5,6-CONDENSED 3-NITROPYRIDINES FROM HETEROCYCLIC AMINES AND NITROMALONALDEHYDE

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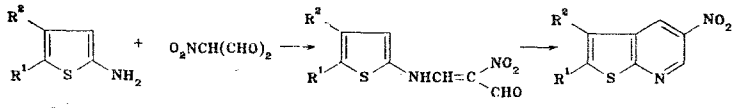
UDC 547.734'822.7'853.7'859.1'732'743.4'722.1.07:543.422

The reaction of nitromalonaldehyde with 2-aminothiophenes leads to 5-nitrothieno-[2,3-b]pyridines. The analogous reaction with 3-aminopyrroles leads to 6-nitropyrrolo[3,2-b]pyridines. The analogous reaction with 4- and 5-aminopyrazoles leads to 6-nitropyrazolo[4,3-b]pyridines and 5-nitropyrazolo[3,4-b]pyridines, respectively. Enamines are formed as intermediates. 3- and 5-Aminopyrazoles which are unsubstituted at N-1 are converted to 3-nitropyrazolo[1,5-a]pyrimidines. The nitro derivatives obtained may be reduced to the corresponding amines.

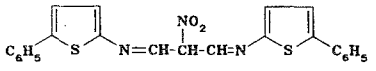
Aniline reacts with nitromalonaldehyde to form 3-nitroquinoline [1, 2]. Several derivatives of aminopyrimidine, 2-aminopyrrole, 5- and 6-aminoindole also undergo this cyclocondensation [3].

In the framework of a study of the preparation of nitroheteroaromatic compounds from nitroolefins [4, 5], we used previously obtained heteroaromatic amines [6] in reactions with nitromalonaldehyde (II) (as its sodium salt).

2-Aminothiophenes (I) react with II even at room temperature to form a mixture of stereomeric enamines III which cyclize in perfluoroacetic acid or acetic acid to give 5-nitro[2,3-b]pyridines IV. The separation of enamines III is not always possible since products IV are formed (in 50-60% yield) upon their heating in acetic acid at reflux.



I a-c II III a-c IV a, b

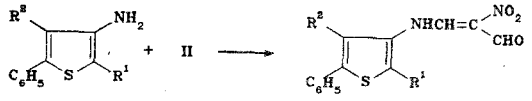


V

I, III, IV a R^1=CH_3, R^2=H; b R^1=$COOC_2H_5$, R^2=CH_3; c R^1—R^2=—$(CH_2)_4$—

2-Amino-5-phenylthiophene reacts with both aldehyde groups to form linear diimine V.

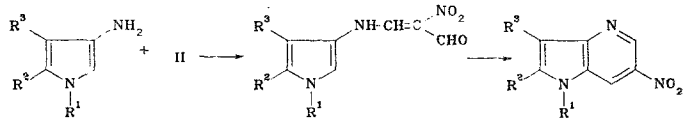
3-Aminothiophenes VI also react with aldehyde II to form enamines VII. These enamines, however, do not cyclize despite the presence of free "ortho" positions.



VI a, b VII a, b

VI, VII a R^1=$COOC_2H_5$, R^2=H; VIb R^1=COOH, R^2=CN; VIIb R^1=H, R^2=CN

3-Aminopyrroles VIII may be readily converted to 6-nitropyrrolo[3,2-b]pyridines in 80-90% yield in one step by heating with aldehyde II in acetic acid at reflux. However, the separation of enamines IXa-c and their subsequent cyclization are possible.



VIII a-c IX a, b X a, c

VIII—X a R^1=C_6H_5, R^2=H, R^3=$CONH_2$; b R^1=p-$CH_3OC_6H_4$, R^2=H, R^3=$CONH_2$; (VIIIб R^3=CN); c R^1=C_6H_5, R^2=CH_3, R^3=CN

Technical University, Dresden, German Democratic Republic 8027. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1471-1475, November, 1983. Original article submitted October 26, 1982; revision submitted May 11, 1983.

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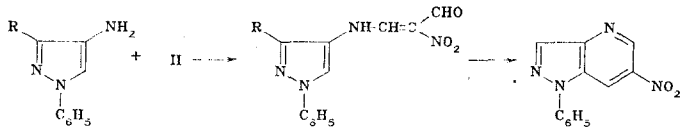
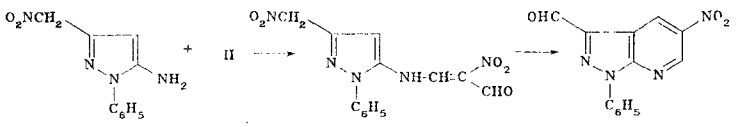
4-Aminopyrazoles XI react with II by the same pathway in two steps to form 6-nitropyrazolo[4,3-b]pyridines (XIII).



