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2,3-DIMETHOXY-6-NITRO-9-(γ-DIETHYLAMINO-β-HYDROXYPROPYLAMINO)ACRIDINE[1]

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The nitroacridine V,[1] 2,3-dimethoxy-6-nitro-9-(γ-diethylamino-β-hydroxypropylamino)acridine, was reported by German investigators (1) to exhibit chemotherapeutic activity in experimental and clinical typhus infections. The results of later work in this country show that this compound has a beneficial effect in both experimental rickettsial (2) and viral infections (3). These findings make this compound desirable as a standard drug in comparative testing programs.

Although the steps in the synthesis of V have been outlined (1), no detailed description of its preparation or physical properties has been published.[2] Attempts in this laboratory to carry out the outlined synthesis under conditions that are described in the chemical literature for similar acridine compounds were unsuccessful. A satisfactory laboratory procedure is described in this paper. The compound thus obtained was identical with the German material.[3]

When the Ullman reaction between 2-chloro-4-nitrobenzoic acid (I) and 4-aminoveratrole (II) was carried out in *n*-amyl alcohol at 140° or in nitrobenzene at 140° according to usual procedures, only dehalogenation of the 2-chloro-4-nitrobenzoic acid to 4-nitrobenzoic acid resulted. No 2-(3,4-dimethoxyphenylamino)benzoic acid, (III) was obtained. This result is similar to that observed by Goldberg and Kelly (4) with this chloronitrobenzoic acid and *p*-phenylenediamine in the Ullman reaction. These workers found, however, that the desired 2-(4-aminophenylamino)-4-nitrobenzoic acid was obtained in isopropyl alcohol at 80°. Albert and Gledhill (5) obtained 2-(4-ethoxyphenylamino)-4-nitrobenzoic acid in good yield from the Ullman reaction between 2-chloro-4-nitrobenzoic acid and *p*-phenetidine in boiling *n*-butyl alcohol. Using these conditions in our laboratory, the reaction of I and aminoveratrole (II) was unsuccessful; in isopropyl alcohol at 80° no reaction occurred. Yields of III up to 34% were obtained, however, when *n*-amyl alcohol was employed and the temperature carefully regulated between 95–100°. The substitution of copper acetate or copper sulfate for the copper powder led to lower yields of III. In all cases where the temperature was high enough to bring about reaction some dehalogenation occurred and *p*-nitrobenzoic acid resulted.

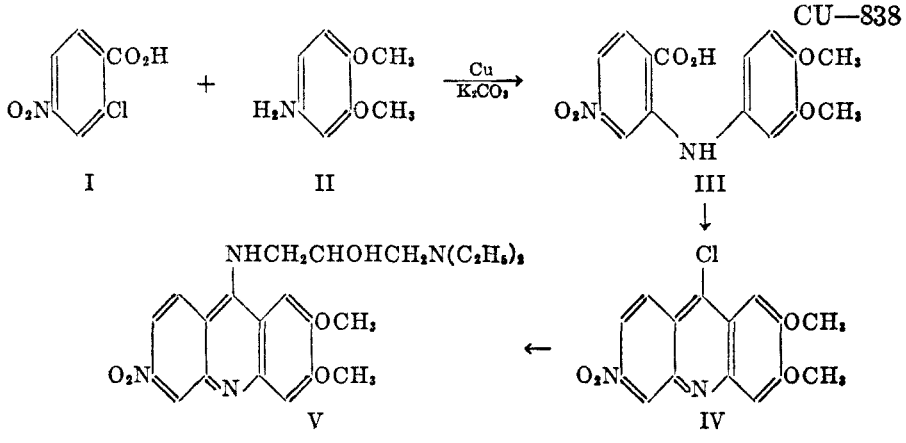
[1] This compound has been designated "nitroakridin 3582" in the report of the German work (1) and in reports in this country (2, 3).

[2] Water-soluble, neutral salts have been reported in the patent literature, German Patent 632,733 (1936); U. S. Patent 2,092,114 (1937) and reference is made to uses of the compound, Eisleb, *cf. Chem. Abstr.*, **31**, 5802 (1937), Keller, *cf.*, *Chem. Abstr.*, **36**, 6688 (1942).

