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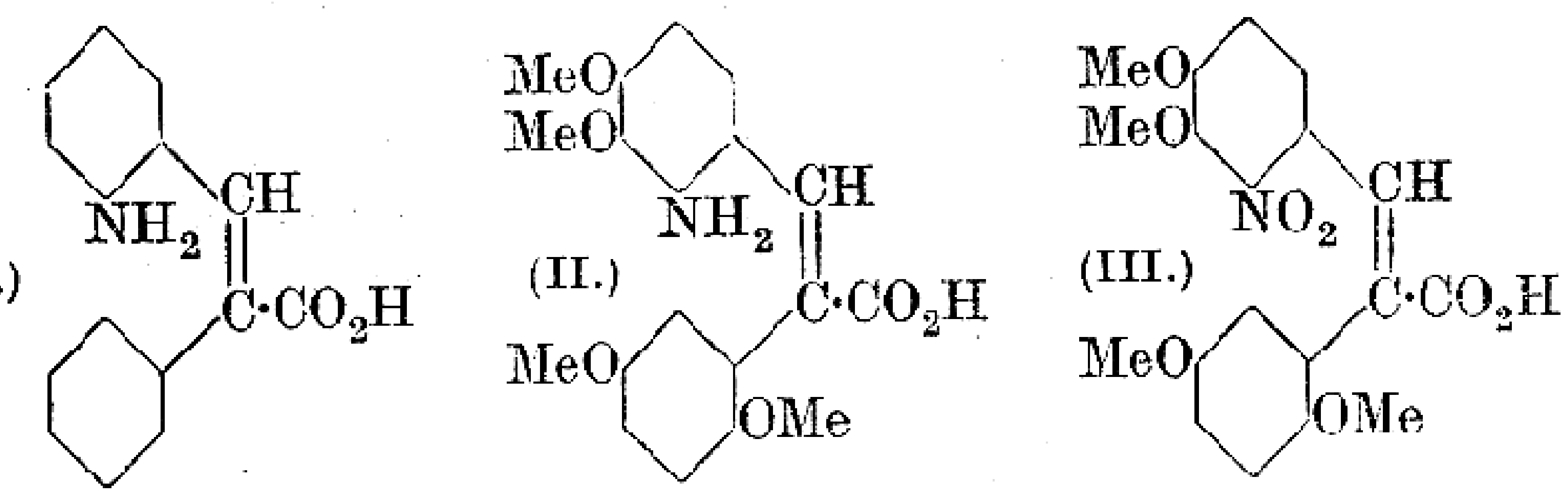
The Isomeric 2-Amino-α-arylcinnamic Acids.

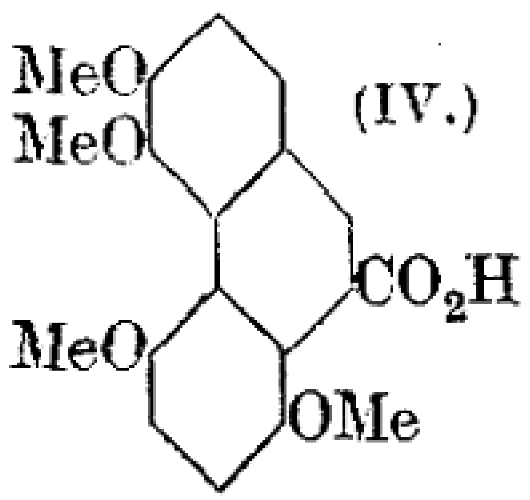
By John Masson Gulland and Cyril Joseph Virden.

