Preparation of Novel Heterocyclic Systems from Isatoic Anhydrides

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Isatoic anhydride (**1a**) and 5-chloroisatoic anhydride (**1b**) were treated with 2-(1-methylhydrazino)ethanol (**2**) to produce 2-aminobenzoic acid 2-(2-hydroxyethyl)-2-methylhydrazide (**3a**) and its 5-chloro analog **3b**, respectively. Treatment of **3a** and **3b** with carbon disulfide gave, respectively, 2,3-dihydro-3-[(2-hydroxyethyl)methylamino]-2-thioxo-4-(1*H*)quinazolinone (**4a**) and its 6-chloro analog **4b**. Compounds **4a** and **4b** afforded 5,6-dihydro-5-methyl-2-thioxo-4*H*,8*H*-[1,3,5,6]oxathiadiazocino[4,5-*b*]quinazolin-8-one (**5a**) and its 10-chloro analog **5b**, respectively, upon treatment with thiophosgene. Compound **5a** could be produced directly from **3a** and thiophosgene. Treatment of **4a** and **4b** with trifluoroacetic anhydride followed by potassium carbonate gave 3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3-*b*]quinazolin-6-one (**7a**) and its 8-chloro analog **7b**, respectively. Treatment of **4a** with thionyl chloride also gave **7a**, but **4b** and thionyl chloride afforded a mixture of **7b** and 8-chloro-3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one (**10**). The dimethyl analogs of **4a** and **4b** (**13a** and **13b**) upon treatment with thiophosgene afforded 3,4-dihydro-2,2,4-trimethyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one (**14a**) and its 8-chloro analog **14b**, respectively.

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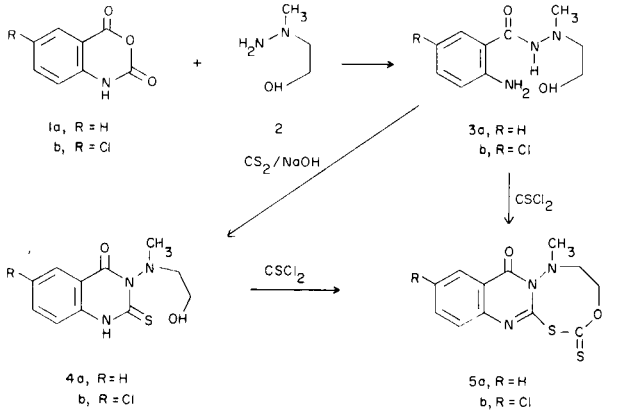
Isatoic anhydride and its derivatives are important starting materials for the synthesis of a variety of heterocyclic systems. We have used isatoic anhydrides in the preparation of benzotriazepines (1-3), quinazolinones (4), and quinazolinobenzoxazinediones (5). In this report we describe the ring-opening reactions of isatoic anhydrides with 2-(1-methylhydrazino)ethanols, which provided starting materials for the preparation of oxathiadiazocinoquinazolinones, thiadiazinoquinazolinones, and oxadiazinoquinazolinones.

Treatment of isatoic anhydride (**1a**) and 5-chloroisatoic anhydride (**1b**) with 2-(1-methylhydrazino)ethanol (**2**) in dimethylformamide gave the respective hydrazides **3a** and **3b** (Scheme I). Cyclization of **3a** with thiophosgene yielded a novel tricyclic heterocycle, namely, 5,6-dihydro-6-methyl-2-thioxo-4*H*,8*H*-[1,3,5,6]oxathiadiazocino[4,5-*b*]-quinazolin-8-one (**5a**). However, under milder conditions, the cyclization of **3a** to **5a** could be done in stepwise fashion. Thus, treatment of **3a** with carbon disulfide afforded 2,3-dihydro-3-[(2-hydroxyethyl)methylamino]-2-thioxo-4(1*H*)quinazolinone (**4a**). Subsequent treatment of **4a** with thiophosgene then gave **5a**. In similar fashion, the 10-chloro analog of **5a** (**5b**) was prepared from hydrazide **3b**.

Quinazolinones **4a** and **4b**, which we viewed as isolated intermediates in the conversions of **3a** and **3b** to **5a** and **5b**, respectively, also turned out to be interesting precursors to other tricyclic systems. Treatment of **4a** and **4b** with trifluroracetic anhydride followed by treatment of the isolated trifluoroacetyl compounds with potassium carbonate gave, respectively, 3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3-*b*]quinazolin-6-one (**7a**) and its 8-chloro analog **7b** (Scheme II). Infrared spectra of the intermediate trifluoroacetyl compounds showed that they were, indeed, *O*-trifluoroacetyl (**6**) and not *S*-trifluoroacetyl (**8**) intermediates. S-Ethyl trifluorothioacetate displays a carbonyl stretching frequency at 1700 cm^{-1}, while the carbonyl frequency for ethyl trifluoroacetate falls at 1790 cm^{-1} (6). Our trifluoroacetyl intermediates displayed carbonyl bands at 1790 cm^{-1}. It is recognized that the *O*-trifluoroacetyl intermediates (**6**) are more logical precursors to **7a** and **7b** than the *S*-trifluoroacetyl intermediates (**8**). However, the initial formation of **8** followed by base-induced acyl transfer to **6** could also have been envisioned in the overall conversions of **4a** and **4a** to the respective thiadiazinoquinazolinones **7a** and **7b**.

