The Synthesis of Imidazothienodiazepines and Imidazopyrazolodiazepines

R. Ian Fryer, James V. Earley and Armin Walser*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

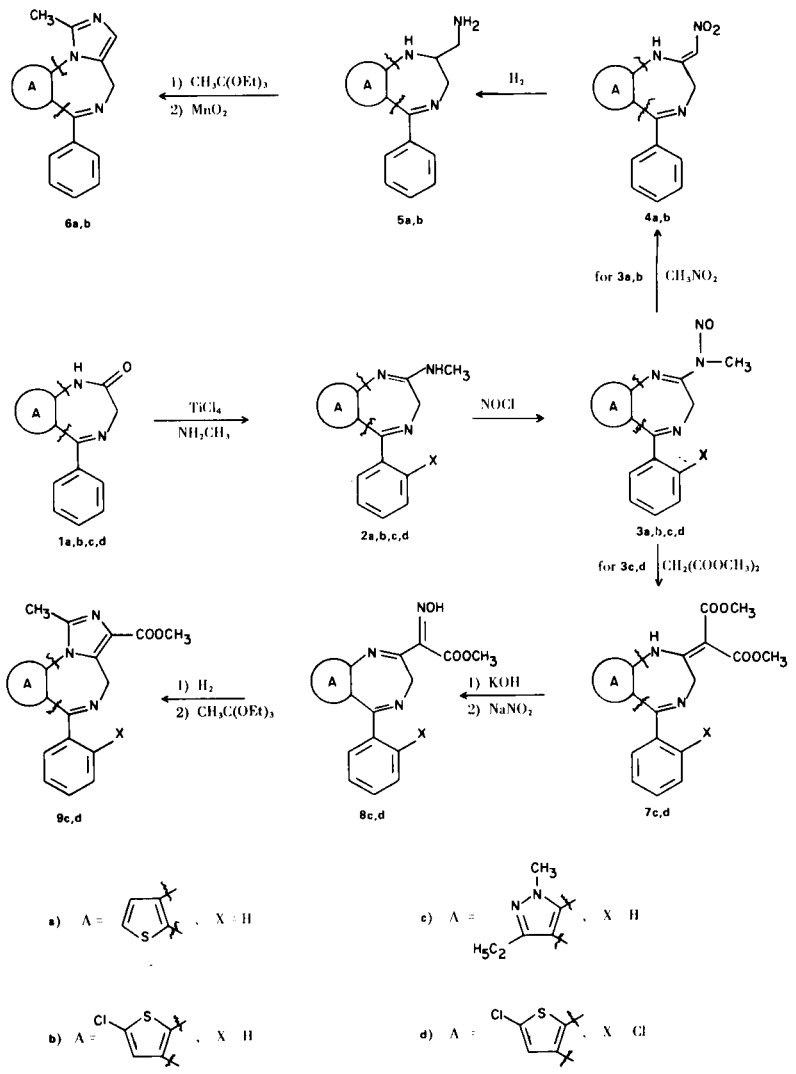
Received November 18, 1977

The thieno[3,2-*e*][1,4]diazepin-2-one (**1a**), the thieno[2,3-*e*][1,4]diazepin-2-one (**1b**), the pyrazolo[3,4-*e*][1,4]diazepin-2-one (**1c**) and a chloro analog of **1b**, compound **1d**, were each converted to derivatives of the novel tricyclic ring systems 4*H*-imidazo[1,5-*a*]thieno[2,3-*f*][1,4]-diazepine, 4*H*imidazo[1,5*a*]thieno[2,3*f*][1,4]diazepine and 4*H*-imidazo[1,5-*a*]pyrazolo[4,3-*f*]-[1,4]diazepine. Depending on the substituents desired on the imidazo ring, two different synthetic pathways were employed.

J. Heterocyclic Chem., 15, 619 (1978).

As part of out continuing interest in the synthesis of novel tricyclic diazepine derivatives bearing an imidazo ring fused to the 1,2-positions of the diazepine ring, (2,3) we have synthesized derivatives of three novel tricyclic ring systems; 4*H*-imidazo[1,5-*a*]thieno[3,2-*f*][1,4]diazepine, 4*H*-imidazo[1,5-*a*]thieno[3,2-*f*][1,4]-diazepine and 4*H*-imidazo[1,5-*a*]pyrazolo[4,3-*f*[1,4]diazepine. In each instance the imidazo ring was constructed from the readily available bicyclic diazepin-2-one precursors, compounds **1a** (4), **1b** (5), **1c** (6), and **1d** (7) (Scheme 1). Using our previously described procedures, the 2-ones were converted to the amidines **2a-d** (8) and then to the *N*-nitrosoamidines **3a-d** (9). The utility of such nitrosoamidines for the formation of carbon-carbon

