Summary and Conclusions

1. A study of the relative effect of polarized and non-polarized light on the decomposition of cocaine has been made, in which (a) several concentrations of cocaine hydrochloride were used; (b) two methods of obtaining a polarized radiation were used; (c) the times of irradiation ranged from one to twelve hours; (d) the effect was tested on goldfish and *Lupinus albus.*
2. The conclusion is drawn that polarized radiations have no selective action in the decomposition of cocaine hydrochloride.
3. Cocaine is slowly decomposed by light.
4. Obvious sources of error which we have tried to eliminate are: the variability of individual goldfish, the tolerance that goldfish develop to cocaine and the effect of traces of impurity in the water.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF KITASATO INSTITUTE]

THE SYNTHESIS OF CERTAIN ACRIDINE COMPOUNDS

BY KONOMU MATSUMURA

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In continuation of work on the preparation of certain acridine derivatives for bactericidal examination,[1] this paper deals with the preparation of the following compounds.

V. 9-Amino-3,6-dimethoxy-acridinium-methyl Chloride

9-Amino derivatives of acridine compounds are now attracting considerable interest in the field of medicine. Of these, Rivanol (2-ethoxy-6,9-diamino-acridine-hydrochloride) is the only product now employed in practice. The compound described here was prepared as a further contribution to the study of this kind of compounds.

Diphenylmethane, prepared from benzyl chloride, benzene and aluminum chloride by Radziewanowski's method,[2] was first converted into 3,6-diamino-acridone (I) by nitration, oxidation, and subsequent reduction by Schöpff's[3] and Staedel's[4] methods, respectively, with a little modification. 3,6-Diamino-acridone was then converted into 9-amino-3,6-dimethoxy-acridine (II) by hydrolysis with 50% sulfuric acid, methylation with dimethyl sulfate, chlorination with phosphorus pentachloride and subsequent amidation with ammonia. 9-Amino-3,6-dimethoxy-acridine on acetylation, treatment with *p*-toluene-methyl-sulfonate, and subsequent hydrolysis with hydrochloric acid, gave 9-amino-3,6-dimethoxy-acridinium-methyl chloride (IV).

[1] Matsumura, THIS JOURNAL, **49**, 810 (1927).

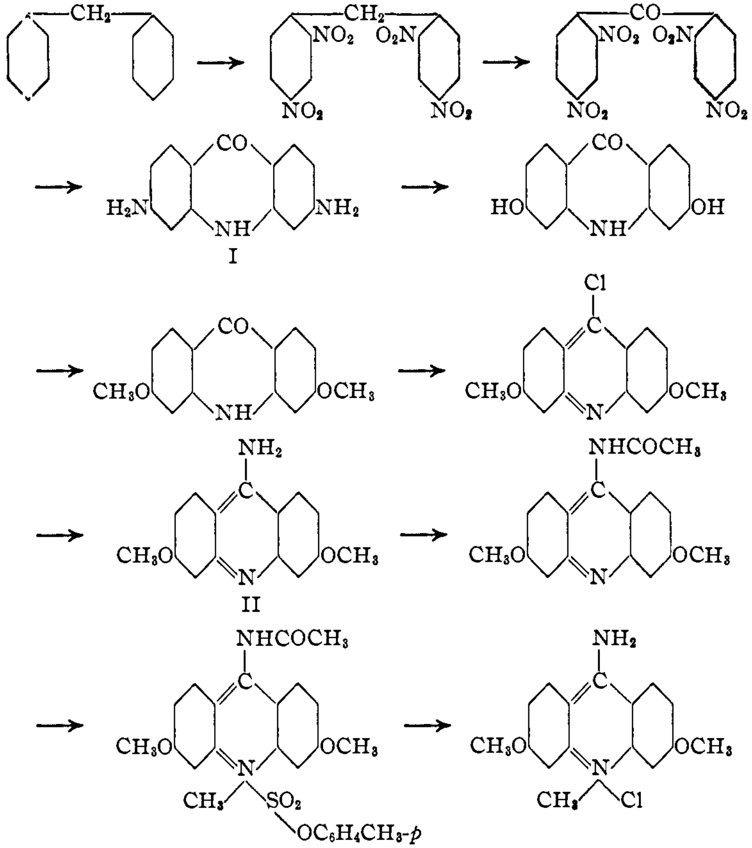
[2] Radziewanowski, *Ber.*, **28**, 1136 (1895).

