Synthesis of 2,4′-Dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic Acids: X-Ray Structure of 1-Benzyl-3′-(4-chlorophenyl)-2,4′-dioxospiro-[indoline-3,2′-thiazolidine]-5′-acetic Acid

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The title compounds have been prepared by the cyclocondensation of mercaptosuccinic acid with isatin-3-imines. The 1-benzyl derivatives have been synthesized by simultaneously reacting 1-benzylisatin, substituted anilines and mercaptosuccinic acid. The structure of the products has been confirmed by X-ray diffraction measurements.

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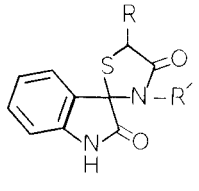
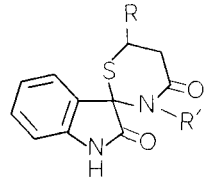
We have earlier reported the cyclocondensation of 2-mercaptopropanoic acid [1] and 3-mercaptopropanoic acid [2] with isatin-3-imines to give spirothiazolidinones **1a** and spirothiazinones **2a**, respectively. We now wish to

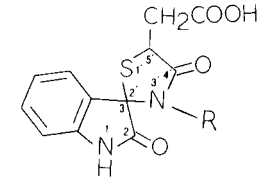


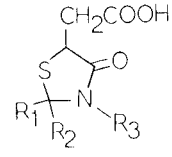
1a R = CH_3
1b R = CH_2COOH



2a R = H
2b R = COOH

report the cyclocondensation of isatin-3-imines with mercaptosuccinic acid **3**. The cyclocondensation of isatin-3-imines with mercaptosuccinic acid is of particular interest owing to the possibility of obtaining either **1b** or **2b** as an exclusive product or as a mixture of the two isomers. Cyclization along the shorter carbon chain would give 2,4′-dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic acid (**1b**) as the product, whereas, the isomeric 2,4′-dioxospiro-[indoline-3,2′-tetrahydro-1,3-thiazine]-6′-carboxylic acid (**2b**) would be formed if condensation occurred along the three carbon chain. The reaction of mercaptosuccinic acid with various other Schiff bases and hydrazones has been reported to give 4-oxothiazolidine-5-acetic acids **4** in general [3-22]. In our search we have found only one report of the six membered isomeric 4-oxotetrahydro-1,3-thiazine-6-carboxylic acid (**5**) being formed. This has been reported [3] for the cyclization reation with mercaptosuccinic acid leading to products **4a** and **5a**. The structures of the products reported [3-22] have been established, in general, on the basis of infrared data.





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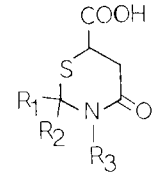

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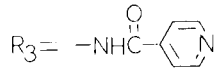
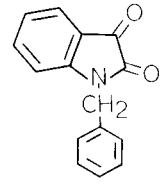
4a, 5a: R_1 = H, R_2 = 

R_3 = 



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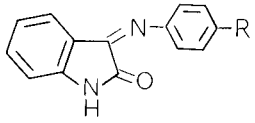
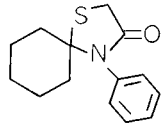


6	R
a	CH_3
b	OCH_3
c	Cl
d	Br
e	H
f	m-CF_3

We report here the first example of a spiro product being prepared from the cyclocondensation reaction of mercaptosuccinic acid with a Schiff base or a hydrazone. Following the general procedure described earlier [1,2] the isatin-3-imines **6a-f** were condensed with mercaptosuccinic acid in toluene under reflux [23], with azeotropic removal of the water formed, to give, as shown in Table 1, the spiro compounds **7a-f**. Equimolar amounts of 1-benzylisatin (**8**) and substituted aniline, and slight excess of mercaptosuccinic acid, when refluxed in toluene, gave products **9a-f**, as shown in Table 2.



