383. *An Attempted Synthesis of Primetin.*

By S. SUGASAWA.

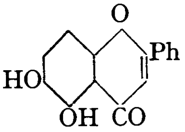
PRIMETIN isolated from *Primula modesta* by Hattori and Nagai (*J. Chem. Soc. Japan*, 1930, **51**, 162) is a dihydroxyflavone, $C_{15}H_{10}O_4$, and its constitution as 5 : 6-dihydroxyflavone (I) was deduced from the results of hydrolysis by means of alcoholic potassium hydroxide, whereby benzoic acid alone was obtained, a phenolic product, probably hydroxyquinol, suffering further change owing to its easy oxidisability; furthermore, one of the two hydroxyl groups is resistant towards methylating agents, and the absorption spectrum of the substance resembles that of 6-hydroxyflavone.

According to Rodionow, Kanewskaja, and Kupinskaja (*Ber.*, 1929, **62**, 2563) hemipinimide affords 5 : 6-dimethoxyanthranilic acid as the main product, when it is treated with potassium hypochlorite under certain conditions; this acid should be convertible into 6-hydroxy-2 : 3-dimethoxyacetophenone (III), a suitable intermediate in the synthesis of 5 : 6-dihydroxyflavone by the general method of Allan and Robinson (J., 1924, **125**, 2192; 1925, **127**, 181, *et seq.*). The project was, however, unsuccessful and 5 : 8-dihydroxyflavone (IV) was probably obtained, assuming that primetin is indeed 5 : 6-dihydroxyflavone.

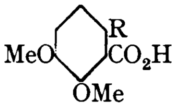
The direct substitution of the amino-group in 5 : 6-dimethoxyanthranilic acid by a hydroxyl group has failed. Also the attempted oxidation of this acid to 2-methoxy-*p*-benzoquinone-3-carboxylic acid (V) afforded a brown amorphous substance (probably the quinone) which decomposed at about 202—205°, but owing to the unfavourable yield this method was not developed. The amino-group was easily replaced by bromine, but when the 6-bromo-2 : 3-dimethoxybenzoic acid (VI) was treated with boiling aqueous sodium acetate and copper acetate, the corresponding hydroxy-acid (VII) was not obtained (compare Hurtley, J., 1929, 1870) and *o*-veratric acid was the only product isolated; a result which is rather unexpected, although a somewhat similar case is reported by Baker, Kirby, and Montgomery (J., 1932, 2876), who obtained pyrogallol and its methyl ethers when they treated 4-iodopyrogallol trimethyl ether with aqueous sodium hydroxide.

When 6-*iodo*-2 : 3-*dimethoxybenzoic acid* (IX) was treated with sodium benzyloxide in benzyl-alcoholic solution, 6-*benzyloxy*-2 : 3-*dimethoxybenzoic acid* (X) was obtained in good yield. The chloride of this acid was converted into 6-*benzyloxy*-2 : 3-*dimethoxyacetophenone* (XI) by means of methylzinc iodide. The debenzylation of the ketone was effected by means of hydrochloric acid in acetic acid solution, but, as the resulting phenolic compound was only obtained in small quantity and would not crystallise, the product was immediately fused with benzoic anhydride and sodium benzoate; a bright yellow substance, m. p. 129—130°, was ultimately isolated. This substance and its derivatives do not tally with primetin or its methyl ether and on demethylation a yellow amorphous substance was obtained, m. p. 179—180° (primetin has m. p. 230°). Owing to lack of material the investigation was discontinued at this stage; it is conceivable that during the debenzylation, not only the benzyl group, but also the methoxyl group ortho to acetyl was removed and the 2 : 6-dihydroxy-3-methoxyacetophenone (XII) thus formed yielded 5-hydroxy-8-methoxyflavone (XIII) on ring closure as the main, if not the sole product, and in that case the isomeric 5-hydroxy-6-methoxyflavone (XIV) (*O*-methylprimetin) might not have been isolable owing to the relatively small quantity produced.

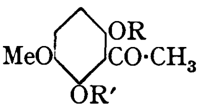
Experiments on the hydrolysis of the benzyloxy-group under milder condition are in progress.



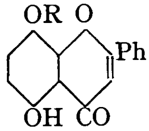
(I.)



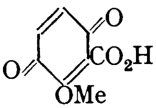
(II, R = NH_2.)
(VI, R = Br.)
(VII, R = OH.)
(IX, R = I.)
(X, R = O·CH$_2$Ph.)



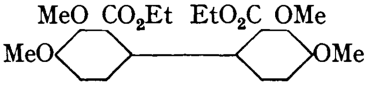
(III, R = H; R′ = Me.)
(XI, R = CH$_2$Ph; R′ = Me.)
(XII, R, R′ = H.)



