SYNTHESIS OF ESTERS OF SUBSTITUTED 3-AMINOPYRROLE-2-CARBOXYLIC ACIDS FROM THIOACRYLAMIDES AND GLYCINE ESTERS*

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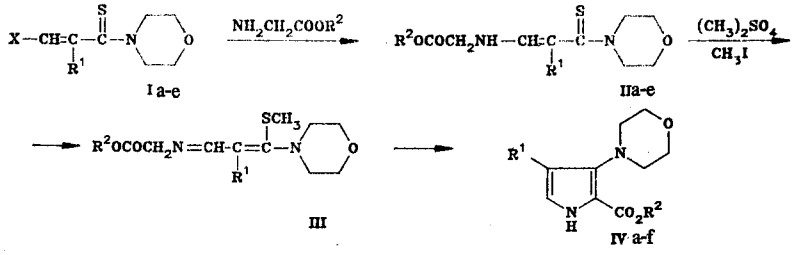
Morpholides of 3-[(alkoxycarbonylmethyl)amino]thioacrylic acids and esters of 3-morpholinopyrrole-2-carboxylic acids have been obtained from glycine esters and morpholides of 3-hydroxy- and 3-(dimethylamino)thioacrylic acids.

Morpholides of 3-hydroxy and 3-aminothiocarboxylic acids (I) are readily obtained by the iminoformylation of thioacetomorpholides [2]. We have shown [3] that the amino and hydroxy groups at the $C_{(3)}$ atom in the amides (I) are readily replaced by residues of amines and hydrazines. In the latter case, as the result of cyclization of the 3-hydrazinothioacrylmorpholides with the evolution of hydrogen sulfide it is possible to obtain 5-morpholinopyrazoles [2].

The aim of the present work was to obtain pyrroles in a similar manner from the thioamides (I) and aminoacetic acid esters. In boiling methanol, the group X of the thioamides (I) is readily replaceable by a residue of the amino acid ester through its amino group, forming with high yields the bright yellow morpholides of 3-[(alkoxycarbonylmethyl)amino] thioacrylic acids. In contrast to the 3-hydrazinothioacrylamides the thioamides (II) did not undergo intramolecular cyclization with the formation of the corresponding pyrrolecarboxylic acid esters (IV) in the presence of bases. The base obviously acts not on the methylene group but on the nitrogen atom of the glycine residue. The methylation of the sulfur atom with dimethyl sulfate or methyl iodide led to the formation of methylthio derivatives with a single mobile hydrogen atom at the methylene group. Intramolecular cyclization was carried out, without previous purification of the methylthio compounds, by the addition of a sodium alcoholate or triethylamine to the reaction mixture.



Ia, c–e X=$(CH_3)_2N$, b X=OH; Ia, b, IIa, b, IVa, b $R^1=C_6H_5$, Ic, IIc, IVc, d R^1= =4-$CH_3C_6H_4$; Id, IId, IVe R^1=4-$CH_3OC_6H_4$; Ie, IIe, IVf R^1=4-ClC_6H_4; IIa, d, e, IVa, c, e, f $R^2=CH_3$, IIb, c, IVb, d $R^2=C_2H_5$

Under these conditions, with the evolution of methyl mercaptan, esters of 3-morpholinopyrrole-2-carboxylic acids (IV) were formed. The structure of the pyrroles (IV) and of the thioamides (II) was confirmed by PMR and mass spectroscopy. The introduction of a methyl substituent into the amino group of the glycine ester prevented a reaction with the thioamide (I) leading to the formation of 1-methylpyrroles, although in similar syntheses of pyrroles

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TABLE 1. Morpholides of 3-[(Alkoxycarbonylmethyl)amino]-thioacrylic Acids (II)

Compound	mp*, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IIa†	147—149	60,0	6,3	8,7	10,0	$C_{16}H_{20}N_2O_3S$	60,0	6,3	8,7	10,0	80
IIb‡	131—133	61,0	6,6	8,4	9,6	$C_{17}H_{22}N_2O_3S$	61,0	6,6	8,4	9,6	87
IIc‡	132—134	62,0	7,0	8,0	9,2	$C_{18}H_{24}N_2O_3S$	62,0	7,0	8,0	9,2	96
IId**	158—160	58,3	6,2	8,0	9,2	$C_{17}H_{22}N_2O_4S$	58,3	6,2	8,0	9,2	49
IIe	148—150	54,2	5,4	7,9	9,0	$C_{16}H_{19}ClN_2O_3S$	54,2	5,4	7,9	9,0	90

*Compounds (IIa-d) were crystallized from methanol and (IIe) from propan-2-ol.

†Mass spectrum: m/z 320, 287, 234, 233, 232 (100%), 231, 199, 174, 157, 147, 130, 102.

‡PMR spectrum ($CDCl_3$), ppm (IIb): 1.19 (3 H, t, CH_3); 3,49 (4 H, m, CH_2); 3.81 (2 H, d, CH_2); 3.81 (4 H, m, CH_2); 4.08 (2 H, q, CH_2); 5.33 (1 H, m, NH); 6.38 (1 H, d, CH); 7.09 (5 H, m, C_6H_5); (IIc): 1.19 (3 H, t, CH_3); 2.19 (3 H, s, CH_3); 3.50 (4 H, m, CH_2); 3.84 (4 H, m, CH_2); 3.80 (2 H, d, CH_2); 4.08 (2 H, q, CH_2); 5.28 (1 H, m, NH); 6.94 (4 H, s, C_6H_4); 6.26 (1 H, d, CH).

