SYNTHESIS OF NOVEL THIAZOLES BEARING HYDRAZINE, THIOSEMICARBAZIDE, THIAZOLE, AND THIAZOLIDINONE MOIETIES

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UDC 542.91:547.789

Thiazolecarboxylate esters (I) and (II) react with hydrazine hydrate to give the acid hydrazides (III) and (IV), which then react with KSCN and PhNCS to give high yields of the thiosemicarbazides (V)-(VIII). Cyclocondensation of the thiosemicarbazide (V) with 3-phenyl-3-chloro-2-oxopropionic acid derivatives gives compounds with two thiazole moieties (IX)-(XIV). The reaction of the phenylthiosemicarbazides (VII) and (VIII) with chloroacetyl chloride and (or) chloroacetic acid affords the thiazolidinonethiazoles (XV) and (XVI).

Some thiazoles display high biological activity [1, 2]. It was therefore of interest to obtain novel compounds with thiazole moieties. We here report the synthesis of such compounds, by successive reactions of fucntionally substituted 5-phenylthiazoles.

Reaction of methyl 3-phenyl-3-chloro-2-oxopropionate with the appropriate thioamides has given the 2-substituted 4-methoxycarbonyl-5-phenylthiazoles (I) and (II) [3], which on heating with excess hydrazine hydrate in ethanol afford the thiazolecarbohydrazides (III) and (IV). Reaction of (III) and (IV) with potassium thiocyanate in hydrochloric acid has given the thiazolecarboxylic acid thiosemicarbazides (V) and (VI), and with phenyl isothiocyanate in absolute ethanol on boiling for 4 h, the phenylthiosemicarbazides (VII) and (VIII). Replacement of the methyl group in the 2-position of thiazole (V) by phenyl has a marked effect on the chemical shifts (CS) of the amino-group protons in the PMR spectra of (V) and (VI), the broadened singlet for the $H_2NC(S)$ group being shifted from 3.36 to 7.46 ppm, while the protons of the C(S)NHNHC(O) group are scarcely affected (see Experimental). In the IR spectra of (V) and (VI), the absorption bands (AB) in the 1300-1700 cm^{-1} region are virtually identical, whereas in the 3150-3450 cm^{-1} region, the AB due to N–H stretching vib-

TABLE 1. Spectral (IR and PMR) Data for Hydrazides of 5-Phenylthiazolecarboxylic Acid

Compound	IR spectrum (ν, cm^{-1}, vaseline paste)	PMR spectrum (δ, ppm, $CDCl_3$).
(IX)	1700 (C=O amide), 1725 (C=O ester), 3075, 3150 (NH bonded)	2,63 s (CH_3), 3,63 s (OCH_3), 7,06–7,56 m ($2C_6H_5$, 2NH)
(X)	1710 (C=O, sh), 3060, 3170 (NH bonded); 3370 (NH_2 free)	1,10 t (CH_3 in OCH_2CH_3), 2,63 s (CH_3), 4,03 q (CH_2 in OCH_2CH_3), 7,00–7,63 m ($2C_6H_5$, NH), 11,00 br.s (HNC(O))
(XI)	1700 (C=O amide), 1715 (C=O ester), 3075, 3135 (NH bonded), 3390 (NH_2 free)	0,66 t (CH_3 in $OCH_2CH_2CH_3$), 1,06–1,66 m (CH_2 in $OCH_2CH_2CH_3$), 2,63 s (CH_3), 3,30 t (OCH_2 in $OCH_2CH_2CH_3$), 7,06–7,63 m ($2C_6H_5$, NH), 11,00 br.s (HNC(O))
(XII)	1710 (C=O, sh), 3075, 3160 (NH bonded); 3365 (NH free)	1,00 d ($2CH_3$ in $OCH(CH_3)_2$), 2,63 s (CH_3), 4,63–5,16 m (CH in $OCH(CH_3)_2$), 7,00–7,56 m ($2C_6H_5$, NH), 11,00 br.s (HNC(O))
(XIII)	1700 (C=O amide), 1715 (C=O ester), 3075, 3135 (NH bonded), 3390 (NH free)	0,66 d ($2CH_3$ in $OCH_2CH(CH_3)_2$), 1,30–2,00 m (CH in $OCH_2CH(CH_3)_2$), 2,63 s (CH_3), 3,80 d (OCH_2), 7,03–7,63 m ($2C_6H_5$, NH), 16,13 br.s (HNC(O))
(XIV)	1670 (C=O amide), 3200 (NH free)	0,76 and 1,06 2 t ($2CH_3$ in $(CH_3CH_2)_2N$), 2,63 s (CH_3), 2,76–3,63 m ($2CH_2$ in $(CH_3CH_2)_2N$), 7,00–7,63 m ($2C_6H_5$, NH), 9,50 br.s (HNC(O))

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Science Center, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2832-2836, December, 1991. Original article submitted August 1, 1990.

