Simple Synthetic Routes to 5-(3,6-Dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-diones and their Derivatives

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Two different synthetic routes to 5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-diones are described. The reaction sequences represent a facile entry into these series of isatin derivatives.

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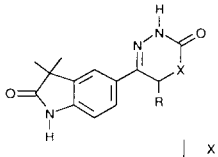
In the search for new cardiotonic drugs, interesting new biochemical properties [1] have been shown for compound **1** in which the pyridazinone ring of the cardiotonic indolidan [2] was replaced by the thiadiazinone moiety. In the course of this work, the effect of substitution in the 3-position of the indolone ring, and in particular, the result of the formal oxidation of this position to give isatin **2** (and its derivatives), was studied.

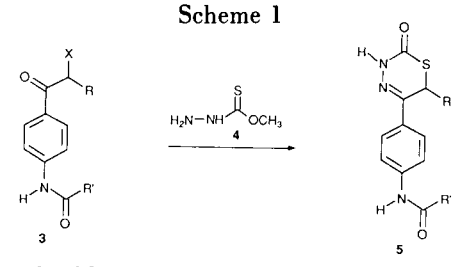


	X	R
Indolidan	CH_2	H
1	S	CH_3

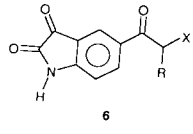
Formula 1

The difficulty in synthesizing compound **2** is related to the way of obtaining the thiadiazinone ring. The general route to form thiadiazinones like **5** utilizes a cyclization of an α-halogenated ketone **3** with *O*-methyl thiocarbazate **4** [3,4]. The haloketone is itself prepared by a classical Friedel-Crafts reaction between the appropriate anilide and an α-haloacyl chloride (Scheme 1).

Scheme 1

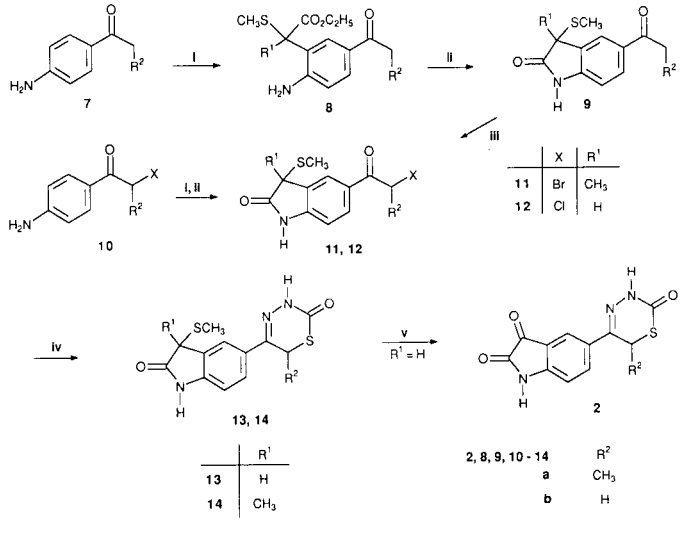


Due to the likely difficulties in obtaining 5-(haloacyl) isatin **6** (isatin equivalent of **3**) and performing selective reactions on this molecule, the synthesis of compound **2** was achieved in an indirect manner, starting from a 4-substituted aniline **7** to give substituted and protected isatin **9** using the Gassman and van Bergen procedure [5,8] (Scheme 2).



Formula 2

Scheme 2



	X	R^1
11	Br	CH_3
12	Cl	H

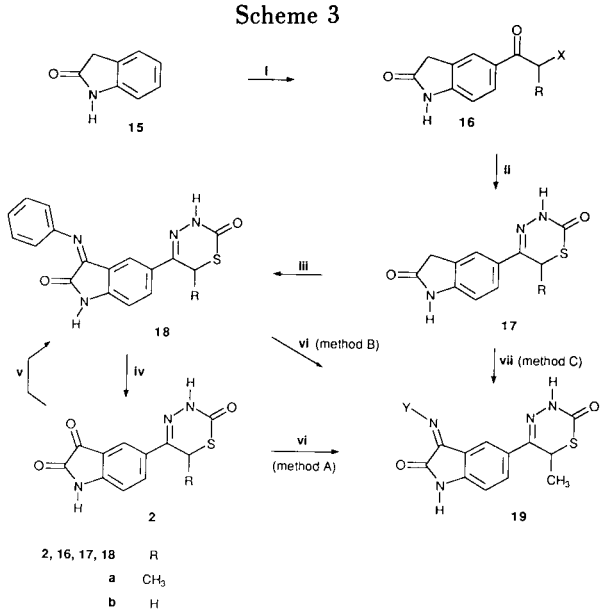
	R^1
13	H
14	CH_3

	R^2
2, 8, 9, 10 - 14 a	CH_3
b	H

i: 1. *t*-BuOCl, CH_2Cl_2, −65°; 2. ethyl methylthioacetate [10]; 3. triethylamine; **ii**: HCl 2 *M*, rt; **iii**: bromine, $CHCl_3$, 0-5°; **iv**: **4**, acetonitrile, reflux; **v**: 1. NCS, CH_2Cl_2, room temperature; 2. Hg(II)O, $BF_3 \cdot OEt_2$, THF, water.

Starting from 1-(4-aminophenyl)-2-chloropropanone **10a** [9] this well described procedure allowed the synthesis of **2** in good overall yield. It is worthy of note that the Gassman condensation works even in the presence of reactive functionalities such as ketones and α-bromoketones. Although this route worked well we were interested in developing an even more expedient alternative. This new route took advantage of the reactivity of the 3-position of indolones with electrophiles [11], in this instance nitrosobenzene [12] (Scheme 3). Under Friedel-Crafts conditions (aluminum chloride, DMF, 80°) indolone **15** reacts with 2-chloropropanoyl chloride to give **16a** in 97% yield. Cyclization of this α-chloroketone with *O*-methyl thiocarbazate **4** [3,4] in the presence of trifluoroacetic acid as catalyst gives **17a** in 87% yield. Nitrosobenzene is then condensed with **17a** in presence of piperidine as catalyst to give **18a** in 80% yield. The active methylene group of the thiadiazinone does not interfere during this reaction. An acidic deprotection of the imine gives rise to the isatin **2a** in 82% yield with the thiadiazinone ring unaffected. However, this reaction has to be conducted carefully since thiadiazinones easily lead to rearrangement products (*i.e.* *N*-aminothiazoles) under strong acidic hydrolysis [13a,13b].