Scheme I



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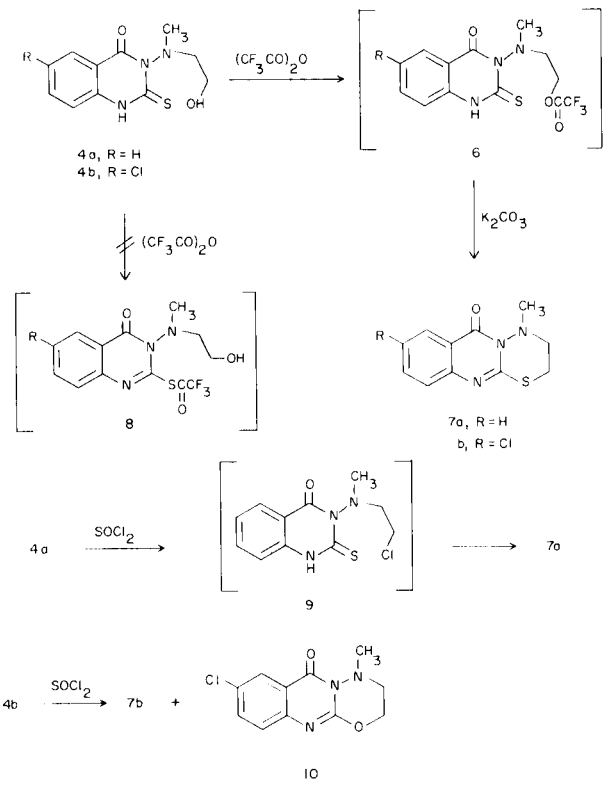
Compound **7a** was also produced by treating **4a** with thionyl chloride. Good evidence for **9** being an intermediate in this transformation was obtained from an experiment in which **7a** was purified by column chromatography, where a crude sample of **9** (presumably unstable with respect to **7a**) was isolated (see Experimental Section and Reference 4). Treatment of **4b** with thionyl chloride gave a mixture of **7b** and 8-chloro-3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one

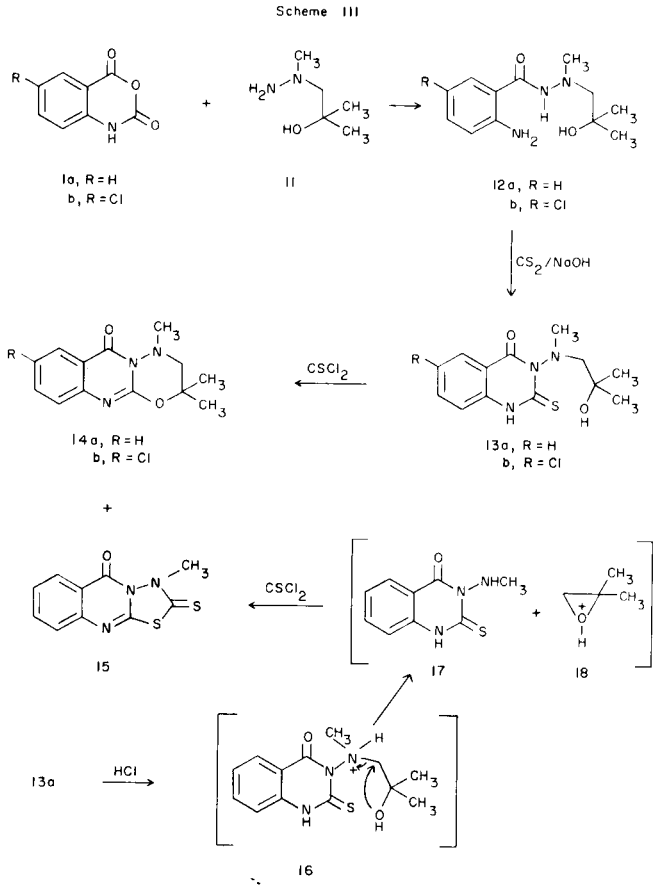
Scheme II



(10), which were separated by column chromatography. We anticipated the possibility of oxadiazine formation from **4a** or **4b** and thionyl chloride, since thionyl chloride should be reactive toward thiols as well as alcohols (7).

Treatment of isatoic anhydrides **1a** and **1b** with 1-(1-methylhydrazino)-2-methyl-2-propanol **(11)** gave hydrazides **12a** and **12b**, respectively, as indicated in Scheme III. Cyclization of **12a** and **12b** with carbon disulfide yielded the respective 2-thioxo-4(1*H*)quinazolinones **13a** and **13b**. Thus, the preparation of **13a** and **13b** was strictly analogous to the preparation of **4a** and **4b**. However, the reactions of **13a** and **13b** with thiophosgene were markedly different from their counterparts in Scheme I. Instead of yielding oxathiazocines, these reactions produced, respectively, 3,4-dihydro-2,2,4-trimethyl-2*H*,6*H*-[1,3,4]oxadiazino-[2,3-*b*]quinazolin-6-one **(14a)** and its 8-chloro derivative **14b**. With compounds **4a** and **4b**, the primary alcohols may react preferentially with thiophosgene to yield chloro thioformates **(19)**, which then cyclize to the oxathiadiazocines upon internal attack of the thiols (Scheme IV). With tertiary carbinols **13a** and **13b**, however, the thiols may perferentially react with thiophosgene to yield chloro dithioformates **(20)**, which then cyclize upon internal attack of the carbinols with extrusion of carbon disulfide and hydrogen chloride.

