Synthesis and Spectral Data of Pyrido[2,3-*e*]-*as*-triazines

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The pyrido[2,3-*e*]-*as*-triazine and its 3-phenyl derivatives were prepared *via* cyclisation with polyphosphoric acid of suitable 3-substituted 2-aminopyridines obtained by reduction of the corresponding 2-nitropyridines. The 3-substituted 2-nitropyridines were obtained by action of hydrazine or benzoylhydrazide with the appropriate 3-halo-2-nitropyridines; only 3-fluoro-2-nitropyridine leads to the 3-substituted 2-nitropyridines. This experimental results are in agreements with the CNDO and MNDO calculations.

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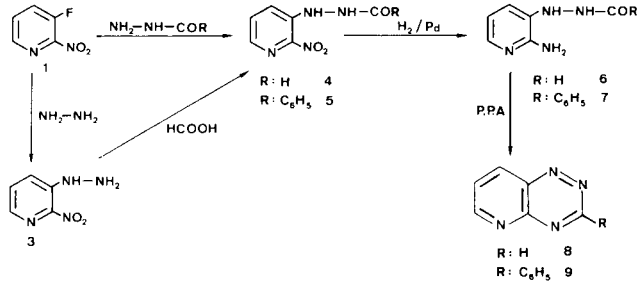
There are four possible pyrido-*as*-triazines, if those with bridgehead nitrogen atoms are excluded. The synthesis of three of them are described in the literature [1] [2] [3].

The preparation of a number of derivatives of pyrido-[2,3-*e*]-*as*-triazines has been reported [2] [4] [5] but the parent heterocycle is unknown.

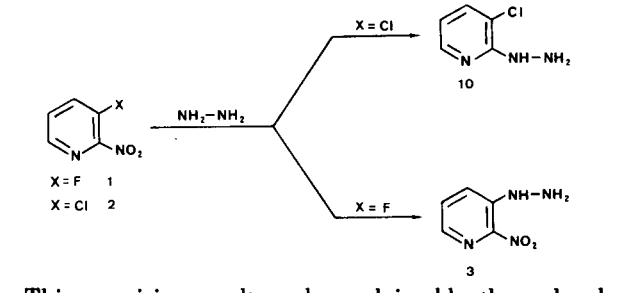
We have successfully prepared the pyrido[2,3-*e*]-*as*-triazine (**8**) and its 3-phenyl derivatives **9** starting with 2-nitro-3-hydrazinopyridine (**3**).

Scheme I



Compound **3** is prepared by treatment of appropriate 2-nitro-3-halopyridines with ethanolic hydrazine hydrate. Treatment of 3-chloro-2-nitropyridine (**2**) with hydrazine hydrate affords 2-hydrazino-3-chloropyridine (**10**) whereas under same conditions 3-fluoro-2-nitropyridine (**1**) leads to 2-nitro-3-hydrazinopyridine (**3**) [8].

Scheme II



This surprising result can be explained by the molecular orbital theory.

The characteristics of the electronic structure: net charge Q_r, π-charge q_r and covalent term χ_r [Table 1] of the 3-halo-2-nitropyridines **1** and **2** were investigated by the use of quantum semi-empirical methods (CNDO, MNDO).

The molecular geometries of compounds **1** and **2** were calculated by the MNDO method.

In the halonitropyridines **1** and **2** the energy levels of the π^*-antibonding orbital (E_{π^*}) are not far and it should not be safe in ignoring it. The contribution of all π^*-antibonding orbitals would instead be assessed to determine the covalent term χ_r (see Experimental) of the Klopman and Salem's equation [9].

The net charges Q_r and π-charges q_r (Table 1) calculated by CNDO and MNDO methods indicate that a charge controlling reagent will attack on C_2 (substitution or nitro group) for **2** and on C_3 (substitution of fluoro for **1**). The covalent terms χ_r by CNDO and MNDO methods reveal that an orbital controlling reagent will attack on the same sites, that is C_2 for **2** and C_3 for **1**.

In the empirical classification of hard and soft donors (bases) established by Pearson [10] it was noticed that hydrazine characterized as hard reagent tends to react *via* charge control.

