200 mg. of the spiro compound IXa and 500 mg. of chromic acid in 5 cc. of glacial acetic acid was boiled under reflux for 2 hr. The mixture was cooled, diluted with water and the neutral product was isolated with ether in the usual way. Crystallization of the product from ethanol gave 65 mg. of fluorenone, m.p. 80–82°, undepressed on admixture with an authentic sample (m.p. 82–83°).

Spiro-(cyclopropane-1,9′-fluorene) (IXb).—A solution of triphenylphosphinemethylene was prepared by adding 24 cc. of a 1 *N* ethereal solution of butyllithium to a suspension of 8.9 g. (25 millimoles) of methyltriphenylphosphonium bromide[13] in 100 cc. of ether with swirling under nitrogen. The mixture was shaken for 2 hr., fluorenone (1.44 g.) in 25 cc. of ether was added and the reaction was then carried out exactly as described above. The product dissolved in benzene was filtered through 100 g. of alumina to remove triphenylphosphine oxide. The eluate was evaporated to dryness, dissolved in pentane and chromatographed on 100 g. of alumina. Elution with pentane and crystallization from methanol yielded 302 mg. of the spiro compound IXb, m.p. 50–55°. A sample, further purified by crystallization from methanol and high-vacuum sublimation, showed m.p. 68–70°; λ_{max} 226, 268, 292 and 303 mμ (log ε 4.30, 4.20, 3.92 and 4.02, respectively). There was no depression in m.p. on admixture with an authentic specimen (m.p. 70–71°)[6] and the infrared spectra were identical.

Further elution of the column with petroleum ether (b.p. 65–70°) yielded 520 mg. of triphenylphosphine.

REHOVOTH, ISRAEL

(13) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954).

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyphosphoric Acid as a Reagent in Organic Chemistry. IX.[1] Cyclization to Diaminoacridines[2]

BY H. R. SNYDER AND MILTON S. KONECKY[3]

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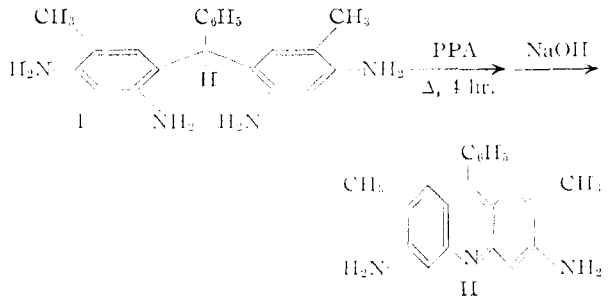
In the presence of a little hydrogen chloride, tetraaminodiarylmethane derivatives such as I are cyclized and aromatized to diaminoacridine derivatives by polyphosphoric acid at 165°. The method appears superior to the usual two-step procedure for effecting this change. In an attempt to use *p*-toluenesulfonic acid in place of hydrogen chloride, di-*p*-tolyl sulfone was produced.

Since there is evidence that polyphosphoric acid acts as a cyclodeamination reagent,[4,5] its applicability to the synthesis of diaminoacridines by the cyclization of suitable tetramine precursors has been considered.

When the cyclization in polyphosphoric acid of the dihydrochloride salt of the tetraaminoditolylphenylmethane (I) was attempted, the diaminoacridine, benzoflavin (II), was obtained directly in reasonably good conversion (48%) and excellent



net yield (83%). The cyclization in polyphosphoric acid may constitute a better general method than that recorded in the literature.[6] The hot reaction melt is poured into cold water and the red phosphate salt of II precipitates. The acid salt is collected by filtration and treated with excess base; the free diaminoacridine base obtained is of excellent purity. Both cyclization and aromatization are accomplished in the polyphosphoric acid medium.

Since the heating of the dihydrochloride salt of I in polyphosphoric acid resulted in the generation of hydrogen chloride with concomitant foaming, the cyclization was repeated under the same conditions except that the free tetramine I was used. Surprisingly, the percentage conversion to benzoflavin (II) was only about one-half that obtained with the dihydrochloride. When hydrogen chloride was generated *in situ* by the periodic addition of solid sodium chloride to the tetramine I in polyphosphoric acid, the percentage conversion (33%) was intermediate between that obtained with the tetramine only and that obtained with the dihydrochloride salt.

