybenzaldehyde (9 g.) gave the hydroxy-acid (13·5 g.) as straw-coloured needles, m. p. 183—184° (from alcohol). *Method B*. Decomposition of the diazonium salt from *trans*-*m*-amino-α-phenylcinnamic acid (15 g.) gave the acid (5 g.) as light brown needles (from benzene), m. p. 187°, not depressing the m. p. of the foregoing product. Methylation of this acid (2·2 g.) gave the *trans*-methoxy-acid (1·8 g.), colourless needles (from alcohol), m. p. 195°.

cis-m-*Hydroxy-α-phenylcinnamic Acid*.—Diazotisation and decomposition of the *cis*-*m*-amino-acid (2·5 g.) gave the cis-m-*hydroxy-acid* (0·75 g.), fine colourless needles (from benzene), m. p. 134° (Found: C, 74·6; H, 4·9%). Methylation gave cis-m-*methoxy-α-phenylcinnamic acid* (0·4 g.), colourless needles (from benzene), m. p. 86° (Found: C, 75·7; H, 5·6%).

cis- *and* trans-p-*Nitro-α-phenylcinnamic Acid*.—Bakunin's method (*loc. cit.*) gave, from *p*-nitrobenzaldehyde (30 g.), a nitro-acid of m. p. 217° (18 g.), believed to be *trans*, and one of m. p. 143° (5 g.).

trans-p-*Amino-α-phenylcinnamic Acid*.—Reduction of the *p*-nitro-acid of m. p. 217° (10 g.) with ferrous sulphate and ammonia gave the *amino-acid* (6 g.), mustard-coloured needles (from alcohol), m. p. 213° (Found: C, 74·8; H, 5·5; N, 6·0. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·9%). A form of this acid melting at 208° was obtained on subsequent occasions. The *trans*-configuration was established by diazotisation and reduction to *trans*-α-phenylcinnamic acid, m. p. and mixed m. p. 172°.

trans-p-*Hydroxy-α-phenylcinnamic Acid*.—*Method A*. Perkin–Oglialoro condensation of *p*-hydroxybenzaldehyde (10 g.) gave the acid (16·5 g.), colourless needles (from alcohol), m. p. 223°. *Method B*. Decomposition of the remarkably stable diazonium salt from the foregoing amino-acid (9·3 g.) gave the hydroxy-acid (6 g.), m. p. 222°, not depressed by the foregoing product, but this is not proof of identity in this case. Addition of the methyl ether of the second product (colourless needles, m. p. 190°) did not depress the m. p. of the methyl ether of the first product (m. p. 188°).

cis-p-*Amino-α-phenylcinnamic Acid*.—Reduction of the *p*-nitro-acid of m. p. 143° (12 g.) gave two amino-acids. The cis-*acid* (4·5 g.), less soluble and hence first to separate, had m. p. 220°, cream-coloured needles (from alcohol) (Found: C, 74·9; H, 5·3; N, 5·85%). The more soluble acid (3·6 g.), m. p. 206°, did not depress the m. p. of *trans*-*p*-amino-α-phenylcinnamic acid. The less soluble acid (1·1 g.) on diazotisation and reduction gave *cis*-α-phenylcinnamic acid (0·35 g.), m. p. and mixed m. p. 133°. Irradiation of the *trans*-*p*-amino-acid (20 g. in 600 ml. of alcohol) in a quartz flask with ultraviolet light for 50 hr. gave the *cis*-acid (6·4 g.), m. p. 221°, which separated from solution during the irradiation. Diazotisation of this acid and treatment with cupro-cupri-sulphite reagent and sodium nitrite solution (*Org. Synth.*, 1948, **28**, 52) gave *cis*-*p*-nitro-α-phenylcinnamic acid, m. p. 127° (but 143° on remelting). Reduction of this nitro-acid gave only *trans*-*p*-amino-α-phenylcinnamic acid, m. p. 208°, confirmed by a mixed m. p. and high solubility.

cis-p-*Hydroxy-α-phenylcinnamic Acid*.—Decomposition of the very stable diazonium salt of the *cis*-*p*-amino-acid (2 g.) gave the *hydroxy-acid* (1 g.), m. p. 222°, long colourless needles from alcohol (Found: C, 75·1; H, 5·0%). Addition of this acid did not depress the m. p. of the *trans*-acid. Methylation gave the *cis*-*p*-methoxy acid, m. p. 123°, colourless needles from alcohol.

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