Pyrrolo[2,1-*c*][1,4]benzodiazepines. Synthesis of New Cyclic Amidines and Fused[*a*]triazolo, Tetrazolo and Oxadiazolo Derivatives

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We report the practical synthesis of new cyclic amidines from thiolactams and the preparation of fused[*a*]triazolo, tetrazolo and oxadiazolo derivatives *via* hydrazidines and oximes, in the pyrrolo[2,1-*c*]-[1,4]benzodiazepine series.

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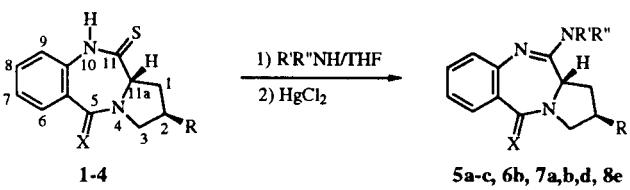
The pyrrolo[2,1-*c*][1,4]benzodiazepines such as anthramycin [1], tomaymycin [2], sibiromycin [3] and DC-81 belong to a class of antitumor antibiotics which are biosynthetically derived from *Streptomyces* species. They are thought to exert their antitumor activity through covalent binding *via* a linkage of an amine moiety from the electrophilic carbinolamine-bearing C-11 position to an N-2 of guanine within the minor groove of DNA [4]. In view of the importance of the carbinolamine functionality, we recently prepared new pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives [5,6] which were evaluated for *in vitro* DNA binding through thermal denaturation studies [7]. Some of these compounds caused a significant increase in melting for calf thymus DNA (*eg*, 0.7° for **11**), possibly due to non-covalent interaction with bases positioned at the bottom of the minor groove in the DNA double helix. In order to extend our study, we present in this paper the preparation of new tricyclic and tetracyclic pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives, analogous to compound **11**. We recently described the preparation of monothiolactams of type **1**, **2** and dithiolactams of type **3**, **4** [8,9]. These thiolactams were synthesized to supplement the lack of reactivity of the corresponding dilactams. Treatment of **1**, **2**, **3** and **4** with 5 equivalents of a primary or secondary amine (dimethylamine) in refluxing tetrahydrofuran, in the presence of 1,3 equivalents of mercuric chloride led in high yields to the cyclic amidines **5a-c**, **6b**, **7a,b,d** and **8e** respectively (Scheme 1).

Scheme 1

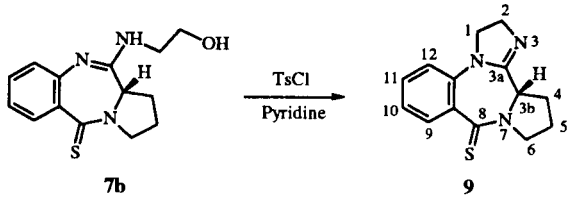


1-4 **5a-c, 6b, 7a,b,d, 8e**

1, X = O, R = H
2, X = O, R = $OCOCH_3$
3, X = S, R = H
4, X = S, R = $OCOCH_3$
5a, X = O, R = H, R' = H, R" = CH_3
5b, X = O, R = H, R' = H, R" = CH_2CH_2OH
5c, X = O, R = H, R' = R" = CH_3
6b, X = O, R = $OCOCH_3$, R' = H, R" = CH_2CH_2OH
7a, X = S, R = H, R' = H, R" = CH_3
7b, X = S, R = H, R' = H, R" = CH_2CH_2OH
7d, X = S, R = H, R' = H, R" = cyclopentyl
8e, X = S, R = $OCOCH_3$, R' = H, R" = CH_2CO_2Et

The cyclic hydroxyamidine **7b** treated with 1.5 equivalents of *p*-toluenesulfonic acid chloride gave the tetracyclic compound **9**. This reaction was conducted at room temperature in pyridine (Scheme 2). The structure of **9** was supported by the following analysis of the ir and nmr spectra. The ir spectrum of **9** exhibited no NH and OH absorptions. The ^1H nmr spectrum showed no exchangeable signal in deuterium oxide. This structure was also confirmed by a mass spectrum and an elemental analysis.

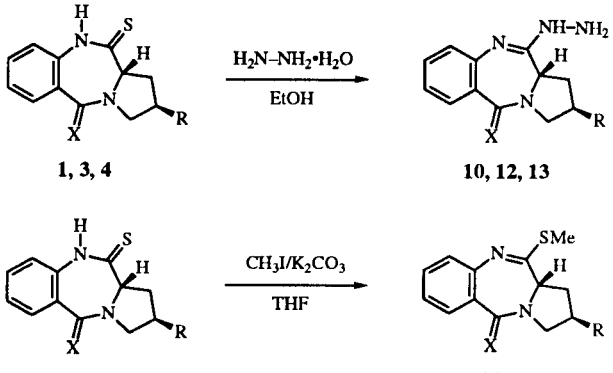
Scheme 2



7b **9**

The thiolactams **1**, **3**, and **4** were converted in good yields to the 11-hydrazinopyrrolo[2,1-*c*][1,4]benzodiazepines **10**, **12**, and **13** by the action of hydrazine

Scheme 3



1, 3, 4 **10, 12, 13**

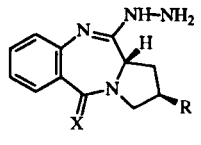
1, 3 **14, 16**

1, **10** and **14**, X = O, R = H
3, **12** and **16**, X = S, R = H
4, X = S, R = $OCOCH_3$
13, X = S, R = OH

hydrate in ethanol at room temperature. During this reaction, the acetoxy group of compound **4** was hydrolized, affording the cyclic 2-hydroxy-hydrazidine **13** (Scheme 3). Treatment of the monothiolactam **1** and the dithiolactam **3** with iodomethane in tetrahydrofuran at room temperature, in the presence of potassium carbonate gave the corresponding methylthioimino ethers **14** and **16**.

