Thiazolo[4,3-*c*][1,4]benzodiazepines. II. Synthesis of Fused[*a*]triazolo, Tetrazolo and Oxadiazolo Derivatives

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We report the practical synthesis of the first fused[*a*]triazolo, tetrazolo and oxadiazolothiazolo[4,3-*c*]-[1,4]benzodiazepine-5,11-diones *via* hydrazidines and oximes.

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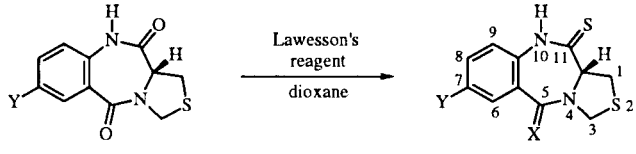
The antitumor activity of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBD) such as anthramycin, tomaymycin, neothramycins A and B [1] is thought to be exerted through a covalent binding *via* an aminal linkage from the electrophilic carbinolamine-bearing C-11 position to an N-2 of guanine within the minor grove of DNA [2]. In view of the importance of the carbinolamine functionality, we recently prepared new PBD derivatives [3] [4] among which some showed a good DNA binding [5] [6]. In order to extend our study to the thiazolo[4,3-*c*][1,4]benzodiazepine series, we described in a preceding paper [7] the synthesis of some amidines prepared *via* the monothiolactams and dithiolactams **2a-e**, obtained from thiazolo-[4,3-*c*][1,4]benzodiazepine-5,11-diones **1a-e** by treatment with Lawesson's reagent (Scheme 1).

Scheme 1

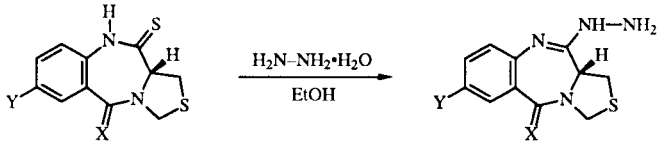


1a-e **2a-e**

1a, 2a, Y = H, X = O
1b, 2b Y = Cl, X = O
1c, 2c, Y = H, X = S
1d, 2d, Y = Cl, X = S
1e, 2e, Y = CH_3, X = S

We present in this paper the preparation of new tricyclic and tetracyclic diazepine derivatives from these thiolactams. These were converted to the 11-hydrazino-thiazolo-[4,3-*c*][1,4]benzodiazepines **3a-e** in good yields, by the action of hydrazine hydrate in ethanol at room temperature (Scheme 2).

Scheme 2

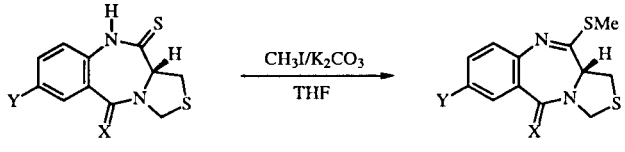


2a-e **3a-e**

2a, 3a, Y = H, X = O
2b, 3b Y = Cl, X = O
2c, 3c, Y = H, X = S
2d, 3d, Y = Cl, X = S
2e, 3e, Y = CH_3, X = S

Treatment of thiolactams **2a,b** and dithiolactams **2c-e** with iodomethane in tetrahydrofuran at room temperature, in presence of potassium carbonate gave the 11-methylthio-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepines **4a-e** (Scheme 3).

Scheme 3

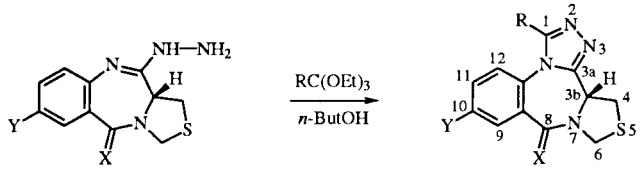


2a-e **4a-e**

4a, Y = H, X = O
4b, Y = Cl, X = O
4c, Y = H, X = S
4d, Y = Cl, X = S
4e, Y = CH_3, X = S

The hydrazines **3a-e** treated with triethyl orthoformate [8] in refluxing *n*-butanol gave the triazoles **5a-c, f-g,** while **3c** by the action of triethyl orthoacetate and triethyl orthobenzoate led to the corresponding substituted triazoles **5d** and **5e** (Scheme 4).

Scheme 4

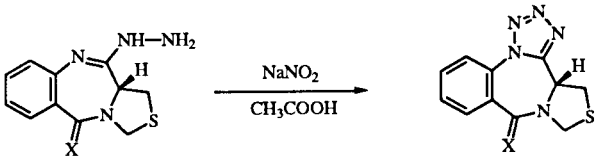


3a-e **5a-g**

5a, Y = H, X = O, R = H
5b, Y = Cl, X = O, R = H
5c, Y = H, X = S, R = H
5d, Y = H, X = S, R = Me
5e, Y = H, X = S, R = Ph
5f, Y = Cl, X = S, R = H
5g, Y = Me, X = S, R = H

The action of 1.5 equivalents of sodium nitrite on the hydrazines **3a,c** in 10% acetic acid gave at room temperature in good yields the new thiazolo[4,3-*c*][1,2,3,4]tetrazolo[1,5-*a*][1,4]benzodiazepines **6a,c** (Scheme 5).