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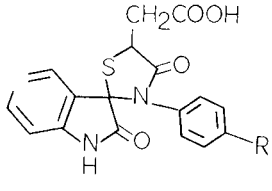
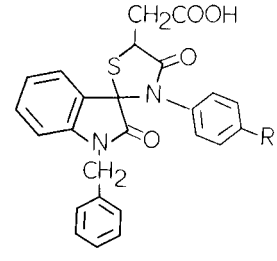


7a-f



9	R
a	Cl
b	H
c	Br
d	OCH_3
e	CH_3
f	C_2H_5

Table 1

7	R	time, hours	MP, °C [a]	Yield %	Formula	Analyses % Calcd.(Found) C	H	Spectral data ir (potassium bromide)
a	CH_3	5	221-222 [b]	69	$C_{19}H_{16}N_2O_4S$	61.94 (61.95)	4.38 (4.52) [c]	3600-2900, 3200, 1730, 1670, 1620 cm^{-1}
b	OCH_3	6	222-224	43	$C_{19}H_{16}N_2O_5S$	59.36 (59.56)	4.20 (4.29)	3600-2910, 3250, 1720, 1670, 1670, 1615 cm^{-1}
c	Cl	5	193-195	69	$C_{18}H_{13}ClN_2O_4S$	55.60 (55.33)	3.37 (3.44) [d]	3500-2875, 3200, 1720-1680, 1640 cm^{-1}
d	Br	6	195-197	33	$C_{18}H_{13}BrN_2O_4S$	49.89 (49.73)	3.02 (3.13)	3600-3000, 3225, 1720, 1675, 1640 cm^{-1}
e	H	5	185-188	50	$C_{18}H_{14}N_2O_4S$	61.00 (60.87)	3.98 (4.04)	3500-2800, 3200, 1700, 1670, 1610 cm^{-1}
f	(*m*-CF_3)	5	241-243	63	$C_{19}H_{13}F_3N_2O_4S$	54.02 (54.04)	3.10 (3.12)	3550-2850, 1730-1710, 1670, 1620 cm^{-1} [e]

[a] Recrystallized from ethanol/water. [b] Recrystallized from ethyl acetate/hexane. [c] Nigrogen: Calcd. 7.61, Found: 7.56. [d] Dried at 110° *in vacuo* for 24 hours. [e] pmr (acetone-d_6): **7f**, δ 4.47 (t, H, J = 7 Hz), 3.35 (d, 2H, J = 7 Hz).

ms: m/e(%) **7a**, 368.0824 ($C_{19}H_{16}N_2O_4S$, 100.000), 340.0881 ($C_{18}H_{16}N_2O_3S$, 75.83, M^+-CO), 324.0923 ($C_{18}H_{16}N_2O_2S$, 18.34, M^+-CO_2), 322.0774 ($C_{18}H_{14}N_2O_2S$, 5.52), 309.0695 ($C_{17}H_{13}N_2O_2S$, 5.24, M^+-CH_2COOH), 295.0902 ($C_{17}H_{15}N_2OS$, 52.96), 290.1051 ($C_{18}H_{14}N_2O_2$, 5.27), 268.0656 ($C_{15}H_{12}N_2OS$, 6.88), 240.0719 ($C_{14}H_{12}N_2S$, 74.26), 239.0637 ($C_{14}H_{11}N_2S$, 13.89), 237.1026 ($C_{15}H_{13}N_2O$, 95.84), 236.0943 ($C_{15}H_{12}N_2O$, 24.62), 235.0871 ($C_{15}H_{11}N_2O$, 16.80), 208.0998 ($C_{14}H_{12}N_2$, 91.17), 207.0918 ($C_{14}H_{11}N_2$, 22.54), 107.0736 (C_7H_9N, 16.88), 91.0548 (C_7H_7, 59.44), 89.0395 (C_7H_5, 11.95), 77.0402 (C_6H_5, 13.59), 65.0401 (C_5H_5, 47.26).

