[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ANDHRA UNIVERSITY]

Synthesis of Chromones. III. Furano and Pyrono Derivatives of Chromone

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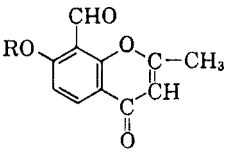
Starting from 8-formyl-7-hydroxy-2-methylchromone, the synthesis of 2-methylfurano(7,8,2′,3′)chromone is effected. Its 3-acetyl derivative was synthesized using 5-acetyl-4-hydroxybenzofuran. A number of α-, and γ-pyrono derivatives of 2-methylchromone of the type A and B have also been synthesized starting from 8-formyl- and 8-acetyl-7-hydroxy-2-methylchromones respectively.

A previous paper[1] deals with the synthesis of some derivatives of 7-hydroxy-2-methylchromone. The present communication reports the synthesis of 2-methylfurano(7,8,2′,3′)chromone (I) and 2-methyl-3-acetylfurano(7,8,2′,3′) chromone (II) and some α-, and γ-pyrono derivatives of 2-methylchromone.

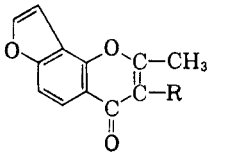
8-Formyl-7-hydroxy-2-methylchromone[1] (III) was condensed with ethyl bromoacetate, yielding 8-formyl-7-*O*-carbethoxymethyl-2-methylchromone (IV) as a liquid, characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Hydrolysis of IV with dilute alkali in the cold gave the corresponding carboxylic acid (V), while hydrolysis using strong hot alkali gave I, cyclization and decarboxylation taking place simultaneously during the course of hydrolysis. Compound I could also be produced by cyclizing V using acetic anhydride and anhydrous sodium acetate. Alternative methods of synthesis of I have also been explored. Karanjic acid[2] (VI) was converted into its methyl ester VII and subsequently condensed with acetone in presence of sodium under the conditions of the Claisen reaction, yielding 5-ω-acetylaceto-4-hydroxybenzofuran (VIII). Attempts to cyclize VIII to produce I brought about decomposition of the diketone, resulting in the isolation of VI. The other easily available starting material was 5-acetyl-4-hydroxybenzofuran (IX) which was obtained (1) from hydrolysis of pongamol[3] and (2) by its synthesis using 2,4 - dihydroxy - 3 - formylacetophenone[4] and passing through the stage: 4-*O*-carbethoxymethyl-3-formyl-2-hydroxyacetophenone its carboxy derivative and cyclization with decarboxylation.

When IX was condensed with acetic anhydride and anhydrous sodium acetate under the conditions of the Kostanecki reaction, II was obtained, further characterized by the ready formation of its 2,4-dinitrophenylhydrazone. Deacetylation of II to yield I could not be achieved.

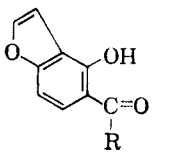
Condensation of III with acetic anhydride and sodium acetate under the conditions of the Perkin reaction, yielded 2-methyl-α-pyrono(7,8,6′,5′) chromone (X), while condensation with diethyl malonate, ethyl acetoacetate, and cyanoacetic ester gave 3′-carbethoxy, 3′-acetyl or 3′-cyano-2-methyl-α-pyrono(7,8,6′,5′) chromones, XI, XII, and XIII, respectively. Hydrolysis of XI with alkali yielded the 3′-carboxy derivative. These α-pyrono-chromones are colorless crystalline substances exhibiting prominent visible fluorescence effects in alcoholic, alkaline alcoholic, and concentrated sulfuric acid solutions.



