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NITROPYRIDINES. 1. HANTZSCH SYNTHESIS OF NITROPYRIDINES AND THEIR QUATERNARY SALTS

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Previously unknown 1,4-dihydropyridines containing acetyl, amide, benzoyl, ester, and cyano groups together with a nitro group were synthesized with preparative yields by a two-component Hantzsch synthesis based on 2-nitro-1,3-diphenylpropenone and various enamines. The nitrodihydropyridines were aromatized with sodium nitrite in acetic acid. The quaternary salts of low-basicity pyridines were produced with dimethyl sulfate and methyl fluorosulfonate.

Keywords: 5-nitro-1,4-dihydropyridines, nitropyridines, quaternary salts of nitropyridines.

1,4-Dihydropyridines with a nitro group in the pyridine ring have potential biological activity. Thus, compounds that are effective antagonists for histamine H_2- and H_3-receptors [1, 2] and Ca antagonists [3-5] and also possess cardiotonic and vasodilator activity [6, 7] and antitumor [8] and herbicidal [9] activity have been found in the series of nitropyridines. Medicinal preparations based on substituted nitrodihydropyridines are used for the treatment of blood circulation system and thrombosis [10], hypertension, atherosclerosis, and stenocardia [11-13]. All this explains the interest in the production of new representatives of 1,4-dihydropyridines with a nitro group in the pyridine ring.

Our interest in the synthesis of new 2-methyl-5-nitro-4,6-diphenylpyridines **4** arose from systematic investigations into the recyclization of quaternary pyridinium salts [14, 15], which included study of the effect of their structure on the direction of recyclization.

A two-component Hantzsch synthesis, based on separation of the Knoevenagel and Michael stages in which separately prepared nitrochalcone **1** (acceptor) and enamines **2a-d** (donors) are used, proved the most suitable for the synthesis of unsymmetrical 1,4-dihydropyridines in that it eliminates the possibility of the formation of cyclocondensation side products.

We found that the dihydropyridines **3a-d** are formed with preparative yields if the reaction is conducted in acetic acid at room temperature with the starting compounds **1** and **2** in a molar ratio of 1:1. Most of the dihydropyridines are precipitated from the acetic acid on completion of the reaction.

In the ^{1}H NMR spectra of these compounds the signal of the 4-H proton is in the region of 5.05-5.52 ppm, while that of the proton attached to the pyridine nitrogen atom is in the region of 6.04-6.44 ppm (Table 1).

The dihydropyridines **3a**,**c**,**d** are easily oxidized by sodium nitrite in acetic acid at 60-70°C. Compound **3b** is oxidized by sodium nitrite at room temperature. 3-Carbamoyl-2-methyl-5-nitro-4,6-diphenylpyridine (**4d**) was obtained by partial hydrolysis of the nitrocyanopyridine **4c** in sulfuric acid. In the ^{1}H NMR spectrum of the

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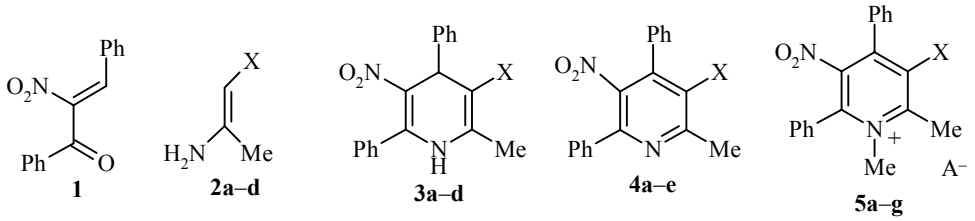

1 **2a–d** **3a–d** **4a–e** **5a–g**

2-5 a X = COMe, **b** X = $COOCH_2Me$, **c** X = CN, **d** X = COPh; **4, 5 e** X = $CONH_2$;
5 f X = COMe, **g** X = $COOCH_2Me$, **a** A = ClO_4, **b,c,e** A = $MeSO_4$, **d,f,g** A = FSO_4

nitroamide **4e** in the regions of 7.73 and 8.02 ppm it is easy to identify the signals of the *cis* and *trans* protons of the amide group in the respective configurational isomers, which appear in the spectrum as broad singlets of equal intensity.

