

CONSTITUTION OF PATULETIN

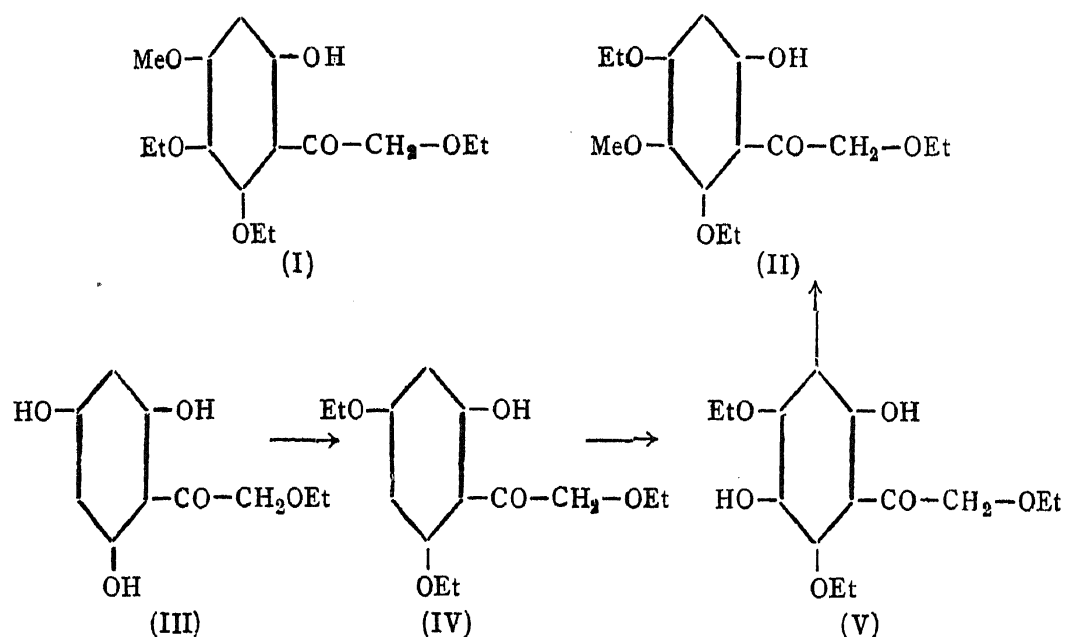
Part III. A Study and Synthesis of O-Pentaethyl Patuletin

BY L. RAMACHANDRA ROW AND T. R. SESHADRI

(From the Department of Chemistry, Andhra University)

