[From the Department of Organic Chemistry, Research Division, Sharp and Dohme, Inc.]

THE SYNTHESIS OF 3-HYDROXYCINCHONINIC ACID AND CERTAIN OF ITS DERIVATIVES

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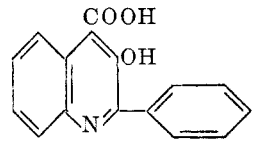
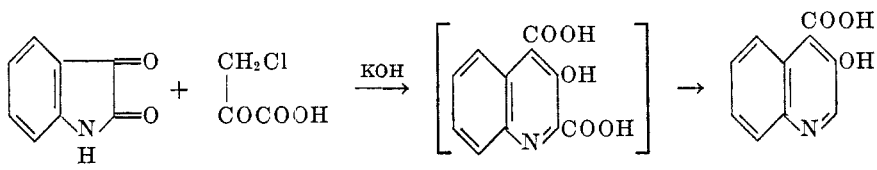
3-Hydroxy-2-phenylcinchoninic acid (HPC) and certain of its derivatives exhibit a number of interesting pharmacological properties (2, 3, 4, 6, 7, 10–13, 18, 23, 24, 26, 27). Blanchard, *et al.* (3) have shown that the 2-phenyl group is



not essential for activity and have reported that 3-hydroxycinchoninic acid (I) is as active pharmacologically as HPC and that it is less toxic. However, an extensive study of this compound was not possible because of the low yield of I obtained in the three-step synthesis employed by these investigators; moreover, the method is not suitable for the preparation of many derivatives of this compound.

In our laboratories, we have found that I is readily prepared by the Pfitzinger reaction using isatin and chloropyruvic acid. The expected product, 3-hydroxy-



I

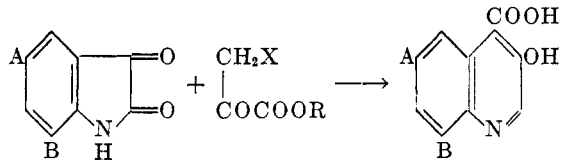
quinoline-2,4-dicarboxylic acid, apparently undergoes decarboxylation under the reaction conditions and I is obtained in yields up to 71 %. The greater lability of the carboxyl group in the 2-position over that in the 4-position is not unexpected since quinoline-2,4-dicarboxylic acid (17) is known to undergo selective decarboxylation (19) to cinchoninic acid. However, the presence of a 3-hydroxy group increases the ease of decarboxylation of both adjacent carboxyl groups since I also loses carbon dioxide under conditions where cinchoninic acid is stable.

Bromopyruvic acid or its ethyl ester was successfully used in place of the chloropyruvic acid and the reaction was readily extended to substituted isatins in place of the parent compound. Seven isatins, 5-chloro-, 5-bromo-, 5-iodo-, 5-methyl-, 5-methoxy-, 7-carboxy-, and 5,7-dichloro-isatin, were converted to the corresponding 3-hydroxycinchoninic acids by this method. Since aqueous solutions of the salts of 3-hydroxycinchoninic acids exhibit fluorescence under untraviolet light, it was possible to follow the progress of the reaction by removing samples of the reaction mixture at various intervals and estimating the

amount of fluorescence. When the reaction was applied to 7-methoxy-4-methylisatin no fluorescence was observed in the reaction mixture and only the starting isatin was isolated. A test reaction with 4-chloro-7-methoxyisatin likewise exhibited no fluorescence; this was assumed to indicate lack of reaction. 3-Hydroxy-6-methoxycinchoninic acid (VII) was demethylated to 3,6-dihydroxycinchoninic acid (VIII) using boiling 48% hydrobromic acid. A summary of the successful preparations appears in Table I.