Table 1

Net Charges Q_r, π-charges q_r, Covalent Term χ_r of Substituted Carbons in Compounds **1** and **2**

Method	Compound	Indices Atom$_r$	Q_r	q_r	χ_r
CNDO	**1**	C_2	+0.0830	1.0538	0.6919
		C_3	+0.2126	0.9946	0.6954
	2	C_2	+0.1434	0.9969	0.7089
		C_3	+0.0469	1.0289	0.5971
MNDO	**1**	C_2	+0.0076	0.9690	0.7699
		C_3	+0.1606	0.9626	0.8660
	2	C_2	+0.0566	0.9860	0.6829
		C_3	−0.0156	1.0701	0.4163

The CNDO as MNDO calculations predict that 3-hydrazino-2-nitropyridine (**3**) will be prepared exclusively by action of hydrazine hydrate with 3-fluoro-2-nitropyridine **1** and so are in agreement with the experimental results.

Reaction of **3** with formic acid leads to 3-formylhydrazino-2-nitropyridine (**4**) while compound **5** is obtained by direct substitution of fluorine with benzoylhydrazide.

Selective reduction of the nitro group with palladium-on-carbon used as catalyst gives **6** and **7** in good yield. These compounds were not kept for a prolonged period nor purified because they are sensitive to air oxidation and very hygroscopic.

The intramolecular cyclodehydration of 2-amino-3-acylhydrazinopyridines **6** and **7** with polyphosphoric acid is an extension of the Bischler synthesis of the benzo-*as*-triazines [6] [7].

EXPERIMENTAL

The covalent term χ_r of an atom r for compounds **1** and **2** was calculated with the equation:

$$\chi_r = \Sigma_n \frac{C_{rn}^2}{E_{HO} - E_{\pi_n^*}}$$

C_{rn}: Coefficient of the atomic orbital of atom r in the π^*-antibonding orbital n.

E_{HO}: Energy of the frontier orbital HOMO of hydrazine.

E_{π^*n}: Energy of the π^*-antibonding orbital n.

3-Fluoro-2-nitropyridine (**1**).

A solution of nitrite sodium (5 g, 0.072 mole) in water (10 ml) was added dropwise to a stirred mixture of 3-amino-2-nitropyridine (10 g, 0.072 mole) in 34% fluoroboric acid (35 ml). During addition the temperature was maintained between -8° and -2°. The stirring was continued for 0.5 hours. The suspension was filtered and the solid washed with 34% fluoroboric acid (9 ml), then with ether (20 ml) and dried at 25°/4 torr for 12 hours to give 15 g of a pale grey solid of the fluoroborate salt (87%). The dry solid was decomposed by heating to 115-120°. After decomposition the remaining oil was treated with a solution of sodium hydrogenocarbonate 10% (20 ml) and the mixture was extracted with chloroform (four 100 ml portion). The combined extracts were dried (magnesium sulfate) filtered and the chloroform removed under reduced pressure to yield the crude 3-fluoro-2-nitropyridine (**1**) as a yellow oil which tends to crystallize (3 g, 45% of crude product). The crude product was used for the next step; **1** can be purified by sublimation, mp 35°; nmr (deuteriochloroform): δ 7.8 (m, 2H, H_4, H_5), 8.45 (m, 1H, H_6).

Anal. Calcd. for $C_5H_3FN_2O_2$: C, 42.20; H, 2.11; N, 19.72. Found: C, 42.3; H, 2.3; N, 20.1

3-Hydrazino-2-nitropyridine (**3**).

A solution of hydrazine hydrate (1 g, 0.02 mole) in ethanol (15 ml) was added dropwise to a stirred solution of 3-fluoro-2-nitropyridine (1.42 g, 0.01 mole) in ethanol (10 ml). During the addition the temperature of mixture was maintained at 0°. After 1 hour the 3-hydrazino-2-nitropyridine (**3**) was isolated by filtration and recrystallized from mixture water-ethanol (50-50) to give 0.75 g (80%) as orange crystals, mp 180°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.4 (m, 3H, NH-NH_2), 7.5 (dd, 1H, H_5, J_{4-5} = 8, J_{5-6} = 6), 7.65 (m, 1H, H_6), 8.05 (dd, 1H, H_4, J_{4-6} = 2).

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.96; H, 3.89; N, 36.36. Found: C, 39.1; H, 3.6; N, 36.0.

3-Formylhydrazino-2-nitropyridine (**4**).

