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

Substitution in the Benzopyrone Series. I. Sulfonation of Some Chromone, Flavone, and Isoflavone Derivatives

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The sulfonation of 2,3-dimethylchromone gave the 6-sulfonyl chloride and 6-sulfonic acid. The structures of both were proven by oxidation to 5-sulfosalicylic acid. 7-Hydroxy-2-methylchromone and 7-hydroxyflavone gave the 8- and 6,8-disulfonic acids, the structures of both monsulfonic acids being proved by nitration to known nitro compounds. The structures of the disulfonic acids in both the cases were proven by alkaline hydrolysis to sulfonic acids of resacetophenone, which on bromination yielded the known bromo compounds. The flavone also gave the 6,8,2′-trisulfonic acid, the structure of which was proven by alkaline hydrolysis, when *o*-sulfobenzoic acid was obtained. 7-Methoxy-2-methylchromone gave only the 8-sulfonic acid which was nitrated to the corresponding 8-nitro compound.

7-Hydroxy-2-methyl- and 7-hydroxy-2-phenyl-iso-flavone were sulfonated first in the 8-, and then in 6,8-positions giving also the corresponding disulfonyl chlorides. Both the mono- and the di-sulfonic acids were hydrolyzed to the sulfonic acids of 2,4-dihydroxyphenyl benzyl ketone, the structures of which were determined by bromination to the known bromo derivatives. 5-Hydroxy-2-methylchromone and 5-hydroxyflavone gave 8- and 6,8-disubstituted acids, as was shown by their nitration to the known nitro compounds. Hydrolysis of the chromone disulfonic acid gave resorcinol 4,6-disulfonic acid. 5-Hydroxyflavone also gave the 6,8,2′-trisulfonic acid which was hydrolyzed to give *o*-sulfobenzoic acid. 5-Methoxy-2-methylchromone gave only the 8-sulfonic acid which was nitrated to the known nitro compound.

In continuation of the work carried on in our laboratory regarding the substitution reactions of benzopyrones, the sulfonation of a number of chromone, flavone, and isoflavone derivatives has been investigated. A perusal of literature[1,2] shows that very little and no systematic work has been done on the subject.

The sulfonation was carried out with chlorosulfonic acid, when in addition to the sulfonic acids, the sulfonyl chlorides were also obtained in some cases. The sulfonic acids were identified by the analysis of their barium salts and wherever possible by the preparation of crystalline derivatives with benzyl-isothiourea hydrochloride. The sulfonyl chlorides could be easily hydrolyzed to the corresponding sulfonic acids or were obtained by heating the sodium sulfonates with an excess of chlorosulfonic acid. This interconversion showed that the sulfonic acid and the sulfonyl chloride groups had entered the benzopyrone nucleus in the same positions. Sulfonanilides were prepared to characterize the sulfonyl chlorides.

Table I describes the experimental conditions under which the different chromones, flavones, and isoflavones were sulfonated.

Attempts to prove the structure of (A) by nitration and hydrolysis were unsuccessful. However, the oxidation of its sodium salt with alkaline permanganate gave the known 5-sulfosalicylic acid[3] showing that the sulfonic acid group in 2,3-dimethylchromone had entered the "6" position. The sulfonyl chloride (B) was hydrolyzed to (A) by boiling with water thus showing the presence of the sulfonyl chloride group also in the "6" position. No di- or tri-sulfonated products could be obtained from this chromone even under very drastic experimental conditions.

The position of the sulfonic acid group in (C) was determined by its nitration when the known 7-hydroxy-2-methyl-8-nitrochromone[6] was obtained. On alkaline hydrolysis, (C) gave a sulfonic acid of resacetophenone which on bromination yielded 3,5-dibromoresacetophenone.[4] For purposes of comparison, direct sulfonation of resacetophenone was carried out when a sulfonic acid different from the above was obtained. The structure of this sulfonic acid was proved to be resacetophenone-5-sulfonic acid, since upon bromination the known 5-bromoresacetophenone[5] was obtained. On nitrating the disulfonic acid (D), the known 7-hydroxy-2-methyl-6,8-dinitrochromone[6] was obtained thus establishing the positions of sulfonic acid groups.

The sulfonic acid group in (E) was shown to be in the "8" position by nitration to give the known 7-methoxy-2-methyl-8-nitrochromone.[6] Sulfonation of the methoxy chromone at higher temperatures or with an excess of chlorosulfonic acid was accompanied by demethylation as indicated by the ferric chloride coloration given by the sulfonated products.

