Grignard reagent and the reaction was completed as before. The product was recrystallized from benzene–petroleum ether (40–60°) as colorless crystals, m.p. 177°, yield 1.8 g. It gave a blue-violet color with concentrated sulfuric acid.

Anal. Calcd. for $C_{24}H_{17}NO$: C, 85.9; H, 5.1; N, 4.2. Found: C, 86.3; H, 5.3; N, 4.0.

Hydrolysis of Vc. The compound (0.5 g.) in 50 cc. of ethyl alcohol was hydrolyzed with 8 cc. of concentrated hydrochloric acid as before. The product was precipitated by the addition of water and recrystallized from petroleum ether (80–100°) as colorless crystals, m.p. 168°, yield 0.4 g. It gave a purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.2; H, 5.1.

Action of α-naphthylmagnesium bromide on VIc. Magnesium (0.3 g.) and α-bromonaphthalene (2 g.) were used in the preparation of α-naphthylmagnesium bromide as before. A solution of 1 g. of VIc in 30 cc. of dry benzene was added and the reaction was completed as before. The product was recrystallized from benzene as colorless crystals, m.p. 261°, yield 0.8 g. It gave a brown color with concentrated sulfuric acid.

The melting point was not depressed on admixture with an authentic sample prepared as in Ref. 4.

Anal. Calcd. for $C_{34}H_{24}O_2$: C, 87.9; H, 5.2. Found: C, 88.4; H, 5.5.

Benzoylation of Vc. Vc (0.5 g.), pyridine (10 cc.), and benzoyl chloride (8 cc.) were heated on the water bath for 2 hr., then poured into 60 cc. of dilute hydrochloric acid. The product was treated as in the case of benzoylation of Va.

The oily product was triturated with petroleum ether (40–60°), cooled in ice to solidify, and filtered from the oily part. It was recrystallized from benzene–petroleum ether (40–60°) in colorless crystals, m.p. 241°, yield 0.3 g. It gave an emerald-green color with concentrated sulfuric acid.

Anal. Calcd. (for monobenzoyl) $C_{31}H_{21}NO_2$: C, 86.7; H, 4.8; N, 3.2; (for dibenzoyl) $C_{38}H_{25}NO_3$: C, 84.0; H, 4.6; N, 2.6. Found: C, 84.2; H, 4.7; N, 2.6.

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ABBASSIA, CAIRO, EGYPT

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

Substitution in the Benzopyrone Series. IV. Sulfonation of Coumarin Derivatives

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The sulfonation of 7-hydroxy-3,4-dimethylcoumarin, its methyl ether, 7-hydroxy-4-methyl-6-ethylcoumarin, its methyl ether, 7-hydroxy-3,4-dimethyl-6-ethylcoumarin and its methyl ether, with chlorosulfonic acid is described. The structures of the sulfonated products have been established, by oxidation, bromination, or nitration to give known compounds.

The present work was undertaken with a view to studying the reactivity of some substituted 7-hydroxycoumarins and their methyl ethers upon sulfonation.[1]

The products of sulfonation were characterized as described previously[2] by their conversion to crystalline derivatives. Table I describes the experimental conditions and the results obtained on the sulfonation of different coumarin derivatives with chlorosulfonic acid. From the results of the sulfonation, it is observed that in 7-hydroxycoumarins, the *6* position is the most reactive, positions *3* and *8* being next in order of reactivity. It is also interesting to note that the *8* position is not favorable for the formation of sulfonyl chlorides. In the case of 7-methoxycoumarins also, the order of reactivity is $6 > 3$. The substitution in the *8* position is always accompanied by demethylation.

