Synthesis of 1,3,4-Thiadiazin-2-one and 1,3,4-Selenadiazin-2-one Derivatives as New Cardiotonic Drugs

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The synthesis of the new heterocycle 1,3,4-selenadiazin-2-one is described, based on the preparation of the analogue heterocycle 1,3,4-thiadiazin-2-one. The related cyclization between an α-haloketone and a thiocarbazate cannot readily be employed within the selenium series. Therefore a new route was developed based upon a diazotization/hydrolysis sequence of the related 2-amino-1,3,4-selenadiazine.

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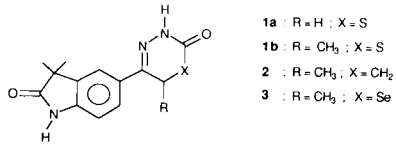
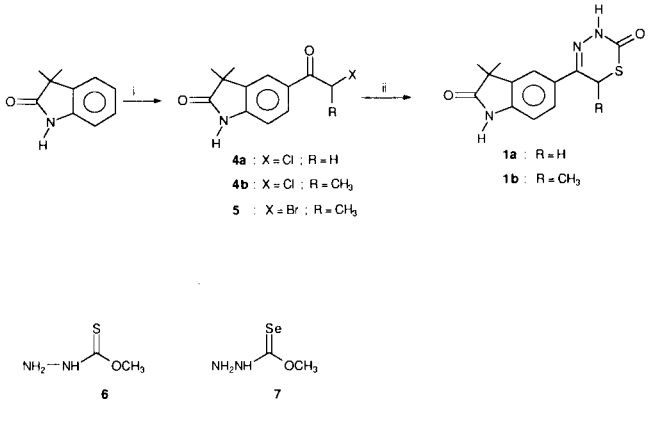
Promising cardiotonic activity obtained with 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3,3-dimethyl-2*H*-indol-2-one **1** [1-3] prompted us to synthesize analogues of this compound by modifying the heteroatoms in the thiadiazinone ring. The methylene equivalent, *i.e.* the 4,5-dihydropyridazin-3(2*H*)-one **2** was previously synthesized by Robertson's group [4]. The present paper describes the preparation of compound **1** and develops the synthesis of the novel 3,6-dihydro-1,3,4-selenadiazin-2-one ring system, examplified by compound **3**.



Formula I

Thiadiazinones were initially built up by a classical sequence involving a Friedel-Crafts reaction between a 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one [4] and an α-halocarboxyl halide, and subsequent condensation with *O*-methylthiocarbazate **6** [5-8] (Scheme I). It was shown that catalyzing the latter reaction with trifluoroacetic acid improved the yields.

Scheme I



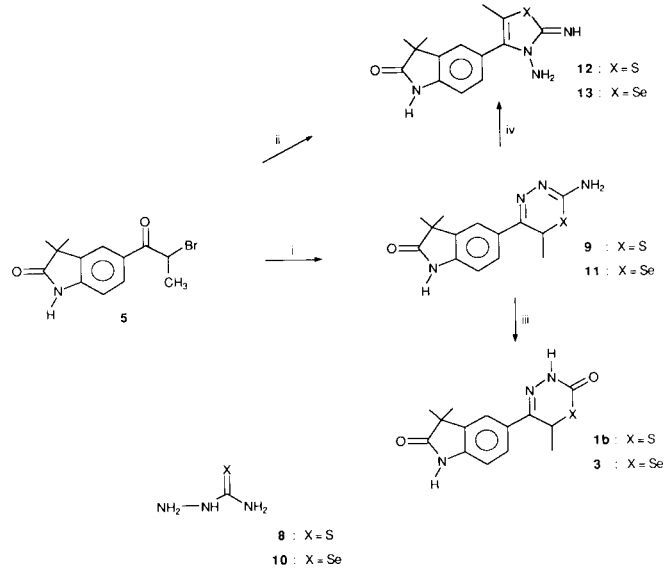
i : $AlCl_3$, RCHXCOCl, DMF, 70° ; ii : **6**, CH_3CN, reflux.