Scheme 3



2, 16, 17, 18 R
a CH_3
b H

19a	$-NHC_6H_5$	**i**	$-NH-p-C_6H_4-CH_3$
b	-OH	**j**	$-NHCH_2C_6H_5$
c	$-NHCSOCH_3$	**k**	$-NHC_6H_{11}$
d	$-NHCSNH_2$	**l**	$-NHC_6F_5$
e	$-NH_2$	**m**	-NH-3-pyridyl
f	$-OC_6H_5$	**n**	$-NH-p-C_6H_4-COOH$
g	NH-2-imidazole	**o**	$-NH-p-C_6H_4-CF_3$
h	$-NHCOOCH_3$		

i: RCHXCOCl, $AlCl_3$, DMF, 80°; **ii**: **4**, acetonitrile, reflux; **iii**: nitrosobenzene, piperidine, MeOH, 60°; **iv**: $BF_3 \cdot OEt_2$, CH_3COOH, room temperature; **v**: aniline, EtOH, reflux; **vi**: hydrazine or amine, solvent, reflux; **vii**: aniline, $NaNO_2$, HCl, 0° or room temperature.

Initial biological results for **2** proved to be of interest and led to the preparation of many derivatives of this compound [14], based on the specific chemical properties of isatin [15]. The following examples describe the synthesis of hydrazone and imine derivatives **19** from compound **2a**. Condensation of **2a** under mild conditions with amines, hydrazines and hydrazides (refluxing in ethanol) gives the expected 3-alkyl- or 3-aryl-imino or 3-hydrazino-indol-2-ones **19a-h** in moderate to good yields (Method A, Scheme 3).

This synthesis could be shortened by direct condensation of the hydrazine with the 3-phenyliminoindol-2-one **18a** (Method B,, Scheme 3). This route (used for **19i-n**), not only proved to be more convenient (shorter route, easier purification), but also gave higher yields. For some compounds (*e.g.* **19o**) the required hydrazine is not well described in the literature. Thus although 2-trifluoromethyl phenylhydrazine is readily available, the 4-substituted derivative has been described only once [16] without full synthetic details (14% yield) and attempts to obtain a pure sample of the compound were unsuccessful. A more convenient procedure for **19o** involved a coupling reaction between an aryl diazonium salt and the indolone **17a** [17,18] (Method C, Scheme 3). Towards this end, attempts to react the phenyldiazonium salt prepared from aniline (sodium nitrite, water, hydrochloric acid), with the indol-2-one **17a** not only were successful, but showed good overall yields (60% yield for **19a**) compared to the previous method. In the same manner, the 4-trifluoromethylphenylhydrazonium salt, prepare *in situ* from 4-trifluoromethylaniline, gave the expected compound **19o** in 51% yield. This last approach can be used generally, but clearly is very appropriate when the required hyrazines are not available. It does not require initial reduction of the aryldiazonium salt prior to reaction and allows the preparation of hydrazone derivatives **19** in a single step from the indolone **17** without going through an isatin intermediate.

The efficient synthesis of **2** and **19**, detailed in this paper, will allow the biological properties of this isatin and its derivatives to be fully evaluated. This work is presently in progress.

EXPERIMENTAL

Melting points were taken in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The nmr spectra were recorded in deuteriochloroform or DMSO-d_6 on a Brucker ACE 200 MHz spectrometer; chemical shifts were recorded in units (ppm relative to tetramethylsilane as the internal standard). The ir spectra were of samples in potassium bromide, recorded using a Shimadzu IR408 model spectrometer. Microanalytical data were provided by the Physical and Analytical Service Unit of the SmithKline Beecham Pharmaceutical Research Laboratories at Harlow, Great Britain.

Ethyl 2-[[3-(1-Oxoethyl)-6-amino]phenyl]-2-methylthiopropionate (**8b**).

To a stirred solution of 11.9 g (97 mmoles) of 1-(4-aminophenyl)ethanone in 300 ml of methylene chloride at −65° was added dropwise a solution of 9.55 g (88 mmoles) of *t*-butyl hypochlorite in 40 ml of dichloromethane. After 10 minutes, 13 g (0.1 mole) of ethyl methylthioacetate [10] dissolved in 30 ml of methylene chloride was added in a 45 minute period; stirring at −65° was continued for 1 hour. Subsequently 8.8 g (88 mmoles) of triethylamine in 40 ml of methylene chloride was added. After addition was completed, the cooling bath was removed and the solution was allowed to warm to room temperature. A 100 ml portion of water was added and the organic layer was separated and washed with an additional 100 ml portion of water. The organic layer was treated with charcoal, dried over magnesium sulfate and evaporated to dryness; 7 g of **8b** was isolated after trituration with ether and standing 48 hours at 0°. The mother liquor afforded another 4.0 g crop. The resulting isolated compound was used in the next step without further purification.

1,3-Dihydro-3-methyl-3-methylthio-5-(1-oxoethyl)-2*H*-indol-2-one (**9b**).

A mixture of 7 g (26 mmoles) of ethyl 2-[[3-(1-oxoethyl)-6-amino]phenyl]-2-methylthiopropionate **8b** and 40 ml of aqueous 2*M* hydrochloric acid was stirred for 2 hours at room temperature. Filtration and washing with water yielded 5.2 g (85%) of 1,3-dihydro-3-methyl-3-methylthio-5-(1-oxoethyl)-2*H*-indol-2-one **9b**, mp 165°; ir (potassium bromide): NH 3250, CO 1735, 1695, 1670, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): 1.55 (s, 3, CH_3), 1.90 (s, 3, CH_3S), 2.50 (s, 3, CH_3CO), 7.00 (d, 1, Ar, J = 8 Hz), 8.00 (s, 1, Ar), 8.10 (d, 1, Ar, J = 8 Hz), 10.90 (s, 1, N*H*).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.29; H, 5.62; N, 5.88.

1,3-Dihydro-3-methyl-3-methylthio-5-(1-oxopropyl)-2*H*-indol-2-one (**9a**).

