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REACTION OF 5(4H)-THIAZOLONES WITH DIAZOMETHANE

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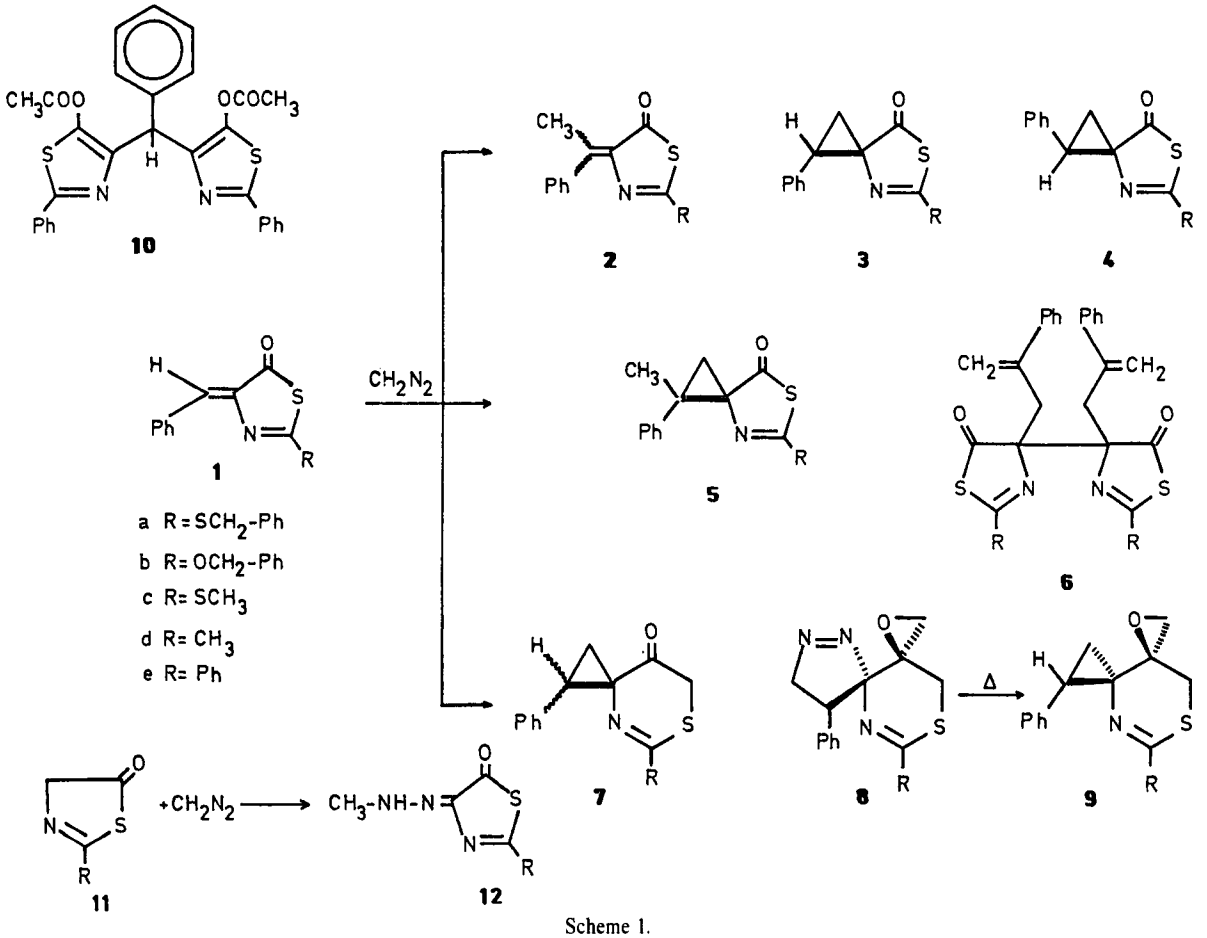
Abstract—The reaction of diazomethane with several (*Z*)-2-substituted-4-benzylidene-5(4H)-thiazolones (**1**) (2-substitution: SCH_2Ph, OCH_2Ph, SCH_3, CH_3, Ph), under two different conditions, has been studied. In benzene at 45° *Z*) and (*E*)-2-substituted-1-phenyl-7-oxo-6-thia-4-azaspiro[2.4]hept-4-enes (**3**, **4**) were mainly obtained. In ether at 0°, ring enlargement reactions took place, giving 2-substituted-8-phenyl-10-oxa-1-thia-3,5,6-triaza-dispiro[4.4.0.2]dodeca-2,5-dienes (**8**) in very good yields, together with small quantities of 5-substituted-1-phenyl-8-oxo-6-thia-4-azaspiro[2.5]oct-4-enes (**7**) and also **3** and **4**. The 2-phenyl derivative of **1** gave no ring expansion products, but instead 4,4'-Bi[2-phenyl-4-(2-phenylallyl)-5(4H)-thiazolone] (**6**) was obtained. Treatment of 2-substituted-5(4H)-thiazolones (2-substitution: SCH_2Ph, OCH_2PH, SCH_3, Ph) led to unexpected 2-substituted-4-(methyl-diazanylidene)-5(4H)-thiazolones (**12**). The ^1H NMR spectra have been analyzed by an iterative computer method, and the computed values obtained have been used to deduce the stereochemistry of the spiro-derivatives.