The structure of (F) was proven by its nitration to the corresponding known 8-nitroflavone.[6] Alkaline hydrolysis of (F) gave resacetophenone-3-sulfonic acid thus confirming the position of sulfonic acid group in (F). Attempts to nitrate (G) were unsuccessful. On alkaline hydrolysis, however, it gave resacetophenone-3,5-disulfonic acid which in turn

(1) Suter, *Organic Chemistry of Sulfur*, John Wiley & Sons, Inc., New York, 1948.
(2) Kruger, *Ber.*, **56**, 487 (1923).
(3) Meldrum and Shah, *J. Chem. Soc.*, **123**, 1988 (1923).
(4) Dahse, *Ber.*, **41**, 1621 (1908).
(5) Desai and Ekhlas, *Proc. Indian Acad. Sci.*, **8**, 516 (1938).
(6) Mehta, Jadhav, and Shah, *Proc. Indian Acad. Sci.*, **29a**, 314 (1949).

TABLE I

SULFONATION OF CHROMONE, FLAVONE, AND ISOFLAVONE DERIVATIVES

Substance	Ref.*	Chlorosulfonic acid, moles	Temp., °C.	Time in hours	Product of Sulfonation
2,3-Dimethylchromone	a	8	140	4	-6-Sulfonic acid (A) and -6-Sulfonyl chloride (B)
7-Hydroxy-2-methylchromone	b	4	100	2	-8-Sulfonic acid (C)
7-Hydroxy-2-methylchromone		8	100	2	Unidentified substance containing S and Cl, m.p. 225° (decomp.) + (C)
7-Hydroxy-2-methylchromone		8	140	6	-6,8-Disulfonic acid (D)
7-Methoxy-2-methylchromone	c	4	100	2.5	-8-Sulfonic acid (E)
7-Hydroxyflavone	d	4[a]	60	4	-8-Sulfonic acid (F)
7-Hydroxyflavone		6	140	6	-6,8-Disulfonic acid (G) $ClSO_3H$ ↓ 4 moles, 140°, 2 hours
7-Hydroxyflavone		15	140	4.5	-6,8,2′-Trisulfonic acid (H)
7-Hydroxy-2-methylisoflavone	e	2[b]	100	4	-8-Sulfonic acid (I)
7-Hydroxy-2-methylisoflavone		6	140	6	-6,8-Disulfonic acid (J) and -6,8-Disulfonyl chloride (K)
7-Hydroxy-2-methylisoflavone		10	140	6	-Trisulfonic acid
7-Hydroxy-2-phenylisoflavone	e	4[b]	100	4	-8-Sulfonic acid (L) (accompanied by original isoflavone)
7-Hydroxy-2-phenylisoflavone		2[a]	60	2	-6,8-Disulfonic acid (M)
7-Hydroxy-2-phenylisoflavone		10	140	6	-6,8-Disulfonyl chloride (N) and -Trisulfonic acid
5-Hydroxy-2-methylchromone	f	1[a]	60	2	-8-Sulfonic acid (O)
		5	100	2	-6,8-Disulfonic acid (P)
5-Methoxy-2-methylchromone	g	1[a]	60	1	-8-Sulfonic acid (Q)
5-Hydroxyflavone	h, i	1[a]	60	1.5	-8-Sulfonic acid (R)
5-Hydroxyflavone		6	140	6	-6,8-Disulfonic acid (S)
5-Hydroxyflavone		10	140	6	-6,8-Disulfonyl chloride (T) $ClSO_3H$ ↓ 4 moles, 140°, 2 hours
5-Hydroxyflavone		15	140	4.5	-6,8,2′-Trisulfonic acid (U)

* The letters in the parentheses indicate references to the methods of preparation, which are as follows: (a) Petschek and Simonis, *Ber.*, **46**, 2014 (1913). (b) Kostanecki and Rozycki, *Ber.*, **34**, 106 (1901). (c) Mehta, Jadhav, and Shah, *Proc. Indian Acad. Sci.*, **29A**, 314 (1949). (d) Rangaswamy and Seshadri, *Proc. Indian Acad. Sci.*, **10A**, 6 (1939); Joshi and Thakor, *J. Univ. Bombay*, **22** (**5**), 21 (1954). (e) Robinson and Baker, *J. Chem. Soc.*, **127**, 1984 (1925). (f) Limaye and Kelkar, *J. Indian Chem. Soc.*, **12**, 788 (1935); Rasāyanam, **1**, 24 (1936). (g) Naik, Mehta, Thakor, Jadhav, and Shah, *Proc. Indian Acad. Sci.*, **38A**, 31 (1953). (h) Baker, *J. Chem. Soc.*, 1954 (1934). (i) Sugasawa, *J. Chem. Soc.*, 1484 (1934). [a] In chloroform. [b] In nitrobenzene.

gave the known 3,5-dibromoresacetophenone[4] on bromination. The trisulfonic acid (H) which can also be obtained by sulfonation of (G) gave on hydrolysis with alkali a 60% yield of *o*-sulfobenzoic acid,[7] showing that the third sulfonic acid group had probably entered the 2′ position.[8] It is interesting to note that this sulfonic acid group in the 2′ position is readily eliminated by boiling with water.

