

## NITROAZINES.

### 20.\* SIMPLE SYNTHESIS OF NITROPYRAZOLOPYRIDINES FROM ALIPHATIC NITROSYNTHONS AND AMINOPYRAZOLES.

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*Two variants of a synthesis for nitropyrzolo[3,4-*b*]pyridines from aminopyrazoles and two- or three-carbon nitrosynthons are examined.*

Derivatives of pyrazolo[3,4-*b*]pyridine include inhibitors of cyclic AMP-phosphodiesterases, anti-inflammatory, psychopharmacological agents, and antimetabolites [2-5], the most interesting being compounds with free NH groups [3, 4]. The basic method for the preparation of these heterocyclic systems is acid catalyzed condensation of N-substituted aminopyrazoles with  $\beta$ -dicarbonyl compounds [3]. The oxidation of blocked 1-aryl- or heterarylmethylene substituents in the pyrazole portion of the molecules is used for the synthesis of 1H-pyrazolo[3,4-*b*]pyridines [3, 4].

We have investigated the possibility of using aliphatic nitro compounds in the preparation of 5-nitropyrzolo[3,4-*b*]pyridines. Two variants of cyclization with nitrosynthons containing two and three carbon atoms have been examined.

A few examples are known of the use of three-carbon nitrosynthons are known: nitromalonic aldehyde has been used for the construction of the pyrazolo[3,4-*b*]pyridine system with the nitro group in the pyridine residue. 1-Methyl- and 1-phenyl-5-nitro-pyrazolo[3,4-*b*]pyridines have been synthesized by heating 1-substituted aminopyrazoles with nitromalonic aldehyde in acetic or polyphosphoric acid [6, 7].



We have developed a simpler and more general method for the synthesis of 5-nitropyrzolo[3,4-*b*]pyridines which permits the preparation of compounds with (Ia-e) and without (If-h) substituents at nitrogen. Compounds Ia-h are formed when the aminopyrazoles IIa-h are heated for a short time with the sodium salt of nitromalonic aldehyde in water or aqueous DMSO without an acid catalyst (Scheme 1, Table 1). The pyrazolo[3,4-*b*]pyridines If-h containing free NH groups, which are inaccessible by other methods, are easily obtained in a single step in this way.

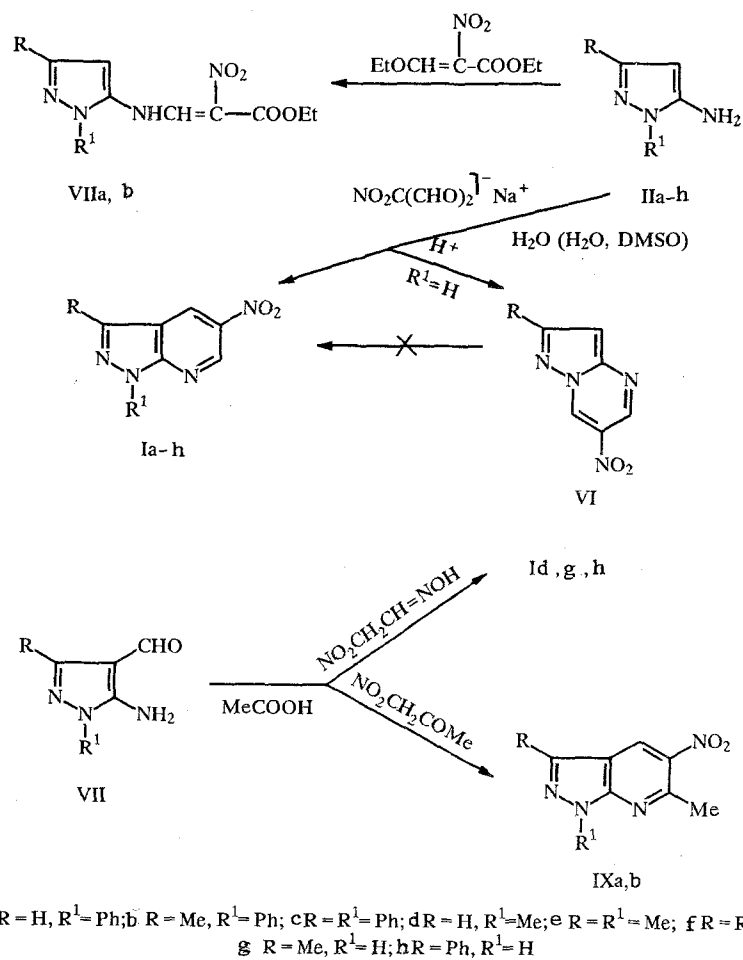
\*For Communication 19 see [1].

