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SYNTHESIS AND PROPERTIES OF N-METHYL-MORPHOLINIUM 6-METHYL-4-(4-PYRIDYL)-5-PHENYLCARBAMOYL-3-CYANO-1,4-DIHYDRO-PYRIDINE-2-THIOLATE

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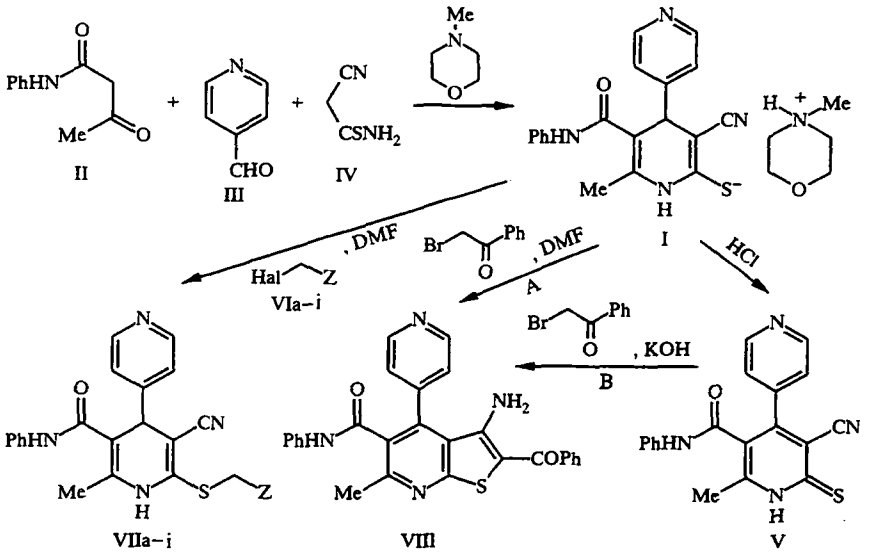
Condensation of acetoacetic acid anilide, 4-pyridyl aldehyde, cyanothioacetamide and N-methylmorpholine gave N-methylmorpholinium 6-methyl-4-(4-pyridyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate from which were obtained the corresponding substituted pyridinethiones, 2-alkylthio-1,4-dihydropyridines and 3-amino-2-benzoyl-6-methyl-4-(4-pyridyl)-5-phenylcarbamoylthieno[2,3-b]pyridine.

Derivatives of 3-cyano-2(1H)-pyridine-chalkogenones with 4-pyridyl substituents are known to have cardiotonic properties [1-5]. Methods for their synthesis include interaction of 4-pyridylmethylenecyanothioacetamide with acetylacetone [6] or acetoacetic ester [7]. the reaction of 5-(4-pyridyl) substituted 2-chloro-3-cyanopyridines with sodium alkoxides [8] and the interaction of α,β-enaminoketones with cyanothioacetamide [9].



VI, VIIa Hal = Cl, Z = Ph; b Hal = Cl, Z = $CONH_2$; c Hal = I, Z = $(CH_2)_4CH_3$ d Hal = Cl, Z = PhNHCO; e Hal = I, Z = H; f Hal = Cl, Z = 4-BrC_6H_4NHCO; g Hal = I, Z = CH_3; h Hal = Br, Z = Et; i Hal = Br, Z = 4-ClC_6H_4

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TABLE 1. ^{1}H NMR and IR Spectra of Compounds VIIa-i

Compound	IR spectrum, ν, cm^{-1}			H NMR spectrum, δ, ppm								
	NH	CN	CONH	CONH, s	NH, s	pyridyl		Ph, m	4-H, s	SCH_2	6-CH_3, s	Z
						α and α'-H, d	β and β'-H, d					
VIIa	3300	2190	1670	9,65	9,28	8,46	7,51	7,32	4,71	4,30 s	2,10	6,98 m (Ph)
VIIb	3264, 3380	2192	1670	10,11	9,74	8,53	7,60	7,27	4,83	3,74 s	2,12	7.92 and 7.75, two br. s. (NH_2)
VIIc	3284	2190	1665	9,71	9,27	8,54	7,55	7,20	4,80	3,01 m	2,13	1,26 m ($(CH_2)_4$), 0,87 t (CH_3)
VIId	3315	2188	1674	9,74	9,61	8,47	7,60	7,20*	4,84	3,99 s	2,12	10,39 s (CONH), 7,20* (Ph)
VIIe	3300	2194	1650	9,73	9,19	8,68	7,49	7,20	4,72	2,63† s	2,09	—
VIIf	3348	2200	1662	9,72	9,53	8,48	7,56*	7,25	4,83	3,97 s	2,11	10,50 s (CONH), 7,56* (C_6H_4)
VIIg	3330	2188	1675	9,71	9,28	8,53	7,49	7,24	4,79	3,02 m	2,10	1,21 t (CH_3)
VIIh	3305	2190	1660	9,72	9,28	8,51	7,53	7,20	4,77	2,97 m	2,10	0,95 t (CH_3), 1,54 m (CH_2)
VIIi	3330	2192	1673	9,67	9,31	8,49	7,45	7,35	4,75	4,30 s	2,11	7,01 m (C_6H_4)