Scheme 5

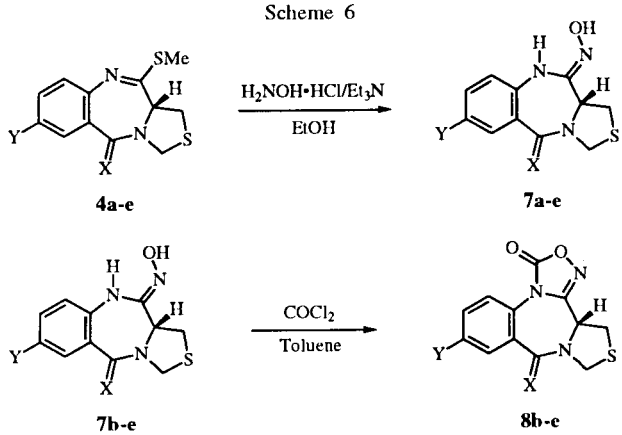


3a,c **6a,c**

3a, 6a, X = O
3c, 6c, X = S

The methyliminothioethers **4a-e** treated with 3 equivalents of hydroxylamine hydrochloride in the presence of triethylamine in refluxing ethanol [9] gave the corresponding 11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepines **7a-e** in good yields (Scheme 6). Compound **7b** led to the original 10-chlorothiazolo[4,3-*c*][1,2,4]oxadiazolo[4,3-*a*]-[1,4]benzodiazepine-1,8-dione (**8b**) by treatment with phosgene in refluxing toluene. This structure was supported by the following analysis of the ir and nmr spectra. The ir spectrum of **8b** exhibited effectively a strong carbonyl absorption at 1765 cm^{-1} and no absorption between 2900 and 3500 cm^{-1}. The ^{1}H-nmr spectrum exhibited no exchangeable proton signal upon deuteration. Application of this pathway to the 11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepines **7c-e** gave the 1-oxothiazolo[4,3-*c*][1,2,4]oxadiazolo-[4,3-*a*][1,4]benzodiazepines **8c-e**.

Scheme 6



4a-e **7a-e**

7b-e **8b-e**

7a, Y = H, X = O
7b, 8b, Y = Cl, X = O
7c, 8c, Y = H, X = S
7d, 8d, Y = Cl, X = S
7e, 8e, Y = Me, X = S

The antitumor activity of compouds **5b**, **5c**, **5d**, **5g**, **6a**, **7c**, **7d**, **8b**, **8c** and **8d** is currently evaluated by the National Cancer Institute, Bethesda, Maryland.

EXPERIMENTAL

General Methods.

Melting points were taken on a Köfler block and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. Nmr spectra were recorded on a Jeol FX 200 using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

1,2,3,11a-Tetrahydro-11-hydrazino-5*H*-thiazolo[4,3-*c*][1,4]-benzodiazepin-5-one (**3a**).

A solution of 1,2,3,10,11,11a-hexahydro-5*H*-thiazolo[4,3-*c*]-[1,4]benzodiazepin-5-one-11-thione (**2a**) (1 g, 0.0040 mole) and hydrazine monohydrate (1.55 ml, 0.0320 mole) in ethanol (30 ml) was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the oily residue was taken up in water. The precipitate was collected, dried and recrystallized from water to yield 0.75 g (76%) of **3a** (white solid), mp 194°; ir (potassium bromide): ν 3400 and 3320 (NH), 1645 (C=O), 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.74 (d, J_{H6H7} = 7.81 Hz, H_6), 7.45 (t, J_{H8H9} = J_{H8H7} = 7.66 Hz, H_8), 7.28 (d, J_{H9H8} = 7.89 Hz, H_9), 7.12 (t, J_{H7H8} = J_{H7H6} = 7.78 Hz, H_7), 6.41 (m, NH and NH_2), 4.92 (d, J_{gem} = 10.26 Hz, H_{3a}), 4.64 (m, H_{3b} and H_{11a}), 3.94 (d, J_{gem} = 10.27 Hz, H_{1a}), 3.41 (m, H_{1b}); ms: m/z 248 (26), 215 (18), 154 (42).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.18; H, 4.83; N, 22.56. Found: C, 53.05; H, 5.02; N, 22.43.

1,2,3,11a-Tetrahydro-7-chloro-11-hydrazino-5*H*-thiazolo[4,3-*c*]-[1,4]benzodiazepin-5-one (**3b**).