Scheme III

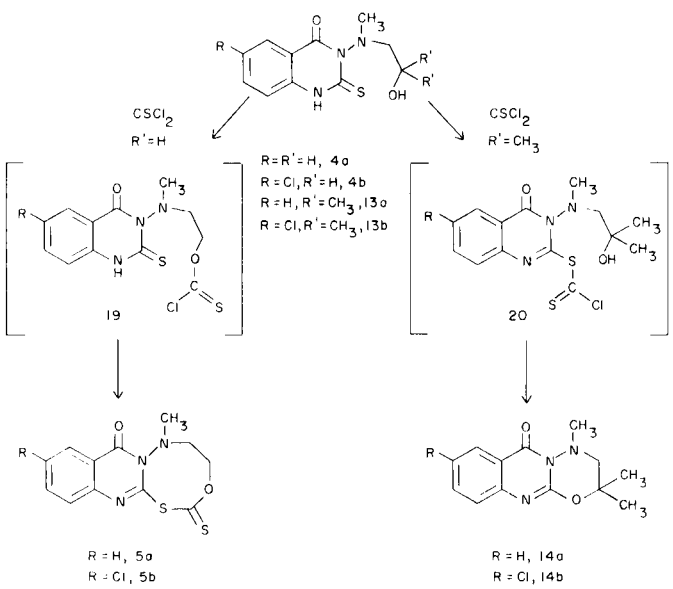


A second product, namely 2,3-dihydro-3-methyl-2-thioxo-6*H*-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-6-one **(15)**, was isolated from the treatment of **13a** with thiosphosgene. A rationale for the formation of **15** is presented in Scheme III, where protonation of **13a** gives **16**, which undergoes loss of the sidechain to yield intermediate **17** as shown. The formation of **15** from **17** and thiophosgene would be expected.

The nmr spectra of compounds **13a** and **13b** were interesting, in that two C-methyl signals (singlets) were observed for each. Perhaps the sidechains are hydrogen-bonded to the nuclei in these compounds, which would allow for the non-equivalence of the methyl groups. The *C*-methyl groups in compounds **12a** and **12b**, by way of contrast, were equivalent.

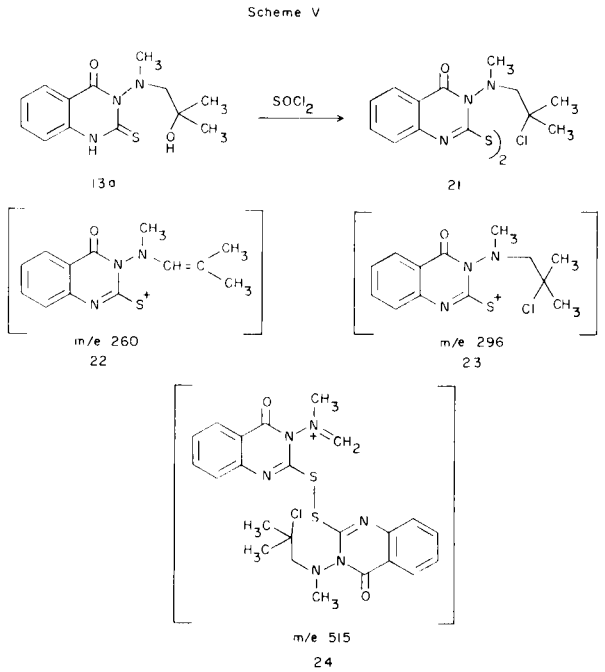
In completing our investigation on various modes of cyclization for compounds **4a, 4b, 13a,** and **13b**, we

Scheme IV



treated **13a** with thionyl chloride. We did expect results different from those seen with **4a**, since a tertiary chloride should form more slowly than a primary chloride, and should undergo displacement less readily than a primary chloride. [Thionyl chloride will convert tertiary carbinols to tertiary chlorides (9), as will anhydrous hydrogen chloride (10).] Treatment of **13a** with thionyl chloride led to a mixture from which a small amount of a pure component, m.p. 201-203°, was isolated. The infrared and nmr spectra and elemental analysis were consistent with **21**, the structure to which we assigned this component. The mass spectrum was also consistent with **21**, although a parent peak was not observed. All fragment masses were assignable to structures in our proposed fragmentation Scheme. Proposed structures for three of the observed fragment masses (**22-24**) are shown in Scheme V.