[3] We are indebted to Dr. J. E. Smadel, of the Army Medical School, who supplied a sample of the German material to Dr. Bettylee Hampil of the Department of Virus Research of these laboratories.

The preparation of III through the Ullman reaction of 2-amino-4-nitrobenzoic acid (9) and 4-iodoveratrole (11) was unsuccessful. Also, the reaction of I and 4-acetylaminoveratrole (12) was unpromising; a small amount of an uncharacterized product resulted.

The direct cyclization of III to the 9-chloroacridine IV, proceeded smoothly (yield, 70%) using phosphoryl chloride according to the procedure of Magidson and Grigorowsky (6). The German synthesis (1) of IV apparently involved the intermediate 9-acridone which was then converted to the 9-chloroacridine. The reaction of γ-diethylamino-β-hydroxypropylamine with IV in phenol by the method of Magidson and Grigorowsky (7) gave a 67% yield of V.



I II III

V IV

EXPERIMENTAL PART[4, 5]

The 2-chloro-4-nitrobenzoic acid I, was prepared by procedures in the literature (9); *o*-toluidine → 2-amino-4-nitrotoluene (77%) (8) [or *p*-nitrotoluene (13)] → 2-chloro-4-nitrotoluene (64%) (9) → I (42%) (6). 4-Aminoveratrole (II) was obtained by the method of Clark (10); veratrole → 4-nitroveratrole (96%) → II (54%).

2-(3,4-Dimethoxyphenylamino)-4-nitrobenzoic acid (III). A mixture of 340 cc. of distilled *n*-amyl alcohol, 25 g. (0.124 mole) of 2-chloro-4-nitrobenzoic acid and 25 g. of anhydrous potassium carbonate was placed in a 1-liter, three-necked flask that was fitted with a stainless steel leaf stirrer and a "Glascol" heater. A small quantity of the alcohol was allowed to distill to remove any water present. The potassium salt of the acid formed a flocculent precipitate during this process. The mixture was cooled to 95° and 31.8 g. (0.21 mole) of aminoveratrole and 0.75 g. of copper powder added. This mixture was heated with good stirring at 95–100° for ten hours. After standing overnight the reaction mixture was added to 500 cc. of ether and filtered. The solid was washed by resuspension in ether, the mixture filtered, and the solid washed on the filter with ether. The dark solid was extracted three times with boiling water (total volume, 1 liter) and the insoluble material discarded. The extract was treated with charcoal. The filtrate from the charcoal was heated to boiling and made just acid to Congo Red by the dropwise addition of dilute hydrochloric acid. The yellow-orange solid that separated was removed immediately from the boiling solution and washed with hot water and dried, yield, 13.66 g., (34.3%), m.p. 222–224°. A sam-

[4] All melting points are uncorrected for stem exposure.

[5] All analyses were performed by Mr. K. B. Streeter, and the Misses Ruth M. Lynch and Thelma V. Plank, of these laboratories.

ple was purified by repeated recrystallization from 50% alcohol and from acetic acid and water, m.p. 227.5–228°.

Anal. Calc'd for $C_{15}H_{14}N_2O_6$: C, 56.61; H, 4.43; N, 8.80; CH_3O, 19.50.
Found: C, 55.78; H, 4.64; N, 8.71; CH_3O, 18.73.

On cooling and further acidification of the aqueous extract, additional solid separated. This consisted principally of *p*-nitrobenzoic acid.

2,3-Dimethoxy-6-nitro-9-chloroacridine (*IV*). A mixture of 12 g. (0.036 mole) of 2-(3,4-dimethoxyphenylamino)-4-nitrobenzoic acid and 120 cc. of freshly distilled phosphoryl chloride was refluxed gently for 2.5 hours. The excess phosphoryl chloride was removed under reduced pressure while heating in a warm water-bath. The residue was treated with crushed ice and the resulting yellow solid was removed, washed with water, then suspended in dilute aqueous sodium bicarbonate solution and the suspension stirred until effervescence ceased. The mixture was filtered and the solid washed with water and dried. The product was recrystallized from 225 cc. of hot reagent pyridine, yield, 8.14 g. (70.7%), m.p. 252–253° dec. The melting point is not exactly reproducible and depends upon the rate of heating.