[3] M. Schöpff, *ibid.*, **27**, 2318 (1894).

[4] Staedel, *Ann.*, **218**, 339 (1883)

The methyl iodide of 9-acetamino-3,6-dimethoxy-acridine (III) was obtained by direct combination of the components, but its scanty solubility in water made it disadvantageous in practice for physiological study.

The yields in all these steps of the synthesis are generally good enough for technical operation. The whole process of the synthesis is represented by the following scheme.



Experimental Part

2,4,2',4'-Tetranitrodiphenylmethane.—The following modification of M. Schöpff's[3] method was used: 135 g. of finely powdered potassium nitrate was dissolved in 700 g. of concd. sulfuric acid below 30° during about three-quarters of an hour. 50 g. of diphenylmethane (b. p. 260°) was introduced into the solution under constant stirring during one and one-half hours at 10–25°. The mixture was then gradually warmed to 70° on the sand-bath and kept at that temperature for half an hour under stirring and then allowed to stand. After being cooled, it was poured into 4 liters of ice water, when a light yellow precipitate was obtained which was filtered and washed.

After being dried, it was boiled with 200 cc. of alcohol, filtered while hot and recrystallized from 400 g. of boiling glacial acetic acid, giving large prisms of light yellow color; m. p. 173°; yield, 81 g. (77%) after recrystallization.

2,4,2′,4′-Tetranitrobenzophenone.—For the preparation of this compound by Staedel's method, the following procedure was found to be the best. To the boiling solution of 17 g. of tetranitrodiphenylmethane in 270 g. of glacial acetic acid, 25 g. of chromic oxide was gradually introduced from the upper end of the cooler during half an hour, and kept boiling for two and one-half hours longer.

Next day the separated crystals were filtered from glacial acetic acid, washed with glacial acetic acid, then with water and with alcohol, giving slightly yellowish prisms; m. p. 232°; yield, 16.5 g. (93%). The melting point is not in agreement with Staedel's and Schöpff's descriptions (m. p. 225°). The lower melting point may perhaps be due to the presence of unaltered mother substance.

3,6-Diamino-acridone.—An attempt to reduce the nitro derivative to diamino-acridone by tin metal and concd. hydrochloric acid led to the formation of much tar, from which only a small amount of the diamino-acridone could be isolated. It was abandoned then and Schöpff's method[3] was used in entirety. This process gave almost colorless needles, which are unaltered at 320°; yield, 10.7 g. (97%) from 18 g. of tetranitrobenzophenone.

3,6-Dihydroxy-acridone.—Attempts to convert the amine into the corresponding hydroxyl compound by the usual method of heating the diazotized solution of the amine led to the formation of much disagreeable black-violet coloring matter, from which only a small amount of dihydroxy-acridone could be extracted, whereas the direct hydrolysis by sulfuric acid was found very satisfactory.

Twelve g. of 3,6-diamino-acridone, 50 cc. of water and 40 g. of concd. sulfuric acid were heated in an enameled autoclave at 195° for six hours. After being cooled, the contents consisted of a light brown colored cake and a slightly colored liquid. The cake was dissolved in an excess of dilute sodium hydroxide solution and after filtration precipitated again with dilute hydrochloric acid. It was recrystallized from boiling glacial acetic acid or better from boiling alcohol, giving almost colorless thin plates or columns of silky luster. It was unaltered at 320°.

The solution in conc. sulfuric acid gives pure blue fluorescence. It is fairly soluble in hot alcohol, in hot glacial acetic acid and acetone, very difficultly in nitrobenzene and insoluble in water, benzene and ether; yield, 10.2 g. (85%).

Anal. Subs., 0.0940: N_2, 5.2 cc. (16°, 760 mm.). Calcd. for $C_{13}H_9O_3N$: N, 6.17. Found: N, 6.44.

3,6-Dimethoxy-acridone.—To a boiling solution of 9 g. of 3,6-dihydroxy-acridone, 4.6 g. of potassium hydroxide and 5 cc. of water, in 50 cc. of alcohol, 12 cc. of dimethyl sulfate was added from the upper end of the cooler in three separated portions.