Scheme I

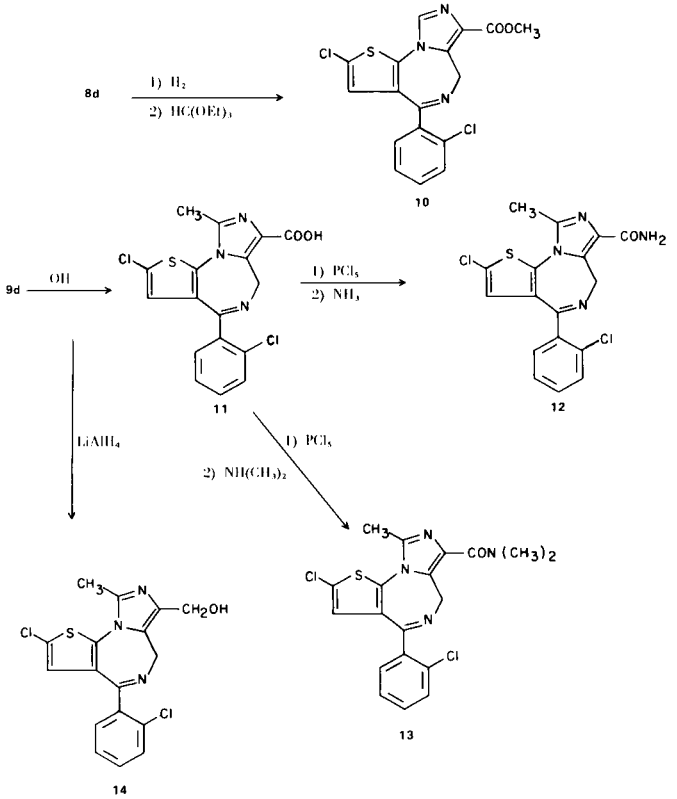


bonds by condensation with carbanions has by now been well established (1,3,10). The carbanion selected, depends on the substitution desired on the imidazo ring. Abitrarily we chose to treat **3a** and **3b** with the anion of nitromethane to give the nitromethylene compounds **4a** and **4b** while compounds **3c** and **3d** were treated with the anion of malonic ester to give the malonylidene derivatives **7c** and **7d**.

Reduction of the nitromethylene group of **4a,b** using hydrogen over a Raney nickel catalyst afforded the primary amines **5a,b** which were condensed with triethyl-orthoacetate to yield dihydroimidazothienodiazepines. The dihydro compounds were not characterized but oxidized directly to the end products **6a,b** by treatment with activated manganese dioxide.

The use of the malonylidene compounds (**7c,d**) offered at least three distinct advantages over the nitromethylene derivatives (**4a,b**). First the use of nitromethane in organic solvents is a potentially hazardous reagent (used under the conditions described in the experimental section we have encountered no difficulties). A second advantage is that the penultimate intermediate is at the "correct" oxidation state such that the orthoacetate condensation product does not require the rather low yield manganese dioxide oxidation reaction in order to introduce the second double bond. Finally, these intermediates (**7c,d**) lead to end products functionalized in the 3-position.

Scheme 2



The malonylidene esters 7c,d were decarboxylated with potassium hydroxide and then nitrosated in situ to afford the oxime esters **8c,d**. Reduction with zinc/acetic acid (for **8c**) or with hydrogen over Raney nickel (for **8d**) gave the glycinylidene derivatives which again were not isolated (11), but were converted directly to the end products (**9c,d**) by treatment with triethyl orthoacetate.

By using triethyl orthoformate instead of orthoacetate, compound **8d** was converted to the corresponding 1*H*-imidazodiazepine, compound **10** (Scheme 2). Hydrolysis of the ester **9d** with methanolic potassium hydroxide gave the free acid **11** while lithium aluminum hydride reduction afforded the expected alcohol **14**. The acid was readily converted, *via* the acid chloride, to both the primary and tertiary amides **12** and **13**, respectively.

EXPERIMENTAL (12)

2-Methylamino-5-phenyl-3*H*-thieno-[3,2-*e*][1,4]diazepine (**2a**).

A mixture of 10 g. (0.036 mole) of 1,3-dihydro-5-phenylthieno-[3,2-*e*][1,4]diazepine-2-(2H)one (**1a**) (4) in 50 ml. of benzene and 300 ml. of tetrahydrofuran was stirred in an ice bath and saturated with methylamine gas. A solution of 9.48 g. (0.05 mole) of titanium tetrachloride in 50 ml. of benzene was added dropwise to the mixture. After the addition was complete, the mixture was stirred on the ice bath for 15 minutes. The ice bath was then replaced with a heating mantle and the mixture refluxed for 0.5 hour. The mixture was cooled and 100 g. of ice was carefully added. The mixture was filtered and the residue was washed with tetrahydrofuran. The filtrates were combined, dried and evaporated. The product was collected by means of dichloromethane to yield 8.6 g. of **2a** as pale yellow prisms, m.p. 223-227°. From the concentrated mother liquors an additional 1.0 g. was obtained, for a total yield of 9.6 g. (92.5%). The analytical sample was recrystallized from dichloromethane, m.p. 227-229°.

Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46. Found: C, 66.02; H, 5.04; N, 16.53.

7-Chloro-2-methylamino-5-phenyl-3*H*-thieno[2,3-*e*][1,4]diazepine (**2b**).

A mixture of 7.7 g. (0.0278 mole) of 7-chloro-1,3-dihydro-5-phenylthieno[2,3-*e*][1,4]diazepin-2-(2*H*)one (**1b**) (5), 50 ml. of benzene and 250 ml. of tetrahydrofuran was stirred in an ice bath and saturated with methylamine gas. To this mixture was added a solution of tetanium tetrachloride (7.38 g., 0.0389 mole) in 50 ml. of benzene from a dropping funnel. After the addition was complete, the mixture was stirred in the ice bath for 15 minutes. The ice bath was then replaced by a heating mantle and the reaction mixture was refluxed for 20 minutes. The mixture was cooled and 100 g. of ice was carefully added. The mixture was then filtered, and the residue washed with tetrahydrofuran. The filtrates were combined, dried and evaporated. The product was collected by means of dichloromethane/ether to yield 5.5 g. (68.4%) of **2b** as pale yellow prisms, m.p. 246-249°. The analytical sample was recrystallized from dichloromethane, m.p. 247-250°.

Anal. Calcd. for $C_{14}H_{12}ClN_3S$: C, 58.03; H, 4.17; N, 14.50. Found: C, 58.20; H, 4.14; N, 14.46.

3-Ethyl-1-methyl-7-methylamino-4-phenyl-1*H*,6*H*-pyrazolo[3,4-*e*]-[1,4]diazepine (**2c**).

A solution of 6.8 g. (0.0255 mole) of 3-ethyl-6,8-dihydro-1-methyl-4-phenyl-1*H*-pyrazolo[3,4-*e*][1,4]diazepin-7(7*H*)one (**1c**) (6) in 125 ml. of dry tetrahydrofuran and 50 ml. of dry benzene was cooled in an ice bath and methylamine was bubbled in until the solution was saturated. A solution of 6.3 g. (0.0331 mole) of titanium tetrachloride in 20 ml. of benzene was then added dropwise with stirring, and after 18 hours at room temperature the mixture was refluxed for 30 minutes. The solution was cooled, and treated with 4 g. of ice. The reaction mixture was filtered and the precipitate was washed with tetrahydrofuran and then with dichloromethane. The combined filtrates were evaporated to dryness and the residue was crystallized from a mixture of methanol and ether, and recrystallized from a mixture of dichloromethane and ether to give 5.8 g. (81%) of **2c** as off-white prisms, m.p. 218-221°.

Anal. Calcd. for $C_{16}H_{19}N_5$: C, 68.30; H, 6.81; N, 24.89. Found: C, 68.33; H, 6.71; N, 24.90.

7-Chloro-5-(2-chlorophenyl)-2-methylamino-3*H*-thieno[2,3-*e*][1,4]-diazepine (**2d**).

A solution of 50 g. (0.161 mole) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydrothieno[2,3-*e*][1,4]diazepin-2-(2H)one (**1d**) (7) in 900 ml. of dry tetrahydrofuran and 300 ml. of dry benzene was cooled in an ice bath, and methylamine was bubbled in until the solution was saturated. A solution of 40 g. (0.209 mole) of titanium tetrachloride in 100 ml. of benzene was added dropwise with stirring. After 4 hours at room temperature a few grams of ice was added and the reaction mixture was filtered. The precipitate was washed several times with hot tetrahydrofuran, and the combined filtrates were evaporated. The residue was partitioned between 250 ml. of dichloromethane and 200 ml. of water, and filtered. The dichloromethane solution was separated, dried, and evaporated. This residue and the precipitate were recrystallized from a mixture of tetrahydrofuran and ethanol to give 34 g. of product. An additional 8 g. was obtained from the mother liquor. Thus the total yield amounted to 42 g. (81%). A sample was recrystallized for analysis from a mixture of tetrahydrofuran and hexane to give pale yellow prisms, m.p. 259-262°.

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3S$: C, 51.86; H, 3.42; N, 12.96. Found: C, 52.16; H, 3.39; N, 12.91.

2-(*N*-nitroso-*N*-methylamino)-5-phenyl-3*H*-thieno[3,2-*e*][1,4]diazepine (**3a**).