During the course of an investigation aimed to the synthesis of 1-aminocyclopropanecarboxylic acids[1] we reacted 4 - benzylidene - 2 - benzylthio - 5(4H) - thiazolone (**1a**) with diazomethane, obtaining a mixture of two main crystalline products, i.e. the desired spirothiazolone **3a** and a second substance **8a**[2]. After several attempts, we were able to prepare either compound at will, by simply changing the reaction conditions. Thus, when **1a** was treated with a benzene solution of diazomethane at 45° the spirothiazolone **3a** was obtained in 45% yield. On the contrary, addition of **1a** to a cold solution of ethereal diazomethane resulted in spontaneous crystallization of **8a** in 65% yield. An analogous reaction of diazomethane with 2-benzyloxy-4-benzylidene-5(4H)-oxazolone has been recently reported.[3]

Since compounds **8a** and **9a**, obtained by heating of the



Scheme 1.

former, could be of interest in connection with the chemistry of cephalosporins, we have investigated the behavior of some readily available substituted thiazolones on similar treatments.

RESULTS AND DISCUSSION

To prepare the starting thiazolones **1**[4] we either condensed N-thioacyl-glycines with benzaldehyde in acetic anhydride (compounds **1a–c**, **1e**)[1,5] or treated the corresponding 4-benzylidene-5(4H)-oxazolone with thioacetic acid (compounds **1d–e**).[6] Compound **1e** was first made from thiohyppuric acid and benzaldehyde, but the resulting material contained always unacceptable amounts of unwanted product **10** (see Experimental section). However, treatment of 4-benzylidene-2-phenyl-5(4H)-oxazolone with thioacetic acid gave readily pure **1e**.

In order to study the behavior of compounds **1** with diazomethane, the reaction was allowed to occur in each case under two different conditions: (A) dropping a benzene solution of diazomethane into a benzene solution of the corresponding thiazolone at 45°, thus trying to minimize multiple additions, and (B) adding the proper thiazolone on a large excess of ethereal diazomethane at 0°. The results are summarized in the Scheme and Table 1.

It can be seen that method A prevents the ring expansion of the thiazolone moiety, the spiroderivatives **3** and **4** being the major products of the reaction. In the case **b**, a low yield of the dihydrothiazine **8b** is produced, accordingly to that given by other thiazolones with identical substitution at C-2[1] and in contrast with the corresponding oxazolone, which yielded only the tricyclic product analogous to **8b**.[3]

When addition was made as in method B the ring enlargement occurred in most of the cases in good yields, **8** being the bulk of the reaction. Compound **1e** gave no expansion products. Instead, a double out-of-ring insertion of CH_2, probably followed by oxidative dimerization, led to the unexpected compound **6e**, whose structure, assigned from usual spectroanalytical data, was supported by X-ray crystal analysis.[7] A similar dimerization has been described by Barrett *et al.*[8] to explain the formation of blue pigment trichotomine from 2-phenyl-4-(2'-carboxyethyl)-5(4H)-thiazolone and L-tryptophan.

When compounds **8a** and **8c** were heated up to their m.p., rapid evolution of N_2 took place, giving respectively **9a** and **9c** in 75% yield. Under the same conditions **8b** and **8d** decomposed into a complex mixture not investigated.

We further tried to carry out the reaction on thiazolones lacking any substituent at C-4. The necessary starting compounds **11** were prepared by cyclization of the corresponding N-thioacyglicines. Reaction of **11** with excess of cold ethereal diazomethane afforded N-methylhydrazones (**12**). This unusual addition is, at the best of our knowledge, the first reported reaction of diazomethane to form a methyl hydrazone.

On the other hand, compound **3a** was allowed to stand with diazometane under conditions of method B, but no reaction was detected after a week of treatment, the starting material being recovered unchanged.

All these results indicate that substitution both at C-2 and C-4 play a very important role on the expansion reaction. However, more work will be necessary before those differences in reactivity can be rationalized.