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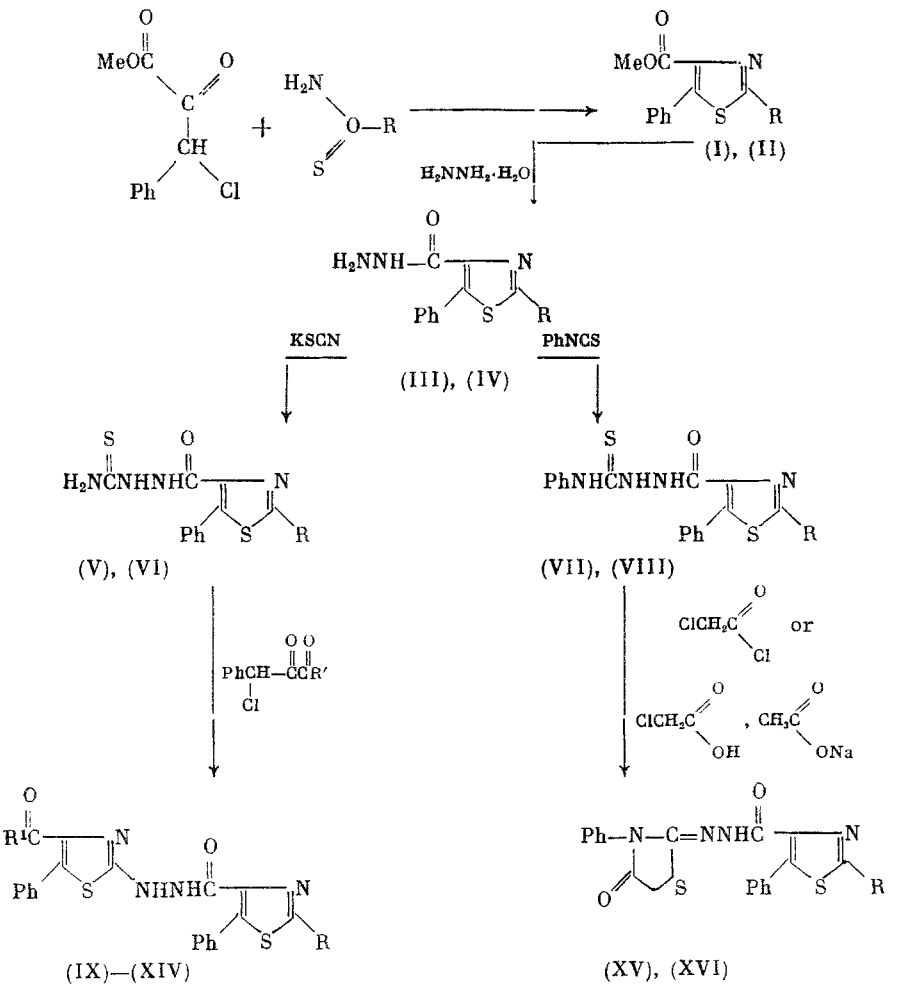

R = Me (I), (III), (V), (VII), (XV); Ph (II), (IV), (VI), (VIII), (XVI); R = = Me, R^1 = OMe (IX); R = Me, R^1 = OEt (X); R = Me, R^1 = OPr (XI); R = Me, R^1 = OPr-*i* (XII); R = Me, R^1 = OBu-*i* (XIII); R = Me, R^1 = NEt_2 (XIV).

