[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, RECORDATI, S.P.A.]

Selective *ortho* and *meta* Migration of an Acyl Group in the Fries Rearrangement of Creosol Esters

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It has been shown that in the acylation of creosol by the boron trifluoride/carboxylic acids method involving the Fries rearrangement, it is possible to obtain selectively, by varying the temperature, *ortho* or *meta* migration of the acyl group.

In the chemical literature some examples are known of *meta* migration of an acetyl group in the Fries rearrangement of phenolic esters.[1,2,3] T. Reichstein[1] was first able to recognize the formation of a *meta* isomer in the rearrangement of acetyl guaiacol. Recently Ballio and Almirante[4] published a short note on some other cases of *meta* migration in acetyl derivatives of 2-methoxy-4-methylphenol (creosol (I)), 2-methyl-4-methoxyphenol and 2,4-dimethylphenol. In the case of creosol, these authors report[4] the formation of both *ortho-* and *meta-* isomers in the ratio 3:1. These data may be questioned on the basis of the work of Manske and Ledingham,[2] in which the formation of the *meta-* isomer alone is reported. Because we were interested in some creosol derivatives, we have taken the opportunity to reexamine the results obtained by the earlier authors[2,4] in order to clear up the conflicting data.

We have repeated the Fries rearrangement on acetyl creosol and our results confirm those of Manske and Ledingham. We were not able to isolate any *ortho-* isomer, but only the *meta* one. Ballio and Almirante, at our request, kindly furnished us with some physical characteristics of the two isomers, not reported in their short communication. To solve the question of the formation of both isomers, we attempted to modify the reaction conditions and to employ the direct acylation of creosol by the Friedel-Crafts procedure. In the latter case, too, the only product isolated was the *meta-* isomer, as acetyl derivative.

At this juncture, we thought to attempt the acylation of phenolic derivatives by the Meerwein method,[5] extensively used by Kindler and coworkers,[6] *i.e.*, the acylation with carboxylic acids in the presence of boron trifluoride, which, as Kindler[6] has pointed out, involves a true Fries rearrangement. This procedure also offers the possibility, by working at different temperatures, to obtain one of the two normally occurring *ortho/para-* isomers. By means of this procedure we attempted to obtain selectively, by varying the temperature, products of *ortho* and *meta* migration in the Fries rearrangement of acetic and propionic esters of creosol. This reaction was extensively studied on acetylcreosol in the range of temperature from 25 to 160°. Between 25–80°, only the *meta-* isomer was obtained, with decreasing yield from 90 to 56%. Between 100–120° the two isomers were formed in a ratio (*ortho/meta*) which varies from 1:4.5 to 4:1. Above 120° only the *ortho-* isomer, as 2,3-dihydroxy-5-methylacetophenone, was isolated. These results are summarized in the Table I.

TABLE I

PER CENT YIELD OF *ortho-* AND *meta-* ISOMERS AT DIFFERENT TEMPERATURES

Temperature	*ortho-* Isomer	*meta-* Isomer
25	—	90
40	—	75
60	—	68
80	—	56.6
100	18	40
120	25	10
140	60	—
160	78	—

The yields were calculated detracting the recovered creosol.