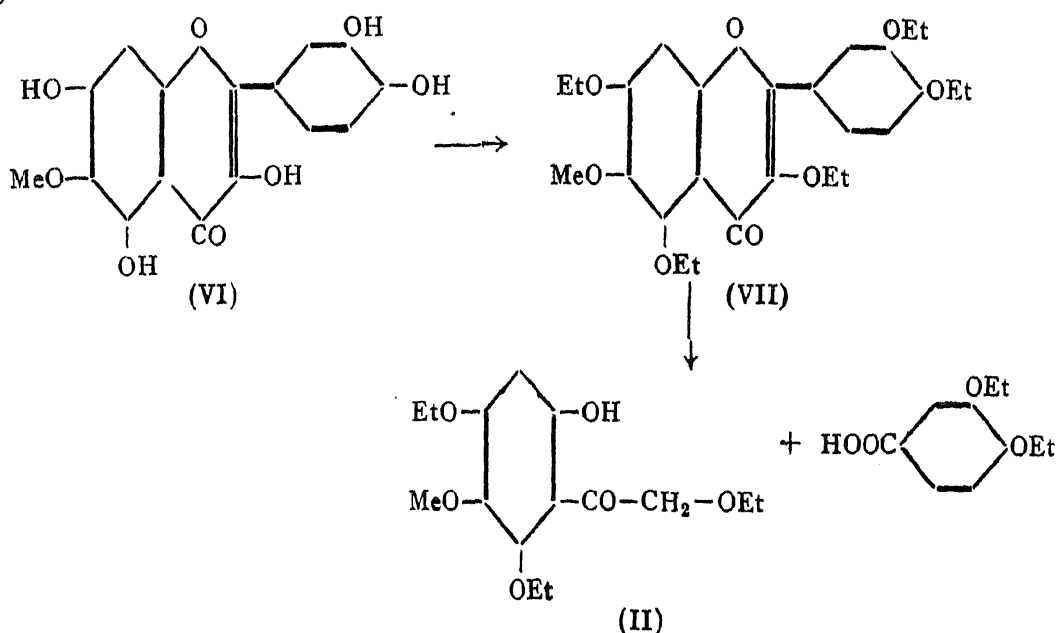
Received January 17, 1946

IN Part I¹ patuletin, $C_{16}H_{12}O_8$, the colouring matter of *Tagetes patula*, was shown to be a mono-methyl ether of quercetagenin. From a study of its properties and reactions and from a comparison with related compounds, the methoxyl was considered to be in the 6-position. This point has now been further investigated through the study and synthesis of pentaethyl patuletin and definite conclusions arrived at. For this purpose patuletin is fully ethylated by means of ethyl iodide and anhydrous potassium carbonate in anhydrous acetone medium. The penta-ethyl ether is obtained as a colourless crystalline compound in good yield. When subjected to fission by means of alcoholic potash, it yields an acid which is identified to be *O*-diethyl protocatechuic acid both by analysis and by comparison with an authentic sample. The formation of this acid as one of the products of degradation confirms the idea that the methoxyl should be situated in the benzopyrone part. As the second product, an orthohydroxy acetophenone is also isolated. It is not identical with quercetagenin tetraethyl ether² and is found to contain three ethoxyl groups and one methoxyl.



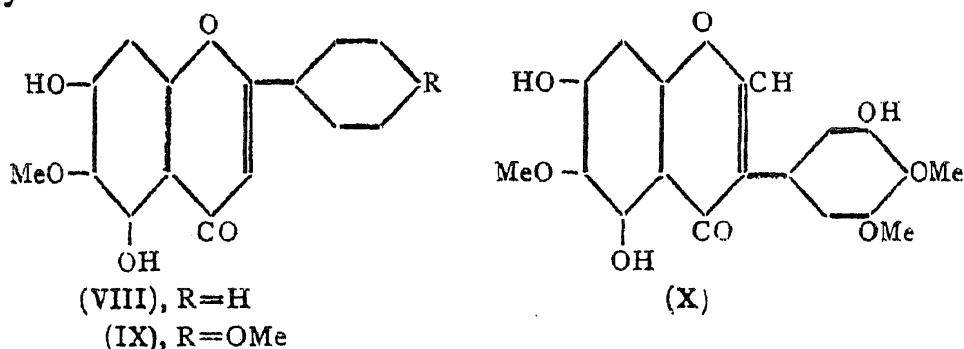
Since the properties of patuletin indicate that the 3- and 5-positions carry hydroxyl groups there are only two possible constitutions for the above

mentioned ketone: (1) ω :5:6-triethoxy-4-methoxy-2-hydroxy-acetophenone (I) corresponding to the 7-methoxy formula for the flavonol and (2) ω :4:6-triethoxy-5-methoxy-2-hydroxy acetophenone (II) corresponding to the 6-methoxy formula. A ketone with the second alternative constitution has now been synthesised starting from phloroglucinol by the general methods described in Part II.³ Phloroglucinol is converted into ω -ethoxy-phloracetophenone (III) which is subjected to partial ethylation to yield ω :4:6-triethoxy-2-hydroxy-acetophenone (IV). This is found to be the same as the ketone obtained by Perkin⁴ by the alkali degradation of quercetin-pentaethyl ether and called also hydroxy-fisetol-triethyl-ether. The above-mentioned procedure constitutes a convenient method for its synthetic preparation. Oxidation of this ketone with alkaline persulphate introduces a hydroxyl in the 5-position yielding the *p*-dihydroxy-ketone (V) whose constitution is based on well-known analogies and also supported by its properties. By further partial methylation with dimethyl sulphate and potassium carbonate is obtained a product, the reactions and properties of which indicate that it has the constitution (II). This synthetic ketone is found to be identical with the degradation product from pentaethyl patuletin. Further condensation of the synthetic ketone with *O*-diethyl protocatechuic anhydride and sodium *O*-diethyl protocatechuate yields a compound identical with penta-ethyl patuletin. Therefore the position of the methoxyl group in the ethyl ether and consequently in patuletin is definitely fixed as the 6 and this is in agreement with all the properties and reactions of patuletin already described. The above-mentioned transformations could then be represented as given below:



The presence of methyl ether groups in the several available positions of anthoxanthins and related anthocyanins should be of interest. In the

more fundamental 5:7-hydroxy series such as quercetin and others, the methoxyl is found commonly in the 3- and 7-positions and also in the side-phenyl nucleus. The preferential methylation of the 6-hydroxyl in patuletin is remarkable. This seems to be peculiar to the 5:6:7-arrangement of the hydroxyls. Among flavones, oroxylin-A (VIII)⁵ found in *Oroxylum indicum* and 6:4'-dimethyl ether of scutellarein (IX)⁶ found in the flowers of *Linaria vulgaris* could be mentioned. In the *iso*-flavone series irigenin (X)⁷ is also a 6-methyl ether.