It seemed likely that a non-volatile, strong acid would exert the same influence on the reaction as hydrogen chloride and, since it would not be removed from the reaction mixture, perhaps would be effective in catalytic quantities. However, when a mixture of *p*-toluenesulfonic acid and the tetramine I was heated in polyphosphoric acid, the conversion was lowered. The crude reaction product was a low-melting mixture from which *p,p′*-ditolyl sulfone and benzoflavin (II) were isolated with the aid of adsorption chromatography.

The isolation of the ditolyl sulfone suggested the possibility that polyphosphoric acid could be used as a reagent for the preparation of sulfones from sulfonic acids. A successful test of this supposition was accomplished when *p*-toluenesulfonic acid was heated in polyphosphoric acid under the same conditions as in the diaminoacridine cyclization and the sulfone was obtained in 28% yield.

In order to explore the scope of the cyclization in polyphosphoric acid to diaminoacridines, the syn-

(1) For the preceding paper concerning cyclization with polyphosphoric acid see D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(2) Part of this work was supported by a grant [AT(11-1)-311] from the Atomic Energy Commission.

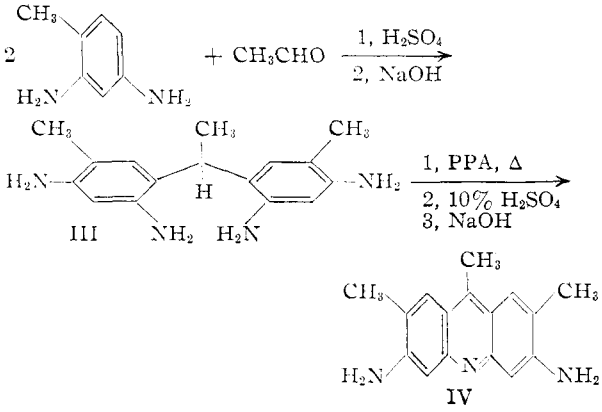
(3) Texas Co. Fellow, 1956–1957.

(4) H. Kissman, D. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952).

(5) C. Elston, Thesis, Doctor of Philosophy, University of Illinois, 1954.

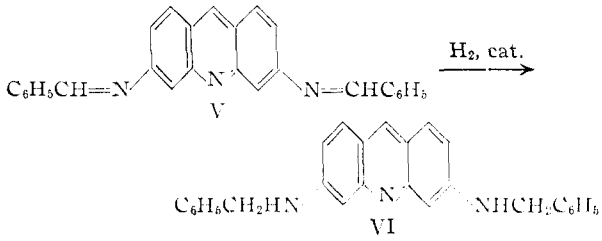
(6) R. Meyer and R. Gross, *Ber.*, **32**, 2352 (1899).

thesis of tetraaminoditolylethane (III) and its cyclization product 2,7,9-trimethyl-3,6-diaminoacridine (IV) was undertaken. The preparation of both of these compounds is described in a German patent,[7] but neither has been characterized.



Diaminotoluene and acetaldehyde were condensed in sulfuric acid solution, and the tetramine III was isolated as a tan, crystalline solid. In the cyclization of III, because the phosphoric acid salt of IV is highly soluble in water, difficulty in the isolation of the product was experienced at first. However, when the polyphosphoric acid melt was poured into 10% sulfuric acid, an acid salt of IV was precipitated, and the isolation of the product was simplified.

In another phase of these studies of diaminoacridines, 3,6-bis-benzylidenediaminoacridine (V) was reduced catalytically to 3,6-bis-N-benzyldiaminoacridine (VI). Whether the anil groups are



attacked in preference to the acridine nucleus, or whether the initial product is a dihydroacridine that is reoxidized during the isolation, is not known.