TABLE I

3-HYDROXYCINCHONINIC ACIDS



No.	A	B	X	R	YIELD,[a] %	M.P.,[b] °C.	FORMULA	ANALYSIS					
								Carbon		Hydrogen		Nitrogen	
								Calc'd	Found	Calc'd	Found	Calc'd	Found
			Cl	H	64[c]								
I	H	H	Br	H	39[d]	224	$C_{10}H_7NO_3$[e]	63.49	63.04	3.73	3.78	7.41	7.36
			Br	C_2H_5	38								
II	Cl	H	Cl	H	79	225–226	$C_{10}H_6ClNO_3$	53.71	53.27	2.70	2.76	6.26	6.20
III	Br	H	Br	H	40	233–234	$C_{10}H_6BrNO_3$	44.80	44.60	2.26	2.23	5.22	5.18
IV	I	H	Br	H	32	239–241	$C_{10}H_6INO_3$	38.12	38.13	1.92	2.11	4.45	4.44
V	Cl	Cl	Cl	H	85[f]	238–240	$C_{10}H_5Cl_2NO_3$	46.54	46.87	1.95	2.15	5.43	5.39
VI	CH_3	H	Cl	H	24	222–224	$C_{11}H_9NO_3$	65.02	65.12	4.47	4.47	6.89	6.89
			Br	H	14								
VII	OCH_3	H	Cl	H	57	227	$C_{11}H_9NO_4$	60.27	59.98	4.14	4.31	6.39	6.45
			Br	H	55								
VIII	OH	H	—	—	96[g]	290	$C_{10}H_7NO_4$	58.54	58.85	3.44	3.59	6.83	6.87
IX	H	COOH	Br	H	21[h]	240–241[i]	$C_{11}H_7NO_5$	56.66	56.66	3.03	2.88	6.01	6.04

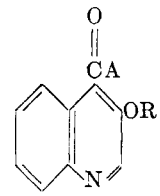
[a] The yields reported are for the crude products initially isolated from the reaction mixture. [b] The compounds usually decarboxylate upon heating, thus to obtain a reproducible decomposition point it is necessary to insert the samples in a preheated bath which is being heated at a constant rate. The melting points reported are uncorrected values obtained by inserting the samples at about 10° below the value recorded and heating at a rate of 1° per 10 seconds. [c] This value is the average of four runs that ranged from 51 to 74%. [d] This value is the average of four runs that ranged from 31 to 51%. [e] *Anal.* Calc'd: Neut. equiv., 189. Found: Neut. equiv., 182. [f] Final purification was by recrystallization from 2-methoxyethanol. [g] This compound was prepared by demethylation of VII as described in the experimental section. [h] Large quantities of a by-product which was very difficult to separate from IX was formed in this reaction. Fractional precipitation followed by recrystallization from 5 *N* HCl then from dimethylformamide gave pure material. In a second run using chloropyruvic acid purification was unsuccessful. [i] The melt quickly resolidified giving a solid which remelted at 279–281°.

A group of German workers (9) have investigated the reaction of isatin and chloropyruvic acid and obtained I in a one-step process; no details or physical properties are available but a complete structure proof of the product is claimed. This information was not available when the present work was underway.

Several functional derivatives of 3-hydroxycinchoninic acid were prepared. The methyl (X) and ethyl (XI) esters were prepared from I using sulfuric acid and the appropriate alsohol. The amide (XII) and the dimethylamide (XIII) were prepared from the methyl ester (X) and the appropriate amine. The 3-acetoxy derivative (XIV) and the more stable 3-butyryloxy derivative (XV)

TABLE II

3-HYDROXYCINCHONINIC ACID DERIVATIVES



No.	A	R	YIELD,[a,b] %	M.P.,[c] °C.	FORMULA	ANALYSIS					
						Carbon		Hydrogen		Nitrogen	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
X	OCH_3	H	94	130–132	$C_{11}H_9NO_3$	65.02	65.00	4.47	4.63	6.89	6.91
XI	OC_2H_5	H	48	69–71	$C_{12}H_{11}NO_3$	66.35	66.05	5.10	5.13	6.45	6.21
XII	NH_2	H	99	252–253	$C_{10}H_8N_2O_2$	63.82	63.75	4.29	4.25	14.89	14.87
XIII	$N(CH_3)_2$	H	34[d]	124–128	$C_{12}H_{12}N_2O_2$	66.65	66.49	5.59	5.54	12.96	12.95
XIV	OH	$COCH_3$	76	210.5	$C_{12}H_9NO_4$	62.33	62.14	3.92	3.93	6.06	6.11
XV	OH	$CO(CH_2)_2CH_3$	40	175–176	$C_{14}H_{13}NO_4$	64.85	64.75	5.05	5.07	5.40	5.41

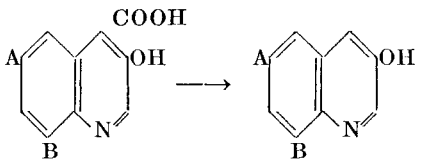
[a] The yields reported are for the crude products isolated from the reaction mixture. [b] Details of the syntheses are given in the experimental section. [c] The melting points are uncorrected values obtained by inserting the sample in a bath preheated to 10 to 15° below the recorded value and heating 1° per 10 seconds. [d] Once recrystallized material.

were prepared from I and the required acid anhydride. The 3-acyloxy derivatives are of interest because of the analogy of I and XIV to salicylic acid and aspirin. Physical and analytical data concerning the functional derivatives appear in Table II.

