These pathways are the successive detachment from M^+ of two or three hydrogen atoms in the case of compounds with functional or hydrocarbon substituents. In addition, competitive splitting out of HCN and a substituent from M^+, as well as CN and HCN particles from the principal rearranged ions, is observed.

EXPERIMENTAL

The mass spectra of I-VIII were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples into the ion source at ionizing-electron energies of 50 and 12 eV, a cathode emission current of 1.5 mA, an accelerating voltage of 2 kV, and a vaporization temperature of 140-160°C. The benzimidazoles were obtained by the methods in [4, 11]. 2-Phenylbenzimidazole with a deuterium label at the nitrogen atom was obtained by the method in [12]. The degree of exchange determined by mass spectrometry was 50%.

LITERATURE CITED

1. W. Pool, H. Harwood, and Ralstone, J. Am. Chem. Soc., 59, 178 (1937).
2. E. Brown and N. Campbell, J. Chem. Soc., No. 4, 1699 (1938).
3. R. Elderfield (editor), "Benzimidazoles," in: Heterocyclic Compounds, Vol. 5, Wiley.
4. Benzimidazoles. Review Information, Series: The Manufacture of Monomers [in Russian], Scientific-Research Institute of Technical and Economic Research of the State Committee of the Council of Ministers of the USSR for Chemistry, Moscow (1978).
5. S.-O. Lawesson, E. Schroll, J. H. Bowie, and R. G. Cooks, Tetrahedron, 24, 1875 (1968).
6. R. A. Khmel'nitskii, A. P. Krasnoshchek, and V. I. Vysotskii, Izv. Timiryazev. Sel'skokhoz. Akad., No. 6, 178 (1968).
7. R. A. Khmel'nitskii, A. N. Kost, K. Kondal-Reddi, and V. I. Vysotskii, Zh. Org. Khim., 5, 1153 (1969).
8. R. A. Khmel'nitskii, Yu. A. Efremov, and N. V. Fedyainov, Izv. Timiryazev. Sel'skokhoz. Akad., No. 3, 199 (1978).
9. T. Nishiwaki, J. Chem. Soc., C, No. 4, 428 (1968).
10. Amer. Petrol. Inst. Res. Project 44, Mass Spectral Data, New York (1952-1967).
11. P. N. Preston, Chem. Rev., 74, 279 (1974).
12. A. M. Bellocq, C. Perchard, A. Novak, and M.-L. Josien, J. Chem. Phys., 62, 1334 (1965).

REACTION OF CYCLIC THIOUREAS WITH CHLOROACYLPIPERAZINES

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S-Alkylation products are formed in the reaction of tetrahydropyrimidine-2-thione and hexahydro-1,3-diazepine-2-thione with chloroacylpiperazines in dimethylformamide at room temperature; dihydrothiazolo[3,2-a]pyrimidine and tetrahydrothiazolo[3,2-a]-[1,3]diazepine systems are obtained in refluxing ethanol. It is shown that the S-alkyl derivatives are very readily converted to condensed systems.

In a continuation of our research on the synthesis of new substances with hypotensive properties we have synthesized a number of different piperazine derivatives that contain pharmacophoric residues, viz., aminoalkyl, methoxybenzoyl, hydroxyaminoalkyl, and diphenylcarbamoyl. The next step in our research was to obtain piperazine compounds with an isothioureide residue, which is bioisosteric with respect to the guanidine grouping [1, 2].

We have previously accomplished the synthesis of imidazolinylthio- and benzimidazolylthioacylpiperazines by the reaction of imidazolidine-2-thione and benzimidazole-2-thione with chloroacylpiperazines in refluxing absolute ethanol [11].

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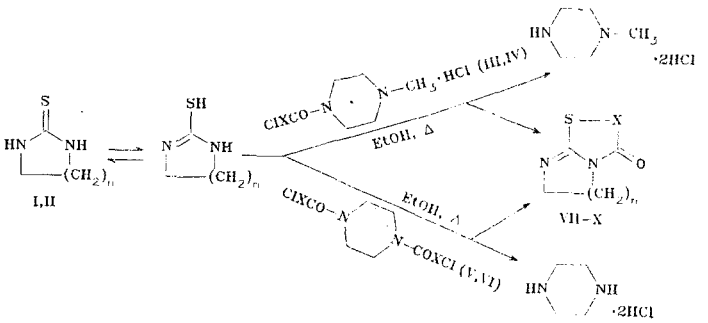
In the present communication we present the results of an investigation of the reaction of cyclic thioureas [tetrahydropyrimidine-2-thione (I) and hexahydro-1,3-diazepine-2-thione (II)] with chloroacylpiperazines [1-methyl-4-chloroacetylpiperazine hydrochloride (III), 1-methyl-4-(2-chloropropionyl)piperazine hydrochloride (IV), 1,4-bis(chloroacetyl)piperazine (V), and 1,4-bis(2-chloropropionyl)piperazine (VI)] in refluxing absolute ethanol – under conditions similar to those in the reaction of benzimidazole- and imidazolidine-2-thione.