The isoflavones were found to be more reactive than the corresponding flavones. Hydrolysis of both (I) and (L) gave 2,4-dihydroxyphenyl benzyl ketone. The structure of the latter was proved by bromination which gave the known 5-bromo ketone.[5] Hence, the hydrolysis product of (I) and (L) was 2,4-dihydroxyphenyl benzyl ketone-3-sulfonic acid. The disulfonic acids (J) and (M) were hydrolyzed to 2,4-dihydroxyphenyl benzyl ketone-3,5-disulfonic acid, which was brominated to the known 3,5-dibromo compound.[5,10] The structures of the trisulfonic acids of the isoflavones could not be definitely established.

Compared to the sulfonation of the 7-hydroxychromones and flavones that of the 5-hydroxy compounds was found to take place more readily. The position of sulfonic acid groups in (O), (P), and (Q) were proved by their nitration to the corresponding known nitro compounds.[11,12] Hydrolysis of (P) with alkali yielded the known resorcinol-4,6-disulfonic acid.[13] Sulfonation of 5-methoxy-2-methylchromone under more drastic conditions than described in the Table I was accompanied by demethylation. The structures of the sulfonic acids (R) and (S) were determined by nitrating them to give the known nitro compounds.[11] The disulfonyl chloride

(7) Clarke and Dreger, *Org. Syntheses*, **Coll. Vol. 1**, 2nd ed., 14 (1941).

(8) *o*-Sulfobenzoic acid forms a di-derivative with S-benzyl-iso-thiourea hydrochloride. The *para*-isomer forms only a mono derivative while no crystalline derivative is formed with *m*-sulfobenzoic acid.[9]

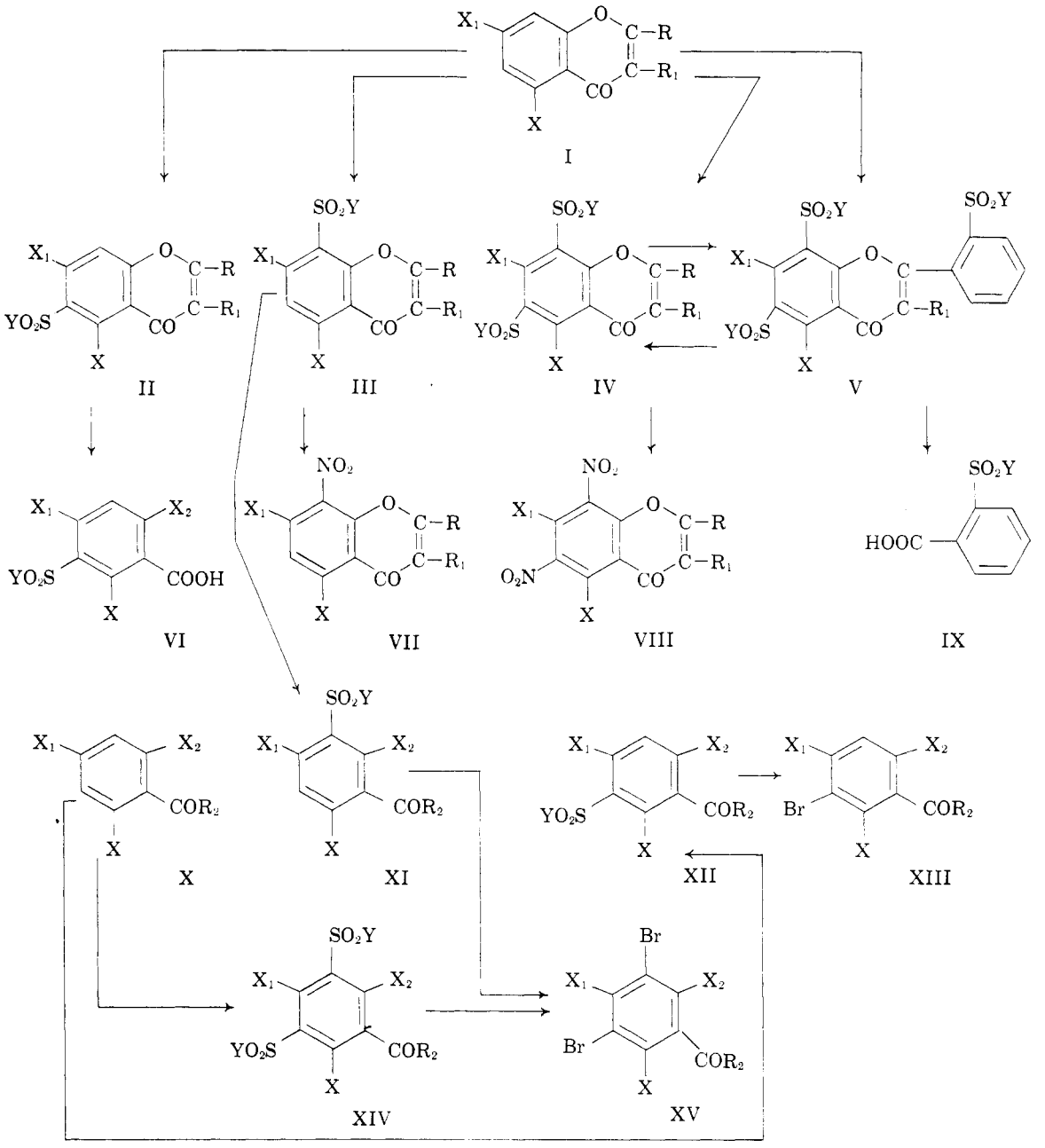
(9) Campaigne and Suter, *J. Am. Chem. Soc.*, **64**, 3041 (1942).

