obtained from fraction II. There was obtained 1.4 g. of yellow powder, m. p. 140–143°.

For analysis the 5.4 g. of product was purified by dissolving in about one liter of refluxing ether. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated to about 30–40 cc. The mixture containing the product, already partly precipitated, was cooled in ice and filtered. The pure product consisted of a light yellow powder, m. p. 143–144°.

Anal.[4] Calcd. for $C_{20}H_{16}O_4$: C, 74.98; H, 5.04. Found: C, 74.97; H, 5.24.

Cyclization.—Two grams of the quinone adduct was refluxed in 50 cc. of 6% methanolic hydrogen chloride for sixteen hours. The quinone went into solution slowly and, on cooling, the mixture crystallized to give a product (1.6 g.) of m. p. 141–143°. Two recrystallizations from methanol gave shiny yellow platelets, m. p. 144–145°.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.52; H, 5.52.

It is interesting to note that the cyclized product gave an apparent exaltation of melting point when mixed with a sample of starting material. A mixture of the two quinones (each melting at 144°) softened at 140° but melted completely at 151–155°.

The cyclized product was further differentiated from the starting material by the fact that in cold alcoholic alkali, the former did not give the deep red color characteristic of the free hydroxy-group present in the uncyclized quinone.

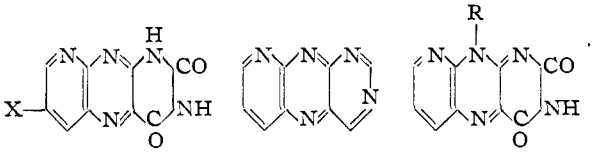
(4) Microanalyses were carried out by Mr. E. F. Shelberg, chief microanalyst, Abbott Research Laboratories.

ORGANIC CHEMISTRY DEPARTMENT
ABBOTT RESEARCH LABORATORIES
NORTH CHICAGO, ILLINOIS RECEIVED JANUARY 17, 1949

Some 9-Aza-alloxazines

BY J. BENJAMIN ZIEGLER[1]

During the course of a program of research in these laboratories it became necessary to synthesize some compounds of type (I). Substances of this structure



(Ia) X = H
(Ib) X = Cl

II

III

which may be considered to be derived from the parent compound, pyrido-[2.3-b] pyrimido-[5.4-e]pyrazine[1a] (II) appear not to have been synthesized previously, although certain closely similar 10-alkyl-9-aza-isoalloxazines (or 10-alkyl-9-aza-flavins) (III) have been prepared by Rudy and Majer.[2a,b]

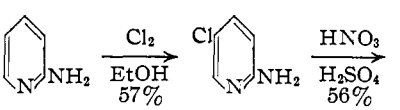
It is to be expected that condensation of 2,3-diaminopyridines with alloxan under the proper conditions would result in the removal of two molecules of water with the formation of tricyclic compounds of type I. Rudy and Majer have shown[3] that condensation of 2,3-diaminopyridine with alloxan in water or dilute acids yields bicyclic compounds formed by the removal of only one molecule of water. The reaction of *o*-phenylenediamine with alloxan with the removal of two molecules of water to yield alloxazine proceeds readily under these conditions.[4] Apparently the diminished reactivity of the 2-amino group in 2,3-diaminopyridine is responsible for the failure to remove the second molecule of water in this case.

The condensation of 2,3-diaminopyridine with alloxan in glacial acetic acid was investigated; however, the product obtained was one formed by the removal of only one molecule of water from the reactants. It is probably the 2-hydroxy-8-azaquinoxaline-3-carboxureide described by Rudy and Majer.[3]

It has been shown[2a,5] that boric acid is an effective condensing agent in reactions of this type. Condensation of 2,3-diaminopyridine with alloxan in a solution of boric acid in glacial acetic acid finally led to a product having the composition of the desired 9-aza-alloxazine (Ia). It was a dense, sandy, reddish-brown crystalline powder insoluble in water but soluble in dilute ammonia water, from which solution it could be precipitated by acidification with acetic acid. It did not melt up to 300° but at about 270° the color changed from reddish-brown to yellow.

Interestingly enough an attempt to synthesize 7-chloro-9-aza-alloxazine (Ib) by condensation of 2,3-diamino-5-chloropyridine with alloxan under these same conditions did not succeed, the product obtained being one formed by the removal of only one molecule of water. Apparently the 2-amino group is still further deactivated by the chlorine atom in the para-position. Substitution of boron trifluoride etherate for the boric acid, however, led to the desired result. The 7-chloro-9-aza-alloxazine was an orange-tan crystalline powder similar in appearance and properties to the parent 9-aza-alloxazine.