XI a, b XII a, b XIII a, b

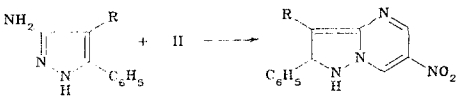
XI—XIII a R=$CONH_2$; b R=C_6H_5CO

By analogy, 5-aminopyrazole (XIV) may react with aldehyde II to give enamine XV. The condensation of this enamine in perfluoroacetic acid is accompanied by the Nef reaction and the final cyclization product is 1-phenyl-5-nitropyrazolo[3,4-b]pyridine-3-carbaldehyde (XVI).



XIV XV XVI

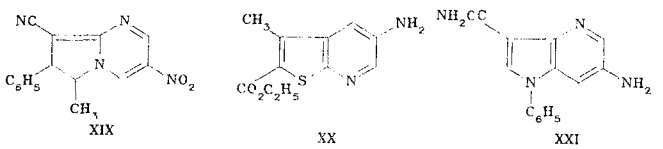
5-Aminopyrazole which does not have a substituent at N-1 condenses with the participation of an endocyclic nitrogen atom to give 3-nitropyrazolo[1,5-a]pyrimidine (XVIII) [7]. This reaction is also found when there is no substituent at C-4 (compound XVIIb).



XVII a, b XVIII a, b

XVII, XVIII a R=CN; b R=H

Another example of this type of reaction is the formation of 3-nitropyrrolo[1,2-a]pyrimidine (XIX) from 2-amino-3-cyano-5-methyl-4-phenylpyrrole.



XIX XX XXI

Amines XX and XXI may be obtained from IVb and Xa by reduction of the nitro groups in the cyclization products.

EXPERIMENTAL

The melting points were determined on a Boëtius heating stand. The IR and UV spectra were taken on Specord-75 and Specord UV-VIS spectrometers, respectively. The NMR spectra were taken on a Bruker spectrometer at 90 MHz.

The synthesis of most of the starting reagents was described in our previous work [6]. Compound VIa was obtained from β-chlorosuccinonitrile and ethyl thioglycolate, mp 103°C [8]. Compound VIb was prepared from α-cyano-β-chlorosuccinonitrile and thioglycolic acid, mp 289-292°C [9]. Aminopyrroles VIIIa (mp 169-172°C), VIIIb (mp 174-176°C), and VIIIc (mp 137-140°C) were obtained by saponification and subsequent decarboxylation of known esters [6, 10]. The synthesis of aminopyrazole XIV (mp 110-112°C) was described in our previous work [11]. The synthesis of aminopyrazole XVIIa was described in previous work [10, 12]. Compound XVIIb was obtained from β-chlorosuccinonitrile and hydrazine (mp 126-128°C) [13].

3-(Heterylamino)-2-nitropropenals (III, VII, IX, XII, and XV, Table 1). A sample of 0.01 mole heterylamine or its salt (I, XIV) was dissolved in 100 ml 10% hydrochloric acid [an additional 200 ml ethanol was added in the case of 3-aminothiophenes VI; aminopyrroles VIII were dissolved in 100 ml acetic acid and aminopyrazoles XI were dissolved in a mixture of 30 ml acetic acid and 200 ml 10% hydrochloric acid]. A solution of 0.01 mole sodium salt of malonaldehyde in 15 ml water was added to this solution and maintained for 30 min. The precipitate formed was filtered off, washed with water, and recrystallized.