EXPERIMENTAL

Ethylation of patuletin.—A solution of patuletin (1.0 g.) in anhydrous acetone (80 c.c.) was treated with ethyl iodide (1.5 c.c.) and anhydrous potassium carbonate (10 g.). The mixture was refluxed gently and ethyl iodide (1.5 c.c. each time; total 6 c.c.) was added at intervals of eight hours. After 30 hours, the potassium salts were separated by filtration and washed with warm acetone. The salt residue was completely soluble in water and yielded no precipitate on acidifying with dilute hydrochloric acid. The acetone filtrate was concentrated on a water-bath to about 5 c.c. and left in the ice-chest. After 24 hours, pale brown crystals separated out. The solid was filtered and washed with a small quantity of acetone. When crystallised twice from alcohol using a small quantity of animal charcoal, it came out in the form of colourless prismatic rods melting at 127–8°. Yield: 0.75 g. The pentaethyl ether was insoluble in warm aqueous alkali and gave no ferric chloride colour in alcoholic solution. It was easily soluble in acetone and ethyl acetate and moderately soluble in alcohol and benzene (Found: C, 66.6; H, 7.1; $C_{26}H_{32}O_8$ requires C, 66.1 and H, 6.8%. Total OC_2H_5 and OCH_3 expressed as OCH_3 , 39.5; penta-ethoxy-monomethoxy-flavone requires 39.4%).

Alkaline degradation of *O*-pentaethyl-patuletin (VII).—*O*-Pentaethyl-patuletin (0.6 g.) was refluxed with 7% absolute alcoholic potash (20 c.c.) on a water-bath for 6 hours. The solvent was removed under vacuum and the concentrate diluted with water (75 c.c.). The solution was then acidified with hydrochloric acid and the product was extracted repeatedly with ether.

The ethereal solution was shaken thrice with dilute sodium bicarbonate solution.

The ketonic part (II):—On evaporating the ether solution a pale yellow oil was obtained which solidified on scratching with a glass-rod. When crystallised twice from aqueous alcohol, it was obtained in the form of pale yellow rhombohedral plates melting at 86–87°. Yield: 0.15 g. It dissolved in sodium hydroxide giving a pale yellow solution. With ferric chloride, a reddish brown colour was obtained in alcoholic solution (Found: C, 60.6; H, 7.7; $C_{15}H_{22}O_6$ requires C, 60.4 and H, 7.4%).

Acid part.—The sodium bicarbonate extract when acidified with hydrochloric acid, yielded a white crystalline solid. It crystallised from hot water in the form of long rectangular rods melting at 165–66° and as identified to be *O*-diethyl-protocatechuic acid. It did not depress the melting point of a pure sample of the diethyl ether prepared by ethylating ethyl protocatechuate with ethyl iodide and potassium carbonate in anhydrous acetone medium and hydrolysing the resulting ethyl *O*-diethyl protocatechuate with alkali (Found: C, 63.0; H, 7.0; $C_{11}H_{14}O_4$ requires C, 62.9 and H, 6.7%).

ω -Ethoxy-phloracetophenone (III).—Anhydrous phloroglucinol (7.0 g.) and ethoxy acetonitrile⁸ (7.0 c.c.) were condensed under the conditions of Hoesch synthesis following the method used for phloracetophenone.⁹ The product crystallised from hot water in the form of stout rhombohedral prisms melting at 197–8°. Yield: 7.5 g. It was easily soluble in alcohol, acetone and ether, and gave a reddish violet colour with ferric chloride in alcoholic solution (Found in a sample dried at 110–20° for three hours: C, 56.9; H, 5.8; $C_{10}H_{12}O_5$ requires C, 56.6 and H, 5.7%).

