[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. XIV. The Reaction of 4-Hydroxycoumarin with Aromatic Acid Chlorides[1]

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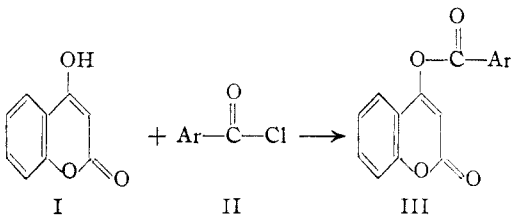
The reaction of 4-hydroxycoumarin (I) in pyridine with a variety of aromatic acid chlorides has been studied. The initial product formed was found to be the corresponding ester (III). None of the esters derived from benzoic acid derivatives were found to rearrange to the corresponding 3-acyl-4-hydroxycoumarin as in the aliphatic series[2]; however, the acetoxybenzoic acid esters of 4-hydroxycoumarin did rearrange to yield 3-acetyl-4-hydroxycoumarin (IX). The yield of IX was found to be enhanced by the presence of chloride ion. A mechanism for the formation of 3-acetyl-4-hydroxycoumarin has been proposed.

The reaction of 4-hydroxycoumarin (I) with aliphatic acid chlorides, together with the mechanism for this reaction was reported in the last paper of this series.[2] It would be supposed *a priori* that an analogous reaction would occur between 4-hydroxycoumarin and aromatic acid chlorides, but this was not the case.

As was found in the case of the aliphatic acid chlorides, the reaction of 4-hydroxycoumarin with aromatic acid chlorides (II) for 1 minute at 0° in pyridine, containing a catalytic amount of piperidine,[3] yielded the corresponding ester (III) in nearly quantitative yields. The esters, which were



I II III

recrystallized from ethanol or ethanol–water, except where indicated, are listed in Table I.

TABLE I

ESTERS OF 4-HYDROXYCOUMARIN

Ester R = coumarin	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Benzoyloxy-R	100	127–129	$C_{16}H_{10}O_4$	72.2	72.4	3.8	3.8
4-(*o*-Acetoxybenzoyloxy)-R	100	121–123	$C_{18}H_{12}O_6$	66.7	66.7	3.7	4.0
4-(*m*-Acetoxybenzoyloxy)-R	100	128–129	$C_{18}H_{12}O_6$	66.7	66.8	3.7	3.9
4-(*p*-Acetoxybenzoyloxy)-R	95	162–164	$C_{18}H_{12}O_6$	66.7	66.8	3.7	4.0
4-(*o*-Methoxybenzoyloxy)-R	97	121–123	$C_{17}H_{12}O_5$	69.0	68.9	4.1	4.3
4-(3,4-Diacetoxybenzoyloxy)-R	96	155–156	$C_{20}H_{14}O_8$	62.9	62.8	3.7	3.8
4-(3,4,5-Triacetoxybenzoyloxy)-R[a]	100	170–174	$C_{22}H_{16}O_{10}$	60.0	59.9	3.6	4.0
4-Phenylacetoxy-R[b]	98	156–158 (d)	$C_{17}H_{12}O_4$	72.8		4.3	
4-Cinnamoyloxy-R	100	156–158	$C_{18}H_{12}O_4$	74.0	74.2	4.1	4.3

[a] This compound could be recrystallized from ethanol only after it had been recrystallized several times from acetone–Skellysolve C. [b] Although this product could be purified to some extent by precipitating it out of benzene solution by the addition of ethanol, no solvent was suitable for recrystallizing it; as a result, it was never obtained analytically pure. The structure of this compound was inferred by the fact that it rearranged into its isomer, 3-phenylacetyl-4-hydroxycoumarin, as is indicated later. In addition, this compound decomposed slightly on standing.

Aliphatic acid chlorides have been shown to react with 4-hydroxycoumarin in pyridine at 37° for 48 hours to yield the corresponding 3-acyl-4-hydroxycoumarin.[2] However, the aromatic acid chlorides, except for phenylacetyl chloride, did not give rise to the analogous compounds. The acetoxy derivatives of benzoyl chloride which were studied did, however, yield 3-acetyl-4-hydroxycoumarin (IX). The proposed mechanism for this reaction is indicated below, using acetylsalicyl chloride (IV) as an example of the acetoxybenzoyl chloride.