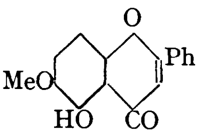
(IV, R = H.)
(XIII, R = Me.)



(V.)



(VIII.)



(XIV.)

EXPERIMENTAL.

6-*Bromo*-2 : 3-*dimethoxybenzoic Acid* (VI).—5 : 6-Dimethoxyanthranilic acid (2 g.), dissolved in an excess of 15% hydrobromic acid, was diazotised by means of sodium nitrite (0·8 g.) in 3 c.c. of water, the solution was poured into one prepared from crystallised copper sulphate (1·5 g.), sodium bromide (4 g.), sulphuric acid (1·5 g.), copper powder (1 g.), and water (15 c.c.), and the whole was kept at *ca.* 20° for 5—6 hours; the evolution of nitrogen then ceased and a brown viscous oil was precipitated. This was isolated by means of ether (yield, 2·5 g.), but was not crystallised. The *anilide*, prepared for characterisation, crystallised from ethyl acetate–light petroleum in thin, light, colourless needles, m. p. 135—137° (Found : N, 4·3. $C_{15}H_{14}O_3NBr$ requires N, 4·2%).

According to Hurtley (*loc. cit.*) *o*-bromobenzoic acid is easily converted into salicylic acid by boiling with aqueous sodium acetate and cupric acetate. This method was applied to the above bromo-acid (6 g.) (crude substance), which was neutralised with sodium hydroxide (0·9 g.) in water (100 c.c.) and after the addition of sodium acetate (10 g.) and copper acetate (1 g.) the mixture was refluxed for 1 hour. The product, a light yellow crystalline powder (3 g.), crystallised from ethyl acetate–light petroleum in thin plates, m. p. 120—121° alone or when mixed with a specimen of *o*-veratric acid prepared from 6-iodo-2 : 3-dimethoxybenzoic acid by catalytic reduction (Found : C, 59·3; H, 5·4. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%).

6-*Iodo*-2 : 3-*dimethoxybenzoic Acid* (IX).—5 : 6-Dimethoxyanthranilic acid (6 g.), dissolved in an excess of 10% sulphuric acid, was diazotised by means of sodium nitrite (2·4 g.) in water (10 c.c.), and the solution added to one made from potassium iodide (30 g.) and concentrated sulphuric acid (20 c.c.) diluted with water (80 c.c.). After an hour, the liquid was heated for 30 minutes at 60—70° until the evolution of nitrogen had ceased; the *iodo-acid* separated as a heavy oil, which was collected by means of ether (yield, 8 g.). The substance crystallised from ethyl acetate–light petroleum in stout plates, m. p. 137—138° (Found : C, 35·5; H, 3·2. $C_9H_9O_4I$ requires C, 35·1; H, 2·9%), readily soluble in organic solvents with the exception of light petroleum.

6-*Benzyloxy*-2 : 3-*dimethoxybenzoic Acid* (X).—Sodium (1·1 g.) was dissolved in benzyl alcohol (60 c.c.), the iodo-acid (7 g.) in the same solvent (*ca.* 20 c.c.) and copper powder (0·5 g.) were added, and the whole was heated (oil-bath, 130—150°) for 3—4 hours. On cooling, the product was poured into water, benzyl alcohol was removed by means of ether, and the filtered alkaline solution was acidified; a yellow oil separated and soon solidified. The *acid* crystallised from aqueous methyl alcohol in nearly colourless prisms (4—4·5 g.) m. p. 128—129° (Found : C, 66·1; H, 5·3. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·5%).

6-*Benzyloxy*-2 : 3-*dimethoxyacetophenone* (XI).—A mixture of the foregoing acid (4 g.) with thionyl chloride (3 g.) was heated at 50—60° until the evolution of hydrogen chloride had ceased and a light brown liquid was obtained. The excess of thionyl chloride was removed under diminished pressure and a solution of the residue in dry benzene was again evaporated; the acid chloride solidified when kept over potassium hydroxide in a vacuum. It crystallised from benzene and light petroleum as aggregates of prisms, m. p. 75—76°, but the purification was accompanied by much loss of substance. Therefore the solid acid chloride, thoroughly washed with benzene–light petroleum (1 : 5), was used in the following experiment.

