tion potentials. Cystine, glycine, alanine, phenylalanine, leucine, histidine and valine were found to catalyze this action, while glutamic acid, aspartic acid and tyrosine did not affect it. This division of amino acids according to physicochemical properties closely parallels their division *in vivo* according to their specific dynamic actions.

ROCHESTER, MINNESOTA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF KITASATO INSTITUTE]

THE SYNTHESIS OF CERTAIN QUINOLINE AND ACRIDINE COMPOUNDS

BY KONOMU MATSUMURA

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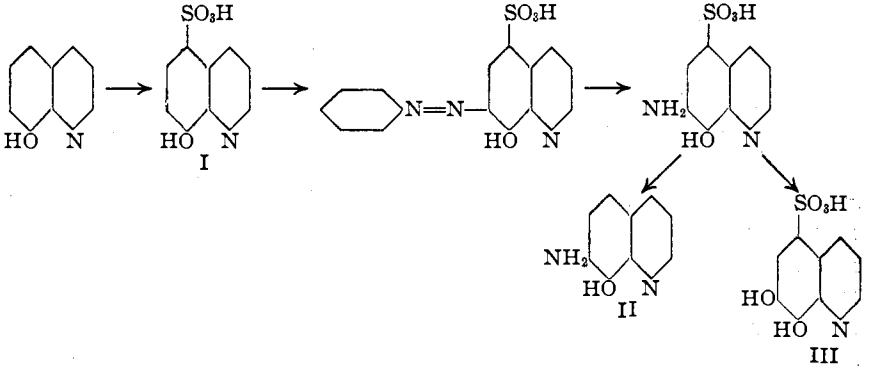
In a study of the physiological action of certain derivatives of quinoline and acridine, the author has prepared a number of compounds related to yatren (the sodium salt of 7-iodo-8-hydroxyquinoline-5-sulfonic acid) which is at present much used in medicine. This paper is a report of these preparations.

I. 7-Amino-8-hydroxyquinoline and Related Compounds

Of the amino derivatives of 8-hydroxyquinoline, the 5-amino-8-hydroxyquinoline was prepared by Kostanecki,[1] and by Fischer and Renouf.[2] The author has prepared the 7-amino-8-hydroxyquinoline using the reactions represented by the following scheme.



8-Hydroxyquinoline-5-sulfonic acid (I) was first prepared by Claus and Posselt,[3] who state that it has no definite melting point but begins to decompose at 270°. The product obtained in the present work by sulfonating 8-hydroxyquinoline by the Claus method melts at 322–323°. Al-

[1] Kostanecki, *Ber.*, **24**, 152 (1891).

[2] Fischer and Renouf, *Ber.*, **17**, 1643 (1884).

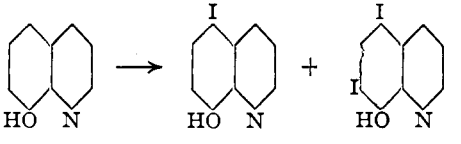
[3] Claus and Posselt, *J. prakt. Chem.*, [2] **41**, 33 (1890).

though this is not in agreement with Claus' description, it seems highly probable that the two compounds are the same. That this compound is not 8-hydroxyquinoline-7-sulfonic acid is shown by the following facts. The amino compound prepared from it melted at 124° and gave a mixed melting point of 102–105° with the 5-amino-8-hydroxyquinoline of Kostanecki (m. p., 143°). It must, therefore, be 7-amino-8-hydroxyquinoline, showing that in the parent substance the sulfonic acid group could not have occupied Position 7.

The 7,8-dihydroxyquinoline-5-sulfonic acid (III) has been shown by Claus and Baumann[4] to be among the decomposition products of yatren obtained when a solution of the latter is heated at 100° for several hours, but it could not be isolated in a pure state. In the present work, it was obtained in a comparatively pure state by the diazotization of 7-amino-8-hydroxyquinoline-5-sulfonic acid and the decomposition of the diazo compound in warm, concentrated sulfuric acid.

