219. *The Influence of Substituents on the Mercuration of Coumarins.*

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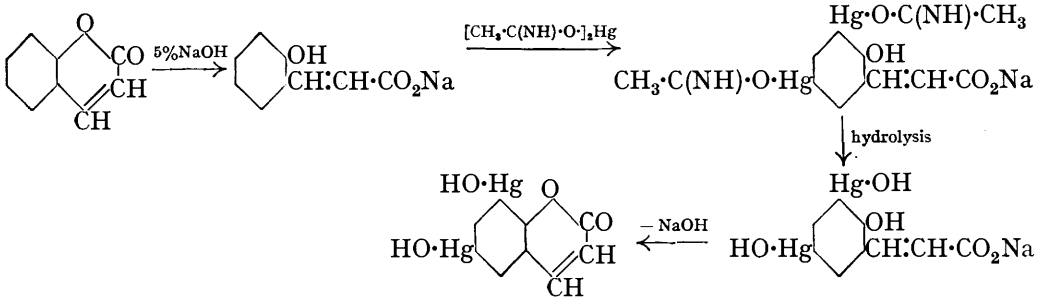
MERCURY acetamide, which has been used as a mercurating agent for compounds containing a reactive methylene group (Naik and Shah, *J. Indian Chem. Soc.*, 1931, **8**, 29), is effective also in the mercuration of coumarins. It does not attack these directly, but only after the action of 5% sodium hydroxide solution upon them. The course of the reaction with coumarin may be represented by the scheme on p. 1044.

Mercury acetamide has thus been made to react with the following substances (the numbers in parentheses indicate the compounds referred to in the tables) : (1) coumarin, (2) 7-hydroxy-4-methyl-, (3) 7-amino-4-methyl-, (4) 4 : 7-dimethyl-, (5) 5 : 6-dihydroxy-4-methyl-, (6) 6-hydroxy-4-methyl-, (7) 6-nitro-, (8) 4 : 6-dimethyl-, (9) 4 : 8-dimethyl-, (10) 7-hydroxy-4 : 5-dimethyl-, (11) 7-hydroxy-4-methyl-3-allyl-, (12) 7-hydroxy-3-benzyl-

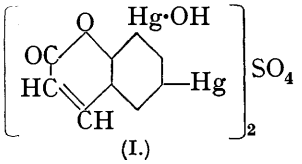
4-methyl-, (13) 7-hydroxy-4-phenyl-, (14) 3-carbethoxy-, (15) 3-acetyl-, (16) 3-benzoyl-coumarin, (17) ketodicoumarin, (18) thiocoumarin, (19) 6-methyl-1 : 2-α-naphthapyrone,



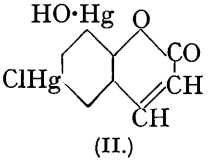
(20) 6-methyl-3 : 4-β-naphthapyrone. The effect of substituents in the coumarin ring on their mercuration is well marked. When the oxygen of the carbonyl group is replaced by sulphur, mercuration takes place in alcoholic solution without the aid of alkali. Coumarins containing a carbethoxy- or a carbomethoxy-group in position 3 give dimercury derivatives, but those containing a benzoyl group or $CO{\cdot}C_9H_5O_2$ (as in ketodicoumarin) in this position give only monomercurated compounds. Substituents in position 4 have scarcely any influence, dimercury derivatives being produced. When position 5 or 7 is occupied by a hydroxy- or an amino-group, dimercury derivatives are obtained, but 7-methylcoumarin gives a monomercury derivative only. When position 6 is substituted different products are obtained according to the nature of the substituent: with a methyl substituent, a monomercury derivative is obtained; a nitro-substituent is expelled and a monomercury derivative produced; a hydroxy-substituent is converted into O·Hg·OH. A coumarin with methyl in position 8 yields a monomercury derivative substituted in position 6. 6-Methyl-1 : 2-α- and -3 : 4-β-naphthapyrone yield each only a monomercury derivative.

All these compounds are more or less soluble in dilute sodium hydroxide solution. The carbon–mercury link is not broken by cold dilute hydrochloric acid. They do not give mercuric sulphide readily on treatment with hydrogen sulphide. Potassium iodide solution decomposes them with the quantitative liberation of alkali hydroxide.