Starting from 4-aminopropiophenone and using the methods described for **8b** and **9b** afforded, without isolation of the intermediate ethyl 2-[[3-(1-oxopropyl)-6-amino]phenyl]-2-methylthiopropionate **8a**, the desired compound **9a**, overall yield, 59%, mp 168°; ir (potassium bromide): NH 3250, CO 1738, 1695, 1682, 1622 cm^{-1}; ^1H nmr (deuteriochloroform): 1.24 (t, 3, CH_3CH_2, J = 7.3 Hz), 1.27 (s, 3, CH_3), 1.94 (s, 3, CH_3S), 2.99 (q, 2, CH_3CH_2, J = 7.3 Hz), 7.01 (d, 1, Ar, J = 6.5 Hz), 7.94 (d, 1, Ar, J = 6.5 Hz), 7.97 (s, 1, Ar), 8.94 (s, 1, N*H*).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.94; H, 6.09; N, 5.75.

5-[(2-Bromo-1-oxo)ethyl]-1,3-dihydro-3-methyl-3-methylthio-2*H*-indol-2-one (**11b**).

A solution of 1.17 g (4.9 mmoles) of 5-acetyl-1,3-dihydro-3-methyl-3-methylthio-2*H*-indol-2-one **9b** in 20 ml of chloroform was cooled to 0-5°. Bromine (0.8 g) in 5 ml of chloroform was added dropwise. The solution was allowed to return to room temperature (15 minutes) and washed twice with 50 ml of water, then successively with 50 ml of a saturated aqueous solution of sodium hydrogen carbonate and 50 ml of brine. The organic layer was dried over magnesium sulfate and evaporated to dryness. Trituration with ethyl ether afforded 1.0 g of compound **11b**, yield 64%, mp 122°; ir (potassium bromide): NH 3150, CO 1735, 1675, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): 1.60 (s, 3, CH_3C), 1.92 (s, 3, CH_3S), 4.87 (A_2B_2, 2, J_{aa} = 2.8 Hz, J_{ab} = 10.1 Hz, CH_2Br), 7.00 (d, 1, J = 7.9 Hz, Ar), 7.95 (s, 1, Ar), 7.97 (d, 1, J = 7.9 Hz, Ar), 11.04 (s, 1, N*H*).

Anal. Calcd. for $C_{12}H_{12}BrNO_2S$: C, 45.87; H, 3.85; N, 4.61. Found: C, 45.68; H, 3.75; N, 4.57.

5-[(2-Bromo-1-oxo)propyl]-1,3-dihydro-3-methyl-3-methylthio-2*H*-indol-2-one (**11a**).

The same procedure as for **11b** was used to prepare **11a** from **9a** giving a crude product which was used without further purification.

5-[(2-Chloro-1-oxo)propyl]1,3-dihydro-3-methylthio-2*H*-indol-2-one (**12a**).

A solution of 20 g (0.11 mmoles) of 1-(4-aminophenyl)-2-chloropropanone **10a** [9] in 290 ml of methylene chloride was cooled to −65°. *t*-Butyl hypochlorite (11.80 g, 0.11 mole) in 40 ml of methylene chloride was added dropwise. Stirring was continued for 15 minutes. A solution of 14.6 g (0.11 mole) of ethyl methylthioacetate [10] in 40 ml of methylene chloride was then added dropwise at −65°. Stirring was continued for 1.5 hours at this temperature. Triethylamine (11 g, 0.11 mole) in 40 ml of methylene chloride was then added and the reaction temperature slowly raised to ambient. After addition of 100 ml of water the reaction mixture was extracted three times with 100 ml of methylene chloride. The organic layer was washed twice with 100 ml of water and concentrated. The oily residue was taken up in 100 ml of ethyl ether and 50 ml of aqueous 2*M* hydrochloric acid was added. After stirring overnight, the aqueous layer was extracted three times with 75 ml of ethyl acetate. The combined organic layers were washed twice with 100 ml of water, decolorized with charcoal and dried over magnesium sulfate. Elimination of the solvent afforded 16.0 g of an oil used in the next step without further purification. A small amount was purified for analytical purpose by column chromatography (silica, eluent: hexane/ethyl acetate: 1/1), yield of crude product 64%, oil; ir (film): NH 3250, CO 1700, 1620 cm^{-1}; ^1H nmr (deuteriochloroform): 1.75 (d, 3, CH_3CH, J = 6.5 Hz), 2.08 (s, 3, CH_3S), 4.35 (s, 1, CH_3SCH), 5.22 (q, 1, $CHCH_3$, J = 6.5 Hz), 7.03 (d, 1, Ar, J = 8.7 Hz), 8.05 (m, 2, Ar), 9.34 (s, 1, N*H*).

5-[(2-Chloro-1-oxo)ethyl]-1,3-dihydro-3-methylthio-2*H*-indol-2-one (**12b**).

Starting from 1-(4-aminophenyl)-2-chloroethanone **10b** [19] and ethyl methylthioacetate [10], the procedure used for compound **12a** afforded the desired product, yield 50%, mp 175°; ir (potassium bromide): NH 3250, CO 1725, 1685, 1605 cm^{-1}; ^1H nmr (DMSO-d_6): 2.00 (s, 3, CH_3S), 4.54 (s, 1, CH_3SCH), 5.09 (s, 2, CH_2Cl), 6.98 (d, 1, Ar, J = 8 Hz), 7.90 (m, 2, Ar), 10.94 (s, 1, N*H*).

Anal. Calcd. for $C_{11}H_{10}ClNO_2S$: C, 51.67; H, 3.94; N, 5.48. Found: C, 51.59; H, 4.08; N, 5.72.

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methylthio-2*H*-indol-2-one (**13a**).