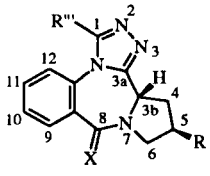
The cyclic hydrazidines **10-13** treated with triethyl orthoformate in refluxing 1-butanol gave the triazoles **18a**, **19a**, **20a** and **21a** respectively. In the same manner, compounds **10** and **11** [5], by the action of triethyl orthobenzoate led to the corresponding substituted triazoles **18b** and **19b**. The tetrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines **22-25** were easily obtained from the cyclic hydrazidines **10-13** by the action of 1.5 equivalents of sodium nitrite in 10% acetic acid. This reaction was accomplished during 1 hour at room temperature (Scheme 4).

Scheme 4

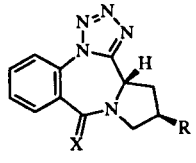


10-13

$R''C(OEt)_3$, 1-Butanol; NaN_3, CH_3COOH



18a-b, 19a-b, 20a, 21a



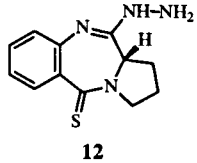
22-25

10, **18** and **22**, X = O, R = H
11, **19** and **23**, X = O, R = OH
12, **20** and **24**, X = S, R = H
13, **21** and **25**, X = S, R = OH

a, R''' = H **b**, R''' = phenyl

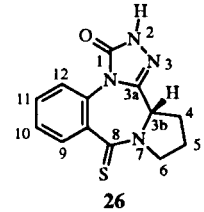
By the action of phosgene in refluxing toluene followed by treatment in alkaline medium, the cyclic hydrazidine **12** afforded the triazolone **26** (Scheme 5). The ir spectrum

Scheme 5



12

$COCl_2$, Toluene

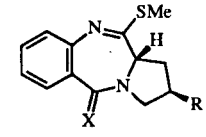


26

of compound **26** exhibited a strong carbonyl absorption at 1680 cm^{-1} and a NH absorption at 3300 cm^{-1}. The ^1H nmr spectrum showed an exchangeable proton signal upon deuteration at 11.2 ppm.

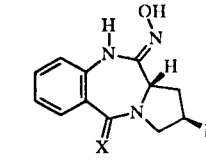
The methylthioimino ether **15** [8] reacted with 3 equivalents of hydroxylamine hydrochloride [10] to give the 11-hydroxyimino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **27** in good yield. This reaction was accomplished in refluxing ethanol in the presence of 1 equivalent of triethylamine. Application of this pathway to the methylthioimino ethers **16** and **17** [8] gave the corresponding C11-oximes **28** and **29**. Compounds **27-29** afforded the pyrrolo[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepine-1,8-diones **30-32** by treatment with phosgene [11] in refluxing toluene (Scheme 6).

Scheme 6



15-17

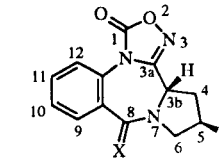
H_2N–OH•HCl/Et_3N, EtOH



27-29

$COCl_2$, Toluene

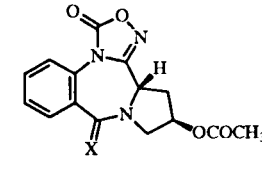
15, **27** and **30**, X = O, R = $OCOCH_3$
16, **28** and **31**, X = S, R = H
17, **29** and **32**, X = S, R = $OCOCH_3$



30-32

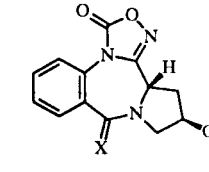
The 5-acetoxypyrrolobenzodiazepines **30** and **32** were easily converted to the 5-hydroxy compounds **33** and **34** by the action of 1.2 equivalents of potassium carbonate in refluxing methanol. No isomerization occured during this reaction (Scheme 7).

Scheme 7



30, 32

K_2CO_3, MeOH



33, 34

30 and **33**, X = O
32 and **34**, X = S

The antitumor activity of compounds **5a**, **6b**, **8e**, **12**, **18a**, **21a**, **24** and **30** was evaluated by the National Cancer

Institute, Bethesda, Maryland. However, none of these compounds showed any satisfactory activity. Other products in this series are under investigation in continuation of our structure-activity studies.

EXPERIMENTAL

General Methods.

Melting points were taken on a Köfler plate and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. The 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. Experimental protocols for the synthesis of compounds **11**, **15** and **17** are described in references [5] and [8].

1,2,3,11a-Tetrahydro-11-alkylamino-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-ones **5a-d**.

General Procedure.

To a solution of 1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one-11-thione (**1**) (1 g, 0.0043 mole) and the appropriate amine (5 equivalents) in boiling tetrahydrofuran (50 ml), was added mercuric chloride (1.5 g, 0.0056 mole). The reaction mixture was stirred for 1 hour, filtered and evaporated to dryness under reduced pressure. The oily residue was taken up in ethyl acetate (100 ml) and washed with an aqueous solution of sodium thiosulfate (2 x 80 ml). The organic layer was dried (magnesium sulfate) and evaporated *in vacuo*. The solid residue was recrystallized to give **5a-d**.

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

When monomethylamine was used, white crystals (69%) were obtained, mp 174° (ethanol); ir (potassium bromide): ν 3280 (NH), 1635 (C=O), 1600 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.78 (d, J_{H6H7} = 8.1 Hz, H6), 7.45 (t, J_{H8H9} = J_{H8H7} = 7.2 Hz, H_8), 7.12 (m, H_7 and H_9), 6.94 (s, NH), 3.93 (m, H_{1a}), 3.45 (m, H_{3a}), 3.04 (m, H_{3b}), 2.76 (s, CH_3), 2.45 (m, H_{1a}), 2.12 (m, H_{1b}), 1.72 (m, H_{2a} and H_{2b}); ms: m/z, 229 (46), 200 (28), 154 (16), 138 (20).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.90; H, 6.70; N, 18.15.