rations in the $H_2NC(S)NHNH$ group are different. The thiosemicarbazide (VI) shows three characteristic AB at 3180, 3300, and 3440 cm^{-1}, whereas in the spectrum of (V) AB are present at 3150, 3190, 3270, 3330, and 3430 cm^{-1}. One method used to introduce thiazole and thiazolidine moieties into a molecule is by reaction of thiosemicarbazides with α-haloketones. There are literature reports of thiosemicarbazides with 4-chlorophenyl [4], 2,4-dichlorophenyl [5, 6], salicyl [7], (1H-benzotriazolo)methylcarboxy [8], and benzofuran groups [9]. There have, however, been no reports of such reactions with thiosemicarbazides having thiazole substituents. The presence in the 4-position of thiazoles (V)-(VIII) of a thiosemicarbazide or phenylthiosemicarbazide residue enables new heterocyclic moieties to be introduced into the molecule. It has been found that the reaction of 2-methyl-5-phenylthiazolecarboxylic acid 1'-thiosemicarbazide (V) with functionally substituted α-chloroketones, recently obtained by the authors [10], is of the Hansch type, giving 2-[2'(2"-methyl-5"-phenylthiazolecarbonyl)hydrazo]-5-phenylthiazolecarboxylic acids (IX)-(XVI). The IR and PMR spectral features of (IX)-(XIV), together with their yields and physical properties, are shown in Tables 1 and 2.

The introduction of a thiazolidine ring into the 4-position of (VII) and (VIII) was effected in two ways, namely by reacting phenylthiosemicarbazides (VII) and (VIII) with chloroacetyl chloride in boiling dichloromethane, or with chloroacetic acid in the presence of sodium acetate in ethanol. When the reaction was carried out with chloroacetyl chloride, the yields of the products, N-(3'-phenyl-4'-oxo-1',3'-thiazolidin-2'-ylidene)hydrazides of 2-methyl(or phenyl)-5-phenylthiazoline-4-carboxylic acid (XV, XVI), were 20-25% greater.

The structures and compositions of all the products (III)-(XVI) were confirmed by IR and PMR spectroscopy, and by elemental analysis.

TABLE 2. Physicochemical Data of Hydrazides of 5-Phenylthiazolecarboxylic Acid

Compound	Yield, %	Solvent for recrystallization	Mp, °C	Found/Calculated, %				Empirical formula
				C	H	N	S	
(IX)	71	Ethanol	221–222	57,34 58,67	3,99 3,99	12,33 12,43	14,29 14,23	$C_{22}H_{18}N_4O_3S_2$
(X)	67	Acetone	191–192,5	58,95 59,48	4,27 4,30	12,15 12,05	13,76 13,80	$C_{23}H_{20}N_4O_3S_2$
(XI)	73	Acetone	194–195	59,85 60,15	4,45 4,59	11,67 11,70	13,35 13,40	$C_{24}H_{22}N_4O_3S_2$
(XII)	69	Acetone	188–190	59,90 60,25	4,48 4,59	11,75 11,70	13,46 13,40	$C_{24}H_{22}N_4O_3S_2$
(XIII)	63	Acetone	171–172,5	60,45 60,98	4,77 4,87	11,35 11,37	13,00 13,02	$C_{25}H_{24}N_4O_3S_2$
(XIV)	77	Washed with ether	97–98	65,00 65,36	5,49 5,44	15,35 15,24	6,72 6,98	$C_{25}H_{25}N_5O_2S_2$

EXPERIMENTAL

PMR spectra were recorded on a Varian T-60 spectrometer (internal standard TMS), and IR spectra on a UR-20 spectrometer (Vaseline paste).

Methyl 2-Methyl-5-phenylthiazolecarboxylate (I). A solution of 42.4 g (0.2 mole) of methyl 3-phenyl-3-chloro-2-oxopropionate and 15.0 g (0.2 mole) of thioacetamide in 150 ml of ethanol was boiled with stirring for 3 h. The ethanol was then removed under reduced pressure, and the residue treated with 100 ml of 5% aqueous sodium bicarbonate, and extracted with ether (3 × 100 ml). The organic layer was dried over $MgSO_4$, the ether removed, and the residue recrystallized from hexane to give 33 g (82%) of (I), mp 80-81.5°C. IR spectrum (ν, cm^{-1}): 1715 (C=O). PMR spectrum (δ, ppm, CCl_4): 2.63 s (CH_3), 3.66 s (OCH_3), 7.10-7.33 m (C_6H_5). Found, %: C 61.71, H 4.72, N 5.90, S 13.71. $C_{12}H_{11}NO_2$. Calculated, %: C 61.80, H 4.71, N 6.00, S 13.74.

Methyl 2,5-Diphenylthiazolecarboxylate (II) was obtained as for (I), yield 87%, mp 89-90°C. IR spectrum (ν, cm^{-1}): 1720 (C=O). PMR spectrum (δ, ppm, $CDCl_3$): 3.83 s (OCH_3), 7.23-8.00 m ($2C_6H_5$). Found, %: C 69.49, H 4.44, N 4.83, S 10.74. $C_{17}H_{13}NO_2S$. Calculated, %: C 69.17, H 4.71, N 4.74, S 10.84.