*Signals overlap.

†SCH_3 signal.

TABLE 2. Characteristics of the Compounds Synthesized, VIIa-i

Compound	Molecular formula	(Found, %) / (Calculated, %) C	H	N	S	mp, °C (solvent for recrystallization)	Yield, %
VIIa	$C_{26}H_{22}N_4OS$	71.10 71,21	4.95 5,06	12.84 12,78	7.50 7,31	150...152 (*i*-PrOH)	79
VIIb	$C_{21}H_{19}N_5O_2S$	62.30 62,21	4.68 4,72	17.35 17,27	7.80 7,91	242...244 (*i*-PrOH)	86
VIIc	$C_{25}H_{28}N_4OS$	69.50 69,41	6.48 6,52	12.80 12,95	7.60 7,41	168...170 (ethanol)	65
VIId	$C_{27}H_{23}N_5O_2S$	67.28 67,34	4.75 4,81	14.60 14,54	6.79 6,66	210...212 (AcOH)	67
VIIe	$C_{20}H_{18}N_4OS$	66.30 66,28	4.90 5,01	15.32 15,46	8.91 8,85	119...121 (ethanol)	86
VIIf	$C_{27}H_{22}BrN_5O_2S$	57.92 57,86	3.80 3,96	12.66 12,50	5.65 5,72	239...241 (n-butanol)	75
VIIg	$C_{21}H_{20}N_4OS$	66.88 67,00	5.20 5,35	14.97 14,88	8.64 8,52	105...107 (ethanol)	81
VIIh	$C_{22}H_{22}N_4OS$	67.57 67,67	5.70 5,68	14.39 14,35	8.10 8,21	139...141 (ethanol)	78
VIIi	$C_{26}H_{21}ClN_4OS$	65.93 66,02	4.30 4,48	11.90 11,85	6.82 6,78	218...220 (n-butanol)	69

In this work we have developed a method for the synthesis of the previously unknown N-methylmorpholinium 6-methyl-4-(4-pyridyl)-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate (I) by the three component condensation of the anilide of acetoacetic acid (II), 4-pyridylaldehyde (III) and cyanothioacetamide (IV) in ethanol at 20°C in the presence of N-methylmorpholine. The structure of the I was confirmed spectroscopically. Its IR spectrum contained an absorption corresponding to a conjugated cyano group and another corresponding to the NHCO unit at 2188 and 1655 cm^{-1} respectively. The ^1H NMR spectrum of the thiolate I contains signals for the hydrogens of the aromatic ring, the N-methylmorpholinium cation and the 6-CH_3 (see Experimental section) together with signals for the protons of the dihydropyridine ring at 9.28 (s, NH) and 4.57 ppm (s, 4-H).

Treatment of salt I with dilute aqueous hydrochloric acid gave the thione (V) which reacted with the halides (VIa-i) in DMF solution to give the corresponding 2-alkylthio-1,4-dihydropyridines (VIIa-i). Interestingly when phenacyl bromide was used as the alkylating agent only the bicyclic product, substituted thieno[2,3-*b*]pyridine (VIII), was obtained (method A). The same product was obtained when the thione V reacted with phenacyl bromide in the presence of KOH (method B).

The structures of compounds V, VII, and VIII are in agreement with ^1H NMR and IR spectroscopic results (see Experimental section, Table 1).