The thiolactam **2b** (1.2 g, 0.0042 mole) was converted to **3b** using the procedure for the preparation of **3a**. This gave 0.85 g (71%) of **3b** (white crystals), mp 206° (ethanol); ir (potassium bromide): ν 3340, 3310 and 3285 (NH), 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.64 (d, J_{H6H8} = 1.92 Hz, H_6), 7.41 (dd, J_{H8H9} = 7.91 Hz, J_{H8H6} = 1.96 Hz, H_8), 7.25 (d, J_{H9H8} = 7.97 Hz, H_9), 6.51 (m, NH and NH_2), 4.72 (d, J_{gem} = 10.03 Hz, H_{3a}), 4.49 (m, H_{3b} and H_{11a}), 3.66 (m, H_{1a} and H_{1b}).

Anal. Calcd. for $C_{11}H_{11}N_4OSCl$: C, 46.73; H, 3.92; N, 19.82. Found: C, 46.72; H, 3.81; N, 19.71.

1,2,3,11a-Tetrahydro-11-hydrazino-5*H*-thiazolo[4,3-*c*][1,4]ben-zodiazepine-5-thione (**3c**).

The dithiolactam **2c** was converted to **3c** using the procedure for the preparation of **3a**. This gave 1.95 g (79%) of **3c** (yellow crystals), mp 215° (water); ir (potassium bromide): ν 3420 and 3300 (NH), 1630 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.08 (d, J_{H6H7} = 8.15 Hz, H_6), 7.41 (t, J_{H8H9} = J_{H8H7} = 7.89 Hz, H_8), 7.20 (d, J_{H9H8} = 7.91 Hz, H_9), 7.07 (t, J_{H7H8} = J_{H7H6} = 8.03 Hz, H_7), 6.64 (m, NH and NH_2), 5.12 (d, J_{gem} = 11.89 Hz, H_{3a}), 4.87 (m, H_{3b} and H_{11a}), 3.81 (d, J_{gem} = 11.72 Hz, H_{1a}), 3.39 (m, H_{1b}).

Anal. Calcd. for $C_{11}H_{12}N_4S_2$: C, 49.96; H, 4.45; N, 21.19. Found: C, 50.13; H, 4.39; N, 21.07.

1,2,3,11a-Tetrahydro-7-chloro-11-hydrazino-5*H*-thiazolo[4,3-*c*]-[1,4]benzodiazepine-5-thione (**3d**).

The dithiolactam **2d** (1.5 g, 0.0050 mole) was converted to **3d** as for the preparation of **3a**. This gave 1.2 g (81%) of **3d** (yellow crystals), mp 256° (2-propanol); ir (potassium bromide): ν 3350 and 3240 (NH), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.93 (s, H_6), 7.43 (d, J_{H8H9} = 8.28 Hz, H_8), 7.14 (d, J_{H9H8} = 8.36 Hz, H_9), 6.21 (m, NH and NH_2), 5.10 (d, J_{gem} = 11.72 Hz, H_{3a}), 4.89 (m, H_{3b} and H_{11a}), 3.78 (d, J_{gem} = 11.23 Hz, H_{1a}), 3.34 (m, H_{1b}).

Anal. Calcd. for $C_{11}H_{11}N_4S_2Cl$: C, 44.22; H, 3.71; N, 18.75. Found: C, 44.06; H, 3.54; N, 18.94.

1,2,3,11a-Tetrahydro-7-methyl-11-hydrazino-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepine-5-thione (**3e**).

The dithiolactam **2e** (1 g, 0.0036 mole) was converted to **3e** using the procedure for the preparation of **3a**. This gave 0.65 g (66%) of **3e** (yellow crystals), mp 226° (ethyl acetate); ir (potassium bromide): ν 3365, 3280 and 3245 (NH), 1610 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.79 (s, H_6), 7.32 (m, H_8 and H_9), 6.44 (m, NH and NH_2), 5.02 (d, J_{gem} = 11.43 Hz, H_{3a}), 4.83 (m, H_{3b} and H_{11a}), 3.84 (d, J_{gem} = 11.34 Hz, H_{1a}). 3 39 (m, H_{1b}), 2.38 (s, CH_3); ms: m/z 278 (46), 245 (24), 180 (19).

Anal. Calcd. for $C_{12}H_{14}N_4S_2$: C, 51.77; H, 5.07; N, 20.13. Found: C, 51.64; H, 5.26; N, 20.30.

1,2,3,11a-Tetrahydro-11-methylthio-5*H*-thiazolo[4,3-*c*][1,4]-benzodiazepin-5-one (**4a**).