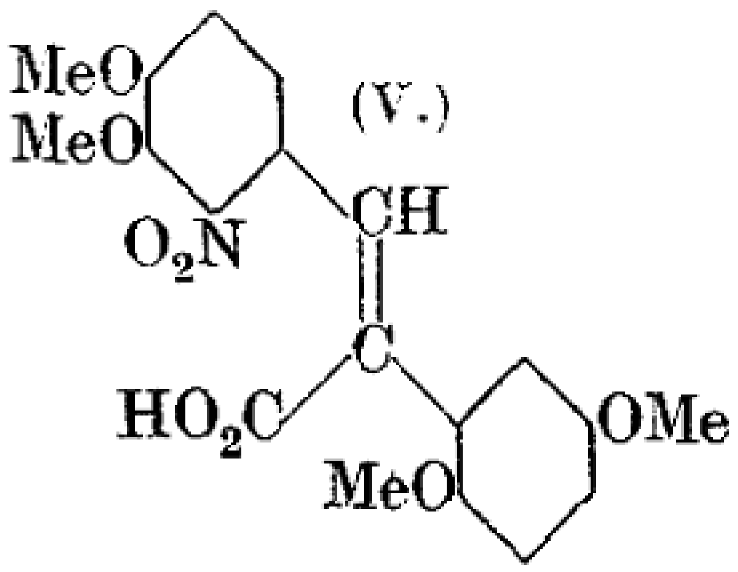
Pschorr (*Ber.*, 1896, **29**, 496) observed that 2-amino-α-phenylcinnamic acid (I) exists in two interconvertible isomeric forms, one yellow, the other colourless. Stoermer and Prigge (*Annalen*, 1915, **409**, 23) confirmed this observation, but did not examine the isomerides more closely, and other workers who have prepared 2-amino-α-arylcinnamic acids make no mention of such isomerism. During an investigation into the constitution of thebenine (this vol., p. 921), we had occasion to prepare 2-amino-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (II), and found that it occurs in two forms, one yellow, the other colourless. This communication is an account of the experiments which have been carried out up to the present time in order to elucidate the nature of this isomerism.

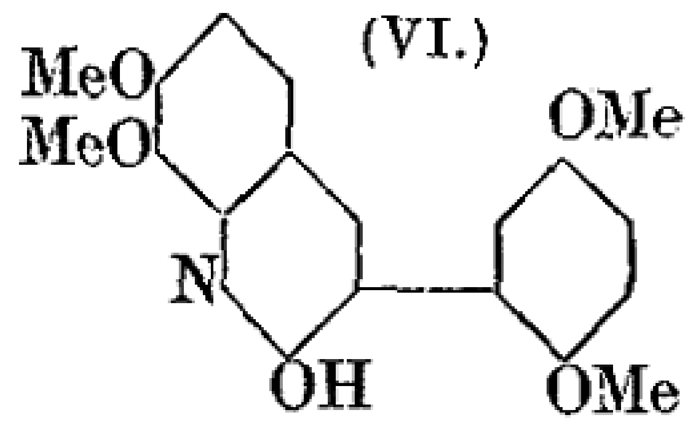


(I.) (II.) (III.)

