157. *Synthesis of Rhamnazin.*

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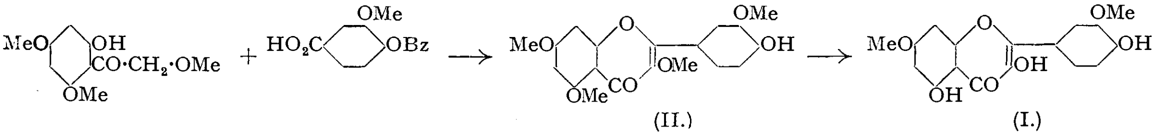
The synthesis of rhamnazin (I) has been effected by condensing 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone with the anhydride and sodium salt of benzoylvanillic acid and subjecting the tetramethyl ether of quercetin (II) thus obtained to partial demethylation with aluminium chloride in nitrobenzene solution.

Rhamnazin (I) occurs in Persian berries with rhamnetin and quercetin (Perkin and Geldard, *J.*, 1895, **67**, 500). Its constitution as the 7 : 3′-dimethyl ether of quercetin was established by Perkin and Allison (*J.*, 1902, **81**, 470). The synthesis has now been effected following in general the procedure adopted in the case of izalpinin (Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1945, **22**, A, 383). 2-Hydroxy-ω : 4 : 6-trimethoxyacetophenone is condensed with the anhydride and sodium salt of benzoylvanillic acid according to the method of Allan and Robinson. The resulting 3 : 5 : 7 : 3′-*tetramethyl ether* (II) of quercetin is subjected to partial demethylation using aluminium chloride in nitrobenzene solution. The synthetic compound has all the properties of rhamnazin and the identity has been confirmed by the preparation of the acetyl and benzoyl derivatives.



A new procedure has been adopted for the preparation of benzoylvanillic acid, by oxidising benzoylvanillin with potassium permanganate in acetic acid solution. The product is then obtained more readily pure and in better yields than by older methods (Tiemann and Kraaz, *Ber.*, 1882, **15**, 2068; Heap and Robinson *J.*, 1926. 2342) in which the separation of by-products causes difficulty.

Experimental.

Benzoylvanillic Acid and Anhydride.—Benzoylvanillin (10 g.) was dissolved in glacial acetic acid (100 c.c.) and aqueous potassium permanganate (7 g. in 150 c.c. of water) gradually added during the course of an hour with vigorous stirring, the temperature being kept at 70—80°. Precipitated manganese dioxide was dissolved by passing sulphur dioxide, and the solution treated with a large volume of water. The acid that separated was filtered off and washed with water. One crystallisation from alcohol yielded colourless prismatic needles, m. p. 174—176°; yield, 7 g. A second crystallisation raised the m. p. to 177—178°.

Dry pyridine (8 c.c.) was added to a solution of benzoylvanilloyl chloride (Heap and Robinson, *loc. cit.*) (5 g.) in anhydrous ether. After 2½ hours in the ice-chest, small pieces of ice and ice-cold dilute hydrochloric acid were added and the mixture was stirred vigorously; a pale cream coloured solid then separated. It was filtered off, washed with ice-cold hydrochloric acid followed by ice water, and dried in a vacuum desiccator; yield, 4 g.

*4′-Hydroxy-*3 : 5 : 7 : 3′*-tetramethoxyflavone* (II).—An intimate mixture of 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone prepared by the partial methylation of 2 : 4 : 6-trihydroxy-ω-methoxyacetophenone (Row and Seshadri, *Proc. Ind. Acad. Sci.*, 1946, **23**, A, 23) (1 g.), benzoylvanillic anhydride (5 g.), and sodium benzoylvanillate (2 g.) was heated under vacuum at 180° for 3 hours. The solid cake was taken out, finely powdered, and refluxed with alcoholic potash (50 c.c. of 10% solution) till it completely dissolved. The solvent was then removed under reduced pressure and the solid residue dissolved in water (150 c.c.). The clear yellowish-brown solution was saturated with carbon dioxide. The yellow solid which separated was filtered off, washed, and crystallised from alcohol; yield, 1·2 g. After a second crystallisation it formed very pale yellow rectangular plates and prisms, m. p. 200—201° (Found : C, 63·8; H, 5·3. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). The *compound* dissolved in aqueous sodium hydroxide or sodium carbonate to give a stable yellow colour. With ferric chloride it produced no characteristic colouration. Its solution in concentrated sulphuric acid had a yellow colour with green fluorescence.

A portion of the above compound (0·2 g.) was methylated by refluxing a solution in anhydrous acetone with methyl sulphate (0·5 c.c.) and potassium carbonate (3·0 g.) for 6 hours. The methyl ether separated as colourless narrow rectangular plates, m. p. 152—153°. The mixed m. p. with an authentic sample of quercetin pentamethyl ether was not depressed.

The tetramethyl ether of quercetin (0·2 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and a few drops of pyridine. The *acetate* was crystallised twice from alcohol from which it separated in colourless flat needles, m. p. 178—180° (Found : C, 62·9; H, 5·3. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

3 : 5 : 4′-*Trihydroxy*-7 : 3′-*dimethoxyflavone* (*Rhamnazin*).—The tetramethoxyflavone (II) (1·0 g.) was dissolved in dry nitrobenzene (8 c.c.), treated with a solution of anhydrous aluminium chloride (2 g.) in the same solvent (8 c.c.), and kept in a boiling water-bath for 1½ hours. The product was then cooled and excess of light petroleum added. The brown precipitate was filtered off, washed thoroughly with light petroleum, and dried. It was then treated with dilute hydrochloric acid, and the mixture heated nearly to boiling and filtered. The solid product was washed twice with hot alcohol (5 c.c.) to remove any unconverted original compound. The yellow residue (0·8 g.) was then crystallised from glacial acetic acid. Further purification was effected by crystallisation from toluene from which it separated in glistening pale yellow rectangular prisms, m. p. 215—216° (Found : C, 61·6; H, 4·4; OMe 19·3. Calc. for $C_{17}H_{14}O_7$: C, 61·8; H, 4·2; OMe, 18·8%).

The compound in alcoholic solution gave an olive-green colour with ferric chloride and an orange-red precipitate with alcoholic lead acetate. In aqueous alkali it dissolved to an orange solution. In concentrated suphuric acid it formed a yellow solution with a brilliant green fluorescence.

The compound (0·3 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and a few drops of pyridine for 1 hour. The white solid that separated out on pouring the reaction mixture into water was collected, washed, and purified by crystallisation successively from alcohol and benzene–light petroleum. The pure acetate formed colourless narrow rectangular plates and flat needles, m. p. 154—155°.

Acetylrhamnazin (0·15 g.) was dissolved in alcohol (10 c.c.) and treated with concentrated hydrochloric acid (2 c.c.). The clear solution was heated on a water-bath for 10 minutes during which time a yellow crystalline solid separated. This was filtered off, washed with a little hot alcohol, and crystallised from toluene from which it separated in pale yellow rectangular prisms, m. p. 215—216°, identical with the original rhamnazin; yield, 0·1 g.

A solution of synthetic rhamnazin (0·1 g.) in aqueous sodium hydroxide was shaken vigorously with benzoyl chloride (0·5 c.c.) till the odour of the chloride disappeared. The solid benzoyl derivative was collected, washed with dilute alkali followed by water, and crystallised from ethyl acetate–light petroleum; it formed rectangular prisms, m. p. 205—207°; yield, 0·1 g.

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