Scheme V



EXPERIMENTAL

Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B Spectrophotometer, nmr with Varian T-60, Varian EM360A and Perkin-Elmer R32 (90 MHz) spectrometers, and mass spectra with a Finnigan GC/MS Model 3000D (electron impact and chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by Dow Analytical Laboratories, Midland, MI, and Midwest Microlab, Ltd., Indianapolis, IN.

Materials.

2-(1-Methylhydrazino)ethanol (**2**), b.p. 87-95° (14 mm) [lit. (11) b.p. 110° (43 mm); lit. (12) b.p. 59-62° (0.2 mm)], and 1-(1-methylhydrazino)-2-methyl-2-propanol (**11**), b.p. 80-84° (13 mm) [lit. (13) b.p. 80-84° (13 mm)] were prepared using the procedure described by Trepanier and Sprancmanis (13).

2-Aminobenzoic Acid 2-(2-Hydroxyethyl)-2-methylhydrazide (**3a**).

To a thick paste of 81.6 g. (0.500 mole) of isatoic anhydride (**1a**) and 25 ml. of dimethylformamide was added 45.1 g. (0.500 mole) of 2-(1-methylhydrazino)ethanol (**2**). Evolution of carbon dioxide was noticeable. The mixture was heated on the steambath (*ca.* 4 hours) until gas evolution ceased. The mixture was cooled, diluted with water, and the solid was collected and recrystallized (2-propanol) to yield 41.0 g. (39%) of **3a**, m.p. 173-175°; ir (Nujol): 3420, 3330, 3230, 1655 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 9.35 (s, 1H, NH), 7.40-7.30 (m, 1H, aromatic), 7.26-7.03 (m, 1H, aromatic), 6.80-6.40 (m, 2H, aromatic), 6.20 (broad s, 2H, NH_2), 4.43 (s, 1H, OH), 2.73 (s, 2H, CH_2), 2.70 (s, 3H, NCH_3), 1.10 [s, 6H,$C(CH_3)_2$]; ms (70 eV chemical ionization, methane): *m/e* 210 ($M^+ + 1$).

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.39; H, 7.22; N, 20.08. Found: C, 57.36; H, 7.03; N, 20.12.

2-Amino-5-chlorobenzoic Acid 2-(2-Hydroxyethyl)-2-methylhydrazide (**3b**).

To a thick paste of 98.8 g. (0.500 mole) of 5-chloroisatoic anhydride (**1b**) and 20 ml. of dimethylformamide was added 45.1 g. (0.500 mole) of **2**. The mixture was heated at 70° until gas evolution ceased. The mixture was cooled, diluted with water, and the solid was collected and recrystallized (ethanol) to yield 45.8 g. (38%) of **3b**, m.p. 176-178°; ir (Nujol): 3425, 3320, 3250, 1620 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 9.48 (s, 1H, NH), 7.43 (d, J = 2.5 Hz, 1H, H at 5-position), 7.25-7.08 (m, 1H, H at 4-position), 6.73 (d, J = 8 Hz, 1H, H at 3-position), 6.35 (broad s, 2H, NH_2), 4.35 (s, 1H, OH), 2.71 (s, 2H, CH_2), 2.67 (s, 3H, NCH_3), 1.09 [s, 6H, $C(CH_3)_2$].

Anal. Calcd. for $C_{10}H_{14}ClN_3O_2$: C, 49.28; H, 5.79; N, 17.24. Found: C, 49.10; H, 5.76; N, 17.05.

2,3-Dihydro-2-[(2-hydroxyethyl)methylamino]-2-thioxo-4(1*H*)quinazolinone (**4a**).

A solution of 24.9 g. (0.119 mole) of **3a** in 300 ml. of ethanol, 75 ml. of carbon disulfide and 20 ml. of 50% sodium hydroxide solution was heated at reflux for 8 hours, after which time tlc (silica gel; 9:1, chloroform:methanol) showed the absence of **3a**. The solution was concentrated and the residue was partitioned between chloroform and water. The aqueous layer was neutralized with acetic acid and the organic layer was separated, washed with water, dried (sodium sulfate) and concentrated to a small volume. Addition of a small volume of ether yielded a solid which was collected and air-dried to yield 27.1 g. (91%) of **4a**, m.p. 198-199°; ir (Nujol): 3220 (NH), 1685 (C=O) cn $^{-1}$; nmr (DMSO-d_6): δ 12.67 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.03-7.77 (m,

1H, aromatic), 7.77-7.00 (m, 3H, aromatic), 4.30 (t, J=5 Hz, 1H, OH,deuterium oxide-exchangeable), 3.70-3.20 (m, 4H, CH_2CH_2), 2.96 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.40; H, 5.30; N, 16.63.

6-Chloro-2,3-dihydro-3-[(2-hydroxyethyl)methylamino]-2-thioxo-4(1*H*)-quinazolinone (**4b**).

