Synthesis of Certain 5-Nitropyridine Derivatives Structurally Related to Some Chemotherapeutic Agents

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The condensation of 2-chloro-5-nitropyridine with 1-aminohydantoin, sulfaguanidine, and semicarbazide is described. With sulfaguanidine the N^4 derivative was always obtained even under the conditions supposed to afford the N^1 derivative. With semicarbazide the condensation in all cases yielded a disubstitution product even when equimolecular amounts of the reactants were used. With aminohydantoin the condensation was effected in 1 per cent hydrochloric acid while in 10 per cent acid no condensation took place, and the haloheterocycle was hydrolyzed to the corresponding hydroxy compound. On the other hand, attempts to condense the halonitropyridine with 3-amino-2-oxazolidone were unsuccessful.

In recent years, heterocycles with a nitro group in position 5- gained success as antimicrobials, *e.g.*, nitrofurans (1), and as amebicides, *e.g.*, 2-diethanolamino-5-nitropyridine (2, 3). As a consequence the authors decided to synthesize compounds having the 5-nitropyridyl radical together with different side chains in position 2- in the hope that the new products would show superior amebicidal action[1] with lower toxicity. For the synthesis of such compounds 2-chloro-5-nitropyridine was condensed with certain amino derivatives.

2-Chloro-5-nitropyridine was prepared from 2-aminopyridine by a procedure derived from the method of Phillips (4), and that of Caldwell (5). The aminopyridine was first nitrated to the corresponding nitraminopyridine which was then rearranged with concentrated sulfuric acid to 2-amino-5-nitropyridine and its isomer the 3-nitro derivative, with the former predominating. The crude 5-nitro compound was then converted to the hydroxy derivative by treatment with sodium nitrite in presence of dilute sulfuric acid (4, 5). The chloronitropyridine was finally obtained from the hydroxy compound by reacting with phosphorus pentachloride in the presence of a small amount of the oxychloride.

Phillips reported that when sulfanilamide was condensed with 2-chloro-5-nitropyridine according to (*a*) Bobranski's (6) and (*b*) Ullmann's conditions (7), the reaction afforded the N^4 derivative in the former case and a mixture of the N^4 and N^1 derivatives in the latter case. However, when the sulfaguanidine was condensed with 2-chloro-5-nitropyridine adopting the two procedures mentioned above, the authors obtained the same product in both cases. This was shown qualitatively to be the N^4 derivative since it failed to diazotize and this conclusion was confirmed by ultraviolet analysis.[2] The absorption spectrum of the condensation product in methanol shows 2 maxima at 263.5 mμ (log ϵ 4.28), and 368 mμ (log ϵ 4.44). The former band is attributed to absorption of sulfanilamido chromophore ($\lambda_{max.}$ 262 mμ; log ϵ 4.25, in ethanol) (8), while the latter may be ascribed to the absorption of the *N*-substituted 2-amino-5-nitropyridine. The absorption in methanolic 2 *N* hydrochloric acid shows 2 maxima at 266.5 mμ (log ϵ 4.01) and 364 mμ (log ϵ 4.30). The hypsochromic shift and the hypochromic effect are due to salt formation. Such a phenomenon is observed in all aromatic amines (*cf.* the absorption spectra of *p*-nitroaniline in ethanol and in HCl). The absorption spectrum in 1 *N* sodium hydroxide shows 3 bands: 337.5 mμ (log ϵ 4.18), 295 mμ (log ϵ 3.92), and 465 mμ (log ϵ 4.46). The latter band which is indicative of a highly conjugated system may be ascribed to the aci-form I of the N^4 derivative which is expected to be present in the alkaline medium (I).

The strong bathochromic shift observed in alkaline solution indicates that the condensation product is the N^4 derivative and not the N^1, since the latter is expected to be insoluble in alkali and possesses identical spectra both in alkaline and neutral solutions.

Condensation of 2-chloro-5-nitropyridine with 1-aminohydantoin in dry pyridine, according to a method reported by Whitmore *et al.* (9), resulted in decomposition of the aminohydantoin with liberation of ammonia (confirmed qualitatively) which caused ammonolysis of the halonitropyridine yielding 2-amino-5-nitropyridine. The same happened when 1-aminohydantoin was replaced with 3-amino-2-oxazolidone. However, when the condensation of the aminohydantoin and the aminooxazolidone with 2-chloro-5-nitropyridine was conducted in aqueous hydrochloric acid in the presence of ethanol following Banks' directions (10), in 10% acid, the haloheterocycle was hydrolyzed to the corresponding hydroxy compound while with 1% acid the condensation was successful with the former amine and with the latter the starting materials were recovered unaffected. Furthermore, in the case of aminooxazolidone, no success attended Mangini's method (11–13), which consists of heating the reactants under reflux with absolute alcohol in presence of fused sodium acetate.

2-Chloro-5-nitropyridine was condensed with semicarbazide by refluxing together equimolecular quantities of the 2 reactants in the presence of 1% hydrochloric acid and ethanol. From the reaction mixture a high melting substance was isolated. It was obvious from the microanalytical data that 2 molecules of the halonitropyridine had condensed with 1 molecule of semicarbazide. Theoretically, 5 structures are possible for such a condensation product (II).

