Synthesis and Antileukemic Activity of Spiro[indoline-3,2′-thiazolidine]-2,4′-diones

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Received June 3, 1987

A number of spiro[indoline-3,2′-thiazolidine]-2,4′-diones have been prepared *via* the cyclocondensation of isatin-3-imines with α-mercaptoacids. 1-Benzyl-5′,5′-dimethylspiro[indoline-3,2′-thiazolidine]-2,4′-diones were prepared by simultaneously refluxing 1-benzylisatin, α-mercaptoisobutyric acid and various anilines in toluene. 3′-(4-Chlorophenyl)-5,5′-dimethylspiro[indoline-3,2′-thiazolidine]-2,4′-dione was active in the P388 and the L1210 leukemia screen tests. A number of analogs of the active spiro compound have been prepared and submitted for antileukemic screening. Anticonvulsant screening results of related compounds are also included.

J. Heterocyclic Chem., **24**, 1637 (1987).

Isatin-3-imines have been shown to undergo cyclocondensation reaction with thiolactic acid [1], mercaptosuccinic acid [2], 3-mercaptopropanoic acid [3,4] and mercaptoacetic acid [5-12] to give spiro oxindoles such as **1**, **2**, **3** and **4** respectively. We wish to report here the preparation of 5′,5′-dimethylspiro[indoline-3,2′-thiazolidine]-2,4′-diones *via* the cyclocondensation of isatin Schiff bases with α-mercaptoisobutyric acid. The diverse biological activity associated with thiazolidinones [13,14] and isatin derivatives [14-17] provides a motive to examine the potential of compounds such as **1**, **2**, **3** and **4** as biologically active agents. In our search for compounds of medicinal interest, a number of spiro[indoline-3,2′-thiazolidine]-2,4′-diones were synthesized and submitted for antileukemic [18] and anticonvulsant [1,19] screening.

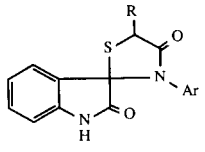
Reaction of isatin (**5**) and substituted isatins **6-10** with a variety of substituted anilines gave the isatin Schiff bases **11-27** (see experimental). Following the general procedure described earlier [1-3], the isatin-3-imines **11-15** were condensed with α-mercaptoisobutyric acid in toluene under reflux, with azeotropic removal of the water formed to give as shown in Table 1, the spiro products **28-32** respectively. Spiro compounds **33-36** were prepared by simultaneously refluxing 1-benzylisatin (**37**), the appropriate aniline and α-mercaptoisobutyric acid in toluene. The spiro compounds were characterised on the basis of spectral data and elemental analyses. The pmr (deuteriochloroform) spectrum of **30** exhibited two signals at δ 1.98 (s, 3H) and δ 1.78 (s, 3H) for the gem dimethyl groups. The methoxy protons appeared at δ 3.66 (s, 3H). Signals at δ 1.90 and δ

Table 1

5′,5′-Dimethylspiro[indoline-3,2′-thiazolidine]-2,4′-diones **28-36**

						Analyses %			
						Calcd.		Found	
No.	R	R′	Mp, °C [a]	Yield %	Formula [f]	C	H	C	H
28	H	H	282-283	53	$C_{18}H_{16}N_2O_2S$	66.64	4.97	66.47	4.97
29	H	CH_3	230-231 [b]	62	$C_{19}H_{18}N_2O_2S$	67.43	5.36	67.11 [c]	5.54
30	H	OCH_3	275-276	54	$C_{19}H_{18}N_2O_3S$ [g]	64.38	5.12	64.50	5.18
31	H	Br	239-240	30	$C_{18}H_{15}BrN_2O_2S$ [h]	53.60	3.75	53.59	3.78
32	H	C_2H_5	188-189 [d]	48	$C_{20}H_{20}N_2O_2S$	68.15	5.72	68.31	5.65
33	$CH_2C_6H_5$	H	170-171	53	$C_{25}H_{22}N_2O_2S$	72.43	5.35	72.20	5.31
34	$CH_2C_6H_5$	CH_3	229-230 [e]	48	$C_{26}H_{24}N_2O_2S$	72.87	5.64	72.86	5.65
35	$CH_2C_6H_5$	C_2H_5	199-200	57	$C_{27}H_{26}N_2O_2S$	73.27	5.92	73.37	5.90
36	$CH_2C_6H_5$	OCH_3	167-168	67	$C_{26}H_{24}N_2O_3S$	70.24	5.44	70.28	5.49