Nitrosyl chloride was introduced into a solution of 7.8 g. (0.03 mole) of **2a** in 100 ml. of dichloromethane and 40 ml. of pyridine cooled in ice water. The reaction was monitored by thin layer chromatography and when the starting material had disappeared the nitrosyl chloride addition was terminated and the reaction mixture was partitioned between dichloromethane and water. The dichloromethane solution was dried and evaporated. Crystallization of the residue from dichloromethane/hexane yielded 7.9 g. (91%) of **3a** as yellow crystals, m.p. 156-159°. The analytical sample was recrystallized from ether/hexane, m.p. 158-160°.

Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.13; H, 4.25; N, 19.70. Found: C, 59.34; H, 4.20; N, 19.74.

7-Chloro-2-(Nitroso-*N*-methylamino)-5-phenyl-3*H*-thieno[2,3-*e*]-[1,4]diazepine (**3b**).

Nitrosyl chloride was introduced into a solution of 5.8 g. (0.02 mole) of **2b** in 100 ml. of dichloromethane and 50 ml. of pyridine until the reaction was complete according to thin layer chromatography. The mixture was partitioned between water and toluene. The organic phase was dried and evaporated. Crystallization of the residue from ether/hexane yielded 4.7 g. (80%) of **3b** as yellow crystals, m.p. 108-110°. An analytical sample was recrystallized from ether/hexane, m.p. 111-113°.

Anal. Calcd. for $C_{14}H_{11}ClN_4OS$: C, 52.75; H, 3.48; N, 17.58. Found: C, 52.73; H, 3.43; N, 17.81.

3-Ethyl-1-methyl-7-(*N*-nitroso-*N*-methylamino)-4-phenyl-1*H*,6*H*-pyrazolo[3,4-*e*][1,4]diazepine (**3c**).

Nitrosyl chloride was bubbled through a solution of 13.6 g. (0.0484 mole) of **2c** in 200 ml. of dichloromethane and 20 ml. of pyridine for 15 minutes at 0°. Additional nitrosyl chloride was added at room temperature after 1 hour and 3 hour intervals for a period of 5 minutes. After 4 hours, the reaction mixture was poured into a mixture of ice and dilute sodium bicarbonate solution with stirring. The layers were separated and the aqueous layer was extracted with 75 ml. of dichloromethane. The combined organic layers were washed with 100 ml. of water, dried over anhydrous sodium sulfate and evaporated. Toluene was added and the reaction was evaporated again. The residue was crystallized from a mixture of dichloromethane and ether and recrystallized from a mixture of dichloromethane, ether and petroleum ether to give 12.3 g. (82%) of **3c** as yellow prisms, m.p. 120-122°.

Anal. Calcd. for $C_{16}H_{18}N_6O$: C, 61.92; H, 5.85; N, 27.08. Found: C, 62.13; H, 5.81; N, 27.31.

7-Chloro-5-(2-chlorophenyl)-2-(*N*-nitroso-*N*-methylamino)-3*H*-thieno[2,3-*e*][1,4]diazepine (**3d**).

A mixture of 40 g. (0.123 mole) of **2d**, 700 ml. of dichloromethane and 350 ml. of pyridine was cooled in an ice bath and nitrosyl chloride was bubbled in for 20 minutes with stirring. After 1 hour it was bubbled in for 5 minutes more and then 600 ml. of water was added slowly. The dichloromethane layer was separated, washed with 200 ml. of water, dried over anhydrous sodium sulfate and evaporated to dryness. The oil was dissolved in dichloromethane and filtered through 400 g. of Florisil. This was eluted with dichloromethane, and then ether. Crystallization of the dichloromethane fraction from a mixture of ether and petroleum ether gave 34 g. of product, and 6 g. more was obtained from the ether fraction for a 92% yield. A sample was recrystallized for analysis from a mixture of ether and petroleum ether to give **3d** as yellow prisms, m.p. 104-107°.

Anal. Calcd. for $C_{14}H_{10}Cl_2N_4OS$: C, 47.60; H, 2.85; N, 15.86. Found: C, 47.73; H, 2.74; N, 15.93.

1,2-Dihydro-2-nitromethylene-5-phenyl-3*H*-thieno[3,2-*e*][1,4]diazepine (**4a**).

A mixture of 15 ml. of nitromethane, 4.5 g. of potassium *t*-butoxide and 60 ml. of *N*,*N*-dimethylformamide which had been stirred for 10 minutes at room temperature was treated with 5.7 g. (0.02 mole) of **3a**. After the addition, the reaction mixture was stirred under nitrogen and heated on the steam bath for 10 minutes. After acidification with 4 ml. of glacial acetic acid the mixture was partitioned between dichloromethane/toluene and saturated sodium bicarbonate solution. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from methanol yielded 2.6 g. (45%) of **4a** as yellow crystals with m.p. 160-163°. An analytical sample was recrystallized from methanol, m.p. 163-164°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2S$: C, 58.94; H, 3.89; N, 14.73. Found: C, 59.00; H, 3.86; N, 14.99.

