PYRIDINE DERIVATIVES

PART V.* ON FLUORO-NITROPYRIDINES[1]

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ABSTRACT

2-Fluoro-5-nitropyridine has been synthesized and its properties compared with 2,4-dinitro-fluorobenzene. Absorption spectra are given. The highly reactive compound was used to prepare well defined derivatives from alcohols, amines, and amino acids.

In conjunction with other studies in the pyridine series we were interested in the synthesis and properties of some fluoro-nitropyridines, which are 'structurally analogous' to the well known dinitro-fluorobenzenes.

The preparation of the 2- and 3-fluoropyridines from the amines has been effected by: (*a*) diazotation in 60% hydrofluoric acid (4,2), (*b*) decomposition of the fluoborates (Schiemann reaction) (9), (*c*) decomposition of the fluosilicates (1). We have obtained 2-fluoro-5-nitropyridine from 2-amino-5-nitropyridine in 20–30% yield by method (*a*); methods (*b*) and (*c*) gave only traces. However, attempts to obtain other fluoro-nitropyridines by these methods were unsuccessful. From 2-amino-3-nitropyridine only the 2-hydroxy derivative was obtained by methods (*a*) or (*b*) and 4-fluoro-3-nitropyridine was not obtained from the 4-amino derivative. The failure of 4-aminopyridine to give 4-fluoropyridine has been reported (9).

As the fluorine in 2-fluoro-5-nitropyridine (NFP) shows the expected high reactivity, some precautions are necessary in its isolation. It gave 2-methoxy-5-nitropyridine (4) with sodium methoxide, or, more slowly with 10% aqueous methanol. From NFP and *o*-toluidine, glycine ethylester or phenylalanine, the corresponding N-substituted 2-amino-5-nitropyridines were obtained. Though NFP had advantages over 2-chloro-5-nitropyridine, which gave no such derivative with glycine ester, it is inferior to 2,4-dinitrofluobenzene for the characterization of phenols (12): with low melting xylenols, NFP gave only oily ethers.

Ultraviolet Absorption Spectra

The comparison of 2-fluoro-5-nitropyridine with the (corresponding) 1-fluo-2,4-dinitrobenzene could not be made, since the latter shows only end-absorption. However, it was interesting to compare the spectra of the fluoropyridines with the fluoro-nitrobenzenes.

It is known (8) that introduction of fluorine has very little effect on the general shape of the pyridine curve; it produces only a slight bathochromic and hyperchromic shift. These shifts fit very well in the pattern proposed by Spiers and Wibaut (11) for halopyridines.

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**The paper "Synthesis of 3-hydroxy-2-alkylpyridines", Can. J. Chem. 31: 564. 1953, is regarded as Part IV of this series.*

On the contrary, introduction of fluorine in nitrobenzene changes the shape of the absorption curve considerably (Fig. 1). Nitrobenzene shows one maximum at 255 mμ, which is also the sole maximum in the symmetrically substituted *p*-fluoro-nitrobenzene. In the ortho- and meta-compounds this maximum is shifted towards shorter wave lengths, and a second maximum occurs near 280 mμ.