II. 5-Iodo-8-hydroxyquinoline

Although the 5-bromo- and 5-chloro-8-hydroxyquinolines are known, the corresponding iodine compound has, curiously enough, never been prepared. Claus,[5] in attempting to iodinate 8-hydroxyquinoline, observed that half of the hydroxyquinoline remained unchanged while the other half gave 5,7-di-iodo-8-hydroxyquinoline. A mono-iodo derivative could not be isolated. In the present work, an aqueous solution of the sodium salt of 8-hydroxyquinoline was treated at room temperature with iodine and potassium iodide, the three compounds being used in equimolecular proportions. The product was found to be a mixture of mono- and di-iodo derivatives of 8-hydroxyquinoline. Conditions under which



the mono-iodo derivative alone could be produced were not found. Iodination, even at temperatures below 0°, always gave some di-iodo compound as a by-product. The position of the iodine atom in the mono-iodo-8-hydroxyquinoline was not proved but, by analogy with the corresponding chloro and bromo derivatives, it seems highly probable that it is in Position 5.

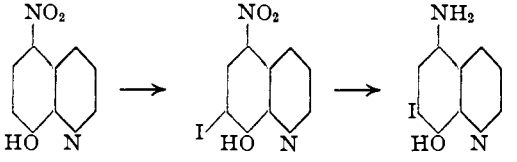
III. 7-Iodo-5-amino-8-hydroxyquinoline

Considerable interest attaches to the physiological action of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, which differs from yatren only in having

[4] Claus and Baumann, *J. prakt. Chem.*, [2] **55**, 465 (1897).

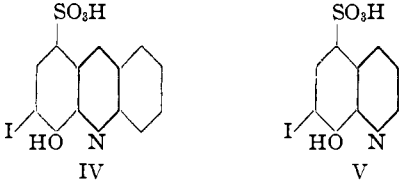
[5] Claus, Ger. pat. 78,880 (1898).

an amino group in Position 5 in place of a sulfonic acid group. It was synthesized according to the following scheme.



IV. 3-Iodo-4-hydroxy-acridine-1-sulfonic Acid (IV)

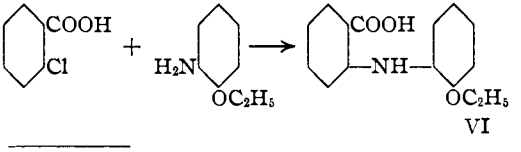
The constitution of this compound in the acridine series corresponds to that of loretin (V), the valuable pharmaceutical product in the quinoline series. It was prepared from 4-hydroxy-acridine by sulfonation and sub-



IV V

sequent iodination, a method similar to that used in the preparation of loretin.[6] Moreover, in analogy with loretin, the sulfonic acid group and the iodine atom introduced into the acridine nucleus were assumed to occupy Positions 4 and 2, respectively. In the preparation of 4-hydroxy-acridine, *o*-phenetidine was first condensed with *o*-chlorobenzoic acid to form 2-ethoxy-2′-carboxylic diphenylamine (VI). This compound was then treated for 15 minutes with seven times its weight of concd. sulfuric acid on a boiling water-bath. The product was found to be a mixture of about equal amounts of 4-ethoxy- and 4-hydroxy-acridones.

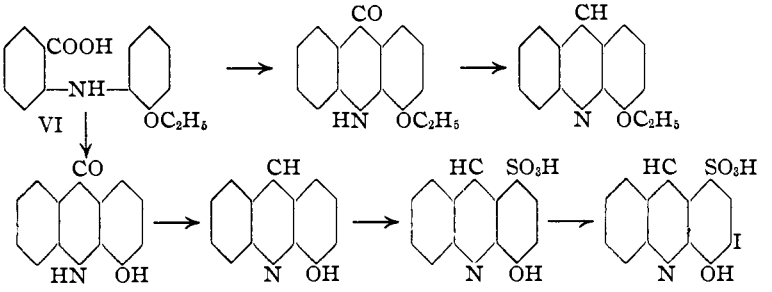
The melting point and other properties of the hydroxy-acridone thus obtained agreed with that of 4-hydroxy-acridone which had previously been prepared by Ullmann[7] by demethylation of 4-methoxy-acridone with aluminum chloride. The ethoxy- and hydroxy-acridones thus prepared were converted into the corresponding acridines by reduction with sodium in amyl alcohol. The synthesis was carried out according to the following scheme.



VI

[6] Ref. 4, p. 457.

[7] Ullmann, *Ann.*, **355**, 343 (1907).



