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SYNTHESIS OF FLAVONOLS ANOLOGOUS TO QUERCETIN EMPLOYING THE BAKER-VENKATARAMAN REACTION

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ABSTRACT--ω-Methoxy-C-methylphloracetophenone was prepared by the condensation of C-methylphloroglucinol with methoxyacetic acid-boron trifluoride complex. Using a modification of the Baker-Venkataraman reaction, the treatment of the ketone with 3, 4-dimethoxybenzoyl chloride (veratroyl chloride) in the presence of anhydrous potassium carbonate in boiling acetone gave 6-methyl-5, 7-dihydroxy-3, 3', 4'-trimethoxylflavone (IV) which on demethylation with aluminum bromide in benzene gave pinoquercetin. Treatment of the ketone with 3, 4, 5-trimethoxy benzoyl chloride (trimethylgalloyl chloride) under similar conditions gave 6-methyl-5, 7-dihydroxy-3, 3', 4', 5'-tetramethoxyflavone (VI) which on demethylation with aluminium bromide in benzene gave pinomyricetin. Compounds IV and VI are of interest because of the presence of the 3-methoxy and 5-hydroxy group in the flavone skeleton. Such compounds have been shown in the past to have potent antiviral activity against rhinovirus infection.

A great improvement in the synthesis of flavonoids was the discovery by Baker (1933) in England as well as by Venkataraman and Mahal (1933), simultaneously and independently, of the rearrangement of ortho-aroyloxyacetophenones to ortho-hydroxydibenzoylmethanes in the presence of bases, such as anhydrous potassium carbonate in boiling toluene or sodamide in ether at 0°C. Various bases including sodium ethoxide and sodium have also been used. Wheeler et al. (1948) made an extensive study of this transformation using different bases and solvents and found that pyridine is the best solvent and that stronger bases favor higher yields of dibenzoylmethane (Fig. 1). They also drew conclusions regarding the probable mechanism of the reaction, namely that it is a base-catalyzed intramolecular-type Claisen condensation effected by a wide variety of bases including potassium hydroxide in pyridine and triphenylmethyl anion. Further proof of the intramolecular nature of the transformation was provided by Wheeler and Gowan (1950) and Schmid and Banholzer (1954), using benzoyl chloride with C^{14}-labeled carbon in the carbonyl group.

Since the dibenzoylmethanes are readily convertible to the flavones by treatment with sulfuric acid, the procedure via the dibenzoylmethanes is often more convenient than the traditional Allan-Robinson reaction for flavone synthesis. The Allan-Robinson reaction consists of the high-temperature fusion of an ortho-hydroxyacetophenone with an aromatic acid anhydride in the presence of the sodium or potassium salt of the aromatic acid (Allan and Robinson, 1924).

Ponderosa pine bark has been examined by a number of workers (Kurth and Hubbard, 1951; Kurth et al., 1954) and has been found to contain the flavonols quercetin and myricetin and the flavanonol taxifolin (2,3-dihydroquercetin; Fig. 2).

An investigation of the Ponderosa coloring matter by Kurth et al. (1956) yielded substantially different results. In addition to taxifolin and quercetin, two hitherto unknown flavonols, 6-methylquercetin and 6-methylmyricetin, were isolated which were given the names pinoquercetin and pinomyricetin, respectively (Fig. 2). These structures were assigned on the basis of elaborate degradation studies on the methyl ethers of the flavonoids obtained by the methylation of the crude coloring matter and chromatography over alumina (Kurt et al., 1956). In the present work, pinoquercetin and pinomyricetin have been synthesized and shown to be identical with the natural products.

MATERIALS AND METHODS

C-Methylphloroglucinol (I)--C-Methylphloroglucinol was prepared according to the method of Shriner and Hull (1945:228) by treatment of phloroglucinol with 40% formaldehyde in presence of hydrochloric acid followed by reduction of the hexahydroxydiphenyl methane formed, by means of zinc and 15% sodium hydroxide solution.

