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SYNTHESIS AND SOME PROPERTIES OF AMIDES OF 4-CARBOXYMETHYL-2-THIOLENE 1,1-DIOXIDE

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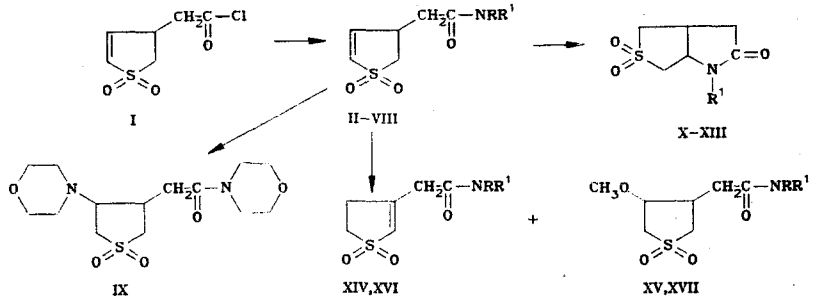
Amides of 4-carboxymethyl-2-thiolene 1,1-dioxide were obtained with aliphatic, heterocyclic, and aromatic amines. A study was carried out on the reactions of these amides with various nucleophilic reagents.

Actinonine analogs with a 1,1-dioxothiolane ring [1] and amides of thiolane 1,1-dioxide have been reported to have pesticide activity [2]. Amides of 4-carboxymethyl-2-thiolene 1,1-dioxide have not been described. We synthesized these compounds by the reaction of the acid chloride of the corresponding acid I, described in our previous work [3], with amines in 1:2 ratio at room temperature in acetone or dioxane solution.

Argyle et al. [4] have reported that the double bond in 2-thiolene 1,1-dioxides is active in nucleophilic addition, although acrylamines [5] and acid amides [6] add only with difficulty. However, as shown in our work, the intramolecular cyclization of N-alkyl- and aryl-amides of 4-carboxymethyl-2-thiolene 1,1-dioxide proceeds rather readily. Thus, a mixture of amides II-V and lactams X-XIII is formed upon reaction with ammonia, primary amines, aniline and p-substituted aniline derivatives (see Table 1). These lactams are the major reaction products if amides II-V are heated for 1 h in an equimolar amount of aqueous alkali.



II—V, XI—XV R=H; II, X, XIV, XV R^1=H; III, XI R^1=*t*-Bu; IV, XII R^1=Ph; V, XIII R^1=*p*-$CH_3C_6H_4$; VI R=R^1=Et; VII R—R^1=C_5H_{10}; VIII, IX, XVI, XVII R—R^1=C_4H_8O

Other addition reactions occur as readily: The reaction of I with excess morpholine leads to addition of the amine at the double bond of amide VIII to form sulfone IX, while heating amides II and VIII with sodium methylate gives both isomerization products XIV and XVI and addition products XV and XVII, as indicated by thin-layer chromatography.

Products XVI and XVII were identified by their thin-layer chromatographic R_f values. The position of the double bond in II-VIII was supported by the finding of a PMR signal for the two vicinal protons which form an AB quartet centered at 6.5-6.8 ppm, J_{AB} = 6.5-7.0 Hz. The complex multiplets with intensity 1H centered at 4.45, 4.65, 5.09, and 5.0 ppm in the PMR spectra of X-XIII were assigned to the proton at the carbon atom bound to the lactam ring nitrogen. The spectrum of X also has a broad NH proton singlet at 7.8 ppm. Of the two possible structures for amide XIV (3-thiolene or 2-thiolene 1,1-dioxide), the latter was as-