In the preparation of the acridone if the concd. sulfuric acid was kept for a shorter time (five minutes) on the water-bath, 4-ethoxy-acridone was the sole product. If the heating was continued for 30 minutes there resulted a water-soluble product, but this compound was not further investigated.

Experimental Part

8-Hydroxyquinoline-5-sulfonic Acid.—Fourteen and one-half g. of 8-hydroxyquinoline was dissolved gradually during the course of an hour in seven times its weight of fuming sulfuric acid (containing 4% of sulfur trioxide) at a temperature not exceeding 10°. After standing for 24 hours at 8°, the mixture was poured over 400 g. of crushed ice. A copious precipitate was obtained. It was filtered off, washed well with cold water and recrystallized from hot, dil. hydrochloric acid (about 5%). The crystals are large, almost colorless needles, melting at 322–323° and containing water of crystallization which is driven off by drying at 100°; yield, 25 g., or 96%.

7-Azobenzene-8-hydroxyquinoline-5-sulfonic Acid.—Twenty-four g. of 8-hydroxyquinoline-5-sulfonic acid was coupled with an equivalent quantity of diazobenzene chloride in alkaline solution. The compound was obtained in needles of a dark red color which darken at 267° and melt at 310°. It is slightly soluble in hot alcohol and insoluble in water, benzene and chloroform; yield, 31 g., or 94%.

Anal. Calcd. for $C_{15}H_{11}O_4N_3S$: N, 12.8. Found: 12.7.

The Sodium Salt formed orange-colored needles fairly soluble in water.

7-Amino-8-hydroxyquinoline-5-sulfonic Acid.—The sodium salt of 7-azobenzene-8-hydroxyquinoline-5-sulfonic acid prepared from 24 g. of 8-hydroxyquinoline-5-sulfonic acid, was dissolved in 500 cc. of hot water and reduced with 64 g. of crystallized stannous chloride and 160 cc. of concd. hydrochloric acid (d., 1.19) by the method of Witt.[8] The tin double salt which was salted out from the reduction mixture was dissolved in hot water and treated with hydrogen sulfide. The free base, which was precipitated admixed with tin sulfide, was extracted several times with boiling, dil. acetic acid. The united extracts, on cooling, deposited long, orange needles which were recrystallized from dil. hydrochloric acid. The compound was insoluble in ether, benzene and chloroform and was slightly soluble in water and hot alcohol. It did not melt at 310°. It dissolved in sodium acetate solution to give a Bordeaux red color. Its alkaline solution darkened with an excess of alkali. It loses its water of crystallization (one mole) on drying at 110° and takes on a more reddish color. With ferric chloride the yellow aqueous solution becomes violet; yield, 14 g.

Anal. Calcd. for $C_9H_8O_4N_2S.H_2O$: C, 47.0; H, 3.5; N, 12.2; S, 13.3; H_2O, 7.0. Found: C, 45.0; H, 3.7; N, 12.1; S, 12.1; H_2O, 6.9.

[8] Witt, *Ber.*, **21**, 3472 (1888).

7-Acetylamino-8-hydroxyquinoline-5-sulfonic Acid.—Two and four-tenths g. of 7-amino-8-hydroxyquinoline-5-sulfonic acid, 2 g. of anhydrous sodium acetate, 1.1 g. of acetic anhydride and 7 g. of toluene were refluxed on a water-bath for one hour and, after evaporating the toluene under diminished pressure, some water was added to dissolve the acetyl compound. The deep brown solution, after filtration, was acidified with dil. hydrochloric acid (Congo red). On standing overnight it deposited light yellow prisms which were filtered off and washed well with water. The compound was insoluble in ether and difficultly soluble in water, hot alcohol and hot chloroform; m. p., 277°, with decomposition; yield, 3.3 g.

Anal. Calcd. for $C_{11}H_{10}O_5N_2S$: S, 11.3. Found: 10.4.

7-(*p*-Nitrobenzoylamino)-8-hydroxyquinoline-5-sulfonic Acid.—Two and eight-tenths g. of 7-amino-8-hydroxyquinoline-5-sulfonic acid and 1.1 g. of sodium carbonate were dissolved in 25 cc. of water, and 2 g. of *p*-nitrobenzoyl chloride was added. The mixture was stirred for three hours at room temperature. The slightly colored, homogeneous paste thus formed was acidified with dil. hydrochloric acid, filtered, washed with water and alcohol and then with ether. The compound crystallized from hot water in slightly yellowish, fibrous needles melting at 297° with decomposition. It was insoluble in benzene, ether and alcohol; yield, 3.5 g.

