[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, INSTITUTE OF SCIENCE, UNIVERSITY OF BOMBAY]

Stability of Coumarinic Acids[1]

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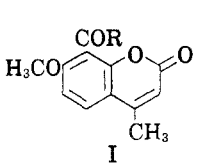
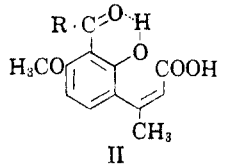
Experimental evidence is furnished to substantiate the interpretation made by Crawford and Rasburn[6] of the stability of the coumarinic acids derived from coumarins having "acidic" substituents in the 8-position. The isomerization of 5-hydroxy-4-methyl-8-nitrocoumarin to 5-hydroxy-4-methyl-6-nitrocoumarin anticipated on the basis of the interpretation has been successfully effected.

Several coumarinic acids have been isolated from coumarins having "acidic" substituents in the 8-position,[3] whereas the isolation of a stable coumarinic acid from coumarins having "acidic" substituents in positions other than 8 has apparently not been accomplished. Dey and Krishnamurty[3d] employed this observation in the effective separation of the mixture of 8-nitro- and 6-nitrocoumarins. During the formylation[4] of some hydroxycoumarin derivatives, we observed that 8-formyl-5,7-dimethoxy-4-methylcoumarin furnished a stable *cis* acid, *viz.* 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid, on warming with alkali and then acidifying, whereas 6-formyl-5,7,-dimethoxy-4-methylcoumarin was recovered on identical treatment. The stability of this and other coumarinic acids derived from coumarins having "acidic"[3c] substituents in the 8-position has been interpreted[5] as due to the failure to lactonize because of the creation of an intromolecular hydrogen bond between the "acidic" (which usually happens to be chelate-forming) substituent in the 8-position and the hydroxyl group generated from the pyrone ring on treatment with alkali. Recently, while the present communication was being prepared, an interesting paper[6] appeared wherein the authors furnish the same interpretation. We record our observations to substantiate this interpretation and also report an isomerization anticipated because of the intramolecular hydrogen bond.

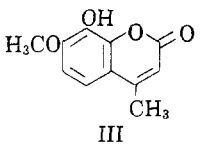
3-Acetyl-4-methoxy-β-methylcoumarinic acid (II, R = CH_3) prepared earlier by Limaye and Sathe[7] along with the corresponding *trans* acid, and 3-formyl-4-methoxy-β-methylcoumarinic acid (II, R = H) revert to their parent coumarins (I) on crystallizing from acetic acid or on standing at room temperature in alcohol containing a few drops of concentrated hydrochloric acid. This is consistent with the view[8] that the intramolecular hydrogen bond is weakened in the presence of protons, *i.e.* in an acidic medium. Dakin oxidation of both these coumarinic acids (II) furnished 8-hydroxy-7-methoxy-4-methylcoumarin (III) and not the corresponding 3-hydroxycoumarinic acid derivative; lactonization has taken place presumably because of the low stability of the *cis* acid resulting from the replacement of the earlier hydrogen bond by a comparatively weak hydrogen bond of the catechol type.



I



II



III

The *cis* acids derived from 8-formyl-5,7-dimethoxy-4-methylcoumarin and 5-methoxy-4-methyl-8-nitrocoumarin (described later) are apparently more stable as they failed to revert to their parent coumarins on crystallizing from acetic acid or on standing in alcoholic hydrochloric acid; however, they reverted in the presence of 80% sulphuric acid. The hydrogen peroxide oxidation of 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid furnished 8-hydroxy-5,7-dimethoxy-4-methylcoumarin.

Interesting evidence in favor of the interpretation is provided by the failure to isolate a stable coumarinic acid (V) from 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (IV) where the hydroxyl group in the 7-position can form a hydrogen bond

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(3) (a) W. v. Miller and F. Kinkelin, *Ber.*, **22**, 1706 (1889); (b) A. Clayton, *J. Chem. Soc.*, **97**, 1388 (1910); (c) L. A. Jordan and J. F. Thorpe, *J. Chem. Soc.*, **107**, 387 (1915), (d) B. B. Dey and P. Krishnamurty, *J. Ind. Chem. Soc.*, **4**, 197 (1927).

(4) R. M. Naik and V. M. Thakor, unpublished results.

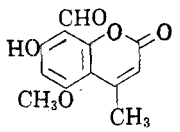
(5) R. M. Naik, Ph.D. thesis, Univ. of Bom., August 1955.

(6) M. Crawford and J. W. Rasburn, *J. Chem. Soc.*, 2155 (1956).

