

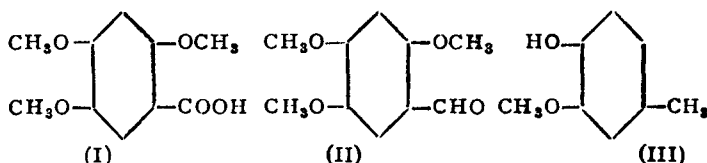
A NEW SYNTHESIS OF ASARONIC ACID AND ALDEHYDE AND THEIR DERIVATIVES

BY S. RAJAGOPALAN, T. R. SESHADRI, F.A.SC., AND S. VARADARAJAN

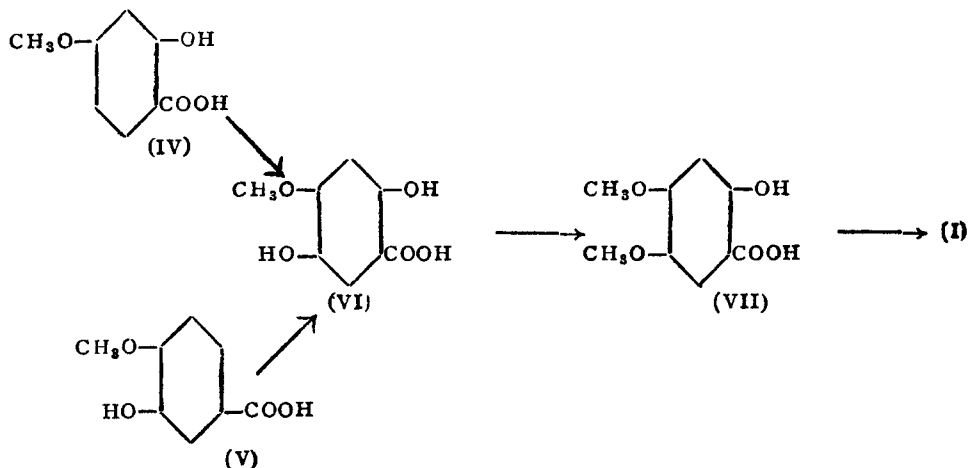
(From the Department of Chemistry, Andhra University, Waltair)

Received July 4, 1949

SAMPLES of asaronic acid (I) and aldehyde (II) were required in connection with the identification of certain degradation products of naturally occurring compounds in this laboratory. Apart from the oxidation of asarylic aldehyde and asarone^{1, 7, 8} asaronic acid was also made in the past² starting from creosol (III) and following a number of steps.

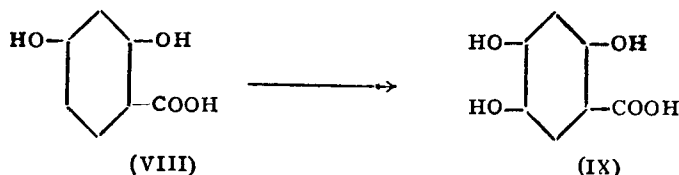


The preparation becomes considerably simplified by employing Elbs persulphate method³ of oxidation. Either 4-O-methyl resorcylic acid (IV) or isovanillic acid (V) could be used for this purpose, the product being 2:5-dihydroxy-4-methoxy benzoic acid (VI). This could be methylated in stages yielding 4:5-dimethoxy-2-hydroxy benzoic acid (VII) and finally asaronic acid (I). The samples thus prepared agree in every respect with the description in the literature of asaronic acid. The dimethoxy-salicylic acid (VII) is an important degradation product of dehydro-deguelin⁴ and

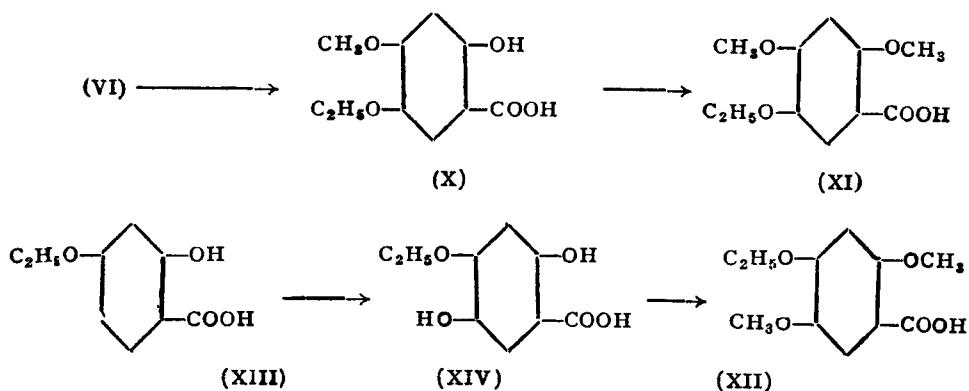


was originally synthesised by Head and Robertson⁵ starting from veratrol. The present synthesis constitutes considerable simplification.