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	IR spectrum, cm^{-1}	Found, %		Chemical formula	Calculated, %		Yield, %
			N	S		N	S	
1	2	3	4	5	6	7	8	9
II	172	420, 450, 525, 565, 595, 660, 675, 720, 742, 840, 860, 900, 1024, 1105—1135, 1180, 1217, 1285, 1300—1310, 1420, 1620—1660, 1770, 2860, 2950, 3005, 3105, 3200—3395	8,1	18,5	$C_6H_9NO_3S$	8,0	18,3	92
III	108	435, 480, 520, 598, 651, 730, 780, 900, 1038, 1100, 1140, 1208—1225, 1285—1318, 1361, 1390, 1452, 1550, 1603, 1670, 2940, 2970, 3062, 3385	5,9	14,0	$C_{10}H_{17}NO_3S$	6,0	13,8	89
IV	135	425, 440, 510—520, 585, 605, 655, 695, 715, 725—730, 810, 820—830, 910, 945, 970, 1030, 1060, 1102, 1130, 1178, 1202, 1255, 1285—1300—1365, 1405—1410, 1440, 1490, 1542, 1598, 1685, 3002, 3085, 3340	5,6	12,8	$C_{12}H_{13}NO_3S$	5,6	12,8	91
V	142	425, 440, 500, 520, 575, 600, 650, 695, 710, 720, 740, 775, 830—840, 860, 900, 945, 970, 1060, 1095, 1140, 1178, 1208, 1255, 1290, 1305, 1320, 1365, 1410, 1509, 1545, 1600, 1688, 2940, 3020, 3140, 3210—3285, 3340	5,0	12,2	$C_{13}H_{15}NO_3S$	5,3	12,1	95
VI	65	415, 445, 500, 590, 600, 615, 655, 723, 748, 785—795, 870, 900, 948, 975, 1085, 1110—1140, 1220—1243, 1290—1320, 1350, 1365—1380, 1410, 1440—1475, 1490, 1640, 1728, 2890, 2945, 2990, 3085	6,3	14,0	$C_{10}H_{17}NO_3S$	6,1	13,8	87
VII	113	420, 445, 465, 530, 580, 600, 645, 655, 740, 770, 830—850, 875, 950, 970, 1015—1025, 1060, 1110—1125—1140, 1200, 1220, 1260, 1248—1352, 1410, 1440—1470, 1625, 2870, 2940, 3010, 3030, 3050, 3080	5,8	12,9	$C_{11}H_{17}NO_3S$	5,8	13,2	86
VIII	158	410, 445, 515, 545, 565, 580, 600, 625, 645, 655, 730, 750, 770, 840, 870, 900, 950, 980, 1030, 1070, 1105, 1125—1140, 1205—1225, 1250, 1280, 1305, 1360, 1405, 1440—1470, 1600—1640, 2750, 2870, 2930—2970, 3080	5,8	13,6	$C_{10}H_{15}NO_4S$	5,7	13,9	86
IX	129	450, 500, 525, 570, 605, 640, 660, 730, 790, 795, 840, 875, 910, 945, 1000, 1015, 1035, 1070, 1110, 1130, 1160, 1190, 1210, 1270, 1295, 1360, 1445, 1635, 2855, 2935—2970	8,5	9,6	$C_{14}H_{24}N_2O_5S$	8,4	9,6	70
X	192	435, 465, 520—545, 575, 605, 680, 705, 760, 855, 880, 900, 960, 1030, 1050, 1125, 1170, 1210, 1240, 1290, 1320, 1385, 1425, 1760, 2860, 2935, 2965, 3020, 3390	8,0	18,8	$C_6H_9NO_3S$	8,0	18,3	81
XI	195	430, 455, 495, 510, 530, 575, 595, 620, 660, 720, 745, 795, 825, 835, 875, 940, 955, 990, 1030, 1050, 1100—1115, 1140, 1195, 1230, 1260—1270, 1300—1310, 1338, 1365, 1400, 1475, 1685, 2940, 2990—3010	6,0	13,8	$C_{10}H_{17}NO_3S$	6,0	13,8	97
XII	177	440, 470, 500, 530, 555, 585, 655, 695, 720, 740, 765, 790, 845, 895, 920, 950, 1000, 1025, 1070, 1110, 1120, 1155, 1190, 1210, 1240, 1290, 1305, 1340, 1390, 1455, 1500, 1590, 1690, 2950, 2980, 3020	5,4	12,8	$C_{13}H_{15}NO_3S$	5,6	12,8	99

signed since only one signal is seen in the ^{13}C NMR spectrum for the methylene group carbon in the α position to the SO_2 group (at δ 53.2 ppm).