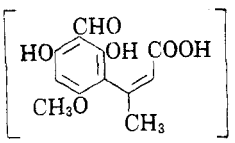
(7) D. B. Limaye and N. R. Sathe, *Rasayanam*, **1**, 30 (1936); *Chem. Abstr.* **31**, 2212 (1937).

(8) V. M. Thakor, *Curr. Sci.*, **22**, 118 (1953).

with the formyl group leaving the hydroxyl group from the pyrone ring free to lactonize.



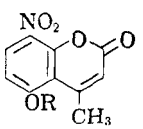
IV



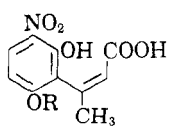
V

Clayton[3b] isolated a stable *cis* acid from 7-hydroxy-8-nitrocoumarin and its stability has been attributed[6] to double chelation as in the case of 2-nitroresorcinol. However, 7-methoxy-4-methyl-8-nitrocoumarin, prepared by Pechmann condensation of 2-nitroresorcinol with ethyl acetoacetate and subsequent methylation, failed to give a stable coumarinic acid. This is in agreement with the recorded[6] failure to isolate a *cis* acid from 7-methyl-8-nitrocoumarin and may be due to the interference of the methoxyl in the 7-position with the coplanarity of the 8-nitro substituent—a condition necessary for maximum chelation.

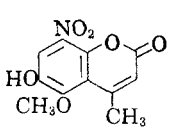
If the stability of the *cis* acids under consideration were to be attributed to the intramolecular hydrogen bond, then complete isomerization of a 5-hydroxycoumarin derivative with a chelate-forming substituent in the 8-position to the corresponding 5-hydroxycoumarin with the substituent in the 6-position by means of alkali would be expected. This would also confirm that the conditions employed consistently throughout led to the formation of *cis* acids only as the isomerization would not be possible in case of the *trans* acid. With these considerations in view, the nitration of 5-hydroxy-4-methylcoumarin was reinvestigated. In contrast to the observations of Parekh and Shah,[9] two mononitro isomers, m.p. 265° and m.p. 188–189°, were isolated. The structure of 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) has been assigned to the isomer, m.p. 265° as (i) its methyl ether (VI, R = CH_3) yielded stable 6-methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3) on treatment with alkali—a characteristic of coumarins with an "acidic" substituent in the 8-position, (ii) the Elbs oxidation of VI (R = CH_3) furnished 6-hydroxy-5-methoxy-4-methyl-8-nitrocoumarin (VIII) in good yield indicating the 6-position to be



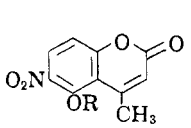
VI



VII



VIII



IX

vacant, since the oxidation of coumarins[10] proceeds smoothly in the 6-position which is *para* to the hydroxyl group of the pyrone ring.

The alternative structure of 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) has been assigned to the other isomer, m.p. 188–189°. Parekh and Shah[11] prepared this substance by Pechmann condensation of 4-nitroresorcinol with ethyl acetoacetate and gave m.p. 209–210°. However, an attempt to repeat their work using anhydrous aluminum chloride met with failure. The observed demethylation of 5-methoxy-4-methyl-6-nitrocoumarin (IX, R = CH_3) with alkali is unusual; however, instances of such demethylation of the methoxyl groups in *ortho* and sometimes *para* positions to the nitro groups by alkali are known in the literature.[12] The nitration of 5-methoxy-4-methylcoumarin afforded only one isomer, identical with 5-methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3).

When 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) was warmed with alkali and then acidified, 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) alone was isolated, indicating that complete isomerization took place presumably through the *cis* acid (VII, R = H). The hydroxyl in the 5-position takes part in lactonization since the original hydroxyl is involved in hydrogen bond formation. The action of alkali on a 5-hydroxycoumarin derivative with any substituent other than chelate-forming in the 8-position, may also bring about at least partial isomerization due to the greater ease with which the hydroxyl group in the 5-position can lactonize. However, *complete* isomerization and at the same time the formation of the stable coumarinic acid from its methyl ether would be a reliable criterion for the existence of chelation.

EXPERIMENTAL[13]

3-Acetyl-4-methoxy-β-methylcoumarinic acid. (11, R = CH_3) 8-Acetyl-7-methoxy-4-methylcoumarin (2 g.) was heated on a steam bath with sodium hydroxide (20 c.c., 5%) for about 15 min., when the whole of the substance went into solution. The product which separated on cooling and gently acidifying, was crystallized from alcohol as light green flakes, m.p. 162° (decomp.), yield 1.5 g. Limaye and Sathe[7] prepared it along with the *trans* acid by drastic and prolonged boiling with concentrated alkali and gave m.p. 163°. While acidifying, unless care is taken to avoid both generation of heat and addition of excess of hydrochloric acid, the coumarinic acid partially reverts to the parent coumarin. This reversal also takes place when the coumarinic acid is crystallized from acetic acid or on keeping it at room temperature with alcohol containing few drops of hydrochloric acid.