It was proposed that 4-hydroxycoumarin reacted with the acetoxybenzoyl chloride to yield the corresponding ester (V). A nucleophilic attack of pyridine (B:) on the carbonyl carbon of the acetoxy group presumably gives rise to the intermediate VI. The 4-hydroxycoumarin anion (VIII) was then formed by cleavage of the aryloxy grouping through the electron shift indicated. Further reaction of VIII with the acetylpyridinium cation (VII), by the mechanism outlined in the last paper of this series,[2] would then yield 3-acetyl-4-hydroxycoumarin.

The formation of the ester V has already been mentioned. If this mechanism is correct, it would be supposed that V would, upon reaction under the same conditions, yield 3-acetyl-4-hydroxycoumarin (IX). This was found to be the case, although, as noted in Table II, the yields are somewhat lower than those obtained with the acid chloride and 4-hydroxycoumarin.

Comparing the two reaction mixtures, that of the acid chloride and 4-hydroxycoumarin, and that of the ester, it is noted that the only difference between the two is the presence of chloride ion in the former (arising from the acid chloride). Using a reaction mixture containing chloride ion, then, it

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(2) H. R. Eisenhauer and K. P. Link, THIS JOURNAL, **75**, 2044 (1953).

(3) See footnote in previous paper (reference 3).

TABLE II

YIELD OF 3-ACETYL-4-HYDROXYCOUMARIN (IX)

Acid chloride	% from acid chloride and 4-hydroxy coumarin 37°/ 48 hr.	100°/ 3 hr.	% from ester V 37°/ 48 hr.	100°/ 3 hr.	100°/ 3 hr. Cl^- present
o-Acetoxybenzoyl	24	34	10	35	33, 34[a]
m-Acetoxybenzoyl	0	0	..	..	..
p-Acetoxybenzoyl	0	21	..	10	21, 23[a]
3,4-Diacetoxybenzoyl	30	48	..	22	46
3,4,5-Triacetoxybenzoyl	30	42	..	38	41

[a] Lithium chloride was used as the source of chloride ion.

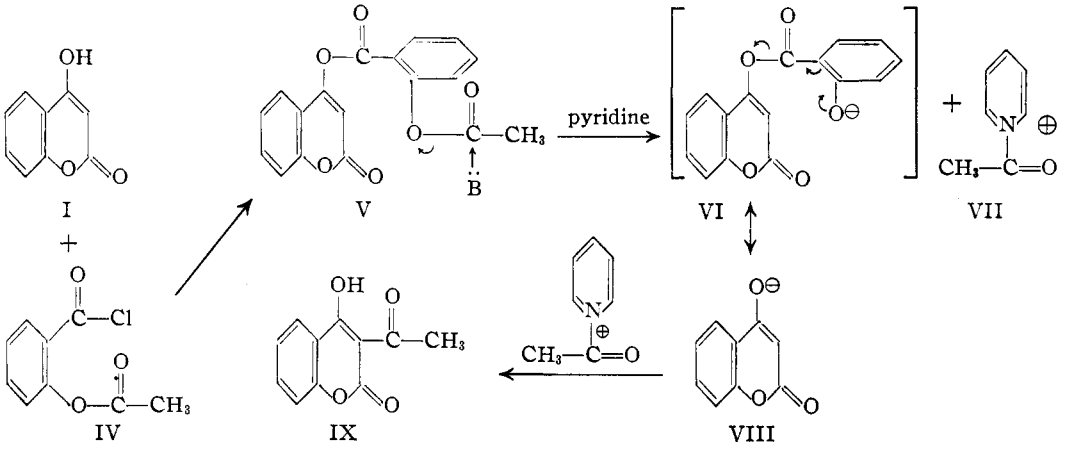
would be expected that the yield of 3-acetyl-4-hydroxycoumarin would be the same starting with the ester or with the acid chloride. To test this hypothesis, the above reactions were repeated with the esters using pyridine saturated with pyridinium hydrochloride. In all cases, it was found that, in the presence of chloride ion, the yield of 3-acetyl-4-hydroxycoumarin from the listed esters was essentially the same as that obtained from the acid chloride and 4-hydroxycoumarin under the same conditions (Table II, last column). The presence of chloride ion in the same manner increased the yield of IX from 10 to 24% with respect to 4-(*o*-acetoxybenzoyloxy)-coumarin (V) at 37° for 48 hours. This latter yield was the same as that obtained from the corresponding acid chloride and 4-hydroxycoumarin under the same conditions.