To a solution of 1,2,3,10,11,11a-hexahydro-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepin-5-one-11-thione (**2a**) (4.5 g, 0.0180 mole) in tetrahydrofuran (90 ml), we added 2 equivalents of methyl iodide (2.2 ml, 0.359 mole) and 3 equivalents of potassium carbonate (7.45 g, 0.0539 mole). The mixture was stirred at room temperature for 15 hours, then filtered and the filtrate was concentrated to dryness. The oily residue was taken up in petroleum ether. The white solid was collected, dried to give 3.7 g (78%) of **4a**, mp 136° (ether); ir (potassium bromide): ν 1635 (C=O), 1605 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.80 (d, J_{H6H7} = 7.83 Hz, H_6), 7.56 (t, J_{H8H9} = J_{H8H7} = 7.79 Hz, H_8), 7.29 (t, J_{H7H8} = J_{H7H6} = 7.80 Hz, H_7), 7.23 (d, J_{H9H8} = 7.80 Hz, H_9), 5.02 (m, H_{3a} and H_{11a}), 4.52 (d, J_{gem} = 11.32 Hz, H_{3b}), 3.52 (m, H_{1a} and H_{1b}), 2.42 (s, CH_3); ms: m/z 264 (56), 215 (22), 169 (35), 137 (40).

Anal. Calcd. for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60. Found: C, 54.31; H, 4.64; N, 10.65.

1,2,3,11a-Tetrahydro-7-chloro-11-methylthio-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepin-5-one (**4b**).

The thiolactam **2b** (4 g, 0.0140 mole) was converted to **4b** as for the preparation of **4a**. This gave 2.85 g (68%) of **4b** (white crystals), mp 134° (ether); ir (potassium bromide): ν 1610 (C=O) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.78 (d, J_{H6H8} = 2.03 Hz, H_6), 7.62 (dd, J_{H8H9} = 8.75 Hz, J_{H8H6} = 2.01 Hz, H_8), 7.28 (d, J_{H9H8} = 8.68 Hz, H_9), 4.62 (d, J_{gem} = 11.27 Hz, H_{3a}), 4.24 (m, H_{3b} and H_{11a}), 3.54 (d, J_{gem} = 11.42 Hz, H_{1a}). 3.28 (m, H_{1b}), 2.46 (s, CH_3).

Anal. Calcd. for $C_{12}H_{11}N_2OS_2Cl$: C, 48.24; H, 3.71; N, 9.38. Found: C, 48.03; H, 3.51; N, 9.19.

1,2,3,11a-Tetrahydro-11-methylthio-5*H*-thiazolo[4,3-*c*][1,4]-benzodiazepine-5-thione (**4c**).

The dithiolactam **2c** (3 g, 0.113 mole) was converted to **4c** using the procedure for the preparation of **4a**. This gave 2.2 g (70%) of **4c** (yellow crystals), mp 142° (ethanol); ir (potassium bromide): ν 1605 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.96 (d, J_{H6H7} = 8.03 Hz, H_6), 7.42 (t, J_{H8H9} = J_{H8H7} = 7.97 Hz, H_8), 7.23 (m, H_7 and H_9), 4.64 (d, J_{gem} = 11.32 Hz, H_{3a}), 4.27 (m, H_{3b} and H_{11a}), 3.34 (m, H_{1a} and H_{1b}), 2.41 (s, CH_3); ms: m/z 280 (34), 230 (62), 184 (18), 136 (28).

Anal. Calcd. for $C_{12}H_{12}N_2S_3$: C, 51.40; H, 4.31; N, 9.99. Found: C, 51.59; H, 4.42; N, 9.78.

1,2,3,11a-Tetrahydro-7-chloro-11-methylthio-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepine-5-thione (**4d**).

The dithiolactam **2d** (2 g, 0.0067 mole) was converted to **4d** using the procedure for the synthesis of **4a**. This gave 1.3 g (62%) of **4d** (yellow crystals), mp 142° (acetone); ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.10 (s, H_6), 7.60 (d, J_{H8H9} = 8.79 Hz, H_8), 7.22 (d, J_{H9H8} = 8.55 Hz, H_9), 5.11 (d, J_{gem} = 12.04 Hz, H_{3a}), 4.81 (m, H_{3b} and H_{11a}), 3.64 (m, H_{1a} and H_{1b}), 2.47 (s, CH_3).

Anal. Calcd. for $C_{12}H_{11}N_2S_3Cl$: C, 45.78; H, 3.52; N, 8.90. Found: C, 45.65; H, 3.31; N, 8.78.

1,2,3,11a-Tetrahydro-7-methyl-11-methylthio-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepine-5-thione (**4e**).

The dithiolactam **2e** (3 g, 0.0107 mole) was converted to **4e** using the method of preparation of **4a**. This gave 2.1 g (67%) of **4e** (yellow crystals), mp 140° (ether); ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.78 (s, H_6), 7.22 (d, J_{H8H9} = 8.74 Hz, H_8), 7.06 (d, J_{H9H8} = 8.80 Hz, H_9), 5.12 (d, J_{gem} = 11.88 Hz, H_{3a}), 4.82 (d, J_{gem} = 11.79, H_{3b}), 4.75 (m, H_{11a}), 3.51 (d, J_{gem} = 11.92, H_{1a}), 3.28 (m, H_{1b}), 2.52 (s, CH_3), 2.45 (s, SCH_3).