Since the various published syntheses[6] of 2,3-diaminopyridine are unsatisfactory for one reason or another we have developed a new synthesis of this difficultly accessible diamine which is believed to possess some advantage over the older methods. The procedure starts with the readily available 2-aminopyridine and proceeds to 2,3-diaminopyridine with an over-all yield of about 20% by a three-step process which is outlined below



(1) Present address: Ciba Pharmaceutical Products, Inc., Summit, N. J.

(1a) R. I. 1872. Patterson and Capell, "The Ring Index," Reinhold Publishing Co., 1940, p. 254.

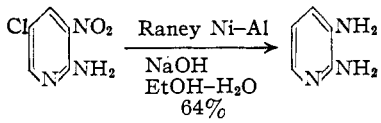
(2) (a) Rudy and Majer, *Ber.*, **71**, 1243–1248 (1938); (b) *ibid.*, **72**, 933–939 (1939).

(3) Rudy and Majer, *Ber.*, **71**, 1323–1332 (1938).

(4) Kühling, *Ber.*, **24**, 2363–2369 (1891).

(5) Kuhn, Reinemund, Weygand and Ströbele, *Ber.*, **68B**, 765–774 (1935).

(6) (a) Tschitschibabin and Kirsanow, *Ber.*, **60**, 766–776 (1927); (b) Konopnicki and Plazek, *ibid.*, **60B**, 2045–2047 (1927); (c) von Schickh, Binz and Schulz, *ibid.*, **69**, 2593–2605 (1936).



The last reaction indicated is an extension of the work of Schwenk and co-workers[7] who had demonstrated the preparative value of this dehalogenation reaction in the benzene series.

Acknowledgment.—The author is indebted to Dr. Joseph R. Stevens for helpful advice and encouragement.

Experimental[8]

(1) **2,3-Diaminopyridine**[6a] **from 2-Amino-3-nitropyridine.**[9]—A solution of 2.0 g. of 2-amino-3-nitropyridine in 150 ml. of 95% ethanol was shaken at room temperature with 0.1 g. of platinum oxide in the presence of hydrogen at an initial pressure of 40 lb./sq. in. After about fifteen minutes absorption of hydrogen had ceased; the pressure drop was 4 lb. (theoretical, 3.4 lb.). The hydrogenation bottle was evacuated and filled with carbon dioxide gas and 5 ml. of concentrated hydrochloric acid was added to the solution. The catalyst was then removed by filtration and the red solution was concentrated *in vacuo* to small volume. Ten ml. of water was added to the residue and the solution was saturated with potassium carbonate, precipitating a dark oil. This oil was taken up in ether and the aqueous layer was extracted exhaustively with ether. The combined ethereal solutions were dried over anhydrous potassium carbonate and concentrated to dryness. The pinkish-gray residue weighed 1.4 g. (89%) and melted at 112–113°. After recrystallization from benzene, pinkish-gray needles were obtained; m.p. 113–114°. The unrecrystallized picrate melted at 258° with decomposition.

(2) **2,3-Diamino-5-Chloropyridine.**[6a]—A suspension of 2.0 g. of 2-amino-3-nitro-5-chloropyridine[10] and 0.1 g. of platinum oxide in 250 ml. of ethanol at 40–45° was shaken with hydrogen gas at an initial pressure of 40 lb./sq. in. Absorption of hydrogen was complete after fifteen minutes, during which time the pressure drop was 3.5 lb. (2.8 lb., the theoretical amount). The hydrogenation bottle was evacuated and filled with carbon dioxide gas. After adding 5 ml. of concentrated hydrochloric acid the catalyst was removed by filtration and the solvent was removed under reduced pressure. The crystalline mush was dissolved in about 10 ml. of water, made alkaline with 3 *N* sodium carbonate solution and chilled overnight in the refrigerator. The solid was collected on a Büchner funnel, washed with a little water and air-dried. There was obtained 1.5 g. of grayish-tan crystals, m. p. 172–173°. Tschitschibabin and Kirsanow[6a] give m. p. 164.5–165°.