ω -4:6-Triethoxy-2-hydroxy-acetophenone (IV).— ω -Ethoxy-phloracetophenone (2.1 g., 1 mol.) was refluxed in anhydrous acetone solution (80 c.c.) with ethyl iodide (1.8 c.c., 2.2 mol.) and anhydrous potassium carbonate (6 g.) for 12 hours. At the end of the reaction, the acetone was distilled off and the residue treated with water (100 c.c.). The precipitate was filtered and washed with water. It was sparingly soluble in aqueous alkali. In an attempt to remove any fully ethylated ketone that might be present, the crude product was dissolved in ether and the solution extracted with 5% aqueous sodium hydroxide. The recovery was small and incomplete even after six extractions. On acidifying the alkaline solution with hydrochloric acid, a colourless crystalline solid separated out. It was crystallised twice from alcohol when ω :4:6-triethoxy-2-hydroxy-acetophenone (IV) was obtained in the form of thin flat needles and plates melting at 96–97°. Yield, 0.4 g.

When the remaining ether was evaporated to dryness and the residue (1.0 g.) crystallised from alcohol the same substance was obtained. The reactions and the melting points were identical and there was no depression in the mixed melting point. Thus the product of ethylation seems to consist entirely of the hydroxy-triethoxy ketone (IV) and the fully ethylated product was not present in detectable amounts.

The substance was easily soluble in alcohol, acetone and benzene. It gave a brownish red colour with ferric chloride in alcoholic solution. It was not easily soluble in aqueous sodium hydroxide and gave a sparingly soluble sodium salt (Found: C, 62.7; H, 7.8; OC_2H_5 , 49.9; $\text{C}_{14}\text{H}_{20}\text{O}_5$ requires C, 62.7; H, 7.5 and OC_2H_5 , 50.4%).

For purposes of comparison an authentic sample of the above ketone was prepared from quercetin (0.3 g.) in the following manner. The flavonol was ethylated by boiling for 30 hours in anhydrous acetone solution with ethyl iodide (2 c.c.) and anhydrous potassium carbonate (2 g.). The penta-ethyl ether thus obtained was subjected to fission using absolute alcoholic potash (3 c.c. 7%) and refluxing for six hours. After adding excess of water, it was extracted with ether. From the ether solution, by shaking with aqueous sodium bicarbonate was separated *O*-diethyl-protocatechuic acid. The residual ether solution on evaporation gave a good yield of hydroxy-fisetol-triethyl ether. In every respect it was identical with the synthetic sample described above and the mixed melting point was undepressed.

ω : 4 : 6-Triethoxy-2 : 5-dihydroxy-acetophenone (V).—To a mechanically stirred suspension of ketone (IV) (2.7 g.) in water (50 c.c.) was added aqueous sodium hydroxide (5% 50 c.c.) slowly. Only part of the ketone went into solution immediately and the rest dissolved completely only towards the end of the reaction. The mixture was then cooled to 15° and potassium persulphate (4.1 g. in 100 c.c. of water) and aqueous sodium hydroxide (5%, 50 c.c.) were added alternately during three hours while maintaining the mechanical stirring all the while. After the addition, the solution was left at room temperature for 20 hours. The insoluble portion was then filtered off and the alkaline filtrate neutralised with hydrochloric acid. The unreacted ketone (0.8 g.) separated out and was removed by filtration. The filtrate was treated with concentrated hydrochloric acid (20 c.c.) and kept on a boiling water-bath for about 15 minutes. An oily layer separated out on cooling and it solidified slowly into a dark brown sticky crystalline mass. It was dissolved in ether and treated with petroleum ether till turbidity appeared. On leaving it aside for about 15 minutes, a small amount of a dark brown sticky impurity separated out and the clear yellow solution could

be decanted. On evaporation it yielded yellowish brown crystals which when recrystallised from hot water came out in the form of broad square plates melting at 101–103°. A second crystallisation from aqueous alcohol raised the melting point to 103–04° which could not be improved further. Yield, 0.6 g. With alcoholic ferric chloride it developed a transient green colour which changed rapidly to yellowish brown and finally to deep red in the course of half-an-hour. It did not give any precipitate with neutral lead acetate in alcoholic solution (Found: C, 59.0; H, 6.7; $C_{14}H_{20}O_6$ requires C, 59.2 and H, 7.0%).

ω : 4:6-Triethoxy-5-methoxy-2-hydroxy-acetophenone (II).—A solution of the dihydroxy-ketone (V) (1.0 g., 1 mol.) in anhydrous benzene (60 c.c.) was treated with dimethyl sulphate (0.5 g., 1.1 mol.) and anhydrous potassium carbonate (3 g.) and the mixture refluxed for 12 hours. Towards the end of the reaction, the benzene layer developed a dark brown colour. The potassium salts were then filtered off and washed thrice with warm benzene. The filtrate was cooled and extracted thrice with aqueous sodium hydroxide (5%, 25 c.c.). When acidified with hydrochloric acid, the clear alkaline extract deposited an almost colourless crystalline solid. After two crystallisations from aqueous alcohol it was obtained as colourless long rectangular plates melting at 85–86°. Yield, 0.4 g. It did not depress the melting point of the ketone obtained from the degradation of *O*-pentaethyl patuletin. It gave a pale reddish brown colour with ferric chlorolride in alcoholic solution (Found: C, 60.6; H, 7.6; $C_{15}H_{22}O_6$ requires C, 60.4 and H, 7.4%. Found total OEt and OMe calculated as methoxyl 40.9; the formula requires 41.6%).