8-Hydroxy-7-methoxy-4-methylcoumarin (111). To the solution of the preceding coumarinic acid (0.4 g.) in sodium hydroxide (4 c.c., 4%) at 0°, hydrogen peroxide (1.6 c.c.,

(9) N. B. Parekh and R. C. Shah, *J. Ind. Chem. Soc.*, **19**, 335 (1942).

(10) S. M. Sethna, *Chem. Revs.*, **49**, 91 (1951).

(11) N. B. Parekh and R. C. Shah, *J. Ind. Chem. Soc.*, **19**, 340 (1942).

(12) (a) Robert Burwell, *Chem. Revs.*, **54**, 662 (1954); (b) R. M. Naik *et. al. Proc. Ind. Acad. Sci.*, **38A**, 32 (1953).

(13) Melting points are uncorrected and were taken in open capillary tubes.

30%) was added dropwise with stirring, and the reaction mixture left for 1 hr. when white needles separated. It was acidified and the product which separated was crystallized from alcohol as thin white needles, m.p. 156° (0.2 g.).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.3; H, 4.7.

It does not give any color with alcoholic ferric chloride but dissolves in dilute alkali. It was methylated with dimethyl sulfate by the potassium carbonate-acetone method to the known 7,8-dimethoxy-4-methylcoumarin. Recently Desai and Parghi[14] reported the preparation of 8-hydroxy-7-methoxy-4-methylcoumarin and stated its melting point as 145°. It is probable that their product is a mixture containing traces of 7,8-dihydroxy-4-methylcoumarin.

8-Formyl-7-methoxy-4-methylcoumarin (I, R = H) was prepared by methylation of 8-formyl-7-hydroxy-4-methyl-coumarin and crystallized from alcohol as thin plates, m.p. 242°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.2; H, 4.8.

3-Formyl-4-methoxy-β-methylcoumarinic acid (II, R = H). One gram of I (R = H) was heated for 15 min. on a steam bath with sodium hydroxide (10 c.c., 5%) and the solution was cooled and gently acidified. The pale yellow product which separated was crystallized from alcohol as pale yellow prisms. It shrinks and then melts at 237°, but does not depress the m.p. of 8-formyl-7-methoxy-4-methylcoumarin, presumably indicating the ring closure which takes place before it melts.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 60.7; H, 5.0.

It completely dissolves in sodium bicarbonate with effervescence and gives a purple-brown color with alcoholic ferric chloride. On standing in acetic acid or alcoholic hydrochloric acid, it reverts to the original coumarin (I, R = H).

The Dakin oxidation of 3-formyl-4-methoxy-β-methylcoumarinic acid (II, R = H) (0.2 g.) in sodium hydroxide (4 c.c., 2%) with hydrogen peroxide (1 c.c., 6%) furnished 8-hydroxy-7-methoxy-4-methylcoumarin (III) described earlier.

8-Hydroxy-5,7-dimethoxy-4-methylcoumarin. Hydrogen peroxide (2 c.c., 6%) was added dropwise to a solution of 3-formyl-4,6-dimethoxy-β-methylcoumarinic acid (0.2 g.) in sodium hydroxide (4 c.c., 2%) at 0°, and the reaction mixture was left at 0° for 2 hr. The color changed from orange-red to greenish-brown and later to light yellow. On acidification, a pale yellow product separated, which crystallized from alcohol as brown prisms, 0.08 g., m.p. 258°.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.3; H, 5.0.

With alcoholic ferric chloride it gives a faint brown color which changes to pale green on standing.

Action of sodium hydroxide on 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (IV). The sodium salt which separated on addition of 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (0.5 g.) to sodium hydroxide (5 c.c., 5%), dissolved on heating on a steam bath for 15 min. The salt did not separate on cooling presumably indicating the opening of the pyrone ring. The solution was gently acidified and the product which separated was identified as the original coumarin (IV). No trace of stable coumarinic acid derivative could be isolated.