The synthesis of the amino-acids (II) follows the usual stages. 2 : 5-Dimethoxybenzaldehyde, prepared by introducing the aldehydo-group into *p*-dimethoxybenzene, condenses with hippuric acid, yielding the azlactone, 5-*keto*-2-*phenyl*-4-(2′ : 5′-*dimethoxybenzylidene*)-4 : 5-*dihydro-oxazole*, which is converted into α-*benzamido*-2 : 5-*dimethoxycinnamic acid* by heating for a short time with dilute hydrochloric acid or sodium hydroxide. Prolonged alkaline hydrolysis of the azlactone yields 2 : 5-*dimethoxyphenylpyruvic acid*, which is oxidised by hydrogen peroxide to 2 : 5-dimethoxyphenylacetic acid. When the sodium salt of this acid is condensed with 2-nitroveratraldehyde (Pisovschi, *Ber.*, 1910, **43**, 2137), trans-2-*nitro*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic acid* (III) is formed, together with a small amount of 2-nitro-3 : 4-dimethoxycinnamic acid (this vol., p. 931). The reduction of the acid (III) with ferrous sulphate and ammonia yields a mixture of two 2-*amino*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic acids* (II), A, m. p. 219°, which is colourless, and B, m. p. 167°, which is yellow; the marked difference of solubility in alcohol provides an easy method of separation. These acids are interconvertible: the addition of an excess of sodium acetate to a solution of either in dilute hydrochloric acid precipitates the acid B, and either acid, uncontaminated by the other, may readily be obtained at will when an ammoniacal solution of A or B is treated with acetic acid under conditions which are described in the experimental section. Both these acids must have the *trans*-configuration for the following reasons. In the first place, both yield 3 : 4 : 5 : 8-*tetramethoxyphenanthrene*-9-*carboxylic acid* (IV) when a methyl-alcoholic solution of the diazonium sulphate is boiled. When the acid (IV) is heated with glacial acetic acid in a sealed tube, it loses carbon dioxide and forms 3 : 4 : 5 : 8-*tetramethoxyphenanthrene*. Secondly, the corresponding *cis*-amino-acid exists only in alkaline solution. Thus, *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (III) is partly converted into *cis-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid* (V) when an aqueous solution of its sodium salt is exposed to ultra-violet light, and the reduction of the barium salt of this acid (V) with ferrous sulphate yields a solution from which hydrochloric acid precipitates 7 : 8 : 2′ : 5′-*tetramethoxy-3-phenylcarbostyril* (VI) (compare Stoermer, *loc. cit.*, p. 18). The same carbostyril derivative is formed from the amino-acids (II), either by exposing an alcoholic solution of B to ultra-violet light, or by heating A or B with acetic anhydride and a trace of sulphuric acid.


(IV.)


(V.)


(VI.)

The difference in colour of alcoholic solutions of the acids A (almost colourless) and B (bright yellow) indicates that the isomerism is not due merely to dimorphism, and the molecular weights of the acids confirm this deduction. The acid B, m. p. 167°, proved to be unimolecular in camphor (Rast, *Ber.*, 1922, **55**, 1051), as was to be expected from its lower melting point and the close resemblance of its properties to those of other 2-amino-α-arylcinnamic acids. The acid A, m. p. 219°, on the other hand, was bimolecular, and therefore it became important to determine the molecular weights in other solvents, and to ascertain the effect of adding a small amount of one form to a saturated solution of the other (compare Sidgwick, J., 1915, **107**, 672). The sparing solubility of the acid A restricted the choice of solvent: in benzene, for example, it is practically insoluble. In azobenzene, the acids A and B were associated, but at comparable concentrations the observed values for the molecular weights of A were approximately twice those of B. In acetic acid, the acids A and B were readily soluble and both appeared to be unimolecular; the values for A were consistently low, but it should be noted that this acid retains moisture, which cannot be eliminated without causing decomposition.

In acid or alkaline solutions the unimolecular form of the 2-amino-α-arylcinnamic acids predominates. (The properties of the hydrochloride and chloroplatinate of Pschorr's colourless amino-acid, *loc. cit.*, are also those of the corresponding derivatives of the yellow form, and we consider that these are all salts of the unimolecular yellow form.) In neutral solvents, on the other hand, the bimolecular is the stable form, and we have observed that in benzene or azobenzene the acid B changes into the acid A in a comparatively short time.

The precise nature of the bimolecular form of these acids can be elucidated only by the further study of this and other cases of the isomerism. Since the analytical data for Pschorr's acid indicate that it is anhydrous, it is not possible on the basis of the available evidence to decide whether the water of crystallisation of the acid A is essential for the production of the bimolecular form, or whether the A type is composed intrinsically of two molecules of the B type, and we wish therefore to record the facts, and to postpone the discussion of the theoretical question until a later publication.

Experimental.

