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NITROPYRIDINES. 2*. HANTZSCH SYNTHESIS OF NITRO- AND DINITROPYRIDINES

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The interaction of α,β-unsaturated nitro ketones and various enamines leads to the synthesis of 5-nitro-1,4-dihydropyridines containing acetyl, amide, benzoyl, ester, and cyano groups in position 3, and also unsymmetrical 3,5-dinitro-1,4-dihydropyridines. Aromatization of the nitrodihydropyridines was carried out with sodium nitrite in acetic acid.

Keywords: 3,5-dinitrodihydropyridines, 5-nitro-1,4-dihydropyridines, nitro ketones, nitropyridines, nitrochalcones.

The synthesis of nitropyridines by the Hantzsch reaction is effected by the cyclocondensation of α,β-unsaturated nitro ketones (condensation products of aromatic aldehydes with nitroacetone and nitroacetophenone) with various enamines.

The availability of nitroacetone and nitroacetopheone enables them to be considered as valuable raw materials in the synthesis of nitropyridines [2], possessing potential biological activity.

Nitroacetone [3, 4] and nitroacetophenone [5] used in the work were obtained by the condensation of nitromethane with acetaldehyde and benzaldehyde (the Anri reaction). The nitroalcohols obtained were oxidized with sodium dichromate.

The condensation of nitroacetophenone with aromatic aldehydes proceeds readily and the corresponding nitrochalcones **1** are formed in preparative yield [6].

Nitroacetone may interact with aromatic aldehydes at both the methyl and the methylene group. Under alkaline catalysis conditions the aldol condensation product is formed only at the methyl group. To obtain condensation products at the methylene group a less reactive Schiff's base of the aromatic aldehyde is used. In this way condensation products at the methylene group are formed in good yield only in the reaction of nitroacetone with Schiff's bases of an aromatic aldehyde containing an acceptor group in the nucleus [7], the yield of 2-nitro-1-phenyl-1-buten-3-one **1a** was only 26%. Because of the low yield of chalcone **1a,** the cyclocondensation of benzylideneacetoacetic ester with the enamine of nitroacetone **2f** was used for the synthesis of nitrodihydropyridine **3d** (variant B) (Scheme 1).

The condensation of benzylidenenitroacetone **1a** with aminocrotonic ester (variant A) in acetic acid at room temperature and an equimolar ratio of initial reactants leads to nitrodihydropyridine **3d** in 56% yield. On condensation by variant B under analogous conditions pyridine **3d** is formed with a yield of 40%. We also note that the enamine of nitroacetone **2f** [8], obtained by the transamination of 2-dimethylamino-1-nitro-1-propene

* For Part 1 see [1].

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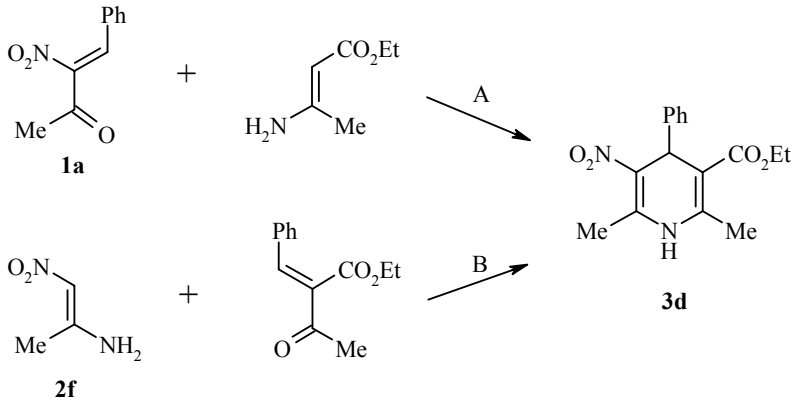
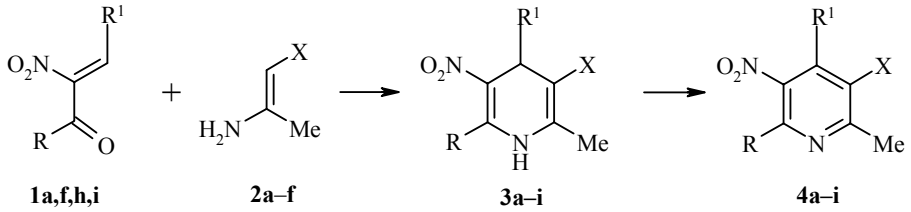
Scheme 1



[9], the condensation product of dimethylacetamide diethylacetal with nitromethane, is a more difficultly available compound compared with benzylidenenitroacetone **1a** even allowing for the low yield of the latter. We therefore used variant A for cyclocondensation in the synthesis of 2,6-dimethyl-1,4-dihydropyridines **3a-e**.