5-Hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) *and 5-hydroxy-4-methyl-6-nitrocoumarin* (IX, R = H). Nitric acid (2 c.c., *d* 1.42) was added with stirring to 5-hydroxy-4-methylcoumarin (0.2 g.) suspended in glacial acetic acid (5 c.c.) at 10° and the mixture left at 0° for 30 min. The substance slowly went into solution and later yellow glistening needles separated. On pouring the contents in cold water, a yellow product was obtained. It was crystallized from a little excess of acetic acid in clusters of thick needles of 5-hydroxy-4-methyl-8-nitrocoumarin, m.p. 265° (decomp.).

Anal. Calcd. for $C_{10}H_7NO_5$: N, 6.3. Found: N, 6.1.

With alcoholic ferric chloride it gives a pale orange color comparable to that of *p*-nitrophenol. Its methyl ether (VI, R = CH_3) crystallized from acetic acid as flocculent white needles, m.p. 225°.

Anal. Calcd. for $C_{11}H_9NO_5$: N, 6.0. Found: N, 6.2.

The mother liquor from the above crystallization on evaporation yielded 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) which crystallized from alcohol as shining yellow needles. It was twice recrystallized, m.p. 188–189°.

Anal. Calcd. for $C_{10}H_7NO_5$: N, 6.3. Found: N, 6.2.

It gives a blood red color with alcoholic ferric chloride. Parekh and Shah[11] gave m.p. 209–210° for this substance, whereas the melting point of the substance obtained by us could not be raised even after several crystallizations. Its methyl ether (IX, R = CH_3) crystallized from alcohol as thin white needles, m.p. 148°.

Anal. Calcd. for $C_{11}H_9NO_5$: N, 6.0. Found: N, 6.2.

When dissolved in 5% sodium hydroxide by warming on a steam bath, cooled, and then acidified, 5-hydroxy-4-methyl-6-nitrocoumarin (IX, R = H) was isolated indicating the demethylation[12] which took place with alkali.

5-Methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3). 5-Methoxy-4-methylcoumarin (0.2 g.) was added in small lots to nitric acid (2 c.c., *d* 1.42) at 20°. The substance went into solution and the reaction mixture turned greenish-brown. After 15 min., the contents were poured into crushed ice. The product which separated was crystallized twice from acetic acid in needles, m.p. 225°. The melting point was not depressed when mixed with 5-methoxy-4-methyl-8-nitrocoumarin (VI, R = CH_3) obtained above. The 6-nitro isomer could not be detected.

6-Methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3), was obtained by heating 5-methoxy-4-methyl-8-nitrocoumarin (0.1 g.) on a steam bath for 15 min. with sodium hydroxide (5 c.c., 5%) and acidifying. The coumarinic acid crystallized from alcohol as crisp yellow plates, m.p. 182° (efferv.).

Anal. Calcd. for $C_{11}H_{11}NO_6$: N, 5.5. Found: N, 5.7.

It gives red color with alcoholic ferric chloride. It reverts to the original coumarin when kept with sulphuric acid (80%).

6-Hydroxy-5-methoxy-4-methyl-8-nitrocoumarin (VIII). To a cooled (0°) solution of 5-methoxy-4-methyl-8-nitrocoumarin (0.7 g.) in sodium hydroxide (6 c.c., 10%) (obtained after warming), a saturated solution of potassium persulfate (0.8 g.) was added dropwise with stirring and the reaction mixture left overnight in a refrigerator. It was acidified and unreacted 6-methoxy-3-nitro-β-methylcoumarinic acid (VII, R = CH_3) was removed by filtration. The filtrate was heated for 1 hr. with more hydrochloric acid when pale yellow crystalline product separated. It crystallized from alcohol as thin light yellow needles, 0.2 g., m.p. 232°.

Anal. Calcd. for $C_{11}H_9NO_6$: N, 5.6. Found: N, 5.8.

It does not give any color with ferric chloride but dissolves in dilute alkali. It does not effervesce with sodium bicarbonate.

Isomerization of 5-hydroxy-4-methyl-8-nitrocoumarin (VI, R = H) *to 5-hydroxy-4-methyl-6-nitrocoumarin* (IX, R = H). 5-Hydroxy-4-methyl-8-nitrocoumarin (0.2 g.) was heated on a steam bath for 15 min., with sodium hydroxide (10 c.c., 5%). The solution was cooled and gently acidified. The product separated was crystallized from alcohol as thin needles, m.p. 188–189°. The melting point was not depressed when mixed with 5-hydroxy-4-methyl-6-nitrocoumarin obtained earlier. No other product could be isolated along with it.

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(14) R. D. Desai and J. V. Parghi, *J. Ind. Chem. Soc.*, **33**, 661 (1956).