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

With 2-aminoethanol, white crystals (74%) were obtained, mp 181° (ether); ir (potassium bromide): ν 3300 (NH), 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.71 (d, J_{H6H7} = 7.8 Hz, H_6), 7.35 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.02 (m, H_7 and H_9), 6.92 (m, NH), 4.51 (m, OH), 3.64 (m, H_{11a}), 3.34 (m, H_{3a} and OCH_2), 3.05 (d, J_{gem} = 11.2 Hz, H_{3b}), 2.99 (m, NCH_2), 2.48 (m, H_{1a}), 2.11 (m, H_{1b}), 1.75 (m, H_{2a} and H_{2b}); ms: m/z 259 (32), 241 (18), 206 (24).

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 65.02; H, 6.45; N, 16.39.

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

When dimethylamine was used, white crystals (70%) were obtained, mp 184° (2-propanol); ir (potassium bromide): ν 1630 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.71 (d, J_{H6H7} = 7.8 Hz, H_6), 7.38 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.14 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 7.04 (d, J_{H9H8} = 7.8 Hz, H_9), 3.88 (m, H_{11a}), 3.39 (d, J_{gem} = 11.5 Hz, H_{3a}), 3.08 (d, J_{gem} = 11.4 Hz, H_{3b}), 2.95 (s, 2 CH_3), 2.55 (m, H_{1a}), 2.14 (m, H_{1b}), 1.88 (m, H_{2a} and H_{2b}).

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.19; H, 6.96; N, 17.26.

1,2,3,11a-Tetrahydro-2-acetoxy-11-(2-hydroxyethylamino)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**6b**).

To a solution of 1,2,3,10,11,11a-hexahydro-2-acetoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one-11-thione (**2**) (1.5 g, 0.0052 mole) and 2-aminoethanol (1.6 ml, 0.026 mole) in boiling tetrahydrofuran (50 ml), was added mercuric chloride (1.8 g, 0.0067 mole). The reaction mixture was stirred for 1 hour, then filtered and tetrahydrofuran was removed under reduced pressure. The solid residue was taken up in chloroform (120 ml) and washed with an aqueous solution of sodium thiosulfate. The organic layer was dried (calcium chloride) and evaporated *in vacuo*. The white solid was recrystallized from ether to give 1.20 g (72%) of **6b**, mp 182°; ir (potassium bromide): ν 3350 (OH), 3290 (NH), 1750 (C=O), 1635 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.81 (d, J_{H6H7} = 7.7 Hz, H_6), 7.45 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.21 (m, NH), 7.18 (m, H_7 and H_9), 6.02 (s, OH), 5.27 (m, H_{2b}), 4.22 (m, H_{11a}), 3.68 (m, H_{3a} and OCH_2), 3.34 (m, H_{3b}), 2.78 (m, H_{1a} and NCH_2), 2.19 (m, H_{1b}), 2.03 (s, CH_3); ms: m/z 317 (28), 273 (42), 198 (16), 164 (21).

Anal. Calcd. for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.42; H, 5.86; N, 13.08.

1,2,3,11a-Tetrahydro-11-alkylamino-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5-thiones **7a,b,d**.

General Procedure.

A solution of 1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dithione (**3**) (1 g, 0.004 mole) and the appropriate amine (5 equivalents) in tetrahydrofuran (40 ml) was heated at reflux. Mercuric chloride (1.4 g, 0,0052 mole) was added to the reaction mixture and it was allowed to stir at reflux for 1 hour. Then, the mixture was filtered and the tetrahydrofuran evaporated to dryness under reduced pressure. The oily residue was taken up in ethyl acetate (100 ml) and washed with an aqueous solution of sodium thiosulfate (2 x 80 ml). The organic layer was dried (magnesium sulfate) and evaporated *in vacuo*. The solid residue was recrystallized to give **7a,b,d**.

1,2,3,11a-Tetrahydro-11-methylamino-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5-thione (**7a**).

With monomethylamine, yellow crystals (71%) were obtained, mp 212° (ethanol); ir (potassium bromide): ν 3310 (NH), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.10 (d, J_{H6H7} = 7.7 Hz, H_6), 7.41 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.24 (m, NH), 7.14 (m, H_7 and H_9), 4.12 (m, H_{11a}), 3.38 (m, H_{3a}), 3.19 (m, H_{3b}), 2.79 (d, J_{CH_3NH} = 4.4 Hz, CH_3), 2.51 (m, H_{1a}), 2.39 (m, H_{1b}), 1.64 (m, H_{2a} and H_{2b}).

Anal. Calcd. for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13. Found: C, 63.81; H, 6.08; N, 17.19.

1,2,3,11a-Tetrahydro-11-(2-hydroxyethylamino)-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5-thione (**7b**).

When 2-aminoethanol was used, yellow crystals were obtained (68%), mp 216° (acetonitrile); ir (potassium bromide): ν 3310 (NH), 1610 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.22 (d, J_{H6H7} = 7.8 Hz, H_6), 7.63 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.41 (m, NH), 7.30 (m, H_7 and H_9), 5.34 (s, OH), 4.20 (m, H_{11a}), 3.62 (m, H_{3a}), 3.56 (m, OCH_2), 3.39 (m, H_{3b} and NCH_2), 2.53 (m, H_{1a}), 1.96 (m, H_{1b}), 1.79 (m, H_{2a} and H_{2b}); ms: m/z 275 (10), 229 (42), 187 (24).

Anal. Calcd. for $C_{14}H_{17}N_3OS$: C, 61.07; H, 6.22; N, 15.26. Found C, 61.02; H, 6.13; N, 15.16.

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

With cyclopentylamine, yellow crystals were obtained (71%), mp 220° (ether); ir (potassium bromide): ν 3290 (NH), 1615 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.07 (d, J_{H6H7} = 7.8 Hz, H_6), 7.34 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.14 (m, H_7 and H_9), 6.74 (d, J_{NHCH} = 5.5 Hz, NH), 4.07 (m, H_{11a}), 3.95 (m, CH), 3.78 (m, H_{3a}), 3.44 (m, H_{3b}), 2.59-2.37 (m, H_{1a} and H_{1b}), 2.32-1.56 (m, H_{2a}, H_{2b} and 4 CH_2).

Anal. Calcd. for $C_{17}H_{21}N_3S$: C, 68.19; H, 7.07; N, 14.03. Found: C, 68.28; H, 6.99; N, 14.02.