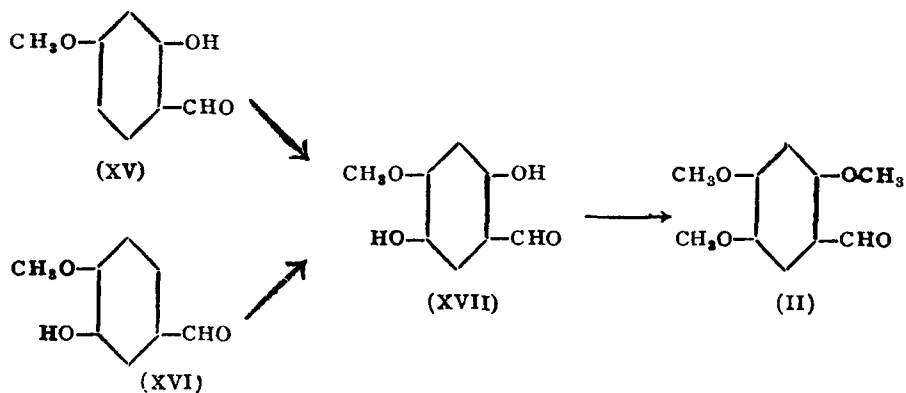
For the above purposes β -resorcylic acid (VIII) itself can be directly employed. It undergoes oxidation but the yield of the oxidation product, *i.e.*, 2: 4: 5-trihydroxy benzoic acid (IX)⁶ is rather poor. It can be methylated to asaronic acid (I).



Further the new method is convenient for preparing the mixed (ethyl methyl) ethers of hydroxyquinol carboxylic acid that have been used by Head and Robertson⁷ in connection with the constitution of aesculin. By the partial ethylation of 2: 5-dihydroxy-4-methoxy benzoic acid (VI) and subsequent methylation 2: 4-dimethoxy-5-ethoxy benzoic acid (XI) is obtained. Its isomer, 2: 5-dimethoxy-4-ethoxy benzoic acid (XII) can be prepared from the 4-ethyl ether of β -resorcylic acid (XIII)¹⁰ by subjecting it to oxidation with potassium persulphate and finally methylating it fully.



Similar procedures can be adopted also for the preparation of asarylic aldehyde¹ (II) starting from resorcylic aldehyde monomethyl ether (XV) or from isovanillin (XVI). Good yields are obtained in their oxidation with persulphate producing 2: 5-dihydroxy-4-methoxy benzaldehyde (XVII) which can be methylated to yield asarylic aldehyde (II). This trimethoxy benzaldehyde was prepared earlier from the ethers of hydroxyquinol by employing the Gattermann reaction.^{7, 8}



EXPERIMENTAL

2:5-Dihydroxy-4-methoxy benzoic acid (VI)

(i) 2-Hydroxy-4-methoxy-benzoic acid was conveniently prepared by methylating resorcylic acid (24 g., 1 mole) with dimethyl sulphate (17 c.c., 1.1 mole) and excess of aqueous alkali (80 c.c. of 20%).

To a solution of 2-hydroxy-4-methoxy benzoic acid (10.0 g.) in aqueous sodium hydroxide (8.0 g. in 90 c.c.) cooled to 10°, was added dropwise an aqueous solution of potassium persulphate (17.0 g. in 300 c.c.) with stirring, in the course of 4 hours. After allowing to stand for 24 hours at room temperature the solution was neutralised with dilute hydrochloric acid and extracted with ether repeatedly to remove the unreacted compound. To the remaining aqueous solution was added concentrated hydrochloric acid (60 c.c.) and sodium sulphite (8.0 g.) and the mixture kept in a water-bath at 80° for 30 minutes. The solution was cooled and extracted with ether. On distilling off ether from the extract a brown solid was left. This crystallised from aqueous alcohol as colourless rectangular rods melting at 201° (decomp.). Yield, 3.5 g. With alcoholic ferric chloride it gave a blue colour which changed to green and finally faded. (Found: C, 47.2; H, 5.0; Loss on drying at 110° in vacuo 8.8%, C₈H₈O₅, H₂O requires C, 47.5; H, 5.0 and loss 8.9%.)