Methylzinc iodide was prepared from activated zinc (4 g.) and methyl iodide (4·5 g.) in pure ethyl acetate (2 g.) and toluene (4 g.), and to this solution, cooled in melting ice, the acid chloride (from 4 g. of the acid), dissolved in pure toluene, was introduced with shaking. The whole was kept for 1 hour and worked up in the usual manner; the crystalline *substance* obtained (*ca.* 2 g.), recrystallised from ethyl acetate–light petroleum, formed pale yellow, rhombic plates, m. p. 90—91° (Found : C, 70·7; H, 6·6. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

5-*Hydroxy*-8-*methoxyflavone* (XIII) (?).—A solution of the foregoing benzyloxydimethoxyacetophenone (2 g.) in acetic acid (50 c.c.) was heated on a steam-bath and hydrochloric acid (6 c.c., *d* 1·16) was gradually introduced with shaking; after 30 minutes' heating, a further volume of hydrochloric acid (3 c.c.) was added and the whole was finally boiled for 2—3 minutes over a gauze. The pseudo-acidic fraction of the product was isolated as a brown viscous oil (*ca.* 1 g.), which was directly heated with benzoic anhydride (5 g.) and sodium benzoate (3 g.) at 190—195° for about 3 hours. Ethyl alcohol (50 c.c.) was then added and, after 30 minutes' refluxing, water was introduced and the alcohol evaporated. The insoluble *substance* was collected, washed, and recrystallised from alcohol, being ultimately obtained as bright yellow leaflets or long hairy needles, m. p. 129—130° (Found : C, 71·4; H, 5·0. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). The alkaline filtrate was saturated with carbon dioxide and the separated brown material was extracted with alcohol containing a little hydrochloric acid. The yellow leaflets, m. p. 125—128°, obtained when the filtered solution was cooled proved to be identical with the substance first obtained.

This flavone develops a bluish coloration with alcoholic ferric chloride and, as it has the composition $C_{16}H_{12}O_4$ and gives an acetyl derivative, must contain a hydroxyl group. Evidently the debenzylation under the condition described above also produced demethylation and from the 2 : 6-dihydroxy-3-methoxyacetophenone thus obtained, 5-hydroxy-8-methoxyflavone was preferably formed on ring-closure. The isomeric 5-hydroxy-6-methoxyflavone (XIV) might have been formed at the same time, but it was not possible to isolate this compound.

When (XIII) was acetylated by means of acetic anhydride and pyridine, a nearly colourless *acetyl* derivative was obtained, which formed very pale yellow prisms, m. p. 146—147°, from ethyl acetate (Found : C, 69·6; H, 4·7. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). The flavone (XIII) (0·3 g.) was refluxed with an excess of hydriodic acid (*d* 1·7) and a little acetic anhydride for about 2 hours. The dark precipitate became yellow when treated with sulphurous acid and crystallised from ethyl alcohol in grains, m. p. 179—180°. The substance is probably 5 : 8-dihydroxyflavone (IV); the addition of an aqueous solution of bleaching powder to its alcoholic solution caused the appearance of a green coloration, which very soon turned into dirty brown, probably owing to the formation of a *p*-quinone derivative. Under such conditions, *o*-dihydroxy-compounds in this series generally give rise to rather stable green colorations.

o-*Veratric Acid.*—This acid, required for a comparison (above), was obtained by the following method, which incidentally affords a confirmation of the constitution assigned to the dimethoxyanthranilic acid from hemipinimide. 6-Iodo-2 : 3-dimethoxybenzoic acid (1 g.), palladium–calcium carbonate catalyst (5 g.; compare Busch and Stoeve, *Ber.*, 1916, **49**, 1063), and 10% alcoholic potash (50 c.c.) were mixed and shaken in hydrogen for 50 minutes, 1 mol. of the gas being absorbed. The resulting *o*-veratric acid (0·4 g.) crystallised from ethyl acetate–light petroleum in needles, m. p. 121—122°.

Ethyl 3 : 4 : 3′ : 4′-*Tetramethoxydiphenate* (VIII).—As a tetramethoxydiphenic acid might have been produced in some of the processes described above, its synthesis was attempted. The iododimethoxybenzoic acid (IX) (1·5 g.) was mixed with thionyl chloride (1·5 g.) and, after heating on a steam-bath, the excess of the reagent was removed in a vacuum, and the acid chloride was then treated with an excess of alcohol. After distillation of the alcohol the brown syrupy ester was collected by means of ether and then mixed with copper powder (2·5 g.) and heated in an oil-bath at 250° for 1 hour. The reaction product was extracted with hot alcohol (charcoal) and, on cooling, the new *ester* crystallised in colourless prisms; after recrystallisation, it had m. p. 124—125° (yield, 0·5 g.) (Found : C, 62·9; H, 6·2. $C_{22}H_{26}O_8$ requires C, 63·2; H, 6·2%).

The hydrolysis of this ester with boiling alcoholic potash was attempted, but without success, the greater part of the ester being recovered unchanged. This great resistance to the action of hydrolysing agents is doubtless due to the fact that both ortho-positions with respect to the carbethoxyl groups are occupied by substituents.

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