1a, 3, 4 a–e R^1 = Ph, R = Me; **1f, 3, 4 f, g** R^1 = R = Ph; **1, 3, 4 h** R^1 = 4-$MeOC_6H_4$, R = Ph; **i** R^1 = 2-Fu, R = Ph; **2–4 a** X = COMe; **b** X = COPh; **c** X = CONHPh; **d** X = COOEt; **e** X = CN; **f** X = NO_2, **3, 4 g** X = CONHPh; **h, i** X = COOEt

When using the two-component Hantzsch synthesis 1,4-dihydropyridines **3b-i** begin to precipitate from the reaction mixture after a few hours. Their yield at a reaction time of 15-20 h is 50-70%. Chromatographic purification was required only for the isolation of 2-acetyl-5-nitro-1,4-dihydropyridine (**3a**), the remaining 1,4-dihydropyridines were purified by recrystallization. Aromatization was carried out with $NaNO_2$ in acetic acid at 60-70°C. The spectral characteristics and yields of the compounds synthesized are given in Table 1.

The mass spectra of nitropyridines **4a-c,e,g** (Table 2) were characterized by high, and in some cases maximal intensity for the $M^{+\cdot}$ ion peaks. Fragmentation of the molecular ions leads to the appearance of ions both for nitropyridines and of ions formed by decomposition of the functional substituent. Peaks for $[M\text{-}OH]^+$, $[M\text{-}OH\text{-}NO]^{+\cdot}$, and $[M\text{-}NO_2\text{-}CH_3]^{+\cdot}$ ions were common in the mass spectra of these compounds. Characteristic of nitropyridines **4c,g** was fission of the functional substituent from the molecular ion with the formation of the $[M\text{-}C_6H_5NH]^+$ ion of high intensity, decomposition of which occurs with elimination of ions common for this series of compounds.

On the basis of the data obtained by us it is possible to draw a conclusion on the preparative availability of nitropyridines synthesized according to Hantzsch. These are key compounds in the synthesis of indoles [10, 11] and *m*-terphenyls [12].