Analysis of the mass spectra of compounds **4a-e** showed the general character of the fragmentation of the molecular ion, which does not depend on the functional group X. The main directions of the primary dissociation of the molecular ion are elimination of the NO_2, OH, CO, and CHO groups. All these processes are connected with the presence of the phenyl substituent at the α-position to the pyridine nitrogen atom (Scheme 1, Table 2). Another direction in the dissociation of the molecular ion is the ejection of NO, which is preceded by partial isomerization of the molecular ion to the pyridyl nitrite ion [16].

The dehydrogenation process, accompanied by cyclization to a trinuclear structure, makes an insignificant contribution to the general pattern of the dissociation of the molecular ion.

For the alkylation of the pyridines **4a-e** with two accepting substituents on account of their extremely low basicity we used dimethyl sulfate and methyl fluorosulfonate ("magic methyl"). When the pyridines **4a-c**,**e** are heated with an excess of dimethyl sulfate at 100°C for 20-24 h the corresponding pyridinium methyl sulfates **5b**,**c**,**e** are formed with preparative yields.

Scheme 1

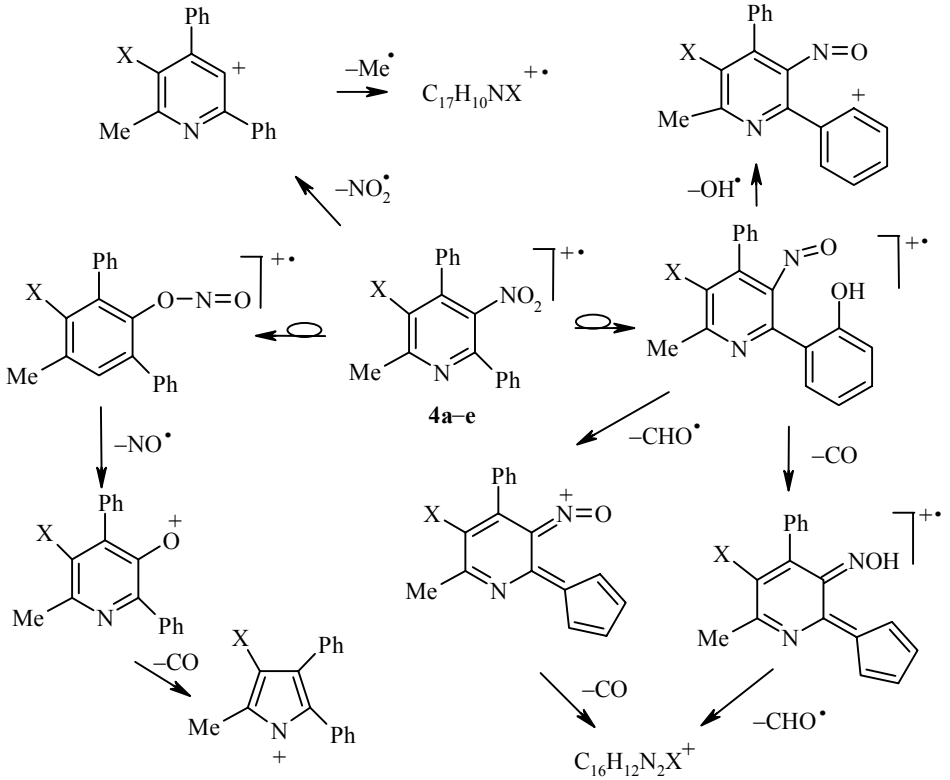

TABLE 1. The Characteristics of the 1,4-Dihydropyridines **3a-d**, the Pyridines **4a-e**, and the Pyridinium Salts **5a-g**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectrum, ν, cm^{-1}	^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz)*	Yield, %
		C	H				
1	2	3	4	5	6	7	8
3a	$C_{20}H_{18}N_2O_3$	71.60 / 71.84	5.28 / 5.43	88-89	3420, 3300 (NH), 1670 (C=O), 1470, 1305 (NO_2)	2.24 (3H, s, 2-CH_3); 2.39 (3H, s, –$COCH_3$); 5.52 (1H, s, 4-H); 6.04 (1H, s, –NH–); 7.24-7.46 (10H, m, 4-, 6-Ph)	84
3b	$C_{21}H_{20}N_2O_4$	69.45 / 69.22	5.71 / 5.53	147-148	3420, 3300 (NH), 1690 (C=O), 1470, 1310 (NO_2)	1.23 (3H, t, –$COOCH_2\underline{CH_3}$, *J* = 7); 2.30 (3H, s, 2-CH_3); 4.09 (2H, q, –$COO\underline{CH_2}CH_3$, *J* = 7); 5.41 (1H, s, 4-H); 6.32 (1H, s, –NH–); 7.17-7.41 (10H, m, 4-, 6-Ph)	74