3-Hydroxyquinoline (XVI) and its derivatives with substituents limited to the benzenoid nucleus have been difficultly accessible, in fact, other than the parent, very few appear in the literature. Since 3-hydroxycinchoninic acid (I) is readily decarboxylated, 3-hydroxyquinoline (XVI) can be obtained in good yields by a two-step process starting with isatin. The decarboxylation reaction was successfully applied to seven of the substituted 3-hydroxycinchoninic acids described in Table I. These reactions and the properties of the compounds pro-

TABLE III

3-HYDROXYQUINOLINES



No.	A	B	YIELD,[a] %	M.P.,[b] °C.	FORMULA	ANALYSIS					
						Carbon		Hydrogen		Nitrogen	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
XVI	H	H	75[c]	200–201[d]	C_9H_7NO	—	—	—	—	—	—
XVII	Cl	H	87[e]	254–255	C_9H_6ClNO	60.18	60.19	3.37	3.53	7.80	7.78
XVIII	Br	H	76[f]	237–238	C_9H_6BrNO	48.24	48.12	2.70	2.77	6.25	6.27
XIX	I	H	73[g]	248–255	C_9H_6INO	39.88	39.96	2.23	2.23	5.17	5.14
XX	Cl	Cl	88[h]	282–283.5	$C_9H_5Cl_2NO$	50.50	50.32	2.35	2.46	6.54	6.53
XXI	CH_3	H	100[i]	181–182	$C_{10}H_9NO$	75.45	75.46	5.70	5.54	8.80	8.76
XXII	OCH_3	H	84[i]	199.5–201.5	$C_{10}H_9NO_2$	68.56	68.55	5.18	5.11	8.00	7.93
XXIII	H	COOH	99[j]	279–280	$C_{10}H_7NO_3$	63.49	63.13	3.73	3.85	7.41	7.32

[a] The yields reported are for the crude products isolated from the reaction mixture. [b] The melting points are taken by inserting the sample in a bath preheated to 10 to 15° below the recorded temperature and heating at about 1° per 10 seconds. [c] This is the average of five runs that ranged from 69 to 87%. [d] Mills and Watson (15) report m.p. 198°. [e] Purified by recrystallization from ethanol. [f] Purified by recrystallization from an ethyl acetate-isopropyl alcohol or ethyl acetate-methanol mixture. *Anal.* Calc'd: Br, 35.67. Found: Br, 35.58. [g] Purified by recrystallization from ethanol. *Anal.* Calc'd: I, 46.82. Found: I, 46.72. [h] Purified by recrystallization from a mixture of methanol and ethyl acetate. *Anal.* Calc'd: Cl, 33.13; Found: Cl, 33.22. [i] Purified by recrystallization from xylene, then from ethyl acetate. [j] This compound requires a much longer time (2.5 hours) for complete decarboxylation to occur. Purification is carried out by recrystallization from glacial acetic acid. Last traces of acetic acid are very difficult to remove from the crystals.

duced are summarized in Table III. This synthesis offers a simple attractive method for obtaining many of this type of 3-hydroxyquinoline.

One quaternary derivative of XVI, 1-methyl-3-hydroxyquinolinium methylsulfate (XXIV), was prepared. This compound is of interest because of its low mouse toxicity and very strong fluorescent properties in ultraviolet light.

EXPERIMENTAL

PYRUVIC ACID DERIVATIVES

Pyruvic acid. Material purchased from the Matheson Co. was fractionated and the fraction boiling at 49.5–50.5 at 4 mm. was used in subsequent reactions.

Chloropyruvic acid was prepared in excellent yields by the method of Garino and Muzio (8) from pyruvic acid and sulfuryl chloride. The material prepared by removing the excess sulfuryl chloride by distillation and storing the residue in an evacuated desiccator over sodalime was satisfactory for use in the Pfitzinger reaction.

Bromopyruvic acid was prepared by the bromination of pyruvic acid according to the method of Springson and Chargaff (21). As with the chloro derivative, the crude product was used without further purification for subsequent reactions.

Ethyl pyruvate was synthesized from pyruvic acid and absolute ethanol according to the procedure of Stekol (22). The yield of material boiling at 40–42° at 9 mm. was 59%.

