

Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine Derivatives
with Potential CNS Activity (1,2)

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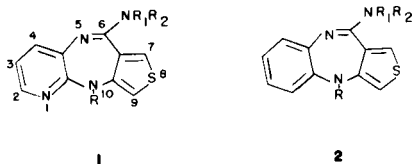
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Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepines (**1a-d**) were synthesized to investigate their potential CNS activity. Synthesis of the desired ring system was effected by condensation of 2,3-diaminopyridine (**3**) with methyl tetrahydro-4-oxo-3-thiophenecarboxylate (**4**). Structural assignment of the major condensation product **5** was determined by comparison of ¹H nmr absorptions of **5** with those of related methyl lactam derivatives **11** and **14**. A discussion of the possible mechanism leading to **5** in preference to isomeric lactam **6** is presented. Biological evaluation of **1a-d** revealed no interesting properties.

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Discussion.

During the course of developing novel thiophene fused tricyclic ring systems as potential psychotropic agents (4a,b), we undertook the synthesis of 6-alkylamino-10H-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepines (**1**). Our goal

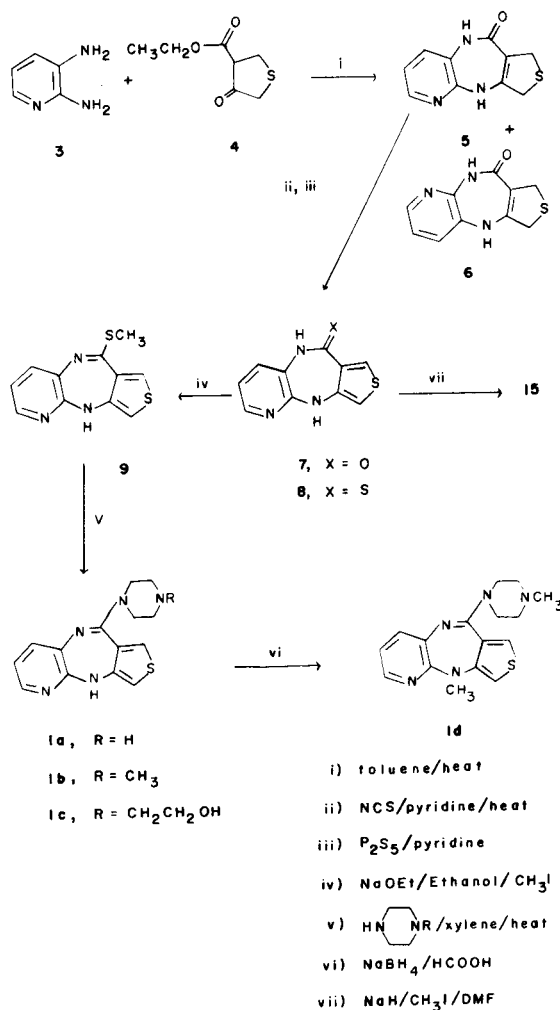


was to prepare novel CNS agents with an improved therapeutic profile similar to that reported for clozapine (**5**) or compounds with mixed action effects similar to those observed for 4*H*-thieno[3,4-*b*][1,5]benzodiazepines (**2**) which we reported previously (4a).

The title compounds **1** were prepared using procedures similar to those reported (4a) for the preparation of **2** (Scheme I). Methyl tetrahydro-4-oxo-3-thiophenecarboxylate (**4**) (**6**) and 2,3-diaminopyridine (**3**) were condensed in refluxing toluene to give an 83% yield of a mixture of lactams **5** and **6** in a ratio of 3:1. The desired lactam **5** was separated by fractional crystallization. It is interesting to note that such separation on the related unsymmetrical benzene derivatives could not be achieved until the lactams were subsequently oxidized (4a). Thiophene **7** was prepared in good yield by oxidation of **5** with *N*-chlorosuccinimide in pyridine. Thiolactam **8**, prepared from **7** and phosphorus pentasulfide, was *S*-alkylated with methyl iodide/sodium ethoxide to give methyl thioether **9**. Reaction of **9** with various piperazines gave the target amidine derivatives **1a-c**. Ring nitrogen substitution was accomplished using the reductive alkylation procedure of Gribble (7) to give **1d**.