Anal. Calcd. for $C_{16}H_{11}O_7N_3S$: S, 8.2. Found: 8.0.

7,8-Dihydroxyquinoline-5-sulfonic Acid.—Two and two-tenths g. of 7-amino-8-hydroxyquinoline-5-sulfonic acid was dissolved in 2 cc. of concd. sulfuric acid, and 20 cc. of water was added. The fine suspension of the free base produced was diazotized at room temperature with 0.7 g. of sodium nitrite, dissolved in 5 cc. of water. After some hours, the clear brown solution deposited the diazo compound in the form of yellow crystals. It was filtered off, washed with a small quantity of water and dried on a plate. It began to decompose at 187° and became a tar at 300°. It was slightly soluble in water; yield, 1.4 g.

To obtain the dihydroxy compound, the solution of 1.2 g. of the diazo compound in 2.5 cc. of concd. sulfuric acid was warmed at 120–150° until the evolution of nitrogen gas had ceased. The reaction mixture was then poured (after cooling) into 25 g. of ice water. The precipitate was filtered, washed with a small quantity of water and recrystallized from acidulated water. It separated in the form of yellow needles melting at 302°, with decomposition. It was insoluble in ether, slightly soluble in hot alcohol and readily soluble in hot water. It reduced Fehling's solution and ammoniacal silver solution in the cold; yield, 0.25 g.

Anal. Calcd. for $C_9H_7O_5NS$: N, 5.8. Found: 5.7.

7-Amino-8-hydroxyquinoline.—A mixture of 3.3 g. of 7-amino-8-hydroxyquinoline-5-sulfonic acid, 100 cc. of water and 6.6 cc. of concd. hydrochloric acid was heated for six hours at 170°, concentrated under reduced pressure and carefully neutralized with crystallized soda. The mixture was then extracted with ether and the ether allowed to evaporate. The compound separated out in slightly brown-colored prisms. It began to decompose at 117° and melted at 124°. It was soluble in alcohol, ether, chloroform and benzene but almost insoluble in water; yield, 2 g.

Anal. Calcd. for $C_9H_8ON_2.H_2O$: N, 16.0. Found: 16.2.

The HYDROCHLORIDE gave short needles from alcohol; m. p., 256°.

The PICRATE gave reddish-brown prisms from alcohol; m. p., 205°, with decomposition.

Anal. Calcd. for $C_9H_8ON_2.2C_6H_3O_7N_3$: N, 18.1. Found: 18.1.

7-Acetylamino-8-hydroxyquinoline.—**Three g.** of finely powdered 7-amino-8-hydroxyquinoline was suspended in a small quantity of ether and the calculated amount of acetic

anhydride, together with some anhydrous sodium acetate, was added to the suspension. After a few days' standing with occasional shaking, the ether was evaporated and some water was added to the residue. The resulting mixture was neutralized with sodium carbonate and extracted with chloroform. The product was recrystallized from ether in colorless needles melting at 177°. It was readily soluble in alcohol, moderately soluble in hot benzene and chloroform but difficultly soluble in ether; yield, 2.5 g.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.9. Found: 14.0.

7-Acetylamino-8-hydroxyquinoline Methyl Iodide.—A solution of 2 g. of 7-acetylamino-8-hydroxyquinoline was refluxed for four hours on a water-bath with 2 cc. of methyl iodide in 15 cc. of methyl alcohol. After evaporating the methyl alcohol and excess of methyl iodide the brown, crystalline residue was recrystallized from hot alcohol. It formed in light yellow needles; m. p., 195°.

Anal. Calcd. for $C_{12}H_{13}O_2N_2I$: I, 36.9. Found: 36.9.

5-Iodo-8-hydroxyquinoline.—Eight and seven-tenths g. of 8-hydroxyquinoline and 2.4 g. of sodium hydroxide were dissolved in a small amount of water and the solution was diluted to 1200 cc. A solution of 15.25 g. of iodine and an equivalent quantity of potassium iodide in 60 cc. of water was then added with constant stirring during the course of an hour and a half. The slightly pink mass which separated was filtered, washed well with water and dried on a plate. It was treated with about 150 cc. of hot alcohol and filtered hot to separate the two iodination products. One of these (*A*) was insoluble in the hot alcohol and remained on the filter, the other (*B*) being recovered from the filtrate on cooling.