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, $CDCl_3$, δ, ppm (*J*, Hz)*	Yield, %
		C	H				
1	2	3	4	5	6	7	8
3a	$C_{15}H_{16}N_2O_3$	66.52 / 66.16	5.89 / 5.92	158-160	3420, 3310 (NH); 1670 (C=O); 1470, 1310 (NO_2)	2.21 (3H, s, 2-CH_3); 2.31 (3H, s, 6-CH_3); 2.45 (3H, s, –$COCH_3$); 5.43 (1H, s, 4-CH); 7.18-7.37 (6H, m, 4-C_6H_5, NH)	77
3b	$C_{20}H_{18}N_2O_3$	71.59 / 71.84	5.28 / 5.43	197-198	3420, 3320 (NH), 1660 (C=O), 1470, 1310 (NO_2)	1.81 (3H, s, 2-CH_3); 2.59 (3H, s, 6-CH_3); 5.50 (1H, s, 4-CH); 6.12 (1H, s, NH); 7.11-7.56 (10H, m, 4-C_6H_5, –COPh)	64
3c	$C_{20}H_{19}N_3O_3$	68.84 / 68.75	5.39 / 5.48	255-257	(KBr disk) 3260, 3180 (NH); 1630 (C=O); 1510, 1300 (NO_2)	2.03 (3H, s, 2-CH_3); 2.55 (3H, s, 6-CH_3); 5.38 (1H, s, 4-CH); 7.02-7.57 (10H, m, 4-C_6H_5, –CONHPh); 9.40 (1H, s, 1-NH); 9.83 (1H, s, –CONHPh)	43
3d	$C_{16}H_{18}N_2O_4$	63.60 / 63.57	6.18 / 6.00	198-200	3430, 3320 (NH); 1700 (C=O), 1480, 1310 (NO_2)	1.22 (3H, t, –$COOCH_2CH_3$, *J* = 7.1); 2.34 (3H, s, 2-CH_3); 2.50 (3H, s, 6-CH_3); 4.10 (2H, q, –$COOCH_2CH_3$, *J* = 7.1); 5.39 (1H, s, 4-CH); 6.36 (1H, s, NH); 7.16-7.32 (5H, m, 4-C_6H_5)	56
3e	$C_{14}H_{13}N_3O_2$	66.21 / 65.87	5.30 / 5.13	173-174	3430, 3320 (NH); 2210 (CN); 1480, 1320 (NO_2)	2.05 (3H, s, 6-CH_3); 2.49 (3H, s, 2-CH_3); 4.99 (1H, s, 4-CH); 6.79 (1H, s, NH); 7.25-7.31 (5H, m, 4-C_6H_5)	62
3f	$C_{18}H_{15}N_3O_4$	63.95 / 64.09	4.39 / 4.48	165-166	3420 (NH); 1490, 1330 (NO_2)	2.48 (3H, s, 2-CH_3); 5.74 (1H, s, 4-CH); 7.24-7.51 (10H, m, 4,6-C_6H_5); 8.14 (1H, br. s, NH)	55
3g	$C_{25}H_{21}N_3O_3$	72.72 / 72.98	5.09 / 5.14	143-145	3420, 3380, 3310 (NH); 1670 (C=O); 1480, 1310 (NO_2)	2.06 (3H, s, 6-CH_3); 5.43 (1H, s, 4-CH); 7.01-7.60 (15H, m, 2,4-C_6H_5, –$CONHC_6H_5$); 9.63 (1H, s, 1-NH); 9.95 (1H, s, –CONHPh)	78
3h	$C_{22}H_{22}N_2O_5$	67.38 / 66.99	5.76 / 5.62	132-134	3440, 3330 (NH); 1700 (C=O); 1470, 1320 (NO_2); 1260 (=C–O–)	1.25 (3H, t, *J* = 7.0, –$CO_2CH_2CH_3$); 2.35 (3H, s, 2-CH_3); 3.78 (3H, s, –OCH_3); 4.12 (2H, q, *J* = 7.0, –$CO_2CH_2CH_3$); 5.40 (1H, s, 4-CH); 6.06 (1H, s, NH); 6.82 (2H, d, *J* = 8.6, H-2',6'); 7.33 (2H, d, *J* = 8.6, H-3',5'); 7.30-7.43 (5H, m, 6-C_6H_5)	46

TABLE 1 (continued)