7-Chloro-1,2dihydro-2-nitromethylene-5-phenyl-3H-thieno[2,3-*e*]-[1,4]diazepine (**4b**).

A mixture of 10 ml. of nitromethane, 35 ml. of *N*,*N*-dimethylformamide and 2.26 g. (0.02 mole) of potassium *t*-butoxide which had been stirred under nitrogen for 10 minutes at room

temperature was treated with 3.2 g. (0.01 mole) of **3b**. After heating for 10 minutes on the steam bath the reaction mixture was acidified by addition of 2 ml. of glacial acetic acid and was partitioned between water and toluene. The toluene layer was washed with water, dried and evaporated. The residue crystallized from ethyl acetate/hexane to yield 2.5 g. of crude product. Purification by chromatography over 40 g. of silica gel using 10% (v/v) of ethyl acetate in dichloromethane gave 2.2 g. (68%) of pure **4b** as yellow crystals, m.p. 154-165°.

Anal. Calcd. for $C_{14}H_{10}ClN_3O_2S$: C, 52.58; H, 3.15, N, 13.14. Found: C, 52.56; H, 3.14; N, 13.16.

2-Aminomethyl-2,3-dihydro-5-phenyl-1*H*-thieno[3,2-*e*][1,4]diazepine Dimaleate (**5a**).

A solution of 1.42 g. (5 mmoles) of **4a** in 200 ml. of ethanol was hydrogenated over Raney nickel (2 teaspoonsful) for 1 hour at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 1,2 g. of maleic acid in 10 ml. of 2-propanol. The salt was crystallized by the addition of ether to yield 1.2 g. (49%) of **5a** as yellow crystals, m.p. 170-173°. The analytical sample was recrystallized from methanol/2-propanol, m.p. 187-189°.

Anal. Calcd. for $C_{14}H_{15}N_3S{\cdot}2C_4H_4O_4$: C, 53.98; H, 4.74; N, 8.58. Found: C, 53.89; H, 4.78; N, 8.78.

2-Aminomethyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-thieno[2,3-*e*][1,4]diazepine Dimaleate (**5b**).

A) A solution of 320 mg. (1 mmole) of **4b** in 20 ml. of ethanol was hydrogenated over Raney nickel for 5 hours at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was chromatographed over 7 g. of silica gel using dichloromethane, methanol, and triethylamine in a ratio of 13:6:1. The clean fractions were combined, evaporated and the residue was treated with maleic acid in 2-propanol. Crystallization of the dimaleate salt from 2-propanol/ether and recrystallization from ethyl acetate/ethanol yielded 65 mg. (12.5%) of **5b** as yellow crystals, m.p. 176-177°.

Anal. Calcd. for $C_{14}H_{14}ClN_3S{\cdot}2C_4H_4O_4$: C, 50.43; H, 4.23; N, 8.02. Found: C, 50.33; H, 4.23; N, 7.91.

B) A solution of 320 mg. (1 mmole) of **4b** in 3 ml. of tetrahydrofuran was added to a suspension of 0.8 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran. After heating to reflux for 5 minutes, the reaction mixture was cooled and treated with 5 ml. of water. The inorganic material was separated by filtration and the filtrate was evaporated. The residue was chromatographed as described above and the pure product was converted to the maleate to give 150 mg. (28%) of dimaleate, m.p. 176-178°.

1-Methyl-6-phenyl-4*H*-imidazo[1,5-*a*]thieno[2,3-*f*][1,4]diazepine (**6a**).

The dimaleate salt of **5a** (1 g., 2 mmoles) was partitioned between dichloromethane and aqueous ammonia. The dichloromethane layer was dried and evaporated. The residue was heated to reflux for 1 hour with 1 ml. of triethyl orthoacetate in 20 ml. of xylene. The solvent was evaporated under reduced pressure and the residue was crystallized from 2-propanol/ether to yield 0.35 g. (62%) of 1-methyl-3a,4-dihydro-6-phenyl-3*H*-imidazo[1,5-*a*]thieno[2,3-*f*][1,4]diazepine, m.p. 150-152°. This material was heated to reflux in 30 ml. of toluene with 3 g. of activated manganese dioxide for 2 hours. The magnanese dioxide was filtered off and washed well with dichloromethane. The combined filtrates were evaporated and the residue was chromatographed over 7 g. of silica gel using 3% (v/v) of ethanol in dichloromethane. The clean fractions were combined and evaporated. Crystallization from dichloromethane/ether and recrystallization from ethyl acetate/hexane yielded 40 mg. (11.5%) of **6a** as white prisms, m.p. 223-225°.