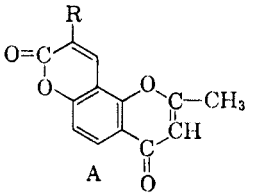
III. R = H
IV. R = CH_2COOEt
V. R = CH_2COOH



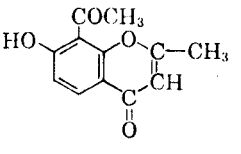
I. R = H
II. R = $COCH_3$



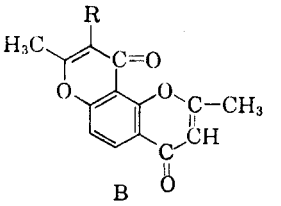
VI. R = OH
VII. R = OCH_3
VIII. R = CH_2COCH_3
IX. R = CH_3



X. R = H
XI. R = COOEt or COOH
XII. R = $COCH_3$
XIII. R = CN



XIV



XV. R = $COCH_3$
XVI. R = H

Condensation of 8-acetyl-7-hydroxy-2-methylchromone (XIV) with acetic anhydride and anhydrous sodium acetate under the conditions of the Kostanecki reaction yielded 2,2′-dimethyl-3′-acetyl-γ-pyrono(7,8,6′,5′) chromone (XV) char-

(1) Ch. Bheemasanakara Rao, G. Subramanyam, and V. Venkateswarlu, *J. Org. Chem.*, **24**, 683 (1959).

(2) T. R. Seshadri and V. Venkateswarlu, *Proc. Ind. Acad. Sci.* (A), **13**, 404 (1941); **17**, 16 (1943). D. B. Limaye, *Abstr. Indian Sci. Cong.*, 118 (1925) and 151 (1926); *Rasāyanam*, 1 (1936) and 119 (1937).

(3) Ch. Bheemasankara Rao and V. Venkateswarlu, *Current Sci. (India)*, **35**, 357 (1956).

(4) H. A. Shah and R. C. Shah, *J. Chem. Soc.*, 133 (1939).

acterized by the ready formation of its 2,4-dinitrophenylhydrazone. XV underwent smooth deacetylation on boiling with aqueous sodium carbonate giving 2,2'-dimethyl-γ-pyrono(7,8,6',5') chromone (XVI).

EXPERIMENTAL

2-Methylfurano(7,8,2',3')chromone (I). III (2 g.) in dry acetone (50 ml.), ethyl bromoacetate (1.2 ml.), and anhydrous potassium carbonate (10 g.) was boiled under reflux on a water bath for 12 hr. On working up the product, IV was obtained as a liquid characterized by the formation of its 2,4-dinitrophenylhydrazone during the first 5 min., which on recrystallization from ethyl acetate appeared as deep orange-red rectangular plates, m.p. 218–19° (dec.).

Anal. Calcd. for $C_{21}H_{18}N_4O_9$: C, 53.7; H, 3.8. Found: C, 53.9; H, 4.1.

Hydrolysis of IV. *(a) With cold dilute alkali.* IV (1 g.) was suspended in potassium hydroxide solution (20 ml., 2%) and left overnight at the laboratory temperature. Acidification of the deep orange solution thus obtained, precipitated V as a yellow solid which on crystallization from methanol appeared as yellow rectangular plates and prisms, m.p. 188–89° (dec.).

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.5; H, 3.8. Found: C, 59.6; H, 4.0.

(V) yielded, during the first 5 min., its 2,4-dinitrophenylhydrazone, which on crystallization from ethyl acetate appeared as deep red prisms, m.p. 220–21°.

Anal. Calcd. for $C_{19}H_{14}N_4O_9$: C, 51.5; H, 3.2. Found: C, 51.6; H, 3.5.

(b) With hot strong alkali. The ester (IV, 1 g.) was heated with aqueous potassium hydroxide (25 ml., 10%) for 0.5 hr. on a boiling water bath, followed by acidification using dilute sulfuric acid, when (I) separated out as a pale yellow solid. Recrystallized from methanol, it appeared as pale yellow slender prisms, m.p. 105–106°. It was insoluble in sodium bicarbonate solution and did not react with 2,4-dinitrophenylhydrazine hydrochloride.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.0; H, 4.0. Found: C, 72.1; H, 4.2.