Screening for biological activity at NIIBIKhS in Kupavna showed that II-V, VII, and VIII have hypotensive activity, while IX and XV display weak antifungal activity.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer in KBr pellets. The PMR spectra were taken on a Tesla BS-487B spectrometer at 80 MHz at room temperature in deuteracetone or

TABLE 1 (Continued)

1	2	3	4	5	6	7	8	9
XIII	217	440, 475, 505, 525, 550, 585, 630, 665, 710, 735, 740, 835, 845, 920, 945, 1070, 1110, 1150, 1185—1195, 1210, 1245, 1295—1310, 1340, 1415, 1510, 1610, 1685, 2950, 2970, 3020	5,5	12,1	$C_{12}H_{13}NO_3S$	5,3	12,1	99
XIV	166	425, 490, 495, 525, 565, 595, 630, 665, 715, 740, 840, 850, 900, 910, 1100, 1140, 1210, 1280, 1315, 1420, 1620—1650, 2780, 2840, 2945, 3100, 3200, 3395	8,0	18,2	$C_6H_9NO_3S$	8,0	18,3	41
XV	110	435, 485, 510, 540, 565, 760, 830, 855, 870, 920, 960, 980, 1040, 1090, 1120—1135, 1190, 1240, 1245, 1365, 1445, 1630, 2780, 2830, 2870, 2920, 2950, 3010	5,2	11,4	$C_{11}H_{19}NO_5S$	5,0	11,6	52

CF_3CO_2H. The internal standard was HMDS. The ^{13}C NMR spectrum was taken on a Bruker WH90 spectrometer at 22.63 MHz at room temperature in DMSO-d_6 with proton decoupling. The chemical shifts were determined relative to the solvent signal (δ 39.6 ppm).

The separation and purity control of the reaction products was carried out by thin-layer chromatography on alumina with grade II activity using 1:12.3 methanol—ether as the eluent.

Acid-Chloride of 4-Carboxymethyl-2-thiolene 1,1-Dioxide (I). A sample of 8.8 g (50 mmoles) 4-carboxymethyl-2-thiolene 1,1-dioxide was added to 10 g (80 mmoles) thionyl chloride and heated until HCl was no longer liberated. Excess thionyl chloride was distilled off and the dry residue (9.5 g) was used for the subsequent reactions.

4-Aminocarbonylmethyl-2-thiolene 1,1-Dioxide (II). Excess gaseous ammonia was passed through a solution of 5.82 g (30 mmoles) acid chloride I in 40 ml acetone cooled with ice water. The precipitate was filtered off. The filtrate was evaporated and crystallization of the dry residue from water gave 1.8 g colorless crystalline product, R_f 0.42.

4-tert-Butylaminocarbonylmethyl-2-thiolene 1,1-Dioxide (III). A sample of 4.5 g (60 mmoles) tert-butylamine was added to a cooled solution of 5.82 g (30 mmoles) acid chloride I in 10 ml acetone. The salt precipitate was filtered off and the filtrate was evaporated. The dry residue was crystallized from aqueous ethanol to give 6.2 g product. Products IV-VIII were obtained by analogy (see Table 1).

3-Morpholino-4-morpholinocarbonylmethylthiolane 1,1-Dioxide (IX). A solution of 2.5 g (10 mmoles) 4-morpholinocarbonylmethyl-2-thiolene 1,1-dioxide (R_f 0.70) in 5 ml morpholine was prepared and heated for 12 h at 110-120°C. Excess morpholine was distilled off. The dry residue was crystallized from methanol to give 2.3 g product, R_f 0.63.

2-Oxo-3a,4,6,6a-tetrahydro-3H-thieno[4,3-d]pyrrole 5,5-Dioxide (X). A sample of 5.25 g (30 mmoles) II was added to a solution of 2 g KOH in 20 ml water. The mixture was heated on a boiling water bath for 1 h, cooled to room temperature, and acidified. The filtrate was evaporated. Crystallization of the dry residue from methanol gave 4.8 g product X, R_f 0.02.

Products XI, XII, and XIII were obtained by analogy (see Table 1).