As a result of the difficulty in obtaining the *O*-methylselenacarbazate **7** (compound not described in the literature), this route to the 1,3,4-selenadiazinone ring system was not attempted. We therefore turned our attention to the transformation of the known 2-amino-1,3,4-selenadiazines (formed by condensation of an α-bromoketone with a 4-alkyl or a 4-aryl selenasemicarbazide [9-11]) into its selenadiazinone analogues.

Initially this transformation was carried out in the sulfur series. The condensation of α-bromoketones with thiosemicarbazide to thiadiazines is well described in the literature [9,12-15], although some authors claim the formation of 1,2,4-triazin-3-thiones as major product [16].

Therefore thiosemicarbazide **8** was condensed with **5** (Scheme II) to give in 70% yield the 2-amino-6*H*-1,3,4-thiadiazine **9** [12]. This reaction works only if it is performed in the presence of trifluoroacetic acid. On the contrary without this catalyst the isolated compound becomes

Scheme II

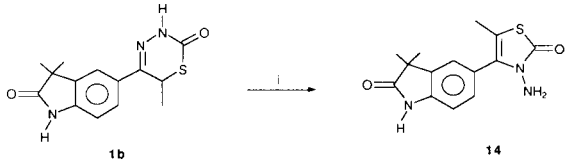


i : **8** or **10**, CH_3CN, CF_3COOH, reflux ; ii : **8** or **10**, CH_3CN, reflux ; iii : DMF, $NaNO_2$, H_2O, CF_3COOH, 40° ; iv : HCl *10N*, reflux.

3-amino-2,3-dihydro-2-imino-1,3-thiazole **12**. Similarly aqueous acidic hydrolysis of the 2-amino-6*H*-1,3,4-thiadiazine **9** leads to the rearrangement product **12** as described in the literature [12] and is not hydrolyzed through a possible iminotautomeric form to thiadiazin-2-one (also 3,6-dihydro-2-oxo-1,3,4-thiadiazine **1b** rearranges to 3-amino-2,3-dihydro-2-oxo-1,3-thiazole **14** (Scheme III)). However the exocyclic nitrogen atom of **9** reacts like an aniline and may be diazotized. Sodium nitrite in acidic media cleanly hydrolyzes that function to the expected oxo group to give compound **1b**.

From the analogous selenasemicarbazide **10**, obtained from potassium selenacyanate and hydrazine [17-18] the same sequence leads to the expected 2-amino-6*H*-1,3,4-selenadiazine **11** in the presence of trifluoroacetic acid, and results in the contracted five membered 3-amino-2,3-dihydro-2-imino-1,3-selenazole ring **13** [19] in the absence of the catalyst. The required 3,6-dihydro-1,3,4-selenadiazin-2(2*H*)-one **3** is then obtained after diazotization of **11** (Scheme II) in a manner identical with the one used in the sulfur series.

Scheme III



1b 14

i : Aqueous *10N* HCl, reflux.

In contrast to the thiadiazinones, however, the yields remain very low. In each reaction involving selena derivatives, elemental selenium was isolated as by-product. No other counterpart of the molecule could be isolated and/or identified. Although the final compounds appear stable under normal conditions of storage, reaction conditions (essentially heat) lead to decomposition.

In conclusion, we have been able to prepare a new selenaheterocycle using a new chemical route. Although this method is limited by its low yields, it is to date the only route to 1,3,4-selenadiazin-2-ones.

Both thiadiazinones **1** and selenadiazinones **3** showed interesting cardiotonic activity as excellent PDE III inhibitors. Moreover they are of particular interest as they possess significant sensitizing properties of myocardial contractile proteins to calcium, a property which was not observed with the pyridazinone equivalent **2**. Biochemical properties are still under evaluation and will be published when completed.

EXPERIMENTAL

Melting points were taken in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were recorded in deuteriochloroform or dimethyl sulfoxide-d_6 on a Brucker ACE 200 MHz spectrometer; chemical shifts are recorded in units (ppm relative to tetramethylsilane as the internal standard). The infrared spectra were of samples in potassium bromide, measured using a Shimadzu IR 408 model spectrometer. Microanalytical data were provided by the Physical and Analytical Service Unit of the SmithKline Beecham Pharmaceutical Research Laboratories at Harlow, Great Britain.