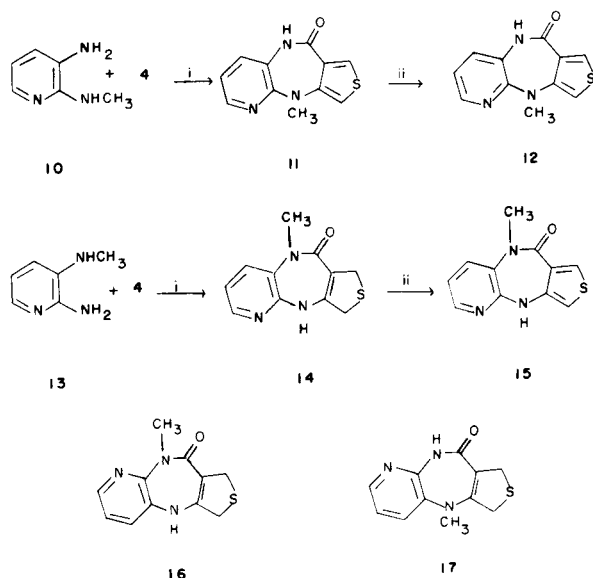
Structural assignment of isomers **5** and **6** was difficult because of their similar spectral properties. Consideration of the nucleophilicity of the 2- and 3-amino groups of **3** as well as previously reported reactions of **3** with β -ketoesters

Scheme I



(**8**) gave no *a priori* expectations for the preferred course of condensation of **3** and **4**. Consequently, related tricyclic derivatives **11** and **14** were prepared to provide insight into the structures of **5** and **6** (Scheme II). When 3-amino-2-

Scheme II



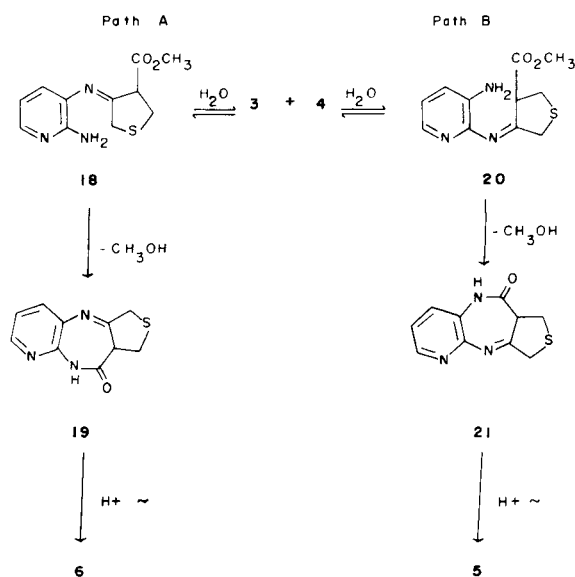
i) toluene/heat
ii) NCS/pyridine/heat

methylaminopyridine (**10**) (**9**) was reacted with **4**, lactam **11** was isolated, albeit in low yield. Similar reaction of 2-amino-3-methylaminopyridine (**13**) (**10**) with **4** provided **14** in moderate yield. Oxidation of **11** and **14** with *N*-chlorosuccinimide/pyridine gave thiophene derivatives **12** and **15** in high yield.