2-Methyl-5-phenylthiazolecarbohydrazide (III). A mixture of 35 g (0.15 mole) of the thiazole (I) and 60 ml of 60% hydrazine hydrate was boiled in ethanol for 5 h, until the solution became colorless. The solid which separated on cooling was filtered off, air-dried, and recrystallized from acetonitrile to give 21 g (60%) of (III), mp 127-129.5°C. IR spectrum (ν, cm^{-1}): 1660 (C=O), 3160, 3225, 3255, 3315 ($NHNH_2$). PMR spectrum (δ, ppm, $CDCl_3$): 2.60 s (CH_3), 3.76 br.s ($NHNH_2$), 6.96-7.50 m (C_6H_5). Found, %: C 56.57, H 4.70, N 18.12, S 13.75. $C_{11}H_{11}N_3OS$. Calculated, %: C 56.65, H 4.71, N 18.01, S 13.74.

Obtained similarly was 2-phenyl-5-phenylthiazolecarbohydrazide (IV). Recrystallized from acetonitrile, mp 171-172°C. IR spectrum (ν, cm^{-1}): 1680 (C=O), 3215, 3265, 3332, 3410 ($NHNH_2$). PMR spectrum [δ, ppm, $C(CD_3)_2SO$]: 4.43 br.s (NH_2), 7.13-8.00 m ($2C_6H_5$), 13.00 br.s (NH). Found, %: C 64.89, H 4.43, N 14.23, S 10.54. $C_{16}H_{13}N_3OS$. Calculated, %: C 65.09, H 4.40, N 14.22, S 10.85.

2-Methyl-5-phenylthiazolecarboxylic Acid Thiosemicarbazide (V). A mixture of 13.8 g (0.057 mole) of (III), 11.4 g (0.11 mole) of KSCN, 80 ml of distilled water, and 60 ml of HCl was boiled for 5 h. The crystals which separated were filtered off, washed with water, and air-dried to give 8.3 g (55%) of (V), mp 222-223.5°C. IR spectrum (ν, cm^{-1}): 1463 (C=S), 1680 (C=O), 3190, 3275, 3330, 3435 (NH_2, NHNH). PMR spectrum [δ, ppm, $(CD_3)_2SO$]: 2.66 s (CH_3), 3.36 br.s (NH_2), 7.13-7.63 m (C_6H_5), 16.03 br.s [NH(O)], 16.80 s [C(S)NH]. Found, %: C 49.27, H 3.98, N 19.14, S 21.82. $C_{12}H_{12}N_4OS_2$. Calculated, %: C 49.31, H 4.10, N 19.16, S 21.94.

Similarly, from (IV) there was obtained 2,5-diphenylthiazolecarboxylic acid thiosemicarbazide (VI), yield 62%, mp 216-217°C. IR spectrum (ν, cm^{-1}): 1690 (C=O), 3180, 3300, 3440 (NH_2, NHNH). PMR spectrum [δ, ppm, $(CD_3)_3SO$]: 7.20-8.16 m ($2C_6H_5$, NH_2), 9.30 br.s [NHC(O)], 10.33 s [NHC(S)]. Found, %: C 57.79, H 5.93, N 15.80, S 18.87. $C_{17}H_{14}N_4OS_2$. Calculated, %: C 57.62, H 5.95, N 15.93, S 18.07.

2-Methyl-5-phenylthiazolecarboxylic Acid 4-Phenylthiosemicarbazide (VII). A mixture of 11.2 g (0.048 mole) of (III) and 6.5 g (0.048 mole) of PhNCS was boiled in absolute ethanol for 4 h. The crystals which separated were filtered off and air-dried, then recrystallized from chloroform to give 10.4 g (87%) of (VII), mp 108-110°C. IR spectrum (ν, cm^{-1}): 1465 (C=S), 1690 (C=O), 3135, 3225 (NHNH). PMR spectrum [δ, ppm, $(CD_3)_2SO$]: 2.70 s (CH_3), 5.93-7.66 m (C_6H_5, NH), 14.70 s [NHC(O)], 15.26 s [NHC(S)]. Found, %: C 58.50, H 4.26, N 14.93, S 16.97. $C_{18}H_{16}N_4OS_2$. Calculated, %: C 58.69, H 4.34, N 15.20, S 17.40.