A solution of 30.0 g. (0.123 mole) of **3b** in 300 ml. of ethanol, 80 ml. of carbon disulfide and 25 ml. of 50% sodium hydroxide solution was heated at reflux for 8 hours. The solution was concentrated and the residue was partitioned between chloroform and water. The aqueous layer was acidified with acetic acid and the organic layer was separated, washed with water, dried (sodium sulfate) and concentrated to a small volume. Addition of a small volume of ether yielded a solid which was collected and air-dried to afford 27.0 g. (77%) of **4b**, m.p. 222-223°; ir (Nujol): 3230 (NH). 1700 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 7.70-6.97 (m, 3H, aromatic), 4.6 (very broad signal, 2H, SH and OH), 3.58-3.10 (m, 4H, CH_2CH_2), 2.83 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{12}ClN_3O_2S$: C, 46.23; H, 4.23; N, 14.70. Found: C, 46.40; H, 4.37; N, 14.51.

Preparation of 5,6-Dihydro-5-methyl-2-thioxo-4*H*,8*H*-[1,3,5,6]-oxathiadiazocino[4,5-*b*]quinazolin-8-one (**5a**). A. From **3a**.

To a mechanically stirred mixture of 7.00 g. (33.4 mmoles) of **3a**, 100 ml. of chloroform and 25 ml. of water at ice bath temperature was added a solution of 5.75 g. (50.0 mmoles) of thiophosgene in 10 ml. of chloroform. Within a few minutes the organic layer became clear and yellow. After 2 hours, the organic layer was separated, washed with water, dried (sodium sulfate) and concentrated to leave 4.10 g. of yellow, foamy solid. Tlc (silica gel; 9:1, chloroform:methanol) showed one major component. Purification by elution through a column of Silica Gel 60 (EM Reagents, 70-230 mesh) with chloroform afforded 2.40 g. (24%) of **5a**, m.p. 122-123°: m.p. 122-123° (benzene-hexane); ir (Nujol): 1685 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.20-7.88 (m, 1H, aromatic), 7.88-7.18 (m, 3H, aromatic), 5.20-4.31 (m, 2H, OCH_2), 3.97-2.90 (m, 5H, NCH_2 and NCH_3, with NCH_3 s at 3.08); ms (70 eV, chemical ionization, methane): m/e 294 ($M^+ + 1$).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 49.15; H, 3.78; N, 14.33. Found: C, 49.00; H, 3.82; N, 14.21.

B. From **4a**.

To a vigorously stirred mixture of 5.02 g. (20.0 mmoles) of **4a**, 100 ml. of chloroform and 20 ml. of water was added a solution of 3.00 g. (26.1 mmoles) of thiophosgene in 10 ml. of chloroform at icebath temperature. After 2 hours of stirring, the organic layer was separated, washed with water, dried (sodium sulfate) and concentrated. The yellow residue was purified by elution through a column of Silica Gel 60 (70-230 mesh, EM Reagents) with chloroform to yield 2.40 g. (41%) of **5a**, m.p. 122-123°, which was identical in all respects with the material prepared as in Part A.

10-Chloro-5,6-dihydro-6-methyl-2-thioxo-4*H*,8*H*-[1,3,5,6]oxathiadiazocino-[4,5-*b*]quinazolin-8-one (**5b**).

To a mechanically stirred mixture of 12.2 g. (50.0 mmoles) of **3b**, 100 ml. of chloroform and 25 ml. of water at ice bath temperature was added a solution of 7.62 ml. (11.5 g., 0.100 mole) of thiophosgene in 10 ml. of chloroform. After 3 hours of stirring the organic layer was separated, washed with water, dried (sodium sulfate) and concentrated to yield a yellow semisolid. Purification by elution through a column of Silica Gel 60 with chloroform afforded 5.82 g. (35%) of **5b**, m.p. 164-165°; ir (Nujol): 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.00-7.83 (m, 1H, aromatic), 7.60-7.00 (m, 2H, aromatic), 5.13-4.20 (m, 2H, OCH_2), 3.97-2.83 (m, 5H, NCH_2 and NCH_3, with NCH_3 s at 3.00).

Anal. Calcd. for $C_{12}H_{10}ClN_3O_2S_2$: C, 43.98; H, 3.07; N, 12.83. Found: C, 44.20; H, 3.11; N, 12.73.

3,4-Dihydro-4-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3-*b*]quinazolin-6-one (**7a**). A. From **4a** and Trifluoroacetic Anhydride.

A solution of 4.00 g. (15.9 mmoles) of **4a** in 25 ml. of trifluoroacetic anhydride was heated at reflux for 75 minutes under a nitrogen atmosphere. The solution was evaporated to dryness and the residue was treated with methylene chloride and concentrated to dryness three times. To the residue was added 5.0 g. of anhydrous potassium carbonate and 50 ml. of acetone, and the mixture was heated on the steambath for 20 minutes. The mixture was concentrated, partitioned between methylene chloride and water, and the organic layer was dried (sodium sulfate) and concentrated. The resulting solid was recrystallized (benzene-hexane) to yield 1.20 g. (32%) of **7a**, m.p. 156-158°; ir (Nujol): 1690 (C=O), 1610 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 8.58-8.34 (m, 1H, aromatic), 8.12-7.38 (m, 3H, aromatic), 4.00-3.45 (m, 4H, CH_2CH_2), 3.13 (s, 3H, CH_3); ms (70 eV, chemical ionization, methane): m/e 234 ($M^+ + 1$), 261 ($M^+ + 29$), 274 ($M^+ + 41$).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 57.00; H, 4.83; N, 17.82.