3c	$C_{19}H_{15}N_3O_2$	71.45 / 71.91	4.91 / 4.76	95-97	3430, 3300 (NH), 2220 (CN), 1500, 1320 (NO_2)	2.10 (3H, s, 2-CH_3); 5.05 (1H, s, 4-H); 6.31 (1H, s, –NH–); 7.26-7.47 (10H, m, 4-, 6-Ph)	77
3d	$C_{25}H_{20}N_2O_3$	75.68 / 75.74	5.11 / 5.09	160-161	3420, 3300 (NH), 1640 (C=O), 1480, 1300 (NO_2)	1.72 (3H, s, 2-CH_3); 5.51 (1H, s, 4-H); 6.44 (1H, s, –NH–); 7.24-7.53 (15H, m, –COPh, 4-, 6-Ph)	64
4a	$C_{20}H_{16}N_2O_3$	72.46 / 72.28	4.70 / 4.85	132-133	1700 (C=O), 1530,1360 (NO_2)	1.99 (3H, s, 2-CH_3); 2.65 (3H, s, –$COCH_3$); 7.29-7.67 (10H, m, 4-, 6-Ph)	62
4b	$C_{21}H_{18}N_2O_4$	69.73 / 69.60	5.19 / 5.01	84-85	1720 (C=O), 1535, 1360 (NO_2)	0.91 (3H, t, –$COOCH_2\underline{CH_3}$, *J* = 7.2); 2.72 (3H, s, 2-CH_3); 4.03 (2H, q, –$COO\underline{CH_2}CH_3$, *J* = 7.2); 7.24-7.66 (10H, m, 4-, 6-Ph)	80
4c	$C_{19}H_{13}N_3O_2$	72.33 / 72.37	4.15 / 4.16	149-150	2230 (CN), 1540, 1360 (NO_2)	2.93 (3H, s, 2-CH_3); 7.37-7.67 (10H, m, 4-, 6-Ph)	60
4d	$C_{25}H_{18}N_2O_3$	75.86 / 76.13	4.68 / 4.60	148-149	1680 (C=O), 1540, 1360 (NO_2)	2.57 (3H, s, 2-CH_3); 7.16-7.72 (15H, m, 4-, 6-Ph, –COPh)	89
4e	$C_{19}H_{15}N_3O_3$	68.76 / 68.46	4.61 / 4.54	283-284	3525, 3400 (NH), 1690 (C=O), 1540, 1350 (NO_2)	2.65 (3H, s, 2-CH_3); 7.36-7.54 (10H, m, 4-, 6-Ph); 7.73 (1H, br. s, –$CONH_2$, *cis*); 8.02 (1H, br. s, –$CONH_2$, *trans*)	90
5a	$C_{21}H_{19}ClN_2O_7$	56.12 / 56.45	4.18 / 4.29	234-236		2.22 (3H, s, 2-CH_3); 2.85 (3H, s, –$COCH_3$); 3.95 (3H, s, 1-CH_3); 7.37-7.70 (10H, m, 4-, 6-Ph)	73
5b	$C_{23}H_{24}N_2O_8S$	56.66 / 56.55	4.96 / 4.95	195-196		0.92 (3H, t, –$COOCH_2\underline{CH_3}$, *J* = 7.1); 2.96 (3H, s, 2-CH_3); 3.40 (3H, s, $CH_3SO_4^-$); 3.96 (3H, s, 1-CH_3); 4.18 (2H, q, –$COO\underline{CH_2}CH_3$, *J* = 7.1); 7.39-7.70 (10H, m, 4-, 6-Ph)	78
5c	$C_{21}H_{19}N_3O_6S$	57.17 / 57.14	4.36 / 4.34	202-203		3.22 (3H, s, 2-CH_3); 3.37 (3H, s, $CH_3SO_4^-$); 4.01 (3H, s, 1-CH_3); 7.55-7.78 (10H, m, 4-, 6-Ph)	75