Table 2

9	R	time, hours	MP, °C [a]	Yield %	Formula	Analyses % Calcd.(Found) C	H	Spectral data ir (potassium bromide)
a	Cl	5	203-204	76	$C_{25}H_{19}ClN_2O_4S$	62.69 (62.80)	4.00 (4.14)	3500-2900, 1720-1690, 1610 cm^{-1}
b	H	3	112-114	74	$C_{25}H_{20}N_2O_4S$	67.55 (67.31)	4.54 (4.67)	3500-2900, 1730-1695, 1670, 1610 cm^{-1}
c	Br	1.5	211-212	75	$C_{25}H_{19}BrN_2O_4S$	57.36 (57.32)	3.66 (3.75)	3500-2900, 1715-1695, 1610 cm^{-1} [c]
d	OCH_3	2.5	221-222	75	$C_{26}H_{22}N_2O_5S$	65.80 (66.01)	4.67 (4.74)	3500-2900, 1715, 1700-1685, 1610 cm^{-1}
e	CH_3	5	225-226	87	$C_{26}H_{22}N_2O_4S$	68.10 (68.01)	4.84 (4.78) [b]	3500-2850, 1710-1700, 1665, 1600 cm^{-1}
f	C_2H_5	2	211-214	72	$C_{27}H_{24}N_2O_4S$	68.62 (68.29)	5.12 (5.04)	3450-2875, 1725-1670, 1620 cm^{-1}

[a] Recrystallized from ethanol/water. [b] Dried at 110° *in vacuo* for 24 hours. [c] ^{13}C nmr (DMSO-d_6): **9c**, δ 176.50, 173.38, 172.40.

That the structure of our products is of type **1b**, vis a vis **2b**, has been established on the basis of spectral data and X-ray diffraction measurements. The ^{13}C nmr spectrum (δ, dimethylsulfoxide-d_6) of **9c** shows carbonyl signals at 176.50 (C-7′), 173.38 and 172.40. Although the carbonyls at C-2 and C-4′ cannot be differentiated on the basis of **13C** nmr, the signals at 173.38 and 172.40 would imply both C-2 and C-4′ to be in a similar skeletal structure: in this case a five membered cyclic structure. This compares reasonably with the ^{13}C shift of C-4 of **10** which exhibited a signal at δ 170.78 [24]. The mass spectrum of **7a** (M^+, $C_{19}H_{16}N_2O_4S$, m/e 368.0824) shows a low intensity peak at 309.0695 (M^+-CH_2COOH,$C_{17}H_{13}N_2O_2S$) suggesting the product to be of type **1b**. The pmr spectrum of **7f** includes two signals, a doublet at δ 3.35 (J = 7 Hz) and a triplet at δ 4.47 (J = 7 Hz) for CH_2 at 6′ and CH at 5′ respectively. The infrared spectral data are presented in Tables 1 and

Table 3

Fractional Atom Co-ordinates (× 10^4) for Non-hydrogen Atoms of **9a**. Standard Deviations are Given in Parentheses.

Atom	x	y	z
S1	3536(2)	8366(2)	6082(3)
CL1	5755(2)	7798(2)	7194(3)
N1	1120(6)	8492(5)	6709(7)
N2	1267(6)	5727(6)	6722(8)
O1	3255(6)	9484(5)	10993(8)
O2	4676(7)	10248(6)	8515(8)
O3	935(6)	10238(5)	7781(7)
O4	784(5)	6890(5)	9084(6)
C1	3528(11)	9752(8)	9579(12)
C2	2354(8)	9499(6)	9273(9)
C3	2819(8)	9545(7)	7406(9)
C4	1549(7)	9497(7)	7303(9)
C5	1898(7)	7613(7)	6233(9)
C6	2136(7)	6948(7)	4646(9)
C7	2634(8)	7261(6)	3038(6)
C8	2770(9)	6444(9)	1766(9)
C9	2442(9)	5344(9)	2106(9)
C10	1934(8)	5004(6)	3737(6)
C11	1794(7)	5841(7)	4965(8)
C12	1225(7)	6725(7)	7588(7)
C13	912(8)	4696(7)	7495(6)
C14	2093(8)	4351(7)	7413(6)
C15	2028(8)	3250(7)	7496(8)
C16	3079(6)	2911(6)	7461(5)
C17	4224(9)	3676(9)	7289(7)
C18	4276(7)	4768(6)	7240(6)
C19	3244(9)	5135(7)	7247(6)
C20	−176(7)	8257(6)	6781(4)
C21	−253(5)	8566(4)	5487(5)
C22	−1507(6)	8450(3)	5608(4)
C23	−2683(4)	7937(5)	7056(3)
C24	−2607(7)	7638(6)	8313(8)
C25	−1344(5)	7774(6)	8193(4)