Table 1. Compounds obtained in the reaction of CH_2N_2 with 2-substituted-4-benzylidene-5(4H)-thiazolones (1)

R / Compd.	a			b			c			d			e		
	Rf	mp(°C)	Method (%)[a] A	B	Rf	mp(°C)	Method (%) A	B	Rf	mp(°C)	Method (%) A	B	Rf	mp(°C)	Method (%) A	B
2	0.48	NC[b]	(15)	(5)	0.45	55-6	10	5	0.45	88-9	10	10	0.39	41-2	10	10				
3	0.43	91-2	45	15	0.40	77-8	40	15	0.40	84-5	40	15	0.24	99-100	45	40	0.45	125-6	65	60
4	0.40	NC	(5)	Tr.	0.28	84-5	20	5	0.30	137-8	20	5	0.14	50-1	20	20	0.43	NC	(5)	Tr.
5													0.18	78-80	10	8				
6																	0.70	160-1	15	25
7	0.15	NC	Tr.	(8)	0.14	66-7	5	10	0.14	NC	(5)	8								
8	0.06	150-1d	Tr.	68	0.03	163-4d	10	60	0.05	131-2d	Tr.	60	0.08	Dec.	Tr.	15				

a Yields are not optimized. Those given in parenthesis are estimated. Tr.=traces.

b Not crystallized or impurified (see Experimental section). Identified by spectral data.

All compounds gave satisfactory microanalyses ($\pm$ 0.4% for C,H,N,S), with the exception of: **2a**, **4a**, **4e**, **7a** which could not be obtained in pure state.

Stereochemical aspects

The thiazolones **1** obtained shown to be *Z*-isomers (vinylic H *ca.* 7.3). Attempts to synthesize *E*-isomers by procedures analogous to those used in the formation of *E*-oxazolones[9,10] were unsuccessful. Preparation of (*E*)-**1e** have been reported by Rao,[6] by treatment of (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone with thioacetic acid. In our hands, however, such treatment always led to the *Z*-thiazolone, whatever stereoisomer was used as the starting material.

^{1}H-NMR spectral data of spirothiazolones are given in Table 2. Geminal protons of cyclopropane ring in derivatives **3** and **4** appear as AB part of ABX systems and show little chemical shift difference. For similar spirooxazolones, we established[10] that protons with syn configuration with respect to the N=C group appear downfield to protons with anti configuration. As the general trend observed in spriooxazolones holds for the spirotiazolone series also, we deduce a *Z*-configuration for compounds **3** (δ H_X *ca.* 3.2) and *E*-configuration for compounds **4** (δ H_X *ca.* 3.6). Coupling constants are in agreement with those assignments. Both sets of reactions are then stereoselective.

Steric problems arisen by dispiroderivatives **8** and **9** were solved by NMR and X-ray crystal studies in **9a**.[11] Again, protons syn to the N=C shown downfield to protons anti in both **9a** and **9c**.

On the same basis, *E*-configuration is tentatively assigned to compounds **7**. Unfortunately in neither case was any of the corresponding stereoisomeric derivatives detected in the reaction mixtures.

EXPERIMENTAL

The melting points were determined on a Kofler Thermopan Reichert apparatus and are uncorrected. IR were performed on a Perkin Elmer 137 E spectrometer in KBr pellets. Data are reported in cm^{-1}. Routine ^{1}H-NMR spectra were recorded for solutions in Cl_3CD on a Perkin Elmer R-12 60 MHz spectrometer. All the chemical shifts are expressed in δ values from Me_4Si as internal standard. ^{13}C-NMR spectra were recorded on a Varian XL-100 spectrometer provided with a Nicolet 1180 data system, in Cl_3CD solution. Silica Gel GF_{254} (E. Merck) was used for both TLC and PLC experiments.

4-Benzylidene-5(4H)-thiazolones (**1**)

Compounds (*Z*)-**1a–c** were prepared by condensation of the corresponding N-thioacylglycines with benzaldehyde.[1,5]

Compound (*Z*)-**1e**

Method A. Thiohippuric acid (0.78 g, 0.004 mol), benzaldehyde (0.42 g, 0.004 mol) and NaOAc (0.4 g) in Ac_2O (1.6 ml) were heated on a steam bath for 1 h. The cold mixture was poured into ice–water, filtered, washed (cold-water), air-dried, and chromatographed on silica gel (benzene) to give **1e** (0.6 g, 58%), m.p. = 132° (EtOAc) (lit[12] 130–2°), and **10** (0.4 g, 37%), m.p. = 138–9° (EtOAc). Calc for $C_{29}H_{22}N_2O_4S_2$: C, 66.15; H, 4.21; N, 5.30; S, 12.15. Found: C, 66.04; H, 4.31; N, 4.98; S, 12.22%. IR 1780 (C=O), 1180 (C–O); ^{1}H-NMR 2.04 (s, 6H, CH_3), 5.99 (s, 1H, CH), *ca.* 7.32 (m, 11H arom.), *ca.* 7.81 (m, 4H arom.); ^{13}C-NMR 20.2 (CH_3), 45.2 (CH), 126.0–133.7 (C arom.), 159.3 (C=N), 167.0 (C=O).