TABLE 1 (continued)

1	2	3	4	5	6	7	8
5d	$C_{26}H_{21}FN_2O_6S$	$\frac{61.59}{61.41}$	$\frac{4.21}{4.16}$	176-178		2.78 (3H, s, 2-CH_3); 4.01 (3H, s, 1-CH_3); 7.19-7.87 (15H, m, 4-, 6-Ph, –COPh)	80
5e	$C_{21}H_{21}N_3O_7S$	$\frac{54.93}{54.89}$	$\frac{4.61}{4.60}$	232-233		2.93 (3H, s, 2-CH_3); 3.39 (3H, s, $CH_3SO_4^-$); 3.95 (3H, s, 1-CH_3); 7.38-7.72 (10H, m, 4-, 6-Ph); 8.17 (1H, br. s, –$CONH_2$, *cis*); 8.23 (1H, br. s, –$CONH_2$, *trans*)	89
5f	$C_{21}H_{19}FN_2O_6S$	$\frac{56.27}{56.50}$	$\frac{4.17}{4.29}$	206-208		2.23 (3H, s, 2-CH_3); 2.86 (3H, s, –$COCH_3$); 3.96 (3H, s, 1-CH_3); 7.35-7.72 (10H, m, 4-, 6-Ph)	75
5g	$C_{22}H_{21}FN_2O_7S$	$\frac{55.67}{55.46}$	$\frac{4.51}{4.44}$	178-179.5		0.93 (3H, t, –$COOCH_2\underline{CH_3}$, J = 7.2); 2.97 (3H, s, 2-CH_3); 3.96 (3H, s, 1-CH_3); 4.18 (2H, q, –$COO\underline{CH_2}CH_3$, J = 7.2); 7.35-7.74 (10H, m, 4-, 6-Ph)	84

* The ^{1}H NMR spectra of compounds **4e** and **5a-g** were recorded in DMSO-d_6.

TABLE 2. The Mass Spectra of the Nitropyridines **4a-c** (m/z, I_{rel}) (Intensities as % of the Intensity of the Maximum Peak)

Com-pound	$M^{+\cdot}$	$[M–H]^+$	$[M–OH]^+$	$[M–CO]^{+\cdot}$	$[M–CHO]^+$	$[M–NO]^+$	$[M–NO_2]^+$	$[M–CO–CHO]^+$	$[M–NO–CO]^+$	$[M–NO_2–CH_3]^{+\cdot}$
4a	332 (100.00)	331 (4.81)	315 (12.79)	304 (9.43)	303 (11.37)	302 (13.40)	286 (6.85)	275 (12.57)	274 (3.38)	271 (32.74)
4b	362 (100.00)	361 (2.95)	345 (4.91)	334 (12.17)	333 (13.90)	332 (2.07)	316 (2.31)	305 (27.00)	304 (18.28)	301 (0.83)
4c	315 (100.00)	314 (13.47)	298 (48.74)	287 (21.79)	286 (25.35)	285 (28.77)	269 (14.21)	258 (59.94)	257 (5.79)	254 (7.77)
4d	394 (47.49)	393 (8.04)	377 (12.86)	366 (6.39)	365 (11.45)	364 (10.29)	348 (2.75)	337 (10.58)	336 (0.79)	333 (—)
4e	333 (100.00)	332 (6.23)	316 (31.67)	305 (15.59)	304 (17.68)	303 (11.41)	287 (10.24)	276 (25.80)	275 (2.09)	272 (4.98)

Pyridinium methyl sulfate **5a** is formed as an oil, and it was therefore converted into the readily crystallizing perchlorate by substitution of the anion. 3-Benzoyl-2-methyl-5-nitro-4,6-diphenylpyridine (**4d**) is not alkylated by dimethyl sulfate, and methyl fluorosulfonate was therefore used for the production of its quaternary salt. In addition to the methyl sulfates, the readily crystallizing fluorosulfonates **5g**,**f** were also obtained from the pyridines **4a**,**b**.