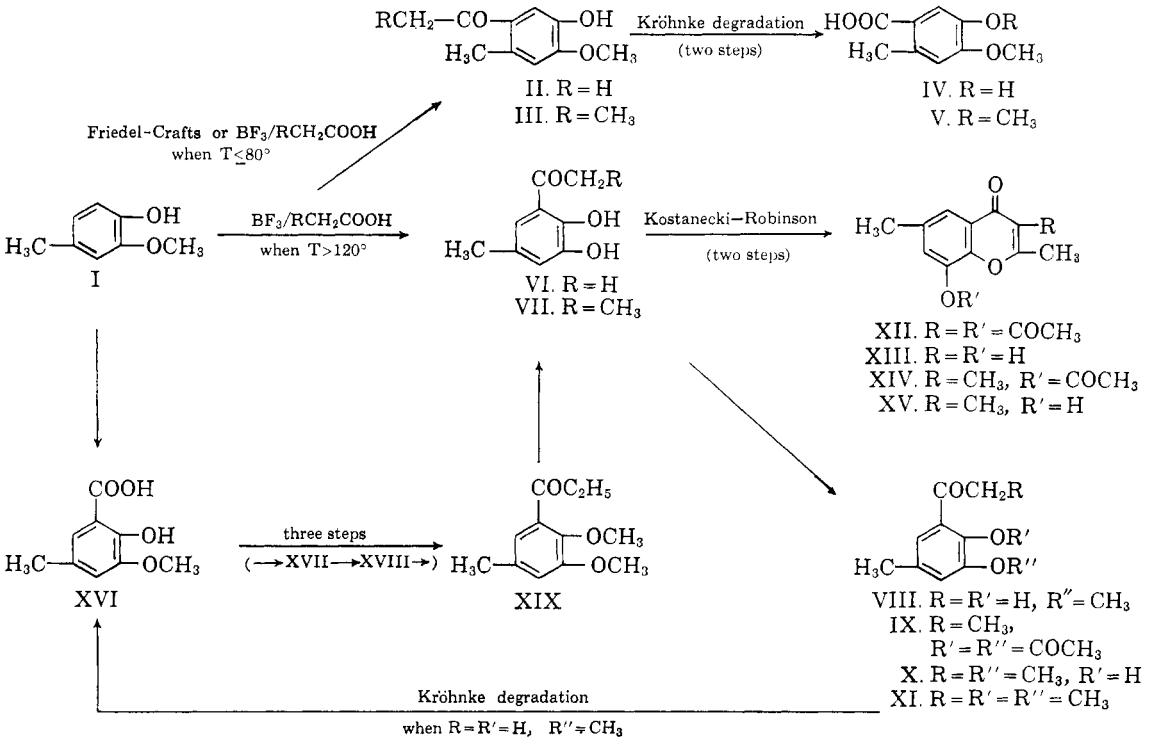
Consequently a temperature of 25° was sufficient to direct the migrating group exclusively in the *meta-* position with the maximum of 90% yield, while at 160° a maximum of 78% of the *ortho-* isomer only was obtained.

The demethylation observed above 120° cannot be regarded as exceptional, since it is well known that the Lewis acids have this capacity even though boron trifluoride is the weakest in the series of boron halides.[7]

The constitution of the *ortho-* and *meta-* isomers thus obtained was rigorously demonstrated by a series of reactions which led to known compounds.

In the case of the *ortho-* isomer derived from propionylcreosol, an independent synthesis was carried out. The experimental work is summarized schematically as follows:

(1) T. Reichstein, *Helv. Chim. Acta*, **10**, 392 (1927).
(2) R. H. Manske and A. E. Ledingham, *Can. J. Research*, 22B, 115 (1944).
(3) A. Ballio, *Gazz. chim. ital.*, **79**, 924 (1949).
(4) A. Ballio and L. Almirante, *Ricerca sci.*, **21**, 85 (1951).
(5) H. Meerwein, *Chem. Ber.*, **66**, 411 (1933).
(6) K. Kindler, H. Oelschläger, and P. Henrich, *Archiv. Pharm.*, **287**, 210 (1954).
(7) R. L. Burwell, Jr., *Chem. Revs.*, **54**, 654 (1954).



By saturating a creosol (I) and acetic or propionic acid mixture (molar ratio 1:2) with boron trifluoride at ice bath temperature, and leaving the reaction mixture stand at room temperature for two days, the 2-methyl-4-methoxy-5-hydroxyacetophenone (II), respectively propiophenone (III), were formed. Compounds II and III were also obtained either by the Fries rearrangement of acetyl- and propionylcreosol or, in the form of their acetyl and propionyl derivatives, by the Friedel-Crafts acylation of I. Compound II, submitted to the Kröhnke degradation,[8] *i.e.*, the formation of carboxylic acids from methyl ketones *via* pyridinium salts, furnished 2-methyl-4-methoxy-5-hydroxybenzoic acid (IV), methylation of which gave 2-methyl-4,5-dimethoxy-benzoic acid (V), identical with that described by Manske and Ledingham.[2]