It was observed that the sulfonation of 7-hydroxy-3,4-dimethylcoumarin at 100° or at lower temperatures gave monosulfonated products I and II, while the disulfonic acid III was obtained with excess of chlorosulfonic acid at higher temperatures. Experiments to prove the constitution of I by the hydrolysis, nitration, and methylation of its sodium salt failed to give definite products. Since the sulfonic acid I could be easily obtained by the hydrolysis of the sulfonyl chloride II, attempts were made to establish the structure of the latter. It is known[3] that halogenation and nitration of sulfonyl chlorides can be effected without modifying the sulfonyl chloride group. Consequently, the bromination of II was carried out and a bromo sulfonyl chloride was obtained. The chlorosulfonation of the known[4] 7-hydroxy-6-bromo-3,4-dimethylcoumarin was attempted under a variety of conditions; however, the product, in all cases, was a sulfonic acid (IV). This bromosulfonic acid was different from that obtained by hydrolysis of the bromo sulfonyl chloride and was assigned the structure, 7-hydroxy-6-bromo-3,4-dimethylcoumarin-8-sulfonic acid. The position of the sulfonyl chloride group in II, however, was determined by demethylation of

(1) C. M. Suter, *Organic Chemistry of Sulfur*, John Wiley and Sons, Inc., New York, 1948, p. 316.

(2) D. V. Joshi, J. R. Merchant, and R. C. Shah, *J. Org. Chem.*, 21, 1104 (1956); J. R. Merchant and R. C. Shah, *J. Ind. Chem. Soc.*, **34**, 35 (1957).

(3) Reference 1, p. 512.

(4) D. Chakravarty and S. M. Mukherjee, *J. Ind. Chem. Soc.*, **14**, 729 (1937).

TABLE I

SULFONATION OF 7-HYDROXYCOUMARINS

Substance	Ref.[a]	Moles of Chlorosulfonic Acid	Temp., °C.	Time of Heating, Hr.		Products
7-Hydroxy-3,4-dimethylcoumarin	9	4.3	80	3	(I)	6-Sulfonic acid and
					(II)	6-sulfonyl chloride
		8.6	130–140	6	(III)	6,8-Disulfonic acid
7-Hydroxy-6-bromo-3,4-dimethylcoumarin	4	Excess	100	2	(IV)	8-Sulfonic acid
7-Methoxy-3,4-dimethylcoumarin	10	4.5	100	2	(V)	6-Sulfonic acid and
					(VI)	6-sulfonyl chloride
		Excess	130–140	4	(III)	(Complete demethylation)
7-Hydroxy-4-methyl-6-ethylcoumarin	11	2	100	2	(VII)	8-Sulfonic acid
		Excess	130–140	6	(VIII)	3,8-Disulfonic acid
7-Methoxy-4-methyl-6-ethylcoumarin	11	4	100	2	(IX)	3-Sulfonic acid and
					(X)	3-sulfonyl chloride
		Excess	130–140		(VIII)	(Complete demethylation)
7-Hydroxy-3,4-dimethyl-6-ethylcoumarin	12	Excess	100 and above	2	(XI)	8-Sulfonic acid
					(XII)	8-Sulfonyl chloride
7-Methoxy-3,4-dimethyl-6-ethylcoumarin	13	Small excess	60	2	(XI)	(Complete demethylation)

[a] The numbers in this column indicate references for methods of preparation.

7-methoxy-3,4-dimethylcoumarin-6-sulfonyl chloride (V) with anhydrous aluminum chloride. The product of this reaction was identical to II.

The sulfonation of 7-hydroxy-3,4-dimethylcoumarin with excess of chlorosulfonic acid at 140° gave only the disulfonic acid. No disulfonyl chloride could be obtained even under different experimental conditions. 3,5-Dinitroresacetophenone was obtained when III was treated with nitric acid in acetic acid at 100°. The breaking up of the coumarin ring has also been observed by Naik and Jadhav[5] during the nitration of 7-hydroxy-3,4-dimethylcoumarin. The structure of the disulfonic acid III was proved by the bromination of its sodium salt which afforded 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin. The latter substance had been synthesized in our laboratory by the Pechmann condensation of 2,4-dibromoresorcinol with ethyl α-methylacetoacetate.