5-(2-Chloroacetyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**4a**).

Aluminum chloride (13.3 g) and DMF (2.2 ml) were stirred at 70° for 15 minutes. After cooling to 40°, 1.5 g (9.3 mmoles) of 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one [4] and 1.1 g (10 mmoles) of 2-chloroacetyl chloride were added and the resulting mixture was stirred at 70° for 1 hour. The mixture was poured onto 100 g of crushed ice and 10 ml of aqueous 10*N* hydrochloric acid, then extracted with 3 portions of 75 ml of ethyl acetate. The organic layer was washed twice with 100 ml of water, dried over magnesium sulfate and evaporated to dryness. Trituration with diethyl ether afforded 1.5 g (68%) of compound **4a** used directly in the next step.

5-[(2-Chloro-1-oxo)propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**4b**).

Using the same conditions as for the preparation of 5-(2-chloroacetyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **4a** and starting from 2-chloropropionyl chloride, the desired compound **4b** was obtained in 53% yield and used in the next step without further purification.

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

Anhydrous aluminum chloride (100 g) and 17 ml of dimethyl formamide were stirred at 70° for 30 minutes. After cooling to room temperature 12 g (74 mmoles) of 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one [4] and 16.1 g (74 mmoles) of 2-bromopropionyl bromide were added and the reaction mixture was stirred at 80° for 1.5 hours. The solution was poured onto 600 g of crushed ice containing 60 ml of aqueous 10*N* hydrochloric acid and stirred for 15 minutes. The mixture was extracted twice with 250 ml of ethyl acetate, the organic phase washed twice with 250 ml of water and dried over magnesium sulfate. The solvent was evaporated to dryness. Trituration of the residue with isopropyl ether afforded 12.5 g of the desired compound **5**, yield 57%, mp 164°; ir (potassium bromide): NH 3300, CO 1730, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): 1.45 (s, 6, CH_3C), 1.91 (d, 3, CH_3CH, J = 6.6 Hz), 5.28 (q, 1, CH_3CH, J = 6.6 Hz), 7.02 (d, 1, Ar, J = 8.1 Hz), 7.92 (d, 1, Ar, J' = 1.6 Hz), 7.95 (dd, 1, Ar, J = 8.1, J' = 1.6 Hz), 9.25 (s, 1, NH).

Anal. Calcd. for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 53.24; H, 4.80; N, 4.75.

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

A mixture of 1.4 g (5.9 mmoles) of 5-(2-chloroacetyl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **4a**, 0.63 g (5.9 mmoles) of *O*-methylthiocarbazate **6** [5-8] and 20 ml of acetonitrile was refluxed for 2 hours. After cooling, the resulting crystalline compound was filtered, washed with 1/1 methanol/water and dried under vacuum to afford 1.1 g of the desired compound **1a**, yield 68%,

mp 280°; ir (potassium bromide): NH 3150, CO 1720, 1680, 1630 cm^{-1}; ^1H nmr (DMSO-d_6): 1.29 (s, 6, CH_3C), 4.2 (s, 2, CH_2S), 6.92 (d, 1, Ar, J = 8 Hz), 7.70 (dd, 1, Ar, J = 8, J' = 1.8 Hz), 7.7 (d, 1, Ar, J' = 1.8 Hz), 10.5 (s, 1, N*H*), 11.42 (s, 1, N*H*).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S \cdot 0.25H_2O$: C, 55.80; H, 4.86; N, 15.02. Found: C, 56.02; H, 4.77; N, 15.37.