TABLE 1. Characteristics of the Compounds Synthesized

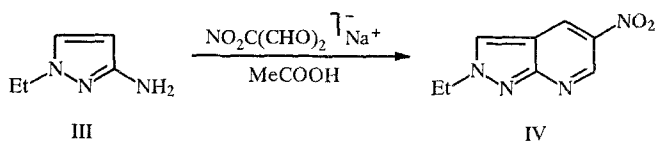
Compound	Molecular formula	mp, °C	IR spectrum (Nujol), $\nu$ , $\text{cm}^{-1}$		$^1\text{H}$ NMR spectrum (DMSO- $d_6$ ), $\delta$ , ppm		Mass spectrum $m/z$ ( $I_{\text{rel}}$ , %)				UV spectrum, $\lambda_{\text{max}}$ , nm (log $\epsilon$ )	Yield, % (method)		
			$\text{NO}_2$	NH	4-H**	6-H**	other signals	( $M+1$ ) <sup>+</sup>	$M^+$	M- $\text{NO}_2$ ( $\phi_2$ )			$\phi_1$ - $\text{R}^1\text{CN}$ ( $\phi_2$ )	$\phi_2$ -HCN
Ia	$\text{C}_{12}\text{H}_8\text{N}_4\text{O}_2$	175...177	—	—	9,29	9,35	7,70...8,30 (5H, m, $\text{C}_6\text{H}_5$ ); 8,40 (1H, s, 3-H)	241 (21,9)	240 (100)	194 (24,6)	167 (6,5)	140 (10,9)	222 (4,10), 240 (4,15), 323 (3,90)	70 (A) 85 (C) 60 (D)
Ib	$\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$	181...183	—	—	9,22	9,32	2,65 (3H, s, $\text{CH}_3$ ); 7,60...8,40 (5H, m, $\text{C}_6\text{H}_5$ )	255 (21,8)	254 (100)	208 (20,3)	167 (14,0)	140 (16,5)	224 (4,21), 242 (4,18), 278 (4,19), 331 (3,90)	75 (B) 85 (C) 75 (D)
Ic	$\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_2$	223...225	—	—	9,35	9,41	7,50...8,40 (10H, m, $\text{C}_6\text{H}_5$ ) <sub>2</sub>	317 (20,2)	316 (100)	270 (28,6)	167 (20,5)	140 (25,9)	266 (4,35), 335 (3,80)	80 (B) 90 (C) 70 (D)
Id	$\text{C}_7\text{H}_6\text{N}_4\text{O}_2$	133...135	—	—	9,10	9,36	4,15 (3H, s, $\text{NCH}_3$ ); 8,35 (1H, s, 3-H)	179 (19,1)	178 (100)	132 (29,5)	105 (22,3)	78 (27,3)	244 (4,00), 263 (4,14), 320 (3,88)	65 (A) 40 (B) 70 (C)
Ie	$\text{C}_8\text{H}_8\text{N}_4\text{O}_2$	137...139	—	—	9,15	9,40	2,65 (3H, s, $\text{CH}_3$ ); 4,10 (3H, s, $\text{NCH}_3$ )	193 (19,9)	192 (100)	146 (20,4)	105 (20,8)	78 (26,5)	243 (4,02), 265 (4,07), 322 (3,89)	70 (A) 50 (B) 80 (C) 65 (A)
If	$\text{C}_6\text{H}_4\text{N}_4\text{O}_2$	195...197	3240	—	9,12	9,35	4,68 (1H, s, NH); 8,36 (1H, s, 3-H)	165 (8,7)	164 (100)	118 (33,7)	91 (20,4)	—	242 (4,12), 257 (4,11), 312 (3,94)	75 (A)
Ig	$\text{C}_7\text{H}_6\text{N}_4\text{O}_2$	190...193	3180	—	9,20	9,40	2,62 (3H, s, $\text{CH}_3$ ); 4,15 (1H, s, NH)	179 (12,4)	178 (100)	132 (30,9)	91 (22,6)	—	242 (4,10), 263 (4,15), 320 (3,88)	75 (A)
Ih	$\text{C}_{12}\text{H}_8\text{N}_4\text{O}_2$	220...222	3100	—	9,25	9,40	4,50 (1H, s, NH); 7,60...8,30 (5H, m, $\text{C}_6\text{H}_5$ )	241 (10,0)	240 (100)	194 (32,1)	91 (19,8)	—	320 (4,10), 240 (4,10), 323 (3,90)	60 (A)
IV	$\text{C}_8\text{H}_8\text{N}_4\text{O}_2$	185...186	—	—	9,25	9,35	1,58 (3H, t, $\text{CH}_3$ ); 5,6 (2H, q, $\text{CH}_2$ ); 8,82 (1H, s, 3H)	255 (21,7)	254 (100)	208 (20,3)	181 (25,7)	—	222 (3,70), 244 (3,90), 275 (4,10), 320 (3,50)	82
IXa	$\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$	—	—	—	9,13	—	8,84 (1H, s, 3-H)	269 (22,9)	268 (100)	222 (12,4)	181 (29,8)	—	225 (3,90), 245 (4,16), 270 (4,32), 330 (3,90)	65
IXb	$\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2$	—	—	—	9,10	—	2,88 (3H, s, $\text{CH}_3$ ); 3,88 (3H, s, $\text{CH}_3$ ); 7,3...8,3 (5H, m, $\text{C}_6\text{H}_5$ )	—	—	—	—	—	—	—