When thiohippuric acid and benzaldehyde (2:1 ratio) were reacted under the same conditions, the yields were **1e**, 40%, **10**, 55%.

Method B. From the corresponding (*Z*)-4-benzylidene-2-phenyl-5(4H)-oxazolone and thioacetic acid.[6]

Compound (*Z*)-**1d** was prepared from (*Z*)-4-benzylidene-2-methyl-5(4H)-oxazolone and thioacetic acid. m.p. = 129–30° (EtOAc). ^{1}H NMR 2.60 (s, CH_3), 7.15 (s, vinylic H).

Compound (*E*)-**1e** has been reported to arise similarly from the corresponding (*E*)-oxazolone.[6a] In our hands, both (*E*) and (*Z*)-4-benzylidene-5(4H)-oxazolones, on treatment with thioacetic acid led to the same (*Z*)-**1e** thiazolone (vinylic H, δ = 7.29 ppm). Attempted preparation of (*E*)-4-benzylidene-5(4H)-thiazolones by procedures analogous to those used in oxazolone chemistry[9] (i.e. isomerization with HBr gas, condensation of benzaldehyde with thiazolonium perchlorate, or polyphosphoric acid) failed.[10]

Addition of CH_2N_2 *to* **1**. *General procedures*

Method A. A benzene solution of CH_2N_2 (100 ml, *ca.* 0.07 mol) was dropped into the corresponding thiazolone **1** (0.02 mol) in benzene (50 ml) at 45°. When evolution of N_2 ceased, the solution was kept at room temperature overnight, a few drops of HOAc added and the solvent removed in vacuo. The residual oil was treated with little ether. Compound **3**, which usually crystallized on cooling, was filtered off and recrystallized. The clear filtered solution was evaporated in vacuo and the residual oil submitted to PLC (*ca.* 100 mg/20 × 20 × 0.15 plate, benzene). Fractions were rechromatrographed when necessary.

Method B. The appropriate thiazolone **1** (0.02 mol) was added portion-wise on magnetically stirred, ice-cooled (0–5°) ethereal diazomethane (100 ml, *ca.* 0.07 mol). The mixture was then left on the cool for 10–12 h, a few drops of HOAc added, with the only exception of case **1d** (see below). The solid deposited at this stage, namely compound **8**, was filtered and recrystallized. The mother liquors were worked up as in method A.

Compound **1d** was treated as above, but addition of HOAc was omitted because **8d** decomposed. Instead, **8d** was filtered and handled in the cold. Attempts at recrystallization resulted also in decomposition. The mother liquors were worked up as in method A.

The following compounds were obtained by either methods A and/or B (see Table 1). In each case, substitution (R) and recrystallization solvent are given.

(2-Substituted)-4-[1-methylbenzylidene]-5(4H)-thiazolones (**2**)

Compound **2a** (2-benzylthio). Evidence for its structure was obtained from a ^{1}H-NMR spectrum with **3a** as impure derivative (compare also with **2b–d**). ^{1}H-NMR 2.50 (s, CH_3), 4.35 (s, CH_2).

Compound **2b** (2-benzyloxy). Pale yellow needles (methanol–EtOAc); ^{1}H-NMR 2.56 (s, CH_3), 5.33 (s, CH_2), *ca* 7.5 (m, 10H arom.).

Compound **2c** (2-methylthio). Long yellow needles (ethanol); IR 1690 (C=O), 1590, 1570 (C=C, C=N); ^{1}H-NMR 2.48 (s, CH_3), 2.65 (s, CH_3), *ca.* 7.3 (m, 3H arom.), *ca.* 7.6 (m, 2H arom.).

Compound **2d** (2-methyl). Yellow microneedles (isopropanol); IR 1680, 1660 (C=O), 1600 (C=C, C=N); ^{1}H-NMR 2.46 (s, CH_3), 2.70 (s, CH_3), *ca.* 7.5 (m, 5H arom.). We also isolated a fraction containing a mixture of **2d**, Rf = 0.39, with a stereoisomeric product, Rf = 0.35; ^{1}H-NMR 2.54 (s, CH_3–C=N), 2.62 (s, CH_3–C=C), 7.4 (m, 5H arom.). Comparison of chemical shifts of both CH_3–C=N and CH_3–C=C groups in compounds **2a–d** with similar oxazolones[13] and also with compounds **3c,d** and **4c,d** suggest a (*Z*)-configuration for **2a–d** and (*E*)-configuration for stereoisomeric derivative of **2d**.