Examination of the ^1H nmr spectrum of **11** revealed two triplet absorptions at δ 4.0 and δ 3.85 for the methylene protons α to sulfur at C-9 and C-7 respectively. The spectra of **5**, **6** and **14** all had singlet absorptions for these methylene protons in the vicinity of δ 3.8. These observations are consistent with the fact that the α methylene groups are nearly equivalent in the non-substituted amine derivatives **5**, **6** and **14**. However, the amine methyl substitution of **11** sterically crowds and deshields the C-9 methylene as compared to C-7 across the ring, causing the methylene protons to become non-equivalent and to split (**11**). These same arguments were used to eliminate alternative isomers **16** and **17** as possible products. In order to relate these results to **5**, the major condensation product in Scheme I, thienolactam **7** was methylated with methyl iodide/sodium hydride to give **15**. Methyl lactam **15** derived in this manner was identical in all respects to the material derived from **4** and **13**.

Since several previous reports of condensation of **3** with β ketoesters have appeared (**8**), it is interesting to examine the apparent preference of the reaction to form **5**, the result of the 2-amine moiety of **3** reacting with the ketone of **4** (Scheme I). Israel and co-workers have noted that con-

Scheme III



densation of **3** with ethyl acetoacetate gives rise to either of the two possible isomeric products by controlling reaction conditions (**8c**). Our present results as well as those of Israel (**8**) might be understood as depicted in Scheme III. Condensation of **3** and **4** under equilibrium conditions (water was not initially removed, see experimental) (**12**) may take place *via* Path A and/or Path B. Presumably Path A is favored due to the more reactive character of the 3-amine giving rise to **18** in preference to **20**. The free amine of **20**, however, is more reactive than that of **18** and ring closure to **21** is thus more facile than ring closure to **19**. As a consequence of the relative irreversibility of this lactam formation, the facile formation of **21** (and hence **5** *via* proton transfer) shifts the equilibrium depicted in Scheme III toward path B and hence **5** forms as the major product of reaction.

The results of biological evaluation of target compounds **1a-d** were discouraging. The compounds were tested in a variety of CNS screens including inhibition of motor activity in rats, antagonism of *d*-amphetamine-induced lethality in grouped mice, antagonism of tetra-benzazine-induced depression and antagonism of pentylenetetrazol-induced convulsions in rats (**13**). All of the test compounds **1** had little or no activity in these evaluations and we have no further interest in compounds of this type.

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin layer chromatographic analysis using Whatman K5F or K6F (5×10 cm) silica gel analytical plates. ^1H nmr

measurements were obtained on a Varian Associates HA-100A spectrometer with tetramethylsilane as the internal standard.

5,7,9,10-Tetrahydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-one (**5**) and 5,7,9,10-Tetrahydro-6*H*-pyrido[2,3-*b*]thieno[3,4-*e*][1,4]diazepin-6-one (**6**).

A solution of 2,3-diaminopyridine (**3**, 10.9 g, 0.100 mole) in toluene (250 ml) was stirred and refluxed while a solution of methyl tetrahydro-4-oxo-3-thiophenecarboxylate (**6**) (**4**, 16.0 g, 0.100 mole) in toluene (200 ml) was added dropwise over a period of 2 hours. Reflux was continued for an additional hour while 260 ml of distillate was collected using a Dean-Stark receiver. The residue was cooled and filtered to give a 3:1 mixture of a yellow solid, 18.2 g (83%). Recrystallization of the solid from dimethyl sulfoxide gave 12.4 g of a 4:1 mixture of **5** and **6** as determined by ¹H nmr analysis. This material was recrystallized carefully from dimethyl sulfoxide containing several drops of water to give pure **5**, 7.3 g (33%), mp 232-234° dec; ir (potassium bromide): 1650 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 8.84 (s, 1H, *NH*), 8.79 (s, 1H, *NH*), 7.69 (dd, 1H, α-pyridyl *H*), 7.10 (dd, 1H, γ-pyridyl *H*), 6.80 (dd, 1H, β-pyridyl *H*), 3.80 (s, 4H, CH₂S).

Anal. Calcd. for C₁₀H₉N₃OS: C, 54.77; H, 4.14; N, 19.16; S, 14.63. Found: C, 54.85; H, 4.08; N, 19.19; S, 14.42.