A mixture of 20 g (crude, 74 mmoles) of 5-[(2-chloro-1-oxo)propyl]-1,3-dihydro-3-methylthio-2*H*-indol-2-one **12a** and 7.9 g (74 mmoles) of *O*-methyl thiocarbazate [3,4] in 300 ml of acetonitrile was refluxed overnight. Concentration followed by trituration in hexane/ethyl acetate 1/1 yielded 18 g of yellow crystals. The filtrate after concentration and chromatography on silica gel (eluent: hexane/ethyl acetate: 1/1) afforded another 2 g crop, yield 88%, mp 159°; ir (potassium bromide): NH 3200, CO 1700, 1620

cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.48 (d, 3, CH_3CH, J = 7 Hz), 2.23 (s, 3, CH_3S), 4.57 (s, 1, CHS), 4.69 (q, 1, CHCH$_3$, J = 7 Hz), 6.91 (d, 1, Ar, J = 8 Hz), 7.70 (d, 1, Ar, J = 8 Hz), 7.75 (s, 1, Ar), 10.72 (s, 1, NH), 11.55 (s, 1, NH).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S_2 \cdot 0.25H_2O$: C, 50.06; H, 4.36; N, 13.47. Found: C, 50.10; H, 4.41; N, 13.46.

1,3-Dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methylthio-2*H*-indol-2-one (**13b**).

Starting from 5-[(2-chloro-1-oxo)ethyl]-1,3-dihydro-3-methylthio-2*H*-indol-2-one **12b** and *O*-methyl thiocarbazate [3,4] and according to the procedure above described for **13a**, the desired compound was obtained, yield: 55%, mp 201-204°; ir (potassium bromide): NH 3200, CO 1715, 1640, 1625 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.99 (s, 3, CH_3S), 4.14 (s, 2, CH_2S), 4.54 (s, 1, CHS), 6.93 (d, 1, Ar, J = 8 Hz), 7.70 (d, 1, Ar, J = 8 Hz), 7.76 (s, 1, Ar), 10.73 (s, 1, NH), 11.46 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S_2 \cdot 0.25H_2O$: C, 48.39; H, 3.89; N, 14.11. Found: C, 48.50; H, 3.84; N, 14.47.

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methyl-3-methylthio-2*H*-indol-2-one (**14a**).

Starting from 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-3-methyl-3-methylthio-2*H*-indol-2-one **11a** and *O*-methyl thiocarbazate [3,4] and according to the procedure described for **13a**, the desired compound was obtained, yield 35%, mp 250°; ir (potassium bromide): NH 3170, CO 1725, 1685, 1620 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.49 (d, 3, CH_3CH, J = 7.2 Hz), 1.58 (s, 3, CH_3), 1.92 (s, 3, CH_3S), 4.74 (q, 1, CHCH$_3$, J = 7.2 Hz), 6.85 (d, 1, Ar, J = 8 Hz), 7.71 (d, 1, Ar, J = 8 Hz), 7.80 (s, 1, Ar), 10.74 (s, 1, NH), 11.55 (s, 1, NH).

Anal. Calcd. for $C_{14}H_{15}N_3O_2S_2 \cdot 0.25H_2O$: C, 51.59; H, 4.79; N, 12.89. Found: C, 51.61; H, 4.81; N, 12.65.

1,3-Dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methyl-3-methylthio-2*H*-indol-2-one (**14b**).

A suspension of 4 g (12.7 mmoles) of 5-[(2-bromo-1-oxo)ethyl]-1,3-dihydro-3-methyl-3-methylthio-2*H*-indol-2-one **11b** and 1.5 g (13.9 mmoles) of *O*-methyl thiocarbazate [3,4] in 40 ml of acetonitrile was refluxed during 2 hours. The mass obtained after concentration was purified by chromatography on silica (ethyl acetate/methylene chloride: 1/1) to yield 1.6 g of the title compound, yield 41%, mp 213°; ir (potassium bromide): NH 3150, CO 1728, 1690, 1635 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.55 (s, 3, CH_3), 1.90 (s, 3, CH_3S), 4.20 (s, 2, CH_2S), 6.90 (d, 1, Ar, J = 8 Hz), 7.70 (d, 1, Ar, J = 8 Hz), 7.75 (s, 1, Ar), 10.75 (s, 1, NH), 11.45 (s, 1, NH).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S_2$: C, 50.80; H, 4.26; N, 13.67. Found: C, 50.48; H, 4.19; N, 13.38.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione (**2a**).

A mixture of 3.30 g (10.8 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methylthio-2*H*-indol-2-one **13a**, 1.89 g (14 mmoles) of *N*-chlorosuccinimide in 250 ml of methylene chloride was stirred overnight at room temperature. After concentration the residue was taken up in a minimum volume of tetrahydrofuran. This solution was added to a suspension of 2.34 g (10.8 mmoles) of mercury(II) oxide, 1.52 g (10.8 mmoles) of boron trifluoride etherate in 75 ml of tetrahydrofuran and 75 ml of water. After 1 hour stirring, 100 ml of chloroform were added and the suspension was filtered. The filtrate was extracted three times with 50 ml of chloroform. The combined organic layers were washed twice with 100 ml of water and dried over magnesium sulfate. The compound was purified by column chromatography (silica, eluent: chloroform/methanol: 97/3), yield 60%, mp 131°; ir (potassium bromide): NH 3280, CO 1745, 1655, 1620 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.52 (d, 3, CH_3CH, J = 7 Hz), 4.62 (q, 1, CHCH$_3$, J = 7 Hz), 6.97 (d, 1, Ar, J = 8 Hz), 7.96 (dd, 1, Ar, J = 8 Hz, J' = 1.5 Hz), 8.10 (d, 1, Ar, J' = 1.5 Hz), 11.18 (s, 1, NH), 11.45 (s, 1, NH).

Anal. Calcd. for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.30; N, 15.26. Found: C, 52.34; H, 3.33; N, 15.13.

5-(3,6-Dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione (**2b**).

Using the same method as for **2a** and starting from 1,3-dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-methylthio-2*H*-indol-2-one **15b** yielded only a low yield of **2b** due to the very low solubility of this latter compound. This molecule was obtained through by route (*vide infra*), but in low yields again for the same reasons of insolubility.

5-[(2-Bromo-1-oxo)propyl]-1,3-dihydro-2*H*-indol-2-one (**16a**).

