PREPARATION AND PROPERTIES OF BETAINES OF 4-PYRIDYL-3,4-DIHYDROPYRIDINE-2-THIONES(1H)

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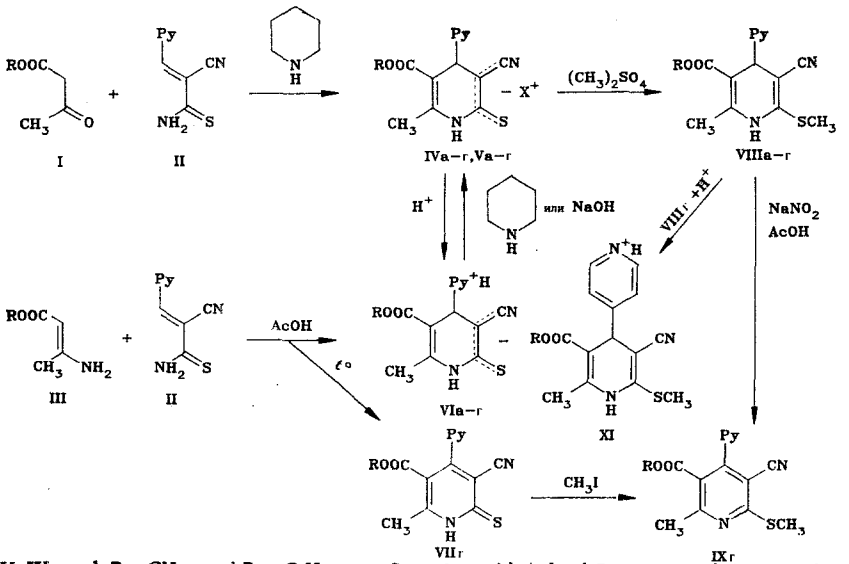
Condensation of 2-cyano-3-pyridylthioacrylamides with esters of acetoacetic or β-aminocrotonic acids yields betaines of 3,5,6-substituted-4-pyridyl-3,4-dihydropyridine-2-thiones(1H). The spectral characteristics of the betaines have been examined and their ionization constants (pK) determined.

We have extended our studies in the area of 3,4-dihydropyridine-2-thiones(1H) [1, 2] by preparing betaines of 6-methyl-5-alkoxycarbonyl-3-cyano-4-(3-pyridyl)- and -(4-pyridyl)-3,4-dihydropyridine-2-thiones(1H) (VI).

We used two routes to the betaines (VI): condensation of 2-cyano-3-pyridylthioacrylamides II with acetoacetic esters I using piperidine as condensing agent, and condensation of the thioamide II with esters of β-aminocrotonic acid III.



IV-IX: a, b R = CH_3, c, d R = C_2H_5; a, c Py = 3-pyridyl, b, d Py = 4-pyridyl; IV a-d: X = piperidine, V a-d: X = Na^+

In the first route, pyridine salts of 6-methyl-5-alkoxycarbonyl-3-cyano-4-(3-pyridyl or 4-pyridyl)-3,4-dihydropyridine-2-thiones(1H) (IV) were isolated as intermediate products. Acidification of the salts IV with an equimolar quantity of hydrochloric acid in ethanol yields the betaines VI. In the second route, the betaines VI are obtained by brief heating of the initial components in acetic acid. In this case small amounts of the pyridine-2-thiones VII are also obtained and if heating is prolonged these become the main products.

The betaines VI are clear yellow compounds (Table 1). Compounds VI differ from compounds VII in their greater polarity (in TLC) and their increased solubility on passing from ethanol to 50% ethanol.

With piperidine or caustic soda, the betaines VI form piperidine or sodium salts of 3,4-dihydropyridine-2-thiones(1H) (IV and V). The betaines VI are not oxidized by atmospheric

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TABLE 1. Characteristics of Compounds IV-IX