(10) By repeating the method of Desai, *et al.*[5] a mixture of bromo compounds was obtained. The conditions had to be modified to get a pure dibromo derivative.

(11) Naik, Mehta, Thakor, Jadhav, and Shah, *Proc. Indian Acad. Sci.*, **38a**, 31 (1953).

(12) Naik and Thakor, *Proc. Indian Acad. Sci.*, **37a**, 774 (1953).

(13) Fischer, *Monatsh.*, **2**, 331 (1881).



(T) could be easily hydrolyzed with water to (S). The trisulfonic acid (U) on boiling with alkali gave (S) and *o*-sulfobenzoic acid[7] showing that the third sulfonic acid group in (U) had probably entered the 2′ position.

EXPERIMENTAL

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

General method for sulfonation. Chlorosulfonic acid was gradually added to the substance with cooling, and the mixture (protected from moisture) was heated. After cooling, the contents were poured over crushed ice. The sulfonyl chlorides usually separated as pasty products which solidified on keeping and crystallized well from benzene. They were characterized by the preparation of their anilides. The filtrate after removal of the sulfonyl chlorides was saturated with sodium chloride when the sodium salt separated in most cases. It was used as such for preparing the derivative with benzyl-iso-thiourea hydrochloride. These derivatives were generally crystallized from dilute alcohol. The barium salt was obtained by concentrating the mother liquor to remove completely the hydrogen chloride and neutralizing the concentrate with barium carbonate. The barium salt was recrystallized from water, dried at 140°, and immediately analyzed. The results are listed in Table II. The yields of the sulfonyl chlorides and sulfonic acids were consistently good in all cases.

Oxidation of (A). *5-Sulfosalicylic acid* (VI, X, X_1 = H; X_2, Y = OH). The sulfonyl chloride (B) was hydrolyzed to (A) (II, R, R_1 = CH_3; X, X_1 = H; Y = OH) by boiling with water and was filtered into a concentrated solution of sodium hydroxide when the sodium salt precipitated. To a solution of 0.5 g. of the sodium salt in 5 ml. of 2 *N* sodium

hydroxide was added dropwise with stirring, 25 ml. of 4% potassium permanganate. The mixture was heated on a steam-bath for one hour. The filtrate was concentrated and acidified with concentrated hydrochloric acid. The product which separated was treated with an alcoholic solution of benzy-liso-thiourea hydrochloride. The derivative crystallized from dilute alcohol and had m.p. 194–196°. The mixture m.p. with the derivative obtained from 5-sulfosalicylic acid[3] showed no lowering.

Anal. Calc'd for $C_{15}H_{16}N_2O_6S_2$: N, 7.30. Found: N, 7.80.

The *barium salt* of 5-sulfosalicylic acid was heated at 140° and analyzed.

Anal. Calc'd for $C_{14}H_{16}BaO_{12}S_2$: Ba, 24.05. Found: Ba, 23.50.