Anal. Calcd. for $C_{13}H_{14}N_2S_3$: C, 53.03; H, 4.79; N, 9.51. Found: C, 53.14; H, 4.71; N, 9.32.

3b,4,5,6-Tetrahydro-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepin-8-one (**5a**).

A solution of 11-hydrazino-1,2,3,11a-tetrahydro-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepin-5-one (**3a**) (0.8 g, 0.0032 mole) and triethyl orthoformate (0.7 ml, 0.0042 mole) in *n*-butanol (30 ml) was heated at reflux. A precipitate was observed after 1 hour. After 2 hours, the mixture was cooled and the white solid was collected, dried and recrystallized from ethanol to yield 0.6 g (72%) of **5a**, mp >260°; ir (potassium bromide): ν 1625 (C=O), 1605 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.96 (s, CH), 7.72 (d, J_{H9H10} = 7.81 Hz, H_9), 7.46 (t, J_{H11H12} = J_{H11H10} = 7.92 Hz, H_{11}), 7.27 (d, J_{H12H11} = 7 87 Hz, H_{12}), 7.14 (t, J_{H10H11} = J_{H10H9} = 7 87 Hz, H_{10}), 4.88 (d, J_{gem} = 10.25 Hz, H_{6a}), 4.66 (m, H_{3b}), 4.55 (d, J_{gem} = 10.55 Hz, H_{6b}), 3.91 (d, J_{gem} = 10.68 Hz, H_{4a}). 3.34 (m, H_{4b}).

Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.98; H, 4.01; N, 21.92.

3b,4,5,6-Tetrahydro-10-chloro-8*H*-thiazolo[4,3-*c*][1,2,4]tri-azolo[4,3-*a*][1,4]benzodiazepin-8-one (**5b**).

The hydrazine **3c** (0.7 g, 0.0025 mole) was converted to **5b** using the procedure for the preparation of **5a**. This gave 0.6 g (83%) of **5b** (white solid), mp > 260° (ether); ir (potassium bromide): ν 1620 (C=O) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 9.24 (s, CH), 7.93 (s, H_9), 7.82 (m, H_{11} and H_{12}), 5.21 (m, H_{6a}), 4.83 (m, H_{6b} and H_{3b}), 4.01 (d, J_{gem} = 11.03 Hz, H_{4a}), 3.74 (m, H_{4b}); ms: m/z 292 (18), 249 (46), 187 (26).

Anal. Calcd. for $C_{12}H_9N_4OSCl$: C, 49.24; H, 3.10; N, 19.14. Found: C, 49.31; H, 3.24; N, 18.99.

3b,4,5,6-Tetrahydro-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepine-8-thione (**5c**).

The hydrazine **3c** (1.7 g, 0.0064 mole) was converted to **5c** using the method of preparation of **5a**. This gave 1.4 g (80%) of **5c** (yellow solid), mp >260° (2-propanol); ir (potassium bromide): ν 1615 (C =N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 9.26 (s, CH), 8.19 (d, J_{H9H10} = 7.81 Hz, H_9), 7.56 (m, H_{10}, H_{11} and H_{12}),

5.43 (m, H_{3b}), 5.21 (d, J_{gem} = 12.06 Hz, H_{6a}), 5.01 (d, J_{gem} = 12.11 Hz, H_{6b}), 4.07 (d, J_{gem} = 11.23 Hz, H_{4a}), 3.83 (m, H_{4b}).

Anal. Calcd. for $C_{12}H_{10}N_4S_2$: C, 52.53; H, 3.67; N, 20.43. Found: C, 52.34; H, 3.80; N, 20.19.

3b,4,5,6-Tetrahydro-1-methyl-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-8-thione (**5d**).

A solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepine-5-thione (**3c**) (0.8 g, 0.0030 mole) and triethyl orthoacetate (0.7 ml, 0.0039 mole) in *n*-butanol (30 ml) was heated at reflux for 3 hours. After cooling, the precipitate was filtered, dried and recrystallized from 2-propanol to give 0.65 g (75%) of **5d** (yellow solid), mp >260°; ir (potassium bromide): ν 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.12 (d, J_{H9H10} = 7.80 Hz, H_9), 7.58 (m, H_{10}, H_{11} and H_{12}), 5.27 (m, H_{3b}), 5.04 (d, J_{gem} = 10.75 Hz, H_{6a}), 4.96 (d, J_{gem} = 10.82 Hz, H_{6b}), 4.05 (d, J_{gem} = 11.13 Hz, H_{4a}), 3.77 (m, H_{4b}), 2.49 (s, CH_3).

Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.19; N, 19.43. Found: C, 54.35; H, 4.26; N, 19.25.

3b,4,5,6-Tetrahydro-1-phenyl-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-8-thione (**5e**).

A solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepine-5-thione (**3c**) (1 g, 0.0038 mole) and triethyl orthobenzoate (1.2 ml, 0.0053 mole) in *n*-butanol (35 ml) was heated at reflux for 3 hours. After cooling, the orange precipitate was collected, dried and recrystallized from ether to give 0.85 g (64%) of **5e**, mp 255°; ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.17-7.01 (m, 9 H), 5.25 (d, J_{gem} = 10.01 Hz, H_{6a}), 5.08 (m, H_{6b} and H_{3b}), 4.06 (d, J_{gem} = 10.28 Hz, H_{4a}), 3.76 (m, H_{4b}).

Anal. Calcd. for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.03; N, 15.99. Found: C, 61.48; H, 4.12; N, 16.15.

3b,4,5,6-Tetrahydro-10-chloro-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-8-thione (**5f**).

The hydrazidine **3d** (1 g, 0.0033 mole) was converted to **5f** using the procedure for the preparation of **5a**. This gave 0.7 g (68%) of **5f** (yellow solid), mp >260° (acetone); ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.27 (s, CH), 8.17 (s, H_9), 7.73 (m, H_{11}, H_{12}), 5.48 (m, H_{3b}), 5.20 (d, J_{gem} = 12.01 Hz, H_{6a}), 4.98 (d, J_{gem} = 11.85 Hz, H_{6b}), 4.08 (d, J_{gem} = 11.71 Hz, H_{4a}), 3.68 (m, H_{4b}).

Anal. Calcd. for $C_{12}H_9N_4S_2Cl$: C, 46.67; H, 2.94; N, 18.14. Found: C, 46.47; H, 3.10; N, 18.13.

3b,4,5,6-Tetrahydro-10-methyl-8*H*-thiazolo[4,3-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-8-thione (**5g**).

The hydrazine **3e** (1.3 g, 0.0047 mole) was converted to **5g** as for the preparation of **5a**. This gave 0.95 g (70%) of **5g** (yellow solid), mp >260° (2-propanol); ir (potassium bromide): ν 1625 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.19 (s, CH), 7.98 (s, H_9), 7.51 (m, H_{11} and H_{12}), 5.19 (m, H_{3b} and H_{6a}), 4.94 (d, J_{gem} = 11.81 Hz, H_{6b}), 3.91 (m, H_{4a} and H_{4b}), 2.38 (s, CH_3).

Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.19; N, 19.43. Found: C, 53.93; H, 4.09; N, 19.56.

3b,4,5,6-Tetrahydro-8*H*-thiazolo[4,3-*c*][1,2,3,4]tetrazolo[1,5-*a*][1,4]benzodiazepin-8-one (**6a**).

To a solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepin-5-one (**3a**) (1 g, 0.0040 mole) in 10% acetic acid (40 ml) we added sodium nitrite (0.4 g, 0.0060 mole). The resultant solution was stirred to room temperature for 1 hour. The white precipitate was filtered, dried and recrystallized from 2-propanol to give 0.7 g (67%) of **6a**, mp 246°; ir (potassium bromide): ν 1630 (C=O), 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.98 (d, J_{H9H10} = 7.81 Hz, H_9), 7.72 (m, H_{10}, H_{11} and H_{12}), 5.41 (m, H_{3b}), 4.74 (m, H_{6a} and H_{6b}), 4.01 (d, J_{gem} = 10.25 Hz, H_{4a}), 3.78 (m, H_{4b}); ms: m/z 259 (70), 229 (29), 169 (36).

Anal. Calcd. for $C_{11}H_9N_5OS$: C, 50.96; H, 3.50; N, 27.01. Found: C, 51.09; H, 3.34; N, 26.91.

3b,4,5,6-Tetrahydro-8*H*-thiazolo[4,3-*c*][1,2,3,4]tetrazolo[1,5-*a*][1,4]benzodiazepine-8-thione (**6c**).

The hydrazine **3c** (0.9 g, 0.0034 mole) was converted to **6c** using the procedure for the preparation of **6a**. This gave 0.7 g (74%) of **6c** (yellow needles), mp 240° (ethanol); ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.21 (d, J_{H9H10} = 8.18 Hz, H_9), 7.67 (m, H_{10}, H_{11} and H_{12}), 5.62 (m, H_{3b}), 5.24 (d, J_{gem} = 11.90 Hz, H_{6a}); 4.91 (d, J_{gem} = 11.81 Hz, H_{6b}), 3.95 (m, H_{4a} and H_{4b}).

Anal. Calcd. for $C_{11}H_9N_5S_2$: C, 47.98; H, 3.29; N, 25.43. Found: C, 48.10; H, 3.14; N, 25.23.

1,2,3,10,11,11a-Hexahydro-11-hydroxyimino-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepin-5-one (**7a**).