Since the difference in the yields of IX obtained in the case of the reaction between 3,4,5-triacetoxybenzoyl chloride and 4-hydroxycoumarin (and the rearrangement of the corresponding ester) at 100°/3 hours does not appear to be significant, it would be supposed that, here too, the *chloride effect* was not apparent at this higher temperature.

As is indicated in Table II, the yields of 3-acetyl-4-hydroxycoumarin are increased by a rise in the temperature in the reaction conditions.

As would be expected, no 3-acetyl-4-hydroxycoumarin was obtained from the reaction between *m*-acetoxybenzoyl chloride and 4-hydroxycoumarin because the electron shift indicated in species VI is not possible in the *m*-isomer.

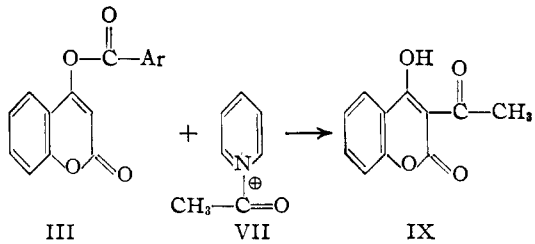
From the mechanism proposed, it would be supposed that the following reaction could occur. To test the validity of this assumption, acetyl chloride was treated with 4-benzoyloxycoumarin (IIIa, Ar = C_6H_5) at 37° for 48 hours in dry pyridine containing a catalytic amount of piperidine. There was in fact obtained a 7% yield of 3-acetyl-4-hydroxycoumarin (IX). It should be noted that, in a control experiment in which acetyl chloride was absent, 4-benzoyloxycoumarin was converted to 4-hydroxycoumarin in 11% yield. Since IX would arise only from this amount of 4-hydroxycoumarin by the mechanism previously indicated,[2] the yield of 3-acetyl-4-hydroxycoumarin with respect to the *available* 4-hydroxycoumarin was thus 62%. It is



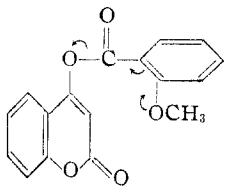
This effect was termed the *chloride effect*. In order to show that this effect was due to chloride ion alone, two of the experiments were repeated using lithium chloride as the source of chloride ion (Table II). The results which were obtained were essentially the same as those in which pyridinium hydrochloride was used as the source of chloride ion.

It is noted that, at 100°/3 hours, the yield of 3-acetyl-4-hydroxycoumarin from 4-(*o*-acetoxybenzoyloxy)-coumarin was, in effect, the same as that obtained from 4-hydroxycoumarin and acetylsalicyl chloride whether chloride ion was present or not. This was interpreted as being due to the fact that the yield of product indicated was the maximum that may be obtained from the reagents under these conditions. In this manner, it would appear that the *chloride effect* disappears at higher temperatures inasmuch as it has already been shown, as noted above, to be operative at 37°/48 hours.

interesting to note that this is approximately the same yield as was obtained in the reaction between 4-hydroxycoumarin and acetyl chloride under the same conditions.[2]

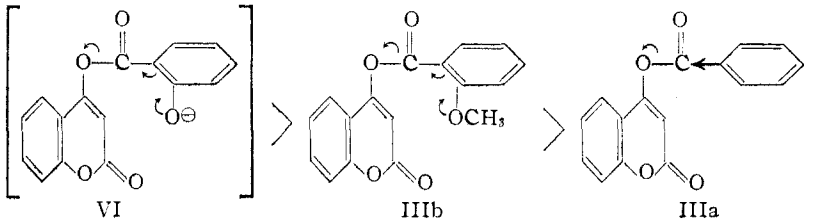


In order to more closely approximate the proposed intermediate VI, this same reaction was repeated using 4-(*o*-methoxybenzoyloxy)-coumarin (IIIb, Ar = *o*-methoxyphenyl). As expected, a somewhat higher yield of IX was realized (10%).