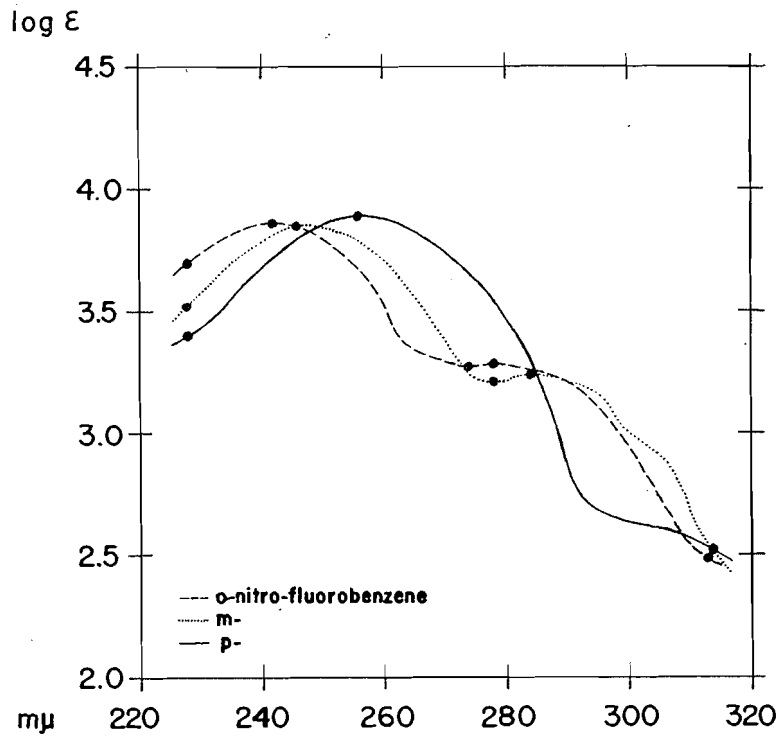

FIG. 1

2- and 4-Nitropyridines also show very distinctly a second maximum in the region of longer wave lengths, whereas this second maximum is absent in 3-nitropyridine (Fig. 2). However if the absorption spectra are measured in an unpolar solvent, e.g. trimethylpentane, instead of in alcohol, 3-nitropyridine also shows a second maximum.*

It is worth while noticing, that NFP shows nearly the same ultraviolet absorption curve as does 3-nitropyridine, the introduction of fluorine producing only a bathochromic effect (Fig. 3).

EXPERIMENTAL**

5-Nitro-2-fluoropyridine (NFP)

Of the several preparative methods tried, the following proved to be the most satisfactory. 2-Amino-5-nitropyridine (10.4 gm.) (3) was dissolved in

*The effect of the solvent on the absorption spectra of heterocyclic bases, e.g. pyridine, is discussed in (8).