A was obtained from hot glacial acetic acid in yellowish needles which began to give off brown fumes at 195° and which melted at 210°. The iodine content of the product was approximately that calculated for the 5,7-di-iodo-8-hydroxyquinoline of Claus; yield, 6.2 g.

Anal. Calcd. for $C_9H_5ONI_2$: I, 64.0. Found: 64.1.

B crystallized from alcohol in colorless prisms melting at 127–128°. The analysis corresponded to that calculated for the mono-iodo derivative; yield, 6.5 g.

Anal. Calcd. for C_9H_6ONI: I, 46.9; N, 5.2. Found: I, 46.5; N, 5.0.

5-Iodo-8-hydroxyquinoline Methyl Iodide.—A mixture of 1 g. of 5-iodo-8-hydroxyquinoline and 1 cc. of methyl iodide was kept at 100° for five hours in a sealed tube. After evaporating the excess of methyl iodide, the product was recrystallized from hot alcohol. It formed in brown needles melting at 142°. The compound was slightly soluble in hot water, insoluble in ether and readily soluble in hot alcohol; yield, 1.3 g.

Anal. Calcd. for $C_{10}H_9ONI_2$: I, 61.5. Found: 61.2.

7-Iodo-5-nitro-8-hydroxyquinoline.—A solution of 9 g. of iodine and an equivalent quantity of potassium iodide in 65 cc. of water was added during the course of an hour to a solution of 6.5 g. of 5-nitro-8-hydroxyquinoline (m. p., 180°) and 4 g. of sodium hydroxide in 1700 cc. of water, the mixture being constantly agitated and kept at room temperature. The product was precipitated from the reaction mixture by acidifying it with dil. sulfuric acid (litmus). The precipitate, after being washed with water and alcohol, crystallized from alcohol in orange needles; m. p., 249°, with decomposition. The compound did not diazotize; yield, 10.3 g.

Anal. Calcd. for $C_9H_5N_2O_3I$: N, 8.9; I, 40.4. Found: N, 9.0; I, 40.3.

7-Iodo-5-amino-8-hydroxyquinoline.—Six and four-tenths g. of 7-iodo-5-nitro-8-hydroxyquinoline, 15 g. of crystallized stannous chloride and 22 g. of concd. hydrochloric acid (d., 1.19) were mixed together and stirred until the orange color disappeared. The tin double salt, consisting of light yellow plates, was dissolved in 800 cc. of warm

water and treated with hydrogen sulfide. From the filtrate from the tin sulfide 7-iodo-5-amino-8-hydroxyquinoline was precipitated by the addition of sodium acetate. It crystallized in yellowish needles (from ether) which softened at about 147° and melted at 157°. It was soluble in dil. hydrochloric acid, sodium hydroxide solution, alcohol, ether and benzene; yield, 2.5 g.

Anal. Calcd. for $C_9H_7N_2OI$: I, 44.7. Found: 44.5.

The HYDROCHLORIDE gave light yellow needles; m. p., 255°, with decomposition. The PICRATE gave reddish-brown needles which decomposed at 159°.

2-Ethoxy-2'-carboxylic-diphenylamine (VI).—A mixture of 15 g. of *o*-chlorobenzoic acid (m. p., 137°, prepared from anthranilic acid by the Sandmeyer reaction), 15 g. of *o*-phenetidine, 15 g. of potassium carbonate, 2 g. of copper bronze and 100 cc. of amyl alcohol was gently refluxed for three hours in an oil-bath. The alcohol was removed by distillation with steam and the residual liquid was filtered while hot. The filtrate was made up to one liter by addition of water and acidified with hydrochloric acid. The diphenylamine carbonic acid separated in greenish-yellow crystals which were filtered while hot and washed with hot water. The compound was recrystallized from alcohol (90%) in yellow needles melting at 160–161°. It was readily soluble in hot alcohol and hot benzene but insoluble in water; yield, 20 g., or 80%.

Anal. Calcd. for $C_{15}H_{15}O_3N$: N, 5.4; C, 70.0; H, 5.8. Found: N, 5.6; C, 70.5; H, 6.1.

