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SYNTHESIS AND PROPERTIES OF THIOCARBAMOYLMETHYLPYRIDINIUM (ISOQUINOLINIUM) YLIDS

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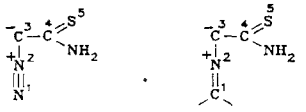
2-(2-Carbethoxy-1-amino-1-thio)ethylenepyradinium(isoqunolinium) ylids were obtained by the reaction of carbethoxycyanomethylpyridinium(isoquinolinium) ylids with hydrogen sulfide. In an alkaline medium they cyclize into 5-mercaptosubstituted imidazo[1,2-a]pyridines(isoquinolines). The structure of the latter compounds was confirmed by PMR and IR spectroscopy.

Thiocarbamolyazomethine ylids are represented in the literature by scattered examples [1-4]. However, on the basis of the known data on the ability of the thio derivatives of heterocyclic azomethine ylids to undergo intramolecular cyclization [3-5], and as the result of the high chemical activity of the thioamide group, it could be expected that the thiocarbamoyl azomethine ylids will serve as convenient starting compounds in the synthesis of condensed heterocycles.

The present article deals with the synthesis and investigation of thiocarbamoylmethylpyridinium(isoquinolinium) ylids and their heterocyclization into imidazole and thiazole derivatives, which are of interest as biologically active compounds [6, 7].

To develop methods of synthesis of thioamides I, we studied the sulfhydrylation of the corresponding nitriles II. We found that the cyano group in compounds II has low reactivity with respect to hydrogen sulfide and only partially converts into the thioamide group when the reaction is carried out at elevated temperature and pressure in the presence of sodium ethylate. Thioamides Ia, b were isolated in yields of from 10 to 40%, while the variation of the catalysts, solvents and the use of a large excess of hydrogen sulfide did not lead to an increase in the degree of conversion of nitrile into thioamide.



In contrast to aliphatic α-diazothioamides, which cyclize into 1,2,3-thiadiazoles even under the conditions of their formation [8], the expected cyclization of thioamides I, which are analogs of α-diazothioamides with isoionic substitution at the 1-position, into thiazoles III did not take place either at elevated temperatures or at various pH values of the medium.

Thioamidates IV were not obtained, from methylaton of thioamides Ia, b by methyl iodide in an ethanolic solution of sodium ethylate, but instead 2-methylthio-3-carbethoxyimidazo[1,2-a]-pyridine (Va) and 2-methylthio-3-arbethoxyimidazo[1,2-a]isoquinoline (Vb) were formed, which, according to the IR and UV spectral data, were identical to the compounds obtained previously by another method [9]. These compounds are probably formed as the result of two

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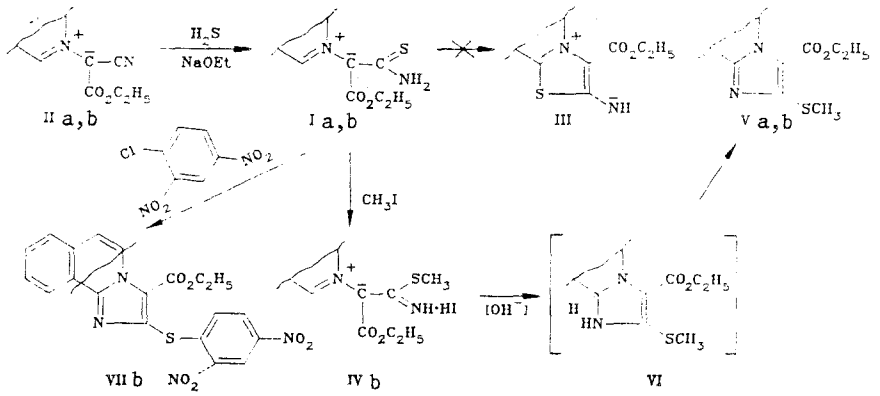


successive reactions: cyclization of the thioamides into imidazolines VI and oxidation of the latter into imidazoles Va, b.

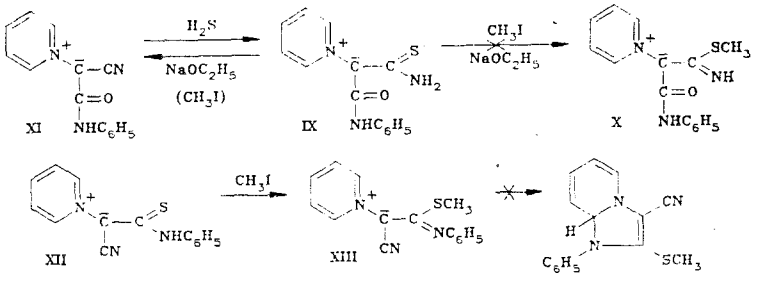
The reaction of thioamide Ib with 2,4-dinitrochlorobenzene proceeds similarly to methylation, and 2-(2,4-dinitrophenylthio)-3-carbethoxyimidazo[1,2-a]isoquinoline (VIIb) is formed as the result. It is noteworthy that thioamide Ia remains unchanged under the conditions of the latter reaction.