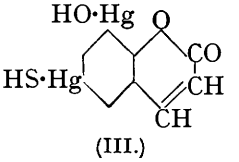
The bishydroxymercuri-compounds are converted into sulphatomercuri-derivatives (I) by 10% sulphuric acid, and their solutions in dilute aqueous sodium hydroxide give chloromercuri-derivatives (II) and mercaptomercuri-compounds (III) when treated with dilute hydrochloric acid and with carbon disulphide, respectively.



(I.)



(II.)



(III.)

Mercuric acetate was made to react with solutions of the coumarins mentioned above in 5% aqueous sodium hydroxide. Its action on coumarin-6-sulphonic acid was also examined. The course of the reaction with coumarin is similar to that depicted above, the final product containing HgOAc in positions 6 and 8.

On treatment with dilute hydrochloric acid and with hydrogen sulphide the bisacetoxymercuricoumarins give results similar to those obtained with the bishydroxymercuricoumarins. Treatment with potassium iodide solution, however, liberates only two equivalents of alkali instead of four:

$$C_9H_4O_2(Hg{\cdot}OAc)_2 + 8KI + 2H_2O \xrightarrow{\text{cold}} C_9H_5O_2(HgOAc) + K_2HgI_4 + CH_3{\cdot}CO_2K + 4KI + KOH + H_2O \xrightarrow{\text{heated}} C_9H_6O_2 + 2K_2HgI_4 + 2CH_3{\cdot}CO_2K + 2KOH.$$

6 : 8-*Bisacetoxymercuricoumarin*, when treated with sodium thiosulphate solution, is

converted into a compound, $C_9H_4O_2<^{Hg}_{Hg}>C_9H_4O_2$ (IV), which readily gives a sulphatomercuri-derivative (compare Dimroth, *Ber.*, 1902, **35**, 2853; Maynard, *J. Amer. Chem. Soc.*, 1924, **46**, 1510; Pesci, *Gazzetta*, 1899, **29**, 394).

The effect of substituents on the mercuration of coumarins by mercuric acetate is, in general, similar to that in the case of mercury acetamide. The main differences are: (1) 6-nitrocoumarin yields 6 : 8-bisacetoxymercuricoumarin; so also does coumarin-6-sulphonic acid; (2) 3-acetyl-4-methylcoumarin gives a bisacetoxymercuri-derivative; (3) 4-phenyl-3-allyl (or benzyl)coumarin yields a hydroxymercuri-acetoxymercuri-derivative. Compounds of the last type, when treated with potassium iodide solution, liberate only three equivalents of potassium hydroxide. 6-Acetoxymercuri-4 : 7-dimethylcoumarin, similarly treated, liberates one equivalent of alkali.

The constitutions assigned to the mercury compounds now described are based on the following considerations:

(1) The mercury-containing substituent has not opened the ethylenic link, because (*a*) the behaviour of the compounds towards sodium carbonate and bicarbonate is like that of coumarin itself, (*b*) cinnamic acid, which contains a double bond in a similar position, is not mercurated when similarly treated (Biilmann, *Ber.*, 1902, **35**, 2576; 1910, **43**, 574), and (*c*) the compounds decolorise potassium permanganate solution as do the coumarins.

(2) The mercury atom has entered the nucleus, because (*a*) all attempts to mercurate coumarin directly failed, but when the hydroxyl group was generated by means of 5% sodium hydroxide solution, the phenolic compound was mercurated at once. A phenolic hydroxyl group not only facilitates mercuration, but also appears to exert an orienting influence (Mameli, *Gazzetta*, 1922, **52**, i, 352; ii, 18, 23, 113; 1926, **56**, 948), mercuration taking place in the *p*- or *o*-positions to it: these become positions 6 and 8 when the coumarin ring is formed. That the mercury is in positions 6 and 8 is further proved by the facts that coumarins with a substituent in position 5 or 7 give dimercurated compounds, whereas those with a substituent in position 6 or 8 give only monomercurated derivatives. (*b*) From a study of known mercury compounds, such as those of *allo*cinnamic acid, it appears that the mercury atom in the nucleus is not removed by dilute hydrochloric acid or hydrogen sulphide (Whitmore, "Monograph on Mercury Compounds"). (*c*) The reaction of the compounds with potassium iodide solution is of the same type as that of the mercurated phenols (Whitmore, *op. cit.*). (*d*) Iodination of dimercurated coumarin gave a *tri-iododihydrocoumarin*, which on oxidation furnished 3 : 5-di-iodosalicylic acid.