1,2,3,11a-Tetrahydro-2-acetoxy-11-(ethylcarbethoxymethyl-amino)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-thione (**8e**).

To a solution of 1,2,3,10,11,11a-hexahydro-2-acetoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dithione (**4**) (2 g, 0.0065 mole) and glycine ethyl ester (3.35 g, 0.0327 mole) in refluxing tetrahydrofuran (60 ml) mercuric chloride (2.30 g, 0.0085 mole) was added. The reaction mixture was stirred for 2 hours, filtered and tetrahydrofuran was removed under reduced pressure. The oily residue was taken up in ethyl acetate (120 ml) and washed with an aqueous solution of sodium thiosulfate (2 x 100 ml). The organic layer was dried (magnesium sulfate) and evaporated *in vacuo*. The solid residue was recrystallized from ethanol to afford 1.70 g (70%) of **8e** as yellow crystals, mp 230°; ir (potassium bromide): ν 3180 (NH), 1740 (C=O), 1720 (C=O), 1605 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.04 (d, J_{H6H7} = 7.8 Hz, H_6), 7.32 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.21 (m, NH), 7.07 (m, H_7 and H_9), 5.24 (m, H_{2b}), 4.33 (m, H_{11a}), 4.10 (q, $J_{CH_2CH_3}$ = 6.8 Hz, OCH_2), 4.04 (m, H_{3a}), 3.91 (m, H_{3b}), 2.80 (s, NCH_2), 2.45 (m, H_{1a} and H_{1b}), 2.06 (s, CH_3), 1.20 (t, $J_{CH_3CH_2}$ = 6.8 Hz, CH_3); ms: m/z 375 (24), 303 (14), 243 (42).

Anal. Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.60; H, 5.61; N, 11.20. Found: C, 57.34; H, 5.79; N, 11.05.

1,2,3b,4,5,6-Hexahydro-8*H*-pyrrolo[2,1-*c*][1,3]imidazo[1,2-*a*]-[1,4]benzodiazepine-8-thione (**9**).

To a solution of 1,2,3,11a-tetrahydro-11-(2-hydroxyethyl-amino)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-thione (**7b**) (0.8 g, 0.0029 mole) in pyridine (25 ml), was added over a period of 10 minutes at 0°, *p*-toluenesulfonyl chloride (0.90 g, 0.0046 mole). After the addition was complete, the solution was stirred at 0° for 30 minutes and allowed to warm to room temperature overnight. The mixture was poured into water and extracted with ethyl acetate (2 x 100 ml). The organic layer was dried (magnesium sulfate) and evaporated to yield 0.45 g (64%) of **9** (yellow crystals), mp 228° (ethanol); ir (potassium bromide): ν 1620 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.92 (d, J_{H9H10} = 7.8 Hz, H_9), 7.70-7.42 (m, H_{10}, H_{11} and H_{12}), 4.58 (m, H_{3b}), 3.48 (m, H_{6a}, H_{6b} and CH_2), 2.92 (m, H_{4a} and CH_2), 2.41 (m, H_{4b}), 2.03 (m, H_{5a} and H_{5b}); ms: m/z 257 (9), 215 (21), 192 (14).

Anal. Calcd. for $C_{14}H_{15}N_3S$: C, 65.34; H, 5.87; N, 16.33. Found: C, 65.12; H, 5.99; N, 16.10.

1,2,3,11a-Tetrahydro-11-hydrazino-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one (**10**).

A solution of 1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-5-one-11-thione (**1**) (3.5 g, 0.0151 mole) and hydrazine monohydrate (5.85 ml, 0.121 mole) in ethanol (65 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 ether to yield 2.75 g (79%) of **10** (white solid), mp 178°; ir (potassium bromide): ν 3370 and 3330 (NH), 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 7.80 (d, J_{H6H7} = 7.8 Hz, H_6), 7.47 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.31 (d, J_{H9H8} = 7.9 Hz, H_9), 7.15 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 6.35 (m, NH and NH_2), 4.64 (m, H_{11a}), 3.34 (d, J_{gem} = 11.2 Hz, H_{3a}), 3.02 (d, J_{gem} = 11.3 Hz, H_{3b}), 2.48 (m, H_{1a}), 2.16 (m, H_{1b}), 1.80 (m, H_{2a} and H_{2b}).

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.44; H, 5.97; N, 24.15.

1,2,3,11a-Tetrahydro-11-hydrazino-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5-thione (**12**).

The thiolactam **3** (3 g, 0.0121 mole) was converted to **12** using the procedure for the preparation of **10**. This gave 2.25 g (76%) of **12** (yellow crystals), mp 198° (ethanol); ir (potassium bromide): ν 3320 and 3290 (NH), 1620 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.08 (d, J_{H6H7} = 7.9 Hz, H_6), 7.52 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.26 (m, H_7 and H_9), 6.81 (m, NH and NH_2), 3.74 (m, H_{11a} and H_{3a}), 3.16 (d, J_{gem} = 11.1 Hz, H_{3b}), 2.51 (m, H_{1a}), 2.21 (m, H_{1b}), 1.92 (m, H_{2a} and H_{2b}).

Anal. Calcd. for $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.74. Found: C, 58.65; H, 5.65; N, 22.92.

1,2,3,11a-Tetrahydro-11-hydrazino-2-hydroxy-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5-thione (**13**).

The dithiolactam **4** (2.5 g, 0.0082 mole) was converted to **13** using the procedure for the preparation of **10**. This gave 1.75 g (83%) of **13** (yellow crystals), mp 202° (2-propanol); ir (potassium bromide): ν 3410 (OH), 3300 and 3245 (NH), 1610 (C=N) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 8.15 (d, J_{H6H7} = 7.8 Hz, H_6), 7.48 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.36-6.90 (m, H_7, H_9, NH and NH_2), 4.98 (s, OH), 4.35 (m, H_{2b} and H_{11a}), 3.60 (d, J_{gem} = 13.7 Hz, H_{3a}), 3.42 (m, H_{3b}), 2.76 (m, H_{1b}), 1.90 (m, H_{1a}).