1	2	3	4	5	6	7	8
3i	$C_{19}H_{18}N_2O_5$	64.22 64.40	5.08 5.12	157-159	3420, 3310 (NH); 1690 (C=O); 1480, 1320 (NO_2)	1.29 (3H, t, J = 7.1, –$CO_2CH_2\underline{CH_3}$); 2.32 (3H, s, 2-CH_3); 4.17 (2H, q, J = 7.1, –$CO_2\underline{CH_2}CH_3$,); 5.61 (1H, s, 4-CH); 6.17 (1H, d, J = 3.1, H-3'); 6.31 (1H, dd, $J_{4'5'}$ = 2.0, $J_{4'3'}$ = 3.1, H-4'); 6.48 (1H, s, NH); 7.29-7.41 (6H, m, 6-C_6H_5, H-5')	62
4a	$C_{15}H_{14}N_2O_3$	67.01 66.66	5.17 5.22	107-108	1700 (C=O); 1520, 1360 (NO_2)	1.91 (3H, s, 2-CH_3); 2.55 (3H, s, 6-CH_3); 2.60 (3H, s, –$COCH_3$); 7.23-7.46 (5H, m, 4-C_6H_5)	
4b	$C_{20}H_{16}N_2O_3$	72.43 72.28	4.90 4.85	161-163	1670 (C=O); 1530, 1370 (NO_2)	2.49 (3H, s, 2-CH_3); 2.66 (3H, s, 6-CH_3); 7.10-7.59 (10H, m, 4-C_6H_5, –COC_6H_5)	52
4c	$C_{20}H_{17}N_3O_3$	68.79 69.15	4.98 4.93	249-250 (with dec.)	3420 (NH); 1680 (C=O); 1530, 1360 (NO_2)	2.58 (3H, s, 2-CH_3); 2.60 (3H, s, 6-CH_3); 7.03-7.39 (10H, m, 4-C_6H_5, –$CONHC_6H_5$); 10.35 (1H, s, –$CO\underline{NH}$Ph)	84
4e	$C_{14}H_{11}N_3O_2$	66.23 66.40	4.33 4.38	121-122	2230 (CN); 1530, 1360 (NO_2)	2.64 (3H, s, 6-CH_3); 2.86 (1H, s, 2-CH_3); 7.34-7.53 (5H, m, 4-C_6H_5)	78
4f	$C_{18}H_{13}N_3O_4$	64.30 64.48	4.00 3.91	130-131	1540, 1360 (NO_2)	2.68 (3H, s, 2-CH_3); 7.30-7.67 (10H, m, 4,6-C_6H_5)	67
4g	$C_{25}H_{19}N_3O_3$	73.65 73.34	4.72 4.68	200-201	3420 (NH); 1680 (C=O); 1540,1360 (NO_2)	2.69 (3H, s, 6-CH_3); 7.03-7.57 (15H, m, 2,6-C_6H_5, –$CONHC_6H_5$); 10.58 (1H, s, –$CO\underline{NH}$Ph)	80
4h	$C_{22}H_{20}N_2O_5$	67.80 67.34	5.29 5.14	103-104	1720 (C=O); 1530, 1360 (NO_2); 1250 (=C–O–)	0.97 (3H, t, J = 7.1, –$CO_2CH_2\underline{CH_3}$,); 2.70 (3H, s, 2-CH_3); 3.79 (3H, s, –OCH_3); 4.06 (2H, q, J = 7.1, –$CO_2\underline{CH_2}CH_3$,); 6.89 (2H, d, J = 8.8, H-2',6',); 7.24 (2H, d, J = 8.8, H-3',5',); 7.39-7.65 (5H, m, 6-C_6H_5)	68
4i	$C_{19}H_{16}N_2O_5$	64.61 64.77	4.49 4.58	116-117	1730 (C=O); 1540, 1360 (NO_2)	1.27 (3H, t, J = 7.1, –$CO_2CH_2\underline{CH_3}$,); 2.71 (3H, s, 2-CH_3); 4.35 (2H, q, J = 7.1, –$CO_2\underline{CH_2}CH_3$); 6.53 (1H, dd, $J_{4'3'}$ = 3.7, $J_{4'5'}$ = 2.0, H-4',); 6.78 (1H, dd, $J_{3'5''}$ = 0.7, $J_{3'4'}$ = 3.7, H-3',); 7.57 (1H, dd, $J_{5'4'}$ = 2.0, $J_{5'3'}$ = 0.7, H-5',); 7.42-7.63 (5H, m, 6-C_6H_5)	40

* ^{1}H NMR spectra of compounds **3c,g** and **4c,g** were recorded in DMSO-d_6, and of **3f** in CD_3CN.

TABLE 2. Mass Spectra of Nitropyridines **4a-c,e,g** (*I*, % of the intensity of the maximum peak)

Compound	*m/z* (*I*, %)*
4a	270 $[M]^{+\cdot}$, (100), 255 $[M–CH_3]^+$ (41), 253 $[M–OH]^+$ (22), 225 $[M–CH_3–NO]^{+\cdot}$ (26), 223 $[M–NO–OH]^{+\cdot}$ (21), 209 $[M–NO_2–CH_3]^{+\cdot}$ (17), 208 $[M–CH_3–OH–NO]^+$ (82), 181 (17), 180 (20), 153 (11), 139 (21), 43 $[CH_3CO]^+$ (73)
4b	332 $[M]^{+\cdot}$ (88), 331 $[M–H]^+$ (43), 315 $[M–OH]^+$ (11), 284 $[M–NO_2–H_2]^+$ (16), 208 $[M–NO–OH–C_6H_5]^+$ (13), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (56)
4c	347 $[M]^{+\cdot}$ (62), 256 (13), 255 $[M–C_6H_5NH]^+$ (82), 225 $[M–C_6H_5NH–NO]^{+\cdot}$ (32), 209 (23), 208 $[M–C_6H_5NH–NO–OH]^+$ (100), 181 (22), 180 $[M–C_6H_5NH–NO–OH–CO]^+$ (26), 153 (17), 140 (11), 139 (20), 77 $[C_6H_5]^+$ (12)
4e	253 $[M]^{+\cdot}$ (100), 236 $[M–OH]^+$ (24), 225 $[M–H_2CN]^+$ (66), 224 $[M–CHO]^+$ (34), 223 $[M–NO]^+$ (16), 208 $[M–OH–NO]^{+\cdot}$ (11), 197 (13), 196 $[M–CO–CHO]^+$ (38), 192 $[M–NO_2–CH_3]^{+\cdot}$ (22), 183 (19), 180 (14), 165 (11), 164 (16), 156 (13), 155 (18), 153 (11), 152 (12), 140 (32), 139 (27), 127 $[C_6H_5C{\equiv}C–CN]^+$ (17), 115 (15), 77 $[C_6H_5]^+$ (16), 76 (11), 63 (11), 51 (12), 43 (24), 42 (11), 39 (12)
4g	409 $[M]^{+\cdot}$ (39), 318 (21), 317 $[M–C_6H_5NH]^+$ (100), 272 $[M–C_6H_5NH–NO–CH_3]^+$ (16), 271 $[M–C_6H_5NH–NO_2]^{+\cdot}$ (63), 270 $[M–C_6H_5NH–NO–OH]^+$ (16)