IIIb, Ar = *o*-methoxyphenyl

A control experiment indicated that, as before, there was a 62% yield of 3-acetyl-4-hydroxycoumarin with respect to the available 4-hydroxycoumarin (arising from the decomposition of the ester). It should be noted that the relatively low yield of IX with respect to the ester is in agreement with the magnitude of the electron shift effecting the cleavage of the ester. Thus the yield of IX from VI was 24%, from IIIb was 10% and from IIIa was 7%.



VI IIIb IIIa

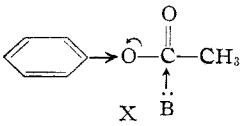
If, as is suggested by the mechanism, pyridine attacks the carbonyl of the acetoxy group in the appropriate 4-hydroxycoumarin ester to yield the acetylpyridinium cation, it should equally do this with other similar compounds containing an acetoxy group. If 4-hydroxycoumarin was present, 3-acetyl-4-hydroxycoumarin should also be formed. A summary of the results is indicated in Table III.

TABLE III

$$\text{Ar-OCOCH}_3 + \text{4-hydroxycoumarin} \xrightarrow{\text{pyridine}} \text{3-acetyl-4-hydroxycoumarin}$$

Ar-OCOCH$_3$	Conditions	Yield of IX, %
Phenyl acetate	37°/48 hr.	0
	100°/18 hr.	2.5
Acetylsalicylic acid	37°/48 hr.	9
Ethyl acetylsalicylate	37°/48 hr.	0
	37°/48 hr., HCl	0
	100°/6 hr.	10
Methyl *p*-acetoxybenzoate	100°/6 hr.	16
o-Nitrophenyl acetate	37°/48 hr.	0

The low yield of product using phenyl acetate (X), even under relatively drastic conditions, might be expected because the electron repulsion of the phenyl group would hinder the cleavage of the C–O bond in the acetoxy residue. However, with the other acetate esters listed in Table III, this effect

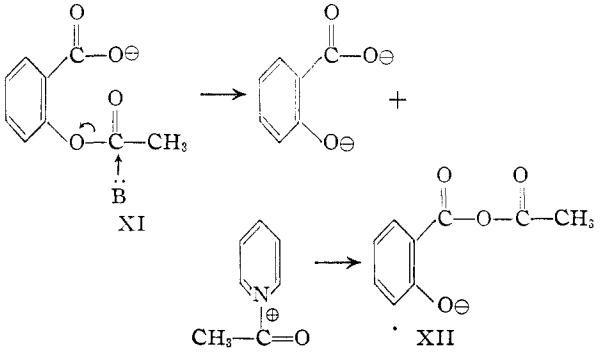


X B

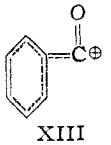
would be overshadowed by the electron-attracting groups in the *o*- or *p*-positions and, in fact, higher yields of 3-acetyl-4-hydroxycoumarin were realized. A control experiment using acetylsalicylic acid (XI) alone showed that it is nearly quantitatively converted into salicylic acid. The low yield of IX obtained was probably due to the competitive reaction between the preparation of IX and the formation of the mixed acid anhydride XII, formed between salicylic acid and acetic acid as indicated below. Although the anhydride XII was not isolated, it should be noted that mixed anhydrides may be formed by the addition of an acid to the pyridinium salt of a second acid chloride.[4]

It is to be noted that *o*-nitrophenyl acetate did not give rise to any 3-acetyl-4-hydroxycoumarin. It was assumed that this was due to the "Ortho Effect."[5] However, the proposed mechanism was supported by the fact that 3-acetyl-4-hydroxycoumarin was produced in most of the cases cited in Table III.