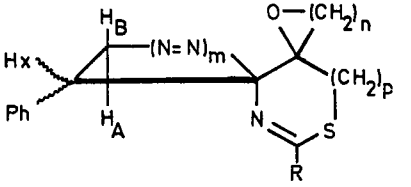
(Z)-(5-substituted)-1-phenyl-7-oxo-6-thia-4-azaspiro[2.4]*hept-4-enes* (**3**). Compound **3a** (5-benzylthio). Yellowish crystals (isopropanol); IR 1710 (C=O). Compound **3b** (5-benzyloxy). White crystals (isopropanol); IR 1720 (C=O). Compound **3c** (5-methylthio). White crystals (isopropanol); IR 1725 (C=O). Compound **3d** (5-methyl). White needles (isopropanol); IR 1710sh, 1690 (C=O). Compound **3e** (5-phenyl). White needles (EtOAc); IR 1700 (C=O).

(E)-(5-substituted)-1-phenyl-7-oxo-6-thia-4-azaspiro[2,4]*hept-4-enes* (**4**). Compound **4a** (5-benzylthio). Evidence for its structure was obtained from a ^{1}H-NMR spectrum of a fraction with **3a**. Compound **4b** (5-benzyloxy). White crystals (isopropanol). Compound **4c** (5-methylthio). White needles (isopropanol); IR 1710 (C=O). Compound **4d** (5-methyl). White crystals (isopropanol); IR 1720sh, 1690 (C=O). Compound **4e** (5-phenyl). Evidence for its structure was obtained from a ^{1}H-NMR spectrum of a fraction with **3e**.

(Z)-1-phenyl-1,5-dimethyl-7-oxo-6-thia-4-azaspiro[2.4]*hept-4-ene* (**5d**). White needles (EtOH); IR 1720 (C=O), 1615 (C=N).

4,4'-Bi-[2-phenyl-4-(2-phenylallyl)5(4H)-thiazolone] (**6e**).

Table 2. ^{1}H NMR spectral parameters, $\nu(\delta)$ and J(Hz) of compounds **3–9**



Comp.	R	Conf.	m	n	p	ν_A	ν_B	ν_X	J_{AB}	J_{AX}	J_{BX}	Other significant parameters
3a	SCH_2Ph	Z	0	0	0	2.42	2.22	3.18	-5.1	8.8	9.6	4.08 (d,CHH-Ph, J=13.1),4.26 (d, CHH-Ph)
3b	OCH_2Ph	Z	0	0	0	2.15	2.14	3.06	-5.3	8.6	9.6	5.10 (d,CHH-Ph, J=11.6),5.20 (d, CHH-Ph)
3c	SCH_3	Z	0	0	0	2.37	2.24	3.13	-4.9	8.6	9.8	2.37 (s, CH_3)
3d	CH_3	Z	0	0	0	2.36	2.17	3.14	-4.8	8.8	9.6	2.30 (s, CH_3)
3e	Ph	Z	0	0	0	2.54	2.35	3.29	-4.9	9.0	9.7	
4a	SCH_2Ph	E	0	0	0	2.42	2.33	3.57	-5.1	9.7	9.1	4.42 (s, CH_2Ph)
4b	OCH_2Ph	E	0	0	0	2.24	2.20	3.39	-5.2	9.7	9.2	5.42 (s, CH_2Ph)
4c	SCH_3	E	0	0	0	2.41	2.33	3.57	-5.2	9.5	9.2	2.58 (s, CH_3)
4d	CH_3	E	0	0	0	2.39	2.31	3.58	-5.3	9.5	9.1	2.46 (s, CH_3)
4e	Ph	E	0	0	0	2.54	2.45	3.78	-5.2	9.8	9.2	
5d	CH_3	Z	0	0	0	2.35	2.18		-4.6			1.74 (s, CH_3-CPh), 2.50 (s, CH_3-C=N)
7a	SCH_2Ph	E?	0	0	1	2.36	2.11	3.33	-4.5	9.6	8.5	3.41 (d, S-CHH-, J=14.3), 3.52 (d, S-CHH-), 3.36 (d, CHH-Ph, J=13.1), 3.75 (d, CHH-Ph)
7b	OCH_2Ph	E?	0	0	1	2.30	1.91	3.22	-4.7	9.4	8.7	3.47 (d, S-CHH-, J=14.7), 3.62 (d, S-CHH-), 4.52 (d, CHH-Ph, J=11.5), 4.87 (d, CHH-Ph)
7c	SCH_3	E?	0	0	1	2.36	2.12	3.29	-4.5	9.4	8.5	1.83 (s, CH_3), 3.38 (d, S-CHH-, J=14.1), 3.52 (d, S-CHH-)