Nitration of (C). *7-Hydroxy-2-methyl-8-nitrochromone* (VII, R = CH_3; R_1, X = H; X_1 = OH). To 0.5 g. of (C) (III, R = CH_3; R_1, X = H; X_1, Y = OH) dissolved in 2.5 ml. of concentrated sulfuric acid was added at 0° 2.5 ml. of nitric acid (*d.* 1.42) with constant stirring. After the reaction mixture was left at 0° for 4 hours, it was poured over ice and the yellow solid obtained was crystallized from alcohol in dark yellow crystals, m.p. 268°. Its mixture m.p. with an authentic sample of 7-hydroxy-2-methyl-8-nitrochromone[6] showed no lowering.

Hydrolysis of (C). Resacetophenone-3-sulfonic acid (XI, R_2 = CH_3; X = H; X_1, X_2, Y = OH). A mixture of 1 g. of (C) and 25 ml. of 6% sodium hydroxide solution was heated on a steam-bath for about 3.5 hours and cooled. The separated product was filtered and dried. It was converted into the S-benzyl-iso-thiuronium derivative, m.p. 172–173°.

Anal. Calc'd for $C_{16}H_{18}N_2O_6S_2$: N, 7.10. Found: N, 7.12.

Bromination of XI. *3,5-Dibromoresacetophenone* (XV, R_2 = CH_3; X = H; X_1, X_2 = OH). The sodium salt of XI was dissolved (500 mg.) in 3 ml. of glacial acetic acid by boiling. To the hot solution 7.5 ml. of a 10% solution of bromine in acetic acid was added with shaking. After five hours the solution was poured into water. The product which separated was crystallized from alcohol, m.p. 173–174°. Its melting point when mixed with 3,5-dibromoresacetophenone prepared according to Dahse[4] showed no depression.

Resacetophenone-5-sulfonic acid (XII, R_2 = CH_3; X = H; X_1, X_2, Y = OH). Resacetophenone (X, R_2 = CH_3; X = H; X_1, X_2 = OH) was kept with chlorosulfonic acid (3 moles) in chloroform medium at 30° for 1.5 hours. The brown oil thus obtained was converted into the *S-benzyl-isothiuronium derivative*, m.p. 166°.

Anal. Calc'd for $C_{16}H_{18}N_2O_6S_2$: N, 7.10. Found: N, 7.04.

The mixture m.p. of this derivative with that of XI showed a lowering.

Bromination of XII. *5-Bromoresacetophenone* (XIII, R_2 = CH_3; X = H; X_1, X_2 = OH). To the aqueous solution of 1 g. of the sodium salt of XII was added 3 ml. of 10% bromine in acetic acid. After keeping the reaction on the steam-bath for 3 hours the contents were poured in ice-cold water when pink crystals were obtained, m.p. 166–167°. The mixture m.p. with 5-bromoresacetophenone prepared according to Desai, *et al.*[5] did not lower.

Nitration of (D). *7-Hydroxy-2-methyl-6,8-dinitrochromone* (VIII, R = CH_3; R_1, X = H; X_1 = OH). To a well cooled solution of 0.5 g. of (D) (IV, R = CH_3; R_1, X = H; X_1, Y = OH) in 8 ml. of concentrated sulfuric acid, 4 ml. of nitric acid (*d.* 1.48) was gradually added and the reaction mixture was left overnight at 30°. When poured over crushed ice a substance separated which, when crystallized from alcohol, gave yellow plates, m.p. 231–233°. The mixture m.p. with an authentic sample of the 6,8-dinitro compound[6] showed no lowering.

Nitration of (E). *7-Methoxy-2-methyl-8-nitrochromone* (VII, R = CH_3; R_1, X = H; X_1 = OCH_3). To a solution of 0.8 g. of (E) (III, R_2 = CH_3; R_1, X = H; X_1 = OCH_3; Y = OH) in 4 ml. of concentrated sulfuric acid cooled to 0°, 4 ml. of nitric acid (*d.* 1.42) was added in such a way that the temperature of the reaction mixture did not rise. After keeping for 3 hours at 0°, it was poured over crushed ice and the product thus obtained was crystallized from alcohol, m.p. 211°. Its mixture melting point with an authentic sample of the 8-nitrochromone[6] did not lower.

Nitration of (F). *7-Hydroxy-8-nitroflavone* (VII, R = C_6H_5; R_1, X = H; X_1 = OH). The nitration of (F) (III, R = C_6H_5; R_1, X = H; X_1, Y = OH) was carried out in the same way as described for (D). The product was crystallized from a pyridine-acetic acid mixture, m.p. 302–304°. The mixture m.p. with an authentic sample[6] did not lower. The hydrolysis of (F) was carried out in exactly the same way as that of (C) when resacetophenone-3-sulfonic acid was obtained.