To a solution of 1,2,3,11a-tetrahydro-11-methylthio-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepin-5-one (**4a**) (0.8 g, 0.0030 mole) in ethanol (30 ml) we added hydroxylamine hydrochloride (0.6 g, 0.0091 mole) and triethylamine (1.7 ml, 0.0121 mole). The mixture was heated to reflux for 4 hours. After cooling to room temperature, the white precipitate was collected, dried and recrystallized from 2-propanol to give 0.45 g (60%) of **7a**, mp 192°; ir (potassium bromide): ν 3360 (OH), 3210 (NH), 1650 (C=N), 1610 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.23 (s, NH), 8.83 (s, OH), 7.66 (d, J_{H6H7} = 7.81 Hz, H_6), 7.35 (t, J_{H8H7} = J_{H8H9} = 7.71 Hz, H_8), 7.24 (d, J_{H9H8} = 7.81 Hz, H_9), 7.02 (t, J_{H7H8} = J_{H7H6} = 7.52 Hz, H_7), 4.87 (d, J_{gem} = 10.74 Hz, H_{3a}), 4.55 (m, H_{3b} and H_{11a}), 3.70 (d, J_{gem} = 11.18 Hz, H_{1a}), 3.25 (m, H_{1b}); ms: m/z 249 (10), 217 (28), 170 (15).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.04; H, 4.25; N, 16.78.

1,2,3,10,11,11a-Hexahydro-7-chloro-11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepin-5-one (**7b**).

The methyliminothioether **4b** (1 g, 0.0033 mole) was converted to **7b** using the procedure for the preparation of **7a**. This gave 0.65 g (68%) of **7b** (white solid), mp 255° (water); ir (potassium bromide): ν 3350 (OH), 3250 (NH), 1655 (C=N), 1610 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.34 (s, NH), 9.07 (s, OH), 7.63 (s, H6), 7.49 (d, J_{H8H9} = 8.79 Hz, H_8), 7.33 (d, J_{H9H8} = 8.79 Hz, H_9), 4.88 (d, J_{gem} = 10.70 Hz, H_{3a}), 4.57 (m, H_{3b} and H_{11a}), 3.68 (d, J_{gem} = 11.02 Hz, H_{1a}), 3.37 (m, H_{1b}).

Anal. Calcd. for $C_{11}H_{10}N_3O_2SCl$: C, 46.57; H, 3.55; N, 14.81. Found: C, 46.43; H, 3.32; N, 14.71.

1,2,3,10,11,11a-Hexahydro-11-hydroxyimino-5*H*-thiazolo-[4,3-*c*][1,4]benzodiazepine-5-thione (**7c**).

The methyliminothioether **4c** (1 g, 0.0036 mole) was converted to **7c** using the procedure for the preparation of **7a**. This gave 0.7 g (74%) of **7c** (yellow crystals), mp 250° (ethanol); ir

(potassium bromide): ν 3320 (NH and OH), 1655 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.33 (s, NH), 8.96 (s, OH), 7.96 (d, J_{H6H7} = 7.82 Hz, H_6), 7.39 (t, J_{H8H9} = J_{H8H7} = 7.63 Hz, H_8), 7.22 (d, J_{H9H8} = 7.71 Hz, H_9), 7.05 (t, J_{H7H8} = J_{H7H6} = 7.72 Hz, H_7), 4.99 (m, H_{3a} and H_{11a}), 4.89 (d, J_{gem} = 10.06 Hz, H_{3b}), 3.51 (m, H_{1a} and H_{1b}); ms: m/z 265 (18), 235 (42), 198 (10).

Anal. Calcd. for $C_{11}H_{11}N_3OS_2$: C, 49.79; H, 4.18; N, 15.84. Found: C, 49.92; H, 4.07; N, 15.68.

1,2,3,10,11,11a-Hexahydro-7-chloro-11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepine-5-thione (**7d**).

The methyliminothioether **4d** (1.2 g, 0.0038 mole) was converted to **7d** using the procedure for the preparation of **7a**. This gave 0.7 g (61%) of **7d** (yellow needles), mp >260° (2-propanol); ir (potassium bromide): ν 3440 (OH), 3200 (NH), 1650 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.40 (s, NH), 9.13 (s, OH), 7.95 (d, J_{H6H8} = 2.44 Hz, H_6), 7.49 (dd, J_{H8H9} = 8.34 Hz, J_{H8H6} = 2.21 Hz, H_8), 7.28 (d, J_{H9H8} = 8.19 Hz, H_9), 5.04 (m, H_{3a}, H_{3b} and H_{11a}), 3.79 (d, J_{gem} = 10.25 Hz, H_{1a}), 3.46 (m, H_{1b}).

Anal. Calcd. for $C_{11}H_{10}N_3OS_2Cl$: C, 44.07; H, 3.36; N, 14.02. Found: C, 44.28; H, 3.21; N, 13.91.

1,2,3,10,11,11a-Hexahydro-7-methyl-11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepine-5-thione (**7e**).