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

A mixture of 1.25 g (4.9 mmoles) of 5-[(2-chloro-1-oxo)-propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **4b**, 0.53 g (5 mmoles) of *O*-methylthiocarbazate **6** [5-8] and 10 ml of acetonitrile was refluxed for 2 hours. After evaporation to dryness the residual oil was purified by chromatography on silica (hexane/ethyl acetate) to yield 0.4 g (28%) of a crystalline compound, mp 268°; ir (potassium bromide): NH 3170, CO 1725, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): 1.28 (s, 6, CH_3C), 1.48 (d, 3, CH_3CH, J = 7.1 Hz), 4.70 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 6.92 (d, 1, Ar, J = 8.1 Hz), 7.65 (dd, 1, Ar, J = 8.1, J' = 1.5 Hz), 7.7 (d, 1, Ar, J' = 1.5 Hz), 10.59 (s, 1, N*H*), 11.58 (s, 1, N*H*).

Anal. Calcd. for $C_{14}H_{15}N_3O_2S \cdot 0.25H_2O$: C, 57.22; H, 5.32; N, 14.30. Found: C, 57.24; H, 5.22; N, 14.76.

5-(2-Amino-6-methyl-6*H*-1,3,4-thiadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**9**).

A mixture of 1.4 g (4.7 mmoles) of 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **5**, 430 mg (4.7 mmoles) of thiosemicarbazide **8**, 540 mg (1 molar equivalent) of trifluoroacetic acid and 20 ml of acetonitrile was refluxed for 2 hours. The precipitate was filtered off, washed with 10 ml of acetonitrile, and dried under vacuum to give compound **9** as a salt of trifluoroacetic acid (yield 70%). To obtain the free base, this salt was suspended in 40 ml of water, then treated with aqueous 0.1*N* solution of sodium hydroxide, and extracted twice with 30 ml ethyl acetate. The combined organic phases were washed twice with 25 ml of water, dried over magnesium sulfate and concentrated under vacuum. The residual solid was triturated with diethyl ether, and dried under vacuum at 40°, overall yield 18%, mp 215°; ir (potassium bromide): NH 3400-3100, CO 1695, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): 1.18 (d, 3, CH_3CH, J = 7.1 Hz), 1.28 (s, 6, CH_3C), 4.40 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 6.69 (m, 2, NH_2), 6.89 (d, 1, Ar, J = 8.1 Hz), 7.68 (dd, 1, Ar, J = 8.1, J' = 1.7 Hz), 7.85 (d, 1, Ar, J' = 1.7 Hz), 10.52 (s, 1, N*H*).

The same reaction performed under the same conditions but in the absence of trifluoroacetic acid led to 1,3-dihydro-5-(3-amino-2,3-dihydro-5-methyl-2-imino-1,3-thiazol-4-yl)-3,3-dimethyl-2*H*-indol-2-one **12** (*vide infra*).

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3,3-dimethyl-2*H*-indol-2-one (**1b**) from **9**.

A mixture of 1 g (2.3 mmoles) of 5-(2-amino-6-methyl-6*H*-1,3,4-thiadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **9**, 10 ml of DMF and 1.14 g (10 mmoles) of trifluoroacetic acid was cooled to 0°. A cold solution of 300 mg (4.6 mmoles) of sodium nitrite in 5 ml of water was added portionwise while maintaining the temperature below 5°. The mixture was heated to 40° for 15 minutes, then concentrated to dryness. The residue was suspended in 50 ml of ethyl acetate, washed twice wit 50 ml of water and the solution was dried over magnesium sulfate. After concentration, the residue was triturated with diethyl ether and dried under vacuum, yielding 300 mg (30%) of a compound identical with that obtained by the previous method.

5-(2-Amino-6-methyl-6*H*-1,3,4-selenadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**11**).