EXPERIMENTAL

^1H NMR spectra of DMSO-D_6 solutions with TMS as internal standard were recorded on a Bruker WP-100 SU (100 MHz) instrument. IR spectra of Nujol mulls were recorded with an IRS-29 spectrometer. TLC was carried out on Silufol UV-254 strips with 3:5 acetone-heptane as eluant and development with iodine vapor.

N-Methylmorpholinium 6-Methyl-4-(4-pyridyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate (I). A mixture of 10 mmol of each of anilide II, aldehyde III and cyanothioacetamide (IV) and 15 mmol of N-methylmorpholine was stirred for 6 h at 20°C. The precipitate was filtered off and washed with ethanol and acetone to give compound I (4.0 g, 89%). mp 246-248°C. IR spectrum: 3150 (NH), 2188 (CN), 1655 cm^{-1} (NHCO). ^1H NMR spectrum: 10.36, (1 H, s, NHCO), 9.28 (1 H, s, NH), 8.47 (2 H, d, α and α'-H_{Py}), 7.48 (2 H, d, β and β'-H_{Py}), 7.20 (5 H, m, H_{Ph}), 4.57 (1 H, s, 4-H), 3.75 (4 H, m, CH_2OCH_2), 3.09 (4 H, m, CH_2NCH_2), 2.72 (3 H, s, NCH_3), 2.09 ppm (3 H, s, 6-CH_3). Found, %: C 64.00, H 5.90, N 15.64, S 7.22. $C_{24}H_{27}N_5O_2S$. Calculated, %: C 64.12, H 6.05, N 15.58, S 7.13.

6-Methyl-4-(4-pyridyl)-5-phenylcarbamoyl-3-cyanopyridine-2(1H)thione (V). A suspension of salt I (10 mmol) in ethanol (15 cm^3) was diluted with aqueous hydrochloric acid to pH 3 with stirring, and filtered. The precipitate, which developed over 24 h, was filtered off and washed with ethanol and hexane to give V (yield 2.46 g, 71%). mp 301-303°C. IR spectrum: 3360 (NH), 2230 (CN), 1648 cm^{-1} (NHCO). ^1H NMR spectrum: 10.36 (1 H, s, NHCO), 8.67 (2 H, d, α and

α'-H_{Py}), 7.45 (2 H, d, β and β'-H_{Py}), 7.26 (5 H, m, H_{Ph}), 2.48 ppm (3 H, s, CH_3). Found, %: C 65.81, H 3.98, N 16.24, S 9.16. $C_{19}H_{14}N_4OS$. Calculated, %: C 65.88, H 4.07, N 16.17, S 9.26.

6-Methyl-2-(Z-methylthio)-4-(4-pyridyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridines (VIIa-i). A halide VI (10 mmol) was added to a suspension of salt I (10 mmol) in DMF (10 cm^3), the mixture was stirred for 4 h and then diluted with water (10 cm^3). The precipitate was filtered off and washed with water, ethanol and hexane to give compounds VIIa-i, whose characteristics are given in Tables 1 and 2.

3-Amino-2-benzoyl-6-methyl-4-(4-pyridyl)-5-phenylcarbamoylthieno[2,3-*b*]pyridine (VIII). Method A. Product VIII was obtained from phenacyl bromide by the method described above for the synthesis of compounds VII: yield 3.5 g (75%). IR spectrum : 3150-3300 (NH_2), 1665 cm^{-1} (NHCO). ^1H NMR spectrum: 10.47, (1 H, s, NHCO), 8.74 (2 H, d, α and α'-H_{Py}), 7.80 (2 H, d, β and β'-H_{Py}), 7.10-7.65 (10 H, m, H_{Ph}), 6.75 ppm (2 H, br.s, NH_2). Found, %: C 69.98, H 4.22, N 11.88, S 7.02. $C_{27}H_{20}N_4O_2S$. Calculated, %: C 69.81, H 4.34, N 12.06, S 6.90.

Method B. 10% Aqueous KOH (5.6 cm^3, 10 mmol) was added with stirring to a suspension of thione V (10 mmol) in DMF (10 cm^3) and then phenacyl bromide (10 mmol) was added over 1 min and the mixture was stirred for 4 h. The mixture was then diluted with water (10 cm^3) and the precipitate which formed was filtered off and washed with water, ethanol and hexane to give compound VII identical to that prepared by method A (no depression with a mixed melting point).

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