4-Ethoxy- and 4-Hydroxy-acridone.—Twenty g. of 2-ethoxy-2'-carboxylic-diphenylamine was dissolved in 140 cc. of concd. sulfuric acid and the solution kept in a boiling water-bath for 15 minutes. The solution was cooled and poured into ice water. The yellow solid which separated was filtered off, washed well with water and treated with warm, dil. sodium hydroxide solution (about 1%) to remove the hydroxy-acridone, the ethoxy-acridone remaining undissolved. The latter crystallized from hot acetic acid (50%) in yellow needles melting at 320°, with decomposition. In alcoholic or glacial acetic acid solution it gave a bluish-green fluorescence and in concd. sulfuric acid solution a greenish-blue color; yield, 9 g.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.9. Found: 5.8.

From the above sodium hydroxide solution, crude 4-hydroxy-acridone was precipitated on acidifying with hydrochloric acid. After being made alkaline with sodium carbonate, it was filtered off and washed with water. It crystallized from hot acetic acid (40%) in yellow needles; m. p., 300°; yield, 6 g.

Anal. Calcd. for $C_{13}H_9O_2N$: N, 6.6. Found: 6.4.

4-Ethoxy-acridine.—Nine g. of 4-ethoxy-acridone was reduced by sodium (30 g.) in amyl alcohol (340 cc.). The sodium was added slowly to the boiling alcohol solution and when the reduction was complete (about three and one-half hours), the viscous reaction product was cooled to 100°, water was added with shaking and the strongly alkaline solution was siphoned off, amyl alcohol was steam distilled and the precipitate was collected, washed with water and purified through its picrate. From the picrate the acridine was obtained by decomposition with hydrochloric acid. The acridine formed in yellow needles, melting at 80° and readily soluble in alcohol and ether. A dilute solution in alcohol gave a bluish-green fluorescence; yield (as picrate), 9 g.

Anal. Calcd. for $C_{15}H_{13}ON$: N, 6.3. Found: 6.3.

The HYDROCHLORIDE gave yellow needles; m. p., 220°, with decomposition.

The SULFATE gave yellow needles; m. p., 250°.

The PICRATE gave yellow needles; m. p., 255°.

Anal. Calcd. for $C_{15}H_{13}ON.C_6H_3O_7N_3$: N, 12.4. Found: 12.4.

Methyl Sulfate.—To the solution of 2 g. of 4-ethoxy-acridine in 40 cc. of nitrobenzene, 1.3 cc. of dimethyl sulfate was added at 190°. After cooling, the nitrobenzene and excess of dimethyl sulfate were distilled under reduced pressure. The resinous residue was thoroughly washed with ether and dissolved in alcohol. The tarry precipitate which was formed on addition of ether to the above alcoholic solution crystallized in the course of several days. It formed in orange-yellow, hygroscopic needles; m. p., 189°. The aqueous solution showed a light green fluorescence; yield, 2.5 g.

Anal. Calcd. for $C_{17}H_{19}O_4NS$: S, 9.6. Found: 9.4.

4-Hydroxy-acridine.—This compound was obtained in exactly the same manner as that described for ethoxy-acridine. It formed in yellow, spindle-shaped crystals melting at 117° and soluble in alcohol and ether. The alcoholic solution showed a green fluorescence. In concd. sulfuric acid, it dissolved to give a yellow solution and a green fluorescence.

Anal. Calcd. for $C_{13}H_9ON$: N, 7.2; C, 80.0; H, 4.6. Found: N, 7.2; C, 79.1; H, 4.9.

The HYDROCHLORIDE gave orange needles; m. p., 252° (with decomposition).

The SULFATE gave orange needles; m. p., 240°.

The PICRATE gave orange needles; m. p., 215°.

Anal. Calcd. for $C_{13}H_9ON.C_6H_3O_7N_3$: N, 13.2. Found: 13.1.

4-Hydroxy-acridine-1-sulfonic Acid.—4-Hydroxy-acridine was dissolved in eight times its weight of fuming sulfuric acid (5%) in the cold. After standing for 24 hours at 8° it was poured into ice water. The yellow precipitate thus obtained was filtered off, dissolved in soda and reprecipitated with dil. hydrochloric acid. It formed in yellow columns; m. p., 301°, with decomposition; yield, quantitative.