The cyclic structure of products Va, b and VIIb is confirmed by IR and PMR spectroscopy as well as by mass-spectrometry data. In the IR spectrum of imidazo[1,2-a]pyridine (Va) and imidazo[1,2-a]isoquinolines (Vb, VIIb), a shift of the stretching vibrations band of the carbonyl group is observed in the 1650–1660 cm^{-1} region, characteristic for the zwitterionic structure of ylids Ia, b and IIa, b [10], into a higher-frequency region (1690 cm^{-1}). The PMR spectrum of compounds Va, b differs sharply from the spectra of azomethine ylids Ia, b and IIa, b. Thus, while in the spectrum of thioamide Ib there is a singlet signal in the isoquinoline ring, and a composite multiplet of the aromatic and heterocyclic protons, in the spectrum of imidazo[1,2-a]isoquinoline Vb, the proton signals of the aromatic part of the molecule appear in a stronger field, and two doublets of signals appear at 9.0 and 7.5 ppm, corresponding to the chemical shift of the 5-H and 6-H protons of the azinium part of the condensed heterocycle. The structure of imidazo[1,2-a]isoquinoline Vb was also confirmed by its conversion into the corresponding carbohydrazide VIIIb by reaction with hydrazine hydrate.

The methylation of thioamide Ib proceeds not only in an alkaline but also in an acid medium. When this reaction was carried out in acetic acid. 2-(2-carbethoxy-1-amino-1-methylthio)ethylene isoquinolinium iodide (IVb) was obtained, which cyclized in an alkaline medium into a product, which is identical in its properties, IR and PMR spectra with imidazo[1,2-a]-isoquinoline Vb.

These data indicate that the protonation of the imine nitrogen atom of thioimino ethers leads to the stabilization of the imine structure IV and the reaction of the electron pair of the imino group nitrogen atom with the α-carbon atom of the azinium part of the molecule is the determining step in the cyclization reaction.

In the case of thiocarbamoylpyridinium ylid IX, containing an N-phenylcarbamoyl group, alkylation with methyl iodide in the presence of sodium ethylate results in the initial nitrile XI, and not in the thioimidate X. Attempts to methylate thioamide IX in an acid medium were unsuccessful. The formation of a nitrile from thioamide during alkylation with methyl iodide in alkaline medium, was also observed in the reaction of thioamide Ia with methyl idoide, whereby in addition to the cyclization product, carbethoxycyanomethylpyridinium ylid IIa was isolated from the reaction medium.



Methylation of 1-(2-cyano-1-phenylaminl 1-thio)ethylenepyridinium ylid (XII) in alkaline medium does not result in the cyclic product, but in thioimino ether XIII.

It was thus shown that an S-alkylation of S-arylation is a necessary step to effect the cyclization of thiocarbamoylpyridinium (isoquinolinium) ylids, whereby the thioimino ethers formed cyclize only in the form of three bases. The observed cyclization of thioimino ethers IV provides a new method for the synthesis of 5-mercapto substituted imidazo[1,2-a]pyridines-(isoquinolines).

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord-75 spectrophotometers in KBr tablets. The UV spectra were run in ethanol on a Beckman Model-26 spectrophotometer. The PMR spectra were obtained in DMSO-D_6 on Perkin-Elmer R-12B (60 MHz) and Bruker WP-80 (80 MHz) spectrometers, using TMS as an internal standard. The course of the reactions and the pure state of the compounds were monitored by TLC on Silufol UV-254 plates in chloroform-ethanol (9:1) (A), chloroform-benzene (9:1) (B), propanol-3 N ammonia (3:1) (C), and chloroform-acetonitrile (9:1) (D) solvent systems. The mass spectra were recorded on a MAT-311A mass-spectrometer under standard conditions.

Compounds IIa, b were synthesized by methods described in [10, 11].