From the following facts, it appears that the mercury-containing substituent in position 6 is more reactive than that in position 8: (*a*) the reaction of a bishydroxymercuricoumarin with potassium iodide solution liberates two equivalents of potassium hydroxide in the cold and two more on heating; (*b*) in the reactions with carbon disulphide, dilute hydrochloric acid, and 10% sulphuric acid, only one of the two substituents is attacked; (*c*) 6-nitrocoumarin on mercuration is converted into 6-hydroxymercuricoumarin.

Experimental.

The coumarins required for the work were prepared mostly by the condensation of phenols with β-ketonic esters in presence of sulphuric acid; a few were obtained by the condensation of salicylaldehyde with β-ketonic esters in presence of piperidine. For the preparation of 7-hydroxy-3-allyl- and -3-benzyl-coumarin phosphorus oxychloride was used as condensing agent, with excellent results (Naik and Trivedi, *J. Indian Chem. Soc.*, 1929, **6**, 801).

6 : 8-*Bishydroxymercuricoumarin.*—Coumarin (2 g.) was dissolved in 5% sodium hydroxide solution (100 c.c.), and the excess of alkali neutralised with dilute acetic acid. The yellow precipitate obtained on addition of a solution of mercury acetamide (Scholler and Schrauth, *Ber.*, 1909, **42**, 784) (10 g.) in water was washed with water, alcohol, and ether (Table I, No. 1).

6 : 8-*Bishydroxymercuricoumarin* is insoluble in most organic solvents, but dissolves in dilute aqueous sodium hydroxide. A suspension (0·3365 g.) in water (50 c.c.) was treated with a solution of potassium iodide (3 g.), and the liberated alkali titrated (phenolphthalein) against 0·0686*N*-hydrochloric acid; in the cold 1·90 equivs., and after heating a further 2·05 equivs.,

were neutralised. The total of 3·95 equivs. indicates that the rupture of the C–Hg link was complete.

The addition of dilute hydrochloric acid to a solution of the mercury compound in aqueous hydroxide gave a white bulky precipitate, consisting of the *chloromercuri*-compound (II), which was washed with water and alcohol (Found : Cl, 6·3. $C_9H_5O_3Hg_2Cl$ requires Cl, 5·9%).

Heated for ½ hour in 10% sulphuric acid, the mercuration product gave a white precipitate, the *sulphatomercuri*-compound (I), which was washed with water and alcohol (Found : S, 2·9. $C_{18}H_{10}O_{10}Hg_4S$ requires S, 2·65%).

A few drops of carbon disulphide were added to an alkaline solution of the mercuration product, the mixture was shaken for a few minutes, and the excess of alkali neutralised with dilute acetic acid. The yellow precipitate obtained (Table III, No. 1) was washed with water, alcohol, and ether.

The mercuration product was heated with 0·1*N*-iodine for 15 minutes. The brown precipitate formed was crystallised from alcohol (Found : I, 71·9. $C_9H_5O_2I_3$ requires I, 72·4%) and oxidised with alkaline potassium permanganate; 3 : 5-di-iodosalicylic acid, m. p. 220—222°, was produced.

6-*Hydroxymercurithiocoumarin*.—Thiocoumarin (1 g.), dissolved in alcohol, was treated with an alcoholic solution of mercury acetamide (5 g.). The yellow product (Table I, No. 18) was washed with hot water, alcohol, and ether.

6 : 8-*Bisacetoxymercuricoumarin*.—Mercuration of coumarin with mercuric acetate was carried out in aqueous solution through the neutral sodium salt. The yellow precipitate (Table II, No. 1) was washed with alcohol and ether. It was in soluble in all organic solvents, but soluble in dilute sodium hydroxide solution.

Its suspension (0·516 g.) in water was treated with a solution of potassium iodide (2 g.) and the liberated alkali was titrated against 0·0492*N*-hydrochloric acid; in the cold 15·5 c.c., and hot, a further 17·5 c.c., of the acid were required. In all, 2·03 equivs. of the alkali were liberated, indicating the complete rupture of the C–Hg link.

The bisacetoxymercuri-compound (1 g.), suspended in a solution of sodium thiosulphate, was heated for ½ hour, and kept for 8 days. The black precipitate which had formed was removed, and the filtrate boiled for 2 hours. The red precipitate (IV) thus produced was

TABLE I.

Reaction Products of Coumarins and Mercury Acetamide.