A second crop of crystals obtained from the above filtrate by the addition of water (4.0 g, 18%) was a 2:3 mixture of **5** and **6**, mp 211-218° dec. No attempts to isolate **6** as a pure isomer were made.

5,10-Dihydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-one (**7**).

To a cooled slurry of 5,7,9,10-tetrahydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-one (**5**, 21.9 g, 0.1 mole) in pyridine (200 ml) was added *N*-chlorosuccinimide (13.4 g, 0.1 mole) in portions while maintaining a temperature between 15-20°. After the final addition, the mixture was heated on a steam bath for 20 minutes and then poured into ice and water (2 l) with vigorous stirring. The mixture was filtered to give **7** (18.6 g, 86%) as a tan solid, mp 280-4° dec; ir (potassium bromide): 1650 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 9.75 (brs, 1H, *NH*), 8.80 (brs, 1H, *NH*), 8.04 (d, 1H, thiophene *H*), 7.70 (dd, 1H, α-pyridyl *H*), 7.30 (dd, 1H, γ-pyridyl *H*), 6.82 (dd, 1H, β-pyridyl *H*) and 6.65 (d, 1H, thiophene *H*).

Anal. Calcd. for C₁₀H₇N₃OS·½ H₂O: C, 53.08; H, 3.56; N, 18.57; S, 14.17. Found: C, 53.46; H, 3.58; N, 18.80; S, 14.17.

5,10-Dihydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-thione (**8**).

A mixture of 5,10-dihydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-one (**7**, 5.4 g, 0.025 mole), phosphorus pentasulfide (2.2 g, 0.01 mole) in pyridine (50 ml) was stirred and refluxed for 4 hours. The mixture was concentrated to a thick oil, 5% sodium carbonate (60 ml) and methanol (5 ml) were added and the mixture was stirred overnight. The solid was collected, washed with water and dried to give 4.5 g (94%) of **8** as a light brown solid, mp 263-267° dec.

Anal. Calcd. for C₁₀H₇N₃S₂: C, 51.48; H, 3.03; N, 18.01; S, 27.49. Found: C, 51.47; H, 3.08; N, 17.77; S, 27.30.

6-(Methylthio)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine (**9**).

To an alcoholic solution of sodium ethoxide (prepared from 0.24 g, 0.01 g atom of sodium in 40 ml of ethanol) was added 5,10-dihydro-6*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-thione (**8**, 2.3 g, 0.01 mole) and methyl iodide (1 ml). The mixture was stirred overnight, diluted with water and extracted with chloroform. The combined organic extracts were filtered through a magnesium silicate cake and concentrated to give a solid which was recrystallized from methanol to give **9** as yellow crystals, 1.5 g (60%), mp 138-141°; ir (potassium bromide): 1621 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 7.83 (dd, 1H, α-pyridyl *H*), 7.54 (d, 1H, thiophene *H*), 7.38 (dd, 1H, γ-pyridyl *H*), 7.09 (brs, 1H, *NH*), 6.85 (dd, 1H, β-pyridyl *H*), 6.19 (d, 1H, thiophene *H*), 2.49 (s, 3H, CH₃S).

Anal. Calcd. for C₁₁H₉N₃S₂: C, 53.41; H, 3.67; N, 16.99; S, 25.93. Found: C, 53.28; H, 3.89; N, 17.01; S, 25.83.

6-(1-Piperazinyl)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine Fumarate (**1a**).