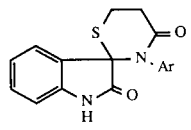
[a] Recrystallized from ethanol. [b] A part of the sample melted at 212-213°. [c] Nitrogen: Calcd. 8.28, Found 8.10. [d] Recrystallized from toluene-hexane. [e] Recrystallized from toluene. [f] All compounds exhibited ir spectra consistent with the structure shown. [g] Pmr (deuteriochloroform): **30** δ 7.45 (N*H* Broad), 7.21-6.61 (aromatic), 3.66 (s, 3H), 1.98 (s, 3H), 1.78 (s, 3H). [h] Pmr (acetone-d_6): **31** δ 7.55 (N*H* broad), 7.35-6.61 (aromatic), 1.90 (s, 3H), 1.71 (s, 3H).



1 R = CH_3

2 R = CH_2COOH

4 R = H



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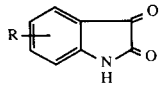


5 R = H

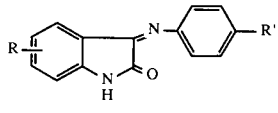
6 R = 5 - CH_3

7 R = 7 - CH_3

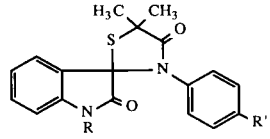
8 R = 5 - Cl

9 R = 5 - I

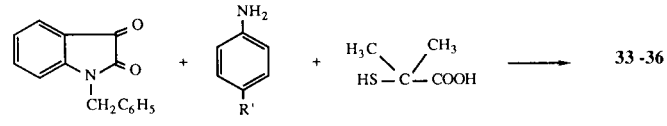
10 R = 5 - Cl, 7 - CH_3



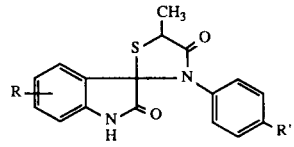
	R	R'
11	H	H
12	H	CH_3
13	H	OCH_3
14	H	Br
15	H	C_2H_5
16	5 - CH_3	Cl
17	5 - CH_3	F
18	5 - CH_3	I
19	5 - CH_3	Br
20	5 - CH_3	OCH_3
21	5 - CH_3	m - Cl
22	5 - CH_3	m - CF_3
23	7 - CH_3	Cl
24	5 - I	Cl
25	5 - Cl	Cl
26	5 - Cl, 7 - CH_3	Cl
27	5 - Cl	CH_3



	R	R'
28	H	H
29	H	CH_3
30	H	OCH_3
31	H	Br
32	H	C_2H_5
33	$CH_2C_6H_5$	H
34	$CH_2C_6H_5$	CH_3
35	$CH_2C_6H_5$	C_2H_5
36	$CH_2C_6H_5$	OCH_3



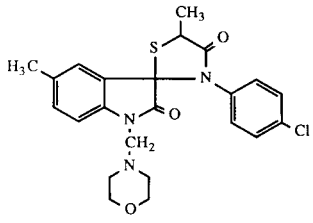
37



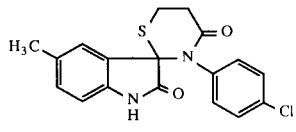
	R	R'
38	5 - CH_3	Cl
39	5 - CH_3	F
40	5 - CH_3	I
41	5 - CH_3	Br
42	5 - CH_3	OCH_3
43	5 - CH_3	m - Cl
44	5 - CH_3	m - CF_3
45	7 - CH_3	Cl
46	5 -I	Cl
47	5 - Cl	Cl
48	5 - Cl, 7 - CH_3	Cl
49	H	Cl
50	5 - Br	Cl
51	5 -NO_2	Cl
52	5 - Cl	CH_3
53	H	OH

1.71 were also present in the pmr (acetone-d_6) spectrum of **31** indicating the presence of the gem dimethyl groups. The signals attributable to the indole protons in **30** and **31** appeared at δ 7.45 and δ 7.55 (broad) respectively.