2 : 5-*Dimethoxybenzaldehyde.*—After several unsatisfactory attempts to introduce the aldehydo-group into quinol by the method of Tiemann and Müller (*Ber.*, 1881, **14**, 1986), the modification of the Gattermann aldehyde synthesis recommended by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373; 1924, **46**, 1518) was found to be satisfactory. The conditions which have already been detailed (this vol., p. 929) were closely adhered to, and the pure aldehyde was obtained in a yield of 70% of that theoretically possible.

5-*Keto*-2-*phenyl*-4-(2′ : 5′-*dimethoxybenzylidene*)-4 : 5-*dihydro-oxazole.*—This azlactone is obtained by heating together on a boiling water-bath 2 : 5-dimethoxybenzaldehyde (10 g.), hippuric acid (12 g.), fused sodium acetate (12 g.), and acetic anhydride (20 c.c.). The orange product is washed with cold alcohol and repeatedly boiled with water (yield, 75%); further treatment is unnecessary for the next stage. The *azlactone* crystallises from acetic acid, ethyl acetate, or ethyl alcohol, from which it separates in orange needles, m. p. 170—172° (Found: N, 4·4. $C_{19}H_{15}O_4N$ requires N, 4·5%).

α-Benzamido-2 : 5-dimethoxycinnamic Acid,

$C_6H_3(OMe)_2{\cdot}CH{:}C(NHBz){\cdot}CO_2H$.

—When the azlactone is boiled for a short time with alcoholic hydrochloric acid or with dilute sodium hydroxide, a clear solution is obtained which deposits this *acid* on cooling or acidification, respectively. It separates from alcohol in colourless needles, m. p. 195—196° (Found in material dried at 100°: N, 4·5. $C_{18}H_{17}O_5N$ requires N, 4·3%). The azlactone is regenerated by boiling with acetic anhydride.

2 : 5-*Dimethoxyphenylpyruvic acid*, $C_6H_3(MeO)_2{\cdot}CH_2{\cdot}CO{\cdot}CO_2H$, is

obtained in 76% yield when the azlactone is hydrolysed by boiling 10% sodium hydroxide solution for 12 hours, and the product is separated from benzoic acid by the sulphur dioxide method of Haworth, Perkin, and Rankin (J., 1924, **125**, 1686). It separates from glacial acetic acid in cream-coloured octahedra, m. p. 166—170° (decomp.), which are rather readily soluble in methyl alcohol or acetone, but sparingly soluble in benzene (Found: C, 58·8; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%).

3-*Hydroxy*-2′ : 5′-*dimethoxy* - 2 - *benzylquinoxaline*.—2 : 5 - Dimethoxyphenylpyruvic acid (2 g.) and *o*-phenylenediamine (1 g.) in ethyl alcohol (5 c.c.) are heated on the water-bath for a few minutes. On cooling, the clear solution deposits colourless needles, which after recrystallisation from ethyl alcohol melt at 179—180°, and retain half a molecule of alcohol when dried in a vacuum desiccator (Found: loss at 120°, 7·1; N, 8·8. $C_{17}H_{16}O_3N_2,\frac{1}{2}EtOH$ requires loss, 7·2; N, 8·8%).

2 : 5-Dimethoxyphenylacetic acid, $(MeO)_2C_6H_3\cdot CH_2\cdot CO_2H$, is obtained (yield, 80%) when a solution of 2 : 5-dimethoxyphenylpyruvic acid (5 g.) in ice-cold sodium hydroxide (35 c.c. of 2*N*) is oxidised by perhydrol (5·5 c.c. made up to 20 c.c.). Next day the pure acid is precipitated in colourless needles by dilute sulphuric acid. It crystallises from benzene in plates, m. p. 123°, which dissolve readily in alcohol, ether, and acetone (Found: C, 60·8; H, 6·0. Calc.: C, 61·2; H, 6·1%). Wolkow and Baumann (*Z. physiol. Chem.*, 1892, **15**, 214) give m. p. 124·5°. The *sodium* salt is prepared by evaporating to dryness a solution of the acid in the calculated amount of aqueous sodium carbonate.