2-(2-Carbethoxy-1-amino-1-thio)ethylenepyridinium Ylid (Ia, $C_{10}H_{12}N_2O_2S$. Hydrogen sulfide was passed for 2 h, with cooling to 0°C, into a solution of sodium ethylate, obtained from 0.06 g (2.6 mmole) of metallic sodium in 10 ml of absolute ethanol, then 0.5 g (2.6 mmoles) of cyanomethylpyridinium ylid IIa was added, and the mixture was held for 4 h in a sealed ampule at 75°C. The ampule was cooled, the precipitate was filtered off, and crystallized from ethanol. Bright yellow crystals, yield 10%. Mp 178-179°C (dec.), R_f(A) 0.48.

2-(2-Carbethody-1-amino-1-thio)ethyleneisoquinolinium Ylid (Ib, $C_{14}H_{14}N_2O_2S$) was obtained in a similar way as thioamide Ia at ratio of cyanomethylisoquinolinium ylid IIb – sodium, equal to 10:1. Orange crystals, yield, 40%, mp 172-173°C (dec), R_f(A) 0.68.

2-(2-Carbethoxy-1-amino-1-methylthio)ethyleneisoquinolinium iodide (IVb, $C_{15}H_{16}N_2O_2S \cdot HI$). A 0.3-g portion (1.0 mmole) of methyl iodide was added to a solution of 0.25 g (1.0 mmole) of thioamide IIb in 5 ml of glacial acetic acid, and the reaction mixture was boiled for 2 h. It was then cooled, the precipitate was filtered off and crystallized from ethanol. Yellow crystals, yield 60%, mp 199-201°C (dec.), R_F(B) 0.73.

2-Methylthio-3-carbethoxyimidazo[1,2-a]pyridine (Va).$C_{11}H_{11}N_2O_2S$). A 0.21-g portion (0.7 mmole) of thioamide IIa was suspended in a solution of 0.02 g (0.7 mmole) of sodium in 20 ml of absolute ethanol, and 0.15 g (1.0 mmole) of methyl iodine was added after 30 min. The reaction mixture was stirred for 20 h at room temperature, then evaporated under vacuum, and water was added to the residue. The precipitate that separated out was filtered off, and crystallized from ethanol. Colorless crystals, yield 15%, mp 123-125°C (dec.) R_f(D) 0.66.

2-Methylthio-3-carbethoxyimidazo[1,2-a]isoquinoline (Vb) $C_{15}H_{14}N_2O_2S$). A 0.5-g portion of thioamide IIb was suspended in a sodium ethylate solution obtained from 0.04 g (1.8 mmole) of metallic sodium in 40 ml of absolute ethanol, and after 30 min, 0.3 g (2.0 mmoles) of methyl iodide was added. The mixture was stirred for 1 h at room temperature, the precipitate was filtered off and crystallized from ethanol. Colorless crystals, yield 30%, mp 142-145°C (dec.) (according to the data in [9], 154°C). R_f(B) 0.3. UV spectrum (in ethanol), λ_{max} (log ε): 272 nm (4.75), 3.18 nm (3.88).

B) A 0.5 g portion (1.0 mmole) of iodide IVb in a solution of 0.03 g (1.3 mmole) of sodium in 40 ml of absolute ethanol was stirred for 1 h. The precipitate was filtered off, and crystallized from ethanol. Colorless crystals.

2-(2,4-Dinitrophenylthio)-3-carbethoxyimidazo[1,2-a]isoquinoline (VIIb, $C_{20}H_{14}N_4O_6S$). A 0.5 g portion (1.8 mmole) of thioamide IIb was suspended in a solution of sodium ethylate, obtained from 0.04 g (1.8 mmole) of metallic sodium in 50 ml of absolute ethanol, and after 30 min 0.36 g (1.8 mmole) of 2,4-dinitrochlorobenzene was added. The mixture was stirred for 5 h at room temperature, the precipitate was filtered off and crystallized from an acetone-water (3:2) mixture. Yellow crystals, yield 32%, mp 238-240°C (dec.). R_f(B) 0.3.