Anal. Calcd. for $C_{13}H_9O_4NS$: S, 11.6. Found: 12.4.

3-Iodo-4-hydroxy-acridine-1-sulfonic Acid.—One g. of 4-hydroxy-acridine-1-sulfonic acid, 0.25 g. of potassium carbonate and 0.6 g. of potassium iodide were dissolved in 30 cc. of hot water, and one g. of bleaching powder (25%) was added with constant stirring to the boiling solution. The thick, yellow paste which resulted was cooled and acidified with dil. hydrochloric acid (5%) at 0°. After being allowed to stand overnight, it was filtered, dissolved in soda, reprecipitated with dil. hydrochloric acid and washed with small quantities of water. It consisted of yellow needles which gave off iodine fumes at 240° and melted at 264°, with decomposition. It was moderately soluble in water and slightly soluble in hot alcohol.

Anal. Calcd. for $C_{13}H_8O_4NSI$: I, 31.7. Found: 31.5.

This research was carried out under the supervision of Professor S. Hata. Certain of the substances obtained are being tested pharmacologically at Kitasato Institute under the direction of Professor Hata and Dr. T. Hachiya.

Summary

The following compounds in the quinoline series have been described: 7-azobenzene-8-hydroxyquinoline-5-sulfonic acid, 7-amino-8-hydroxyquinoline-5-sulfonic acid, 7,8-dihydroxyquinoline-5-sulfonic acid, 7-amino-8-hydroxyquinoline, 5-iodo-8-hydroxyquinoline, 7-iodo-5-nitro-8-hydroxyquinoline and 7-iodo-5-amino-8-hydroxyquinoline; in several of these cases suitable derivatives such as the picrate, the acetate and the hydrochloride have been also described.

The following compounds connected with the acridine syntheses have been characterized: 2-ethoxy-2-carboxylic-diphenylamine, 4-ethoxy-acridone, 4-hydroxy-acridone, 4-ethoxy-acridine, 4-hydroxy-acridine, 4-hydroxy-acridine-1-sulfonic acid and 3-iodo-4-hydroxy-acridine-1-sulfonic-acid.

TOKYO, JAPAN

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

THYMOLBENZEIN, 4-HYDROXY-3-ISOPROPYL-6-METHYL-BENZOPHENONE AND SOME OF THEIR DERIVATIVES

BY W. R. ORNDORFF AND H. T. LACEY[1]

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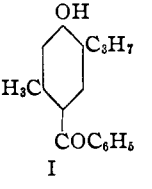
In connection with the investigation of the phthaleins and related substances underway in this Laboratory it seemed desirable to study thymolbenzein, the mother substance of thymolphthalein,[2] thymoltetrachlorophthalein[3] and thymolsulfonephthalein.[4] Since thymolbenzein had not been made, the purpose of this investigation was to prepare it, to study it and to make derivatives of it characteristic of the benzeins.

Thymolbenzein was made by the action of benzotrichloride upon thymol with the subsequent decomposition of the hydrochloride thus formed. A benzophenone derivative, 4-hydroxy-3-*iso*propyl-6-methylbenzophenone (I), was also obtained. The benzotrichloride probably first reacts with



I

one molecule of thymol to form 4-hydroxy-3-*iso*propyl-6-methyldiphenyldichloromethane, which gives the ketone (I) on hydrolysis. The diphenyldichloromethane derivative then reacts with another molecule of thymol, or benzotrichloride reacts with two molecules of thymol to form the unstable chloride of the carbinol form of thymolbenzein, which immediately rearranges to form the stable hydrochloride of thymolbenzein. The latter is either a carbonium (II) or an oxonium (III) salt. It de-

[1] From a dissertation presented by H. T. Lacey, Grasselli Fellow in Chemistry for 1925–1926, to the Faculty of the Graduate School of Cornell University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Traube, *Arch. Pharm.*, [3] **23**, 536 (1887). Sørensen, *Ergebnisse Physiol.*, **12**, 383 (1912).

[3] Cornwell and Esselstyn, THIS JOURNAL, **49**, 826 (1927).

[4] Lubs and Clark, *J. Wash. Acad. Sci.*, **5**, 614 (1915); **6**, 481 (1916). Orndorff and Cornwell, THIS JOURNAL, **48**, 981 (1926).