No.	Coumarin derivative produced.	Formula.	Colour.	Temp. of colour change.	% Hg found.	% Hg calc.
1	6 : 8-Bishydroxymercuri-	$C_9H_6O_4Hg_2$	Yellow	225°	69·6	69·2
2	7-Hydroxy-6 :8-bishydroxymercuri-4-methyl-	$C_{10}H_8O_5Hg_2$	Orange	270	65·3	65·7
3	7-Amino-6 : 8-bishydroxymercuri-4-methyl-	$C_{10}H_9O_4NHg_2$	Deep red	253	65·4	65·8
4	6-Hydroxymercuri-4 : 7-dimethyl-	$C_{11}H_{10}O_3Hg$	Light yellow	261	52·0	51·3
5	5-Hydroxy-6-oxyhydroxymercuri-8-hydroxymercuri-4-methyl-	$C_{10}H_8O_6Hg_2$	Deep yellow	160	64·2	64·1
6	Oxyhydroxymercuri-4-methyl-	$C_{10}H_8O_4Hg$	Brown	218	50·4	51·0
7	6-Hydroxymercuri-	$C_9H_6O_3Hg$	Yellowish-brown	218	55·4	55·2
8	8-Hydroxymercuri-4 : 6-dimethyl-	$C_{11}H_{10}O_3Hg$	Light yellow	198	51·1	51·3
9	6-Hydroxymercuri-4 : 8-dimethyl-	$C_{11}H_{10}O_3Hg$	Yellowish-brown	243	50·9	51·3
10	7-Hydroxy-6 : 8-bishydroxymercuri-4 : 5-dimethyl-	$C_{11}H_{10}O_5Hg_2$	Buff	—	64·8	64·4
11	7-Hydroxy-6 : 8-bishydroxymercuri-4-methyl-3-allyl-	$C_{13}H_{12}O_5Hg_2$	Deep orange-red	—	62·2	61·8
12	7-Hydroxy-6 : 8-bishydroxymercuri-3-benzyl-4-methyl-	$C_{17}H_{14}O_5Hg_2$	Deep red	272	56·8	57·2
13	7-Hydroxy-6 : 8-bishydroxymercuri-4-phenyl-	$C_{15}H_{10}O_5Hg_2$	Deep red	260	59·3	59·7
14	6 : 8-Bishydroxymercuri-3-carboxy-	$C_{10}H_6O_6Hg_2$	Lemon-yellow	251	65·0	64·3
15	6 : 8-Bishydroxymercuri-3-acetyl-	$C_{11}H_8O_5Hg_2$	Yellow	—	64·1	64·5
16	6-Hydroxymercuri-3-benzoyl-	$C_{16}H_{10}O_4Hg$	Deep yellow	230	42·8	42·4
17	6 : 6′-Bishydroxymercuriketodi-	$C_{19}H_{10}O_7Hg_2$	Yellow	235	53·6	53·3
18	6-Hydroxymercuri-thio-	$C_9H_6O_2SHg$	Yellow	—	52·7	52·9
19	Hydroxymercuri-6-methyl-1 : 2-α-naphthapyrone	$C_{14}H_{10}O_3Hg$	Light red	161	47·6	47·0
20	Hydroxymercuri-6-methyl-3 : 4-β-naphthapyrone	$C_{14}H_{10}O_3Hg$	Light yellow	188—198	47·4	47·0

TABLE II.

Reaction Products of Coumarins and Mercuric Acetate.