Similarly, from (IV) there was obtained 2,5-diphenylthiazolecarboxylic acid 4-phenylthiosemicarbazide (VIII), yield 98%, mp 176-177.5°C. IR spectrum (ν, cm^{-1}): 1685 (C=O), 3190, 3450 (NH, NHNH). PMR spectrum [δ, ppm, $(CD_3)_2SO$]: 4.26 br.s (NH), 6.93-8.16 m ($3C_6H_5$), 9.66 s [NHC(O)], 10.43 br.s [NHC(S)]. Found, %: C 64.10, H 4.09, N 12.97, S 14.71. $C_{23}H_{18}N_4OS_2$. Calculated, %: C 64.18, H 4.10, N 13.02, S 14.88.

Methyl 2-[2'-(2"-Methyl-5"-phenylthiazolecarbonyl)hydrazo]-5-phenylthiazolecarboxylate (IX). A mixture of equimolar amounts of methyl 3-phenyl-3-chloro-2-oxopropionate and thiosemicarbazide (V) was boiled for ~3 h with stirring in absolute ethanol until the solution became colorless, and the crystals which had separated were filtered off and recrystallized (Table 2).

Similarly, from the appropriate derivatives of 3-phenyl-3-chloro-2-oxopropionic acid and thiosemicarbazide (V) there were obtained compounds (X)-(XIV), data for which are given in Tables 1 and 2.

2-Methyl-5-phenylthiazoline-4-carboxylic Acid N-(3'-Phenyl-4'-oxo-1',3'-thiazolidin-2'-ylidene)hydrazide (XV). Method 1. A mixture of 1.5 g (0.004 mole) of the phenylthiosemicarbazide (VII) and 0.9 g (0.008 mole) of chloroacetyl chloride was boiled in 30 ml of dichloromethane for 10 h. The solvent was removed under reduced pressure, and the residue treated with 40 ml of diethyl ether. The crystals were filtered off to give 1.5 g (90%) of (XV), mp 101-102.5°C. IR spectrum (ν, cm^{-1}): 1705 (C=O), 1640 (C=N). PMR spectrum (δ, ppm, $CDCl_3$): 2.66 s (CH_3), 3.83 s (CH_2), 6.83-7.60 m ($2C_6H_5$). Found, %: C 58.76, H 4.05, N 13.56, S 15.89. $C_{20}H_{16}N_4O_2S_2$. Calculated, %: S 58.82, H 3.91, N 13.71, S 15.70.

Method 2. A mixture of 1.2 g (0.003 mole) of the phenylthiosemicarbazide (VII) and 1.3 g (0.016 mole) of sodium acetate was boiled for 5 h in 40 ml of acetic acid, then poured onto ice water and kept for 2 days. The crystals which had separated were filtered off and washed with ether to give 0.8 g (67%) of (VII).

Similarly, using Method 1 there was obtained 94%, and by Method 2, 71% of 2,5-diphenylthiazoline-4-carboxylic acid N-(3'-phenyl-4'oxo-1',3'-thiazolidin-2'-ylidene)hydrazide (XVI), mp 120-122°C. IR spectrum (ν, cm^{-1}): 1700 (C=O), 1650 (C=N). PMR spectrum (δ, ppm, CD_2Cl_2): 3.86 s (CH_2), 6.73-7.93 m ($3C_6H_5$), 9.66 br.s (NH). Found, %: C 62.97, H 3.76, N 12.30, S 12.87. $C_{25}H_{18}N_4O_2S_2$. Calculated, %: C 63.83, H 3.82, N 11.90, S 13.63.

LITERATURE CITED

1. N. N. Mel'nikov, K. P. Novozhilov, and T. N. Pylova, Chemical Plant Protectants [in Russian], Khimiya, Moscow (1980), p. 263.
2. M. D. Mashkovskii, Medicinals [in Russian], Meditsina, Moscow (1984), Part 1, p. 202; Part 2, pp. 8, 9, 291, 346.
3. V. A. Mamedov, I. A. Nuretdinov, and D. N. Sadkova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2854 (1990).
4. H. Sard, P. C. Meltzer, and R. K. Razdan, J. Heterocycl. Chem., 22, No. 2, 361 (1985).
5. B. N. Goswami, J. C. S. Kataky, and J. N. Baruah, J. Indian. Chem. Soc., 61, No. 6, 530 (1984).
6. B. N. Goswami, J. C. S. Kataky, and J. N. Baruah, J. Heterocycl. Chem., 21, No. 4, 1225 (1984).
7. I. Chaabar and O. O. Ji, J. Indian Chem. Soc., 61, No. 6, 523 (1984).
8. S. M. El-Khaws and N. S. Habib, J. Heterocycl. Chem., 26, No. 1, 177 (1989).