TABLE 1. Characteristics of Compounds Synthesized

Compound	Mp, deg C	λ_{max}, nm (log ϵ) (in ethanol)	Found, %				Chemical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
IIIa[a]	154—157	224 (3,92), 280 (3,77), 387 (4,20)	45,7	3,6	12,7	15,2	$C_8H_8N_2O_3S$	45,5	3,8	13,2	15,1	90
IIIb	198—191	224 (4,01), 268 (3,91), 391 (4,20)	46,8	4,3	9,7	11,7	$C_{11}H_{12}N_2O_5S$	46,5	4,2	9,8	11,3	82
IIIc	179—181	228 (3,96), 278 (3,91), 398 (4,08)	52,2	4,9	10,7	12,4	$C_{11}H_{12}N_2O_3S$	52,4	4,8	11,1	12,7	45
IVa[b]	144—146	220 (4,04), 264 (4,36), 292 (3,87)	49,6	3,0	14,2	16,6	$C_8H_6N_2O_2S$	49,5	3,1	14,4	16,5	95, 83[c]
IVb[d]	127—129	225 (3,85), 272 (4,54), 306 (3,80)	49,4	3,9	10,1	11,5	$C_{11}H_{10}N_2O_4S$	49,6	3,8	10,5	12,0	86, 81[c]
VIIa	215—218	245 (3,98), 314 (4,30), 380 (4,27)	55,4	4,3	8,0	9,6	$C_{16}H_{14}N_2O_5S$	55,5	4,1	8,1	9,3	82
VIIb[e]	224—226	227, 278, 251	56,2	3,2	14,2	10,8	$C_{14}H_9N_3O_3S$	56,2	3,0	14,0	10,7	34
IXa[e]	200—203	247, 301, 383	56,1	4,5	18,9	—	$C_{14}H_{12}N_4O_4$	56,0	4,0	18,7		87
IXb	203—205	240 (4,10), 302 (4,16), 388 (4,17)	54,0	4,9	16,2		$C_{15}H_{14}N_4O_5$	54,5	4,3	16,9		71
Xa	274—276	248 (4,32), 265 (4,24), 320 (3,92), 339 (3,87)	59,1	3,5	19,7		$C_{14}H_{10}N_4O_3$	59,6	3,6	19,8		80, 89[c]
Xb[e]	245—247	248 (4,31), 270 (4,20), 319 (3,83), 339 (3,76)	57,0	4,4	17,4		$C_{15}H_{12}N_4O_4$	57,7	3,9	17,9		90
Xc	182—185	244 (4,25), 266 (3,99), 334 (4,09)	58,2	3,5	17,6	10,0	$C_{15}H_{10}N_4O_2S$	58,1	3,3	18,1	10,3	87[c]
XIIa	255—260	308 (4,08), 381 (4,29)[g]	51,9	3,8	23,2		$C_{13}H_{11}N_5O_4$	51,9	3,7	23,2		93
XIIb	255—258	260 (4,28), 288 (4,29), 381 (4,37)	62,7	3,8	15,2		$C_{19}H_{14}N_4O_4$	63,0	3,9	15,5		92
XIIIa	230—235	307 (4,01), 393 (4,08)[g]	55,5	3,5	24,5		$C_{13}H_9N_5O_3$	55,1	3,2	24,7		75
XV[h]	130—135	224 (4,02), 262 (3,88)	49,3	3,5	22,1		$C_{13}H_{11}N_5O_5$	49,2	3,5	22,1		83
XVI	247—251	278 (4,17), 317 (3,88)[g]	54,3	4,0	19,1		$C_{13}H_8O_3 \cdot H_2O$	54,6	3,5	19,6		63

[a]PMR spectrum: 2.74 (3H, d, J = 0.9 Hz, CH_3), 6.60 (1H, m, 3-H), 6.80 (1H, d, 4-H), 8.05 (0.2H, d, J = 14.4 Hz, =CH), 8.50 (0.4H, d, J = 3.5 Hz, =CH), 8.70 (0.4H, d, J = 3.5 Hz, =CH), 10.15 (0.2H) and 10.20 (0.8 H, d, J = 3.5 Hz, CHO), 11.40 (0.2 H, d, J = 14.4 Hz, NH), 12.40 ppm (0.8 H, d, J = 13.5 Hz, NH). [b]PMR spectrum: 2.67 (d, J = 1.5 Hz, CH_3), 7.05 ppm (d, J = 1.5 Hz, 3-H). [c]By method B. [d]PMR spectrum: 1.34 (t, CH_3), 4.40 (q, CH_2), 2.73 (s, 2-CH_3), 8.55 (d, J = 2.2 Hz, 4-H), 9.36 ppm (d = 2.2 Hz, 6-H). [e]PMR spectrum: 6.71 (m, C_6H_5), 7.19 (d, J = 0.9 Hz, 2-H), 7.40 (d, J = 0.9 Hz, 5-H), 7.57 (d) and 8.16 (1H, q, =CH), 9.12 (d) and 9.25 (1H, s, CHO), 12.12 and 12.25 ppm (1H, d, NH). [f]PMR spectrum: 3.85 (s, CH_3), 7.17 and 7.65 (d, C_6H_4), 7.59 (s, NH_2), 8.52 (d, J = 3 Hz, 7-H), 8.73 (s, 2-H), 9.38 ppm (d, J = 3 Hz, 5-H). [g]In DMF. [h]PMR spectrum: 7.74 (5H, m, C_6H_5), 8.50 (0.3H, d, J = 16 Hz, =CH), 9.0 (0.35H, d, J = 4 Hz, =CH), 9.15 (0.35H, d, J = 4 Hz, =CH), 9.35 (1H, s, 5-H), 9.95 (0.3H, s, CHO), 10.02 (0.7 H, d, J = 4 Hz, CHO), 12.6 (0.3 H, d, J = 16 Hz, NH), 12.8 ppm (0.7H, d, J = 16 Hz, NH).