The sulfonation of 7-methoxy-3,4-dimethylcoumarin, at 100° or at lower temperatures, gave monosulfonated products V and VI. Attempts to prove the structures of V by nitration or hydrolysis failed to give definite results. Bromination of its sodium salt, however, gave a bromo compound free from sulfur which melted at 208–210°. The latter was not known, and attempts to prove its constitution by hydrolysis were unsuccessful. The position of the sulfonic acid group in V was established by the oxidation of its sodium salt with alkaline potassium permanganate. The product of this oxidation was 2-methoxy-4-hydroxy-benzenesulfonic acid, which did not give any coloration with alcoholic ferric chloride, but was easily converted to the known 2,4-dimethoxy-benzenesulfonic acid[6] by methylation. As a point of interest, the sulfonation of resorcinol mono methyl ether was carried out, affording a mono sulfonic acid different from the above. The product gives a violet coloration with alcoholic ferric chloride solution. It was therefore assigned the constitution 2-hydroxy-4-methoxy-benzenesulfonic acid.

At higher temperatures, and with excess of chlorosulfonic acid or with fuming sulfuric acid, 7-methoxy-3,4-dimethylcoumarin gave a disulfonic acid in which the methoxyl group was completely demethylated (III). The product gave a positive ferric chloride test and was converted to 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin by bromination of its disodium salt.

The sulfonation of 7-hydroxy-4-methyl-6-ethylcoumarin required controlled experimental conditions. Only mono- (VII) and di- (VIII) sulfonic acids were obtained. No sulfonyl chlorides, however, could be prepared.

The sulfonic acid (VII) gave a blue coloration with alcoholic ferric chloride solution. This color test indicated[7] that the sulfonic acid group in (VII) was in the position *ortho* to the hydroxyl group; that is, the sulfonation had taken place in the *8* position. The constitution of (VIII) was determined by bromination in acetic acid medium which afforded 7-hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin. The structure of the latter was confirmed by its conversion by alkaline hydrolysis, to a bromo coumarilic acid (A).

The sulfonation of 7-methoxy-4-methyl-6-ethylcoumarin at 100°, led to the formation of monosulfonated products (IX) and (X). At higher tempera-

(5) A. R. Naik and G. V. Jadhav, *J. Ind. Chem. Soc.*, 26, 245 (1945).

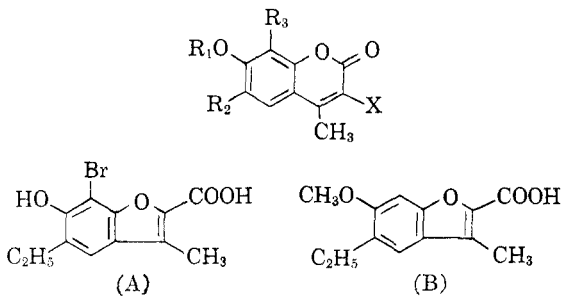
(6) C. M. Suter and H. L. Hansen, *J. Am. Chem. Soc.*, 55, 2080 (1933).

(7) S. Soloway and S. H. Wilen, *Anal. Chem.*, 24, 979 (1952).

tures, complete demethylation occurred as shown by the fact that the disulfonic acid formed gave upon bromination 7-hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin. The structure of (IX) was established by its conversion, by bromination to 7-methoxy-3-bromo-4-methyl-6-ethylcoumarin. The structure of the latter was determined by its conversion to the related coumarilic acid (B).

Only monosulfonated products (XI) and (XII) were obtained by the sulfonation of 7-hydroxy-3,4-dimethyl-6-ethylcoumarin. The sulfonic acid (XI) gave an intense coloration with alcoholic ferric chloride solution showing that the sulfonic acid group in (XI) had entered the *8* position. The bromination of (XI) gave 7-hydroxy-8-bromo-3,4-dimethyl-6-ethylcoumarin, the structure of the latter being confirmed by the fact that it was recovered unchanged on boiling with sodium carbonate.

The sulfonation of 7-methoxy-3,4-dimethyl-6-ethylcoumarin was accompanied by complete demethylation, and the corresponding hydroxy coumarin sulfonic acid XI was obtained.