Hydrolysis of (G). *Resacetophenone-3,5-disulfonic acid* (XIV, R_2 = CH_3; X = H; X_1, X_2, Y = OH). The sulfonic acid (G) (IV, R = C_6H_5; R_1, X = H; X_1, Y = OH) was hydrolyzed in the same way as (C).

Bromination of (XIV). *3,5-Dibromoresacetophenone* (XV). To a solution of 0.5 g. of the sodium salt of XIV in 3 ml. of acetic acid, 7.5 ml. of 10% bromine in acetic acid was gradually added with shaking. After leaving at 30° for 6 hours the reaction mixture was poured in water. The bromo compound was crystallized from alcohol in pink needles, m.p. 173–174°. Its mixture m.p. with 3,5-dibromoresacetophenone[4] did not lower.

Hydrolysis of (H). *o-Sulfobenzoic acid* (IX, Y = OH). The hydrolysis of 0.5 g. of the trisodium salt of (H) (V, R_1, X = H; X_1, Y = OH) with 20 ml. of 10% sodium hydroxide was complete when refluxed for 1 hour. The reaction mixture was acidified with hydrochloric acid and treated with barium chloride, when 125 mg. of an insoluble barium salt was obtained. This was converted into the sodium salt for preparing the *S-benzyl-iso-thiuronium derivative*. The derivative separated first as an oil which solidified on keeping. On crystallizing from dilute alcohol it melted at 204–205°.

Anal. Calc'd for $C_{23}H_{26}N_4O_5S_3$: N, 10.49. Found: N, 10.40.

This derivative was found to be that of *o*-sulfobenzoic acid since it showed no lowering in melting point when mixed with the derivative of *o*-sulfobenzoic acid prepared according to Campaigne and Suter.[9]

Hydrolysis of (I) *and* (L). *2,4-Dihydroxyphenyl benzyl ketone 3-sulfonic acid* (XI, R_2 = $CH_2C_6H_5$; X = H; X_1, X_2, Y = OH). A mixture of 1 g. of (I) (III, R = CH_3; R_1 = C_6H_5; X = H, X_1, Y = OH) and 15 ml. of 10% sodium hydroxide was refluxed for 1.5 hours. The solution was acidified with hydrochloric acid and after concentration it was poured into a saturated solution of sodium chloride. The sodium salt was used to obtain the *S-benzyl-iso-thiuronium derivative*. When crystallized from 95% alcohol it melted at 186–187°.

Anal. Calc'd for $C_{22}H_{22}N_2O_6S_2$: N, 5.91. Found: N, 5.92.

2,4-Dihydroxyphenyl benzyl ketone 5-sulfonic acid (XII, R_2 = $CH_2C_6H_5$; X = H; X_1, X_2, Y = OH). To a cooled solution of 0.5 g. of 2,4-dihydroxyphenyl benzyl ketone[5] (X, R = $CH_2C_6H_5$; X = H; X_1, X_2 = OH) in 10 ml. of chloroform, 0.5 ml. of chlorosulfonic acid was gradually added taking care that the temperature of the mixture did not rise above 25°. The contents were shaken in a mechanical shaker for 1.5 hours and the brown oil which separated was poured over crushed ice. The sulfonic acid was isolated by concentrating the aqueous solution and was converted to the *S-benzyl-iso-thiuronium derivative* which gave silvery-white plates from alcohol, m.p. 206–207°.

Anal. Calc'd for $C_{22}H_{22}N_2O_6S_2$: N, 5.91. Found: N, 5.93.

The mixture m.p. of this derivative showed a definite lowering when mixed with the derivative obtained from the hydrolysis of (I) and (L).

Bromination of XII. *5-Bromo-2,4-dihydroxyphenyl benzyl ketone* (XIII, R_2 = $CH_2C_6H_5$; X = H; X_1, X_2 = OH). To 0.5 g. of the sodium salt of XII, bromine (1 mole) in acetic acid was added and the reaction mixture was kept on the steam-bath for 20 minutes. After pouring into ice-water a yellow solid separated which when crystallized from alcohol