Experimental[8]

Preparation of the Tetraaminoditolylphenylmethane (I).—The method was developed from that of Meyer and Gross.[6] Into a 500-ml., round-bottomed flask equipped with a reflux condenser were placed 18.3 g. (0.15 mole) of 2,4-diaminotoluene and 29.3 g. (0.15 mole) of 2,4-diaminotoluene dihydrochloride, which was prepared by dissolving the free amine in ether and bubbling in dry hydrogen chloride. Then *ca.* 150 ml. of 95% ethanol was added, and the mixture was heated on a steam-bath to effect solution. The solution was cooled to *ca.* 60°, and 15.2 ml. (0.15 mole) of benzaldehyde was added. The solution was then heated under gentle reflux on a steam-bath for 2.5 to 3 hours. A somewhat fluffy, ivory colored solid separated during the heating period. After cooling to room temperature the solid was collected by suction filtration, rinsed with ethanol, and dried. The ethanol filtrate was reserved. The ivory solid (52.5 g., 86.5%) melted with decomposition at 241–245°. The ethanol filtrate was evaporated to dryness under vacuum on a rotary concentrator. A brown, solid residue, which weighed *ca.* 8.4 g., was deposited. The residue was suspended in water and 6 *N* hydrochloric acid was added until solution was complete. The solution was boiled with *ca.* 1.5 g. of Darco, filtered hot, and cooled. When the solution was treated with excess base, a tan precipitate of the free tetramine separated. The precipitate was collected by suction filtration, washed with water, and dried. The dry precipitate weighed 4.73 g. and, together with the dihydrochloride, raised the total yield of crude product to 95%. An analytical sample was obtained by the washing of the free tetramine first with chloroform and then with hot acetone, and then sublimation of the washed solid at 215° (0.1 mm.). The analytical sample melted with decomposition at 263–265°.

Anal. Calcd. for $C_{21}H_{24}N_4$: C, 75.88; H, 7.28; N, 16.87. Found: C, 76.49; H, 7.05; N, 16.59.

Cyclizations to Benzoflavin in Polyphosphoric Acid. A. From the Dihydrochloride Salt of the Tetramine.—A mixture of 4.10 g. (0.01 mole) of tetraaminoditolylphenylmethane dihydrochloride and 50 g. of polyphosphoric acid (Victor Chemical Works) was warmed to *ca.* 60° in a 100-ml. beaker on a steam-bath to effect suspension. At 60° hydrogen chloride was generated and caused the mixture to foam. The mixture was then heated on a hot-plate, with mechanical stirring, and the rate of heating was controlled for *ca.* 0.5 hour to prevent excessive foaming. Then heat was applied steadily until the temperature reached 165°. The temperature was maintained at 165–170° for 3.5 hours. Most of the hot melt was poured slowly with stirring into 100 ml. of cold water. Immediately, a bright orange solid separated. The remainder of the viscous melt was transferred by water rinses. After cooling, the orange solid was collected, rinsed with water, and the excess water was removed by suction filtration. The orange colored acidic filtrate was reserved. The damp solid, when treated with *ca.* 100 ml. (an excess) of 2 *N* sodium hydroxide solution, changed from orange to yellow in color. The mixture was digested on a hot-plate at 60–70° for 0.5 hour. After cooling, the yellow solid was collected by suction filtration, washed with water, and dried in a vacuum desiccator over potassium hydroxide. The yellow solid (1.50 g., 48% conversion) melted with decomposition at 305–310° (lit.[6] >300°). An analytical sample was obtained by crystallization first from dimethylformamide–water, then from ethanol–water, and finally sublimation at 200° (0.1 mm.).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.60; H, 5.96; N, 13.53.

The orange colored acidic filtrate was treated carefully with 2 *N* sodium hydroxide solution, and at *ca.* *p*H 3, a small amount of orange precipitate was separated by filtration and discarded. The filtrate was then treated with base to *ca.* *p*H 8. The light-yellow solid which separated was collected by suction filtration, washed with water, and dried in a vacuum desiccator over potassium hydroxide. This yellow powder (1.44 g., 43% recovery) melted with decomposition at 225–240° and was identified as the free tetraaminoditolylphenylmethane by its infrared spectrum. Then net yield of benzoflavin, after correction for the recovery of starting material, was 83%.

B. From the Free Tetramine.—A mixture of 3.32 g. (0.01 mole) of tetraminoditolylphenylmethane and 50 g. of polyphosphoric acid was heated, with stirring, on a hot-plate to 165° within a half hour. The temperature was maintained at 165–170° for 3.5 hours. The hot melt was poured into 130 ml. of cold water. After cooling, the orange-red solid which precipitated was collected by suction filtration and washed with water. The acidic filtrate was reserved. The wet solid was treated with an excess (40 ml.) of 2 *N* sodium hydroxide solution, and the mixture was stirred for *ca.* one hour. The yellow solid was collected by suction filtration and dried in a vacuum desiccator over potassium hydroxide. The product (0.75 g., 24% conversion) melted with decomposition at 301–306° (sealed tube).