According to the rules of Pearson and Sonstad [3], S-alkyl derivatives are formed in the reaction of tautomeric thioureas containing two nucleophilic donor centers (nitrogen and sulfur atoms) with alkylating reagents, viz., chloroacylpiperazines. This is precisely what we observed in the reaction of these reagents with imidazolidine-2-thione and benzimidazole-2-thione.

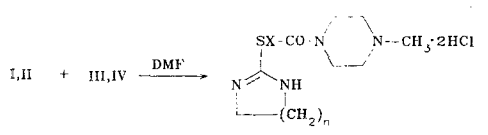
The products of the reaction of thioureas I and II with chloroacylpiperazines in ethanol were not the expected S-alkylated derivatives but rather dihydrothiazolo[3,2-a]pyrimidines VII and VIII and tetrahydrothiazolo[3,2-a][1,3]diazepines IX and X, in addition to the hydrochlorides of the corresponding amines.



I, VII, VIII n=2; II, IX, X n=3; III, V, VII, IX X=> CH_2; IV, VI, VIII, X X=> CH—CH_3

2H,5H-6,7-Dihydrothiazolo[3,2-a]pyrimidin-3(2H)-one (VII), 2H-5,6,7,8-tetrahydrothiazolo[3,2-a][1,3]diazepin-3(2)-one (IX), and the corresponding 2-methyl derivatives VIII and X are formed extremely readily. Complete conversion of the starting substances occurs under the indicated conditions 5-20 min from the instant of homogenization of the reaction mixture in refluxing ethanol (the cyclic thioureas do not dissolve in ethanol at room temperature, and the mixture is initially heterogeneous). The melting points, results of elementary analysis, and data from the IR and PMR spectra are in agreement with the corresponding data for the dihydrothiazolopyrimidines obtained in [4] by the reaction of tetrahydropyrimidine-2-thione with halo esters, as well as by the reaction of this thione with halides of halo acids [5] and tetrahydrothiazolodiazepines synthesized by the reaction of hexahydro-1,3-diazepine-2-thione with halo esters [6].

The 2-tetrahydropyrimidinylthioacylpiperazines and 2-tetrahydro-1,3-diazepinothioacylpiperazines of interest to us are formed in high yields when the reaction is carried out in anhydrous dimethylformamide (DMF) at room temperature.

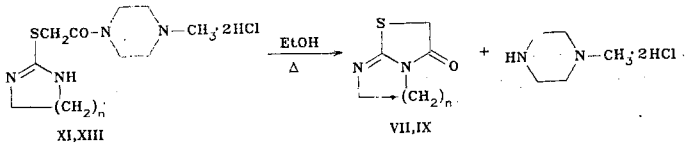


XI, XII n=2; XIII, XIV n=3; XI, XIII X=CH_2; XII, XIV X=$CHCH_3$

The individuality and structures of the S-alkyl compounds obtained were confirmed by the results of elementary, chromatographic, and spectral analysis. The IR spectra of XI-XIV are characterized by the presence of an absorption band at 1620-1640 cm^{-1}, which corresponds to the stretching vibrations of an amide bond (N—C=O). The intense absorption band at 1550-1570 cm^{-1} corresponds to the vibrations of the C=N bond. The bands that are characteristic for ammonium salts have frequencies of 2400-2700 cm^{-1}. 1-Methyl-4-(2-tetrahydropyrimidinylthioacetyl)piperazine dihydrochloride (XI) was refluxed in absolute ethanol for 5 min. Dihydrothiazolopyrimidine VII and N-methylpiperazine dihydrochloride were isolated from the reaction mixture.

TABLE 1. Properties of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %	Reaction time, h
		C	H	N		C	H	N		
XI	216—218	39,9	6,7	16,8	$C_{11}H_{22}Cl_2N_4OS$	40,1	6,7	17,0	80	2
XII	191—193	42,6	6,8	16,1	$C_{12}H_{24}Cl_2N_4OS$	42,0	7,0	16,3	54	4
XIII	200—201	42,1	6,9	16,1	$C_{12}H_{24}Cl_2N_4OS$	42,0	7,0	16,3	58	2
XIV	212—213	43,4	7,2	15,3	$C_{13}H_{26}Cl_2N_4OS$	43,7	7,3	15,7	62	4



XI,XIII VII,IX

Similarly, dihydrochloride XIII is converted to tetrahydrothiazolodiazepine IX and a salt of the amine when it is refluxed in ethanol.