Compound*	T mp,† °C	Found, %				Empirical formula	Calculated, %				Yield, %	
		C	H	N	S		C	H	N	S	A	B
IVa	158—160	61,2	6,6	14,6	8,7	$C_{19}H_{24}N_4O_2S$	61,3	6,6	15,0	8,6	93	87
IVb	173—175	61,1	6,4	14,9	8,5	$C_{19}H_{24}N_4O_2S$	61,3	6,6	15,0	8,6	77	80
IVc	140—142	61,9	6,6	14,3	8,6	$C_{20}H_{26}N_4O_2S$	62,1	6,8	14,5	8,3	63	66
IVd	152—154	61,8	6,7	14,3	8,7	$C_{20}H_{26}N_4O_2S$	62,1	6,8	14,5	8,3	70	65
Va	198—200	54,1	3,9	13,0	10,2	$C_{14}H_{12}NaN_3O_2S$	54,4	3,9	13,6	10,4	92	
Vb	>250	54,2	4,2	13,8	10,9	$C_{14}H_{12}NaN_3O_2S$	54,4	3,9	13,6	10,4	81	
Vc	195—197	55,1	4,6	13,1	9,3	$C_{15}H_{14}NaN_3O_2S$	55,7	4,4	13,0	9,9	66	
Vd	238—240	55,3	4,3	12,7	9,3	$C_{15}H_{14}NaN_3O_2S$	55,7	4,4	13,0	9,9	79	
VIa	186—188	58,2	4,8	14,2	10,9	$C_{14}H_{13}N_3O_2S$	58,5	4,6	14,6	11,2	69	45
VIb	218—220	58,3	4,5	14,6	10,8	$C_{14}H_{13}N_3O_2S$	58,5	4,6	14,6	11,2	69	60
VIc	173—175	60,6	5,2	13,6	10,2	$C_{15}H_{15}N_3O_2S$	59,8	5,0	13,9	10,6	71	60
VId	181—183	60,1	5,2	14,1	10,1	$C_{15}H_{15}N_3O_2S$	59,8	5,0	13,9	10,6	49	69
VIId	244—246	59,3	4,2	14,4	10,4	$C_{15}H_{13}N_3O_2S$	60,2	4,4	14,0	10,7	29	
VIIIa	214—215	59,6	5,0	13,6	10,8	$C_{15}H_{15}N_3O_2S$	59,8	5,0	13,9	10,6	68	
VIIIb	169—170	59,6	4,8	13,9	10,2	$C_{15}H_{15}N_3O_2S$	59,8	5,0	13,9	10,6	70	
VIIIc	226—228	60,9	5,4	13,2	10,2	$C_{16}H_{17}N_3O_2S$	60,9	5,4	13,3	10,2	70	
VIIId	148—150	60,4	5,4	12,9	10,2	$C_{16}H_{17}N_3O_2S$	60,9	5,4	13,3	10,2	73	
IXd	78—80	61,9	4,9	12,9	9,9	$C_{16}H_{15}N_3O_2S$	61,3	4,8	13,4	10,2	61	52

*IVa, b, Va, b, VIa, b, VIIIa, b: R = CH_3. IVc, d, Vc, d, VIc, d, VIId, VIIIc, d, IXd: R = C_2H_5. IVa, c, Va, c, VIa, c, VIIIa, c: Py = 3-pyridyl; IVb, d, Vb, d, VIb, d, VIId, VIIIb, d, IXd: Py = 4-pyridyl.

†Compounds IV-VI, VIII, IX recrystallized from ethanol, VII from nitromethane; Vb, with decomp.

TABLE 2. IR and UV Spectra of Compounds IV-X

Compound	IR spectra ν, cm^{-1}			UV spectra, λ, nm
	C=O	C≡N	N—H	
IVa	1685	2172	3110, 3178, 3216	261, 306, 373 p.
IVb	1696	2177	3104, 3142, 3210	262, 308, 373 p.
IVc	2691	2182	3112, 3158, 3190	261, 308, 373 p.
IVd	1694	2168	3140, 3175, 3255	258, 310, 375p.
Va	1661	2181	3161, 3205, 3372	261, 308, 367p.
Vb	1674	2180	3165, 3205, 3390	259, 309, 370p.
Vc	1659	2177	3158, 3205, 3360	260, 303, 368 p.
Vd	1652	2188	3156, 3192, 3375	258, 309, 372 p.
VIa	1642	2178	3328	258, 310, 342 p.
VIb	1712	2166	3200	258, 312, 340 p.
VIc	1637	2177	3320	256, 314, 338 p.
VId	1705	2176	3204	257, 313, 338 p.
VIIa	1712	2234	3180	247 p., 330, 410
VIIIa	1697	2194	3166	228, 270, 282 p., 358
VIIIb	1702	2194	3155	229, 280, 359
VIIIc	1705	2200	3110	232, 254 p., 286 P., 360
VIIId	1700	2190	3160	227, 270, 358
IXd	1720	2226	—	216, 285, 326 p.

oxygen on standing in solution, thus differing from the 4-aryl-substituted 3,4-dihydropyridine-2-thiones(1H) which are comparatively easily oxidized to the corresponding pyridine-2-thiones-(1H) [2].