Anal. Calcd. for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04. Found: C, 68.60; H, 4.63; N, 14.96.

8-Chloro-1-methyl-6-phenyl-4*H*-imidazo[1,5-*a*]thieno[3,2-*f*][1,4]diazepine (**6b**).

The dimaleate **5b** (0.52 g., 1 mmole) was partitioned between dichloromethane and aqueous ammonia. The dichloromethane solution was dried and evaporated. The residue was heated to reflux for 1 hour with 0.5 ml. of triethyl orthoacetate in 10 ml. of xylene. The crude product obtained after evaporation under reduced pressure was dissolved in 25 ml. of toluene and the solution was heated to reflux for 1.5 hours after addition of 2.5 g. of activated manganese dioxide. The manganese dioxide was then filtered off and the filtrate was evaporated. Chromatography of the residue over 6 g. of silica gel using 4% (v/v) of ethanol in dichloromethane and crystallization of the clean fractions from ether/hexane yielded 12 mg. (4%) of **6b** as white prisms, m.p. 168-170°; ms: m/e 313 (M^+).

(3-Ethyl-1,6,7,8-tetrahydro-1-methyl-4-phenylpyrazolo[3,4-*e*][1,4]diazepin-7-ylidene)propanedioic Acid Dimethyl Ester (**7c**).

A mixture of 14 ml. of dimethyl malonate and 35 ml. of *N,N*-dimethylformamide was treated with 6.5 g. (0.0580 mole) of potassium *t*-butoxide and after stirring for 5 minutes a solution of 5.9 g. (0.019 mole) of **3c** in 10 ml. of *N,N*-dimethylformamide was added. The resulting mixture was heated on the steam bath for 5 minutes, cooled, and 6 ml. of glacial acetic acid was added. The reaction mixture was next poured into 300 ml. of cold water, and after 15 minutes the solution was decanted. The remaining oil was dissolved in 75 ml. of of dichloromethane which was washed with 50 ml. of dilute ammonium hydroxide, dried over anhydrous sodium sulfate and chromatographed through Florisil. The column was eluted first with dichloromethane, then with ether and finally with ethyl acetate. The ether and ethyl acetate fractions were combined and evaporated. The residue was crystallized and recrystallized from methanol to give 1.8 g. (24%) of the diester as off-white rods, m.p. 145-148°.

Anal. Calcd. for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.80; N, 14.65. Found: C, 62.85; H, 5.83; N, 15.03.

[7-Chloro-2,3-dihydro-5-(2-chlorophenyl)-1*H*-thieno[2,3-*e*][1,4]diazepin-2-ylidene]propanedioic Acid Dimethyl Ester (**7d**).

A mixture of 3.4 g. (0.03 mole) of potassium *t*-butoxide, 7 ml. of dimethylmalonate and 20 ml. of *N,N*-dimethylformamide was stirred for 5 minutes under an atmosphere of nitrogen. Following the addition of 3.55 g. (0.01 mole) of **3d**, the mixture was stirred and heated on the steam bath for 5 minutes, acidified by the addition of 3 ml. of acetic acid and the product was precipitated by the slow addition of water. The crystalline material was collected, washed with water and methanol and dissolved in dichloromethane. The solution was dried and evaporated and the residue was crystallized from ethanol to yield 3 g. (70%) of **7d** as off-white prisms. Crystallization from ethanol afforded an analytical sample, m.p. 158-160°.

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_4S$: C, 50.84; H, 3.32; N, 6.59. Found: C, 50.88; H, 3.44; N, 6.63.

1-Ethyl-1,6,7,8-tetrahydro-1-methyl-4-phenyl-pyrazolo[3,4-*e*][1,4]diazepine-7-(hydroxyimino)acetic Acid Methyl Ester (**8c**).

A solution of 1.7 g. (4.45 mmoles) of **7c** in 40 ml. of methanol was treated with 0.56 g. (0.01 mole) of potassium hydroxide, and the solution was refluxed for 2.5 hours. The solvent was

evaporated, and the residue was partitioned between 50 ml. of dichloromethane and 30 ml. of water. The water layer was first acidified with hydrochloric acid then made basic with ammonium hydroxide and extracted with 75 ml. of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and filtered through Florisil. The Florisil was eluted with ether, and then with ethyl acetate. The eluents were combined and evaporated to give 0.9 g. of the crude monoester as an oil. This product was not further purified but was dissolved in 10 ml. of glacial acetic acid and treated with 0.35 g. (5 mmoles) of sodium nitrite while stirring. After 45 minutes the reaction mixture was poured into 100 ml. of water, which was extracted with 75 ml. of dichloromethane. The organic layer was washed with 50 ml. of dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The product was crystallized from a mixture of ethyl acetate and ether. Recrystallization from a mixture of dichloromethane and ether gave 0.4 g. (35%) of the pure material as off-white rods, m.p. 225-227°.