When the acylation of I is accomplished keeping the reaction temperature at 160°, the 2,3-dihydroxy-5-methylacetophenone (VI) and propiophenone (VII) were formed. Compound VI on selective methylation furnished the *ortho*- isomer (VIII) recorded by Ballio and Almirante.[4] Compound VII was characterized through the diacetyl derivative (IX) and the mono and dimethyl ethers, X and XI, respectively.

To confirm the *ortho*- position assumed by the introduced acetyl and propionyl groups, compounds VI and VII were submitted to acylation with acetic anhydride and anhydrous sodium acetate, according to Kostanecki-Robinson procedure, the corresponding chromone derivatives being obtained. Starting from VI the 3-acetyl-8-acetoxy-2,6-dimethyl-chromone (XII) was first isolated, the saponification of which gave the 8-hydroxy-2,6-dimethylchromone (XIII). Analogously from VII was obtained 8-hydroxy-2,3,6-trimethylchromone (XV) *via* the 8-acetoxy derivative (XIV).

The λ_{max} values of ultraviolet spectra of XIII and XV are in good agreement with those observed for the 8-hydroxy-2,3-dimethylchromone, according with the conclusions of Ganguly and Bagchi[9] that a methyl group in the benzene ring of the chromone causes only little variations in the ultraviolet spectra.

The structure of VII was also confirmed with an independent synthesis carried out from creosol. Compound I was transformed by the Marasse modification of the Kolbe-Schmitt reaction[10] into the creosol carboxylic acid (XVI) previously prepared by Baine *et al.*[11] and was subsequently methylated to 2,3-dimethoxy-5-methylbenzoic acid (XVII). The chloride of the latter, XVIII, by reaction with zinc ethyl iodide, furnished 2,3-dimethoxy-5-methylpropiophenone (XIX), identical with compound XI. The demethylation of XIX, with pyridinium chloride, led to 2,3-dihydroxy-5-methylpropiophenone, identical with VII. A mixture melting point of the two products obtained by different routes was not depressed.

(8) F. Kröhnke, *Chem. Ber.*, **66**, 604 (1933).

(9) B. Ganguly and P. Bagchi, *J. Org. Chem.*, **21**, 1415 (1956).

(10) A. S. Lindsey and H. Jeskey, *Chem. Revs.*, **57**, 583 (1957).

(11) O. Baine, *et al*, *J. Org. Chem.*, **19**, 510 (1954).

EXPERIMENTAL

2-Methyl-4-methoxy-5-hydroxyacetophenone (II). A mixture of 20 g. of creosol and 17 g. of acetic acid was saturated with boron trifluoride at ice bath temperature and then kept at 25° for 2 days. The reaction mixture was decomposed by pouring it in sodium acetate solution and the product which separated was collected by filtration, washed with water, and dried. On crystallization from ligroin, 23 g. of a white crystalline solid, m.p. 129–130°, was obtained (0.5 g. of creosol were recovered).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.88. H, 6.35. Found: C, 64.84; H, 6.40.

2-Methyl-4-methoxy-5-hydroxypropiophenone (III). By the same procedure described for compound II, starting from 20 g. of creosol and 21.5 g. of propionic acid, 16.8 g. of III, from ligroin, were obtained. White crystalline product, m.p. 97–99° (5 g. of creosol were recovered).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 66.09; H, 6.83. Found: C, 65.91; H, 7.00.

2-Methyl-4-methoxy-5-hydroxybenzoic acid (IV). Compound II (3.5 g.) was brominated in glacial acetic acid with 3.2 g. of bromine. Removal of the solvent left an oil which was transformed directly, by the action of pyridine, into the corresponding pyridinium salt. The separated product was isolated by filtration, washed with ether, and crystallized from alcohol/ether. There was obtained 2 g. of white crystalline product, m.p. 237–239°.