The betaines VI, like 4-aryl-3,4-dihydropyridine-2-thiones, are easily alkylated. The best results are obtained by alkylation of the piperidine salts of IV with dimethylsulfate. The 2-methylthio-1,4-dihydropyridines VIII which are obtained are oxidized to 2-methylthio-pyridines IX; these can also be prepared by alkylation of the pyridine-2-thiones VII.

The betaine structure of compound VI is supported by the results of IR, and proton and ^{13}C NMR spectroscopy. The IR spectra (Table 2) show absorption bands for the stretching vibrations of C≡N groups for the salts IV and V, and also, for the betaines VI, bands at 2168-2188 cm^{-1}. Thus, the salts IV and V serve as model compounds for corroboration of the betaine structure of compounds VI. In addition, in all the compounds IV-VI there are absorption bands for NH groups; this supports the formation of anions by loss of a proton from the tertiary carbon of the 3,4-dihydropyridine ring.

TABLE 3. Proton NMR Spectra of Compounds IV-VI and VIII (in DMSO-D_6)*

Compound	Chemical shift, δ, ppm					
	4-H	6-CH_3	R—H	Py—H	NH	others
IVa	4,28	2,23	3,44	8,3 (2′-, 6′-H), 7,5—7,2 (4′-, 5′-H)	8,3	3,0 (α-CH_2), 1,6 (β,γ-CH_2)
IVb	4,24	2,24	3,44	8,4 (2′-, 6′-H), 7,06 (3′-, 5′-H)	8,4	2,9 (α-CH_2), 1,6 (β,γ-CH_2)
IVc	4,22	2,17	3,82 (CH_2), 0,97 (CH_3)	8,3 (2′-, 6′-H), 7,4—7,1 (4′-, 5′-H)	8,3	2,9 (α-CH_2), 1,5 (β,γ-CH_2), 5,4 (N^+H_2)
IVd	4,38	2,24	3,89 (CH_2), 1,02 (CH_3)	8,33 (2′-, 6′-H), 7,07 (3′-, 5′-H)	8,0	2,9 (α-CH_2), 1,5 (β,γ-CH_2), 7,6 (N^+H_2)
Va	4,27	2,20	3,44	8,27 (2′-, 6′-H), 7,5—7,1 (4′-, 5′-H)	8,3	
Vb	4,29	2,22	3,44	8,44 (2′-, 6′-H), 7,11 (3′-, 5′-H)	8,4	
Vc	4,27	2,22	3,89 (CH_2), 1,04 (CH_3)	8,29 (2′-, 6′-H), 7,44 (4′-H), 7,24 (5′-H)	8,3	
Vd	4,24	2,22	3,89 (CH_2), 1,04 (CH_3)	8,38 (2′-, 6′-H), 7,04 (3′-, 5′-H)	8,2	
VIa	4,44	2,31	3,51	8,60 (6′-H), 8,49 (2′-H), 8,0—7,7 (4′-, 5′-H)	7,7	
VIb	4,51	2,29	3,45	8,73 (2′-, 6′-H), 7,62 (3′-, 5′-H)	9,0	
VIc	4,47	2,31	3,96 (CH_2), 1,07 (CH_3)	8,58 (6′-H), 8,48 (2′-H), 8,0—7,5 (4′-, 5′-H)	7,7	
VId	4,49	2,29	3,90 (CH_2), 1,03 (CH_3)	8,73 (2′-, 6′-H), 7,61 (3′-, 5′-H)	8,8	
VIIIa	4,58	2,37	3,58	8,47 (2′-, 6′-H), 7,64—7,33 (4′-, 5′-H)	9,55	2,55 (S—CH_3)
VIIIb	4,74	2,44	3,66	8,57 (2′-, 6′-H), 7,22 (3′-, 4′-H)	7,76	2,48 (S—CH_3)
VIIIc	4,71	2,40	4,09 (CH_2), 1,18 (CH_3)	8,49 (2′-, 6′-H), 7,69—7,72 (4′-, 5′-H)	7,48	2,49 (S—CH_3)
VIIId	4,49	2,29	3,92 (CH_2), 1,02 (CH_3)	8,51 (2′-, 6′-H), 7,13 (3′-, 5′-H)	9,5	2,46 (S—CH_3)

*Spectrum NMR of compound VIIIb run in $CDCl_3$.