9. K. M. Basvaraja and Y. S. Agasimundin, Indian J. Chem., 22, No. 5, 458 (1983).
10. V. A. Mamedov, I. A. Nuretdinov, and F. G. Sibgatullina, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2172 (1988).

SYNTHESIS OF NOVEL CONDENSED TRICYCLIC SYSTEMS FROM 2-ALKENYL(ALKYNYL)THIO-3-THIOPHENALDOXIMES

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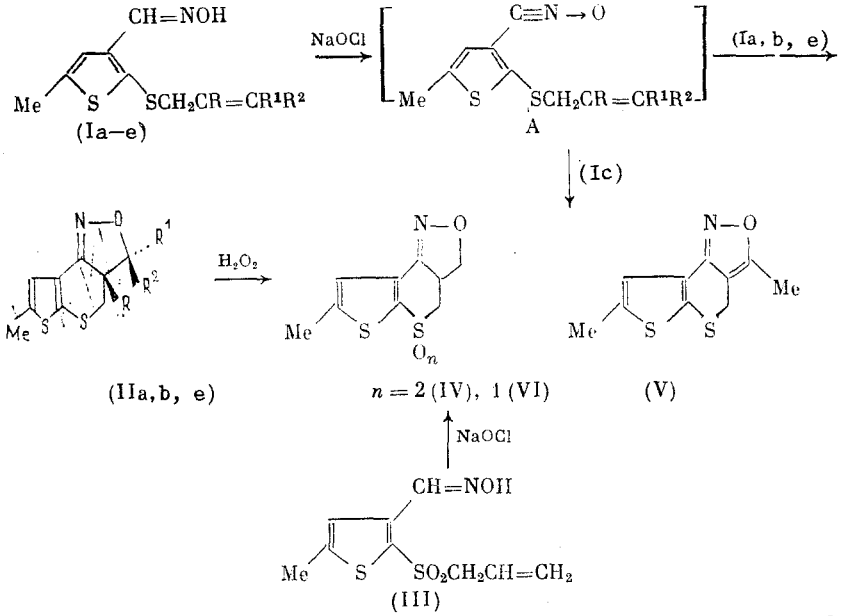
UDC 542.91:541.69:547.733+547.818.1+547.786

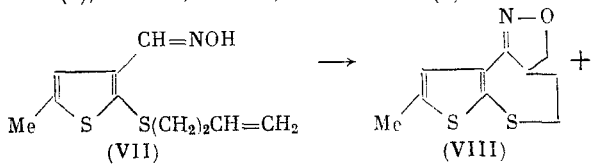
Starting from 2-alkenyl(or alkynyl)thiothiophen-3-aldoximes, some novel tricyclic systems have been obtained which incorporate annelated thiophene, dihydrothiopyran, and isoxazoline or isoxazole rings.

Condensed systems including sulfur and nitrogen heterocycles show a wide spectrum of pharmacological activity [1, 2], polcyclic thiophenes sometimes being more active than their hydrocarbon isosteres [3, 4]. In particular, some thienothiopyrans show high antiglaucoma activity [4].

We have now synthesized some novel tricyclic systems from 2-alkenyl(or alkynyl)thioaldoximes (I) [5]. Treatment of (Ia, b) with an equimolar amount of NaOCl in the two-phase system CH_2Cl_2–H_2O [6] in the absence of a catalyst has given high yields of 7-methyl-3,3a-dihydro[4H]thieno[2,3-b]thiopyrano[4,5-c]isoxazoline (IIa) and its 3,3-dimethyl derivative (IIb). Similarly, from (III) there was obtained the tricyclic 5,5-dioxide (IV). The reac-



R = R^1 = R^2 = H (a); R = H, R^1 = R^2 = CH_3 (b); R = H, R^1 = Me, R^2 = Cl (c); R = = Me, R^1 = R^2 = H (d); R = Me, R^1 = H, R^2 = *i*-PrCOO (e).



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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2837-2842, December, 1991. Original article submitted January 11, 1991.

 0568-5230/91/4012-2474$12.50