In a reactor equipped with a mechanical stirrer and containing 200 g (1.5 moles, 10 equivalents) of aluminum chloride, 35 ml of dry dimethylformamide was added dropwise at 0-5°. The exothermic reaction was then heated to 70° during 30 minutes. When the reaction temperature had decreased to room temperature, 1,3-dihydroindol-2-one (oxindole) (20 g, 0.15 mole) was added portionswise. While maintaining the temperature below 40° with an ice bath, 2-bromopropionyl chloride (27.4 g, 0.16 moles) were added dropwise over a 30 minutes period. The reaction mixture was then left 18 hours at room temperature, then heated to 40° for an hour. When cooled, the mixture was poured on 1 kg of crushed ice. The precipitate was filtered, washed with water and dried under vacuum, yield 97%, mp 164-165°; ir (potassium bromide): NH 3150, CO 1720, 1700, 1670, 1620 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.59 (d, 3, CH_3CH, J = 6.4 Hz), 3.58 (s, 2, CH_2CO), 5.71 (q, 1, CHCH$_3$, J = 6.4 Hz), 6.93 (d, 1, Ar, J = 8.1 Hz), 7.88 (s, 1, Ar), 7.95 (d, 1, Ar, J = 8.1 Hz), 10.84 (s, 1, NH).

Anal. Calcd. for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.42; H, 3.78; N, 5.32.

5-[(2-Chloro-1-oxo)ethyl]-1,3-dihydro-2*H*-indol-2-one (**16b**) [20].

The same reaction conditions described for **16a** were used to prepare 5-[(2-chloro-1-oxo)ethyl]-1,3-dihydro-2*H*-indol-2-one **16b**, starting from 1,3-dihydroindol-2-one and chloroacetyl chloride, yield 95%, mp 240°; ir (potassium bromide): NH 3220, CO 1740, 1710, 1680, 1615 cm^{-1}; lit [20].

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one (**17a**).

A mixture of 38 g (0.142 mole) of 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-2*H*-indol-2-one **16a**, 15.04 g (0.142 mole) of *O*-methyl thiocarbazate [3,4] in 800 ml of acetonitrile was refluxed under stirring for 6.5 hours. After cooling at 0-5°, the crude crystalline product was collected, washed twice with 50 ml of acetonitrile and dried to give 15.23 g of **17a** as white crystals, yield 41% (if one equivalent (0.142 mole) of trifluoroacetic acid is added to the mixture at the beginning of the reaction, the yield can be raised to 87%), mp 270°; ir (potassium bromide): NH 3450, 3200, CO 1690, 1640, 1615 cm^{-1}; ^{1}H nmr (DMSO-d_6): 1.47 (d, 3, CH_3CH, J

= 7.1 Hz), 3.54 (s, 2, CH_2CO), 4.70 (q, 1, C*H*CH$_3$, J = 7.1 Hz), 6.89 (d, 1, Ar, J = 7.9 Hz), 7.66 (d, 1, Ar, J = 7.9 Hz), 7.68 (s, 1, Ar), 10.63 (s, 1, N*H*), 11.60 (s, 1, N*H*).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S \cdot 0.25H_2O$: C, 54.22; H, 4.36; N, 15.81. Found: C, 54.58; H, 4.17; N, 16.01.

1,3-Dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one (**17b**).

A mixture of 61 g (0.29 mole) of 5-[(2-chloro-1-oxo)ethyl]-1,3-dihydro-2*H*-indol-2-one **16b**, 31.8 g (0.30 mole) of *O*-methylthiocarbazate [3,4] in 600 ml of acetonitrile was refluxed under stirring for 6 hours. The crude crystalline product was collected by filtration while warm, washed twice with 200 ml of acetonitrile and twice with 200 ml of diethyl ether, then dried to give 65 g of **17b** as white crystals, yield 87%, mp 320° dec; ir (potassium bromide): NH 3200, CO 1690, 1635, 1615 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): 3.54 (s, 2, CH_2CO), 4.17 (s, 2, CH_2S), 6.88 (d, 1, Ar, J = 8 Hz), 7.66 (d, 1, Ar, J = 8 Hz), 7.68 (s, 1, Ar), 10.62 (s, 1, N*H*), 11.50 (s, 1, N*H*).

Anal. Calcd. for $C_{11}H_9N_3O_2S \cdot 0.4H_2O$: C, 51.92; H, 3.88; N, 16.51. Found: C, 51.87; H, 3.74; N, 16.85.

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one (**18a**).

A. From 5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione (**2a**).

A mixture of 2 g (7.3 mmoles) of 5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione **2a** and 0.68 g (7.3 mmoles) of aniline in 50 ml of ethanol was refluxed for 1 hour. After cooling, yellow crystals were filtered off and dried at 40° under vacuum to give **18a** as a mixture of syn and anti isomers, yield 78%, mp 290°.

B. From 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one (**17a**).

A suspension of 8 g (30.6 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one **17a** in 100 ml of methanol mixture was heated to 60°. Nitrosobenzene (3.6 g, 33.6 mmoles) was added portionswise at this temperature, followed dropwise by 1.6 ml of piperidine neat. The suspension became clear, then a precipitate appeared after a few minutes. Stirring was continued for a further 10 minutes and the suspension was cooled. The precipitate was filtered off, washed twice with 10 ml of ethyl ether and dried under vacuum, yielding 18 g of the desired compound identical with that one obtained by the previous method, yield 80%; ir (potassium bromide): NH 3200, CO 1769, 1735, 1645, 1615 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): (mixture of syn and anti) 1.27 (d, 3 x 0.72, CH_3CH, J = 7.1 Hz), 1.48 (d, 3 x 0.28, CH_3CH, J = 7.1 Hz), 4.07 (q, 0.72, C*H*CH$_3$, J = 7.1 Hz), 4.80 (q, 0.28, C*H*CH$_3$, J = 7.1 Hz), 6.7-8.1 (m, 8, Ar), 11.2 (s, 1, N*H*), 11.57 (s, 0.72, N*H*), 11.68 (s, 0.28, N*H*); ms: 218, 233, 234, 235, 261, 262, 322, 323, 350 (M$^+$), 351, 352; Molecular ion: 350.0823 (theoretical 350.08374 for $C_{18}H_{14}N_4O_2S$).

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.41; H, 4.08; N, 15.92.

1,3-Dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one (**18b**).

A solution of 1,3-dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one **17b** (5 g, 20 mmoles) in 250 ml of methanol/dimethylformamide (1/4) was heated to 60°. Nitrosobenzene (2.35 g, 22 mmoles) was added portionswise at this temperature followed dropwise by 1 ml of piperidine neat. The mixture was heated two hours at this temperature, then filtered while hot. The filtrate was concentrated under vacuum and poured into 1 ℓ of water. Filtration yielded a crystalline residue which after trituration in hot methanol gave 750 mg of the desired compound. Another crop could be obtained by extraction of the filtrate with ethyl acetate. The combined organic layers were washed with water, treated with charcoal and dried over magnesium sulfate.