TABLE II

MELTING POINTS AND ANALYSES OF THE DERIVATIVES OF SULFONIC ACIDS AND SULFONYL CHLORIDES

Sulfonation Product	M.p., °C.	Barium Salt/Sulfonyl Chloride	Analysis Barium/Halogen Calc'd	Found	S-Benzylisothiuronium deriv.	Anilide	M.p., °C.	Analysis Nitrogen Calc'd	Found
(A)	—	$C_{22}H_{18}BaO_{10}S_2$	21.40	20.70	—	—	—	—	—
(B)	157–158	$C_{11}H_9ClO_4S$	13.00	12.90	—	$C_{17}H_{15}NO_4S$	277–279	4.25	3.90
(C)	235 (d)	$C_{20}H_{14}BaO_{12}S_2$	21.20	21.30	$C_{18}H_{18}N_2O_6S_2$	—	178–180	6.60	6.90
(D)	—	$C_{10}H_6BaO_9S_2$	29.20	28.50	—	—	—	—	—
(E)	—	$C_{22}H_{18}BaO_{12}S_2$	20.30	20.20	—	—	—	—	—
(F)	271–273	$C_{30}H_{18}BaO_{12}S_2$[a]	17.76	17.97	$C_{23}H_{20}N_2O_6S_2$	—	201–202	5.79	5.55
(G)	262–263	$C_{15}H_8BaO_9S_2$[b]	25.70	25.32	$C_{31}H_{30}N_4O_9S_4$	—	224	7.78	7.74
(H)	—	$C_{30}H_{14}Ba_3O_{24}S_2$	30.20	29.60	—	—	—	—	—
(I)	208–209	$C_{32}H_{22}BaO_{12}S_2$	17.15	17.20	$C_{24}H_{22}N_2O_6S_2$	—	125	5.60	5.57
(J)	—	$C_{16}H_{10}BaO_9S_2$	25.04	24.74	—	—	—	—	—
(K)[e]	84–85	—	—	—	—	$C_{28}H_{22}N_2O_7S_2$	153 (d)	5.00	4.99
(L)	221–222	$C_{42}H_{26}BaO_{12}S$	14.85	14.96	$C_{29}H_{24}N_2O_6S_2$	—	258–259	5.04	4.99
(M)	—	$C_{21}H_{12}BaO_9S_2$	22.50	22.93	—	—	—	—	—
(N)	99–101	—	—	—	—	$C_{33}H_{24}N_2O_7S_2$	153 (d)	4.48	4.30
(O)	—	$C_{20}H_{14}BaO_{12}S_2$	21.20	21.00	$C_{18}H_{18}N_2O_6S_2$	—	235	6.60	6.30
(P)	—	$C_{10}H_6BaO_9S_2$	29.20	28.40	$C_{26}H_{28}N_4O_9S_4$	—	225–227	8.40	8.80
(Q)	—	$C_{22}H_{18}BaO_{12}S_2$	20.30	19.60	—	—	—	—	—
(R)	154–156	$C_{30}H_{18}BaO_{12}S_2$	17.76	17.96	$C_{23}H_{20}N_2O_6S_2$	—	234–235	5.79	5.54
(S)	151–152	$C_{15}H_8BaO_9S_2$[c]	25.70	25.60	$C_{31}H_{30}N_4O_9S_4$	—	237 (d)	7.78	7.70
(T)	104–105 (d)	—	—	—	—	$C_{27}H_{20}N_2O_7S_2$	280 (d)	5.79	5.75
(U)	—	$C_{30}H_{14}Ba_3O_{24}S_2$	30.20	30.30	—	—	—	—	—

[a] Crystallizes with 2.5 moles of water. [b] Crystallizes with 3 moles of water. [c] Crystallizes with 4 moles of water. [d] Refers to decomposition. [e] Found to be hygroscopic.

gave yellow plates, m.p. 103°. The mixture m.p. with 5-bromo-2,4-dihydroxyphenyl benzyl ketone prepared according to Desai, *et al.*[5] showed no lowering.

The hydrolysis of (L) (III, R, R_1 = C_6H_5; X = H; X_1, Y = OH) was carried out in the same way as for (I) and the same hydrolysis product was obtained.

Bromination of 2,4-dihydroxyphenyl benzyl ketone (X, R_2 = $CH_2C_6H_5$; X = H; X_1, X_2 = OH). (*Cf.* Desai, *et al.*[5] *3,5-Dibromo-2,4-dihydroxyphenyl benzyl ketone* (XV). The ketone (X) was treated with bromine (4 moles) in acetic acid and the reaction mixture was kept on steam-bath for 1 hour. On pouring the contents on ice, a product separated which was crystallized from alcohol, m.p. 150°.

Anal. Calc'd for $C_{14}H_{10}Br_2O_3$: Br, 41.45. Found: Br, 41.25.

Hydrolysis of (J) and (M). *2,4-Dihydroxyphenyl benzyl ketone 3,5-disulfonic acid* (XIV, R_2 = $CH_2C_6H_5$; X = H; X_1, X_2, Y = OH). The method followed was the same as that for (I).