(3) **2,3-Diaminopyridine from 2-Amino-3-nitro-5-chloropyridine.**—A suspension of 2.5 g. of the aminonitrochloropyridine in a solution of 10 ml. of ethanol in 75 ml. of 10% aqueous sodium hydroxide in a 250-ml. three-necked round-bottomed flask fitted with a mechanical stirrer and thermometer was warmed to 60°, and 7.5 g. of Raney nickel–aluminum alloy was added portionwise with stirring and occasional cooling over a period of one-half hour, holding the temperature at 60–65°. An additional 5 ml. of ethanol was added followed portionwise by an additional gram of alloy, holding the temperature at 80–85°. By this time the suspended nitro compound was practically completely dissolved. The cold mixture was filtered and the catalyst washed with a little water. The combined filtrate and washings was saturated with potassium carbonate and extracted exhaustively with ether. Removal of the ether left a residue to 1.17 g. of crude product, m. p. 107–108°. Recrystallization from benzene–petroleum (Nuchar GFO) yielded 1.0 g. of grayish needles, m. p. 111–112°. A mixture melting point with an authentic specimen of 2,3-diaminopyridine prepared from 2-amino-3-nitro-pyridine showed no depression.

(4) **Condensation of 2,3-Diaminopyridine with Alloxan in Glacial Acetic Acid.**—A solution of 0.20 g. of 2,3-diaminopyridine in 10 ml. of glacial acetic acid was added to a solution of 0.32 g. of alloxan monohydrate in 20 ml. of glacial acetic acid and the whole was heated on the steam-bath for thirty minutes. The solution gradually became deep red in color and after about five minutes precipitation of a yellow solid began. After cooling to room temperature the solid was collected on a Hirsch funnel and washed with a little glacial acetic acid. After drying, 0.37 g. of a tan powder was obtained, dec. 260–270°. Dilution of the filtrate with an equal volume of water yielded an additional 0.03 g. of material. The crude was dissolved in dilute ammonium hydroxide, the solution treated with Nuchar W, filtered, and then neutralized with 20% acetic acid. The product was collected on a Hirsch funnel, washed with water and dried; the pale buff crystals dec. 275–280°. A portion in aqueous pyridine gave a pale gray-blue fluorescence under ultraviolet light.

Anal. Calcd. for $C_9H_5O_2N_5$: C, 50.23; H, 2.34; N, 32.55. Calcd. for $C_9H_7O_3N_5$: C, 46.34; H, 3.03; N, 30.05. Found: C, 46.00; H, 3.06; N, 30.25, 30.30.

(5) **9-Aza-alloxazine.**—A solution of 0.67 g. of 2,3-diaminopyridine in 34 ml. of glacial acetic acid was added to a warm solution of 1.1 g. of alloxan monohydrate and 1.3 g. of boric acid in 67 ml. of glacial acetic acid and the whole was heated on the steam-bath for one hour. After a few minutes the orange solution began to deposit a precipitate. The mixture was cooled and the precipitate was collected on a Büchner funnel and washed with a little glacial acetic acid. After drying, the condensation product weighed 1.43 g. After solution in dilute ammonium hydroxide and reprecipitation with acetic acid, the material was collected on a Hirsch funnel and washed with water. After drying, the red-brown crystals weighed 1.16 g. The substance did not melt up to 300°.

Anal. Calcd. for $C_9H_5O_2N_5$: C, 50.23, H, 2.34; N, 32.55. Found: C, 50.05, H, 2.68; N, 32.60.

(6) **Condensation of 2,3-Diamino-5-chloropyridine with Alloxan in Boric Acid–Glacial Acetic Acid.**—A hot solution of 0.9 g. of the diaminochloropyridine in 45 ml. of glacial acetic acid was added to a hot solution of 1.1 g. of alloxan monohydrate and 1.8 g. of boric acid in 90 ml. of glacial acetic acid and the dark red solution was heated on the steam-bath for one hour; on cooling, separation of yellow crystals began. After chilling overnight in the refrigerator the mixture was filtered and the crystalline product was washed with a little glacial acetic acid and dried. The tan crystals, weight 1.6 g., were recrystallized from 250 ml. of boiling glacial acetic acid (Nuchar W). The resulting pale yellow crystals did not melt up to 300°.

Anal. Calcd. for $C_9H_4O_2N_5Cl$: N, 28.06; Cl, 14.20. Calcd. for $C_9H_6O_3N_5Cl$: N, 26.17; Cl, 13.25. Found: N, 25.95; Cl, 13.20, 13.23.