After concentration the residual oil was treated with isopropyl ether and ethyl acetate and led, after vacuum drying, to 830 mg of crystals identical with the previous crop, yield 23%, mp >300°; ir (potassium bromide): NH 3200, CO 1745, 1660, 1615 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): (mixture of syn and anti), 3.86 (s, 1.46, CH_2, syn or anti), 4.25 (s, 0.54, CH_2, syn or anti), 6.8-8.1 (m, 8, Ar), 11.19 (s, 0.3, N*H*), 11.42 (s, 0.7, N*H*), 11.5 (s, 1, N*H*).

Anal. Calcd. for $C_{17}H_{12}N_4O_2S \cdot 0.5H_2O$: C, 59.12; H, 3.79; N, 16.22. Found: C, 59.32; H, 3.78; N, 16.41.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione (**2a**) from 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one (**18a**).

Trifluoroboron etherate (1.54 ml) was added to a suspension of 10 g (28 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one **18a** in 1 ℓ of acetic acid. After 1 hour stirring at room temperature, the mixture was poured in 7 ℓ of water and extracted three times with 800 ml of ethyl acetate. The combined organic layers were washed six times with 600 ml of water and dried over magnesium sulfate. After concentration the residue was washed with methylene chloride (50 ml) yielding 6.4 g of red crystals showing a single spot on tlc (chloroform/methanol: 9/1) with physical data (mp, ir, nmr) identical with the compound obtained by the previous method, yield 82% (*vide supra*).

5-(3,6-Dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione (**2b**).

Starting from 1,3-dihydro-5-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one **18b** and using the same method described for **2a**, the method led to the desired compound, yield 13%, mp >300°; ir (potassium bromide): NH 3180, CO 1745, 1635, 1610 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): 4.22 (s, 1, CH_2S), 6.99 (d, 1, Ar, J = 8.3 Hz), 7.90 (d, 1, Ar, J' = 1.8 Hz), 8.05 (dd, 1, Ar, J = 8.3 Hz, J' = 1.8 Hz), 11.26 (s, 1, N*H*), 11.60 (s, 1, N*H*); accurate mass: $C_{11}H_7N_3O_3S$. Calcd: 261.0208. Found: 261.0210.

Anal. Calcd. for $C_{11}H_7N_3O_3S \cdot H_2O$: C, 47.31; H, 3.25; N, 15.05. Found: C, 47.31; H, 2.62; N, 14.77 [21].

Condensation of Hydrazines with Isatine **2a**. General Procedure (Method A).

A mixture of 5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione **2a** (1 molar equivalent) and the hydrazine (1 molar equivalent as the base) in ethanol (50 ml/g of **2a**) was refluxed during two hours. If the hydrochloride of the hydrazine was used, 1 molar equivalent of potassium carbonate was added to the reaction mixture before starting the heating. After cooling, the crystals were filtered off, triturated in water and dried under vacuum.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-in-

dole-2,3-dione 3-Phenylhydrazone (**19a**).

Method A followed by a complementary purification by column chromatography on silica (eluent: chloroform containing 1% methanol) afforded 58% of yellow crystals, mp 296°; ir (potassium bromide): NH 3150, CO 1692, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): 1.50 (d, 3, CH_3CH, J = 7.1 Hz), 4.83 (q, 1, CH_3CH, J = 7.1 Hz), 6.9-8.1 (m, 8, Ar), 11.26 (s, 1, NH), 11.64 (s, 1, NH), 12.74 (s, 1, NH-N).

Anal. Calcd. for $C_{18}H_{15}N_5O_2S \cdot 0.25H_2O$: C, 58.44; H, 4.22; N, 18.93. Found: C, 58.52; H, 4.19; N, 18.73.

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-hydroxyimino-2*H*-indol-2-one (**19b**).

Method A afforded 34% of yellow crystals, mp 170°; ir (potassium bromide): NH 3200, CO 1725, 1640, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): 1.47 (d, 3, CH_3CH, J = 7.1 Hz), 4.71 (q, 1, CH_3CH, J = 7.1 Hz), 6.96 (d, 1, Ar, J = 8.3 Hz), 7.80 (d, 1, Ar, J = 8.3 Hz), 8.47 (s, 1, Ar), 10.97 (s, 1, NH), 11.63 (s, 1, NH), 13.45 (broad s, 1, OH).

Anal. Calcd. for $C_{12}H_{10}N_4O_3S \cdot 0.5H_2O$: C, 48.15; H, 3.70; N, 18.71. Found: C, 48.08; H, 3.47; N, 18.37.

O-Methyl 2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2-oxo-1*H*-indol-3-ylidene Hydrazine-carbothioate (**19c**).

Method A afforded 71% of orange crystals, mp 245°; ir (potassium bromide): NH 3200, 3150, CO 1700, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): 1.47 (d, 3, CH_3CH, J = 7.1 Hz), 4.17 (s, 3, CH_3O), 4.83 (q, 1, CH_3CH, J = 7.1 Hz), 7.03 (d, 1, Ar, J = 8.3 Hz), 7.87 (dd, 1, Ar, J = 8.3 Hz, J' = 1.8 Hz), 7.93 (d, 1, Ar, J' = 1.8 Hz), 11.57 (s, 1, NH), 11.69 (s, 1, NH), 13.51 (s, 1, NH).

Anal. Calcd. for $C_{14}H_{13}N_5O_3S_2$: C, 46.27; H, 3.61; N, 19.27. Found: C, 46.05; H, 3.56; N, 19.02.

2-[2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2-oxo-1*H*-indol-3-ylidene] Hydrazine-carbothioamide (**19d**).