A mixture of 6-(methylthio)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine (**9**, 2.5 g, 0.01 mole), piperazine (8.6 g, 0.1 mole), acetic acid (3 drops) was refluxed for 24 hours in xylene (15 ml). The solvent was evaporated, the residue was washed with water and dissolved in acetic acid (2*N*, 50 ml). The solution was filtered, the filtrate was made alkaline with ammonium hydroxide and extracted several times with methylene chloride. The combined extracts were dried, filtered and the filtrate evaporated to give a glass (2.8 g). This glass was dissolved in ethanol (30 ml) and treated with an ethanolic solution of fumaric acid (2.3 g, 0.02 mole in 45 ml of ethanol). The fumarate salt was collected and recrystallized from ethanol to give 1.9 g (48%) of **1a** as a yellow solid, mp 202-203° dec; ¹H nmr (DMSO-*d*₆): 7.97 (brs, 1H, *NH*), 7.72 (dd, 1H, α-pyridyl *H*), 7.61 (d, 1H, thiophene *H*), 7.17 (dd, 1H, γ-pyridyl *H*), 6.98 (s, 1H, *NH*), 6.86 (dd, 1H, β-pyridyl *H*), 6.69 (d, 1H, thiophene *H*), 6.48 (s, 2H, fumarate *H*), 3.56 (m, 4H, CH₂NC=N), 3.08 (m, 4H, CH₂NH).

Anal. Calcd. for C₁₄H₁₃N₅S·¾ C₄H₄O₄·¼ H₂O: C, 54.17; H, 4.95; N, 18.58; S, 8.51. Found: C, 54.01; H, 5.01; N, 18.18; S, 8.27.

6-(4-Methyl-1-piperazinyl)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine (**1b**).

A mixture of 6-(methylthio)-10*H*-pyrido[3,4-*b*]thieno[3,4-*e*][1,4]diazepine (**9**, 2.5 g, 0.01 mole), *N*-methylpiperazine (16 ml) and acetic acid (3 drops) was stirred and refluxed for 7.5 hours. The mixture was cooled and poured into ice-water. The yellow solid (**1b**) was collected and recrystallized from alcohol (20 ml) to give 2.2 g (73%) of **1b**, mp 189-191°; ¹H nmr (deuteriochloroform): δ 7.78 (dd, 1H, α-pyridyl *H*), 7.30 (dd, 1H, γ-pyridyl *H*), 7.21 (d, 1H, thiophene *H*), 6.88 (dd, 1H, β-pyridyl *H*), 6.70 (brs, 1H, *NH*), 6.42 (d, 1H, thiophene *H*), 3.58 (s, 4H, CH₂NC=N), 2.52 (t, 4H, CH₂NCH₃), 2.33 (s, 3H, NCH₃).

Anal. Calcd. for C₁₅H₁₇N₅S: C, 60.17; H, 5.72; N, 23.39; S, 10.71. Found: C, 60.09; H, 5.64; N, 23.26; S, 10.72.

4-(10*H*-Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-6-yl)-1-piperazine Ethanol Fumarate (**1c**).

This salt, prepared by the procedure described above for **1a**, using hydroxyethylpiperazine in place of piperazine, was obtained as a yellow solid in 43% yield, mp 192-193° dec; ¹H nmr (DMSO-*d*₆): δ 7.91 (brs, 1H, *NH*), 7.71 (dd, 1H, α-pyridyl *H*), 7.50 (d, 1H, thiophene *H*), 7.18 (dd, 1H, γ-pyridyl *H*), 6.82 (dd, 1H, β-pyridyl *H*), 6.68 (d, 1H, thiophene *H*), 6.58 (s, 2H, fumarate *H*), 3.55 (m, 6H, CH₂O, CH₂NC=N), 2.70 (m, 6H, CH₂N).

Anal. Calcd. for C₁₆H₁₅N₅OS·¾ C₄H₄O₄: C, 54.79; H, 5.33; N, 16.82; S, 7.70. Found: C, 54.99; H, 5.48; N, 16.97; S, 7.87.

10-Methyl-6-(4-methyl-1-piperazinyl)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine Hemifumarate (**1d**).