(ii) Isovanillic acid⁹ (4.0 g.) was subjected to oxidation with aqueous potassium persulphate (8.0 g. in 160 c.c.) in alkaline medium (6.0 g. of sodium hydroxide in 40 c.c. of water). On working up the reaction product as in the above experiment the quinol carboxylic acid was obtained as a brown amorphous solid. After repeated crystallisations from aqueous alcohol it came out as colourless rectangular rods and prisms melting at 201° (decomp.). Yield, 1.4 g. A mixed melting point with the sample obtained above was undepressed.

2-Hydroxy-4:5-dimethoxy benzoic acid (VII)

The above dihydroxy compound (VI) (0.8 g.) in dry benzene (30 c.c.) was refluxed with dimethyl sulphate (0.8 c.c.) and anhydrous potassium carbonate (4.0 g.) for 6 hours. The potassium salts were filtered off and washed with hot benzene. On distilling off the solvent from the filtrate a colourless solid was obtained. When crystallised from water it yielded the methyl ester of 2-hydroxy-4:5-dimethoxy benzoic acid as long prismatic needles melting at 95°. This ester (0.6 g.) was hydrolysed by heating with 5% aqueous alkali (20 c.c.) for half an hour on a boiling water-bath. The product obtained on acidification was crystallised from aqueous alcohol. 2-Hydroxy-4:5-dimethoxy benzoic acid separated out as rhombohedral prisms melting at 210-11° (decomp.).^{4,5} A mixed melting point with 2:5-dihydroxy-4-methoxy benzoic acid was considerably depressed. It gave a violet blue colour with alcoholic ferric chloride. Yield, 0.4 g.

2:4:5-Trimethoxy benzoic acid (Asaronic acid) (I)

2:5-Dihydroxy-4-methoxy benzoic acid (VI) (0.5 g.) in acetone (30 c.c.) was treated with freshly distilled dimethyl sulphate (0.8 c.c.) and anhydrous potassium carbonate (6.0 g.) and the mixture refluxed for 12 hours. The potassium salts were filtered and washed with warm acetone. On removing acetone from the filtrate and adding water to the residue a brown amorphous solid was obtained. This was filtered and hydrolysed by heating with 5% aqueous alkali on a boiling water-bath for half an hour. The resulting product when crystallised from benzene-petroleum ether yielded asaronic acid as colourless needles melting at 143°. ^{1,2} It gave no colour with alcoholic ferric chloride. Yield, 0.4 g.

2:4:5-Trihydroxy benzoic acid (IX)

An ice-cold solution of β -resorcylic acid (VIII) (15.0 g.) in aqueous sodium hydroxide (12.0 g. in 100 c.c.) was treated with aqueous potassium persulphate (30.0 g. in 400 c.c.). After 24 hours the solution was worked up as usual. The product was a brown solid (3.0 g.) and was difficult to purify; after a number of crystallisations from water it yielded hydroxy quinol carboxylic acid as fine needles melting at 217-18° (decomp.).⁶ Mixed melting point with β -resorcylic acid was depressed. The trihydroxy acid gave a violet blue colour with alcoholic ferric chloride. Yield, 1.0 g. When this acid (0.6 g.) in acetone (50 c.c.) was methylated with dimethyl sulphate (1.3 c.c.) and potassium carbonate (10.0 g.) and the resulting ester was hydrolysed with 5% alkali it yielded asaronic acid.

2-Hydroxy-4-methoxy-5-ethoxy benzoic acid (X)

2: 5-Dihydroxy-4-methoxy benzoic acid (VI) (1.0 g.) in acetone (80 c.c.) was treated with freshly distilled diethyl sulphate (1.3 c.c.) and anhydrous potassium carbonate (6.0 g.) and refluxed for 12 hours. The potassium salts were filtered and acetone distilled off from the filtrate. The sticky solid thus obtained was hydrolysed by heating with 5% aqueous sodium hydroxide (40 c.c.) for half an hour. The solution on acidification yielded the monohydroxy acid as an amorphous solid. It crystallised from aqueous alcohol as rectangular rods melting at 194° (decomp.). It gave a stable violet blue colour with alcoholic ferric chloride. Yield, 0.6 g. (Found: C, 56.2; H, 6.0; C₁₀H₁₂O₅ requires C, 56.6; H, 5.7%.)

2: 4-Dimethoxy-5-ethoxy benzoic acid (XI)

The preceding compound (X) (0.1 g.) in acetone (30 c.c.) was methylated with dimethyl sulphate (0.4 c.c.) and anhydrous potassium carbonate (2.0 g.) by refluxing for 24 hours. The resulting product was hydrolysed with 5% aqueous sodium hydroxide (10 c.c.). 2: 4-Dimethoxy-5-ethoxy benzoic acid crystallised from water as rectangular rods melting at 137°.7 It gave no colour with alcoholic ferric chloride.