B. From **4a** and Thionyl Chloride.

A 2.51-g. (10.0 mmoles) quantity of **4a** was slurried with 50 ml. of methylene chloride and 1.43 g. (12.0 mmoles) of thionyl chloride was added. After *ca.* 10 minutes of stirring solution resulted, and after 1 hour a small amount of white solid was present. The mixture was concentrated to a small volume and the white solid was collected (14) and air-dried to yield 1.49 g. of white solid, which appeared to be (by infrared) a hydrochloride salt. This material was partitioned between 1N sodium hydroxide solution and methylene chloride and the organic layer was dried (sodium sulfate) and concentrated to leave 0.750 g. (32%) of **7a**, m.p. 155-156° (benzene-hexane). This material was spectrally identical to the material prepared as in Part A.

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.70; H, 4.77; N, 18.13.

8-Chloro-3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3-*b*]quinazolin-6-one (**7b**). A. From **4b** and Trifluoroacetic Anhydride.

A solution of 4.00 g. (14.0 mmoles) of **4b** in 25 ml. of trifluoroacetic anhydride was heated at reflux for 1 hour. The solution was evaporated to dryness and the residue was treated with methylene chloride and evaporated to dryness three times. To the residue was added 5.0 g. of anhydrous potassium carbonate and 50 ml. of acetone and the mixture was heated at reflux for 30 minutes. The mixture was concentrated and partitioned between methylene chloride and water. The organic phase was dried (sodium sulfate) and concentrated and the resulting solid was recrystallized (benzene-hexane) to afford 2.10 g. (56%) of **7b**, m.p. 193-194°; ir (nujol): 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.23 (d, J = 2 Hz, 1H, aromatic), 7.87-7.37 (m, 2H, aromatic), 3.87-3.27 (m, 4H, CH_2CH_2), 2.97 (s, 3H, CH_3); ms (70 eV, electron impact): m/e 267 (molecular ion).

Anal. Calcd. for $C_{11}H_{10}ClN_3OS$: C, 49.34; H, 3.76; N, 15.69. Found: C, 49.50; H, 3.89; N, 15.97.

B. From **4b** and Thionyl Chloride.

To a slurry of 2.86 g. (10.0 mmoles) of **4b** in 50 ml. of methylene chloride was added 1.43 g. (12.0 mmoles) of thionyl chloride. Solution resulted after *ca.* 15 minutes, and a white solid was present after 1 hour. After 1.5 hours, the mixture was concentrated to a small volume and the solid was collected (2.12 g.). This material was partitioned between methylene chloride and water and the organic phase was dried (sodium sulfate) and concentrated to leave 1.75 g. of solid. Even after two recrystallizations (between-hexane) a mixture of products was apparent by tlc(Silica Gel; 9:1, chloroform:methanol). The 1.75 g. of material was applied, in a minimum volume of chloroform, to a 175-g. column of Silica Gel 60 (70-230 mesh, EM Reagents), and eluted with 3 l. of chloroform to remove 0.990 g. (37%) of **7b**, m.p. 192-193° (benzene-hexane). This material was spectrally identical to the material prepared as in Part A.

Anal. Calcd. for $C_{11}H_{10}N_3OS$: C, 49.34; H, 3.76; N, 15.69. Found: C, 49.24; H, 3.89; N, 15.83.

Subsequent elution of the column with 1.5 l. of 96:4,

chloroform:methanol removed 0.640 g. (25%) of 8-chloro-3,4-dihydro-4-methyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one (**10**), m.p. 196-196.5° (benzene-hexane); ir (Nujol): 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.19 (d, J = 2 Hz, 1H, aromatic), 7.86-7.30 (m, 2H, aromatic), 4.80 (t, J = 5 Hz, 2H, OCH_2), 3.57 (t, J = 5 Hz, 2H, NCH_2), 3.05 (s, 3H, CH_3); ms (70 eV, electron impact): m/e 251 (molecular ion).

Anal. Calcd. for $C_{11}H_{10}ClN_3O_2$: C, 52.49; H, 4.01; N, 16.70. Found: C, 52.54; H, 3.83; N, 16.46.

2-Aminobenzoic Acid 2-(2-Hydroxy-2-methylpropyl)-2-methyl Hydrazide (**12a**).

To a slurry of 163 g. (1.00 mole) of **1a** and *ca.* 100 ml. of dimethylformamide was added 118 g. (1.00 mole) of 1-(1-methylhydrazino)-2-methyl-2-propanol (**11**). After 3 hours of heating on the steambath, the solution was cooled, diluted with water and the resulting precipitate was collected and recrystalized (ethanol) to afford 112 g. (47%) of **12a**, m.p. 149-150°; ir (Nujol): 3460, 3360 and 3220 (NH and OH), 1645 (weak), 1615 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 9.35 (s, 1H, NH), 7.47-7.30 (m, 1H, aromatic), 7.26-7.03 (m, 1H, aromatic), 6.80-6.40 (m, 2H, aromatic), 6.20 (s, 2H, NH_2), 4.43 (s, 1H, OH), 2.73 (s, 2H, CH_2), 2.70 (s, 3H, NCH_3), 1.01 [s, 6H, $C(CH_3)_2$].

