681. *The Structures of Some Supposed Azetid-2 : 4-diones. Part II.* Derivatives of Tartronic Acid.*

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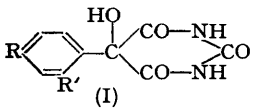
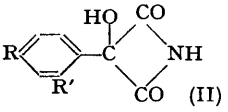
It has been shown by direct comparison with authentic specimens that compounds prepared by the method of Riebsomer *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 3491) from aryltartronic esters and urea or ammonia are not tartronimides but 5-aryloxazolid-2 : 4-diones. Other supposed tartronimides obtained by the alkaline degradation of 5-aryldialuric acids have already been recognised as oxazolid-diones (see *J.*, 1949, addendum to p. 1327).

Alloxan reacts with aromatic amines by condensation with the activated benzene nucleus to form 5-aryldialuric acids (I), a synthesis first recorded by Pellizzari (*Gazzetta*, 1887, **17**, 409; 1888, **18**, 340; 1889, **19**, 397; 1911, **41**, 21). These acids are decomposed when dissolved in aqueous alkalis giving ammonia, carbon dioxide, and new products which Pellizzari formulated as tartronimides (II). Pellizzari's synthesis of dialuric acids from alloxan and aromatic amines was later extended by Boehringer to phenols and aryl ethers and was protected by patents as providing, by alkaline and acid hydrolysis respectively, a route to the aryltartronic acids and the corresponding aromatic aldehydes (cf. " Friedländer," Vol. V, pp. 117, 863; Vol. VI, pp. 158 *et seq.*).

An account is now given of the alkaline degradation of 5-(2 : 4-dimethoxyphenyl)dialuric acid (I; R = R′ = OMe), first prepared by N. M. Green (Thesis, Oxford, 1948). Heating this acid with 10N-aqueous sodium hydroxide gave 2 : 4-dimethoxyphenyltartronic acid,


(I)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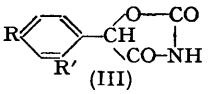
(III)

from which the related mandelic acid was obtained by treatment with warm dilute hydrochloric acid. On the other hand, the product formed on hydrolysis with N-sodium hydroxide contains one active hydrogen per molecule and gives an alkali-insoluble monomethyl ether which does not yield an acetyl derivative, facts excluding the tartronimide structure (II; R = R′ = OMe) but readily explicable on the supposition that it is an oxazolid-2 : 4-dione (III; R = R′ = OMe). This interpretation is in agreement with the comparable observations by Aspelund on other dialuric acids (*Acta Acad. Aboensis Math. et Phys.*, 1939, **11**, No. 7, 4; 1939, **11**, No. 14, 3) of which we then became aware (see *J.*, 1949, addendum to p. 1327).

Riebsomer *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 3491) attempted the preparation of 5-aryldialuric acids by a variation of the Traube synthesis of pyrimidines, using alcoholic solutions of aryltartronic esters, urea, and sodium ethoxide, but unexpectedly obtained compounds of the type $Ar{\cdot}C_3H_2O_3N$. Identical products were again formed, though in very small amounts, when ammonia was substituted for urea, a result which thus led to their representation as tartronimides (Riebsomer *et al.*, *loc. cit.*). Recognition of Pellizzari's supposed tartronimides as oxazolid-diones makes it evident that the products described by the American authors are similarly constituted, a conclusion supported by the concordance of melting point recorded for the supposed phenyltartronimide (Riebsomer *et al.*, *loc. cit.*) and for 5-phenyloxazolid-2 : 4-dione (III; R = R′ = H) (Traube and Ascher, *Ber.*, 1913, **46**, 2082); this has now been confirmed by a mixed melting point with an authentic specimen synthesised from ethyl mandelate and urea.

Similarly, the compound formed on mild alkaline hydrolysis of the newly prepared 5-*p*-methoxyphenyldialuric acid (I; R = OMe, R′ = H) is indistinguishable from 5-*p*-methoxyphenyloxazolid-2 : 4-dione (III; R = OMe, R′ = H) synthesised from 4-methoxymandelamide and ethyl carbonate in alcoholic sodium ethoxide. The formation of oxazolid-diones from aryltartronic esters does not, however, appear to involve the corresponding dialuric acids as intermediates since the 5-(2 : 4-dimethoxyphenyl)dialuric acid is only very slightly affected by alcoholic sodium ethoxide under the conditions of the Riebsomer reaction.