Anal. Calcd. for $C_{15}H_{16}BrNO_4$: C, 53.24; H, 4.77. Found: C, 53.10; H, 4.83.

Two grams of pyridinium salt of ω-bromo-2-methyl-4-methoxy-5-hydroxyacetophenone in 30 ml. of water was added to 20 ml. of 15% sodium hydroxide and the reaction mixture was heated on the steam bath for 15 min. After cooling, the carboxylic acid formed was precipitated from solution by means of dilute hydrochloric acid, collected by filtration and purified by double precipitation.

After crystallization from hot water, 0.9 g. of 2-methyl-4-methoxy-5-hydroxybenzoic acid, m.p. 176–178°, was obtained.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.54. Found: C, 59.32; H, 5.80.

2-Methyl-4,5-dimethoxybenzoic acid (V). To a solution of 0.9 g. of 2-methyl-4-methoxy-5-hydroxybenzoic acid (IV) in 15 ml. of 15% sodium hydroxide was added 1.8 g. of methyl sulfate dropwise. The reaction mixture was heated on the water bath at 40° for 20 min. and then 1.8 g. of methyl sulfate was added. The solution was refluxed for 3 hr., cooled, diluted with water, and acidified with dilute hydrochloric acid.

The separated solid was collected by filtration and dried. On crystallization from ligroin, 0.65 g. of white crystalline product, m.p. 145–147°, was obtained. A mixture melting point of this acid with a sample of that prepared according to Manske and Ledinghan[2] was not depressed.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found C, 61.13; H, 6.02.

2,3-Dihydroxy-5-methylacetophenone (VI). By the procedure outlined for compound II, but keeping the reaction temperature at 160° for 1.5 hr., a mixture of 4.15 g. of creosol and 3.6 g. of acetic acid gave 3.9 g. of light yellow crystalline product from ligroin, m.p. 86–88°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.03; H, 6.07. Found: C, 65.02; H, 6.19. The *diacetate* was a white crystalline product m.p. 100–102°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.46; H, 5.68.

3-Methyl ether (VIII). By methylating 4.5 g. of compound VI with 3.5 g. of methyl sulfate in acetone in the presence of anhydrous potassium carbonate, 0.9 g. of a light yellow crystalline product (from ligroin) m.p. 84–85°, was obtained.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.72. Found: C, 66.59; H, 6.63.

2,3-Dihydroxy-5-methylpropiophenone (VII). By the procedure outlined for compound II but keeping reaction temperature at 160° for 90 min., a mixture of 6.9 g. of creosol and 7.4 g. of propionic acid gave 5.4 g. of light yellow crystalline product, m.p. 83–85°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.51; H, 6.51. The *diacetate* (IX) was a white crystalline product, m.p. 80–82°.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.42; H, 5.84.

3-Methyl ether (X). By methylating 5 g. of compound VII with 3.5 g. of methyl sulfate in acetone in the presence of anhydrous potassium carbonate, 2.1 g. of a yellow crystalline powder, m.p. 69–70°, was obtained. The product was recrystallized from ligroin.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 67.90; H, 7.46.

Dimethyl ether (XI). Light yellow liquid b.p. 103–105°/0.2 mm.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.18; H, 7.74. Found: C, 69.05; H, 7.60.

2,4-Dinitrophenylhydrazone. Orange-yellow solid, m.p. 147–148.5°.

Anal. Calcd. for $C_{18}H_{20}N_4O_6$: N, 14.42. Found: N, 14.50.

3-Acetyl-8-acetoxy-2,6-dimethylchromone (XII). A mixture of 3 g. of 2,3-dihydroxy-5-methylacetophenone (VI), 7 g. of anhydrous sodium acetate, and 10 g. of acetic anhydride was refluxed for 8 hr. By pouring the reaction mixture in water the chromone derivative was isolated. On crystallizing from ethanol, 2 g. of white crystalline product was obtained, m.p. 114–115°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.15. Found: C, 65.42; H, 5.20.