ω-Methoxy-C-methylphloracetophenone (II)--A mixture of C-methylphloroglucinol (20 g), boron trifluoride-methoxyacetic acid complex (100 g) was kept at 28 to 30°C for 24 h and poured over crushed ice (2,500 g). The complex obtained was collected and boiled with water (500 ml) for 1 h, and the product obtained on cooling crystallized from a mixture of ether and petroleum ether as colorless needles (15 g), melting point of 207°C (lit. melting point of 206 to 207°C; Jain and Seshadri, 1954). The substance gave a reddish brown coloration with alcoholic ferric chloride.

6-Methyl-5, 7-dihydroxy-3, 3', 4'-trimethoxyflavone (IV)--A mixture of ω-methoxy-C-methylphloracetophenone (II; 5 g), veratroyl chloride (10 g), anhydrous potassium carbonate (25 g), and acetone (150 ml) was refluxed for 4 h. The solvent was removed by distillation and, after cooling, the pale orange residue was treated with water. The yellow precipitate (a) which separated was filtered. The reddish brown filtrate was saturated with carbon dioxide and left overnight in the refrigerator. The yellow product was filtered, washed with water and crystallized from methanol. The yellow plates (0.9 g) had a melting point of 264°C (found: C, 63.3 and H, 5.1; calculated for $C_{19}H_{18}O_7$: C, 63.7 and H, 5.1%). The substance gave a green color with alcoholic ferric chloride and a pink color with magnesium and hydrochloric acid characteristic of flavonoids.

The yellow precipitate (a) crystallized from aqueous acetic acid in yellow needles (1.5 g), melting point of 210°C (found: C, 64.3 and H,

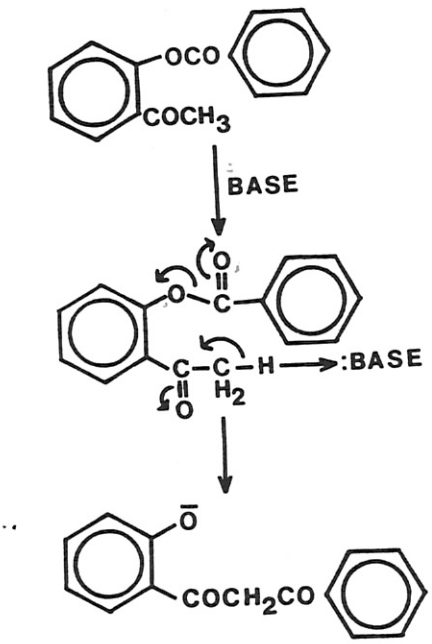

FIG. 1. Dibenzoyl methane.

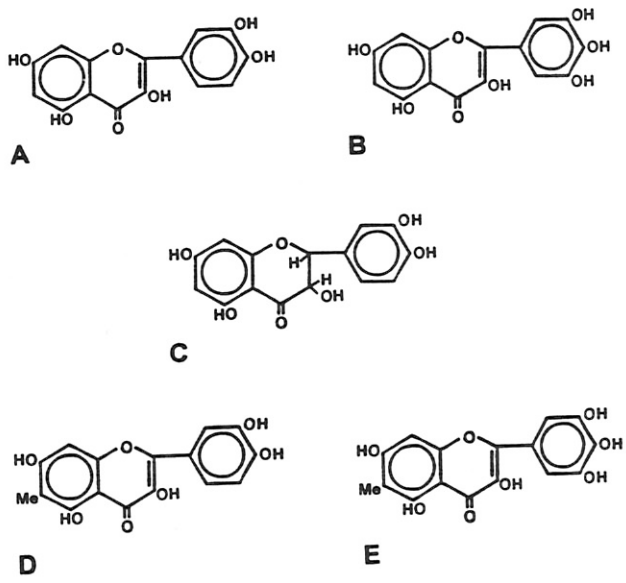

FIG. 2. A) Quercetin, B) taxifolin, C) myricetin, D) pinoquerce (6-methylquercetin), E) pinomyricetin (6-methylmyricetin).