* Part I, preceding paper.

2 : 4-Dimethoxyphenylglyoxal and 2 : 4-dimethoxymandelonitrile have been prepared in connection with the identification of the 5-(2 : 4-dimethoxyphenyl)oxazolid-dione, but owing to unforeseen difficulties in proceeding to the related mandelic acid or amide it was not possible to complete independent syntheses of the hydrolysis products of the dimethoxyphenyl dialuric acid.

Experimental.

5-(2 : 4-*Dimethoxyphenyl*)*dialuric Acid*.—A solution of alloxan hydrate (36 g.) in hot water (35 c.c.) was made up to 85 c.c. with concentrated hydrochloric acid and mixed with resorcinol dimethyl ether (36 g.) dissolved in ethanol (150 c.c.). Hydrogen chloride was then passed into the mixture for ½—1 hour, whereupon it became solid owing to deposition of crystalline 5-(2 : 4-*dimethoxyphenyl*)*dialuric acid* (42 g.). This was collected, washed with alcohol, and dissolved in boiling water, from which it crystallised in needles, m. p. 263—264° (decomp.) (Found : C, 51·8; H, 4·3; N, 9·8. $C_{12}H_{12}O_6N_2$ requires C, 51·4; H, 4·3; N, 10·0%). The dialuric acid can also be crystallised from ethanol; it gives a green colour in concentrated sulphuric acid. It was unchanged (recovery 80%) after being heated at 115—120° for 8 hours with sodium ethoxide (3 equivalents) in ethanol, and no oxazolid-dione could be detected.

2 : 4-*Dimethoxyphenyltartronic Acid*.—A solution of the dimethoxyphenyldialuric acid (12 g.) in 10N-potassium hydroxide (26 c.c.) was evaporated to dryness, with stirring, on a steam-bath. The product was redissolved in water (30 c.c.) and again taken to dryness, the residue then being dissolved in water (30 c.c.) and the solution brought to pH 6·7 by the addition of acetic acid (*ca.* 12 g.). After dilution with alcohol (4 vols.) the solution was left at 0—2° for 48 hours, whereupon a colourless potassium salt (2·2 g., 15%) was precipitated; a further small quantity was deposited on the continued addition of alcohol. The salt (1 g.) was shaken with excess of ethereal hydrogen chloride for 20 minutes, and after filtration the solution was evaporated, the residue of 2 : 4-dimethoxyphenyltartronic acid (0·5 g.), m. p. 128° (effervescence), being dried in a vacuum over phosphoric anhydride. Esterification with diazomethane gave *methyl* 2 : 4-*dimethoxyphenyltartronate*, which crystallised from light petroleum (b. p. 100—120°) in colourless needles, m. p. 95° (Found : C, 54·7; H, 5·5. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·7%).

2 : 4-*Dimethoxymandelic Acid*.—A solution of 2 : 4-dimethoxyphenyltartronic acid, or its potassium salt, in hydrochloric acid (6%) was heated on a steam-bath for ½ hour. The product was extracted with ether, and evaporation of the solvent left 2 : 4-*dimethoxymandelic acid* which crystallised from benzene in shining plates, m. p. 130° (Found : C, 57·1; H, 6·0. $C_{10}H_{12}O_5$ requires C, 56·7; H, 5·7%).

5-(2 : 4-*Dimethoxyphenyl*)*oxazolid*-2 : 4-*dione*.—The dimethoxyphenyldialuric acid (40 g.) was dissolved in N-sodium hydroxide (600 c.c.), and the solution heated on a steam-bath for 20 minutes. The clear liquid was then cooled and acidified, and next day the crystalline product (22—23 g., 65—70%) was collected and crystallised from water. The *dimethoxyphenyloxazolid-dione* was thus obtained as clusters of needles, m. p. 179° (Found : C, 56·0; H, 4·6; N, 5·9%; active H, 0·8 atom; *M*, 236. $C_{11}H_{11}O_5N$ requires C, 55·7; H, 4·7; N, 5·9%; active H, 1 atom; *M*, 237). The oxazolid-dione which is sparingly soluble in cold water dissolves readily in aqueous sodium hydroxide and carbonate. It is a strong acid and can be titrated to phenolphthalein with alkalis (N/10) (Found : equiv., 241). The oxazolid-dione gives a green solution in concentrated sulphuric acid. The silver salt precipitated from an aqueous solution of the sodium compound with silver nitrate is readily soluble in aqueous ammonia and in dilute nitric acid. The oxazolid-dione is oxidised by aqueous permanganate to 2 : 4-dimethoxybenzoic acid, m. p. and mixed m. p. 108°.