A violent reaction occurred at each addition and precipitate was produced. The mixture was boiled for an hour longer. On being cooled, it was made strongly alkaline by the addition of a solution of 4.5 g. of sodium hydroxide in 100 cc. of water. The precipitate of microscopic columns was filtered after standing for one night, washed with water and recrystallized from glacial acetic acid.

It gave almost colorless short needles or plates, unaltered at 320°; its concd. sulfuric acid solution shows a bluish-green fluorescence, and it is fairly soluble in hot alcohol and hot glacial acetic acid, but insoluble in benzene and ether; yield, 7.8 g. (77%).

Anal. Subs., 0.0937: N_2, 4.5 cc. (16°, 759 mm.). Calcd. for $C_{15}H_{13}O_3N$: N, 5.49. Found: N, 5.58.

9-Chloro-3,6-dimethoxy-acridine.—5.1 g. of 3,6-dimethoxy-acridone, 4.6 g. of phosphorus pentachloride and 12 cc. of dry toluene were well mixed into a homogeneous paste. The mixture was gradually warmed to 120–130° during an hour with occasional stirring and kept at that temperature for three hours longer. The toluene and phosphorus oxychloride were driven off by the current of dry air and the material was allowed to cool. The yellow mass thus obtained was treated with ice water, converted into a fine powder, and on making alkaline with dilute aqueous ammonia, free base was obtained; m. p. 152–8°; yield, 5.6 g. The product so obtained is good enough for use in the next step of the synthesis. For the further purification for analytical use, the crude product was dissolved in cold alcohol, and the filtered solution was concentrated in vacuum at room temperature. On addition of cold water to the concd. alcoholic solution, the chlorodimethoxy-acridine separated out as long needles of light yellow color; m. p. 184°. It was easily soluble in alcohol with green fluorescence, difficultly in benzene, almost insoluble in water and the solution in concd. sulfuric acid gave an intense green fluorescence.

Anal. Subs., 0.2833: AgCl, 0.1478. Calcd. for $C_{15}H_{12}O_2NCl$: Cl, 12.98. Found: Cl, 12.88.

The hydrochloride gave yellow needles and is very easily soluble in cold alcohol and rather difficultly in cold water.

9-Amino-3,6-dimethoxy-acridine.—A mixture of 70 cc. of absolute alcohol and 3 g. of copper acetate was strongly cooled by ice and salt and saturated with ammonia (dried through calcium oxide) at 0°. To this solution finely powdered, crude 9-chloro-3,6-dimethoxy-acridine prepared from 5.1 g. of dimethoxy-acridone was added and heated at 140° (24 atm.) in an autoclave for eight hours. After the evaporation of alcohol and excess of ammonia, the residual mass was extracted twice with hot dilute hydrochloric acid and then with hot water. The united hot extracts were made alkaline with dilute aqueous sodium hydroxide, when intensely yellow crystals separated and crystallized as yellow prisms from alcohol; m. p. 268°.

It is fairly soluble in ether, easily in acetone and hot nitrobenzene, sparingly in chloroform, benzene and hot water. The solution in concd. sulfuric acid gives a green fluorescence and on dilution with water a violet-blue fluorescence is shown. The alcoholic solution gives a green fluorescence and on dilution with alcohol a pure blue fluorescence. In dilute hydrochloric acid it is rather difficultly soluble, with violet-blue fluorescence, but is fairly soluble on warming; yield, 3.5 g.

Anal. Subs., 0.0570: CO_2, 0.1486; H_2O, 0.0302. Subs., 0.0796: N_2, 7.3 cc. (11.5°, 760.6 mm.). Calcd. for $C_{15}H_{14}O_2N_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 71.10; H, 5.89; N, 10.90.

The hydrochloride was obtained on addition of an excess of concd. hydrochloric acid to the hot alcoholic solution of the free base and subsequent cooling. It forms light yellow needles which begin to soften at 310° and melt at 315° (decomp.). It is fairly soluble in cold alcohol, rather difficultly in cold water but fairly soluble in hot.

Anal. Subs., 0.3152: 19.6 cc. $N/10$ NaOH. Calcd. for $C_{15}H_{14}O_2N_2\cdot 2HCl$: HCl, 22.32. Found: HCl, 22.70.