It had been noted previously that none of the expected 3-acyl-4-hydroxycoumarins were obtained from the corresponding aromatic acid chlorides as was indicated in the aliphatic series.[6] It is suggested that this was due to the fact that the positive charge on the carbonyl carbon of the aromatic carbonium ion (XIII), when formed, was distributed about the benzene ring by resonance stabilization. Since the positive charge was delocalized from this position, this species was unable to react with the carbanion of 4-hydroxycoumarin as in the aliphatic series.[2] To test this hypothesis, it was shown that phenylacetyl chloride reacted with 4-hydroxycoumarin in pyridine and piperidine to yield 3-phenylacetyl-4-hydroxycoumarin. The corresponding ester, 4-phenylacetoxycoumarin, also rearranged under the same conditions to give this compound. It is significant that delocalization of charge in the phenylacetylcarbonium ion is not possible.



XI XII



XIII

(4) H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949).

(5) L. P. Hammett, "Physical Organic Chemistry," First Edition, McGraw-Hill Book Co., Inc., 1940, p. 204. It was shown that the rate of hydrolysis of substituted benzoic acid esters was much less for the *o*-isomers than for the *m*- or *p*-isomers. This effect was particularly evident in the nitrosubstituted benzoates.

(6) T. Ukita, S. Nojima and M. Matsumoto, THIS JOURNAL, **72**, 5143 (1950).

However, the vinylog of benzoyl chloride, cinnamoyl chloride, did not give rise to 3-cinnamoyl-4-hydroxycoumarin. This would be expected, for again resonance stabilization, and hence delocalization of charge, is possible, thus supporting this hypothesis. The only base-soluble compound isolated from the reaction mixture was β-truxinic acid.

Experimental

Preparation of the Acetates.—Commercial acetylsalicylic acid was used. The remainder of the acetates were prepared by the Chattaway procedure.[7] The yields are indicated in Table IV.

Preparation of the Acid Chlorides.—Commercial benzoyl chloride was used. Most of the other acid chlorides were prepared by the action of a slight excess of phosphorus pentachloride on the acid. After heating the reaction mixture on a steam-bath for 10 minutes, the acid chloride was distilled under reduced pressure (if a liquid) or shaken with dry Skellysolve B, filtered and recrystallized (if a solid). The results are indicated in Table IV.

TABLE IV

ACETATES AND ACID CHLORIDES

Acid	Yield of acetate, %	M.p., °C.	Yield of acid chloride, %	M.p., °C.	B.p., °C.	Mm.
o-Hydroxybenzoic	..	.....	82		100	1
m-Hydroxybenzoic	73	129–131	88		153–155	30
p-Hydroxybenzoic	98	86–88	75		110	0.3
o-Methoxybenzoic	..	.....	84[a]		132–134	20
3,4-Dihydroxybenzoic	92	157–159	35[b]	46–50		
3,4,5-Trihydroxybenzoic	64	172–173	96[c]	98–104		
Phenylacetic	..	.....	64		115–120	20
Cinnamic	..	.....	77		150–155	20

[a] From thionyl chloride. [b] Recrystallized from benzene–Skellysolve A. [c] Recrystallized from xylene.

Preparation of the 4-Hydroxycoumarin Esters.—To 4-hydroxycoumarin (1.0 g.) in dry pyridine (8 ml.) containing piperidine (1 drop) at 0° was slowly added 1.5 equivalents of the acid chloride. One minute after complete addition, the reaction mixture was poured into ice and dilute hydrochloric acid. The precipitate was filtered and washed with water. After shaking the product with 5% sodium bicarbonate solution, it was again filtered, washed and dried. The yield and melting point of the various esters are indicated in Table I.

3-Acetyl-4-Hydroxycoumarin (IX). (a) From 4-Hydroxycoumarin and the Acetylated Hydroxybenzoyl Chlorides.—4-Hydroxycoumarin (1.0 g.) in dry pyridine (8 ml.) containing piperidine (1 drop) reacted with 1.5 equivalents of the acetylated hydroxybenzoic acid chloride for 48 hours at 37° or for 3 hours at 100°. The reaction mixture was then poured into ice and dilute hydrochloric acid. The resulting precipitate was filtered, washed with water and then shaken with 5% sodium hydroxide solution. The extract was acidified with hydrochloric acid and the resulting precipitate, after being filtered and washed with water, was steam distilled to yield 3-acetyl-4-hydroxycoumarin. The yields from the various acetylated hydroxybenzoyl chlorides are indicated in Table II. It should be noted that these are corrected by a factor of the solubility of 3-acetyl-4-hydroxycoumarin in water (37 mg./liter of distillate). The product after steam distillation was essentially pure without recrystallization. The melting point was 133–135°. A mixed melting point with an authentic sample of 3-acetyl-4-hydroxycoumarin was not depressed.