5.0; $C_{28}H_{26}O_{10}$ requires: C, 64.4; H, 5.0% corresponding to the veratroyl ester of flavone IV). The substance gave a green color with 5% alcoholic ferric chloride and a pink color with magnesium and hydrochloric acid.

The veratroyl ester obtained (1.0 g) was boiled with 5% alcoholic potassium hydroxide (100 ml) for 30 min. The solvent was distilled, the residue taken up in water, and the brown solution saturated with carbon dioxide. The yellow precipitate was filtered and crystallized from methanol. The yellow plates (0.5 g) had a melting point of 264°C, identical with the flavone (IV) previously described.

6-Methyl-3, 5, 7, 3', 4'-pentahydroxyflavone (VIII; Demethylation of IV)--The flavone (IV; 0.5 g) was dissolved in hot benzene (150 ml) and a benzene mixture of anhydrous aluminum bromide (2 g) was added. The mixture was refluxed for 3 h. The solvent was removed by distillation, the orange residue treated with dilute hydrochloric acid (1:1, 100 ml), and the mixture heated on a boiling water-bath when the product changed from an orange to a pale yellow color. The suspension was cooled, and the yellow substance was collected and washed with ice-water. It crystallized from aqueous methanol in yellow needles (0.2 g), melting point of 289°C (lit. melting point of pinoquercetin 289°C; Kurth et al., 1955, 1956; found in a sample dried at 150°C at 0.003 mm for 3 h: C, 61.2 and H, 4.2; calculated for $C_{16}H_{12}O_7$: C, 60.7 and H, 3.8%). The substance gave brownish green color with alcoholic ferric chloride.

The flavonol was acetylated with excess of acetic anhydride and a few drops of pyridine. The pentacetate crystallized from ethyl acetate in colorless needles, melting point of 200 to 201°C (lit. melting point of pinoquercetin pentacetate melting point of 201°C; Kurth et al., 1955, 1956).

6-Methyl-5, 7-dihydroxy-3, 3', 4', 5'-tetramethoxyflavone (VI)--A mixture of ω-methoxy-C-methylphloracetophenone (II; 5g), trimethylgalloyl chloride (11.25 g), anhydrous potassium carbonate (30 g) and acetone (150 ml) was refluxed for 4 h. The solvent was removed by distillation and, after cooling, the pale orange-red residue was treated with water (500 ml). The pale yellow precipitate (a) which separated was filtered. The reddish-brown filtrate was saturated with carbon dioxide and left overnight in a refrigerator. The yellow product w collected, washed with water and dried. It crystallized from ethyl acet in pale yellow needles (0.8 g), melting point of 272°C (found: C, 6 and H, 5.4; $C_{20}H_{20}O_8$ requires: C, 61.9 and H, 5.2%). The substance g a pink color with magnesium and hydrochloric acid and a green c with alcoholic ferric chloride.

The yellow precipitate (a) crystallized from aqueous acetic aci yellow needles (1.8 g), melting point of 200°C (found C, 61.4 and H, $C_{30}H_{30}O_{12}$ requires: C, 61.8 and H, 5.2% corresponding to trimethlgalloyl ester of flavone VI). The substance gave a green c with alcoholic ferric chloride and a pink color with magnesium hydrochloric acid.

The trimethylgalloyl ester obtained (1.0 g) was boiled with alcoholic potassium hydroxide (100 ml) for 30 min. The solvent distilled, the residue taken up in water, and the brown solution satu with carbon dioxide. The yellow precipitate was filtered and cry lized from ethyl acetate. The yellow needles (0.5 g) had melting of 272°C, identical with the flavone (VI) previously described.