Anal. Calcd. for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.61; H, 5.41; N, 19.99.

7-Chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]-diazepine-2-(hydroxyimino)acetic Acid Methyl Ester (**8d**).

A mixture of 2.15 g. (5 mmoles) of **7d**, 50 ml. of methanol and 0.7 g. (1.25 mmoles) of potassium hydroxide was heated to reflux under nitrogen for 3 hours. The solvent was partially evaporated and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. The crude [7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2-ylidene]-acetic acid methyl ester obtained was dissolved in 20 ml. of glacial acetic acid. Sodium nitrite, 0.5 g., was added and the mixture was stirred for 15 minutes at room temperature, diluted with water and extracted with dichloromethane. The extracts were washed with water and sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from dichloromethane/ether and recrystallization from tetrahydrofuran/methanol gave 0.45 g. (23%) of **8d** as yellow crystals, m.p. 242-245° dec.

Anal. Calcd. for $C_{16}H_{11}Cl_2N_3O_3S$: C, 48.50; H, 2.80; N, 10.60. Found: C, 48.37; H, 2.33; N, 10.50.

7-Ethyl-1,9-dimethyl-6-phenyl-4*H*,9*H*-imidazo[1,5-*a*]pyrazolo[4,3-*f*][1,4]diazepine-3-carboxylic Acid Methyl Ester (**9c**).

A solution of 0.2 g. (0.567 mmole) of **8c** in 10 ml. of dichloromethane and 0.35 ml. of acetic acid was treated with 0.4 g. of zinc dust. After stirring for 5 minutes the solution was filtered. The zinc was washed with dichloromethane and tetrahydrofuran and the washings were added to the filtrate. The combined filtrates were treated with 0.3 ml. of triethyl orthoacetate in 15 ml. of ethyl acetate and the solvents were removed. The residue was heated under reflux in 15 ml. of ethyl acetate for 1 minute and the solvent was removed. The residue was applied to thick layer silica gel plates which were developed with 10% methanol in ethyl acetate. The band between Rf 0.2-0.4 was removed and washed with methanol. The methanol solution was filtered and evaporated and the residue crystallized from ethyl acetate to give 0.1 g. (49%) of **9c** as white rods, m.p. 187-189°.

Anal. Calcd. for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 66.26; H, 5.80; N, 19.22.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]thieno-[3,2-*f*][1,4]diazepine-3-carboxylic Acid Methyl Ester (**9d**).

A solution of 0.4 g. (1 mmole) of **8d** in 30 ml. of warm tetrahydrofuran and 20 ml. of ethanol was treated with 0.5 teaspoonful of Raney nickel and the mixture was hydrogenated for 45 minutes at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 10 ml. of methanol and treated with 0.4 ml. of triethylorthoacetate and 3 drops of ethanolic hydrogen chloride. After heating to reflux for 10 minutes the solvent was evaporated and the residue was partitioned between dichloromethane and sodium bicarbonate solution. The organic layer was dried and evaporated. Chromatography of the residue over 10 g. of silica gel using dichloromethane ethyl acetate 3:5 (v/v) afforded after crystallization of the residue from ethanol 95 mg. (23%) of **9d** as white prisms, m.p. 211-212°.

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2S$: C, 53.21; H, 3.23; N, 10.34. Found: C, 53.35; H, 3.29; N, 10.45.

8-Chloro-6-(2-chlorophenyl)-4*H*-imidazo[1,5-*a*]thieno[3,2-*f*][1,4]-diazepine-3-carboxylic Acid Methyl Ester (**10**).

A solution of 3.7 g. (0.0093 mole) of **8d** in a mixture of 200 ml. of dry tetrahydrofuran and 120 ml. of methanol was cooled to 10° and 1 teaspoonful of Raney nickel was added. The reaction mixture was hydrogenated at room temperature and at atmospheric pressure until the theoretical amount of hydrogen was taken up (100 minutes), and was then filtered through Celite. The filtrates were treated with 3 ml. (0.0228 mole) of triethylorthoformate and 3 drops of ethanolic hydrogen chloride, and the solution was evaporated to dryness. The residue was dissolved in 100 ml. of methanol and treated with the same quantities of triethylorthoformate and ethanolic hydrogen chloride. The solution was refluxed for 1 hour, evaporated to dryness and the residue was dissolved in 75 ml. of dichloromethane. The solution was washed with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and chromatographed through 125 g. of Florisil. The column was eluted with dichloromethane containing ether (10%, v/v), and then with ether, and finally with ethyl acetate. The ether and ethyl acetate fractions were combined, concentrated and filtered. The product was recrystallized from a mixture of dichloromethane, ethyl acetate and ether to give 1.2 g. (32%) of **10** as white prisms, m.p. 170-175°.