**UV spectrum (in acetonitrile), λ_{max}, nm (log ε): 259 (3.98); 294 (4.38); 382 (3.10).

TABLE 2. Esters of 3-Morpholinopyrrole-2-carboxylic Acids (IV)

Compound	mp*, °C	Found, %			Empirical formula	Calculated, %			Yield, % (method of preparation)
		C	H	N		C	H	N	
IVa†	179—181	67,0	6,2	9,5	$C_{16}H_{18}N_2O_3$	67,1	6,4	9,8	84 (A)
IVb	171—172	68,2	6,8	9,1	$C_{17}H_{20}N_2O_3$	68,0	6,7	9,3	93 (B)
IVc	149—151	68,2	6,5	9,4	$C_{17}H_{20}N_2O_3$	68,0	6,7	9,3	53 (A)
IVd	173—175	68,7	7,4	8,6	$C_{18}H_{22}N_2O_3$	68,8	7,1	8,9	71 (B)
IVe	158—159	64,6	6,4	8,7	$C_{17}H_{20}N_2O_4$	64,5	6,4	8,9	51 (B)
IVf	191—193	60,2	5,4	8,3	$C_{16}H_{17}ClN_2O_3$	59,9	5,4	8,7	51 (A) 63 (B)

*Compounds (IVa, c, e, f) were crystallized from methanol, and (IVb and d) from ethanol.

†PMR spectrum ($CDCl_3$), ppm: 2.93 (4 H, m, CH_2); 3.61 (4 H, m, CH_2); 3.70 (3 H, s, CH_3); 6.68 (1 H, d, CH); 7.25 (5 H, m, C_6H_5); 9.32 (1 H, br. signal, NH). Mass spectrum: m/z 286, 271, 255, 254, 242, 227, 225, 223, 197, 196, 195 (100%), 169, 168, 167, 140, 128, 115.

[4-12] esters of N-methylglycine have sometimes given better results than the unmethylated esters. In our case, after the reaction had been performed, only the starting materials were isolated.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-487C spectrometer (80 MHz) with HMDS as internal standard. Electronic spectra were obtained on a Specord UV-vis spectrometer in acetonitrile at a concentration of the solution of ~10^{-4} M, and mass spectra on a Varian MAT-CH6 spectrometer.

General Procedure for Obtaining Compounds (IIa-e) (Table 1). A solution of 10 mmoles of 3-(dimethylamino)thioacrylic acid morpholide perchlorate (or free 3-hydroxythioacrylic acid morpholide), 10 mmoles of glycine ester hydrochloride, and 20 mmoles of triethylamine in 20 ml of methanol was boiled for 5 min and was poured into ice water. The bright-yellow precipitate of compound (II) was filtered off.

General Procedure for Obtaining the Pyrroles (IVa-f) (Table 2). A. A solution of 10 mmoles of a morpholide (II) and 15 mmoles of dimethyl sulfate in 20 ml of chloroform was boiled for 15 min. After the chloroform had been evaporated off, the residue was dissolved in 20 ml of the alcohol corresponding to the ester and the solution was heated in the boiling water bath for 5 min. Then it was poured into ice water and the colorless crystals of the pyrrole (IV) that deposited were filtered off.

B. A solution of 10 mmoles of the morpholide (II) and 15 mmoles of methyl iodide in 20 ml of the alcohol corresponding to the ester was heated under reflux in the boiling water bath for 20 min. Then 15 mmoles of ethylamine was added to the reaction mixture and heating was continued for 5 min. The solution was poured into ice water and the precipitate of the pyrrole (IV) was filtered off.

LITERATURE CITED

1. J. Liebscher, E. Mitzner, A. Knoll, and H. Z. Hartmann, Z. Chem., 23, 405 (1983).
2. J. Liebscher and A. Berhanu, Synthesis, No. 10, 769 (1982).
3. L. Liebscher, A. Alemayehu, and A. Berhanu, J. Prakt. Chem., 325, 689 (1983).
4. S. Hauptmann, M. Weissenfels, M. Scholz, E.-M. Werner, H.-J. Kohler, and J. Weisflog, Tetrahedron Lett., No. 11, 1317 (1968).
5. S. Hauptmann, M. Scholz, H.-J. Köhler, and H.-J. Hofmann, J. Pract. Chem., 311, 614 (1969).
6. S. Hauptmann, A. Hantschmann, and M. Scholz, Z. Chem., 9, 22 (1969).
7. J.-M. Weber, D. Cagniant, P. Cagniant, and G. Kirsch, J. Heterocycl. Chem., 20, 61 (1983).
8. T. Momose, T. Tamaha, T. Yokota, N. Nagamobo, and K. Yamada, Chem. Pharm. Bull., 26, 2224 (1978).
9. T. Momose, T. Tamaha, and T. Yokota, J. Heterocycl. Chem., 16, 1821 (1977).
10. M.-J. Lim, R.-S. Klein, and J. J. Fox, J. Org. Chem., 44, 3826 (1979).
11. K. Gewald, H. Schäfer, and E. Schindler, GDR Patent No. 138,976; Chem. Abstr., 93, 71547 (1981).
12. S. Mataka, K. Takashi, Y. Tsuda, and M. Tashiro, Synthesis, No. 2, 157 (1982).