6-Methyl-3, 5, 7, 3', 4', 5'-hexahydroxyflavone (IX; Demethyl of VI--The flavone (VI; 0.5 g) was dissolved in hot benzene (150 ml a benzene mixture of anhydrous aluminum bromide (2 g) was a The mixture was refluxed for 3 h. The solvent was remove distillation, the orange-red residue treated with dilute hydrochlori (1:1, 50 ml), and the mixture heated on a boiling water-bath for 3 when the color changed to yellow. The suspension was cooled, a yellow substance was filtered and washed with ice-water. The stance crystallized from aqueous methanol in yellow needles (melting point of 330°C with darkening (lit. melting point of pinomyr melting point of 330°C; Kurth et al., 1955, C, 57.4 and H, 3.9; C_{1} requires: C, 57.8 and H, 3.6%). The substance gave a greenish color with alcoholic ferric chloride, and a green coloration with ac potassium carbonate, characteristic of pinomyricetin.

The flavonol was acetylated with excess of acetic anhydride few drops of pyridine. The hexacetate crystallized from etha

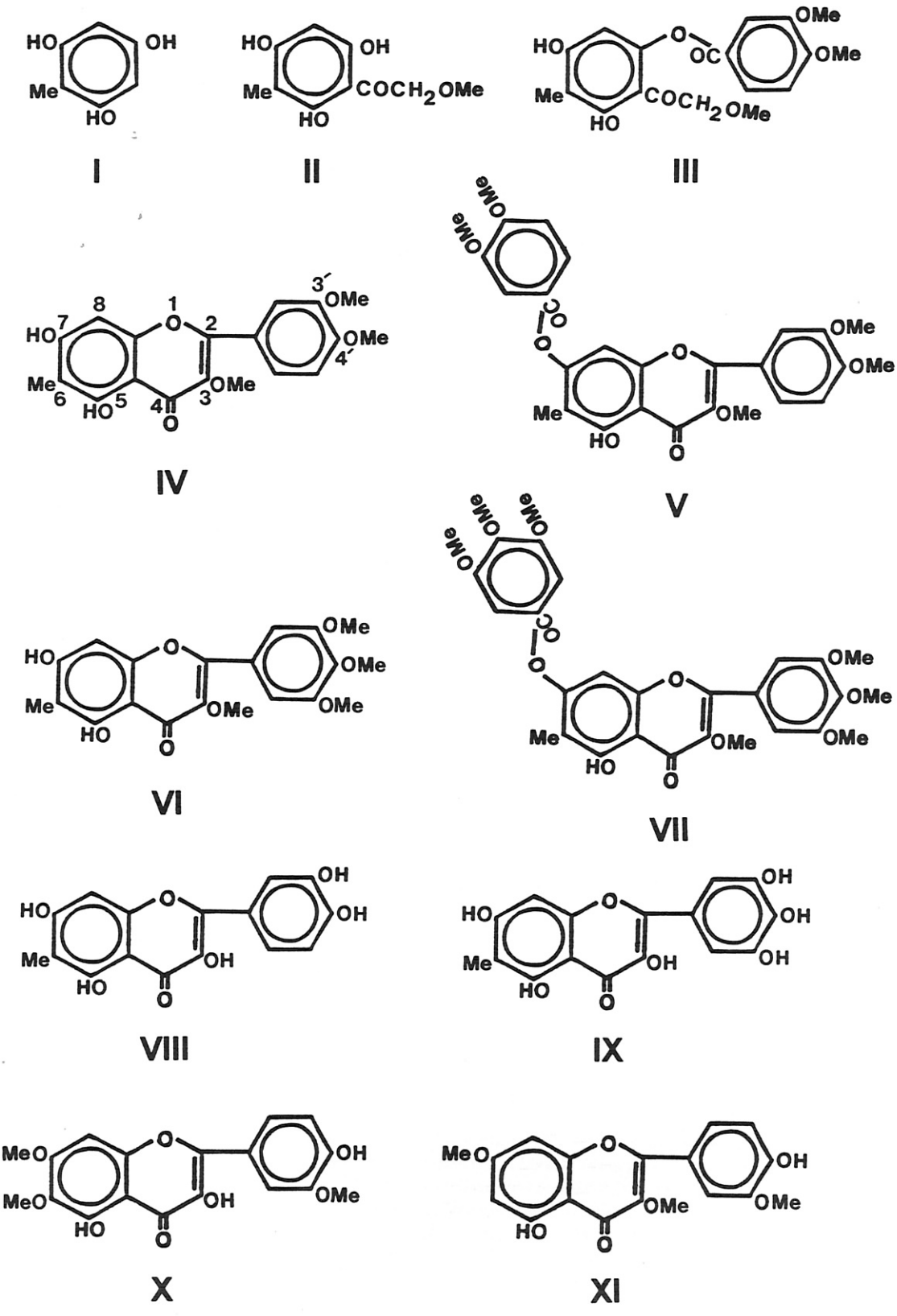

FIG. 3. I) C-Methylphloroglucinol; II) W-methoxy-C-methylphloracetophenone; III) monoester of II; IV) 6-methyl-5,7dihydroxy-3, 3', 4'-trimethoxyflavone; V) 7-veratroyl ester; VI) 6-methyl-5,7-dihydroxy-3, 3', 4', 5'-tetramethoxyflavone; VII) 7-trimethylgalloyl ester; (VIII) 6-methyl-3, 5, 7, 3', 4'-pentahydroxyflavone; IX) 6-methyl-3, 5, 7, 3', 4', 5'-hexahydroxyflavone; X) chrysosplenentin A; XI) chrysosplenetin B.

colorless needles, melting point of 229 to 230°C (lit. melting point of pinomyricetin hexacetate melting point of 230°C; Kurth et al., 1955, 1956).

Results and Discussion

Synthesis of pinoquercetin and pinomyricetin--A modification of the Baker-Venkataraman reaction consists of the treatment of an ortho-hydroxyacetophenone with an aroyl chloride in presence of anhydrous potassium carbonate in boiling acetone. In the present work, when ω-methoxy-C-methylphloracetophenone (II) was treated with an aroyl chloride under the modified Baker-Venkataraman conditions, the reaction proceeded with some unexpected results.