Method A afforded 79% of yellow crystals, mp 300°; ir (potassium bromide): NH 3250, CO 1698, 1648, 1625, 1608 cm^{-1}; ^1H nmr (DMSO-d_6): 1.52 (d, 3, CH_3CH, J = 7.1 Hz), 4.65 (q, 1, CH_3CH, J = 7.1 Hz), 7.02 (d, 1, Ar, J = 8.3 Hz), 7.81 (dd, 1, Ar, J = 8.3 Hz, J' = 1.7 Hz), 8.12 (d, 1, Ar, J' = 1.7 Hz), 8.81 (s, 1, NH), 9.12 (s, 1, NH), 11.43 (s, 1, NH), 11.70 (s, 1, NH), 12.41 (s, 1, NH).

Anal. Calcd. for $C_{13}H_{12}N_6O_2S_2$: C, 44.82; H, 3.47; N, 24.12. Found: C, 44.70; H, 3.49; N, 23.34.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-Hydrazone (**19e**).

Method A afforded 14% of yellow crystals, mp 268°; ir (potassium bromide): NH 3400, 3200, CO 1690, 1620, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): 1.48 (d, 3, CH_3CH, J = 7.1 Hz), 4.77 (q, 1, CH_3CH, J = 7.1 Hz), 6.95 (d, 1, Ar, J = 8.3 Hz), 7.65 (dd, 1, Ar, J = 8.3 Hz, J' = 1.7 Hz), 7.79 (d, 1, Ar, J' = 1.7 Hz), 9.80 (m, 1, NH_2), 10.52 (m, 1, NH_2), 10.93 (m, 1, NH), 11.63 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{11}N_5O_2S$: C, 49.82; H, 3.83; N, 24.21. Found: C, 49.60; H, 3.84; N, 23.82.

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenoxyimino-2*H*-indol-2-one (**19f**).

Method A afforded 41% of yellow crystals, mp 212°; ir (potassium bromide): CO 1735, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): 1.51 (d, 3, CH_3CH, J = 7.0 Hz), 4.79 (q, 1, CH_3CH, J = 7.0 Hz), 7.04 (d, 1, Ar, J = 8.0 Hz), 7.2-7.6 (m, 5, phenyl), 7.94 (dd, 1, Ar, J = 8.0 Hz, J' = 1.7 Hz), 8.51 (d, 1, Ar, J' = 1.7 Hz), 11.2 (m, 1, NH), 11.7 (m, 1, NH).

Anal. Calcd. for $C_{18}H_{14}N_4O_3S \cdot 0.5H_2O$: C, 57.59; H, 4.02; N, 14.92. Found: C, 57.91; H, 3.85; N, 15.16.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-[2-(4,5-Dihydro-1*H*-2-imidazolyl)hydrazone] (**19g**).

Method A afforded 41% of yellow crystals, mp 243° dec; ir (potassium bromide): CO 1680, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): 1.49 (d, 3, CH_3CH, J = 7.1 Hz), 3.34 (s, 4, NCH_2CH_2N), 4.58 (q, 1, CH_3CH, J = 7.1 Hz), 6.88 (d, 1, Ar, J = 8.3 Hz), 7.5-7.7 (m, containing at 7.63, s, 2, NH, NH, and dd, 1, Ar, J = 8.3 Hz, J' = 1.7 Hz), 8.72 (d, 1, Ar, J' = 1.7 Hz), 10.50 (s, 1, NH), 11.58 (s, 1, NH).

Anal. Calcd. for $C_{15}H_{15}N_7O_2S \cdot 1.5H_2O$: C, 46.87; H, 4.72; N, 25.51. Found: C, 46.63; H, 4.83; N, 25.04.

Methyl 2-(2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2-oxo-1*H*-indol-3-ylidene] Hydrazine-carboxylate (**19h**).

Method A afforded 33% of yellow crystals, mp 201°; ir (potassium bromide): NH 3200, CO 1735, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): 1.50 (d, 3, CH_3CH, J = 7.0 Hz), 3.84 (s, 3, CH_3O), 4.81 (q, 1, CH_3CH, J = 7.0 Hz), 6.97 (d, 1, Ar, J = 8.3 Hz), 7.84 (d, 1, Ar, J = 8.3 Hz), 8.34 (s, 1, Ar), 11.02 (s, 1, NH), 11.25 (s, 1, NH), 11.70 (s, 1, NH).

Anal. Calcd. for $C_{14}H_{13}N_5O_4S \cdot 1.5H_2O$: C, 44.91; H, 4.31; N, 18.70. Found: C, 45.06; H, 3.98; N, 18.75.

Condensation of Hydrazine with 3-Phenyliminoindol-2-one **18a**. General Procedure (Method B).

A mixture of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3-phenylimino-2*H*-indol-2-one **18a** (1 molar equivalent), and hydrazine (1.1 molar equivalents) in acetonitrile was refluxed for 2 hours. The mixture was cooled, filtered off and the residue was washed with hot 1/1 methanol/water and dried under vacuum.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-[(4-Methyl)phenylhydrazone (**19i**).

Method B afforded 92% of orange crystals, mp 285°; ir (potassium bromide): CO 1680, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): 1.50 (d, 3, CH_3CH, J = 7.1 Hz), 2.29 (s, 3, CH_3Ar), 4.85 (q, 1, CH_3CH, J = 7.1 Hz), 7.00 (d, 1, Ar, J = 8.3 Hz), 7.20 (d, AB, 2, phenyl, J = 8.4 Hz), 7.39 (d, AB, 2, phenyl, J = 8.4 Hz), 7.73 (dd, 1, Ar, J = 8.3 Hz, J' = 1.8 Hz), 7.99 (d, 1, Ar, J = 1.8 Hz), 11.26 (s, 1, NH), 11.66 (s, 1, NH), 12.74 (s, 1, NH).

Anal. Calcd. for $C_{19}H_{17}N_5O_2S \cdot 0.25H_2O$: C, 59.44; H, 4.59; N, 18.24. Found: C, 59.55; H, 4.47; N, 18.25.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-[(Phenylmethyl)hydrazone] (**19j**).

Method B afforded 24% of yellow crystals, mp 202°; ir (potassium bromide): NH 3200, CO 1665, 1605 cm^{-1}; ^1H nmr (DMSO-d_6): 1.46 (d, 3, CH_3CH, J = 7.0 Hz), 4.7-4.8 (m, 3, CH_3CH + $ArCH_2$), 6.94 (d, 1, Ar, J = 8.3 Hz), 7.2-7.4 (m, 5, phenyl), 7.64 (d, 1, Ar, J = 8.3 Hz), 7.80 (s, 1, Ar), 11.03 (s, 1, NH), 11.37 (s, 1, NH), 11.61 (s, 1, NH).