(A) (B)

$R_1 = R_3 = H$; $X = CH_3$; $R_2 = HSO_3$, SO_2Cl (I and II)
$R_1 = R_3 = H$; $X = CH_3$; $R_2 = R_3 = HSO_3$ (III)
$R_1 = H$; $X = CH_3$; $R_2 = Br$; $R_3 = HSO_3$ (IV)
$R_1 = OCH_3$; $R_3 = H$; $X = CH_3$; $R_2 = HSO_3$, SO_2Cl (V and VI)
$R_1 = X = H$; $R_2 = C_2H_5$; $R_3 = HSO_3$ (VII)
$R_1 = H$; $R_2 = C_2H_5$; R_3, $X = HSO_3$ (VIII)
$R_1 = OCH_3$; $R_2 = C_2H_5$; $R_3 = H$; $X = HSO_3$, SO_2Cl (IX and X)
$R_1 = H$; $R_2 = C_2H_5$; $X = CH_3$; $R_3 = HSO_3$, SO_2Cl (XI and XII)

EXPERIMENTAL

All melting points are corrected and were taken in a sulfuric acid bath. Freshly distilled chlorosulfonic acid was used for sulfonation.

General method for sulfonation. The general method is the same as that described in Part II of this series.[2]

7-Hydroxy-8-bromo-3,4-dimethylcoumarin-6-sulfonyl chloride ($R_1 = H$; $X = CH_3$; $R_2 = SO_2Cl$; $R_3 = Br$). To a solution of 500 mg. of the sulfonyl chloride (II) in 5 ml. of hot acetic acid, was added gradually with shaking, 5 ml. of a 10% solution of bromine in acetic acid. The mixture was heated on a water bath for 40 min. and kept overnight. The product which separated was filtered and crystallized from acetic acid, m.p. 195–196°.

Anal. Calcd. for $C_{11}H_8BrClO_5S$: S, 8.7. Found: S, 8.5.

Demethylation of 7-methoxy-3,4-dimethylcoumarin-6-sulfonyl chloride (VI). Three grams of the sulfonyl chloride was intimately mixed with 12 g. of powdered anhydrous aluminum chloride and the contents (protected from moisture) were heated at 165–170° for 4 hr. The mixture was cooled and ice and hydrochloric acid were added. The pasty residue, after repeated crystallizations from benzene, had a m.p. 193–195° (dec.). Its mixed melting point with the 7-hydroxy-3,4-dimethylcoumarin-6-sulfonyl chloride (II), obtained by direct sulfonation, showed no lowering.

Nitration of 7-hydroxy-3,4-dimethylcoumarin-6,8-disulfonic acid (III). To a solution of 500 mg. of the sulfonic acid obtained by decomposition of its barium salt, in 5 ml. of glacial acetic acid, was added dropwise 2 ml. of nitric acid (*d* 1.42). The mixture was heated on the water bath for 1.5 hr. and poured over ice. The yellow precipitate was crystallized from alcohol, m.p. 167–168°. Its mixed melting point with an authentic sample of 3,5-dinitroresacetophenone[5] showed no lowering.

Bromination of sodium 7-hydroxy-3,4-dimethylcoumarin-6,8-disulfonate (III). To a suspension of 2 g. of the sodium salt in 8 ml. of acetic acid, was added 8 ml. of a 25% solution of bromine in acetic acid, and the mixture heated at 100° for 1 hr. The mixture, on dilution, gave a precipitate which was crystallized from acetic acid as white needles melting at 238°.

Anal. Calcd. for $C_{11}H_8Br_2O_5$: Br, 46.0. Found: Br, 45.7.

Its mixed melting point with 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin prepared by Pechmann condensation of 2,4-dibromoresorcinol with ethyl α-methylacetoacetate showed no lowering.