C-Methylphoroglucinol (I; Fig. 3) was prepared by the method of Shriner and Hull (1945). Condensation of (I) with methoxacetic acid-boron trifluoride complex gave ω-methoxy-C-methylphloracetophenone (II; Fig. 3). Treatment of the ketone (II) with 2 M of 3, 4-dimethoxybenzoyl chloride (veratroyl chloride) in presence of anhydrous potassium carbonate in boiling acetone gave 6-methyl-5, 7-dihydroxy-3, 3', 4'-trimethoxyflavone (IV; Fig. 3) along with its 7-veratroyl ester (V; Fig. 3). Apparently, the monoester of the ketone (III; Fig. 3) was first formed, which cyclized to the flavone (IV). The ester (V; Fig. 3) was easily hydrolysed to the flavone (IV) by alcoholic potassium hydroxide.

When ω-methoxy-C-methlphoracetophenone (II) was treated with 3, 4, 5-trimethoxybenzoyl chloride (O-trimethylgalloyl chloride) in the presence of anhydrous potassium carbonate in boiling acetone, the reaction again proceeded beyond the expected O-acylation stage, and the easily isolable products were 6-methyl-5, 7-dihydroxy-3, 3', 4', 5'-tetramethoxyflavone (VI; Fig. 3) along with its 7-trimethylgalloyl ester (VII; Fig. 3) which was hydrolysed to the flavone (VI) by alcoholic potassium hydroxide.

Demethylation Studies--Demethylation of (IV) with aluminum bromide in benzene gave 6-methyl-3, 5, 7, 3', 4'-pentahydroxyflavone (VIII; Fig. 3) identical with pinoquercetin obtained from the Ponderosa pine bark. Demethylation of (VI) with aluminum bromide in benzene gave 6-methyl-3, 5, 7, 3', 4', 5'-hexahydroxyflavone (IX; Fig. 3) identical with natural pinomyricetin.

Flavonoids Having Antiviral Activity--It may be noted that the compounds (IV) and (VI) obtained by the Baker-Venkataraman reaction on ω-methoxy-C-methylphloracetophenone (II) have a 3-methoxy and a 5-hydroxy group in the flavone skeleton. Tsuchiya et al. (1985) have tested a number of compounds and have concluded that a 3-methoxy and a 5-hydroxy group in the flavone skeleton were both necessary for antiviral activity against the rhinovirus infection.