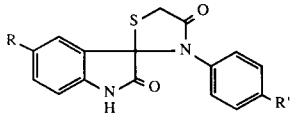
The architecturally novel antitumor antibiotic, Fredericamycin A has a 1,4-diketo*spiro*[4.1]nonane subunit, and is reportedly [20] active *in vivo* against the P388 and L1210 leukemia cell line. This report prompted us to submit for antileukemic screening some of the *spiro*[indoline-3,2'-thiazolidine]-2,4'-diones we had earlier prepared [1].



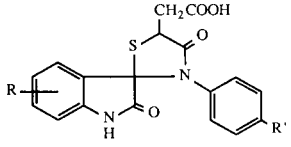
54



55



	R	R'
56	CH_3	Cl
57	H	Cl
58	H	Br
59	H	H



	R	R'
60	5 - CH_3	Cl
61	1 - $CH_2C_6H_5$	C_2H_5
62	1 - $CH_2C_6H_5$	H
63	1 - $CH_2C_6H_5$	OCH_3
64	1 - $CH_2C_6H_5$	Cl
65	H	CH_3

Compounds having an indoline substructure have been shown to possess antitumor activity. We felt that the spiro center in our compounds would contribute spatial characteristics similar to Fredericamycin A, perhaps leading to an active compound. In our preliminary search for a lead compound we found **38** exhibited substantial *in vivo* activity against intraperitoneally implanted murine P-388 lymphocytic leukemia [18]. We therefore decided to investigate the effect of structural modification on the antitumor activity. In our study 3'-(4-chlorophenyl)-5,5'-dimethylspiro[indoline-3,2'-thiazolidine]-2,4'-dione (**38**) served as the lead compound. Systematic variation on **38** has been effected *via* three modifications: variation of 3'-substituted-phenyl, variation at C-5 on the oxindole and variation of the thiazolidine moiety.

In the first category, the 3'-(4-chlorophenyl) substituent has been changed by replacing the chlorine (in **38**) with fluorine (**39**), iodine (**40**), bromine (**41**) and methoxy (**42**). Compound **43** represents a variant of **38** in which the 3'-phenyl group has a chlorine at the *meta* position. In compounds **46**, **47**, **49**, **50** and **51** the methyl at C-5 has been changed to iodine, chlorine, hydrogen, bromine and nitro respectively. In the next set of compounds the thiazolidine moiety in **38** has been modified. Compound **55** is isomeric with **38**, but has a tetrahydro-1,3-thiazine ring instead. In compounds **56** and **60** the 5'-methyl in **38** has been replaced by hydrogen and carboxymethyl respectively.

5'-Methylspiro[indoline-3,2'-thiazolidine]-2,4'-diones **38-53** were prepared by refluxing the appropriate isatin-3-imine with thiolactic acid in toluene with azeotropic removal of the water formed. Following the above procedure isatin-3-imine **16** when allowed to react with 3-mercaptopropanoic acid, mercaptoacetic acid and mercaptosuccinic acid gave **55**, **56** and **60** respectively. The spiro compound **38** when subjected to Mannich condensation with morpholine and formaldehyde gave the 1-morpholinomethyl derivative **54**. Physical properties of previously unreported spiro compounds are listed in Table 2.

The leukemia screen (3PS31) test results are shown in Table 3. Compound **38** had T/C % 141 at 240 mg/Kg and