Oxidation of sodium 7-methoxy-3,4-dimethylcoumarin-6-sulfonate (V). To a solution of 3 g. of the salt in 50 ml. of 2*N* potassium hydroxide solution was added dropwise, with stirring and cooling, 100 ml. of a 4% solution of potassium permanganate. The mixture was heated on a water bath for an hour and filtered. The filtrate was concentrated and acidified with concentrated hydrochloric acid. When the mixture was cooled, a potassium salt separated which gave a crystalline derivative with benzylisothiourea hydrochloride, which melted at 226–228°. It did not give any coloration with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{15}H_{18}N_2O_5S_2$: N, 7.6. Found: N, 7.2.

Methylation of the above oxidation product. One gram of potassium salt was dissolved in 6 ml. of a 10% potassium hydroxide solution and 1 ml. of dimethyl sulfate was added. The mixture was heated on a water bath for 2 hr. When the mixture was acidified, a precipitate was obtained which gave an *S*-benzylisothiouronium derivative (crystallized from dilute alcohol) melting at 183–185°.

Anal. Calcd. for $C_{16}H_{20}N_2O_5S_2$: N, 7.3. Found: N, 7.2.

The *p*-toluidine salt of the methylated product was crystallized from a mixture of alcohol and chloroform, m.p. 197°.

Anal. Calcd. for $C_{15}H_{19}NO_5S$: N, 4.3. Found: N, 4.2.

The mixed melting points of the *S*-benzylisothiouronium derivative and the *p*-toluidine salt with those of resorcinol dimethyl ether-4-sulfonic acid[6] showed no lowering.

Sulfonation of resorcinol monomethyl ether.[8] A mixture of 2.5 ml. of concentrated sulfuric acid and 5 g. of resorcinol monomethyl ether were heated at 90–100° for 30–40 min. The mixture was poured into saturated brine solution and the sodium salt separated. The derivative with benzylisothiourea hydrochloride was crystallized from dilute alcohol, m.p. 127°. It gave a violet coloration with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{15}H_{18}N_2O_5S_2$: N, 7.6. Found: N, 7.8.

7-Hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin ($R_1 = H$; $X = R_3 = Br$; $R_2 = C_2H_5$). 7-Hydroxy-4-methyl-6-ethylcoumarin-3,8-disulfonic acid (VIII) was obtained by decomposition of the barium salt and had m.p. 185°. To a solution of 400 mg. of the acid in 2 ml. of acetic acid was added 5.3 ml. of a 10% solution of bromine in acetic acid, and the mixture was boiled for 30 min. The crystals which separated on cooling were crystallized in needles of m.p. 213–215°. The same product was also obtained by direct bromination of 7-hydroxy-6-ethyl-4-methylcoumarin.

Anal. Calcd. for $C_{12}H_{10}Br_2O_5$: Br, 44.2. Found: Br, 44.3.

(8) B. B. Dey, *J. Ind. Chem. Soc.*, 12, 685 (1935).