(b) **From the 4-(Acetoxybenzoyloxy)-coumarins (V).**—The procedure followed was the same as that indicated in (a) above. The yields are summarized in Table II. In the trials in which chloride ion was present, the pyridine which was used had previously been saturated with pyridinium hydrochloride by passing dry hydrogen chloride into pyridine until solid pyridinium hydrochloride precipitated. When the source of chloride ion was lithium chloride, the pyridinium hydrochloride was replaced by 1.5 molar equivalents of anhydrous lithium chloride.

(c) **From 4-Benzoyloxycoumarin (IIIa) or 4-(*o*-Methoxybenzoyloxy)-coumarin (IIIb) and Acetyl Chloride.**—4-Benzoyloxycoumarin (1.7 g.) or 4-(*o*-methoxybenzoyloxy)-coumarin (2.0 g.) reacted with acetyl chloride (0.7 ml.) in dry pyridine (8 ml.) containing piperidine (1 drop) in the manner indicated in (a) above. The yield of 3-acetyl-4-hydroxycoumarin from 4-benzoyloxycoumarin was 90 mg. (7%) and from 4-(*o*-methoxybenzoyloxy)-coumarin was 120 mg. (10%). Control experiments, in which acetyl chloride was absent, indicated that 110 mg. and 150 mg. of 4-hydroxycoumarin was formed from each of the esters, respectively. This indicated that the yield of 3-acetyl-4-hydroxycoumarin, with respect to the available 4-hydroxycoumarin was 62% in each case.

(d) **From Substituted Phenyl Acetates.**—Commercial acetylsalicylic acid was used. Phenyl acetate and ethyl acetylsalicylate were on hand in this Laboratory. Methyl *p*-acetoxybenzoate was prepared in 86% yield by the Chattaway procedure.[7] The melting point on recrystallization from ethanol was 70–72°. There was obtained an 87% yield of *o*-nitrophenyl acetate from *o*-nitrophenol by a method outlined by Galatis.[8] This material, on recrystallization from benzene–Skellysolve B, melted at 39–40°. A mixed melting point with *o*-nitrophenol (m.p. 45°) was depressed.

4-Hydroxycoumarin (1.0 g.) was treated with 1.5 equivalents of the various phenyl acetates in dry pyridine (8 ml.) containing piperidine (1 drop) under the conditions indicated in Table III. The various yields of 3-acetyl-4-hydroxycoumarin obtained on steam distillation, as in (a) above, are summarized in Table III.

3-Phenylacetyl-4-hydroxycoumarin.—(a) 4-Hydroxycoumarin (2.0 g.) in dry pyridine (16 ml.) containing piperidine (2 drops) was treated with phenylacetyl chloride (2.8 g.) for 3 hours at 100°. The reaction mixture was poured into ice and dilute hydrochloric acid. The resulting precipitate was filtered, washed with water and shaken with 5% sodium hydroxide solution. The precipitate obtained by acidification of the extract was filtered, washed with water and then added to boiling water (100 ml.). The product, which remained undissolved, was recrystallized from ethanol–water, m.p. 120–121°. The yield of 3-phenylacetyl-4-hydroxycoumarin was 0.5 g. (14%).

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.8; H, 4.3. Found: C, 72.6; H, 4.6.

(b) 4-Phenylacetoxycoumarin (2.7 g.) was dissolved in pyridine (8 ml.) containing piperidine (1 drop) and heated at 100° for 3 hours. The yield of 3-phenylacetyl-4-hydroxycoumarin, isolated as indicated in (a) above, was 0.15 g. (6%).

Acknowledgment.—We are indebted to our colleague, Mr. Collin H. Schroeder, for all the carbon and hydrogen analyses. We also wish to express our gratitude to Professors S. M. McElvain and A. L. Wilds of the Chemistry Department of this University for helpful advice and suggestions.

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(7) F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931).

(8) L. C. Galatis, THIS JOURNAL, **69**, 2062 (1947).