Cyclization of (V). A mixture of V (0.5 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (10 ml.) was boiled under reflux for about 2 hr. Decomposition of the cooled reaction mixture with water gave (I) as a pale yellow solid. Recrystallized from methanol, it appeared as pale yellow prisms, m.p. 105–106°. A mixed melting point with a sample of (I) obtained earlier was undepressed.

5-ω-Acetylaceto-4-hydroxybenzofuran (VIII). Sodium powder (1 g.) in dry ether was added with cooling to a mixture of methyl ester of karanjic acid[2] (1 g.) and dry acetone (5 ml.). There was brisk reaction followed by the formation of a fluffy solid. The reaction mixture was then boiled under reflux for about 4 hr. Any excess sodium was then decomposed using small quantities of methanol and the mixture decomposed using dilute acetic acid. The residue obtained was crystallized from petroleum ether when it appeared as colorless needles, m.p. 224–225°, giving a green ferric coloration turning blue in alcoholic solution. A mixed melting point with karanjic acid was considerably depressed. This diketone in ether solution when shaken with an aqueous solution of copper acetate precipitated the copper complex, which on crystallization from chloroform appeared as dull green crystals melting above 300°.

Anal. Calcd. for $C_{12}H_{10}O_4$; C, 66.1; H, 4.6. Found: C, 65.9; H, 4.7.

5-Acetyl-4-hydroxybenzofuran (IX). Pongamol (1 g.) was boiled under reflux for 8 hr. using methyl alcoholic potassium hydroxide (30 ml., 8%). As much of the alcohol as possible was then removed by evaporation, the liquid residue diluted with water, cooled and extracted with ether (A). The aqueous alkaline solution (B) was worked up separately. The ether solution (A) on evaporation left a residue which solidified during the course of 24 hr. Recrystallized from petroleum ether (b.p. 40–60°), it appeared as rectangular plates, m.p. 58–59°, with no positive ferric reaction. This was identified as 5-acetyl-4-methoxybenzofuran by comparison with an authentic sample synthesized earlier[3] and by the preparation of its 2,4-dinitrophenylhydrazone which appeared as orange-red prisms (from alcohol), m.p. 215–16°.

Anal. Calcd. for $C_{17}H_{14}N_4O_6$: N, 15.1. Found: N, 15.0.

Demethylation of 5-acetyl-4-methoxybenzofuran using hydriodic acid in acetic anhydride gave a small quantity of (IX). The aqueous alkaline extract (B) was acidified with dilute sulfuric acid and the precipitated solid extracted with ether, the ether extract washed with aqueous sodium bicarbonate, and the residue obtained after removal of the solvent recrystallized from petroleum ether (b.p. 40–60°), m.p. 86–87°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.5. Found: C, 68.2; H, 4.6.

By synthesis. 2,4-Dihydroxy-3-formylacetophenone[4] (1 g.) dissolved in anhydrous acetone (25 ml.) was boiled under reflux on a water bath after addition of ethyl bromoacetate (1 ml.) and anhydrous potassium carbonate (10 g.). On working up, 4-O-carbethoxymethyl-3-formyl-2-hydroxyacetophenone was obtained as colorless rectangular plates and prisms (from methanol), m.p. 84–85°. Yield, 0.6 g.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. Found: C, 58.4; H, 5.4.

This (1 g.) on hydrolysis using boiling aqueous alkali (20 ml., 2%) during 0.5 hr., followed by acidification gave the carboxylic acid as colorless plates (from ethyl acetate), m.p. 163–164°. Yield, 0.4 g.

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.6; H, 4.2. Found: C, 55.6; H, 4.3.

Cyclization of the above carboxylic acid (0.5 g.) using acetic anhydride (5 ml.) and anhydrous sodium acetate (2 g.) by boiling under reflux during 0.5 hr. gave (IX) as pale yellow needles, m.p. 86–87°. A mixed melting point with the sample obtained earlier was undepressed.