Anal. Calcd. for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.71. Found: C, 60.80; H, 7.86; N, 17.85.

2-Amino-5-chlorobenzoic Acid 2-(2-Hydroxy-2-methylpropyl)-2-methyl hydrazide (**12b**).

The procedure employed was as described for **12a**. On a half-molar scale, the collected product was recrystallized (ethanol) to afford 65.8 g. (48%) of **12b**, m.p. 271-274°; ir (Nujol): 3340, 3330 and 3230 (NH and OH), 1620 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 9.48 (s, 1H, NH), 7.43 (d, J = 2.5 Hz, 1H, H at 6-position), 7.25-7.08 (m, 1H, H at 4-position), 6.73 (d, J = 8 Hz, 1H, H at 3-position), 6.35 (s, 2H, NH_2), 4.35 (s, 1H, OH), 2.71 (s, 2H, CH_2), 2.67 (s, 3H, NCH_3), 1.09 [s, 6H, $C(CH_3)_2$].

Anal. Calcd. for $C_{12}H_{18}ClN_3O_2$: C, 53.04; H, 6.67; N, 15.46. Found: C, 52.80; H, 6.76; N, 15.46.

2,3-Dihydro-3-[(2-hydroxy-2-methylpropyl)methylamino]-2-thioxo-4(1*H*)-quinazolinone (**13a**).

A solution of 29.2 g. (0.123 mole) of **12a** in 300 ml. of ethanol, 80 ml. of carbon disulfide and 25 ml. of 50% sodium hydroxide solution was heated at reflux for 8 hours. After standing overnight, tlc (Silica Gel; 9:1, chloroform:methanol) indicated one clean product. The solution was evaporated and the residue was partitioned between methylene chloride and water. The aqueous phase was acidified with acetic acid and the organic layer was washed with water, dried (sodium sulfate) and concentrated to give a white solid. Trituration with ether and collection of the solid afforded 32.4 g. (94%) of **13a**, m.p. 200-201°: m.p. 201-202° (ethanol); ir (Nujol): 3280, 3180 and 3120 (OH and NH), 1700 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.08-7.93 (m, 1H, aromatic), 7.87-7.65 (m, 1H, aromatic), 7.50-7.25 (m, 2H, aromatic), 4.36 (s, 1H, OH), 3.15 (s, 2H, CH_2), 2.96 (s, 3H, NCH_3), 1.18 (s, 3H, CCH_3), 1.08 (s, 3H, CCH_3).

Anal. Calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.88; H, 6.13; N, 15.04. Found: C, 55.60; H, 5.94; N, 15.21.

6-Chloro-2,3-dihydro-3-[(2-hydroxy-2-methylpropyl)methylamino]-2-thioxo-4(1*H*)quinazolinone (**13b**).

The procedure and scale employed were as described for **13a**, to give 34.1 g. (89%) of **13b**, m.p. 265-267°; ir (Nujol): 3290 (OH), 3170 (NH), 1700 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 7.91 (d, J = 2.5 Hz, 1H, H at 6-position), 7.90-7.72 (m, 1H, H at 4-position), 7.41 (d, J = 8 Hz, 1H, H at 3-position), 4.29 (s, 1H, OH), 3.13 (s, 2H, CH_2), 2.95 (s, 3H, NCH_3), 1.17 (s, 3H, CCH_3), 1.08 (s, 3H, CCH_3).

Anal. Calcd. for $C_{13}H_{16}ClN_3O_2S$: C, 49.75; H, 5.14; N, 13.39. Found: C, 49.80; H, 5.16; N, 13.61.

Treatment of **13a** with Thiophosgene.

To a solution of 7.00 g. (25.1 mmoles) of **13** in 200 ml. of chloroform was added 20 ml. of water and a solution of 3.00 g. (26.1 mmoles) of thiophosgene in 20 ml. of chloroform. After 4 hours of vigorous stirring the organic layer was separated and concentrated to yield a thick paste. Trituration with ether yielded a white solid (0.980 g.) which was dissolved in water. The solution was basified with sodium hydroxide, extracted with chloroform, and the dried (sodium sulfate) extracts were concentrated to an oil which crystallized on standing. The solid was triturated with ether and collected to give 3,4-dihydro-2,2,4-trimethyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one (**14a**), m.p. 124-126°; ir (Nujol): 1695 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.16-7.98 (m, 1H, aromatic), 7.87-7.62 (m, 1H, aromatic), 7.53-7.25 (m, 2H, aromatic), 3.45 (s, 2H, CH_2), 3.03 (s, 3H, NCH_3), 1.55 [s, 6H, $C(CH_3)_2$]; ms (70 eV, chemical ionization, methane): m/e 246 ($M^+ + 1$), 274 ($M^+ + 29$), 286 ($M^+ + 41$).

Anal. Calcd. for $C_{13}H_{15}H_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.52; H, 6.14; N, 17.03.