8-Hydroxy-2,6-dimethylchromone (XIII). Compound XII (1.2 g.) was refluxed for 1 hr. with 12 ml. of 10% sodium carbonate. After cooling and filtering the solution was acidified with dilute hydrochloric acid and the separated solid was collected by filtration. The crude product on crystallizing from ethanol gave 0.9 g. of white crystalline solid, m.p. 260–261°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.30; H, 5.15.

Ultraviolet spectrum in ethanol 95°: λ_{max}: 240 and 321 mμ (inflection at 260 mμ).

2,3,6-Trimethyl-8-acetoxychromone (XIV). By the same procedure employed for compound XII, 4 g. of 2,3-dihydroxy-5-methylpropiophenone (VII), 9 g. of anhydrous sodium acetate and 13 g. of acetic anhydride gave 3.5 g. of 8-acetoxy-2,3,6-trimethylchromone as a white crystalline solid, m.p. 102–104°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.27; H, 5.74. Found: C, 68.18; H, 5.58.

2,3,6-Trimethyl-8-hydroxychromone (XV). Three grams of the acetoxy derivative (XIV), on boiling with an aqueous solution of 10% sodium carbonate for 2 hr., gave 2.1 g. of the corresponding 8-hydroxy derivative. Crystals from aqueous ethanol, m.p. 210–211°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.93. Found: C, 70.60; H, 6.08.

Ultraviolet spectrum in ethanol 95°: λ_{max}: 235 and 320 mμ (a small peak is observable at 255 mμ).

2,3-Dimethoxy-5-methylbenzoyl chloride (XVIII). Thirty-one grams of 2,3-dimethoxy-5-methylbenzoic acid[12] (XVII) and 130 ml. of thionyl chloride were refluxed for 2–3 hr. Removal of the excess thionyl chloride left an oil which solidified on cooling. On crystallizing the crude product from ligroin, 31 g. of light yellow crystalline product, m.p. 60–62°, was obtained.

Anal. Calcd. for $C_{10}H_{11}ClO_3$: C, 55.94; H, 5.16. Found: C, 55.65, 5.23.

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(12) J. H. Fletcher and D. S. Tarbell, *J. Am. Chem. Soc.*, **65**, 1431 (1943).

2,3-Dimethoxy-5-methylpropiophenone (XIX). To a solution of ethyl zinc iodide (prepared according to Mauthner[13] from 35 g. of copper-zinc couple, 73 g. of ethyl iodide, 36.5 g. of toluene, and 18.5 g. of ethyl acetate in presence of a few milligrams of iodine), cooled at 0°, a solution of 30 g. of 2,3-dimethoxy-5-methylbenzoyl chloride (XVIII) in 200 ml. of toluene was added dropwise with stirring. The reaction mixture was left to stand at room temperature for 2 hr., transferred in a separatory funnel, and vigorously shaken with water and with dilute hydrochloric acid. The aqueous layer was extracted twice with ether and the ethereal extracts were added to the toluene layer. After washing with sodium bicarbonate solution, with sodium thiosulfate solution and finally with water, the toluene layer was dried over anhydrous sodium sulfate. Removal of the solvent left an oil which was distilled in vacuum. The fraction boiling at 104–105°/0.2–0.3 mm. was collected. It weighed 20.5 g.

(13) J. Mauthner, *J. prakt. Chem.* (*2*), **103**, 393 (1922).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.18; H, 7.74. Found: C, 69.10; H, 7.70. This product gave the same dinitrophenylhydrazone of XI. A mixture melting point of these derivatives was not depressed.

2,3-Dihydroxy-5-methylpropiophenone. Seven grams of 2,3-dimethoxy-5-methylpropiophenone (XIX) and 21 g. of pyridinium chloride were refluxed for 30 min. By pouring the reaction mixture in water, the demethylated product was isolated. On crystallizing from ligroin, 3.1 g. of 2,3-dihydroxy derivative, m.p. 84–85°, was obtained.