9a ≀	SCH_2Ph	Z	0	1	1	1.48	1.34	2.43	-5.1	7.4	9.5	2.55 (d, -CHH-S, J_{gem}=12.0), 2.74 (d, CHH-oxirane, J_{gem}=4.7), 2.84 (dd, -CHH-oxirane, J=1.6), 3.44 (dd, CHH-S), 3.74 (d, CHH-Ph, J=13.1),3.88 (d,CHHPh)
9c ≀	SCH_3	Z	0	1	1	1.49	1.40	2.44	-5.1	7.4	9.3	2.04 (s, CH_3), 2.59 (d, CHH-S, J_{gem}=12.1), 2.82 (d, CHH-oxirane), 2.91 (dd, CHH-oxirane, J=1.6) 3.51 (dd, CHH-S)
8a	SCH_2Ph		1	1	1	4.63	4.95	3.28	-17.6	7.1	8.4	2.61 (d, -CHH-S, J_{gem}=12.4), 2.80 (d, -CHH-oxirane, J_{gem}=4.7), 3.38 (dd, -CHH-S, J=1.5), 3.52 (dd, -CHH-oxirane), 3.69 (d, CHHPh, J=13.0), 3.91 (d, CHHPh)
8b	OCH_2Ph		1	1	1	4.65	4.92	3.22	-17.6	6.9	8.4	2.63 (d, -CHH-S, J_{gem}=12.6), 2.81 (d, -CHH-oxirane, J_{gem}=4.7), 3.35 (dd, -CHH-S, J=1.6), 3.49 (dd, -CHH-oxirane), 4.69 (d, -CHH-Ph, J=12.1), 4.90 (d, CHHPh)
8c	SCH_3		1	1	1	4.81	5.00	3.33	-17.5	6.4	8.3	2.02 (s, CH_3), 2.77 (d, CHH-S, J_{gem}=12.5), 2.85 (d, CHH-oxirane, J_{gem}=4.1), 3.39 (dd, -CHH-S, J=1.6) 3.47 (dd, -CHH-oxirane)
8d	CH_3		1	1	1	4.67	5.10	3.28	-17.7	7.8	8.6	1.96 (s, CH_3), 2.44 (d, -CHH-S, J_{gem}=12.5), 2.85 (d, -CHH-oxirane, J_{gem}=4.8), 3.54 (dd, -CHH-S, J=1.9), 3.76 (dd, -CHH-oxirane)

Colorless solid (EtOAc); IR 1725, 1710 (C=O), 1625, 1600 (C=C, C=N); ^{1}H-NMR 3.38 (d, 1H, -CHH-, J = 13.4), 4.23 (d, 1H, -CHH-), 5.18 (s, 1H, vinylic), 5.26 (s, 1H, Vinylic); ^{13}C-NMR 36.33 (CH_2), 92.55 (-C-), 118.30 (CH_2=), 126.22-142.17 (C arom.), 165.17 (C=N), 208.77 (C=O).

(5-*Substituted*)-1-*phenyl*-8-*oxo*-6-*thia*-4-*azaspiro*[2.5]*oct*-4-*enes* (7). Compound **7a** (5-benzylthio). Pale yellow syrup. Compound **7b** (5-benzyloxy). Colorless crystals (MeOH); IR 1690 (C=O), 1635 (C=N). Compound **7c** (5-methylthio). Pale yellow syrup; IR 1685 (C=O), 1630 (C=N).

(2 - *Substituted*) - 8 - *phenyl* - 10 - *oxa* - 1 - *thia* - 3,5,6 - *triaza dispiro*[4.4.0.2]*dodeca*-2,5-*dienes* (8). Compound **8a** (2-benzylthio). Tiny white plates (EtOAc); IR 1595 (C=N); ^{13}C-NMR 31.22 (CH_2S), 35.80 (CH_2Ph), 46.42 (CH), 53.05 (CH_2O), 55.80 (-C-O), 83.36 (CH_2N), 102.38 (-C-N), 126.98-136.13 (C arom.), 159.47 (C=N). Compound **8b** (2-benzyloxy). Flocky white needles (EtOAc); IR 1630 (C=N). Compound **8c** (2-methylthio). White crystals (dioxane-isopropanol); IR 1590 (C=N); ^{13}C-NMR 13.98 (CH_3), 31.23 (CH_2S), 46.02 (CH), 52.79 (CH_2O), 55.67 (-C-O), 83.46 (CH_2N), 102.45 (-C-N), 126.89-136.42 (C arom), 159.47 (C=N). Compound **8d** (2-methyl) decomposed on attempted recrystallization.