2: 5-Dihydroxy-4-ethoxy benzoic acid (XIV)

To an ice-cold solution of 2-hydroxy-4-ethoxy benzoic acid¹⁰ (XIII) (3.0 g.) in aqueous sodium hydroxide (1.3 g. in 15 c.c.) was added dropwise potassium persulphate (3.5 g. in 70 c.c. of water) during 4 hours. The reaction product was worked up as usual. The dihydroxy acid crystallised from aqueous alcohol as thin rectangular rods, melting at 202.4° (decomp.). With alcoholic ferric chloride it gave a violet blue colour which slowly changed to green and finally faded. Yield, 0.5 g. (Found: C, 54.2; H, 5.3; C₉H₁₀O₅ requires C, 54.5; H, 5.1%.)

2: 5-Dimethoxy-4-ethoxy benzoic acid (XII)

The above dihydroxy acid (XIV) (1.0 g.) in acetone (100 c.c.) was methylated with dimethyl sulphate (1.8 c.c.) and anhydrous potassium carbonate (5.0 g.) by refluxing for 20 hours. The dimethyl ether crystallised from aqueous alcohol as rectangular rods melting at 130-31°.7 It did not give any colour with alcoholic ferric chloride. Yield, 0.6 g.

2: 5-Dihydroxy-4-methoxy benzaldehyde (XVII)

(i) 2-Hydroxy-4-methoxy benzaldehyde was made earlier by Ott and Nauen¹¹ by the methylation of resorcylic aldehyde with dimethyl sulphate and alcoholic potash. It is now found that the preparation is more conveniently carried out in boiling dry benzene solution (5 hours) with 1.1 mole of dimethyl sulphate and excess of anhydrous potassium carbonate.

2-Hydroxy-4-methoxy benzaldehyde (XV) (5.0 g.) was dissolved in pyridine (5 c.c.) and aqueous sodium hydroxide (4.0 g. in 50 c.c.) and the solution cooled in ice. A solution of potassium persulphate (10.0 g. in 250 c.c. of water) was added dropwise in the course of 4 hours. After 24 hours the product was worked up as usual. It crystallised from alcohol as colourless rectangular plates and prisms melting at 209° (decomp.).⁷ Yield, 1.0 g. With alcoholic ferric chloride it gave a bluish green colour which slowly faded.

(ii) Isovanillin (4.0 g.) in aqueous sodium hydroxide (3.2 g. in 40 c.c.) was treated with potassium persulphate (8.0 g. in 200 c.c.) under conditions identical with those employed above. 2: 5-Dihydroxy-4-methoxy benzaldehyde crystallised from alcohol and melted at 209° (decomp.).⁷ A mixed melting point with the sample obtained in the previous experiment was not depressed. Yield, 1.6 g.

2: 4: 5-Trimethoxy-benzaldehyde (Asarylaldehyde) (II)

The dihydroxy aldehyde (XVII) (0.5 g.) in acetone (40 c.c.) was refluxed for 10 hours with dimethyl sulphate (1.0 c.c.) and potassium carbonate (6.0 g). The reaction product when crystallised from water yielded asarylaldehyde as rectangular rods melting at 114°.^{7, 8} It did not give any colour with alcoholic ferric chloride.

SUMMARY

Asaronic acid is conveniently prepared from 4-O-methyl- β -resorcylic acid and isovanillic acid by oxidation with alkaline persulphate and subsequent methylation. Useful partial methyl ethers and mixed methyl-ethyl ethers are also made by adopting this method. Similarly asarylic aldehyde is obtained from 4-O-methyl- β -resorcylic aldehyde and isovanillin.

REFERENCES

1. Butterloff and Rizza .. *J. Russ. Phy. Chem. Soc.*, 1887, 19, 3.
2. Luff, Perkin and Robinson .. *J.C.S.*, 1910, 1131.
3. Baker .. *Ibid.*, 1948, 2303.
4. Clark .. *J.A.C.S.*, 1931, 2007.
5. Head and Robertson .. *J.C.S.*, 1931, 2432.
6. Thiele and Jaeger .. *Ber.*, 1901, 2840.
7. Head and Robertson .. *J.C.S.*, 1930, 2434.
8. Gattermann and Eggers .. *Ber.*, 1899, 289.
9. Lovecy, Robinson and Sugasawa *J.C.S.*, 1930, 818.
10. Kostanecki and Tambor .. *Ber.*, 1895, 2307.
11. Ott and Nauen .. *Ibid.*, 1922, 920.
- Robinson and Robinson .. *J.C.S.*, 1932, 1441.