To a stirred and cooled mixture of 6-(4-methyl-1-piperazinyl)-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepine (1.2 g, 0.004 mole) in 97% formic acid (14 ml) was added sodium borohydride pellets one at a time (1.35 g, 0.036 mole). The mixture was stirred at room temperature for two days, cooled, diluted with water, made alkaline with ammonium hydroxide and extracted with chloroform. The extracts were dried (magnesium sulfate), filtered and the filtrate was evaporated to an oil. The oil (1.6 g) was dissolved in ethanol (10 ml) and treated with a hot solution of fumaric acid (0.5 g, 0.004 mole) in ethanol (10 ml). The product precipitated upon cooling and was collected by filtration to give 1.2 g of **1d** as a tan solid, mp 201-203° dec; ¹H nmr (DMSO-*d*₆): δ 7.83 (dd, 1H, α-pyridyl *H*), 7.52 (d, 1H, thiophene *H*), 7.20 (dd, 1H, γ-pyridyl *H*), 6.91 (dd, 1H, β-pyridyl *H*), 6.82 (d, 1H, thiophene *H*), 6.65 (s, 2H, fumarate *H*), 3.52 (m, 4H, CH₂NC=N), 3.12 (s, 3H, CH₃N), 2.48 (m, 4H, CH₂NCH₃), 2.38 (s, 3H, CH₃NCH₂).

Anal. Calcd. for C₁₆H₁₉N₅S·½ C₄H₄O₄·½ C₂H₂OH: C, 57.84; H, 6.13; N, 17.75; S, 8.13. Found: C, 57.52; H, 5.85; N, 17.58; S, 8.27.

1,3,4,9-Tetrahydro-4-methyl-10*H*-pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepin-10-one (**11**).

A solution of 2-methylamino-3-aminopyridine (**8**) (3.4 g, 0.027 mole) and methyl tetrahydro-4-oxo-3-thiophenecarboxylate (**6**) (2.9 g, 0.018

mole) in toluene (200 ml) was refluxed for 3 hours during which 100 ml of distillate was collected using a Dean-Stark receiver. The residue was cooled and concentrated to give an oily solid. Recrystallization from ethyl acetate gave **11** (0.38 g, 6%) as a pale yellow solid, mp 240-241°; ir (potassium bromide): 1661 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 9.28 (brs, 1H, NH), 8.00 (dd, 1H, α -pyridyl H), 7.28 (dd, 1H, γ -pyridyl H), 7.06 (dd, 1H, β -pyridyl H), 4.00 (t, 2H, CH_2S), 3.85 (t, 2H, CH_2S), 3.25 (s, 3H, NCH_3).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{OS}$: C, 56.63; H, 4.75; N, 18.01; S, 13.75. Found: C, 56.72; H, 4.77; N, 18.08; S, 13.61.

4,9-Dihydro-4-methyl-10H-pyrido[3,2-*b*]thieno[3,4-*e*]1,4-diazepin-10-one (**12**).

A suspension of 1,3,4,9-tetrahydro-4-methyl-10H-pyrido[3,2-*b*]thieno[3,4-*e*]1,4-diazepin-10-one (**11**, 0.595 g, 0.0026 mole) in pyridine (5 ml) was oxidized with *N*-chlorosuccinimide (0.34 g, 0.0026 mole) using the procedure described above to prepare **7**. The product **12** was obtained (0.395 g, 67%) as an off-white solid, mp 240-241°; ir (potassium bromide): 1672 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 10.02 (brs, 1H, NH), 8.14 (d, 1H, thiophene H), 8.07 (dd, 1H, α -pyridyl H), 7.41 (dd, 1H, γ -pyridyl H), 7.05 (dd, 1H, β -pyridyl H), 6.84 (d, 1H, thiophene H), 3.28 (s, 3H, CH_3N).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{OS}$: C, 57.12; H, 3.92; N, 18.17; S, 13.87. Found: C, 56.77; H, 4.12; N, 18.20; S, 13.75.

1,3,4,9-Tetrahydro-9-methyl-10H-pyrido[3,2-*b*]thieno[3,4-*e*]1,4-diazepin-10-one (**14**).