A mixture of 13.3 g (45 mmoles) of 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **5**, 5.13 g (45 mmoles) of trifluoroacetic acid, 6.21 g (45 mmoles) of selenasemicarbazide **10** [17-18] and 100 ml of acetonitrile was refluxed for 3 hours. The mixture was poured into 1 ℓ water and filtered. The filtrate was then basified with sodium hydrogen carbonate, saturated with sodium chloride and extracted twice with 200 ml of ethyl acetate. The organic phase was washed twice with 100 ml of water, concentrated to dryness and triturated with diethyl ether and ethanol, yield 4.74 g (31%), mp 205° dec; ir (potassium bromide): NH 3380, 3120, CO 1705, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): 1.28 (s, 6, CH_3C), 1.37 (d, 3, CH_3CH, J = 7.1 Hz), 4.46 (q, 1, CH$_3$C*H*, J = 7.1 Hz), 6.80 (m, 2, NH_2), 6.89 (d, 1, Ar, J = 8.2 Hz), 7.67 (dd, 1, Ar, J = 8.2, J' = 1.5 Hz), 7.85 (d, 1, Ar, J' = 1.5 Hz), 10.51 (s, 1, N*H*). The sample showed traces of ethanol as impurities (nmr) and was used in the next step without further purification; ms: molecular ion at 336.0499 (theor, 336.04893 calculated for $C_{14}H_{16}N_4OSe$): m/z = 171, 172, 187, 188, 199, 200, 215, 216, 241, 256 (100%), 257, 336.

Anal. Calcd. for $C_{14}H_{16}N_4OSe \cdot 0.1C_2H_6O$: C, 50.18; H, 4.92; N, 16.48. Found: C, 49.80; H, 4.76; N, 16.07.

When this reaction was performed in DMF and in the absence of trifluoroacetic acid the only product isolated was 1,3-dihydro-5-(3-amino-2,3-dihydro-2-imino-5-methyl-1,3-selenazol-4-yl)-3,3-dimethyl-2*H*-indol-2-one **13** (*vide infra*).

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

A mixture of 2.59 g (7.5 mmoles) of 5-(2-amino-6-methyl-6*H*-1,3,4-selenadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one **11**, 3.42 g (30 mmoles) of trifluoroacetic acid and 30 ml of DMF was cooled to 0°. A cold solution of 0.52 g (7.5 mmoles) of sodium nitrite in 15 ml of water was then added dropwise. After the end of the addition the temperature of the mixture was slowly raised to 40° and maintained at this level for 90 minutes under argon. The mixture was diluted with water (200 ml), saturated with sodium chloride and extracted twice with 50 ml of ethyl acetate. The organic phase was successively washed twice with 50 ml of water, dried over magnesium sulfate, treated with active charcoal and concentrated to dryness to leave an oily residue which gave a crystalline material after trituration with diethyl ether, yield 8.5%, mp 235°; ir (potassium bromide): NH 3200, CO 1705, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): 1.28 (s, 6, CH_3C), 1.69 (d, 3, CH_3CH, J = 7.2 Hz), 4.69 (q, 1, CH$_3$C*H*, J = 7.2 Hz), 6.92 (d, 1, Ar, J = 8.2 Hz), 7.63 (dd, 1, Ar, J = 8.2, J' = 1.7 Hz), 7.75 (d, 1, Ar, J' = 1.7 Hz), 10.59 (s, 1, N*H*), 11.60 (s, 1, N*H*); ms: molecular ion at 337.0339 (theor, 337.03295 calculated for $C_{14}H_{15}N_3O_2Se$): m/z = 172, 186, 200 (100%), 201, 229, 333, 334, 335, 337, 338, 339.

Anal. Calcd. for $C_{14}H_{15}N_3O_2Se$: C, 48.70; H, 4.67; N, 12.17. Found: C, 48.81; H, 4.38; N, 11.92.

1,3-Dihydro-5-(3-amino-2,3-dihydro-2-imino-5-methyl-2-1,3-thiazol-4-yl)-3,3-dimethyl-2*H*-indol-2-one (**12**).

A mixture of 2 g (7.1 mmoles) of 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**5**), 650 mg of thiosemicarbazide and 25 ml of acetonitrile was refluxed for 2 hours. The precipitate was filtered off, washed with water and suspended in

100 ml of water. An aqueous 0.1*N* solution of sodium hydroxide was added dropwise up to *p*H value was 10. The aqueous solution was extracted twice with ethyl acetate (100 ml), the organic phase was washed twice with 50 ml of water, dried over magnesium sulfate and treated with charcoal. Concentration yielded 1.2 g (52%) of a crystalline material, mp 224° (ethyl acetate); (despite extensive vacuum drying the sample retains approximately 0.12 *M* ethyl acetate, established by nmr; ir (potassium bromide): NH 3350, 3180, CO 1695, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): 1.26 (s, 6, CH_3C), 2.33 (s, 3, CH_3C), 4.75 (s, 2, NH_2), 6.85 (d, 1, Ar, J = 8 Hz), 7.34 (d, 1, Ar, J = 8 Hz), 7.46 (s, 1, Ar), 8.25 (s, 1, N*H*), 10.39 (s, 1, N*H*).