Table 2

5'-Methylspiro[indoline-3,2'-thiazolidine]-2,4'-diones **39-48**, **52**

						Analyses %			
						Calcd.		Found	
No.	R	R'	Mp, °C	Yield	Formula [b]	C	H	C	H
39	5-CH_3	F	282-283 [a]	65	$C_{18}H_{15}FN_2O_2S$	63.14	4.42	63.06	4.30
40	5-CH_3	I	273-274 [a]	67	$C_{18}H_{15}IN_2O_2S$	48.01	3.36	48.07	3.41
41	5-CH_3	Br	149-150 [e]	51	$C_{18}H_{15}BrN_2O_2S$	53.60	3.75	53.55	3.90
42	5-CH_3	OCH_3	237-238 [c]	55	$C_{19}H_{18}N_2O_3S$	64.38	5.12	64.48	5.23
43	5-CH_3	*m*-Cl	209-210 [c]	69	$C_{18}H_{15}ClN_2O_2S$	60.24	4.21	60.53	4.30
44	5-CH_3	*m*-CF_3	191-192 [c]	69	$C_{19}H_{15}F_3N_2O_2S$	58.15	3.85	58.37	3.92
45	7-CH_3	Cl	232-233 [c]	61	$C_{18}H_{15}ClN_2O_2S$	60.24	4.21	60.51	4.34
46	5-I	Cl	259-260 [c,d]	45	$C_{17}H_{12}ICIN_2O_2S$	43.37	2.57	43.65	2.63
47	5-Cl	Cl	211-212 [c]	74	$C_{17}H_{12}Cl_2N_2O_2S$	53.83	3.19	53.96	3.21
48	5-Cl,7CH_3	Cl	253-254 [c]	61	$C_{18}H_{14}Cl_2N_2O_2S$	54.97	3.59	54.98	3.92
52	5-Cl	CH_3	222-223 [c]	67	$C_{18}H_{15}ClN_2O_2S$	60.24	4.21	59.97	4.30

[a] Recrystallized from ethanol. [b] All compounds exhibited ir spectra consistent with the structure shown. [c] Recrystallized from ethanol-water. [d] Turns dark 5° before melting.

was confirmed to be active *in vivo* against P388 lymphocytic leukemia. Replacement of the 3'-(4-chlorophenyl) substituent with 3'-(4-*halo*phenyl) led to inactive compounds. Compound **42** having a 3'-(4-methoxyphenyl) group had T/C % 119 at 240 mg/Kg. A compound having T/C % > 125 is considered to be substantially active at the dosage indicated. Substitution of the 5-methyl (on the oxindole) with chlorine (**47**) or bromine (**50**) led to compounds having lower T/C values. The 1-morpholinomethyl derivative of **38** was less potent than the parent compound, and had T/C % 121 at 240 mg/Kg. In order to examine positional requirements of the substituents in **38**, isomer **52** was synthesized. Interchanging of the 5-methyl and 3'-(4-chlorophenyl) substituents with 5-chloro and 3'-(4-methylphenyl) afforded an inactive compound (**52**).

Table 3

Leukemia Screen (3PS31) Test Results [18]

Compound	Doses Tested (mg/Kg) T/C% [a]		
	240	120	60
38	141	126	121 [b]
	133	119	114 [c]
39	87	90	89
40	91	94	103
41	97	96	94
42	119	102	109
47	108	105	105
49	96	103	101
50	100	109	97
51	91	91	91
52	100	96	91
53	94	100	91
54	121	100	113
55	100	95	103
56	100	100	101
60	Tox	96	99
61	Tox	97	94
62	89	95	89
16	95	87	99(Tox) [d]

[a] T/C % is the ratio of the median survival time of the test and control animals expressed as a percentage. A value of > 125 indicates significant antitumor activity at the dosage indicated. [b] T/C % = 103 at 30 mg/Kg. [c] Leukemia screen test repeated. In general a minimal increase in survival of treated animals over controls resulting in a T/C % > 125 is necessary for further work. [d] Toxic at 3.75 mg/Kg. T/C % = 101 at 0.93 mg/Kg.

Modification of the 5'-methylthiazolidine-4'-one moiety (as in **38**) to the *isomeric* tetrahydro-1,3-thiazine-4'-one yielded an inactive compound (**55**). The 5'-methyl substituent seems to be important for activity since the nor analog **56** and compound **60** were also found to be inactive at the doses tested. Isatin-6-imine **16** was inactive against P388 but exhibited considerable cytotoxicity at low doses.

3'-(4-Chlorophenyl)-5,5'-dimethylspiro[indoline-3,2'-thiazolidine]-2,4'-dione (**38**) has also shown activity against L1210 lymphoid leukemia (3LE31) and the mammary xenograft tumor test system 3MBG5. The screening results obtained for **38** against three test systems are shown in Table 4.