A solution of 3-hydrazino-2-nitropyridine (2 g, 0.013 mole) in formic acid (50 ml) was refluxed with stirring for 8 hours. The formic acid was removed under reduced pressure. The brown remaining solid was recrystallized from ethanol to give 1.35 g (57%) of orange crystals, mp 182°; ir: ν max 3300, 2920, 1680 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.35 (m, 2H, NH-NH), 7.55 (m, 1H, H_5), 8.0 (s, 1H, CHO), 7.9-8.25 (m, 2H, H_4, H_6).

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.4; H, 3.3; N, 30.5.

3-Benzoylhydrazino-2-nitropyridine (**5**).

A mixture of 3-fluoro-2-nitropyridine (1.8 g, 0.0126 mole) and benzoylhydrazine (1.8 g, 0.0132 mole) in ethanol (150 ml) was refluxed with stirring for 16 hours. The product was isolated by filtration and recrystallized from ethanol to give 2.5 g (77%) of orange crystals, mp 184°; ir: ν max 3330, 3240, 3090, 1650 cm^{-1}; nmr (dimethyl sulfoxide-d_6): δ 7.55 (m, 5H, H_4, H_5, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.85 (m, 3H, H_6, $H_{2'}$, $H_{6'}$), 9.2 (2H, NH-NH).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.7; H, 3.8; N, 21.4.

3-Acylhydrazino-2-aminopyridines **6** and **7**.

A partial solution of 3-acylhydrazino-2-nitropyridine **4** or **5** (0.01 mole) in ethanol (150 ml) containing 0.5 g of 10% palladium-on-carbon was hydrogenated at atmospheric pressure. Uptake of hydrogen was complete in 1 hour. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. No suitable crystallizing solvent could be found for the product which was very hygroscopic and sensitive to air oxidation. The yields of crude product were about 95%. The crude product was used for the cyclisation.

Pyrido[2,3-*e*]-*as*-triazine (**8**).

A stirred suspension of 3-formylhydrazino-2-aminopyridine (1 g, 0.0065 mole) in polyphosphoric acid (20 ml) was heated at 120° for 7 minutes. The mixture was poured with stirring into a cooled solution of ammonium hydroxide (60 ml, d = 0.89) in water (200 ml). The mixture was extracted with ether (four 50 ml portions). The combined extracts were dried (magnesium sulfate) filtered and ether removed under reduced pressure. Pyrido[2,3-*e*]-*as*-triazine (**8**) was purified by column chromatography on alumina with chloroform as an eluent to give 0.170 g (20%) of product, mp 130°; ir: ν max 1600, 1560, 1500 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.90 (dd, 1H, J_{7-8} = 8, H_7), 8.9 (dd, 1H, J_{6-8} = 2, H_8), 9.4 (dd, 1H, H_6), 10.03 (s, 1H, H_3); ^{13}C nmr (deuteriochloroform): δ 153.3 (C_3, J = 204); 160.5 (C_6, J = 180), 126.6 (C_7, J = 168), 138.4 (C_8, J = 168), 144.1 (C_9), 161.4 (C_{10}); uv: λ max (ε x 10^{-3}) 264 nm (3.1), 308.4 nm (6.1), 456.4 nm (0.26).

Anal. Calcd. for $C_6H_4N_4$: C, 54.55; H, 3.03; N, 42.42. Found: C, 54.7; H, 2.9; N, 42.3.

3-Phenylpyrido[2,3-*e*]-*as*-triazine (**9**).

This compound was prepared from 3-benzoylhydrazino-2-aminopyridine (**7**) in 50% yield by the procedure described above, mp 142°; ^{1}H nmr (deuteriochloroform): 7.6 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.8 (dd, 1H, J = 4, J = 8, H_7), 8.8 (m, 2H, $H_{2'}$, $H_{6'}$), 8.9 (dd, 1H, J = 2, H_8), 9.4 (dd, 1H, H_6); uv: λ max (ε x 10^{-3}), 258 nm (24.6), 357.1 (7.98), 470.4 (0.31).

Anal. Calcd. for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.1; H, 3.7; N, 26.5.

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[11] Melting points are uncorrected. The uv spectra were recorded on a Perkin-Elmer 552 Spectrometer. The ^{1}H and ^{13}C nmr spectra were obtained on Brucker WH 90, Varian EM 360 with TMS as the internal standard in deuteriochloroform and HMDS as a standard in DMSO-d_6. The microanalyses were performed by the microanalyses department of INSCIR-INSA.