The results obtained in this research make it possible to propose a mechanism for the reaction of cyclic thioureas with chloroacylpiperazines in refluxing ethanol. The reaction probably proceeds through the formation of an S-alkyl derivative. The hydrogen chloride present in the reaction medium catalyzes ethanolysis [7] of the amide bond. This results in the formation of a salt of the amine and an ester, which then undergo intramolecular cyclization to give the two-ring compounds.

On the basis of the results that we obtained it may be concluded that perhydrothiazolone has a particularly strong tendency to form condensed systems with tetrahydropyrimidine and tetrahydro-1,3-diazepine.

EXPERIMENTAL

The melting points are indicated without correction. The PMR spectra of solutions of the compounds in D_2O were recorded with a Varian 60 MHz spectrometer with tetramethylsilane as the internal standard. The IR spectra of KBr pellets were recorded with a Unicam SP-200G spectrometer. Thin-layer chromatography (TLC) was carried out on glass plates (5.5 by 2.5 cm) coated with silica gel G (Merck) in a chloroform–acetone system (7:3) with development with iodine vapors.

The starting compounds were obtained as follows: hexahydropyrimidine-2-thione (I) from 1,3-diaminopropane and carbon disulfide by the method in [8], hexahydro-1,3-diazepine-2-thione (II) from 1,4-diaminobutane and carbon disulfide by the method in [9], 1-methyl-4-chloroacetylpiperazine hydrochloride (III) from 1-methylpiperazine and chloroacetyl chloride, and 1-methyl-4-(2-chloropropionyl)piperazine hydrochloride (IV) from 1-methylpiperazine and 2-chloropropionyl chloride by the method in [10]. 1,4-Bis(chloroacetyl)piperazine (V) and 1,4-bis(2-chloropropionyl)piperazine (VI) were obtained by the method in [11] from the corresponding halo acid halides and anhydrous piperazine.

2H,5H-6,7-Dihydrothiazolo[3,2-a]pyrimidin-3(2H)-one (VII). A mixture of 1.6 g (0.01 mole) of tetrahydropyrimidine-2-thione (I) and 2.13 g (0.01 mole) of 1-methyl-4-chloroacetylpiperazine hydrochloride (III) was refluxed for 5 min in 20 ml of absolute ethanol, after which the solvent was removed *in vacuo*, 40 ml of ether was added to the residue, and the mixture was refluxed for 10 min. The precipitate was removed by filtration and washed with ether to give 0.23 g of 1-methylpiperazine dihydrochloride with mp 241-242°C. The ether filtrate was evaporated to dryness, and the residue was allowed to stand at 0°C for 17 h to give 1.3 g (81%) of 2H,5H-6,7-dihydrothiazolo[3,2-a]pyrimidin-3(2H)-one (VII) with mp 57-58°C.

The similar reaction of thiourea I with hydrochloride IV gave 2-methyl-2H,5H-6,7-dihydrothiazolo[3,2-a]pyrimidin-3(2H)-one (VIII) with mp 64-65°C.

The reaction of thiourea II with hydrochloride III gave 2H-5,6,7,8-tetrahydrothiazolo-[3,2-a][1,3]diazepin-3(2H)-one (IX) with mp 90-93°C, whereas the reaction of thiourea II with hydrochloride IV gave 2-methyl-5,6,7,8-tetrahydrothiazolo[3,2-a][1,3]diazepin-3(2H)-one (X) with mp 110-111°C.

2-Methyl-5,6,7,8-tetrahydrothiazolo[3,2-a][1,3]diazepin-3(2H)-one (XI). A mixture of 2.62 g (0.02 mole) of hexahydro-1,3-diazepine-2-thione (II) and 2.67 g of 1,4-bis(2-chloropropionyl)piperazine was refluxed in absolute ethanol for 5 min, after which the mixture was cooled and filtered to give 1.4 g of piperazine dihydrochloride with mp 337°C. The filtrate was evaporated *in vacuo*, and the residue was washed with water to give 2.4 g (65%) of 2-methyl-5,6,7,8-tetrahydrothiazolo[3,2-a][1,3]diazepin-3(2H)-one (X) with mp 110-111°C (chloroform–hexane).

Similarly, the reaction of thiourea II with 1,4-bis(chloroacetyl)piperazine gave IX, whereas the reaction of thiourea I with piperazines V and VI gave VII and VIII, respectively.