Anal. Calc'd for $C_{15}H_{11}ClN_2O_4$: C, 56.54; H, 3.48; N, 8.79; CH_3O, 19.48.
Found: C, 56.24; H, 3.40; N, 8.76; CH_3O, 19.49.

2,3-Dimethoxy-6-nitro-9-(γ-diethylamino-β-hydroxypropylamino)acridine (*V*). A mixture of 21.41 g. (0.067 mole) of 2,3-dimethoxy-6-nitro-9-chloroacridine and 63 g. of phenol was heated in an oil-bath carefully regulated between 85–90° until the solid dissolved. With the temperature maintained at 85–90°, 23 g. (0.158 mole) of γ-diethylamino-β-hydroxypropylamine[6] was added dropwise over a 25-minute period with constant manual stirring. Heating was continued at this temperature with occasional manual stirring for 1.5 hours. A precipitate formed during the addition of the amine but dissolved during one hour. The mixture was cooled and twice its volume of commercial anhydrous alcohol added. This solution was made acid to Congo Red by dropwise addition of concentrated hydrochloric acid. Slightly more than two volumes of ether was added with stirring and the liquid decanted immediately from the oily solid that separated. The solid was washed several times with ether and then dissolved in 1.5 liters of water. To this solution 1.5 liters of alcohol was added and a small quantity of insoluble residue removed and discarded. The filtrate was made basic by the addition of dilute ammonium hydroxide and diluted slowly with three liters of water. After complete precipitation, the red solid was removed, washed with water, and dried, yield, 20.14 g. (67%), m.p. 103°; (the melt resolidified and melted again over a range). A small sample of this material was further purified by suspending in water and adding dilute hydrochloric acid until acid to Congo Red. The solution was diluted with alcohol, treated with charcoal and the product precipitated by addition of ammonia, m.p. 109–115°. This material was found to contain 4.05% water on drying at 100° under vacuum and over phosphorus pentoxide. (Theory for one mole of water 4.04%.) This material was identical with the base recovered from a sample of the German dihydrochloride by treatment of an aqueous solution with dilute ammonium hydroxide.

The anhydrous base was obtained by crystallization from 200 cc. of boiling acetone, 14.8 g., m.p. 166–167°. After recrystallization, the melting point was 168–169°.

Anal. Calc'd for $C_{21}H_{23}N_4O_5$: C, 61.66; H, 6.59; N, 13.08; CH_3O, 14.48.
Found: C, 61.77; H, 6.72; N, 12.83; CH_3O, 14.45.

This material was reconverted to the low-melting hydrate by precipitation from an aqueous acid solution by ammonia.

The dihydrochloride was prepared as follows: The anhydrous base was suspended in the minimum volume of water and dilute hydrochloric acid added until acid to Congo Red. The solution was diluted with a large volume of acetone and allowed to stand for sixteen hours. The yellow solid was removed, washed with acetone and dried at room temperature,

[6] The γ-diethylamino-β-hydroxypropylamine was produced by the Sharples Chemical Corporation and kindly supplied by Dr. R. C. Elderfield of Columbia University.

m.p. 219–220° dec. On drying at 100° (2 mm.) over phosphorus pentoxide it changed from yellow to orange and lost weight corresponding to a dihydrate. (H_2O Calc'd 6.70%. Found 6.82%).

Anal. Calc'd for $C_{22}H_{28}N_4O_5 \cdot 2HCl$: N, 11.17; CH_3O, 12.38.
Found: N, 11.10; CH_3O, 12.39.

SUMMARY

The synthesis of 2,3-dimethoxy-6-nitro-9-(γ-diethylamino-β-hydroxypropylamino)acridine in satisfactory yield is described.

GLENOLDEN, PA.

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