Anal. Calcd. for $C_{12}H_{14}N_4OS$: C, 54.94; H, 5.38; N, 21.36. Found: C, 54.71; H, 5.45; N, 21.14.

1,2,3,11a-Tetrahydro-11-methylthio-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one (**14**).

To a solution of 1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one-11-thione (**1**) (6 g, 0.0259 mole) in tetrahydrofuran (120 ml), was added 2 equivalents of methyl iodide (3.20 ml, 0.0517 mole) and 3 equivalents of potassium carbonate (10.7 g, 0.0777 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 and

recrystallized from ether to give 4.55 g (71%) of **14**, mp 140°; ir (potassium bromide): ν 1640 (C=O), 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.82 (d, J_{H6H7} = 7.8 Hz, H_6), 7.51 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.32 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 7.18 (d, J_{H9H8} = 7.8 Hz, H_9), 4.30 (m, H_{11a}), 3.60 (m, H_{3a} and H_{3b}), 2.71 (m, H_{1a}), 2.49 (s, CH_3), 2.39 (m, H_{1b}), 2.03 (m, H_{2a} and H_{2b}).

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.68; N, 11.36. Found: C, 63.24; H, 5.47; N, 11.22.

1,2,3,11a-Tetrahydro-11-methylthio-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5-thione (**16**).

The thiolactam **3** (5 g, 0.0202 mole) was converted to **16** as described for the preparation of **14**. This gave 3.80 g (72%) of **16** (yellow crystals), mp 148° (ethyl acetate); ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.10 (d, J_{H6H7} = 7.8 Hz, H6), 7.64 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.35 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 7.23 (d, J_{H9H8} = 7.8 Hz, H_9), 4.25 (m, H_{11a}), 3.49 (m, H_{3a} and H_{3b}), 2.64 (m, H_{1a}), 2.43 (s, CH_3), 2.38 (m, H_{1b}), 2.10 (m, H_{2a} and H_{2b}); ms: m/z 262 (42), 214 (16), 170 (26).

Anal. Calcd. for $C_{13}H_{14}N_2S_2$: C, 59.51; H, 5.38; N, 10.68. Found: C, 59.43; H, 5.12; N, 10.47.

3b,4,5,6-Tetrahydro-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepin-8-one (**18a**).

A solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**10**) (2.5 g, 0.0109 mole) and triethyl orthoformate (2.35 ml, 0.0141 mole) in 1-butanol (50 ml) was heated at reflux. After 2 hours, the mixture was cooled and the white solid was collected, dried and recrystallized from ether to yield 1.95 g (74%) of **18a**, mp >260°; ir (potassium bromide): ν 1630 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.03 (s, CH), 7.81 (d, J_{H9H10} = 7.8 Hz, H_9), 7.50 (t, J_{H11H12} = J_{H11H10} = 7.9 Hz, H_{11}), 7.25 (d, J_{H12H11} = 7.8 Hz, H_{12}), 7.17 (t, J_{H10H11} = J_{H10H9} = 7.8 Hz, H_{10}), 3.88 (m, H_{3b}), 3.41 (d, J_{gem} = 11.3 Hz, H_{6a}), 3.01 (d, J_{gem} = 11.4 Hz, H_{6b}), 2.61 (m, H_{4a}), 2.20 (m, H_{4b}), 1.85 (m, H_{5a} and H_{5b}); ms: m/z 240 (12), 197 (46), 135 (21).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.06; H, 5.23; N, 23.18.

3b,4,5,6-Tetrahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-8-one (**19a**).

The cyclic hydrazidine **11** (1 g, 0.0041 mole) was converted to **19a** using the procedure for the preparation of **18a**. This gave 0.80 g (78%) of **19a** (white solid), mp >260° (ethanol); ir (potassium bromide): ν 3320 (OH), 1630 (C=O), 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.13 (s, CH), 7.96 (d, J_{H9H10} = 7.7 Hz, H_9), 7.75-7.62 (m, H_{10}, H_{11} and H_{12}), 5.23 (m, H_{5b}), 5.17 (d, J_{OHH5b} = 3.4 Hz, OH), 4.84 (m, H_{3b}), 3.81 (d, J_{gem} = 12.89 Hz, H_{6a}), 3.50 (dd, J_{gem} = 13.0 Hz, J_{H6bH5b} = 4.4 Hz, H_{6b}), 3.48 (m, H_{4a}), 2.72 (m, H_{4b}).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.81; H, 4.80; N, 21.73.

3b,4,5,6-Tetrahydro-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepine-8-thione (**20a**).

The hydrazidine **12** (1 g, 0.0040 mole) was converted to **20a** using the method for the preparation of **18a**. This gave 0.75 g (72%) of **20a** (yellow crystals), mp >260° (ether); ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.05 (s, CH), 8.16 (d, J_{H9H10} = 7.8 Hz, H_9), 7.65-7.38 (m, H_{10}, H_{11} and H_{12}), 4.85 (m, H_{3b}), 3.54 (m, H_{6a} and H_{6b}), 3.11 (m, H_{4a}), 2.53 (m, H_{4b}), 1.88 (m, H_{5a} and H_{5b}); ms: m/z 256 (20), 213 (46), 180 (12).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 61.07; H, 4.86; N, 22.05.

3b,4,5,6-Tetrahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-8-thione (**21a**).

The cyclic hydrazidine **13** (1.5 g, 0.0057 mole) was converted to **21a** using the procedure for the preparation of **18a**. This gave 1.15 g (75%) of **21a** (yellow crystals), mp >260° (acetone); ir (potassium bromide): ν 3320 (OH), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 9.18 (s, CH), 8.17 (d, J_{H9H10} = 7.8 Hz, H_9), 7.68-7.49 (m, H_{10}, H_{11} and H_{12}), 5.17 (m, H_{5b}), 5.06 (d, J_{OHH5b} = 3.4 Hz, OH), 4.71 (m, H_{3b}), 3.76 (d, J_{gem} = 12.5 Hz, H_{6a}), 3.61 (d, J_{gem} = 12.6 Hz, H_{6b}), 3.27 (m, H_{4a}), 2.65 (m, H_{4b}); ms: m/z 272 (24), 227 (12), 186 (48).