1-Methyl-4-(2-tetrahydropyrimidinylthioacetyl)piperazine Dihydrochloride (XI). A mixture of 1.76 g (0.015 mole) of tetrahydropyrimidine-2-thione (I) and 3.2 g (0.015 mole) of 1-methyl-4-chloroacetylpiperazine hydrochloride (III) in 10 ml of dry DMF was stirred until the solids dissolved (30 min), and the solution was allowed to stand at room temperature for 2 h. The precipitated crystals were removed by filtration and washed with ether to give 3.9 g (80%) of a product with mp 216-218°C (from methanol–ether cooled to 0°C). IR spectrum: 1630 (C=O), 1610 (C=N), and 2420-2700 cm^{-1} ($\overset{+}{N}HCH_3$). PMR spectrum (D_2O): 1.9 (2H, m, CH_2), 2.88 (3H, s, N–CH_3), 3.2-3.8 (12H, m, N–CH_2), and 4.2 ppm (2H, s, S–CH_2–CO). Similarly, the reaction of thiourea II with hydrochloride III gave 1-methyl-4-(2-tetrahydro-1,3-diazepinylthioacetyl)piperazine dihydrochloride (XIII).

1-Methyl-4-[(2-tetrahydro-1,3-diazepinylthio)methyl]acetylpiperazine Dihydrochloride (XI). A mixture of 1.3 g (0.01 mole) of hexahydro-1,3-diazepine-2-thione (II) and 2.27 g (0.01 mole) of 1-methyl-4-(2-chloropropionyl)piperazine hydrochloride in 7 ml of dry DMF was maintained at room temperature for 4 h, after which 70 ml of ether was added, and the mixture was allowed to stand at 0°C for 16 h. The resulting crystals were removed by filtration and washed with ether to give 2.2 g (62%) of a product with mp 212-213°C. IR spectrum: 1635 (C=O), 1600 (C=N), and 2480-2700 cm^{-1} ($\overset{+}{N}HCH_3$). PMR spectrum (D_2O): 1.5 (3H, d, CH–CH_3), 1.8 (4H, m, CH_2), 2.9 (3H, s, N–CH_3), 3.3-3.7 (12H, m, N–CH_2), and 3.98 ppm (1H, q, CH–CH_3).

The reaction of thiourea I with hydrochloride IV was carried out similarly to give 1-methyl-4-[(2-tetrahydropyrimidinylthio)methyl]acetylpiperazine dihydrochloride (XII).

2H,5H-6,7-Dihydrothiazolo[3,2-a]pyrimidin-3(2H)-one (VII). A 1-g (0.003 mole) sample of 1-methyl-4-(2-tetrahydropyrimidinylthioacetyl)piperazine dihydrochloride was refluxed in 5 ml of absolute ethanol for 5 min, after which the mixture was cooled, treated with 60 ml of dry ether, and filtered to give 0.4 g (77%) of 1-methylpiperazine dihydrochloride with mp 243°C. The filtrate was evaporated, and the residue was extracted with ether (two 30-ml portions). The solvent was removed, and the residue was crystallized from hexane to give 0.3 g (56%) of a product with mp 57-58°C, which was identical to the product obtained by the method in [6].

LITERATURE CITED

1. C. W. Thornber, Chem. Soc., Rev., 8, 563 (1979).
2. P. B. W. Timmermans and P. A. van Zwieten, J. Med. Chem., 25, 1389 (1982).
3. R. G. Pearson and J. Songstad, J. Am. Chem. Soc., 89, 1827 (1967).
4. H. S. Chandhary and H. K. Pujari, Indian J. Chem., 10, 766 (1972).
5. S. Groszkowski and M. Skopinska-Szmidt, Polish Patent No. 104845; Chem. Abstr., 95, 81018y (1981).
6. K. Chadha Vijay, H. S. Chandhary, and H. K. Pujari, Aust. J. Chem., 22, 2679 (1969).
7. B. C. Challis and J. A. Chalis, in: Comprehensive Organic Chemistry, Vol. 2, edited by M. O. Sutherland, Pergamon Press, Oxford–New York (1979), p. 957.
8. A. F. McKay and W. G. Hatton, J. Am. Chem. Soc., 78, 1618 (1965).
9. A. F. McKay and M. E. Kreling, Can. J. Chem., 35, 1438 (1957).
10. A. G. Caldwell, L. P. Wallis, and P. L. Barret, West German Patent No. 139504; Chem. Abstr., 58, 13968 (1963).
11. S. Groszkowski, Roczn. Chem., 38, 229 (1964).