(7) **7-Chloro-9-aza-alloxazine.**—A solution of 1.5 g. of 2,3-diamino-5-chloropyridine in 72 ml. of glacial acetic acid was added to a solution of 1.76 g. of alloxan monohydrate and 10 ml. of boron fluoride etherate in 144 ml. of glacial acetic acid. The deep red solution was heated on the steam-bath for three-fourths hour and allowed to stand at room temperature for two days, when a small amount of yellow material had separated. Water was added and most of the acetic acid was removed by steam distillation. The residue, having a volume of about 1 liter was thoroughly chilled in the refrigerator. The solid was isolated by filtration, dissolved in dilute ammonium hydroxide (deep red color), the solution treated with

(7) Schwenk, Papa, Whitman and Ginsberg, *J. Org. Chem.*, **9**, 1–8 (1944).

(8) All melting points are corrected. Microanalyses by Dr. Velmer B. Fish.

(9) Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **47**, 1286–1296 (1915).

(10) Tschitschibabin and Jegorow, *ibid.*, **60**, 683–690 (1928).

Nuchar W, filtered, and acidified with glacial acetic acid. The precipitate was collected on a Büchner funnel, washed with water and dried. The yellowish-brown crystalline powder weighed 1.4 g. It did not melt up to 380°.

Anal. Calcd. for $C_9H_4O_2N_5Cl$: N, 28.06; Cl, 14.20. Found: N, 28.00, 27.95; Cl, 14.21.

J. T. BAKER CHEMICAL CO.
PHILLIPSBURG, NEW JERSEY

RECEIVED NOVEMBER 15, 1948

NEW COMPOUNDS

Quinazoline Derivatives

4-(1,2,3,4-Tetrahydroquinolyl-1)-quinazoline.—Ten grams (0.0685 mole) of 4-quinazolone was refluxed with 22 g. (0.105 mole) of phosphorus pentachloride and 100 ml. phosphorus oxychloride for twenty-four hours. The latter was removed by distillation under diminished pressure; toluene (15 ml.) was added and 10 ml. removed by distillation. Twenty grams (0.139 mole) of 1,2,3,4-tetrahydroquinoline was added and the resulting mixture refluxed for two hours. Dilute hydrochloric acid was added and the upper layer separated and discarded. The addition of dilute sodium hydroxide to the aqueous layer resulted in the separation of a pasty solid. From this the desired product was obtained as bright yellow crystals from ethanol in a yield of 78%; m. p. 130.5–131.5°.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.14; H, 5.79; N, 16.08. Found: C, 77.80; H, 5.74; N, 16.15.

6-Chloro-4-(6-methoxy-1,2,3,4-tetrahydroquinolyl-1)-quinazoline.—In an analogous manner, 10.8 g. (0.060 mole) of 6-chloro-4-quinazolone, 12.7 g. (0.061 mole) of phosphorus pentachloride, 72 ml. phosphorus oxychloride, and 24 g. (0.15 mole) of 6-methoxy-1,2,3,4-tetrahydroquinoline were allowed to react to form the desired quinazoline in a yield of 68%. The product crystallized from an ethanol–ethyl acetate mixture in pale yellow needles, m. p. 106–108°.

Anal. Calcd. for $C_{18}H_{16}ClN_3O$: C, 66.35; H, 4.95. Found: C, 66.15; H, 4.95.

THE VENABLE CHEMICAL LABORATORY
UNIVERSITY OF NORTH CAROLINA GORDON M. GOODALE
CHAPEL HILL, N. C. ROBT. L. MCKEE

RECEIVED JANUARY 26, 1949

Two New Derivatives of 2-Aminofluorene

In an attempt to make 2-aminofluorene derivatives which should produce a more rapid carcinogenic response than that elicited by feeding N-(2-fluorenyl)-acetamide[1] we have prepared N-(2-fluorenyl)-glycine and N-(2-fluorenyl)-hemi-succinamide in the hope that the greater solubility of these compounds in water would lead to the desired action.