Table 4

Screening Results for **38**

Dosage mg/Kg	T/C % [a] 3LE31	3MBG5	3M531
800	—	72	86
400	123	125	93
200	116	85	98
100	116	107	101
50	113	—	96
25	107	—	—

[a] See Table 3 for explanations.

3'-(4-Chlorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione **57** [11] exhibited the ability to protect mice against Metrazol induced seizures [19] at 300 mg/Kg dose level (3/5 protected). Structural variants **31**, **33**, **34**, **35**, **58**, **59**, **63**, **64** and **65** were inactive at 300 mg/Kg in the maximal electroshock seizure and Metrazol tests [19].

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 spectra were recorded on a Hitachi Perkin Elmer Model R-24B instrument. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were carried out by Spang Microanalytical laboratory and Galbraith Laboratories, Inc.

Isatin-3-imines **11-15**.

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 30 minutes. After standing for a few hours at room temperature the products were collected by filtration and recrystallized from ethanol. Melting points for compounds **11-15** were consistent with those reported [3, 6, 21, 22, 23].

Isatin-3-imines **16-27**.

The 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 on a steam bath for one hour. After standing for a few hours at room temperature the products were collected by filtration and recrystallized from ethanol. Compound **16** (86%), mp 289-290°, lit [24] mp >235°; **17** (82%), mp 275°, lit [24] mp 262°; **18** (88%), 266-267°, lit [24] mp >210°; **19**, (83%), mp 282° dec., lit [24] mp >252°; **20** (71%) mp 221-222°, lit [24] mp 218-220°; **21** (72%) mp 204-205°, lit [24] mp

198-199°; **22** (73%) mp 227-229°; **3** (93%) mp 277-278; **24** (84%) mp 258-260°; **25** (89%) mp 267-268°; **26** (92%) mp 282-285°; **27**, (85%) mp >284°.

5',5'-Dimethyl-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'-dione, **28** and Analogs **29-32**.

a) A mixture of **11** (0.007 mole) and α-mercaptoisobutyric acid (0.008 mole) in 50 ml of toluene was refluxed for 15 hours in a Deak-Stark separator. The water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol to give **28** as shown in Table 1.

b) Using the procedure described above, the analogs **29-32** were obtained from imines **12-15** respectively, and are shown in Table 1.

1-Benzyl-5',5'-dimethyl-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'-dione, **33** and Analogs **34-36**.

a) A mixture of 1-benzylisatin [25] (0.004 mole), aniline (0.004 mole) and α-mercaptoisobutyric acid (0.005 mole) in 50 ml of toluene was refluxed for 15 hours and the water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol to give **33** as shown in Table 1.

b) Compounds **34-36** were similarly prepared and are shown in Table 1. In some cases an oil was obtained on evaporation of the solvent. Trituration in ethanol and refrigeration for one hour yielded a solid product.

5'-Methylspiro[indoline-3,2'-thiazolidine]-2,4'-diones **38-53**.

a) Compounds **38**, **49**, **50**, **51** and **53** were prepared as reported earlier [1].

b) A mixture of **17** (0.015 mole) and thiolactic acid (0.017 mole) in 100 ml toluene was refluxed for 10 hours and the water formed was removed azeotropically using a Dean-Stark separator. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol (charcoal) to give **39** as shown in Table 2.

c) Following the procedure described in section (b), isatin-3-imine (number of moles of imine: number of moles of thiolactic acid) **18** (0.012:0.016) gave the spiro product **40** as shown in Table 2. Similarly, **19** (0.008 : 0.0095) gave **41**, **20** (0.007 : 0.0085) gave **42**, **21** (0.014 : 0.017) gave **43**, **22** (0.013 : 0.016) gave **44**, **23** (0.014 : 0.017) gave **45**, **24** (0.011 : 0.015) gave **46**, **25** (0.013 : 0.016) gave **47** and **26** (0.013 : 0.016) gave **48** as shown in Table 2.

d) A mixture of 5-chloroisatin (0.01 mole) and *p*-toluidine (0.01 mole) was refluxed in absolute ethanol for 30 minutes. After standing overnight the product was filtered to give **27**. The imine (**27**), without further purification was refluxed with thiolactic acid (0.01 mole) in toluene for 7 hours in a Dean-Stark separator. The reaction mixture was cooled and the solvent evaporated *in vacuo* to give **52** as shown in Table 2.