Methylation of the oxazolid-dione (II; R = R′ = OMe) with ethereal diazomethane gave 5-(2 : 4-*dimethoxyphenyl*)-3-*methyloxazolid*-2 : 4-*dione*, crystallising from aqueous methanol in colourless needles, m. p. 111—112° (Found : C, 57·4; H, 5·4; N, 5·7; OMe, 24·9; NMe, 7·29. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6; OMe, 24·7; NMe, 11·6%). The *N*-methyl derivative was recovered unchanged after being heated with acetic anhydride for 8 hours.

The solution obtained by heating 5-(2 : 4-dimethoxyphenyl)oxazolid-2 : 4-dione (1 g.) with acetic anhydride (30 c.c.) on a steam-bath for 1 hour was filtered from a small unidentified residue (m. p. 256—260°), evaporated under reduced pressure, and finally dried at 110° over potassium hydroxide. The *acetyl* derivative (0·7 g.), m. p. 124°, when crystallised from alcohol formed needles, m. p. 125° (Found : C, 56·3; H, 4·7; N, 5·1. $C_{13}H_{13}O_6N$ requires C, 55·9; H, 4·7; N, 5·0%). This compound is insoluble in cold aqueous alkalis and its solutions do not form a precipitate with silver nitrate.

5-*Phenyloxazolid*-2 : 4-*dione*.—To a solution of sodium (1·25 g.) in dry ethanol (30 c.c.) were added ethyl mandelate (9 g.) and urea (3 g.). After 2 hours' heating under reflux the mixture was evaporated under reduced pressure and the residue dissolved in water (*ca.* 60 c.c.). Acidification of the filtered solution gave the 5-phenyloxazolidione (6·85 g., 77%), m. p. 103—104°, which on recrystallisation from water gave plates, m. p. 107—108°. Traube and Ascher (*Ber.*, 1913, **46**, 2082), who obtained it from 2-imino-5-phenyloxazolid-4-one, give m. p. 108°. The 3-methyl derivative formed by the action of diazomethane, had m. p. 112—113°. Aspelund (*Finska Kem. Medd.*, 1940, **49**, 49) found m. p. 113° for a specimen synthesised from phenylchloroacetyl chloride and *N*-methyl-*N*′-phenylurea.

Repetition of the preparation from ethyl phenyltartronate and urea (Riebsomer *et al.*, *loc. cit.*) gave 5-phenyloxazolid-2 : 4-dione (16%), m. p. 107—108° alone or mixed with a specimen synthesised from ethyl mandelate, and the *N*-methyl derivative had m. p. and mixed m. p. 112—113°. The preparation of ethyl phenyltartronate (Riebsomer, *loc. cit.*) using 1·2 mols. of stannic chloride affords the tartronate, b. p. 154—16?°/1 mm., in 28% yield.

5-p-*Methoxyphenyldialuric Acid*.—A solution (47 c.c.) containing alloxan hydrate (20 g.) in hot water (10 c.c.) and concentrated hydrochloric acid was added to a mixture of anisole (16 g.) and ethanol (100 c.c.), and the whole saturated with hydrogen chloride. The product which separated after 24 hours at room temperature and a further 2 hours' cooling at 0° consisted of the crude p-*methoxyphenyldialuric acid* (11·5 g., 32%), m. p. 230° (decomp.), and when recrystallised from hot water formed needles, m. p. 239° (decomp.) (Found : C, 53·2; H, 4·0; N, 10·9. $C_{11}H_{10}O_5N_2$ requires C, 52·8; H, 4·0; N, 11·2%).

5-p-*Methoxyphenyloxazolid*-2 : 4-*dione*.—(i) 5-*p*-Methoxyphenyldialuric acid (5·4 g.) was heated in 2N-sodium hydroxide (34 c.c.) on a steam-bath for 30 minutes. The solution was cooled in ice-water and acidified with concentrated hydrochloric acid until precipitation of the p-*methoxyphenyloxazolid*-2 : 4-*dione* (2·1 g., 47%) was complete. Recrystallisation from hot water gave colourless plates, m. p. 135—136° (Found : C, 57·9; H, 4·3; N, 7·0. $C_{10}H_9O_4N$ requires C, 57·95; H, 4·4; N, 6·8%). Dissolved in aqueous alkali and treated with potassium permanganate, the dione (0·2 g.) gave, on acidification and treatment with sulphur dioxide, *p*-anisic acid (0·075 g., 50%), m. p. 181—182°.