**Melting points are corrected. Analyses are by A. Bernhardt, Mühlheim (Ruhr), Germany.

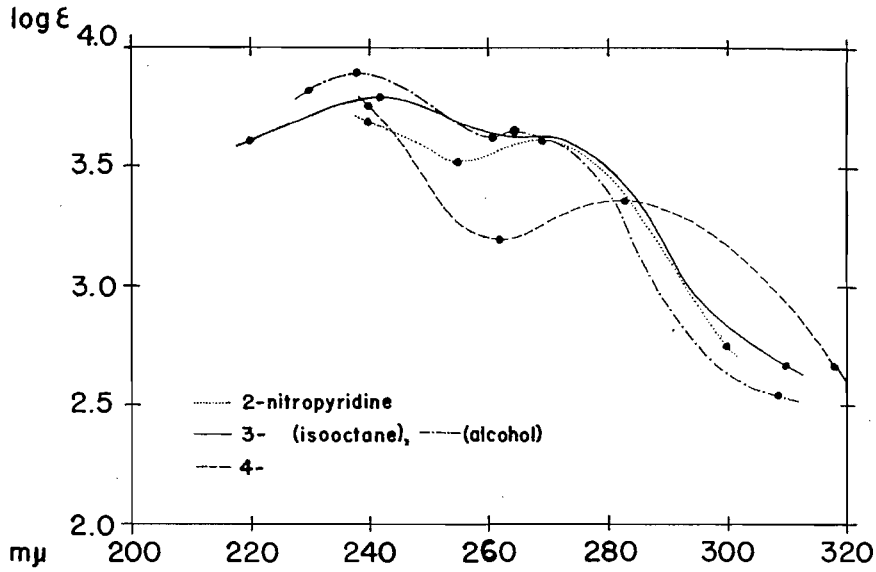

FIG. 2

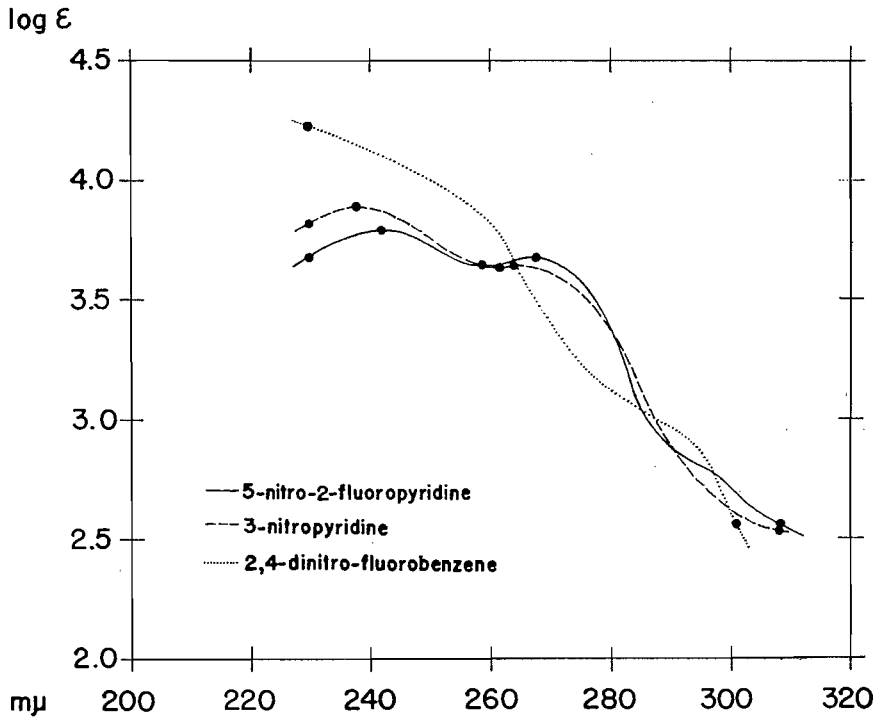

FIG. 3

100 ml. of 60% hydrofluoric acid, cooled to 0°C., and 6.3 gm. sodium nitrite added in small portions to the well stirred solution. After standing overnight

at room temperature, the acid was neutralized with sodium bicarbonate, an excess of sodium bicarbonate added, and the mixture saturated with sodium chloride. The mixture was extracted continuously with ether for 12 hr., the solvent evaporated, and the residue, consisting of NFP and 2-hydroxy-5-nitropyridine, distilled *in vacuo*. The receiver was cooled with dry ice-acetone mixture. NFP is rather volatile, has a characteristic smell, and is a typical lachrymator, even in low concentrations; it also has an irritating action on the skin, like 2,4-dinitro-fluobenzene. Yield 2.3 gm. (i.e. 22%), m.p. 19–21°C.; white prisms; b.p. 79–81°C. at 5–6 mm. Hg. Calc. for $C_5H_3FN_2O_2$: C, 42.26; H, 2.13; N, 19.72%. Found: C, 42.52; H, 2.01; N, 19.60%. $n_D^{23°} = 1.5258$; sp. gr.$\frac{23°}{23°} = 1.410$; found: $R_D = 30.93$. Ultraviolet absorption in 2,2,4-trimethylpentane ($c = 0.00011$): λ_{max} 242 mμ (log $\epsilon = 3.78$); 268 mμ (log $\epsilon = 3.67$) (Fig. 3).

Attempts to prepare NFP by heating 2-chloro-5-nitropyridine with potassium fluoride in a nonpolar solvent, corresponding to the convenient synthesis of 2,4-dinitro-fluorobenzene (5), were unsuccessful.

5-Nitro-2-methoxypyridine

Sodium, 200 mgm. was dissolved in absolute methanol, (5 ml.) the solution was cooled to 10°C. and added to a cooled solution of 420 mgm. NFP in 3 ml. of absolute methanol. A violent reaction set in and was completed by heating the mixture on the steam bath for 30 min. After cooling, the mixture was poured into water and the precipitate collected on a Büchner funnel. After sublimation *in vacuo* (39 mm.), the yield was 425 mgm. (94%); m.p. 104–108°C. After recrystallization from diluted methanol, the m.p. was 109–110°C. The mixed m.p. with an authentic sample was not depressed.