A solution of 2-amino-3-methylaminopyridine (**9**) (2.3 g, 0.0187 mole) and methyl tetrahydro-4-oxo-3-thiophenecarboxylate (**6**) (2 g, 0.0125 mole) in toluene (150 ml) was refluxed for 3 hours during which time 75 ml of distillate was collected in a Dean-Stark trap. The solution was evaporated and the residue was recrystallized from ethyl acetate to give **14** (0.6 g, 20%) as an off-white solid, mp 220-222°; ir (potassium bromide): 1672, 1630 cm^{-1} ; ^1H nmr (DMSO- d_6): 9.10 (brs, 1H, NH), 7.93 (dd, 1H, α -pyridyl H), 7.51 (dd, 1H, γ -pyridyl H), 7.10 (dd, 1H, β -pyridyl H), 3.87 (s, 4H, CH_2S), 3.13 (s, 3H, CH_3N).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{OS}$: C, 56.63; H, 4.75; N, 18.01; S, 13.75. Found: C, 56.39; H, 4.75; N, 17.84; S, 13.96.

4,9-Dihydro-9-methyl-10H-pyrido[3,2-*b*]thieno[3,4-*e*]1,4-diazepin-10-one (**15**). Method A.

Treatment of 1,3,4,9-tetrahydro-9-methyl-10H-pyrido[3,2-*b*]thieno[3,4-*e*]1,4-diazepin-10-one (**14**, 0.233 g, 0.001 mole) in pyridine (2 ml) with *N*-chlorosuccinimide (0.133 g, 0.001 mole) in the manner described above for **7**, gave 0.12 g (55%) of **15** after one recrystallization from aqueous methanol as a tan solid, mp 245-246°; ir (potassium bromide): 1645 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 8.75 (brs, 1H, NH), 8.08 (d, 1H, thiophene H), 7.98 (dd, 1H, α -pyridyl H), 7.65 (dd, 1H, γ -pyridyl H), 7.08 (dd, 1H, β -pyridyl H), 6.76 (d, 1H, thiophene H), 3.34 (s, 3H, CH_3N).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{OS}$: C, 57.12; H, 3.92; N, 18.17; S, 13.87. Found: C, 56.83; H, 3.82; N, 17.91; S, 13.69.

Method B.

A solution of lactam **7** (0.65 g, 0.0030 mole) in dimethylformamide (25 ml) was treated with sodium hydride (0.15 g, 0.0030 mole of a 50%

suspension with mineral oil prewashed with petroleum ether) and the mixture was stirred 15 minutes. Methyl iodide (0.45 g, 0.20 ml, 0.0032 mole) was added and stirring was continued for 2 hours. The reaction was quenched with water (150 ml) and the precipitate was collected by filtration and air dried, 0.68 g (99%). Recrystallization from chloroform-petroleum ether gave the analytical sample of **15**, mp 244-246°, identical in all respects to the material prepared above from 2-amino-3-methylaminopyridine as described above.

Acknowledgement.

The authors wish to thank Dr. W. Gore and staff for the measurement of spectral data, Mr. G. Morton for useful discussions concerning ^1H nmr results and Dr. R. Hargreaves and staff for microanalytical data.

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- (1) For the previous paper in this series see J. B. Press and N. H. Eudy, *J. Heterocyclic Chem.*, **18**, 1261 (1981).
- (2) These compounds are the subjects of the U. S. Patent 4,066,647 (1978); *Chem. Abstr.*, **88**, P136685b (1978).
- (3) Deceased September 5, 1974.
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- (11) For a discussion of such van der Waal deshielding effects see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, Ca., 1964, pp 189-190. A similar -0.1 ppm shift for 1,3 methyl deshielding of a C-4 proton in steroidal systems is discussed.
- (12) In reference 8c, the reaction run without solvent and azeotropic removal of water gave the product with the same orientation observed for **5**.
- (13) Testing results were supplied by Drs. I. P. Day and E. N. Greenblatt of these laboratories. For a description of the test procedures, see reference 4.