The proton NMR spectra of the analogous 4-aryl-substituted 3,4-dihydropyridine-2-thiones X [2] show signals for the 3-H and 4-H protons in the form of doublets, corresponding to two stereoisomers. The spectra of the betaines VI and the salts IV and V show only a singlet for the 4-H proton (Table 3). It should be noted that the signals of the 4-pyridyl radical protons of the betaine VI are shifted downfield in comparison with those of the salts IV and V, which is further support for the betaine structure of compound VI.

In the carbon-13 spectra of betaines VId, and the corresponding Na salts Vd, the C(2) signals are found at 167-164 ppm (Table 4). Comparison of these signals with the C(2) signals from 4-aryl-3,4-dihydropyridines X (191.25 and 189.76, trans- and cis-isomers) [2] shows that the signals from the betaine are shifted markedly downfield, which also precludes the presence of a C=S group. On comparing the carbon-13 spectra of the betaines VId with those of the model compounds V, VIII, and XI, prepared by acidification of VIIId (Table 4), it can be seen that the chemical shifts of the carbons of the pyridine ring are close to those having aprotonated nitrogen atom (compound XI), and the chemical shifts of the carbons of the dihydropyridine ring are close to those in the sodium salt V.

Ionization constants (pK) were determined for the betaines VI and the corresponding 4-aryl derivatives X [2] (Table 5). It has been shown that these compounds in 50% aqueous ethanol behave as acids of average strength. Examination of the ionization constants pK also provides support for the betaine structure for compound VI. We used compounds VIII and X as model compounds. On the strength of [3, 4, p. 21], we assigned the constants pK_1 (4.54 and 5.15) to

TABLE 4. Carbon-13 NMR Spectra (in DMSO-D_6) of Compounds Vd, VId, VIIId, and XI

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	SCH_3	CN	COOEt			$6\text{-}CH_3$	Pyridine		
								CO	CH_2	CH_3		2',6'-H	3',5'-H	4'-H
Vd	167,4	78,3	43,5	97,0	148,7	—	126,6	168,2	59,8	15,2	19,7	157,6	123,1	150,6
VId	164 broad	79 very broad	44,1	97,6 broad	149,7	—	124 broad	167,6	60,0	15,0	19,5	—*	125,3	145,1 broad
VIIId	147,4	87,6	41,7	100,6	148,1	16,9	119,9	167,2	60,7	15,0	19,1	154	123,2	151,3
XI	163,6	85,0	42,7	98,6	148,5	16,0	118,4	165,8	60,1	13,9	18,3	148,1	125,4	142,8

*Signal not observed in view of excessive broadening.

TABLE 5. Ionization Constant (pK) of Betaines VI, 1,4-Dihydropyridines VIII, and 4-Aryl-3,4-dihydropyridine-2-thiones X

Compound	pK_1	pK_2
VIc	4,54±0,04	2,17±0,08
VId	5,15±0,03	2,26±0,07
VIIIc	3,18±0,04	—
VIIId	3,79±0,06	—
6-Methyl-4-phenyl-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2-thione[1H](Xa) [2]	—	4,03±0,05
6-Methyl-4-[4'-nitrophenyl]-5-ethoxycarbonyl-3-cyano-3,4-dihydropyridine-2-thione[1H] (Xb) [2]	—	3,29±0,07

protonation of the 4-pyridyl radical and pK_2 (2.17 and 2.26) to detachment of a proton from the 3,4-dihydropyridine-2-thione residue. It was shown that the pyridine cation, as a strong electron-acceptor, markedly increases the acid strength of compound VI (for VId, pK_2 = 2.6; for Xb, pK_2 = 3.29), but on the other hand, the anion increases the basic character of the nucleophilic center in the 4-pyridyl radical (for VId, pK_1 = 5.15; for VIIId, pK_1 = 3.79).

EXPERIMENTAL

A Perkin-Elmer 580B spectrometer was used to obtain the infrared spectra (in nujol). Ultraviolet spectra were run on a Specord UV-vis in ethanol. A WH 90/DC instrument (90 MHz) was used for the proton NMR spectra, the internal standard being TMS_4; carbon-13 HNMR spectra were run at 22.63 MHz with cyclohexane (δ = 27.44 ppm) as internal standard. The accuracy of the reported chemical shifts was ±0.03 ppm for ^1H and ±0.07 ppm for ^{13}C. Ionization constants were determined by potentiometric titration with a glass electrode [4, p. 108] in 50% aqueous ethanol.