3-Aminocarbonylmethyl-2-thiolene 1,1-Dioxide (XIV). A solution of 0.23 g (10 mmoles) sodium methylate in 10 ml methanol was prepared and 1.7 g (10 mmoles) amide II was added to the solution and heated for 1-2 h at 60-65°C. Thin-layer chromatography indicated a mixture of X (R_f 0.02), XIV (R_f 0.15), and XVII (R_f 0.93). Crystallization from methanol separated 1.1 g white, crystalline XIV, R_f 0.19.

3-Methoxy-4-morpholinocarbonylmethylthiolane 1,1-Dioxide (XV). A sample of 1.3 g (5 mmoles) amide VIII was added to a solution of 0.11 g (5 mmoles) metallic sodium in 10 ml methanol. The mixture was heated for 1-2 h at 60-65°C and the methanol was distilled off. Thin-layer chromatography indicated a mixture of XV (R_f 0.80) and XVII (R_f 0.53). Crystallization from water—ethanol gave 0.75 g XV, R_f 0.80.

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SYNTHESIS AND STRUCTURE OF DERIVATIVES OF 7-OXO-4,5,6,7-TETRAHYDROBENZO[b]-THIOPHENE AND 7-HYDROXYBENZO[b]THIOPHENE

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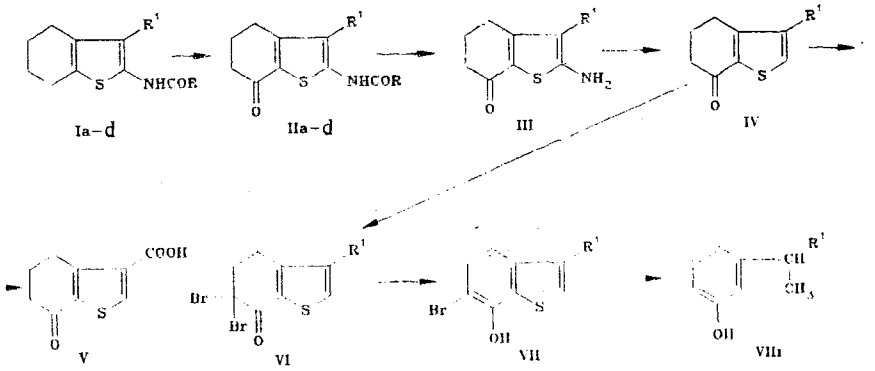
The oxidation of 2-acylamino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophenes gave the corresponding 7-oxotetrahydrobenzo[b]thiophenes and some of the transformations of these compounds were studied. These compounds were used for the synthesis of 3-ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene. The structures of the compounds prepared were established by chemical and spectral methods.

α-Amino derivatives of heterocyclic compounds often display an enhanced tendency to undergo oxidation, thereby giving valuable oxo and hydroxy compounds [1]. We studied the potassium dichromate oxidation of 2-acylamino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophenes Ia-d [2, 3] in acetic acid, which leads to the corresponding 7-oxotetrahydrobenzo[b]thiophenes IIa-d. A subsequent series of transformations (see Scheme) permits preparation not only of various derivatives of 7-oxotetrahydrobenzo[b]thiophenes and 3-ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene (VII), but also phenol VIII by desulfurization of VII. This final step facilitated the proof of the structures of all the compounds synthesized.



I, II a R=CH_3; b R=H; c R=CH_2Cl; d R=C_6H_5; I—IV, VI—VIII R^1=$COOC_2H_5$

The PMR spectrum of Ia has signals for methylene groups at positions 5 and 6 as a complex multiplet centered at 1.78 ppm, while the signals for the methylene groups at positions 4 and 7 appear as triplets at 2.75 and 2.64 ppm, respectively. The assignment of the two latter signals was made by comparison with the spectrum of 2-acetylamino-4,5,6,7-tetrahydrobenzo-[b]thiophene (IX) [3], which does not contain an ethoxycarbonyl group at C-3. The only signal shifted downfield by 0.26 ppm in going from IX to Ia was assigned to the CH_2 group at C-4. The PMR spectrum of the oxidized product IIa was signals for three methylene groups: two triplets (at 2.57 and 3.07 ppm) and a quintet (at 2.16 ppm). This multiplicity is possible only if the carbonyl group is at C-4 or at C-7. Selection of these two positions by comparison of

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