Anal. Calcd. for $C_{17}H_{11}Cl_2N_3O_2S$: C, 52.06; H, 2.83; N, 10.71. Found: C, 52.10; H, 3.07; N, 10.72.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]thieno-[3,2-*f*][1,4]diazepine-3-carboxylic acid (**11**).

To 10 ml. of methanol and 1 ml. of water was added 0.1 g. (0.247 mmole) of **9d** and 0.028 g. (0.493 mmole) of potassium hydroxide. The reaction mixture was refluxed for 2 hours and evaporated. The residue was dissolved in 10 ml. of water, washed with 10 ml. of ether and then acidified with acetic acid. The acid solution was extracted with 30 ml. of dichloromethane, which was dried over anhydrous sodium sulfate, concentrated and cooled. The product was filtered and recrystallized from a mixture of dichloromethane and ether to give 40 mg. (40%) of **11** as white prisms, m.p. 242-247°.

Anal. Calcd. for $C_{17}H_{11}Cl_2N_3O_2S$: C, 52.05; H, 2.83; N, 10.71. Found: C, 52.13; H, 3.06; N, 10.66.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]thieno-[3,2-*f*][1,4]diazepine-3-carboxamide (**12**).

To 0.8 g. (2.04 mmoles) of **11** in 100 ml. of dry dichloromethane cooled in an ice bath was added 0.46 g. (2.2 mmoles) of phosphorus pentachloride. After 30 minutes ammonia was bubbled in for 5 minutes with stirring. After 2 hours, 75 ml. of water was added and the solution was filtered. The dichloromethane was separated, dried and evaporated. The residue was crystallized from ethanol and then combined with the first

precipitate. This was recrystallized from a mixture of chloroform and ethanol to give 0.65 g. (81%) of **12** as white rods, m.p. 300-305°.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_4OS$: C, 52.18; H, 3.09; N, 14.32. Found: C, 52.27; H, 3.12; N, 14.27.

8-Chloro-6-(2-chlorophenyl)-1,*N*,*N*-trimethyl-4*H*-imidazo[1,5-*a*]-thieno[3,2-*f*][1,4]diazepine-3-carboxamide (**13**).

Phosphorus pentachloride, 0.46 g. (2.2 mmoles), was added to a suspension of 0.785 g. (2 mmoles) of **11** in 50 ml. of dichloromethane. After stirring under nitrogen in an ice bath for 30 minutes, dimethylamine was introduced until the reaction mixture was alkaline. It was stirred for 30 minutes at room temperature and washed with saturated sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from ethyl acetate/ether gave white crystals which were recrystallized from ethyl acetate for analysis, m.p. 197-200°.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_4OS$: C, 54.43; H, 3.85; N, 13.36. Found: C, 54.60; H, 3.92; N, 13.10.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*]thieno-[3,2-*f*][1,4]diazepine-3-methanol (**14**).

To 20 ml. of ether under nitrogen was added 38 mg. (1 mmole) of lithium aluminum hydride. The reaction was cooled in an ice bath and 0.2 g. (0.493 mmole) of **9d** was dissolved in 20 ml. of dry tetrahydrofuran and added dropwise with stirring to the reaction mixture. After one hour 5 ml. of ethyl acetate was added followed by 3 ml. of a saturated solution of sodium bicarbonate. The mixture was filtered through Celite, which was then washed with dichloromethane and the combined filtrates were evaporated and crystallized from a mixture of dichloromethane and ether. Recrystallization from the same solvents gave 0.1 g. (53%) of **14** as off-white prisms, m.p. 100-110°, resets, m.p. 190-194°.

Anal. Calcd. for $C_{17}H_{13}Cl_2N_3OS$: C, 53.98; H, 3.43; N, 11.11. Found: C, 54.14; H, 3.47; N, 11.06.

Acknowledgement.

We are indebted to the following members of our Physical Chemistry Department for spectral and elemental analysis: Dr. W. Benz, Dr. F. Scheidl, Dr. W. Toome, Mr. S. Traiman, and Dr. T. Williams.

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(11) See reference 1 for similar examples in which the intermediate amino compounds were characterized.

(12) Melting points were taken microscopically on a hot stage and are corrected. Spectra of all compounds were taken and compared in order to confirm or exclude structural changes. All novel compounds gave spectra compatible with assigned structures. The uv spectra were taken on a Cary Model 14 spectrophometer, nmr spectra with a Varian A-60 instrument, ir spectra on a Beckman IR-9 spectrophotomer and mass spectra using a CEC-21-110B instrument at 70 eV by direct insertion. The yields reported were usually the result of single experiments and were not optimized.