The acidic filtrate was treated with base to *p*H 3; the small amount of red solid that separated was filtered off and discarded. The filtrate was treated with base to *p*H 8, and the light-yellow solid was collected, washed, and dried

(7) Ciba, German Patent 143,893, March 13, 1902; *Friedl.*, **7**, 313 (1903).

(8) Melting point determinations followed by the symbol (K) were made on a Kofler micro-stage melting-point apparatus. All other melting point determinations were uncorrected capillary determinations.

over potassium hydroxide. This yellow powder (1.85 g., 56% recovery) melted with decomposition at 235–238° and was identified as the tetramine by its infrared spectrum. Therefore, the net yield of benzoflavin was 54%.

C. With Addition of Sodium Chloride.—A mixture of 3.32 g. (0.01 mole) of tetraaminoditolylphenylmethane and 50 g. of polyphosphoric acid was heated in a 100-ml. beaker on a hot-plate and stirred mechanically. When the temperature reached 110° (after *ca.* 10 minutes), 0.1 g. of solid sodium chloride was added to the mixture. Immediately, hydrogen chloride was evolved. When the temperature reached 165° in *ca.* 5 minutes, another 0.1 g. of sodium chloride was added. The temperature was maintained at 165–170° for four hours, and the sodium chloride was added periodically during this time, *ca.* once every 20 minutes. The hot melt was poured into 130 ml. of cold water, and the orange precipitate which separated was collected by suction filtration. After treatment with excess base, collection by filtration, and drying, the resultant yellow product (1.03 g., 33% conversion) melted with decomposition at 310°. The recovered tetramine weighed 1.51 g. (45.5% recovery), and the net yield of benzoflavin was 61%.

D. With Addition of *p*-Toluenesulfonic Acid.—A mixture of 50 g. of polyphosphoric acid and 1.90 g. (0.01 mole) of *p*-toluenesulfonic acid monohydrate was stirred manually to effect suspension. Then 3.32 g. (0.01 mole) of tetraaminoditolylphenylmethane was added to the mixture. The mixture was heated on a hot-plate, with mechanical stirring, and the temperature was raised to 165°. The temperature was maintained at 160–170° for 3.5 hours. The hot melt was poured into 150 ml. of cold water. The resultant orange precipitate was collected by suction filtration, treated with excess base, and digested at 70° for 0.5 hour. The yellow solid was collected by suction filtration, washed with water, and dried. The product (1.07 g.) melted with decomposition at 220–263°. About 500 mg. of this solid was chromatographed on an alumina column. A white, crystalline solid, which melted at 129–152° and represented about 15% of the weight of the product of the cyclization, was isolated from the first benzene fractions which came off the column. This white solid was recrystallized from benzene–petroleum ether, and the recrystallized material melted at 156–157.5°. From its infrared spectrum and melting point, it was identified as *p,p'*-ditolyl sulfone. Benzoflavin was isolated from later fractions (ethanol) from the column, but a complete material balance was not accomplished. The recovered tetramine weighed 2.10 g. (62.3% recovery).

***p,p'*-Ditolyl Sulfone.**—A mixture of 5.7 g. (0.03 mole) of *p*-toluenesulfonic acid monohydrate and 50 g. of polyphosphoric acid was heated on a hot-plate and stirred mechanically. The temperature reached 165° within 0.5 hour and was maintained at 165° for three hours. The hot melt was poured into 150 ml. of cold water, and a white solid immediately precipitated. The white, crystalline solid was collected by suction filtration, washed with water, and dried. The crystals (1.05 g., 28%) melted at 152–158° (K) (lit.[9] 159°). An analytical sample was obtained by recrystallization from benzene–petroleum ether, and it melted at 158–160° (K).

Anal. Calcd. for $C_{14}H_{14}SO_2$: C, 68.26; H, 5.72. Found: C, 68.15; H, 5.67.