\* Compounds Ia,b,d,e,g, IV, VIII, IX were purified by crystallization from ethanol, Ic from acetic acid, If from water, and Ih from 50% DMF.

\*\* Ia—e  $J_{46} = 2.4$  Hz, If—h  $J_{46} = 2.2$  Hz, IV  $J_{46} = 2.1$  Hz.



The reaction direction and the product yield depends not only on the nature of the substituent but also on its position in the aminopyrazole. While the 1-R<sup>1</sup>-5-amino derivatives IIa-e react readily with nitromalonic aldehyde, the isomeric product from the condensation of 1-ethyl-3-aminopyrazole (III), 2-ethyl-5-nitropyrazolo[3,4-b]pyridine (IV) was obtained only after prolonged boiling in acetic acid. The reaction did not occur in water or DMSO.



5-Aminopyrazoles without substituents at position 1 react with nitromalonic aldehyde in acidic media with participation of a cyclic nitrogen atom to give derivatives of 6-nitropyrazolo[1,5-a]pyrimidines (VI) [6, 8]. The dependence of the condensation direction on changes in pH and the formation of 5-nitropyrazolo[3,4-b]pyridines when the reaction is carried out without an acid catalyst is apparently connected with a shift of the position of the initial attack from the exocyclic amino group to atom C<sub>(4)</sub> of the pyrazole, which agrees with literature results. It is known, for example, after when 1-benzyl-5-aminopyrazole reacted for many hours in benzene with β-dicarbonyl compounds containing acceptor substituents (trifluoroacetic or oxaloacetic esters) products of C<sub>(4)</sub> substitution were isolated [1-benzyl-4-(2-carbethoxy-1-oxyethyl)pyrazoles] which underwent further condensation to give derivatives of pyrazolo[3,4-b]pyridine [8, 9], whereas in acetic acid the corresponding vinylamines were formed [2].

The scheme for formation of the pyridines If-h via recyclization of initially formed 6-nitropyrazolo[1,5-a]pyrimidines (VI) should be excluded since this conversion requires prolonged boiling of the latter in 15% alcoholic alkali [9]. Not even traces of the pyridines I were obtained when compounds VI were heated with an equimolar amount of NaOH (the formation of alkali is possible from the hydrolysis of nitromalonic aldehyde under the conditions of the condensation reaction).

Condensation of 1-R<sup>1</sup>-5-aminopyrazoles with another three-carbon nitrosynthone, ethyl ethoxymethylenenitroacetate, stopped at the stage of formation of the pyrazolylaminoacrylates VII (Scheme 1). The corresponding nitropyridines were not obtained by heating either in a solvent or in the melt.

The construction of the pyrazolopyridine system with a nitro group in the pyridine residue using a two carbon nitrosynthone was realized in the synthesis of 5-nitropyrazolo[3,4-*b*]pyridines starting from 3-aminopyrazolylaldehydes-4 (VIII). The nitropyridines I and IX (scheme 1) were obtained by heating compounds VIII in acetic acid nitroacetaldoxime, nitroacetone, or ethyl nitroacetate.

The symmetric (1335–1350) and asymmetric (1500–1540 cm<sup>-1</sup>) nitro group stretching vibrations appear in the IR spectra of all the compounds prepared. Apart from signals for the substituents R and R<sup>1</sup>, the <sup>1</sup>H NMR spectra of compounds I and IV contain signals for the pyridine protons in the form of two doublets. The Spin-spin coupling of the *meta*-protons depends on the nature and position of the substituent R<sup>1</sup> at the nitrogen atom in the pyrazole residue (for Ia–e,  $J_{46} = 2.4$  Hz, for If–h,  $J_{46} = 2.2$  Hz, and for IV  $J_{46} = 2.1$  Hz). Comparison of the spectra of compounds Ia,b and IXa,b shows that the 4-H proton resonates at higher field. The molecular ion peak in the mass spectra of compounds I and IV is maximal ( $W_M$  12–20%) which is indicative of the cyclic structure. The first fragmentation step, elimination of NO<sub>2</sub>, is characteristic of nitro compounds. The second fragmentation process, consecutive elimination of HCN and RCN is typical of nitrogen-containing heterocycles and indicates the number of heteroatoms in the molecule.