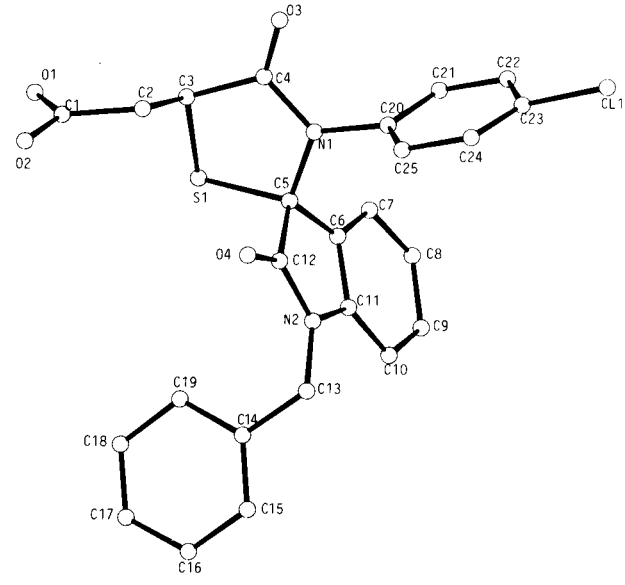


Figure 1 Compound 9a

Table 4

Selected Bond Distances (Å) and Angles (deg) for **9a**

C1-O1	1.26(1)	C4-N1	1.38(2)
C1-O2	1.26(1)	C4-O3	1.19(1)
C1-C2	1.50(2)	N1-C20	1.46(1)
C2-C3	1.52(1)	C23-CL1	1.74(1)
C3-S1	1.82(1)	C6-C7	1.37(1)
C3-C4	1.53(1)	C6-C11	1.38(1)
C5-S1	1.88(1)	C10-C11	1.38(1)
C5-N1	1.46(1)	C11-N2	1.43(2)
C5-C6	1.49(1)	C12-N2	1.37(2)
C5-C12	1.56(1)	C12-O4	1.20(1)
		N2-C13	1.44(2)
C3-S1-C5	94.2(4)	S1-C5-N1	103.0(5)
C4-N1-C5	118.7(8)	S1-C5-C6	111.3(5)
C4-N1-C20	120.9(7)	S1-C5-C12	109.4(5)
C5-N1-C20	119.9(6)	N1-C5-C6	116.9(9)
C11-N2-C12	111.9(8)	N1-C5-C12	113.2(6)
C11-N2-C13	124.8(7)	C6-C5-C12	103.1(7)
C12-N2-C13	123.2(7)	C5-C6-C7	131.1(9)
O1-C1-O2	123.5(9)	C5-C6-C11	109.3(8)
O1-C1-C2	114.9(8)	C7-C6-C11	119.6(8)
O2-C1-C2	121.5(1.0)	N2-C11-C6	109.1(7)
C1-C2-C3	111.8(6)	N2-C11-C10	127.2(9)
S1-C3-C2	114.9(7)	C6-C11-C10	123.7(8)
S1-C3-C4	104.2(6)	N2-C12-O4	127.2(8)
C2-C3-C4	106.8(6)	N2-C12-C5	106.2(7)
N1-C4-O3	122.5(9)	O4-C12-C5	126.6(8)
N1-C4-C3	114.0(8)	N2-C13-C14	113.5(6)
O3-C4-C3	123.3(8)		

2. X-Ray crystallographic measurements were obtained on compound **9a** to establish unequivocally the ring system: the structure of a crystal from **9a** was shown to be 1-benzyl-3′-(4-chlorophenyl)-2,4′-dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic acid (Figure 1).

Positional parameters and their standard deviations are given in Table 3 for non-hydrogen atoms. Selected bond lengths and angles are given in Table 4.