5,6-Condensed 3-nitropyridines (IV, X, XII, XVI, Table 1). A. A sample of 0.01 mole amino aldehyde (III, VII, IX, XII, or XV) was slowly heated to 140°C with stirring with a 10-fold excess of perfluoroacetic acid and the reaction mixture was maintained for 15-20 min

at this temperature. After cooling, 100 g ice was added and the reaction mixture was treated with aqueous ammonia until it became basic. The precipitate formed was filtered off and washed with water.

B. A sample of 0.01 mole hetarylamine (I, VI, VIII, XI, or XIV) was heated with 0.01 mole sodium salt of nitroaldehyde II at reflux in 100 ml acetic acid for 1-2 h. After cooling, the reaction mass was poured into 250 ml water. The precipitate was filtered off and washed with water.

2-Nitro-1,3-bis(5-phenyl-2-thienylamino)propane (V). A solution of 0.01 mole sodium salt of nitromalonaldehyde in 15 ml water was added to a solution of 0.01 mole hydrochloride salt of 2-amino-5-phenylthiophene in a mixture of 10 ml conc. hydrochloric acid and 50 ml DMF. After 20 min, the reaction mass was diluted with 100 ml water. The precipitate was filtered off and washed with water to give V in 65% yield, mp 229-233°C (from pyridine). Found: C, 64.1; H, 4.0; N, 14.5%. Calculated for $C_{23}H_{17}N_3O_2S_2$: C, 64.0; H, 4.0; N, 14.9%.

3-Nitro-7-phenyl-8-cyanopyrazolo 1,5-a pyrimidine (XVIIIa). A sample of 0.015 mole 3-amino-4-cyano-5-phenylpyrazole (XVIIa) was dissolved in 100 ml 10% hydrochloric acid at 40-50°C. A sample of 0.02 mole sodium salt of malonaldehyde in 50 ml water was added to this solution and maintained for 3 h. The precipitate formed was filtered off and washed with water to yield 65% XVIIIa, mp 229-231°C (from acetic acid). IR spectrum (KBr): 2200 (CN), 1550, 1330 cm^{-1} (NO_2). Found: C, 58.3; H, 2.5; N, 26.4%. Calculated from $C_{13}H_7H_5O_2$: C, 58.9; H, 2.7; N, 26.4%.

3-Nitro-7-phenylpyrazolo[1,5-a]pyrimidine (XVIIIb) was obtained analogously to XVIIIa from 0.01 mole 3-amino-5-phenylpyrazole (XVIIb) and 0.015 mole sodium salt of malonaldehyde in 63% yield, mp 299-300°C (from DMF). Found: C, 59.4; H, 314; N, 23.4%. Calculated for $C_{12}H_8N_4O_2$: C, 60.0; H, 3.4; N, 23.3%.

6-Methyl-3-nitro-7-phenyl-8-cyanopyrrolo [1, 2-a]pyrimidine (XIX) was obtained analogously to XVIIIa from 0.01 mole 2-amino-3-cyano-5-methyl-6-phenylpyrrole [6, 14] and 0.012 mole malonaldehyde sodium salt in 89% yield, mp 254-257°C (from dioxane). IR spectrum (KBr): 2210 (CN), 1530, 1340 cm^{-1} (NO_2). PMR spectrum (in DMSO-d_6): 2.63 (s, CH_3), 7.57 (m, C_6H_5), 9.1 (d, J = 3 Hz, 2-H), 9.8 ppm (d, J = 3 Hz, 4-H). Found: C, 64.7; H, 3.8; N, 20.1%. Calculated for $C_{15}H_{10}N_4O_2$: C, 64.7; H, 3.6; N, 20.1%.

Ethyl ester of 5-amino-3-methylthieno[2,3-b]pyridine-2-carboxylic acid (XX). A sample of 10 g zinc dust and 25 ml acetic acid was added to 0.005 mole nitro compound IVb and heated for 30 min at reflux. The hot solution was filtered. The precipitate was washed with two 20-ml portions of hot acetic acid on the filter. A sample of 30 ml water was added to the filtrate. The filtrate was neutralized with aqueous ammonia. The precipitate formed was filtered off to give 37% XX, mp 174-179°C (from ethanol). IR spectrum (KBr): 3270 (NH), 1640 cm^{-1} (CO). Found: C, 55.4; H, 5.6; N, 11.2; S, 13.2%. Calculated for $C_{11}H_{12}N_2O_2S$: C, 55.9; H, 5.1; N, 11.9; S, 13.6%.

6-Amino-1-phenylpyrrolo[3,2-b]pyridine-3-carboxamide (XXI) was prepared analogously to acid XX by the reduction of 0.005 mole nitro compound Xa in 35% yield, mp 180-185°C (from 50% aqueous ethanol). Found: C, 61.8; H, 4.8; N, 20.9%. Calculated for $C_{14}H_{12}N_4O \cdot H_2O$: C, 62.6; H, 5.2; N, 20.7%.

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