Anal. Calcd. for $C_{14}H_{16}N_4OS \cdot 0.12C_4H_8O_2$: C, 58.17; H, 5.71; N, 18.79. Found: C, 57.86; H, 5.66; N, 18.60.

A 2 hour reflux of 5-(2-amino-6-methyl-6*H*-1,3,4-thiadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**9**) in aqueous 10*N* hydrochloric acid led, after the same work-up, to the same compound (**12**) in 30% yield.

1,3-Dihydro-5-(3-amino-2,3-dihydro-2-imino-5-methyl-2-imino-1,3-selenazol-4-yl)-3,3-dimethyl-2*H*-indol-2-one (**13**).

A solution of 1.49 g (5 mmoles) of 5-[(2-bromo-1-oxo)propyl]-1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one (**5**) and 690 mg (5 mmoles) of selenasemicarbazide [17-18] in 20 ml of DMF containing 5 ml of concentrated aqueous ammonia was stirred overnight at room temperature. The mixture was poured into 100 ml water, extracted twice with 75 ml of methylene chloride, washed twice with 100 ml of water and dried over magnesium sulfate. After concentration the residue was triturated with a 1/1 mixture of diethyl ether/ethyl acetate and washed with acetonitrile to yield, after drying at 40° under vacuum, an amorphous material (despite intense drying nmr indicates the presence of 0.1 *M* ethyl acetate), yield 6%, mp 225°; ir (potassium bromide): NH 3380, 3200, CO 1700, 1628 cm^{-1}; ^1H nmr (DMSO-d_6): 1.25 (s, 6, CH_3C), 2.38 (s, 3, CH_3C), 4.96 (s, 2, NH_2), 6.83 (d, 1, Ar, J = 8 Hz), 7.28 (d, 1, Ar, J = 8 Hz), 7.41 (s, 1, Ar), 8.50 (s, 1, N*H*), 10.36 (s, 1, N*H*).

Anal. Calcd. for $C_{14}H_{16}N_4OSe \cdot 0.1C_4H_8O_2$: C, 50.26; H, 4.92; N, 16.28. Found: C, 50.18; H, 4.86; N, 16.08.

1,3-Dihydro-5-(3-amino-2,3-dihydro-5-methyl-2-oxo-1,3-thiazol-4-yl)-3,3-dimethyl-2*H*-indol-2-one (**14**).

A solution of 1 g (3.5 mmoles) of 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)-3,3-dimethyl-2*H*-indol-2-one **1b** in 10*N* aqueous hydrochloric acid (10 ml) was refluxed for one hour. The mixture was poured into 50 ml of water, filtered off and the crude material was dissolved in 50 ml of ethyl acetate and washed with a 2*N* aqueous sodium hydrogenocarbonate solution (50 ml), water (50 ml) and dried over magnesium sulfate. After concentration, the residue was triturated in diethyl ether and dried at 40°, yield 68%, mp 242°; ir (potassium bromide): NH 3350, 3180, CO 1695, 1622 cm^{-1}; ^1H nmr (deuteriochloroform): 1.44 (s, 6, CH_3C), 2.11 (s, 3, CH_3C), 4.38 (s, 2, NH_2), 7.01 (d, 1, Ar, J = 8.6 Hz), 7.16 (s, 1, Ar), 7.18 (d, 1, Ar, J = 8.6 Hz), 8.62 (s, 1, N*H*).

Anal. Calcd. for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.23; N, 14.52. Found: C, 58.36; H, 5.26; N, 14.32.

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