(2-*Substituted*)-5-*phenyl*-8-*oxa*-1-*thia*-3-*aza*-*dispiro*[4.2.0.2]*dec*-2-*enes* (9)

General procedure. 0.5 g of the corresponding **8** were heated in an oil bath up to melting. Rapid evolution of N_2 took place, giving a dark viscous syrup. EtOAc was added to the syrup, from which **9** crystallized in cases **a** and **c**. In cases **b** and **d**, the syrup consisted in a complex mixture of products, not further investigated.

Compound **9a** (2-benzylthio). Tiny pale yellow needles. m.p. = 101-2° (isopropanol). 85%. Calc for $C_{20}H_{19}NOS_2$: C, 67.99; H, 5.38; N, 3.97; S, 18.13. Found: C, 68.07; H, 5.22; N, 3.92; S, 18.17; IR 1595 (C=N); ^{13}C-NMR 18.52 (CH_2 cycloprop.), 30.50 (-CH_2S), 32.49 (Ph-C<), 35.33 (Ph-C-S), 48.42 (>C-N), 53.56 (CH_2O), 54.99 (>C-O), 125.80-137.00 (C arom), 152.07 (C=N).

Compound **9c** (2-methylthio). Pale yellow plates. m.p. = 110-11° (EtOH). 90%. Calc for $C_{14}H_{15}NOS_2$: C, 60.65; H, 5.42; N, 5.05; S, 23.10. Found: C, 60.41; H, 5.46; N, 5.27; S, 23.18% IR 1595 (C=N).

(2-*Substituted*)-5(4*H*)-*thiazolones* (11)

Method A (Based on Boyd[14]). 70% $HClO_4$ (3 g, 0.02 mol) was added dropwise on ice-cooled, stirred Ac_2O (20 ml). To this solution, 0.02 mol of the appropriate N-thioacylglycine was added in portions, and the slurry formed was stirred for 1 h. Et_2O (100 ml) was then added, and the mixture kept in the cold for 2 h. The solid 5(4H)-thiazolonium hydroperchlorate was filtered, washed with Et_2O and stirred several times with sol. of Na_2AcO until all the solid was into solution. The etheral solution was dried (Mg_2SO_4), rapidly evaporated and the residual oil immediately used in the following step without any further purification. Thus were prepared:

Compound **11a**.[5a] IR 1275 (C=O); ^{1}H-NMR 4.45 (s, CH_2Ph), 4.64 (s, CH_2), 7.37 (s, 5H arom.). Compound **11c**. IR 1730 (C=O); ^{1}H-NMR 2.62 (s, CH_3), 4.68 (s, CH_2).

Method B.[12] The N-thioacylglycine (0.01 mol) in CH_2Cl_2 (50 ml) and dicyclohexyl carbodiimide (0.01 mol) were stirred for 45 min. The dicyclohexylurea was filtered off and the solvent removed *in vacuo* to give an oil, immediately used in the following step. In this way were obtained. Compound **11b**, IR 1725 (C=O); ^{1}H-NMR 4.53 (s, CH_2—C=O), 5.48 (s, CH_2Ph), 7.48 (s, Ph), and Compound **11e**,[12] ^{1}H-NMR 4.92 (s, CH_2), *ca.* 7.6 (m, 3H arom.), *ca* 7.9 (m, 2H arom.)

(2-*Substituted*)-4-(*methyl-hydrazono*)5(4*H*)-*thiazolones* (12)

General procedure. An ethereal solution of the corresponding compound **11** (0.01 mol) was added dropwise with stirring on ice-cold ethereal diazomethane (50 ml, *ca.* 0.035 mol). The mixture was then kept in the cold for 4–5 h. Compound **12** crystallized spontaneously. A few drops of HOAc were added, the solvent removed *in vacuo* and the residue recrystallized to give the title compounds. The following derivatives were obtained (R, m.p., recrystallization solvent and yield are given). Compound **12a** (2-benzylthio). Long yellow needles. 169–70° (EtOAc). 75%. Calc for $C_{11}H_{11}N_3OS_2$: C, 49.81; H, 4.18; N, 15.84; S, 24.12. Found: C, 49.88; H, 4.24; N, 15.91; S, 24.47%. IR 3300 (NH), 1680 (C=O); ^{1}H-NMR 3.42 (d, CH_3, J = 4.5 Hz), 6.48 (s, CH_2), 7.38 (s, 5H arom.), *ca.* 7.85 (broad, NH), disappears on shaking with D_2O, whilst the doublet at 3.42 collapses to a singlet; ^{13}C NMR 35.49 (CH_2), 38.22 (CH_3), 127.73–135.11 (C arom.), 140.62 (S-C=N), 165.66 (N-C=N), 184.75 (C=0).