Structures II*a* and II*b* were excluded by the fact that no ammonia evolved when the condensation

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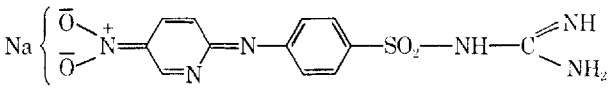
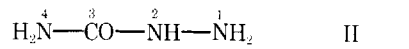
[1] The products at present are under preliminary screening for possible amebicidal action or any other useful pharmacological activity.

[2] The ultraviolet and infrared spectra were run on Spectracord model 4000 A and Infracord model 137 spectrophotometers, respectively.

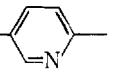


I

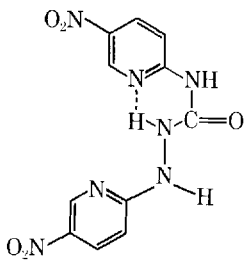


II

IIa = R in 1,1; IIb = R in 1,2; IIc = R in 4,4

IId = R in 2,4; IIe = R in 1,4; R = O_2N- 

product was heated with sodium hydroxide. Obviously, the reasons which prevented the formation of a compound having the structure IIa and IIb would also prevent the formation of IIc or IId. These reasons are probably steric effects. On the other hand, the infrared analysis[2] favored structure IIe and showed that it did exist in the chelated form (III).



III

The observed frequency of about 2985–3080 cm.$^{-1}$ (broad) may be ascribed to the chelated NH (*Reference 14*, p.195), while the sharp band at 3400 cm.$^{-1}$ may be assigned to the NH stretching frequency of the secondary amide (*Reference 14*, p. 176). Furthermore, the carbonyl stretching frequency of 5-nitro-2-acetylaminopyridine was found to occur at 1700 cm.$^{-1}$. Accordingly, the frequency of 1724 cm.$^{-1}$ may be attributed to the amide I band. Finally, the bands at 1997 and 1550 cm.$^{-1}$ may be assigned to the C=N (*Reference 14*, p. 226) and NO_2 (*Reference 14*, p. 250) stretch vibrations, respectively.

EXPERIMENTAL[3]

5-Nitro-2-acetylaminopyridine.—This compound was prepared from 5-nitro-2-aminopyridine by acetylation with acetic anhydride. The product was crystallized from benzene and it melted at 196° as reported (15).

p - (5 - Nitro - 2 - pyridylamino)benzenesulfonylguanidine.—*Method A.*—A mixture of 2-chloro-5-nitropyridine (3.16 Gm.) and sulfaguanidine (4.64 Gm.) was fused at 130–150° for 20 min. (Bobranski's conditions). The solid cake resulting was then extracted with boiling 2 *N* sodium hydroxide solution. The deep red extract was acidified with dilute hydrochloric acid and buffered by the addition of excess saturated solution of sodium acetate. The product which was obtained in 52% yield (3.3 Gm.) melted at 265–266° after 1 crystallization from ethanol.

Anal.[4]—Calcd. for $C_{12}H_{12}N_6O_4S$: C, 42.85; H, 3.57; N, 25.00; S, 9.52. Found: C, 42.90; H, 3.70; N, 24.30; S, 9.80.

Method B.—The above experiment was repeated but in the presence of anhydrous potassium carbonate (2.7 Gm.) and copper powder (0.2 Gm.) and the fusion conducted at 100–130° for 1 hr. (Ullmann's conditions). The solid cake thus obtained was then extracted with hot water, and the aqueous extract was acidified with 2 *N* acetic acid. The product after being crystallized from ethanol melted at 265–266°, and the melting point was not depressed on admixture with a pure specimen prepared by *Method A*.

5′ - Nitro - 2′ - pyridyl - 1 - aminohydantoin and N^1, N^4-Di(5′-nitro-2′-pyridyl) Semicarbazide.—These were prepared by the following general method.

A mixture of equimolecular amounts of 2-chloro-5-nitropyridine and the amino compound[5] (1-aminohydantoin in the former and semicarbazide in the latter) was refluxed with hydrochloric acid solution (1 ml. concentrated HCl, d 1.19, in 80 ml. of water and 20 ml. of ethanol) for 30–32 hr. The reaction mixture was then concentrated under diminished pressure to about 15–20 ml. when the condensation product separated out. The yield in both cases was 25% and the product was crystallized from ethanol.

The former compound melted at 247–249°.

Anal.—Calcd. for $C_8H_7N_5O_4$: C, 40.50; H, 2.95; N, 29.50. Found: C, 40.68; H, 3.05; N, 29.37.

The latter compound did not melt until 350°.

Anal.—Calcd. for $C_{11}H_9N_7O_5$: C, 41.00; H, 2.80; N, 30.70. Found: C, 41.13; H, 2.89; N, 31.02.

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[3] Melting points are uncorrected.

[4] Analyses were performed by Alfred Bernhardt, Germany.

[5] In the case of semicarbazide the 25% yield was obtained when 1 mole was condensed with 2 moles of the haloheterocycle, while with equimolecular amounts poorer yields were obtained.