A mixture melting point with a sample of VII was not depressed.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.40; H, 6.74.

Ultraviolet spectrum of 8-hydroxy-2,3-dimethylchromone in ethanol 95°: λ_{max} 235 and 310 mμ.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Fries Reaction of 2,4-Dichloro-5-methylphenyl Acetate[1]

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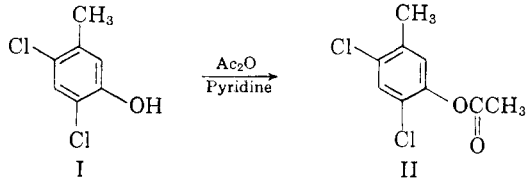
Treatment of 2,4-dichloro-5-methylphenyl acetate (II) with aluminum chloride at 135° gave 3,5-dichloro-2-hydroxy-6-methylacetophenone (III) as the major product and a small amount of 6,8-dichloro-2,5-dimethylchromone (IV). The structure of the former compound was substantiated by converting it to the hydrazone of 2-hydroxy-6-methylacetophenone which was synthesized by an independent method.

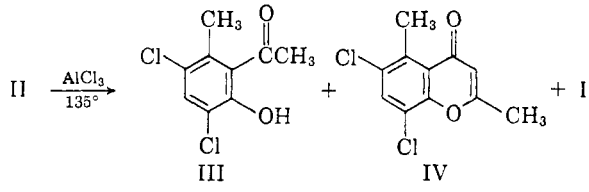
During the synthesis of 2-isoamyl-3,4-dimethylbenzofuran,[3] a degradation product of the antibiotic fumagillin,[4] 2 - hydroxy - 6 - methylacetophenone (XVIII) was considered as a possible starting material. The present paper describes a study of the Fries reaction on 2,4-dichloro-5-methylphenyl acetate (II), and shows that one of the products is 3,5-dichloro-2-hydroxy-6-methylacetophenone (III) by relating it to the hydrazone of 2-hydroxy-6-methylacetophenone, which has been prepared by an unambiguous method.

Acetylation of 2,4-dichloro-5-methylphenol (I) with acetic anhydride–pyridine gave a high yield of the acetate II.



I II

Treatment of the acetate II with aluminum chloride at 135° produced three compounds: the desired 3,5-dichloro-2-hydroxy-6-methylacetophenone (III), 6,8-dichloro-2,5-dimethylchromone (IV), and deacetylated material I.



III IV

The infrared spectrum of IV indicated the presence of a conjugated carbonyl function (1653 cm.$^{-1}$) consistent[5] with the chromone structure (as opposed to a coumarin structure). Moreover, the ultraviolet spectrum (see experimental) was similar to 2-hydroxymethylchromone and 2-methylchromone.[6]

When subjected to basic hydrolysis, IV was converted back to the acetophenone III; no 3,5-dichloro-2-hydroxy-6-methylbenzoic acid was formed—an observation which is characteristic of 5-substituted chromones.[7]

(1) Supported in part by Grant E-1138 of the U. S. Public Health Service.

(2) Abbott Laboratories Fellow, 1960–1961.

(3) D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman, and N. J. McCorkindale, *J. Am. Chem. Soc.*, 82, 1005 (1960).

(4) D. D. Chapman, S. E. Cremer, R. M. Carman, M. Kuntsmann, J. G. McNally, Jr., A. Rosowsky, and D. S. Tarbell, *J. Am. Chem. Soc.*, 82, 1009 (1960).

(5) M. S. Newman and S. Schiff, *J. Am. Chem. Soc.*, 81, 2266 (1959); Coumarins absorb in the 1754–1695 cm.$^{-1}$ region, whereas chromones absorb at 1667–1639 cm.$^{-1}$

(6) T. A. Geissman and J. W. Bolger, *J. Am. Chem. Soc.*, 73, 5875 (1951).

(7) R. C. Elderfield, *Heterocyclic Compounds*, Vol. 2, Wiley, New York, 1951, pp. 258–259.