3'-(4-Chlorophenyl)-5,5'-dimethyl-1-morpholinomethylspiro[indoline-3,2'-thiazolidine]-2,4'-dione (**54**).

A mixture of **38** (1.15 g, 0.0032 mole), morpholine (0.28 g, 0.0032 mole) and 37% formaldehyde (0.29 g) was refluxed in absolute ethanol for 10 hours. The reaction mixture was cooled, the solvent evaporated *in vacuo* and the crude product obtained was recrystallized from ethanol-water to give **54** in 66% yield, mp 186-187°, ir (potassium bromide): 2975, 2925, 2860, 1725, 1700, 1660, 1490, 1340, 1270, 1240, 1120 cm^{-1}.

Anal. Calcd. for $C_{23}H_{24}ClN_3O_3S$: C, 60.32; H, 5.28. Found: C, 59.97; H, 5.37.

3'-(4-Chlorophenyl)-5-methylspiro[indoline-3,2'-tetrahydro-1,3-thiazine]-2,4'-dione (**55**).

A mixture of **16** (0.01 mole) and 3-mercaptopropanoic acid (0.015 mole) in 100 ml of toluene was refluxed for 48 hours and the water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol-water to give analytically pure **55** in 22% yield, mp 267-268°; ir (potassium bromide): 3250, 2950, 1720, 1660, 1640, 1495, 1370 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2S$: C, 60.24; H, 4.21. Found: C, 60.50; H, 4.25.

3'-(4-Chlorophenyl)-5-methylspiro[indoline-3,2'-thiazolidine]-2,4'-dione (**56**).

A mixture of **16** (0.0075 mole) and mercaptoacetic acid (0.009 mole) in 100 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 product obtained was recrystallized from ethanol to give **56** in 57% yield, mp 145-146°, ir (potassium bromide): 3200-3150, 2975, 2925, 1720, 1690, 1620, 1495, 1405, 1350 cm^{-1}; pmr (dimethylsulfoxide-d_6): δ 7.40-6.55 (7H, aromatic), 4.05 (s, 2H, two components), 2.20 (s, 3H).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2S$: C, 59.21; H, 3.80. Found: C, 58.92; H, 4.37.

3'-(4-Bromophenyl)-spiro[indoline-3,2'-thiazolidine]-2,4'-dione (**58**).

Following the procedure described above (for **56**), imine **14** (0.01 mole) and mercaptoacetic acid (0.015 mole) gave **58** in 57% yield, mp (ethanol) 212-213°; ir (potassium bromide): 3200-3150, 3100, 2950, 2925, 1710, 1675, 1605, 1480, 1465, 1350, cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}BrN_2O_2S$: C, 51.21; H, 2.96. Found: C, 51.18; H, 3.05.

Compounds **57** and **59** were prepared as reported [11].

3'-(4-Chlorophenyl)-5-methyl-2,4'-dioxospiro[indoline-3,2'-thiazolidine]-5'-acetic Acid (**60**).

A mixture of **16** (0.015 mole) and mercaptosuccinic acid (0.015 mole) was refluxed in 100 ml toluene for 10 hours, with azeotropic removal of the water formed. The reaction mixture was cooled, the solvent evaporated *in vacuo* and the crude product thus obtained was recrystallized from ethyl acetate-petroleum ether, to give **60** [26] in 51% yield, mp 237-238°, ir (potassium bromide): 3350-2500 (broad), 3225, 3000, 2900, 1730, 1700, 1670, 1620, 1485, 1430, 1390 cm^{-1}, pmr (dimethylsulfoxide-d_6): δ 10.9 (s, COOH), 7.33-6.50 (7H, aromatic), 4.66 (d, J = 5 Hz, H, methine), 4.53 (d, J = 5 Hz, H, methine), 3.08 (d, J = 5 Hz, 2H, CH_2).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4S$: C, 56.64; H, 3.75; N, 6.96. Found: C, 56.21; H, 3.77; N, 6.87.

Compounds **61-65** were prepared as reported earlier [2].

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