Bromination of XIV. *3,5-Dibromo-2,4-dihydroxyphenyl benzyl ketone* (XV, R_2 = $CH_2C_6H_5$: X = H; X_1, X_2 = OH). To a solution of 0.5 g. of the sodium salt of XIV in 10 ml. of acetic acid, bromine (2 moles) in acetic acid was gradually added and the contents were refluxed for 15 minutes on a steam-bath. On pouring into water, a pinkish-white precipitate was obtained, which on crystallization from alcohol melted at 150°. The mixture m.p. with the 3,5-dibromo derivative prepared from the ketone did not show a lowering.

Nitration of (O). *5-Hydroxy-2-methyl-8-nitrochromone* (VII, R = CH_3; R_1, X_1 = H; X = OH). To a suspension of 0.5 g. of (O) (III, R = CH_3; R_1, X_1 = H; X, Y = OH) in 5 ml. of acetic acid at 0°, 3 ml. of nitric acid (*d.* 1.42) was gradually added. The reaction mixture was poured into ice-water after keeping at 30° for 3 hours. When crystallized from acetic acid, tiny brown p'ates were obtained, m.p. 218–220°. Its mixture m.p. with a sample of 5-hydroxy-8-nitro-2-methylchromone[11] was not lowered but with 5-hydroxy-6-nitro-2-methylchromone[12] the mixture gave a definite lowering.

Nitration of (P). *5-Hydroxy-2-methyl-6,8-dinitrochromone* (VIII, R = CH_3; R_1, X_1 = H; X = OH). To a suspension of 0.5 g. of the sodium salt of (P) (IV, R = CH_3; R_1, X_1 = H; X, Y = OH) in 8 ml. of acetic acid was added 5 ml. of nitric acid (*d.* 1.42). The mixture was heated on a steam-bath for 40 minutes and was poured over ice. The separated yellow product was crystallized from acetic acid, m.p. 203–204°. Its mixture m.p. with 5-hydroxy-2-methyl-6,8-dinitrochromone[11] showed no lowering.

Hydrolysis of (P). *Resorcinol-4,6-disulfonic acid.* One gram of the sodium salt of (P) was dissolved in 20 ml. of 10% sodium hydroxide and the solution was boiled for three hours. The white precipitate obtained after acidification was used for preparation of the *derivative with benzyl-isothiourea hydrochloride*, which was crystallized from alcohol, m.p. 226–228°.

Anal. Calc'd for $C_{22}H_{26}N_4O_8S_4$: N, 9.30. Found: N, 9.60.

The melting point of the derivative when mixed with the same derivative of resorcinol-4,6-disulfonic acid[13] showed no depression.

Nitration of (Q). *5-Methoxy-2-methyl-8-nitrochromone* (VII, R = CH_3; R_1, X_1 = H; X = OCH_3). A mixture of 2 ml. of concentrated sulfuric acid and 2 ml. of nitric acid (*d.* 1.42) was added dropwise to the aqueous solution of 0.5 g. of (Q) (III, R = CH_3; R_1, X_1 = H; X = OCH_3; Y = OH) previously cooled to 0°. After 2 hours at 0° the reaction mixture was poured on ice. The product was crystallized from alcohol in white plates, m.p. 174°. The mixture m.p. with 5-methoxy-2-methyl-8-nitrochromone was not lowered.

Nitration of (R). *5-Hydroxy-8-nitroflavone* (VII, R = C_6H_5; R_1, X_1 = H; X = H). To a mixture of 5 ml. of concentrated sulfuric acid and 5 ml. of nitric acid (*d.* 1.4) was added 0.5 g. of (R) (III, R = C_6H_5; R_1, X_1 = H; X, Y = OH) and the contents were left at room temperature for 45 minutes. When poured onto crushed ice a yellow solid separated which, after crystallizing from acetic acid, melted at 225°. This did not lower the mixture m.p. with an authentic sample of 5-hydroxy-8-nitroflavone.[11]

Nitration of (S). *5-Hydroxy-6,8-dinitroflavone* (VIII, R =

C_6H_5; R_1, X_1 = H; X = OH). To a hot solution of 0.5 g. of (S) (IV, R = C_6H_5; R_1, X_1 = H; X, Y = OH) in 25 ml. of acetic acid, 5 ml. of nitric acid (*d.* 1.4) was gradually added with shaking. The reaction mixture was kept on the steam-bath for 1.5 hours and then at room temperature for half an hour. The yellow product which separated after pouring the contents in cold water was crystallized from acetic acid, m.p. 253°. The mixture m.p. with 5-hydroxy-6,8-dinitroflavone[11] showed no lowering.

The constitution of (U) was proven in the same way as of (H) by isolating *o*-sulfobenzoic acid which was characterized by its S-benzylthiuronium derivative.

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