N-(2-Fluorenyl)-glycine.—A solution of 36.2 g. (0.20 mole) of 2-aminofluorene[2] in 750 ml. of hot 95% ethanol was added to a solution of 29.2 g. (0.21 mole) of bromoacetic acid (Eastman Kodak Co.) and 38.8 g. (0.46 mole) of sodium bicarbonate in 500 ml. of water, the mixture heated under reflux on the steam-bath for twelve hours and then diluted with 500 ml. of boiling water. A small insoluble residue in the hot solution was removed by filtration, and the filtrate evaporated to a volume of 800 ml. in vacuum. When cold, it was acidified to *p*H 4 with 6 *N* HCl, and the amorphous brown powder that formed was filtered by suction and washed with 500 ml. of hot water. The crude fluorenylglycine was recrystallized from hot 95% ethanol (with decolorizing carbon (Darco)). After two further recrystallizations from the same solvent the compound was obtained in the form of small rhombic plates with a slight tan coloration; m. p. 157° (dec.) (uncor.); yield, 39 g. (81%).

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.3; H, 5.5. Found: C, 74.8; H, 5.4.

N-(2-Fluorenyl)-hemi-succinamide.—A mixture of 36.2 g. (0.20 mole) of 2-aminofluorene[2] and 24 g. (0.24 mole) of succinic anhydride (E. K.) in 500 ml. of dry benzene was refluxed for seven hours, during which time the succinyl derivative slowly separated from the solution. When cold, the crude product was filtered off and the excess succinic anhydride present in it decomposed by suspending the material in 500 ml. of absolute ethanol and refluxing on the steam-bath for one hour. After twenty-four hours in the cold the pale yellow crystals were collected on a Buchner funnel and washed with 30 ml. of absolute ethanol. The yield of N-(2-fluorenyl)-hemi-succinamide, m. p. 225° (dec.) (uncor.) was 57.5 g. (95%). It formed colorless rhombic plates from acetone, m. p. unchanged.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.6; H, 5.4; N, 5.0. Found: C, 72.6; H, 5.4; N, 5.0.

Dr. Gray H. Twombly, of the Department of Obstetrics and Gynecology of this University, has found that both these compounds are carcinogenically potent in rats.[3]

(1) Wilson, DeEds and Cox, *Cancer Research*, **1**, 596 (1941), and numerous papers by other authors since.

(2) "Organic Syntheses," Coll. Vol. II, New York, N. Y., 1943, p. 448. We have also reduced 2-nitrofluorene conveniently on the large scale with sodium hydrosulfite.

(3) Private communication.

DEPARTMENT OF BIOCHEMISTRY
COLLEGE OF PHYSICIANS AND SURGEONS
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630 WEST 168TH STREET
NEW YORK 32, N. Y. C. H. W. HIRS

RECEIVED JANUARY 31, 1949

p-Cyclopentylacetophenone and *p*-Cyclopentylbenzoic Acid

***p*-Cyclopentylacetophenone.**—Six grams of phenylcyclopentane and 3 g. of acetyl chloride were dissolved in 30 ml. of dry carbon disulfide and 5 g. of aluminum chloride was added gradually. A vigorous reaction ensued, the solution turning orange in color. The mixture was allowed to stand overnight. It was then refluxed for thirty minutes and poured upon ice and dilute hydrochloric acid. The organic layer was washed with water, dried over calcium chloride, and the solvent distilled at ordinary pressure. The residual oil was vacuum distilled. There was obtained 5 g. of a colorless, refractive oil which distilled at 131–135° at 6 mm. When freshly distilled, the product is practically odorless; d^{25}_{25} 1.028, $n^{25}D$ 1.5486; M_D calcd. 56.50; M_D observed 58.14.

Anal. Calcd. for $C_{13}H_{16}O$: C, 84.0; H, 7.96. Found: C, 84.1; H, 7.76.

2,4-Dinitrophenylhydrazone.—This derivative was prepared by the method of Shriner and Fuson.[1] It was obtained as bright orange plates, moderately soluble in alcohol from which it was twice recrystallized; m. p. 165°.

Anal. Calcd. for $C_{19}H_{20}O_4N_4$: C, 62.0; H, 5.43; N, 15.2. Found: C, 61.7; H, 5.39; N, 15.2.

***p*-Cyclopentylbenzoic acid** was prepared from *p*-bromophenylcyclopentane[2] by means of the Grignard reaction followed by carbonation with Dry Ice. The crude acid was twice recrystallized from dilute alcohol. From 2 g. of

(1) Shriner and Fuson, "Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y. 1948, p. 171.

(2) Kleene, THIS JOURNAL, **62**, 2883 (1940).