Compound **12b** (2-benzyloxy). White needles. m.p. = 147–8° (EtOAc). 70% Calc for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.42; N, 16.87; S, 12.85. Found: C, 53.18; H, 4.33; N, 16.62; S, 13.01%. IR 3300 (NH), 1685 (C=O); ^{1}H-NMR 3.43 (d, CH_3, J = 4.5 Hz), 5.57 (s, CH_2), 7.53 (s, 5H arom.), *ca.* 7.8 (broad, NH) D_2O causes disappearance of the signal at 7.8, while the doublet at 3.43 collapses to a singlet.

Compound **12c** (2-methylthio). Yellow microneedles. 98–9° (EtOAc). 73%. Calc for $C_5H_7N_3OS_2$: C, 31.75; H, 3.73; N, 22.21; S, 33.83. Found: C, 31.81; H, 3.63; N, 22.18; S, 34.11%. IR 3265 (NH), 1700, 1680 (C=O); ^{1}H-NMR 2.64 (s, CH_3S), 3.45 (d, CH_3N), *ca.* 8.0 (broad, NH), disappears with D_2O while the doublet at 3.45 collapses to a singlet; ^{13}C-NMR 13.85 (CH_3S), 38.20 (CH_3N), 140.80 (S-C=N), 166.29 (N-C=N), 184.72 (C=O). Compound **12e** (2-phenyl). Yellowish plates. 110–1° (isopropanol). 70%. Calc for $C_{10}H_9N_3OS$: C, 54.79; H, 4.10; N, 19.17; S, 14.61. Found: C, 55.02; H, 4.28; N, 19.31; S, 14.42%. IR 3280 (NH), 1665 (C=O); ^{1}H-NMR 3.48 (d, CH_3), *ca.* 7.5 (m, 3H arom.), *ca.* 7.85 (m, 2H arom.), *ca.* 8.4 (broad, NH), disappears with D_2O, while the doublet collapses to a singlet.

^{1}H-NMR spectral data

The spectra were recorded for solutions in $CDCl_3$ with Me_4Si as internal standard on a Varian EM-390 spectrometer (compounds **2-7**, **11**, **12**) or a Varian XL-100 spectrometer (compounds **8**, **9**) in the frequency-sweep mode. Spectral widths of 900 and 180 Hz or 1000 and 250 Hz were respectively used for the measurements. Analyses of the systems were performed by a Nicolet 1180 data system using an ITRCAL program. The experimental and calculated spectra from the resulting best values matched satisfactorily.

REFERENCES

[1]M. Bernabé, O. Cuevas and E. Fernández Alvarez, (a) *Eur. J. Med. Chem.* **14**, 33 (1979), (b) *Synthesis* 191 (1977).

[2]M. Bernabé, O. Cuevas and E. Fernández Alvarez, *Tetrahedron Lett.* 895 (1977).

[3]J. H. Jones and M. J. Witty, *J. Chem. Soc. Perkin Trans.* I, 858 (1980).

[4]Recent review on thiazolones: G. C. Barrett, *Tetrahedron* **36**, 2023 (1980).

[5]A. H. Cook, G. Harris, I. Heilbron and G. Shaw, *J. Chem. Soc.* 1056 (1948).

[6](a) R. Filler and Y. S. Rao, *J. Org. Chem.* **27**, 3730 (1962), (b) H. Behringer and J. B. Jepson, *Chem. Ber.* **85**, 138 (1952).

[7]C. Foces-Foces, F. H. Cano and S. García-Blanco, *J. Cryst. Molec. Struct.* **8**, 309 (1979).

[8]G. C. Barrett, L. A. Chowdhury and A. A. Usmani, *Tetrahedron Lett.* 2063 (1978).

[9](a) Y. S. Rao and R. Filler, *Synthesis* 749 (1975), (b) I. Arenal, M. Bernabé and E. Fernández Alvarez, *An. Quim.* **77C**, 56 (1981).

[9](a) I. Arenal. Doctoral Thesis. Universidad Complutense de Madrid (1980); (b) I. Arenal, M. Bernabé, E. Fernández Alvarez and S. Penadés, *J. Heterocyclic Chem.* in press.
[10]M. L. Martínez, F. H. Cano and S. García-Blanco, *Acta Crystallogr. Sect. B* **33**, 3913 (1977).
[12]H. Muxfeldt, J. Behling, G. Grethe and W. Rogalski, *J. Am. Chem. Soc.* **89**, 4991 (1967).
[13]C. Cativiela and E. Meléndez, *Synthesis* 832 (1978).
[14]G. V. Boyd and P. H. Wright, *J. Chem. Soc. Perkin Trans.* I, 909 (1972).