Three tautomeric forms are possible for compounds If–h: 1-H-, 2-H-, and 3-H-derivatives of pyrazolo[3,4-*b*]pyridine. The observed similarity of electron impact fragmentation for compounds If, Ia, and Id shows that the proton is attached to a nitrogen atom in the pyrazole residue. A retrodiene decomposition with elimination of the C<sub>2</sub>HNO<sub>2</sub> unit should be observed for the 7-H-tautomer. Comparison of the UV and <sup>1</sup>H NMR spectra of compound IVg with Id, Ie, and IV indicates that the N-unsubstituted derivatives occur in solution as either the 1- or 2-H-isomers.

## EXPERIMENTAL

UV spectra of ethanol solutions were recorded with a Specord UV-vis spectrometer, IR spectra of Nujol mulls with a UR-20 machine, <sup>1</sup>H NMR spectra in DMSO-D<sub>6</sub> with HMDS internal standard with a Bruker WR-90 spectrometer, and mass spectra with a Varian MAT-311 instrument under standard conditions.

**1-R-Nitropyrazolo[3,4-*b*]pyridines, Ia–h (Table 1).** A. A solution of an aminopyrazole IIe–h (0.01 mole) and the monohydrate of the sodium salt of malonic aldehyde (1.6 g, 0.01 mol) in water (15 ml) was boiled for 15 min, cooled, the precipitate filtered off and recrystallized.

B. An aminopyrazole IIa–h (0.01 mol) was dissolved in DMSO or DMF (15 ml), mixed with a solution of the monohydrate of the sodium salt of malonic aldehyde (1.6 g, 0.01 mol) in water (5 ml), heated to 100° C and maintained at this temperature for 15–20 min. The cooled solution was poured into water, the precipitate filtered off and recrystallized.

C. A solution of an aminopyrazole IIa–d, h and the monohydrate of the sodium salt of malonic aldehyde (1.6 g, 0.01 mol) in acetic acid (10 ml) was boiled for 40–60 min, cooled, and the precipitate filtered off and recrystallized.

D. A solution of aminopyrazolylaldehyde VIII (0.01 mol) and nitroacetaldoxime or nitroacetone (0.012 mol) in acetic acid (10 ml) was boiled for 30 min, cooled, the precipitate filtered off and recrystallized.

**2-Ethyl-5-nitropyrazolo[3,4-*b*]pyridine (IV).** A solution of the aminopyrazole III (0.01 mol) and the monohydrate of the sodium salt of malonic aldehyde (1.6 g, 0.01 mol) in acetic acid (20 ml) was boiled for 48 h, evaporated to dryness, and recrystallized from ethanol.

**Ethyl 1-(1-Phenylpyrazolyl-5-amino)-2-nitroacrylate (VIIa, C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>).** A solution of 1-phenyl-5-aminopyrazole (1.6 g, 0.01 mol) and ethyl ethoxymethylenenitroacetate (2.1 g, 0.011 mol) in benzene (40 ml) was boiled for 1h, cooled, and the precipitate filtered off and recrystallized from ethanol to give VIIa (2.5 g, 83%), m.p. 112–115° C. IR spectrum: 1310, 1520 (NO<sub>2</sub>), 1705 (C=O), 3250 cm<sup>-1</sup> (NH). M<sup>+</sup> 316. <sup>1</sup>H NMR spectrum (DMSO-D<sub>6</sub>): 1.15 (3H, t, CH<sub>3</sub>), 4.25 (2H, q, CH<sub>2</sub>), 6.75 (1H, d, 4-H), 7.40–7.60 (5H, m, C<sub>6</sub>H<sub>5</sub>), 7.72 (1H, d, 3-H), 8.20 (1H, br.s, =CH), 10.50 ppm (1H, br.s, NH).

**Ethyl 1-(1-phenyl-3-methylpyrazolyl-5-amino)-2-nitroacrylate (VIIb, C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>)** was obtained analogously to compound VIIa, yield 79%. M.p. 117–110° C. IR spectrum: 1310, 1500 (NO<sub>2</sub>), 1710 (C=O), 3260 cm<sup>-1</sup>

(NH).  $^1\text{H}$  NMR spectrum (DMSO- $\text{D}_6$ ): 1.20 (3H, t,  $\text{CH}_3$ ), 2.25 (3H, s,  $\text{CH}_3$ ), 4.20 (2H, q,  $\text{CH}_2$ ), 6.50 (1H, s, 4-H), 7.45–7.65 (5H, m,  $\text{C}_6\text{H}_5$ ), 8.20 (1H, br.s, =CH), 10.50 ppm (1H, br.s, NH).

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