Ethyl bromopyruvate was prepared in 63% yield by the bromination of the ethyl pyruvate according to the procedure of Ward (25); b.p. 87–97° at 10 mm.

ISATINS

Isatin purchased from the Eastman Kodak Co. was found satisfactory for most purposes; however, better yields and purer products were obtained if this material was either reprecipitated or recrystallized as described in Organic Syntheses (14).

5-Chloroisatin was prepared according to the method of Sandmeyer (20) from *p*-chloroaniline. The yield of *p*-chloroisonitrosoacetanilide was 88%; the yield of 5-chloroisatin was 91%, m.p. 244–245°.

5-Methylisatin was prepared from *p*-toluidine by the Organic Syntheses (14) procedure.

5,7-Dichloroisatin was obtained from the Theodor Schuchardt Co. (Munich, Germany). Three recrystallizations from glacial acetic acid gave pure material, m.p. 223.5–225.5°.

5-Bromoisatin was obtained from the Theodor Schuchardt Co. and was found to be pure enough to be used without further purification.

5-Iodoisatin was prepared by iodination of isatin with iodine monochloride according to the procedure of Musajo (16). The yield was 68%, m.p. 270–272°.

5-Methoxyisatin. *p*-Methoxyisonitrosoacetanilide was prepared in 83–91% yields from *p*-anisidine according to the procedure of Bachman and Picha (1). Ring closure of this intermediate in sulfuric acid as described by these authors (1) gave very poor yields of 5-methoxyisatin. However, if methyl sulfate was used in the reaction mixture according to a procedure supplied by Blanchard (5), yields as high as 58% were obtained, m.p. 198–200°.

4-Methyl-7-methoxyisatin was obtained from the Theodor Schuchardt Co. and used without further purification.

7-Carboxyisatin. When this compound was prepared from anthranilic acid through *o*-carboxyisonitrosoacetanilide, according to the procedure of Sandmeyer (20), an impure product was obtained which was difficult to purify. However, purification by two recrystallizations from pyridine gave material that melted at 275–277°. The yield of crude material was 86%; of twice recrystallized product was 33%.

3-HYDROXYCINCHONINIC ACIDS

A general procedure for the preparation of 3-hydroxycinchoninic acid was devised by substituting an equivalent amount of a substituted isatin in place of the parent compound used in the procedure that follows. An equivalent amount of bromopyruvic acid or ethyl bromopyruvate has been substituted for the chloropyruvic acid. In some cases the potas-

sium salts formed from the isatins are insoluble in the volume specified. In these cases either the halopyruvic acid was added to a suspension of the salts or, preferably, water added until solution was effected at 30–35° and then the halopyruvic acid was added. The reaction involving 5,7-dichloroisatin required a very large volume of water. In general, purification was carried out best by reprecipitation methods; any deviations from this method are noted in Table I, which summarizes the reactions that were carried out.

3-Hydroxycinchoninic acid (I). Recrystallized isatin (644.4 g., 4.38 moles) was dissolved in a hot solution containing potassium hydroxide (1974.7 g., 35.2 moles) and water (3950 ml.). The solution was cooled to 25° and mechanically stirred. Chloropyruvic acid (735 g., 6 moles) was added dropwise over two hours while the temperature was maintained at 22–25° by cooling. The solution was allowed to stand for 6 days at room temperature and then was treated with a saturated solution of sodium bisulfite (containing 153 g., 1.45 moles) in order to prevent the development of color in the product.

The solution was stirred mechanically, cooled to 18° and acidified to Congo Red paper by the gradual addition of concentrated hydrochloric acid (about 2100 ml.). The temperature was maintained at 12–18° with an ice-bath. The yellow solid that separated was removed by filtration, washed with water, and suspended in water (6 l.) containing sulfur dioxide. After stirring for 30 minutes the solid again was separated by filtration.

The wet solid was suspended in water (3.5 l.), stirred, and dissolved by the gradual addition of solid sodium bicarbonate. The solution was treated with a saturated solution of sodium bisulfite (containing 35 g. of solid) and filtered. The filtrate was stirred mechanically and made acid to Congo Red paper by the dropwise addition of concentrated hydrochloric acid. The solid was separated, washed with water, then resuspended in water (1 l.) and again filtered. The solid was suspended in ethanol (700 ml.), separated by filtration, and air-dried. The yield of yellow product was 587 g. (71%). This material is pure enough for most purposes but some samples have been further purified by one or more of four ways: (a) The product was dissolved in aqueous ammonia, treated with decolorizing charcoal, filtered and reprecipitated with hydrochloric acid. (b) It was suspended in acetone or 2-methoxyethanol (Methyl Cellosolve), concentrated hydrochloric acid was added until solution was effected, and then the suspension was treated with decolorizing charcoal, filtered, and precipitated by dilution with water. (c) It was recrystallized, with charcoal treatment, from 5 *N* hydrochloric acid. (d) It was recrystallized from dimethylformamide. A purified sample melts at 224° with decomposition when inserted in a bath preheated to 205° and heated at 1° per 5 seconds. Blanchard (5) reports that material which we have prepared in this manner gave no depression in melting point when mixed with a sample prepared by his method (3).