2-Methyl-3-acetylfurano(7,8,2',3')chromone (II). A mixture of IX (0.5 g.), anhydrous sodium acetate (1 g.), and acetic anhydride (10 ml.) was boiled under reflux at 180–185° for about 6 hr. The residue obtained after working up was crystallized from methanol–petroleum ether (b.p. 40–60°) when it appeared as pale yellow needles, m.p. 118–119° with no positive ferric reaction.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.6; H, 4.4.

This readily formed a 2,4-dinitrophenylhydrazone, which on crystallization from ethyl acetate appeared as orange-red prisms, m.p. 283–284°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.9; H, 3.3. Found: C, 57.1; H, 3.5.

α- and γ-Pyronochromones. 2-Methyl-α-pyrono(7,8,6',5')-chromone. A mixture of III (1 g.), acetic anhydride (10 ml.), and freshly fused sodium acetate (2 g.) was gently boiled under reflux for 10 hr. The cooled reaction mixture was then decomposed using ice water and the solid that had separated out was filtered, dried, and recrystallized from methanol when it appeared as colorless rectangular plates, m.p. 233–234°. A sublimed sample had the same melting point. In alcoholic solution, it exhibits a weak violet fluorescence which becomes deeper on the addition of alkali. In concentrated sulfuric acid, it dissolved to give a colorless solution with a weak blue fluorescence.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.4; H, 3.5. Found: C, 68.6; H, 3.7.

2-Methyl-3'-acetyl-α-pyrono(7,8,6',5')chromone. Condensation of III (0.5 g.) and ethyl acetoacetate (0.32 g.) in presence of piperidine gave the required compound as pale yellow plates (from ethyl acetate–petroleum ether, b.p. 40–60°), m.p. 241–242°. It dissolved in alcohol and alcoholic alkali forming pale yellow solutions having a pale blue fluorescence, while in concentrated sulfuric acid, it gave a

pale orange-yellow solution with a green fluorescence having a bluish tinge.

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.7; H, 3.7. Found: C, 67.0; H, 4.1.

2-Methyl-3'-cyano-α-pyrono(7,8,6',5')chromone. Condensation of III (0.5 g.) with ethyl cyanoacetate (0.28 g.) in presence of piperidine gave the compound which appeared as pale yellow plates, m.p. 196–197° (dec.). In alcohol and concentrated sulfuric acid solutions, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_7NO_4$: C, 66.4; H, 2.8. Found: C, 66.7; H, 3.1.

2-Methyl-3'-carbethoxy-α-pyrono(7,8,6',5')chromone. III (0.5 g.) was condensed with diethyl malonate (0.4 g.) in presence of piperidine and the resulting product crystallized from methanol when it appeared as colorless prisms, m.p. 205–206°. In alcohol, it gave a pale yellow solution with a pale greenish blue fluorescence and with alcoholic alkali deeper greenish blue was observed. In concentrated sulfuric acid it exhibits a weak violet fluorescence.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.0; H, 4.0. Found: C, 64.1; H, 4.2.

2-Methyl-α-pyrono(7,8,6',5')chromone-3'-carboxylic acid. Saponification of the above ester using methanolic alkali in the cold during 24 hr., followed by acidification gave the carboxylic acid, which on crystallization from methanol appeared as colorless rectangular prisms, m.p. 257–258° (dec.). It dissolved easily in sodium bicarbonate solution. In alcoholic solution, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_8O_6$: C, 61.8; H, 2.9. Found: C, 62.0; H, 3.1.