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.24; H, 4.29; N, 20.37.

3b,4,5,6-Tetrahydro-1-phenyl-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-8-one (**18b**).

A solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (**10**) (2 g, 0.0087 mole) and triethyl orthobenzoate (2.55 ml, 0.0113 mole) in 1-butanol (40 ml) was heated at reflux for 3 hours. After cooling, the white precipitate was collected, dried and recrystallized from 2-propanol to give 1.90 g (70%) of **18b**, mp >260°; ir (potassium bromide): ν 1640 (C=O), 1605 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.92-7.27 (m, 9 H), 4.73 (m, H_{3b}), 3.62 (m, H_{6a}), 3.45 (m, H_{6b}), 2.62-2.44 (m, H_{4a} and H_{4b}), 1.95 (m, H_{5a} and H_{5b}).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.14; H, 5.10; N, 17.71. Found: C, 72.31; H, 4.96; N, 17.53.

3b,4,5,6-Tetrahydro-5-hydroxy-1-phenyl-8*H*-pyrrolo[2,1-*c*]-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-8-one (**19b**).

The cyclic hydrazidine **11** (1 g, 0.0041 mole) was converted to **19b** using the procedure for the preparation of **18b**. This gave 1.05 g (78%) of **19b** (white crystals), mp >260° (ether); ir (potassium bromide): ν 3280 (OH), 1635 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.93-7.25 (m, 9H), 5.31 (m, H_{5b}), 4.98 (m, OH), 4.76 (m, H_{3b}), 3.74 (d, J_{gem} = 13.0 Hz, H_{6a}), 3.58 (m, H_{6b}), 3.32 (m, H_{4a}), 2.76 (m, H_{4b}); ms: m/z 332 (24), 274 (8), 186 (31).

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.50; H, 4.99; N, 17.04.

3b,4,5,6-Tetrahydro-8*H*-pyrrolo[2,1-*c*]tetrazolo[1,5-*a*][1,4]-benzodiazepin-8-one (**22**).

To a solution of 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (**10**) (1 g, 0.0043 mole) in 10% acetic acid (40 ml), was added sodium nitrite (0.45 g, 0.0065 mole). The resultant solution was stirred to room temperature for 1 hour. The white precipitate was filtered, dried and recrystallized from ether to give 0.75 g (72%) of **22**, mp 240°; ir (potassium bromide): ν 1620 (C=O), 1600 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.02 (d, J_{H9H10} = 7.8 Hz, H_9), 7.75 (m, H_{10}, H_{11} and H_{12}), 5.18 (m, H_{3b}), 3.66 (m, H_{6a} and H_{6b}), 2.75 (m, H_{4a}), 2.48 (m, H_{4b}), 2.06 (m, H_{5a} and H_{5b}); ms: m/z 241 (20), 211 (8), 156 (19).

Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.86; H, 4.75; N, 28.86.

3b,4,5,6-Tetrahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*]tetrazolo-[1,5-*a*][1,4]benzodiazepin-8-one (**23**).

The cyclic hydrazidine **11** (1.2 g, 0.0049 mole) was converted to **23** using the procedure for the preparation of **22**. This gave 0.85 g (69%) of **23** (white crystals), mp 248° (acetone); ir (potassium bromide): ν 3340 (OH), 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.93 (d, J_{H9H10} = 7.7 Hz, H_9), 7.76-7.58 (m, H_{10}, H_{11} and H_{12}), 5.12 (m, H_{5b}), 4.95 (d, J_{OHH5b} = 3.8 Hz, OH), 4.89 (m, H_{3b}), 3.77 (d, J_{gem} = 12.2 Hz, H_{6a}), 3.61 (m, H_{6b}), 3.42 (m, H_{4a}), 2.85 (m, H_{4b}).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.24; H, 4.47; N, 27.40.

3b,4,5,6-Tetrahydro-8*H*-pyrrolo[2,1-*c*]tetrazolo[1,5-*a*][1,4]-benzodiazepine-8-thione (**24**).

The cyclic hydrazidine **12** (1.5 g, 0.0061 mole) was converted to **24** as for the preparation of **22**. This gave 1 g (65%) of **24** (yellow crystals), mp 253° (ethanol); ir (potassium bromide): ν 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.28 (d, J_{H9H10} = 7.8 Hz, H_9), 7.82 (m, H_{11} and H_{12}), 7.68 (t, J_{H10H11} = J_{H10H9} = 7.7 Hz, H_{10}), 5.10 (m, H_{3b}), 4.93 (m, H_{6a}), 4.71 (m, H_{6b}), 3.82 (m, H_{4a} and H_{4b}), 2.03 (m, H_{5a} and H_{5b}); ms: m/z 257 (16), 228 (46), 184 (22).

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.22. Found: C, 55.87; H, 4.43; N, 27.39.

3b,4,5,6-Tetrahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*]tetrazolo-[1,5-*a*][1,4]benzodiazepine-8-thione (**25**).

The cyclic hydrazidine **13** (1 g, 0.0038 mole) was converted to **25** using the procedure for the preparation of **22**. This gave 0.75 g (72%) of **25** (yellow crystals), mp >260° (ethyl acetate); ir (potassium bromide): ν 3310 (OH), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.19 (d, J_{H9H10} = 7.8 Hz, H_9), 7.69-7.54 (m, H_{10}, H_{11} and H_{12}), 5.16 (m, H_{5b}), 4.92 (m, H_{3b}), 4.87 (d, J_{OHH5b} = 3.7 Hz, OH), 3.78 (m, H_{6a}), 3.59 (m, H_{6b}), 3.48 (m, H_{4a}), 2.82 (m, H_{4b}).

Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.74; H, 4.06; N, 25.62. Found: C, 52.60; H, 3.92; N, 25.39.

1,2,3b,4,5,6-Hexahydro-8*H*-pyrrolo[2,1-*c*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepin-1-one-8-thione (**26**).