Tetraaminoditolylethane.—The method of preparation used was essentially that described in a 1902 patent issued to Ciba[7] although the product was not characterized in the patent. A solution of 97.7 g. (0.8 mole) of 2,4-diaminotoluene in 2000 ml. of water containing 40 g. (0.4 mole) of concentrated sulfuric acid was cooled to 5° in an ice–salt bath. Over a period of 0.5 hour, 17.6 g. (0.4 mole) of cold acetaldehyde was added slowly with stirring. The solution was then stirred for 1.5 hours while the temperature was maintained at 0–10°. The solution was allowed to warm slowly (*ca.* one hour) to 18°. At this point 4 *N* sodium hydroxide solution was added slowly until the *p*H was *ca.* 9. A tan crystalline solid separated. The mixture was stirred occasionally over a 15-minute aging period, and then the tan crystals were collected by suction filtration, washed with water, and dried in a vacuum desiccator over potassium hydroxide. The crystals (73 g., 68%) melted with decomposition at 198–203°. After three recrystallizations from benzene, the analytical sample melted with decomposition at 227–229°.

Anal. Calcd. for $C_{16}H_{22}N_4$: C, 71.06; H, 8.23; N, 20.72. Found: C, 71.54; H, 8.29; N, 20.45.

2,7,9-Trimethyl-3,6-diaminoacridine.—A mixture of 2.71 g. (0.01 mole) of tetraaminoditolylethane, 30 g. of polyphosphoric acid and 0.1 g. of solid sodium chloride was heated, with mechanical stirring, in a 50-ml. beaker on a hot-plate. At *ca.* 125° the tetramine formed a red gummy ball which finally dissolved after an hour. The temperature reached 165° within a half-hour and was maintained at 165–170° for four hours. Small amounts of sodium chloride were added periodically, *ca.* every 20 minutes, during this reaction period. The hot melt was poured cautiously into 70 ml. of 10% sulfuric acid solution. Within a few minutes, bright red crystals began to separate. The mixture was allowed to cool to room temperature, and the red crystalline precipitate was collected by suction filtration. No attempt was made to recover starting material from the filtrate. The precipitate was washed into a beaker with 20 ml. of water, and 2 *N* sodium hydroxide solution was added slowly. At *ca. p*H 4, the precipitate dissolved to give a clear, red solution. At *p*H 7–8, a dark red, oily material separated, and it began to form an orange-yellow solid upon addition of base to *p*H 12–14. The mixture was boiled for several minutes, and the solid became bright yellow in color. When cool, the yellow solid was collected by suction filtration, washed with water, and dried in a vacuum desiccator over potassium hydroxide. The dry solid (0.69 g., 27.5%) melted with decomposition at 295–297° (K). The analytical sample, which was obtained by recrystallization from ethanol and subsequent sublimation, melted with decomposition at 307–311° (K).

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.47; H, 6.82; N, 16.72. Found: C, 76.97; H, 6.59; N, 16.57.

3,6-Bis-N-benzyldiaminoacridine.—The 3,6-bis-benzylidenediaminoacridine used in this reaction was prepared by the method of Glen, Sutherland and Wilson[10] and was recrystallized once from ethanol. A benzene solution of 1.3 g. (0.0036 mole) of 3,6-bis-benzylidenediaminoacridine was treated with Raney nickel and hydrogen at 1000 p.s.i. at room temperature for 21 hours. After hydrogenation, the solution was separated from the catalyst by gravity filtration. The catalyst was rinsed first with two 15-ml. portions of benzene and then two 15-ml. portions of ethanol. The filtrate including the rinses was evaporated to dryness under vacuum on a rotary concentrator. The residue, a golden-yellow solid, weighed 0.61 g. and melted at 183° (K) after sintering at *ca.* 150°.

The solid was dissolved in 30 ml. of refluxing benzene, the solution was cooled, and a negligible amount of insoluble material was removed by filtration. The benzene solution was added to a glass column containing alumina, and the chromatogram was developed. A yellow solid (0.30 g., 23%) which melted at 200–203° (K) was isolated from the 25% chloroform in benzene fractions. After three recrystallizations from ethanol, the golden crystals melted at 202–204° (K).

Anal. Calcd. for $C_{27}H_{23}N_3$: C, 83.25; H, 5.95; N, 10.79. Found: C, 83.65; H, 6.05; N, 10.49.

URBANA, ILL.

(9) H. Meyer, *Ann.*, **433**, 327 (1923).

(10) W. Glen, M. Sutherland and F. Wilson, *J. Chem. Soc.*, 1484 (1936).