2,2'-Dimethyl-3'-acetyl-γ-pyrono(7,8,6',5')chromone (XV). A mixture of XIV (1 g.), anhydrous sodium acetate (2 g.), and acetic anhydride (5 ml.) was boiled under reflux at 180–185° for about 6 hr. The product obtained after working up was crystallized from methanol when it appeared as colorless plates and prisms, m.p. 184–185° (dec.). A sublimed sample, however, melted at 185–186° (dec.). It gave no ferric coloration in alcoholic solution.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2. Found: C, 67.8; H, 4.3. This compound readily gave its 2,4-dinitrophenylhydrazone which on crystallization from ethyl acetate–petroleum ether (b.p. 40–60°) appeared as deep yellow plates and prisms, m.p. 243–244° (dec.).

Anal. Calcd. for $C_{22}H_{16}N_4O_8$: C, 56.9; H, 3.5. Found: C, 56.8; H, 3.7.

2,2'-Dimethyl-γ-pyrono(7,8,6',5')chromone (XVI). 0.5 g. of XV was dissolved in aqueous sodium carbonate solution (2*N*, 50 ml.) and gently boiled under reflux for about 3 hr. The product when worked out was found to be a mixture of (XVI) and its corresponding diketone and hence the product was directly employed for complete cyclization. A solution of the mixture (0.25 g.) in absolute alcohol (5 ml.) containing concentrated hydrochloric acid (2 drops) was refluxed for 5 min. and the solvent removed by evaporation. The residue was then crystallized from methanol when it appeared as yellow prisms, m.p. 260–261°, having no positive reaction with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.6; H, 4.3.

WALTAIR, INDIA

[CONTRIBUTION FROM UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY]

Studies on the Constitution, Stereochemistry, and Synthesis of Aegeline,[1] an Alkaloidal-Amide of *Aegle marmelos* Correa

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Aegeline, a neutral product of *Aegle marmelos* Correa, is shown to have the formula $C_{18}H_{19}O_3N$. It is proved to be *N*-β-hydroxy-β-*p*-methoxyphenylethylcinnamamide from the studies of its acid hydrolysis, hydramine fission, periodic acid oxidation, and other degradative experiments, and also by its synthesis. The stereochemistry and steric stability of the compound are discussed. The characteristic features observed in its ultraviolet and infrared spectra, particularly in the —C=C— stretching region and the "trans band region" at 990–965 cm.$^{-1}$ establish the *trans* configuration of aegeline.

The leaves of *Aegle marmelos* Correa were reported as a source of aegeline, m.p. 176° (yield, 0.09%) by Chatterjee and Bose.[2] The substance showed absorption in the ultraviolet region (λ_{max} at 217 mμ, log ε 4.5328, 223 mμ, log ε 4.5177, and 275 mμ, log ε 4.6053) and contained an alcoholic function. It was earlier believed to be a neutral non-nitrogenous compound from its elementary analysis but later a careful examination of its infrared spectrum (Table I) revealed that aegeline was a conjugated amide. This observation accorded with the ultraviolet spectra measurements which were closely similar to those of *trans-N*-methylcinnamamide (λ_{max} at 216, 222, and 273 mμ, log ε 4.2863, 4.2077, and 4.4038, respectively) thus indicating that the substance did contain nitrogen.[3] In further consonance with this fact, aegeline evolved a strong base having methylamine-like odor when fused with alkali. Thereby, serious doubt was raised as to the correctness of the formula $C_{18}H_{18}O_4$ originally proposed. Several elementary analyses now carefully performed clearly demonstrated that aegeline must possess the formula $C_{18}H_{19}O_3N$. The present communication concerns the studies on its constitution, synthesis, stereochemistry, and steric stability.

For the isolation of aegeline, the previous ether extraction method[2] was followed with some modification. The ethereal mother liquor left after the

(1) Following the convention for terminology, the suffix *e* has been added to aegelin.

(2) A. Chatterjee and S. Bose, *J. Indian Chem. Soc.*, 29, 425 (1952).

(3) A. Chatterjee and S. K. Srimany, *Congress Handbook XVIth International Congress of Pure and Applied Chemistry*, Part II, p. 199 (1957).