One such compound (XI; Fig. 3), isolated by Shimuzu et al. (1969) from the plants of the genus*Chrysosplenium* was shown to have potent antiviral activity, especially against rhinovirus infection. It was assigned the structure (XI) on the basis of degradation studies and was given the name "chrysosplenetin."

The name chrysosplenetin was originally given to the flavonol (X; Fig. 3) isolated from *Chrysosplenium japonicum* by Nakaoki and Morita (1956), who assigned it the structure (X), which has been confirmed by synthesis (Mani et al., 1991). We shall call compound (X) chrysosplenetin A and the compound (XI) chrysosplenetin B. A synthesis of chrysosplenetin B, to verify its structure, is being undertaken in our laboratory using the Baker-Venkataraman reaction on appropriate starting materials.

Literature Cited

ALLAN, J., AND R. ROBINSON. 1924. Synthesis of o-hydroxyactaphenone using the sodium salt of an aromatic acid. J. Chem. Soc., 125:2192.

BAKER, W. 1933. Molecular rearrangement of some o-acyloxy-acetophenone and the mechanism of the production of 3-acychromones. J. Chem. Soc., 1933:1381.

JAIN, A. C., AND T. R. SESHADRI. 1954. Nuclear oxidation in flavones and related compounds. J. Sci. Industrial Res., 13B:539.

----. 1956. Synthetic experiments in the benzopyrone series L. Nuclear methylation of quercetin. Chem. Abstracts, 50:315(g).

KURTH, E. F., AND J. K. HUBBARD. 1951. Extractives from Ponderosa pine bark. Industrial Eng. Chem., 43:896.

KURTH, E. F., S. R. GUPTA, AND T. R. SESHADRI. 1954. Quercetin from fir and pine bark. J. Sci. Industrial Res., 13B:886.

KURTH, E. F., V. RAMANATHAN, AND K. VENKATARAMAN. 1955. The coloring matters of Ponderosa pine bark. Current Sci, 24:157 (Indian).

----. 1956. The coloring matters of Ponderosa pine bark. J. Sci. Industrial Res., 15B:139.

MANI, R. I., P. F. POWERS, AND L. DRUMMOND. 1991. Boron trifluoride in the synthesis of plant phenolics: Synthesis of pinoquercetin and pinomyricetin, flavanols occurring in the Ponderosa pine bark. J. Tennessee Acad. Sci., 66:94-98.

NAKAOKI, T., AND N. MORITA. 1956. Medicinal resources (II). Glycosides of *Chrysoplenium japonicum*. J. Pharmacological Soc. Japan, 76:32.

SCHMID, H., AND K. BANHOLZER. 1954. The intramolecular nature of the Baker-Venkataraman rearrangement. Helv. Chim. Acta., 37:1706.

SHIMUZU, M., ET AL. 1969. Constituents of *Chrysoplenium* plants in Japan. Glycoside of *Chrysoplenium grayaum* and the seasonal variation of its contents. Yakugaku Zasshi, 89(5):702-704 (Japanese).

SHRINER, R. L., AND C. J. HULL. 1945. Isoflavones. II. A synthesis of methylgenistein. J. Organic Chem., 10:228.

TSUCHIYA, Y., ET AL. 1985. Flavones and flavanols exhibiting antiviral activity. Chem. Pharmalogical Bull., 33(9):3881 (English).

VENKATARAMAN, K., AND H. S. MAHAL. 1933. Some 4-styrlcoumins Current Sci., 2:214 (Indian).

WHEELER, T. S., AND J. E. GOWAN. 1950. Further experiments on the Baker-Venkataraman tranformation. J. Chem. Soc., ?:1925.

WHEELER, T. S., F. GOGAN, J. E. GOWAN, AND J. KEANE. 1948 Name index of organic reactions. Sci. Proc. Royal Dublin Soc. 24:291.