The picrate forms yellow columns from alcohol, begins to decompose at 273° and sharply melts at 285° with foaming.

Anal. Subs., 0.0735: N_2, 9.0 cc. (13°, 770 mm.). Calcd. for $C_{15}H_{14}O_2N_2\cdot C_6H_3O_7N_3$: N, 14.49. Found: N, 14.64.

9-Acetamino-3,6-dimethoxy-acridine.—9-Amino-3,6-dimethoxy-acridine and some excess of acetic anhydride, under the addition of sodium acetate, were kept for two hours at 100°. The reaction mixture was poured into water and warmed on the water-bath until completely dissolved. On treating the filtered liquid with aqueous sodium carbonate, the acetyl compound is precipitated as light yellow shining needles from alcohol; m. p. 277–278°.

Anal. Subs., 0.0836: 6.7 cc. (12°, 764 mm.). Calcd. for $C_{17}H_{16}O_3N_2$: N, 9.46. Found: N, 9.55.

9-Acetamino-3,6-dimethoxy-acridinium Methyl Iodide.—1.7 g. of 9-acetamino-3,6-dimethoxy-acridine, 5 cc. of methyl alcohol and 1 g. of methyl iodide were heated at 110° for one and one-half hours in a sealed tube. After evaporating the reaction mixture almost to dryness, the yellow mass was treated with boiling alcohol and filtered cold. It forms yellow plates, very sparingly soluble in hot water with blue fluorescence, and also in boiling alcohol; m. p. 310° (decomp.); the yield was the theoretical.

Anal. Subs., 0.2919: AgI, 0.1575. Calcd. for $C_{18}H_{19}O_3N_2I$: I, 29.00. Found: I, 29.15.

9-Acetamino-3,6-dimethoxy-acridinium Methyl-*p*-toluenesulfonate.—7.1 g. of 9-acetamino-3,6-dimethoxy-acridine was dissolved in 70 cc. of boiling nitrobenzene; 5 g. of *p*-toluene-methyl-sulfonate was added to the solution at a time and allowed to cool. The separated mass was filtered, washed with benzene and then treated with boiling benzene. The benzene-insoluble matter was collected and washed with ether. It formed light yellow needles which began to soften at 250° and melted at 280°. It is fairly soluble in hot water, with blue fluorescence, easily in alcohol and fairly soluble in nitrobenzene; yield, 4.8 g.

Anal. Subs., 0.0859: N_2, 4.5 cc. (12.5°, 768 mm.). Calcd. for $C_{25}H_{26}O_6N_2S$: N, 5.81. Found: N, 6.26.

9-Amino-3,6-dimethoxy-acridinium Methyl Chloride.—A mixture of 4.2 g. of the acetaminodimethoxy-acridinium methyl toluenesulfonate, 15 cc. of water and 30 cc. of concd. hydrochloric acid was boiled for eight hours. After cooling, the separated crystals were filtered off and washed with a little water.

It forms yellow needles, unaltered at 315°, fairly soluble in cold water, with intense blue fluorescence, easily soluble in hot alcohol with violet-blue fluorescence, and concd. sulfuric acid solution gives a weak green fluorescence; yield, 2.7 g.

Anal. Subs., 0.0741: N_2, 5.6 cc. (15°, 766 mm.). Subs., 0.3439: AgCl, 0.1604. Calcd. for $C_{16}H_{17}O_2N_2Cl$: N, 9.20; Cl, 11.66. Found: N, 8.91; Cl, 11.53.

I hereby desire to express my hearty thanks to Professor Hata for the interest which he has kindly taken in this work.

Summary

The following compounds connected with the acridine syntheses have been characterized: 3,6-dihydroxy-acridone, 3,6-dimethoxy-acridone, 9-chloro-3,6-dimethoxy-acridine, 9-amino-3,6-dimethoxy-acridine, 9-acetamino-3,6-dimethoxy-acridine, 9-acetamino-3,6-dimethoxy-acridinium methyl iodide, 9-acetamino-3,6-dimethoxy-acridinium methyl *p*-toluenesulfonate and 9-amino-3,6-dimethoxy-acridinium methyl chloride.

TOKYO, JAPAN