O-Diethyl-protocatechuic anhydride.—Thionyl chloride (2.0 c.c.) was added in small quantities at a time with vigorous shaking to a suspension of *O*-diethyl-protocatechuic acid (8.4 g.) in anhydrous ether (100 c.c.) containing anhydrous pyridine (10 c.c.). Throughout the addition the temperature of the reaction mixture was kept at 0° by cooling in an ice-bath. After the addition was over (30–45 mts.) the flask was left in the refrigerator for three hours and the mixture was shaken with crushed ice and filtered. The granular solid product was then triturated successively with ice-cold water, dilute ice-cold hydrochloric acid and ice-cold sodium carbonate solution (5%). Finally the anhydride was washed with ice-cold water until free from sodium carbonate. It was then pressed between the folds of filter paper and dried *in vacuo* over concentrated sulphuric acid. The crude product melted at 148–49° with slight sintering at 145°. When recrystallised from benzene it was obtained as stout rectangular prisms melting at 149–50°. Yield, 6.5 g (Found: C, 66.1; H, 6.3; $C_{22}H_{26}O_7$ requires C, 65.7 and H, 6.5%).

Synthesis of O-pentaethyl-patuletin.—An intimate mixture of ω :4:6-triethoxy-5-methoxy-2-hydroxy-acetophenone (II) (0.3 g.), O-diethyl-protocatechuic anhydride (1.0 g.) and the sodium salt of O-diethyl-protocatechuic acid (0.5 g.) was heated under reduced pressure at 170–80° for four hours. At the end of the reaction, the solid crust was broken up and refluxed with alcohol (10 c.c.) for about ten minutes. It was then treated with alcoholic potash (1 g. of KOH in 5 c.c. of alcohol) and refluxed for 15 minutes more. As much alcohol as possible was removed under reduced pressure and excess of water added to the residue. A colourless crystalline solid remained undissolved. It was filtered and washed with water till free from alkali and crystallised twice from alcohol when it was obtained in the form of colourless rectangular prismatic rods melting at 128–29°. A third crystallisation was also done but it did not improve the melting point. This substance did not dissolve in warm or cold aqueous alkali and developed no colour with ferric chloride in alcoholic solution. Yield, 0.2 g. (Found: C, 65.7; H, 6.5; $C_{26}H_{32}O_8$ requires C, 66.1 and H, 6.8%. Found total OC_2H_5 and OCH_3 calculated as OCH_3 , 38.9; pentaethoxy-mono-methoxy-flavone requires 39.4%). This product did not depress the melting point of O-pentaethyl-patuletin obtained by the ethylation of patuletin.

The alkaline filtrate left after the separation of the above solid product was saturated with carbon dioxide. A small quantity of dark brown amorphous material was deposited. Since it was too small, it was not studied.

SUMMARY

The constitution of patuletin as 6-O-methyl quercetagetin has been finally established by the study of its penta-ethyl ether which yields O-diethyl-protocatechuic acid and ω :4:6-triethoxy-5-methoxy-2-hydroxy-acetophenone on degradation with alkali. The above ketone and O-pentaethyl-patuletin have been synthesised by unambiguous methods starting from ω -ethoxy-phloroacetophenone.

REFERENCES

1. Row and Seshadri .. *Proc. Ind. Acad. Sci. A*, 1945, **22**, 215.
2. Perkin .. *J.C.S.*, 1913, 209.
3. Row and Seshadri .. *Proc. Ind. Acad. Sci. A*, 1946, **23**, 23.
4. Perkin .. *J.C.S.*, 1912, **28**, 329.
5. Shah, Mehta and Wheeler .. *Ibid.*, 1936, 591.
6. Schmid and Rumpel .. *Monatsh*, 1932, **60**, 8.
7. Baker .. *J.C.S.*, 1928, 1022.
8. Sommelet .. *Ann. Chim. Phys.*, 1906, **8**, 493.
9. *Organic Synthesis* .. *Vol. XV*, p. 70.