3,6-Dihydroxycinchoninic acid (VIII). 3-Hydroxy-6-methoxycinchoninic acid (10.96 g., 0.05 mole) was suspended in redistilled 48% hydrobromic acid (100 ml.) and the mixture was refluxed for 5 hours. The solid quickly dissolved upon heating. The solution was cooled whereby large crystals (probably the hydrobromide of 3,6-dihydroxycinchoninic acid) separated. The crystals were removed and suspended in water which caused a rapid conversion to a yellow amorphous solid. The solid was separated, washed with water, and then with ethanol. After drying the yield was 9.85 g. (96%).

The crude material was dissolved in aqueous sodium bicarbonate, treated with sodium bisulfite (2 g.), filtered, and the filtrate acidified (to *p*H 2) using dilute hydrochloric acid. The solid was removed, washed with water, and dried; yield, 8.8 g. Further purification was effected by recrystallization from 6 *N* hydrochloric acid. The product (probably the hydrochloride salt) was digested with hot water (to decompose the salt), filtered, washed with water, then with alcohol, and dried; the yield of bright yellow product was 7.8 g. The melting point was difficult to determine but relatively consistent values could be observed if a sample was inserted in a bath preheated to 250° and heated 1° per 10 seconds; melting occurred at 252° with rapid resolidification to a solid that melted at 290° (uncorr.).

3-HYDROXYCINCHONINIC ACID DERIVATIVES

Methyl 3-hydroxycinchoninate (X). 3-Hydroxycinchoninic acid (37 g., 0.2 mole) was added slowly, with cooling to concentrated sulfuric acid (105 ml., *d.* 1.84). Absolute methanol

(420 ml.) was added cautiously and the mixture was refluxed for 24 hours. The mixture was cooled, poured onto ice (1 kg.) and the resulting solution was made just alkaline by the addition of solid sodium bicarbonate. The solid that separated was removed, washed with water, and dried. The yield was 34 g. (94%).

Recrystallization, and decolorization with carbon, from a mixture of methanol (300 ml.) and water (35 ml.) gave 21 g. After a second recrystallization, this time from *n*-heptane, 15.5 g. of pale yellow needles remained, m.p. 130–132°.

Ethyl 3-hydroxycinchoninate (XI). 3-Hydroxycinchoninic acid (54 g., 0.286 mole) was esterified using ethanol (600 ml.) and concentrated sulfuric acid (150 ml.) in a manner similar to that described for the methyl ester. The yield was 30 g. (48%). After two recrystallizations from *n*-hexane followed by two recrystallizations from *n*-heptane, 16 g. of light yellow crystals remained, m.p. 69–71°.

3-Hydroxycinchoninamide (XII). Methyl 3-hydroxycinchoninate (15.5 g., 0.076 mole) was dissolved in a methanol solution (125 ml.) containing ammonia (16.5 g., 0.97 mole) and the mixture was heated at 100° in an autoclave for 24 hours. The solution was cooled and the precipitate (10 g.) was removed. Evaporation of the filtrate gave a residue of 3.5 g., bringing the total to 13.5 g. (99%). Two recrystallizations from a mixture of dioxane (7 parts) and methanol (1 part) afforded fine white crystals (7 g.), m.p. 252–253°, when inserted at 245° and heated 1° per 7 seconds.

N,N-Dimethyl-3-hydroxycinchoninamide (XIII). Methyl 3-hydroxycinchoninate (30 g., 0.148 mole) was dissolved in a solution of methanol (250 ml.) and dimethylamine (89 g., 1.98 moles). The mixture was heated at 100° for 24 hours in an autoclave and the resulting solution was evaporated to dryness at reduced pressure. The dark oily residue was dissolved in hot water; upon cooling 11.1 g. (34%) of crystalline product separated. Recrystallization from water afforded 9.75 g. of light yellow prisms, m.p. 124–128°.