All the molecular dimensions are within accepted values. The two S-C distances are 1.82(1) and 1.88(1), the longer value being the bond attached to the carbon at the spiro junction. Bond angles at this junction are in the range 103-117° and the two rings wich meet at the spiro junction are 87° to one another. The *p*-chlorophenyl ring is approximately at right angles to the thiazolidine ring.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B Spectrophotometer. Proton magnetic resonance spectrum was recorded on a Hitachi Perkin Elmer Model R-24B instrument using tetramethylsilane as an internal standard. Carbon magnetic resonance spectra were determined at 20.1 MHz on a Bruker WP80 instrument. Chemical shifts are expressed in parts per million (δ). The mass spectrum was obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska (supported under the NSF Regional Instrumentation Facilities Program). Analyses were carried out by Spang Microanalytical laboratory.

Preparation of Isatin-3-imines **6a-f**.

Isatin (0.01 mole) and the appropriate aniline (0.01 mole) in 30-50 ml of absolute ethanol containing a drop of glacial acetic acid were heated at reflux on a steam bath for under 30 minutes. After standing for a few hours at room temperature, the products were collected in quantitative yields by filtration. Melting points for compound **6a-e** were consistent with those reported [1,2]. Compound **6f**, R = *m*-CF_3, had mp = 240-241° (from ethanol).

Preparation of 3′-(4-Methylphenyl)-2,4′-dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic Acid, **7a** and Analogs **7b-f**.

a) Compound **7a**.

A mixture of **6a** (0.01 mole) and mercaptosuccinic acid (0.012 mole) in 70 ml of toluene was refluxed for 5 hours and the water formed was azeotropically removed. The reaction mixture was cooled to room temperature, the product filtered and recrystallized from ethyl acetate/hexane to give **7a** as shown in Table 1.

b) Compound **7b**.

A mixture of **6b** (0.01 mole) and mercaptosuccinic acid (0.012 mole) in 70 ml of toluene was refluxed for 6 hours and the water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the gummy product obtained was dissolved in 10 ml of ethyl acetate and set aside for 48 hours. The solid product thus obtained was recrystallized from ethanol/water (Table 1).

c) Compounds **7c** and **7d**.

Using the procedure described for the preparation of **7a**, the analogs **7c** and **7d** were prepared and are shown in Table 1.

d) Compounds **7e** and **7f**.

The procedure described for the preparation of **7a** was followed. After refluxion, the reaction mixture was cooled and toluene decanted. The gummy residue was then recrystallized, from ethyl acetate/petroleum ether followed by another recrystallization from ethanol/water, to analytical purity (Table 1).

Preparation of 1-Benzyl-3′-(4-chlorophenyl)-2,4′-dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic acid, **9a** and Analogs **9b-f**.

a) Compound **9a**.

A mixture of 1-benzylisatin (0.005 mole), *p*-chloroaniline (0.005 mole), and mercaptosuccinic acid (0.006 mole) in 40 ml toluene was refluxed for 5 hours and the water formed was removed azeotropically. The reaction mixture was cooled to room temperature, the product filtered and recrystallized from ethanol/water to give **9a** as shown in Table 2.

b) Compounds **9b-f**.

Using the procedure described for the preparation of **9a**, the analogs **9b-f** were prepared and are shown in Table 2.

Crystallography.

Crystal Data: $C_{25}H_{19}O_4N_2SCl$, Formula weight = 478.9, triclinic, space group *P*T, a = 11.751(5), b = 12.500(3), c = 9.249(3)Å, α = 99.2(1), β = 58.6(1), γ = 103.6(1), μ = 1126.24 Å^3, d_{calcd} = 1.443 gcm^{-3}, Z = 2.

X-Ray data were taken at 293K with graphite monochromated MoK_α radiation (λ = 0.71069 Å) on a Stoe Stadi 2 Weissenberg diffractometer using an ω scan with θ_{max} = 30°. Of the 3993 reflections measured, 1769 had $I/\sigma(I) > 3$ and these were used in the calculations. No corretions were made for absorption (t_{max} = 0.980, t_{min} = 0.883).

The structure was solved by direct methods and refined anisotropically by full-matrix least squares refinement for all non-H atoms to R = 0.064 (R_w = 0.064). All H atoms except that attached to C3 were placed from a

difference map, but were not refined. Calculations for structure solution and refinement were carried out using SHELX [25] and for geometry calculations using XRAY [26].

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