To 1,2,3,11a-tetrahydro-11-hydrazino-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5-thione (**12**) (1.2 g, 0.0049 mole) was added phosgene (25 ml, 0.0487 mole) in toluene solution (20%). This mixture was heated to reflux for 1 hour. After evaporation of the solvent, the solid residue was taken up in an aqueous solution of ammonium hydroxide (20 ml). The yellow precipitate was collected, washed with water, dried and recrystallized from ethanol to give 0.90 g (67%) of **26** (yellow crystals), mp 254°; ir (potassium bromide): ν 3300 (NH), 1680 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 11.20 (s, NH), 8.21 (d, J_{H9H10} = 7.8 Hz, H_9), 7.88 (d, J_{H12H11} = 7.7 Hz, H_{12}), 7.62 (m, H_{10} and H_{11}), 5.01 (m, H_{3b}), 4.83 (m, H_{6a}), 4.68 (m, H_{6b}), 3.68 (m, H_{4a} and H_{4b}), 2.01 (m, H_{5a} and H_{5b}); ms: m/z 272 (38), 230 (21), 169 (62).

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.43; N, 20.57. Found: C, 57.18; H, 4.62; N, 20.74.

1,2,3,10,11,11a-Hexahydro-2-acetoxy-11-hydroxyimino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**27**).

To a solution of 1,2,3,11a-tetrahydro-2-acetoxy-11-methylthio-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**15**) (1 g, 0.0033 mole) in ethanol (40 ml), was added hydroxylamine hydrochloride (0.65 g, 0.0099 mole) and triethylamine (1.85 ml, 0.0132 mole). The mixture was heated to reflux for 4 hours. After cooling to room temperature, the white precipitate was collected, dried and recrystallized from ethanol to give 0.60 g (65%) of **27**, mp 228°; ir (potassium bromide): ν 3350 (OH), 3230 (NH), 1740 (C=O), 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.34 (s, NH), 9.13 (s, OH), 7.85 (d, J_{H6H7} = 7.7 Hz, H6), 7.57 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.29 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 7.19 (d, J_{H9H8} = 7.8 Hz, H_9), 5.28 (m, H_{2b}), 4.32 (m, H_{11a}), 3.75 (m, H_{3a} and H_{3b}), 2.78 (m, H_{1a}), 2.69 (m, H_{1b}), 2.03 (s, CH_3).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.32; H, 5.03; N, 14.69.

1,2,3,10,11,11a-Hexahydro-11-hydroxyimino-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5-thione (**28**).

The methyliminothioether **16** (1.5 g, 0.0057 mole) was converted to **28** using the procedure for the preparation of **27**. This gave 1 g (70%) of **28** (yellow solid), mp 242° (2-propanol); ir (potassium bromide): ν 3310 (OH), 3230 (NH), 1615 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.47 (s, NH), 9.02 (s, OH), 8.06 (d, J_{H6H7} = 7.8 Hz, H_6), 7.48 (t, J_{H8H9} = J_{H8H7} = 7.8 Hz, H_8), 7.30 (t, J_{H7H8} = J_{H7H6} = 7.8 Hz, H_7), 7.23 (d, J_{H9H8} = 7.8 Hz, H_9), 4.27 (m, H_{11a}), 3.62 (m, H_{3a} and H_{3b}), 2.73 (m, H_{1a}), 2.44 (m, H_{1b}), 2.06 (m, H_{2a} and H_{2b}); ms: m/z 247 (54), 215 (14), 139 (30).

Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99. Found: C, 58.41; H, 5.43; N, 16.86.

1,2,3,10,11,11a-Hexahydro-2-acetoxy-11-hydroxyimino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5-thione (**29**).

The methyliminothio ether **17** (0.8 g, 0.0025 mole) was converted to **29** using the procedure for the preparation of **27**. This gave 0.50 g (63%) of **29** (yellow solid), mp 246° (ether); ir (potassium bromide): ν 3350 (OH), 3220 (NH), 1735 (C=O), 1615 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.13 (s, NH), 8.97 (s, OH), 8.09 (d, J_{H6H7} = 7.7 Hz, H_6), 7.65 (t, J_{H8H9} = J_{H8H7} = 7.7 Hz, H_8), 7.32 (t, J_{H7H8} = J_{H7H6} = 7.7 Hz, H_7), 7.24 (d, J_{H9H8} = 7.8 Hz, H_9), 5.21 (m, H_{2b}), 4.41 (m, H_{11a}), 3.78 (m, H_{3a} and H_{3b}), 2.80 (m, H_{1a}), 2.68 (m, H_{1b}), 2.05 (s, CH_3).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.08; H, 4.92; N, 13.77. Found: C, 54.91; H, 5.03; N, 13.58.

1,2,3b,4,5,6-Hexahydro-5-acetoxy-8*H*-pyrrolo[2,1-*c*][1,2,4]oxa-diazolo[4,3-*a*][1,4]benzodiazepine-1,8-dione (**30**).

To 1,2,3,10,11,11a-hexahydro-2-acetoxy-11-hydroxyimino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazopin-5-one (**27**) (1.2 g, 0.0041 mole), was added phosgene (21 ml, 0.0415 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 acetone to give 0.90 g (69%) of **30**, mp >260°; ir (potassium bromide): ν 1765 (C=O), 1740 (C=O), 1630 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.85 (d, J_{H9H10} = 8.0 Hz, H_9), 7.54 (m, H_{10}, H_{11} and H_{12}), 5.20 (m, H_{5b}), 4.30 (m, H_{3b}), 3.72 (dd, J_{gem} = 11.8 Hz, J_{H6aH5b} = 3.0 Hz, H_{6a}), 3.48 (dd, J_{gem} = 11.7 Hz, J_{H6bH5b} = 4.5 Hz, H_{6b}), 2.76 (d, J_{gem} = 10.8 Hz, H_{4a}), 2.61 (m, H_{4b}), 2.05 (s, CH_3); ms: m/z 315 (54), 264 (18), 209 (36).

Anal. Calcd. for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 57.33; H, 4.12; N, 13.41.

1,2,3b,4,5,6-Hexahydro-8*H*-pyrrolo[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one-8-thione (**31**).