The filtrate from the 0.980 g. of solid afforded a crop of crystals (380 mg.) which was recrystallized (ethanol) to yield 2,3-dihydro-3-methyl-2-thioxo-6*H*-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-6-one (**15**), m.p. 183-184°; ir (Nujol): 1685 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.28-8.13 (m, 1H, aromatic), 8.04-7.80 (m, 1H, aromatic), 7.75-7.47 (m, 2H, aromatic), 4.26 (s, 3H, CH_3); ms (70 eV, chemical ionization, methane): m/e 250 ($M^+ + 1$), 278 ($M^+ + 29$), 290 ($M^+ + 41$).

Anal. Calcd. for $C_{10}H_7N_3OS_2$: C, 48.17; H, 2.83; N, 16.85. Found: C, 48.20; H, 3.02; N, 17.08.

Treatment of **13b** with Thiophosgene.

To a mixture of 7.84 g. (25.0 mmoles) of **13b** in 200 ml. of chloroform and 30 ml. of water was added 15 ml. of thiophosgene in small increments with icebath cooling (15). After 60 hours the organic layer was separated and concentrated. The resulting solid was triturated with ether and collected to yield 2.50 g. of 8-chloro-3,4-dihydro-2,2,4-trimethyl-2*H*,6*H*-[1,3,4]oxadiazino[2,3-*b*]quinazolin-6-one (**14b**). An additional 0.500 g. of **14b** was obtained from the filtrate by chromatography on Silica Gel (EM Reagents, 70-230 mesh), using 9:1, chloroform:methanol as the eluent. Total yield of **14b** was 3.00 g. (43%), m.p. 218-220° (ethanol); ir (Nujol): 1680 (C=O) cm^{-1}; nmr (trifluoroacetic acid): δ 8.36 (d, J = 2.5 Hz, 1H, H at 7-position), 8.10-7.90 (m, 1H, H at 9-position), 7.64 (d, J = 9 Hz, 1H, H at 10-position); ms (70 eV, chemical ionization, methane): m/e 280 ($M^+ + 1$), 308 ($M^+ + 29$), 320 ($M^+ + 41$).

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.81; H, 5.04; N, 15.02. Found: C, 56.10; H, 5.18; N, 15.16.

Treatment of **13a** with Thionyl Chloride.

To a slurry of 2.79 g. (10.0 mmoles) of **13a** in 50 ml. of methylene chloride was added 1.43 g. (12.0 mmoles) of thionyl chloride. Solution resulted after *ca.* 2 minutes. After 3 hours, the pale yellow solution was concentrated and the residue was triturated with ether to yield 1.00 g. of sticky, yellow solid. The filtrate was partitioned between methylene chloride and 1*N* sodium hydroxide solution. The organic layer was dried (sodium sulfate) and concentrated to leave 1.68 g. of clear, viscous oil. This oil was applied to a 175-g. column of Silica Gel 60 (EM Reagents, 70-230 mesh) and eluted with 1.5 l. of chloroform and 1 liter of 98:2, chloroform:methanol. Early fractions were combined and concentrated to leave 1.14 g. of solid which was recrystallized twice from hexane to yield 80.0 mg. of 2,2'-dithiobis[3-(2-chloro-2-methylpropyl)methylamino]-4(3*H*)quinazolinone (**21**), m.p. 201-203°; ir (Nujol): 1685 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.00-8.17 (m, 1H, aromatic), 7.87-7.64 (m, 1H, aromatic), 7.54-7.30 (m, 2H, aromatic), 4.17-3.42 (m, 2H, CH_2), 3.22 (s, 3H, NCH_3), 1.80 [s, 6H, $C(CH_3)_2$]; ms (70 eV, electron impact): m/e (relative intensity) 515 (03), 474 (06), 396 (12), 354 (07), 321 (23), 296 (20), 260 (100), 218 (53), 179 (90), 162 (70), 83 (100).

Anal. Calcd. for $C_{26}H_{30}Cl_2N_6O_2S$: C, 52.61; H, 5.09; N, 14.16. Found: C, 52.89; H, 5.17; N, 14.24.

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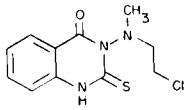
(14) This experiment was repeated on three times the scale and the filtrate at this point was concentrated (3.43 g.) and chromatographed on 175 g. of Silica Gel 60 (70-230 mesh, EM Reagents) with 500 ml. of chloroform and 1 l. of 98:2, chloroform:methanol. Fractions displaying a single spot on tlc (Silica Gel; 9:1, chloroform:methanol) at higher R_f than **7a** were combined and concentrated to leave 0.93 g. of oil which solidified on trituration with ether. Nmr (deuteriochloroform) and ms (70 eV, chemical ionization, methane) clearly indicated a 1:4 ratio of **7a** and **9**. Ms for **9**: m/e 270 ($M^+ + 1$), 298 ($M^+ + 29$), 310 ($M^+ + 41$).



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(15) When **13b** was treated with an equivalent amount of thiophosgene for two hours as was **13a**, work-up of the reaction mixture yielded mainly starting material (**13b**).