No.	Coumarin derivative produced.	Formula.	Colour.	Decomposition.	% Hg found.	% Hg calc.
1	6 : 8-Bisacetoxymercuri-	$C_{13}H_{10}O_6Hg_2$	Yellow	248°	60·85	60·5
2	7-Hydroxy-6 : 8-bisacetoxymercuri-4-methyl-	$C_{14}H_{12}O_7Hg_2$	Deep yellow	208	58·6	57·9
3	7-Amino-6 : 8-bisacetoxymercuri-4-methyl-	$C_{14}H_{13}O_6NHg_2$	Deep red	270	58·45	57·9
4	6-Acetoxymercuri-4 : 7-dimethyl-	$C_{13}H_{12}O_4Hg$	Faint pink	—	46·1	46·3
5	5-Hydroxy-6-oxyacetoxymercuri-8-acetoxymercuri-4-methyl-	$C_{14}H_{12}O_8Hg_2$	Deep yellow	145	56·9	56·5
6	6 : 8-Bisacetoxymercuri-	$C_{13}H_{10}O_6Hg_2$	Yellow	—	59·85	60·5
7	6-Oxyacetoxymercuri-4-methyl-	$C_{12}H_{10}O_5Hg$	Brown	230	45·6	46·1
8	8-Acetoxymercuri-4 : 6-dimethyl	$C_{13}H_{12}O_4Hg$	Yellowish	238	46·7	46·3
9	6-Acetoxymercuri-4 : 8-dimethyl-	$C_{13}H_{12}O_4Hg$	—	—	46·6	46·3
10	7-Hydroxy-6 : 8-bisacetoxymercuri-4 : 5-dimethyl-	$C_{15}H_{14}O_7Hg_2$	Yellow	210	56·9	56·6
11	7-Hydroxy-6-hydroxymercuri-8-acetoxymercuri-4-methyl-3-allyl-	$C_{15}H_{14}O_6Hg_2$	Orange-yellow	212	58·4	57·9
12	7-Hydroxy-6-hydroxymercuri-8-acetoxymercuri-3-benzyl-4-methyl-	$C_{19}H_{16}O_6Hg_2$	Deep red	—	54·6	54·05
13	7-Hydroxy-6-hydroxymercuri-8-acetoxymercuri-4-phenyl-	$C_{17}H_{12}O_6Hg_2$	Deep red	—	55·8	56·2
14	6 : 8-Bisacetoxymercuri-3-carboxy-	$C_{14}H_{10}O_8Hg_2$	Yellow	260	57·0	56·65
15	6 : 8-Bisacetoxymercuri-3-acetyl-	$C_{15}H_{12}O_7Hg_2$	Yellow	215	57·4	56·8
16	6-Acetoxymercuri-3-benzoyl-	$C_{18}H_{12}O_5Hg$	Deep yellow	190	39·2	39·3
17	6 : 6′-Bisacetoxymercuriketodi-	$C_{23}H_{14}O_9Hg_2$	Yellow	192	47·5	47·9
18	6-Acetoxymercuri-thio-	$C_{11}H_8O_3SHg$	Pink	252	47·9	47·6
19	Acetoxymercuri-6-methyl-1 : 2-α-naphthapyrone	$C_{16}H_{12}O_4Hg$	Light red	220	42·1	42·7
20	Acetoxymercuri-6-methyl-3 : 4-β-naphthapyrone	$C_{16}H_{12}O_4Hg$	Light yellow	196	42·3	42·7
21	6 : 8-Bisacetoxymercuri- (from coumarin-6-sulphonic acid)	$C_{13}H_{10}O_6Hg_2$	Yellow	—	61·0	60·5

TABLE III.

Reaction Products of Mercurated Coumarins (Table I) and Carbon Disulphide.

No.	Coumarin derivative produced.	Formula.	Colour.	Decomposition.	% S found.	% S calc.
1	6-Mercaptomercuri-8-hydroxymercuri-	$C_9H_6O_3SHg_2$	Yellow	182°	5·3	5·4
2	7-Hydroxy-6-mercaptomercuri-8-hydroxymercuri-4-methyl-	$C_{10}H_8O_4SHg_2$	Deep red	187	4·85	5·10
16	6-Mercaptomercuri-3-benzoyl-	$C_{16}H_{10}O_3SHg$	Red	—	6·9	6·6
17	6 : 6′-Bismercaptomercuriketodi-	$C_{19}H_{10}O_5S_2Hg_2$	—	—	8·5	8·2
19	Mercaptomercuri-6-methyl-1 : 2-α-naphthapyrone	$C_{14}H_{10}O_2SHg$	—	—	7·7	7·3

collected, washed with alcohol, and dried. It became black at about 195° (Found : Hg, 58·5. $C_{18}H_8O_4Hg_2$ requires Hg, 58·1%).

Action of Iodine on 7-Hydroxy-6 : 8-bisacetoxymercuri-4-methylcoumarin.—The compound (1 g.), suspended in water (50 c.c.), was treated slowly with a solution of iodine and heated until no further absorption was observed. The product, crystallised from alcohol, melted at 172° (Found : I, 68·6. $C_{10}H_7O_3I_3$ requires I, 68·5%).

6-Acetoxymercurithiocoumarin.—When alcoholic solutions of thiocoumarin (1 g.) and mercuric acetate (5 g.) were mixed, a pinkish precipitate (Table II, No. 18) separated; it was washed with alcohol and ether.

The authors express their gratitude to the Government of His Highness the Maharaja Gaekwar of Baroda for a grant.

THE COLLEGE, BARODA (INDIA). [*Received, February 13th,* 1934.]