Anal. Calcd. for $C_{19}H_{17}N_5O_2S \cdot 0.25H_2O$: C, 59.44; H, 4.59; N, 18.24. Found: C, 59.49; H, 4.50; N, 18.28.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-(Cyclohexylhydrazone) (**19k**).

Method B afforded 54% of yellow crystals, mp 217°; ir (potassium bromide): NH 3150, CO 1675, 1635 cm^{-1}; ^1H nmr (DMSO-d_6): 1.0-2.1 (m, 13, including cyclohexyl ring and d, at 1.47 ppm, 3, C*H*$_3$CH, J = 7.1 Hz), 3.5-3.7 (m, 1, C*H*N), 4.78 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 6.95 (d, 1, Ar, J = 8.2 Hz), 7.64 (dd, 1, Ar, J = 8.3 Hz, J' = 1.6 Hz), 7.80 (d, 1, Ar, J' = 1.6 Hz), 11.03 (s, 1, N*H*), 11.16 (d, 1, N*H*, J = 5.3 Hz), 11.61 (s, 1, N*H*).

Anal. Calcd. for $C_{18}H_{21}N_5O_2S$: C, 58.20; H, 5.70; N, 18.85. Found: C, 58.29; H, 5.71; N, 18.53.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-(Pentafluorophenylhydrazone) (**19l**).

Method B afforded 92% of yellow crystals, mp 285°; ir (potassium bromide): NH 3250, CO 1700, 1620, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): 1.47 (d, 3, C*H*$_3$CH, J = 7.1 Hz), 4.78 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 7.02 (d, 1, Ar, J = 8.3 Hz), 7.77 (d, 1, Ar, J = 8.3 Hz), 7.88 (s, 1, Ar), 11.47 (s, 1, N*H*), 11.65 (s, 1, N*H*), 12.51 (s, 1, N*H*).

Anal. Calcd. for $C_{18}H_{10}F_5N_5O_2S \cdot 0.5H_2O$: C, 46.56; H, 2.39; N, 15.08. Found: C, 46.54; H, 2.26; N, 15.06.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-(3-Pyridylhydrazone) (**19m**).

Method B afforded 64% of yellow crystals, mp 275°; ir (potassium bromide): CO 1700, 1620, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): 1.50 (d, 3, C*H*$_3$CH, J = 7.1 Hz), 4.84 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 7.01 (d, 1, Ar, J = 8.3 Hz), 7.37-7.44 (m, 1, pyridine), 7.77 (d, 1, Ar, J = 8.3 Hz), 7.90-7.95 (m, 1, pyridine), 8.03 (s, 1, Ar), 8.27 (m, 1, pyridine), 8.79 (m, 1, pyridine), 11.31 (s, 1, N*H*), 11.68 (s, 1, N*H*), 12.63 (s, 1, N*H*).

Anal. Calcd. for $C_{17}H_{14}N_6O_2S \cdot H_2O$: C, 53.11; H, 4.19; N, 21.86. Found: C, 52.87; H, 3.88; N, 21.49.

4-[2-[5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2,3-dihydro-2-oxo-1*H*-indol-3-ylidene]hydrazino]benzoic Acid (**19n**).

Method B afforded 95% of yellow crystals, mp >320°; ir (potassium bromide): OH 3500, NH 3200, CO 1690, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): 1.50 (d, 3, C*H*$_3$CH, J = 7.1 Hz), 4.85 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 7.02 (d, 1, Ar, J = 8.3 Hz), 7.56 (d, A*B*, 2, phenyl, J = 8.7 Hz), 7.77 (dd, 1, Ar, J = 8.3 Hz, J' = 1.7 Hz), 7.95 (d, A*B*, 2, phenyl, J = 8.7 Hz), 8.03 (d, 1, Ar, J' = 1.7 Hz), 11.35 (s, 1, N*H*), 11.67 (s, 1, N*H*), 12-13 (m, 1, COOH), 12.80 (s, 1, N*H*).

Anal. Calcd. for $C_{19}H_{15}N_5O_4S \cdot H_2O$: C, 53.39; H, 4.01; N, 16.38. Found: C, 53.88; H, 3.71; N, 16.45.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-Phenylhydrazone (Method C) (**19a**).

Aniline (400 mg, 4.3 mmoles) in 10 ml of water containing 2.5 ml of aqueous concentrated hydrochloric acid was diazotized at 0-5° with a cold solution of 300 mg (4.3 mmoles) of sodium nitrite in 8 ml of water. The resulting solution was added dropwise to a solution of 1.0 g (3.8 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one **17a** in 20 ml of ethanol and 20 ml of DMF. The mixture was stirred for one hour at room temperature. The precipitate was filtered off, washed with methylene chloride and methanol and dried under vacuum to give a compound with analytical data (mp, ir, nmr) identical with these obtained by the previous method, Yellow crystals, yield 60%.

5-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-1*H*-indole-2,3-dione 3-[4-Trifluoromethylphenylhydrazone] (**19o**).

A solution of 1 g (6.2 mmoles) of 4-trifluoromethylaniline in 16 ml of water containing 7 ml of aqueous 10*M* hydrochloric acid was diazotized at 0-5° with a cold solution of 430 mg (6.3 mmoles) of sodium nitrite in 8 ml of water. This resulting solution was added dropwise to a solution of 1.62 g (6.2 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-2*H*-indol-2-one **17a** in 20 ml of ethanol and 25 ml of DMF. After two hours stirring at room temperature the precipitate was filtered off, washed with methylene chloride and hot methanol and dried under vacuum, yield: 51%, mp >300°; ir (potassium bromide): CO 1705, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): (mixture of syn and anti), 1.52 (2d, 3, C*H*$_3$CH), 4.83 (m, 1, CH$_3$C*H*), 6.9-8.5 (m, 7, including 4H, phenyl ring and 3H, Ar), 10.9-12.8 (m, 3, 3 x N*H*).

Anal. Calcd. for $C_{19}H_{14}F_3N_5O_2S \cdot 0.5H_2O$: C, 51.58; H, 3.42; N, 15.83. Found: C, 51.75; H, 3.34; N, 15.54.

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