The methyliminothioether **4e** (1 g, 0.0034 mole) was converted to **7e** using the procedure for the preparation of **7a**. This gave 0.6 g (63%) of **7e** (orange crystals), mp >260° (acetone); ir (potassium bromide): ν 3380 (OH), 3220 (NH), 1660 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.22 (s, NH), 8.81 (s, OH), 7.82 (s, H_6), 7.21 (m, H_8 and H_9), 5.06 (m, H_{3a} and H_{3b}), 4.87 (m, H_{11a}), 3.69 (d, J_{gem} = 10.72 Hz, H_{1a}), 3.36 (m, H_{1b}), 2.26 (s, CH_3).

Anal. Calcd. for $C_{12}H_{13}N_3OS_2$: C, 51.59; H, 4.69; N, 15.04. Found: C, 51.84; H, 4.74; N, 14.95.

1,2,3b,4,5,6-Hexahydro-10-chloro-8*H*-thiazolo[4,3-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepine-1,8-dione (**8b**).

To 1,2,3,10,11,11a-hexahydro-7-chloro-11-hydroxyimino-5*H*-thiazolo[4,3-*c*][1,4]benzodiazepin-5-one (**7b**) (1 g, 0.0035 mole), we added phosgene (20 ml, 0.04 mole) in toluene solution (20%). The solution was heated to reflux for 2 hours. After cooling to room temperature, the white precipitate was collected, dried and recrystallized from ether to give 0.7 g (64%) of **8b**, mp 225°; ir (potassium bromide): ν 1765 (C=O), 1630 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.84 (m, H_9, H_{11} and H_{12}), 5.18 (m, H_{3b}), 4.77 (m, H_{6a} and H_{6b}), 3.68 (d, J_{gem} = 10.28 Hz, H_{4a}), 3.55 (m, H_{4b}); ms: m/z 309 (28), 265 (12), 249 (21).

Anal. Calcd. for $C_{12}H_8N_3O_3SCl$: C, 46.54; H, 2.60; N, 13.57. Found: C, 46.52; H, 2.57; N, 13.46.

1,2,3b,4,5,6-Hexahydro-8*H*-thiazolo[4,3-*c*][1,2,4]oxadiazolo-[4,3-*a*][1,4]benzodiazepin-1-one-8-thione (**8c**).

The oxime **7c** (1.2 g, 0.0045 mole) was converted to **8c** using the procedure for the preparation of **8b**. This gave 0.8 g (61%) of **8c** (yellow crystals), mp 232° (ether); ir (potassium bromide): ν 1770 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.06 (d, J_{H9H10} = 8.26 Hz, H_9), 7.59 (m, H_{10}, H_{11} and H_{12}), 5.32 (m, H_{3b}), 5.22 (d, J_{gem} = 10.92 Hz, H_{6a}), 4.90 (d, J_{gem} = 11.15 Hz, H_{6b}), 3.67 (m, H_{4a} and H_{4b}).

Anal. Calcd. for $C_{12}H_9N_3O_2S_2$: C, 49.47; H, 3.11; N, 14.42. Found: C, 49.48; H, 3.22; N, 14.38.

1,2,3b,4,5,6-Hexahydro-10-chloro-8*H*-thiazolo[4,3-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one-8-thione (**8d**).

The oxime **7d** (0.8 g, 0.0027 mole) was converted to **8d** as for the preparation of **8b**. This gave 0.65 g (75%) of **8d** (yellow crystals), mp 232° (ethanol); ir (potassium bromide): ν 1760 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.10 (d, J_{H9H11} = 2.39 Hz, H_9), 7.75 (m, H_{11} and H_{12}), 5.45 (m, H_{3b}), 5.19 (d, J_{gem} = 11.72 Hz, H_{6a}), 4.92 (d, J_{gem} = 12.01 Hz, H_{6b}), 3.70 (m, H_{4a} and H_{4b}).

Anal. Calcd. for $C_{12}H_8N_3O_2S_2Cl$: C, 44.24; H, 2.47; N, 12.90. Found: C, 44.39; H, 2.29; N, 12.96.

1,2,3b,4,5,6-Hexahydro-10-methyl-8*H*-thiazolo[4,3-*c*][1,2,4]-oxadiazolo[4,3-a][1,4]benzodiazepin-1-one-8-thione (**8e**).

The oxime **7e** (1 g, 0.0036 mole) was converted to **8e** using the procedure for the preparation of **8b**. This gave 0.7 g (64%) of **8e** (yellow crystals), mp 234° (ether); ir (potassium bromide): ν 1775 (C=O), 1615 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.96 (s, H_9), 7.59 (m, H_{11} and H_{12}), 5.28 (m, H_{3b} and H_{6a}), 4.95 (d, J_{gem} = 11.72 Hz, H_{6b}), 3.73 (m, H_{4a} and H_{4b}), 2.48 (s, CH_3); ms: m/z 305 (34), 261 (8), 199 (40), 164 (21).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S_2$: C, 51.13; H, 3.63; N, 13.76. Found: C, 50.89; H, 3.49; N, 13.88.

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