Condensation of 2-Nitroveratraldehyde with 2 : 5-Dimethoxyphenylacetic Acid. trans-2-*Nitro*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic Acid* (III) *and* trans-2-*Nitro*-3 : 4-*dimethoxycinnamic Acid*.—A mixture of sodium 2 : 5-dimethoxyphenylacetate (10 g.), 2-nitroveratraldehyde (Pisovschi, *Ber.*, 1910, **43**, 2137) (30 g.), and acetic anhydride (200 g.) is heated at 100° for 60 hours. Water is then added to destroy the acetic anhydride, and the residual oil is repeatedly extracted with small quantities of boiling dilute sodium carbonate solution. On cooling, the combined extracts deposit long silky needles of sodium *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamate. These are ground with concentrated hydrochloric acid; the *acid* obtained, after being washed and dried (13·5 g.), crystallises from ethyl alcohol in bright yellow, hexagonal plates, m. p. 204—205° (Found: C, 58·9; H, 4·9. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9%).

Acidification with concentrated hydrochloric acid of the alkaline mother-liquor from which the sodium salt has separated (above) precipitates *trans*-2-nitro-3 : 4-dimethoxycinnamic acid (1·5 g.), which crystallises from ethyl alcohol in colourless needles, m. p. 229° with softening from 216°. There is no depression in the melting point of a mixture of this acid with the cinnamic acid obtained by the condensation of 2-nitroveratraldehyde and malonic acid (compare this vol., p. 932). The amount of this acid which is produced in the condensation described above increases rapidly with rise in temperature, and in earlier experiments it was observed that when the reaction took place at 140° equal weights of the two acids were produced.

The Isomeric trans-2-*Amino*-3 : 4 : 2′ : 5′-*tetramethoxy*-α-*phenylcinnamic Acids, A and B* (II).—A hot solution of *trans*-2-nitro-3 : 4 : 2′ : 5′-tetramethoxy-α-phenylcinnamic acid (13·0 g.) in dilute ammonia (100 c.c.) is added carefully (frothing) to a hot reducing mixture previously prepared by the addition of ammonia (*d* 0·880; 120 c.c.) to a solution of ferrous sulphate (83·6 g.) in hot water (150 c.c.); the mixture is heated on the water-bath for 30 minutes. After the ferrosoferric oxide has been thoroughly washed with dilute ammonia, the combined filtrate and washings are cooled and just acidified with glacial acetic acid. The product separates as a gummy mass which rapidly crystallises; on recrystallisation from ethyl alcohol, the acid A (7·5 g.) separates in colourless needles. From the alcoholic mother-liquor, when evaporated to small bulk and cooled, the acid B is obtained as yellow needles (0·5 g.). The quantity of this acid increases, and the amount of A decreases correspondingly, if an excess of acetic acid is used in precipitating the product of the reduction.

The *acid B* is purified by dissolving it in cold, dilute hydrochloric acid (charcoal) and precipitating it by the addition of sodium acetate solution. After being washed with water and dried on porous tile, it crystallises from ethyl alcohol in yellow needles, m. p. 167° (Found in material heated at 100°: C, 62·6, 62·3; H, 5·6, 5·7; N, 3·8; OMe, 33·2. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9; N, 3·9; 4OMe, 34·5%). The somewhat low percentage of carbon indicates the retention of traces of moisture, which are lost only by heating to 140° (Loss at 140°: 0·6, 0·7%. Found in material dried at 140°: C, 63·5; H, 6·0%). The acid forms a yellow solution in dilute hydrochloric acid and a colourless solution in dilute sodium hydroxide or carbonate or ammonia, and is precipitated from these by the addition of sodium acetate or acetic acid respectively. It dissolves rather readily in methyl or ethyl alcohol, forming a bright yellow solution, but is sparingly soluble in cold benzene. It was converted into an uncrystallisable gum when a 0·1% aqueous solution was boiled under reflux for 12 hours.