* Peaks with $I > 10\%$ are given.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) spectrometer in solution in $CDCl_3$, DMSO-d_6, and CD_3CN, internal standard was TMS. The IR spectra were recorded on a Specord IR 75 instrument in chloroform. Mass spectra were obtained on a Varian MAT 212C instrument using direct insertion of samples into the ion source, ionizing voltage was 70 eV. A check on the progress of reactions and the purity of the compounds obtained was carried out by TLC on Silufol UV 254 plates, eluent was benzene (for compound **4f**), chloroform (for compounds **4d,e,h,i**), chloroform–ethyl acetate, 9 : 1 (for compounds **3e-g**, **4a,b,g**), and chloroform–ethyl acetate, 1:1 (for compounds **3a-d**, **3h-i**, **4c**). The melting points of all compounds except **3c** and **4c** were determined on a Boetius hot stage, for **3c** and **4c** in capillaries to determine the melting point of the crystalline substance.

Nitroisopropanol was obtained as described in [3], nitroacetophenone by the procedure of [5], the chalcones of nitroacetophenone by the method of [6, 1], 2-amino-1-nitro-1-propene **2f** by the method of [8], and nitropyridine **4d** was described in [13].

Nitroacetone. A solution of conc. H_2SO_4 (19.6 ml) in water (9.8 ml) was added dropwise to a mixture of nitroisopropanol (20.0 g, 0.19 mol) and $Na_2Cr_2O_7$ (30.0 g, 0.11 mol) in water (20 ml) cooled to 0°C, at such a rate that the temperature of the reaction mixture did not exceed 10°C. After adding all the acid, the mixture was stirred a further 2 h, then water (60 ml) was added, and the mixture extracted with $CHCl_3$ (3 × 20 ml). The extract was washed with saturated NaCl solution, and dried over $MgSO_4$. After removing the solvent in vacuum, nitroacetone (15.7 g, 80%) was obtained, which crystallized on cooling, was then diluted with absolute ether, and filtered off. The snow-white crystals had mp 47°C [3,4]. Crystalline nitroacetone was stored in the refrigerator for 2 weeks.

2-Nitro-1-phenyl-1-buten-3-one (1a). Nitroacetone (5.15 g, 0.05 mol) was added to a solution of benzylidenebutylamine (8.1 g, 0.05 mol) in acetic anhydride (25 ml) with cooling. The precipitated white crystals went back into solution again after a short time. The reaction mixture was left for 1 day at ~20°C, and then poured into water. The precipitated oil crystallized on cooling for several hours. The crystals were washed with a small quantity of CCl_4, and filtered off. Compound **1a** (2.48 g, 26%) of mp 106°C was obtained [7].

Nitrodihydropyridines 3a-i (General Procedure). A solution of nitrochalcone **1** (10 mmol) and the appropriate enamine **2** (10 mmol) in glacial CH_3COOH (15 ml) was left at room temperature for 15-20 h. The acetic acid was distilled in vacuum, and the residue recrystallized from ethanol. Nitrodihydropyridine **3a** was purified by flash chromatography on a dry column [14] (Silicagel L 5/40 μ sorbent).

Oxidation of Nitrodihydropyridines 3a-i into Nitropyridines 4a-i (General Procedure). Sodium nitrite (3 mmol) was added in portions with stirring to a suspension of the appropriate dihydropyridine **3a-i** in glacial CH_3COOH (6 ml) at 60-70°C. After adding all the oxidizing agent the reaction mixture was stirred for 1 h further at the same temperature. The reaction mixture was cooled to room temperature, and diluted to 4 volumes with water and ice. The precipitated crystals of pyridines **4a-i** were filtered off, washed with water, dried, and recrystallized from ethanol.

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