The oxime **28** (0.80 g, 0.0032 mole) was converted to **31** using the procedure for the preparation of **30**. This gave 0.55 g (63%) of **31** (yellow crystals), mp >260° (ether); ir (potassium bromide): ν 1770 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.02 (d, J_{H9H10} = 7.9 Hz, H_9), 7.61 (m, H_{10}, H_{11} and H_{12}), 4.27 (m, H_{3b}), 3.62 (m, H_{6a} and H_{6b}), 2.71 (m, H_{4a}), 2.43 (m, H_{4b}), 2.10 (m, H_{5a} and H_{5b}).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.01; H, 4.20; N, 15.51.

1,2,3b,4,5,6-Hexahydro-5-acetoxy-8*H*-pyrrolo[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one-8-thione (**32**).

The oxime **29** (0.90 g, 0.0029 mole) was converted to **32** using the procedure for the preparation of **30**. This gave 0.65 g (65%) of **32** (yellow crystals), mp >260° (acetonitrile); ir (potassium bromide): ν 1765 (C=O), 1730 (C=O), 1615 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.04 (d, J_{H9H10} = 7.8 Hz, H_9), 7.56 (m, H_{10}, H_{11} and H_{12}), 5.16 (m, H_{5b}), 4.29 (m, H_{3b}), 3.76 (dd, J_{gem} = 11.5 Hz, J_{H6aH5b} = 2.9 Hz, H_{6a}), 3.50 (dd, J_{gem} = 12.0 Hz, J_{H6bH5b} = 4.4 Hz, H_{6b}), 2.79 (m, H_{4a}), 2.31 (m, H_{4b}), 2.08 (s, CH_3).

Anal. Calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.38; H, 3.93; N, 12.69. Found: C, 54.19; H, 4.10; N, 12.41.

1,2,3b,4,5,6-Hexahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepine-1,8-dione (**33**).

A solution of 1,2,3b,4,5,6-hexahydro-5-acetoxy-8*H*-pyrrolo-[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepine-1,8-dione (**30**) (0.80 g, 0.0025 mole) and potassium carbonate (0.40 g, 0.0030 mole) in methanol (30 ml) was heated at reflux for 2 hours. After evaporation of the solvent under reduced pressure, the solid residue was taken up in water (80 ml). The white precipitate was collected, dried and recrystallized from ethanol to give 0.60 g (87%) of **33**, mp 254°; ir (potassium bromide): ν 3340 (OH), 1760 (C=O), 1650 (C=O), 1610 (C=O), 1610 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.81 (d, J_{H9H10} = 7.8 Hz, H_9), 7.50 (m, H_{10}, H_{11} and H_{12}), 5.08 (s, OH), 4.38 (m, H_{5b}), 4.28 (m, H_{3b}), 3.67 (m, H_{6a}), 3.50 (dd, J_{gem} = 11.8 Hz, J_{H6bH5b} = 4.4 Hz, H_{6b}), 2.69 (d, J_{gem} = 10.9 Hz, H_{4a}), 2.59 (m, H_{4b}); ms: m/z 273 (26), 228 (54), 184 (10).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.03; N, 15.38. Found: C, 57.36; H, 3.88; N, 15.20.

1,2,3b,4,5,6-Hexahydro-5-hydroxy-8*H*-pyrrolo[2,1-*c*][1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one-8-thione (**34**).

The acetoxy compound **32** (0.50 g, 0.0015 mole) was converted to **34** using the procedure for the preparation of **33**. This gave 0.35 g (84%) of **34** (yellow crystals), mp 250° (ethanol); ir (potassium bromide): ν 3350 (OH), 1755 (C=O), 1620 (C=N) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.07 (d, J_{H9H10} = 7.8 Hz, H_9), 7.48 (m, H_{10}, H_{11} and H_{12}), 5.04 (OH), 4.32 (m, H_{5b}), 4.20 (m, H_{3b}), 3.62 (m, H_{6a}), 3.51 (d, J_{gem} = 11.9 Hz, H_{6b}), 2.60 (d, J_{gem} = 11.2 Hz, H_{4a}), 2.46 (m, H_{4b}).

Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.98; H, 3.81; N, 14.53. Found: C, 54.17; H, 4.03; N, 14.29.

REFERENCES AND NOTES

[1] W. Leimgruber, V. Stefanovic, F. Schenker, A. Karr and J. Berger, *J. Am. Chem. Soc.*, **87**, 5791 (1965).

[2] K. Arima, M. Kohsaka, G. Tamura, H. Imanaka and H. Sakai, *J. Antibiot.*, **25**, 437 (1972).

[3] J. D. Leber, J. R. E. Hoover, K. G. Holden and S. M. Hecht, *J. Am. Chem. Soc.*, **110**, 2992 (1988).

[4] L. H. Hurley, T. Reck, D. E. Thurston, D. R. Langley, K. G. Holden, R. P. Hertzberg, J. R. E. Hoover, G. Gallagher, L. F. Faucette, S. M. Mong and R. K. Johnson, *Chem. Res. Toxicol.*, **1**, 258 (1988).

[5] M. P. Foloppe, S. Rault and M. Robba, *Tetrahedron Letters*, **33**, 2803 (1992).

[6] M. P. Foloppe, E. Caballero, S. Rault and M. Robba, *Eur. J. Med. Chem.*, **27**, 291 (1992).

[7] M. P. Foloppe, S. Rault, D. E. Thurston, T. C. Jenkins and M. Robba, *Eur. J. Med. Chem.*, **31**, 407 (1995).

[8] M. P. Foloppe, S. Rault, I. Rault and M. Robba, *Heterocycles*, **36**, 63 (1993).

[9] A. C. Gillard, S. Rault, M. Boulouard and M. Robba, *J. Heterocyclic Chem.*, **32**, 1741 (1995).

[10] F. Eloy and R. Levaers, *Chem. Rev.*, **2**, 155 (1962).

[11] A. C. Gillard, S. Rault, M. Boulouard and M. Robba, *J. Heterocyclic Chem.*, **33**, 275 (1996).