A solution of 300 mgm. NFP in 8 ml. of dilute methanol (15% v/v) was kept for 12 hr. at room temperature, after which no more crystals precipitated. Yield of 5-nitro-2-methoxypyridine 15 mgm., m.p. 109–110°. Calc. for $C_6H_6N_2O_3$: N, 18.18; OCH_3, 20.14%. Found: N, 18.05; OCH_3, 20.20%.

N-(5-nitropyridyl-2)-o-toluidine

A mixture of 600 mgm. NFP and 600 mgm. *o*-toluidine was heated on the steam bath for two hours; the solid content of the flask was recrystallized from 70 ml. 10% hydrochloric acid with a little charcoal, and then twice from dilute alcohol; m.p. 137–139°C., mixed melting point with a sample prepared from 2-chloro-5-nitropyridine was not depressed. Yield almost quantitative. Calc. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84%. Found: C, 63.12, 62.83; H, 4.74, 4.76%.

Ethyl N-(5-nitropyridyl-2)-aminoacetate

A solution of 250 mgm. of glycine ethyl ester hydrochloride and 336 mgm. of sodium bicarbonate in 5 ml. water was added to a solution of 284 mgm. of NFP in 10 ml. of ethanol. After standing at 5°C. for five hours the precipitation of white needles began. They were collected the next day and had a melting point of 140–145°C.; crude yield 425 mgm. After purification by recrystallization from dilute alcohol the melting point was 142–143°C. Calc. for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66%. Found: C, 47.94; H, 5.00; N, 18.72%.

N-(5-nitropyridyl-2)-β-phenylalanine

Phenylalanine (330 mgm.) and sodium bicarbonate (336 mgm.) were dissolved in 15 ml. water and mixed with a solution of 284 mgm. NFP in 5 ml. alcohol. After 15 hr. at room temperature the solvents were removed *in vacuo* at 30°C., and the residue recrystallized several times from absolute methanol. Brownish-yellow plates, yield 291 mgm. (52%), m.p. 183–185°C. Calc. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63%. Found: C, 58.42; H, 4.63; N, 14.47%.

Ultraviolet Absorption Spectra

The fluoro-nitrobenzenes and dinitrobenzenes were prepared from the nitroanilines in a Schiemann reaction according to Org. Synth., Coll. Vol. II, p. 225. The nitropyridines were prepared by oxidation of the aminopyridines with hydrogen peroxide in oleum (6, 7, 10). The spectra were measured in 2,2,4-trimethylpentane ('isooctane') unless otherwise stated.

o-Nitro-fluorobenzene b.p. 86–87°C. at 10–11 mm. Hg (c = 0.00015);
λ_{max}: 242 mμ (log ϵ = 3.86), 278 mμ (log ϵ = 3.27).

m-Nitro-fluorobenzene b.p. 53–54°C. at 1–2 mm. Hg. (c = 0.00021);
λ_{max}: 246 mμ (log ϵ = 3.87), 284 mμ (log ϵ = 3.23).

p-Nitro-fluorobenzene b.p. 86–88°C. at 12–14 mm. Hg (c = 0.00021);
λ_{max}: 256 mμ (log ϵ = 3.88).

2-Nitropyridine m.p. 70–71°C., in 95% ethanol (c = 0.00014);
λ_{max}: 269 mμ (log ϵ = 3.60).

3-Nitropyridine m.p. 35–36°C., (c = 0.00014);
λ_{max}: 238 mμ (log ϵ = 3.88), 264 mμ (log ϵ = 3.64). In 95% ethanol (c = 0.00016), λ_{max}: 242 mμ (log ϵ = 3.78).

4-Nitropyridine m.p. 49–51°C., in 95% ethanol (c = 0.00013):
λ_{max}: 282 mμ (log ϵ = 3.35).

ACKNOWLEDGMENT

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