It should be noted that the pyridines **4a-d** that we synthesized from the nitro aliphatic precursors by the Hantzsch reaction can probably not be obtained by other known methods.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) with TMS as internal standard. The IR spectra were obtained on a Specord IR-75 instrument (in chloroform). The mass spectra were recorded on a Varian MAT 212C instrument with direct injection of the samples into the ion source at ionization potential 70 eV. The reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates with 9:1 chloroform–ethyl acetate (compounds **3a-d**), chloroform (compounds **4a-d**), and 6:3:1 chloroform–ethyl acetate–ethanol (compound **4e**) as eluents. The melting points of compounds **3a-d**, **4a**,**c**,**d**, and **5b**,**d**,**g** were determined on a Boetius instrument, and the others were determined on an instrument for determination of the melting points of crystalline substances.

Nitroacetophenone was obtained by the method in [17].

1,3-Diphenyl-2-nitropropenone (1). A mixture of nitroacetophenone (4.00 g, 25 mmol), benzaldehyde (4.24 g, 40 mmol), β-alanine (0.188 g), and glacial acetic acid (4 ml) in benzene (40 ml) was boiled for 3 h in a flask fitted with a Dean–Stark tube. The reaction mixture was washed with water (3 × 5 ml), the benzene was removed under vacuum, and the product was recrystallized from ethanol. We obtained 3.85 g (63%) of the nitrochalcone **1**; mp 92°C [18]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.34 (1H, s, –CH), 7.98-7.35 (10H, m, arom.).

General Procedure for the Production of Nitrodihydropyridines 3a-d (Table 1). A solution of compound **1** (2.53 g, 10 mmol) and the respective enamine **2** (10 mmol) in glacial acetic acid (15 ml) was left at room temperature for 20 h. The acetic acid was distilled under vacuum, and the residue was recrystallized from ethanol. The nitrodihydropyridine **3a** was purified by flash chromatography on a dry column (Silicagel L 5/40 μ) with gradient elution (hexane, chloroform, 9:1 chloroform–ethyl acetate).

General Procedure for the Oxidation of Nitrodihydropyridines 3a-d to Nitropyridines 4a-d (Table 2). To a suspension of the respective dihydropyridine **3a-d** (2 mmol) in glacial acetic acid (6 ml) at 60-70°C (at room temperature for **3b**) with stirring we added in parts sodium nitrite (3 mmol). When all the oxidizing agent had been added, the reaction mixture was stirred at the same temperature for a further 1 h, cooled to room temperature, diluted four times with water and ice, and neutralized with ammonia. The crystals of the pyridines **4a-d** that separated were filtered off, washed with water, dried, and recrystallized from ethanol.

3-Carbamoyl-2-methyl-5-nitro-4,6-diphenylpyridine (4e). A solution of the pyridine **3c** (0.63 g, 2 mmol) and concentrated sulfuric acid (10 ml) was heated on a water bath for 1 h. The mixture was cooled to room temperature and poured into a mixture of water and ice. The precipitate was filtered off, dried, and recrystallized from ethanol.

Nitropyridinium Methyl Sulfates (5a-c,e) (General Procedure for the Alkylation of Nitropyridines with Dimethyl Sulfate). A mixture of the respective pyridine **4a-c**,**e** (5 mmol) and freshly distilled dimethyl sulfate (1.9 ml, 20 mmol) was heated at 100°C for 20-24 h. The mixture was cooled and washed with dry ether (3 × 10 ml). The ether was decanted. If the oil did not crystallize (as in the case of **5a**), the residue was dissolved in water (5 ml), and a saturated aqueous solution of 1.5 g of sodium perchlorate was added. The crystallized salt was filtered off, dried, and recrystallized from ethanol.

Nitropyridinium Fluorosulfonates (5d,f,g) (General Procedure for the Alkylation with Methyl Fluorosulfonate). A solution of the respective pyridine **4a**,**b**,**d** (5 mmol) in chlorobenzene (15 ml) was cooled to 0°C. A solution of methyl fluorosulfonate (15 mmol) in chlorobenzene (3 ml) was added drop by drop with stirring. After 10 min the cooling was removed, and the reaction mixture was left at room temperature for 48 h. The crystals that separated were filtered off, washed with dry ether, and recrystallized from ethanol.

The characteristics of the obtained salts **5a-g** are given in Table 1.

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