3-Acetoxycinchoninic acid (XIV). 3-Hydroxycinchoninic acid (37.8 g., 0.2 mole) was suspended in acetic anhydride (120 ml.) and the mixture was heated to boiling. Within 5 minutes the solid had dissolved. After cooling, the solid that separated was removed. The product was washed with a little acetic anhydride and then with ether. The yield was 35.1 g. (76%). Recrystallization from acetic anhydride gave 26 g. of white product, m.p. 210° when inserted at 205° and heated at 1° per 10 seconds. Further purification could be carried out by recrystallization from a mixture of dry dimethylformamide and ethyl acetate. The fine white crystals melted at 210.5° when heated as previously described.

3-Butyryloxycinchoninic acid (XV). 3-Hydroxycinchoninic acid (20 g., 0.1 mole) was refluxed with butyric anhydride (100 ml.) until solution was effected. The solution was filtered and cooled. The solid that separated was removed and washed with hexane. The yield was 11 g. (40%), m.p. 170–171° when inserted in a bath at 160° and heated 1° per 5 seconds. Three recrystallizations from ethyl acetate gave white crystals, m.p. 175–176° when determined as before.

3-HYDROXYQUINOLINE DERIVATIVES

A general procedure for the preparation of substituted 3-hydroxyquinolines was devised by substituting an equivalent amount of a substituted 3-hydroxycinchoninic acid in place of I in the procedure that follows. In the case of the 8-carboxy derivative (XXIII), it was necessary to reflux for 2.5 hours. Table III summarizes the decarboxylations that were carried out. Since the methods of purification of the products varied, these details have been recorded in the notes to the table.

3-Hydroxyquinoline (XVI). 3-Hydroxycinchoninic acid (50 g., 0.264 mole) (I) was added portionwise over 3 to 5 minutes to boiling nitrobenzene (350 ml.). Boiling was continued for 3 to 5 minutes longer and the dark solution was filtered. The gray-brown solid that separated upon cooling was separated, thoroughly washed with hexane, and dried. The yield was 33.4 g. (87%), m.p. 165–172°.

A number of methods of purification of the crude material have been investigated since recrystallization alone was not satisfactory. The best procedure was as follows: The crude

material was suspended in water (100 ml.) and dissolved by stirring and adding the minimum quantity of dilute hydrochloric acid. (The solution may be treated with decolorizing carbon and filtered at this point.) The solution was stirred mechanically and very dilute ammonium hydroxide was added dropwise until the *p*H 5.0 was reached (measured with "Hydrion" paper). The mixture was filtered and the small quantity of precipitate discarded. The filtrate was treated with more ammonium hydroxide to *p*H 7.0. The precipitated solid was separated, washed with a little water, and dried. The recovery was about 80%, m.p. 192–194°. One recrystallization from ethyl acetate gave an 80% recovery, m.p. 194–196.5°. Two more recrystallizations gave white needles, m.p. 200–201° (corr.).

3-Hydroxy-1-methylquinolinium methylsulfate (XXIV). 3-Hydroxyquinoline (13.05 g., 0.09 mole) was dissolved in boiling ethyl acetate (300 ml.) and methyl sulfate (18.9 g., 0.15 mole) added. The mixture was refluxed for 25 minutes during which time an oily product separated. Upon cooling a solid formed, which was separated after 12 hours. The yield was 23.7 g. (97%), m.p. 163–168°. Three recrystallizations from ethanol gave 17.4 g. of light yellow crystals which melted at 145–150°, resolidified, and remelted at 163–165.°

Anal. Calc'd for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16; S, 11.82.
Found: C, 49.03; H, 4.93; N, 5.15; S, 11.78.

Acknowledgment. The analytical data presented in this paper were obtained by Mr. Kermit B. Streeter and his staff.

SUMMARY

3-Hydroxycinchoninic acid (I) has been synthesized by the reaction of isatin with chloro- or bromo-pyruvic acid under the conditions of the Pfitzinger reaction. Seven substituted 3-hydroxycinchoninic acids, the 6-chloro-, 6-bromo-, 6-iodo-, 6-methyl-, 6-methoxy-, 8-carboxy- and 6,8-dichloro- derivatives were produced in an analogous manner using substituted isatins. The methyl and ethyl esters, the amide and dimethylamide, the 3-acetoxy-, 3-butyryloxy-, and 6-hydroxy- derivatives of (I) were prepared by conventional methods. The 3-hydroxycinchoninic acids were decarboxylated to produce the corresponding substituted 3-hydroxyquinolines.

WEST POINT, PA.

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