(ii) (cf. Wallingford, U.S.P. 2,338,220; *Chem. Abs.*, 1944, **38**, 3666). To a solution of sodium (0·4 g.) in ethanol (7 c.c.), ethyl carbonate (3 g.) and an ethanolic solution (40 c.c.) of 4-methoxymandelamide (3 g.) were added and the mixture was heated under reflux for 2 hours. The precipitated sodium salt was collected and dissolved in water, the solution on acidification depositing the 5-*p*-methoxyphenyloxazolid-2 : 4-dione. With a further small amount obtained by concentration of the alcoholic filtrate, shaking with water, and filtration from insoluble 4-methoxymandelamide (0·2 g.) followed by acidification, the yield was 2·15 g. Crystallisation from water gave clusters of plates, m. p. 135—136° alone or mixed with a specimen derived from the dialuric acid.

Methylation of the oxazolid-dione with ethereal diazomethane gave 3-*methyl*-5-p-*methoxyphenyloxazolid*-2 : 4-*dione*, glistening plates (from alcohol), m. p. 141—142° (Found : C, 59·7; H, 5·2; N, 6·7. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

2 : 4-*Dimethoxyphenylglyoxal*.—2 : 4-Dimethoxyacetophenone (Perkin, Robinson, and Turner, *J.*, 1908, **93**, 1108) gives a *semicarbazone* crystallising from ethanol and having m. p. 206° (Found : C, 55·8; H, 6·3; N, 17·5. $C_{11}H_{15}O_3N_3$ requires C, 55·7; H, 6·4; N, 17·7%). The ketone (30 g.) was oxidised in dioxan with selenious acid as described for acetophenone (*Org. Synth.*, **15**, 67). After removal of the solvent under reduced pressure the residue was thrice extracted with hot water (3 × 170 c.c.), but the desired product failed to separate from the aqueous solution (charcoal) even after concentration. It was therefore extracted with chloroform, and the product (30 g.) eventually solidified (m. p. 99°) but was not readily recrystallised.

It was characterised by the *semicarbazone*, light yellow plates, m. p. 205—206°, from ethanol (Found : C, 52·6; H, 5·4; N, 16·6. $C_{11}H_{13}O_4N_3$ requires C, 52·6; H, 5·2; N, 16·7%). A mixed m. p. with dimethoxyacetophenone semicarbazone was *ca.* 186°. The 2 : 4-dimethoxyphenylglyoxal, unlike the isomeric 2 : 6-dimethyl ether (Fuson, McKeever, Rabjohn, and Gray, *J. Amer. Chem. Soc.*, 1943, **65**, 1028), failed to undergo rearrangement in alkaline conditions to the corresponding mandelic acid.

2 : 4-*Dimethoxymandelonitrile*.—A solution of potassium cyanide (21 g., 4 mols.) in water (55 c.c.), mixed with 2 : 4-dimethoxybenzaldehyde sodium bisulphite compound (21 g., 1 mol.), was cooled in ice-water and shaken with benzene (50 c.c.) until two clear layers were obtained. The benzene solution was then separated, washed with water, and finally treated with anhydrous magnesium sulphate. When completely dry, the filtered solution was diluted with light petroleum to turbidity and left at 0°. After 5 days the crystalline product (5·65 g.) was collected, and a further quantity (2·7 g.) obtained by evaporation of the solution to dryness and crystallisation from benzene–light petroleum. The 2 : 4-*dimethoxymandelonitrile* (8·35 g., 55%), m. p. 65—66°, when recrystallised from light petroleum formed colourless needles, m. p. 66—67° (Found : C, 62·1; H, 6·05; N, 7·2. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·2%). Various attempts to convert the nitrile into derivatives of 2 : 4-dimethoxymandelic acid were unsuccessful. Cold concentrated hydrochloric acid led to a product insoluble in aqueous alkali. Solutions in concentrated sulphuric acid, and in ethereal hydrogen chloride containing an equivalent of alcohol, when poured into water gave nitrogenous products from which, however, no mandelamide was isolated. Reactions between resorcinol dimethyl ether and ethyl mesoxalate (cf. Riebsomer, *loc. cit.*) or ethoxalyl chloride in presence of various catalysts also failed.

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