The main characteristics of the prepared compounds are set out in Tables 1-5.

Piperidine Salt of 6-Methyl-5-alkoxycarbonyl-3-cyano-4-pyridyl-3,4-dihydropyridine-2-thione(1H) (IV). A. A mixture of 10 mmoles acetoacetic ester I and 10 mmoles 2-cyano-3-pyridylthioacrylamide II was heated and stirred at 50°C, partially dissolved in 20 ml absolute ethanol, 2 ml (25 mmoles) piperidine added, and the reaction mixture filtered hot. The filtrate was cooled to 0°C and the white, finely crystalline product filtered off and washed with cold ethanol and ether. Yield 70-77% compound IV.

B. A mixture of 5 mmoles betaine VI and 0.5 ml (10 mmoles) piperidine in 10 ml absolute ethanol was stirred 15-30 min at room temperature and cooled to 0°C. The reaction product was filtered off and washed with cold ethanol. Yield 65-87% compound IV.

Sodium Salt of 6-Methyl-5-alkoxycarbonyl-3-cyano-4-pyridyl-3,4-dihydropyridine-2-thiones (1H) (V). A mixture of 5 mmoles betaine VI heated in 2 ml 3 N NaOH (6 mmoles) and 15 ml ethanol was filtered and cooled to 0°C. The precipitated solid was filtered off and washed with cold ethanol. Yield 66-92% compound V.

Betaines of 6-Methyl-5-alkoxycarbonyl-3-cyano-4-pyridyl-3,4-dihydropyridine-2-thiones(1H) (VI). A. To 20 ml of 0.5 N hydrochloric acid in ethanol at 50-60°C, 10 mmoles of the piperi-

dine-salt IV was added and dissolved with vigorous stirring. The solution was filtered hot, cooled to 0°C, and the precipitate filtered off and washed with cold ethanol and water. Yield 49-71% compound VI.

B. A mixture of 10 mmoles of an ester of β-aminocrotonic acid III and 10 mmoles 2-cyano-3-pyridylthioacrylamide was heated on a water bath with 20 ml absolute ethanol and 10 ml glacial acetic acid until dissolved, filtered and cooled to 20°C. A small amount of product VII separated. The filtrate was cooled to 0°C and the precipitate filtered off and washed with cold ethanol and water. Yield 45-69% compound VI.

6-Methyl-5-ethoxycarbonyl-3-cyano-4-(4-pyridyl)-pyridine-2-thione(1H) (VIId). A mixture of 10 mmoles of the ethyl ester of β-aminocrotonic acid III, 10 mmoles 2-cyano-3-pyridylthioacrylamide II in 20 ml absolute ethanol, and 10 ml glacial acetic acid was heated 1 h on a water bath and filtered. The filtrate was kept at 0°C for 24 h and the precipitate filtered off. Yield 0.87 g (29%) compound VIId.

2-Methylthio-6-methyl-5-alkoxycarbonyl-3-cyano-4-(4-pyridyl)-1,4-dihydropyridine (VIII). A mixture of 10 mmoles freshly prepared piperidine salt IV and 1.2 ml (15 mmoles) dimethyl sulfate in 20 ml absolute ethanol was stirred for 1 h at room temperature. The reaction mixture was poured into water, ammonia added to pH 5-6 and the precipitate filtered off. Yield 68-73% compound VIII.

2-Methylthio-6-methyl-5-ethoxycarbonyl-3-cyano-4-(4-pyridyl)-pyridine (IX). A. A mixture of 0.6 g (2 mmoles) ester VII and 0.3 ml (5 mmoles) methyl iodide in 10 ml 0.5% sodium ethoxide was heated on a water bath for 5 min. The mixture was cooled, poured into ice-cold water, acidified to pH 6-7 and the precipitate filtered off. Yield 0.45 g (61%) compound IXd.

B. A mixture of 0.63 g (2 mmoles) 1,4-dihydropyridine VIII in 3 ml glacial acetic acid was heated to 50-60°C and 0.35 g (5 mmoles) sodium nitrite added. The reaction mixture was cooled, poured into ice-cold water, neutralized with ammonia and the precipitate filtered off. Yield 0.33 g (52%) compound IX.

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