TABLE 1. Spectral Characteristics of Synthesized Compounds*

Compound	IR spectrum (KBr), cm^{-1}			PMR spectrum (in DMSO-D_6), δ, ppm	Mass spectrum, m/z (%)
	C=O	C≡N	NH		
Ia	1650	—	3250, 3380	8,7 (3H, m); 7,98 (2H, m); 3,95 (2H, q, CH_2); 1,0 (3H, t, CH_3)	224 (47), 223 (27), 177 (13), 80 (100), 79 (30)
Ib	1660	—	3270, 3370	9,93 (1H, s, 1-H); 8,39 (6H, m); 3,93 (2H, q, CH_2); 1,0 (3H, t, CH_3)	274 (54), 273 (35), 227 (21), 143 (46), 130 (100)
IIa	1655	2190	—	9,1 (2H, m); 7,95 (3H, m); 4,1 (2H, q, CH_2); 1,22 (3H, t, CH_3)	—
IIb	1650	2170	—	10,0 (1H, s, 1-H); 8,3 (6H, m); 4,2 (2H, q, CH_2); 1,25 (3H, t, CH_3)	—
IVb	1655	—	3210	10,2 (1H, s, 1-H); 8,3 (6H, m); 4,1 (2H, q, CH_2); 2,5 (3H, s, SCH_3); 1,06 (3H, t, CH_3)	288 (49), 286 (81), 241 (100), 213 (28), 168 (96)
Va	1690	—	—	9,15 (1H, d, 5-H); 7,4 (3H, m); 4,37 (2H, q, CH_2); 2,6 (3H, s, SCH_3); 1,37 (3H, d, CH_3)	236 (94), 191 (22), 189 (22), 164 (63), 163 (100), 131 (34)
Vb	1690	—	—	9,0 (1H, d, 5-H); 8,6 (1H, m); 7,8 (3H, m); 7,5 (1H, d, 6-H); 4,4 (2H, q, CH_2); 2,7 (3H, s, SCH_3); 1,4 (3H, t, CH_3)	286 (100), 214 (37), 213 (50), 181 (41), 128 (59)
VIIb	1690	—	—	9,1 (1H, s); 8,95 (1H, d, 5-H); 8,2 (2H, m); 7,75 (5H, m); 4,3 (2H, q, CH_2); 1,1 (3H, t, CH_3)	438 (46), 392 (16), 365 (23), 302 (32), 128 (100)
VIIIb	1650	—	3170, 3300	8,9 (1H, d, 5-H); 7,75 (4H, m); 7,3 (1H, d, 6-H); 2,8 (3H, s, SCH_3)	—
IX	1620	—	3280, 3435	—	—
XI	1620	2145	3315	—	—
XIII	—	2150	3450	8,9 (2H, m); 7,8 (3H, m); 6,9 (5H, m); 2,15 (3H, s, SCH_3)	267 (14), 266 (10), 220 (100), 141 (50), 77 (94)

*The data of the element analysis (C, H, N, S) correspond to the calculated values. For compounds IIa, b the elemental analysis was not carried out.

2-Methylthioimidazo[1,2-a]isoquinoline-3-carbohydrazide (VIIIb, $C_{13}H_{12}N_4OS$). A 5-ml portion of a 25% solution of hydrazine hydrate was added to a solution of 0.3 g (1 mmole) of imidazo[1,2-a]isoquinoline Vb in 10 ml of ethanol. The mixture was boiled for 3 h, cooled, the precipitate was filtered off and crystallized from ethanol. Colorless crystals, yield 30%, mp 164-167°C (dec.), Rf(A) 0.64.

2-(2-N-Phenylcarbamoyl-1-amino-1-thio)ethylenepyridinium Ylid (IX, $C_{14}H_{13}N_3OS$). Hydrogen sulfide was passed for 2 h, with cooling to 0°C, into a suspension of 1.5 g (6.0 mmoles) of pyridinium ylid XI in a mixture of 150 ml of toluene and 0.64 g (6.0 mmoles) of triethylamine. The reaction mixture was heated for 4 h in a sealed ampule at 100°C. The ampule was then cooled, the precipitate was filtered off, washed with acetone and ether, and crystallized from ethanol. Yellow crystals, yield, 27%, mp 155-157°C (dec.), Rf(C) 0.5.

1-N-Phenylcarbamoyl-1-cyanopyridinium Ylid (XI, $C_{14}H_{11}N_3O$). A 1.52-g portion (15.0 mmoles) of triethylamine was added gradually, with stirring, to a mixture of 2 g (12.0 mmoles) of cyanomethylpyridinium chloride [11] and 1.79 g (15.0 mmoles) of phenyl isocyanate in 50 ml of toluene. After 2 h, the precipitate that separated out was filtered off and crystallized twice from acetone. Bright-yellow crystals, yield 48%, mp 169-172°C (dec.) Rf(S) 0.64.

2-(2-Cyano-1-phenylamino-1-methylthio)ethylenepyridinium Ylid (XIII, $C_{15}H_{13}N_3S$). A 0.5-g portion (2.0 mmoles) of thioamide XII [1] was suspended in a solution of 0.07 g (3.0 mmoles) of sodium in 30 ml of absolute ethanol, and after 30 min 0.43 g (3.0 mmoles) of methyl iodide was added. The reaction mixture was stirred for 3 h at room temperature, water was added, the precipitate was filtered off and crystallized from ethanol. Dark-red crystals, yield 62%, mp 144-147°C (dec.), Rf(C) 0.8.

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