TABLE II

DERIVATIVES OF SULFONIC ACIDS AND SULFONYL CHLORIDES

Sulfonation Product	M.P., °C.	Barium Salt or Sulfonyl Chloride	Analysis Barium Halogen Calcd.	Found	S-Benzylisothiouronium Derivative	Anilide	M.P., °C.	Analysis Nitrogen % Calcd.	Found
I	—	$C_{22}H_{18}BaO_{12}S_2$	20.3	20.2	$C_{19}H_{20}N_2O_6S_2$	—	222–224	6.4	6.4
II	193–195 (dec.)	$C_{11}H_9ClO_5S$	12.3	11.9	—	$C_{17}H_{15}NO_5S$	198–200	4.1	4.3
III	—	$C_{11}H_8BaO_9S_2$	28.3	27.8	—	—	—	—	—
IV	—	—	—	—	$C_{19}H_{19}BrN_2O_6S_2$	—	191–192	5.4	5.4
V[a]	—	$C_{24}H_{22}BaO_{12}S_2$	19.5	19.5	$C_{20}H_{22}N_2O_6S_2$	—	266	6.2	6.5
VI	200–202	$C_{12}H_{11}ClO_5S$	11.7	11.6	—	$C_{18}H_{17}NO_5S$	241–243	3.9	4.1
VII	—	$C_{24}H_{22}BaO_{12}S_2$	19.5	19.0	$C_{20}H_{22}N_2O_6S_2$	—	159–161	6.2	6.4
VIII	—	$C_{12}H_{10}BaO_9S_2$	27.5	27.3	$C_{28}H_{32}N_4O_9S_4$	—	230–232	8.0	8.4
IX	—	$C_{26}H_{26}BaO_{12}S_2$	18.8	18.1	$C_{21}H_{24}N_2O_6S_2$	—	178	6.0	6.2
X	196–197 (dec.)	$C_{13}H_{13}ClO_5S$	11.2	11.0	—	$C_{19}H_{19}NO_5S$	197	3.7	3.9
XI	—	$C_{26}H_{26}BaO_{12}S_2$	18.8	18.2	$C_{21}H_{24}N_2O_6S_2$	—	198–200	6.0	6.4
XII[b]	135–137	$C_{13}H_{13}ClO_5S$	11.2	10.6	—	$C_{19}H_{19}NO_5S$	260	3.7	3.3

[a] The free sulfonic acid crystallized from concentrated hydrochloric acid and had m.p. 186° (dec.) (Found: S, 11.6. $C_{12}H_{12}O_6S$ requires: S, 11.3%). [b] The free sulfonic acid crystallized from dilute hydrochloric acid and had m.p. 170–172° (Found: S, 10.1. $C_{13}H_{14}O_6S$ requires: S, 10.7%).

6-Hydroxy-7-bromo-5-ethyl-3-methylcoumarilic acid (A). Four hundred milligrams of the above dibromo coumarin was refluxed with 20 ml. of 1*N* potassium hydroxide solution for 2 hr. The filtrate, on acidification, deposited a violet substance which crystallized from dilute acetic acid, m.p. 186–188° (dec.). It dissolved in sodium bicarbonate readily.

Anal. Calcd. for $C_{12}H_{11}BrO_4$: Br, 26.7. Found: Br, 25.9.

7-Hydroxy-8-bromo-4-methyl-6-ethylcoumarin (R_1 = X = CH_3; R_2 = C_2H_5; R_3 = H). One gram of sodium 7-methoxy-4-methyl-6-ethylcoumarin-3-sulfonate (IX) was suspended in 5 ml. of acetic acid and a solution of bromine in acetic acid (2 equivalents) was added. The mixture was heated on a water bath for 15 min., filtered, and cooled. The crystals which separated were recrystallized from acetic acid affording white needles melting at 171–173°. The same compound was also obtained by the direct bromination of 7-methoxy-4-methyl-6-ethylcoumarin.

Anal. Calcd. for $C_{13}H_{13}BrO_3$: Br, 26.9. Found: Br, 26.7.

6-Methoxy-5-ethyl-3-methylcoumarilic acid. Five hundred milligrams of the above bromo compound was boiled with 20 ml. of 1*N* potassium hydroxide for 5 hr. The substance, which separated on acidification, was crystallized from acetic acid as needles of m.p. 220° (dec.). It gave a violet coloration with concentrated sulfuric acid.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.4. Found: C, 66.9; H, 6.8.

7-Hydroxy-3,4-dimethyl-8-bromo-6-ethylcoumarin (R_1 = H; X = CH_3; R_3 = Br; R_2 = C_2H_5). One gram of the sulfonic acid (XI) was suspended in 6 ml. of acetic acid and 6 ml. of a 10% solution of bromine in acetic acid was added. After heating the mixture at 100° the crystals which separated were recrystallized and the product was obtained as white needles of m.p. 226–228°.

Anal. Calcd. for $C_{13}H_{13}BrO_3$: Br, 26.9. Found: Br, 27.4.

The same compound was also obtained by bromination of 7-hydroxy-3,4-dimethyl-6-ethylcoumarin.

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