The Synthesis of 5,10-Dihydro- and 2,3,5,10-Tetrahydrothiazolo-[3,2-*b*][2,4]benzodiazepines, 1,2,3,4,7,12-Hexahydrobenzothiazolo-[3,2-*b*][2,4]benzodiazepine, and 9,14-Dihydro-6*H*-[1]benzothiopyrano-[4',3':4,5]thiazolo[3,2-*b*][2,4]benzodiazepine *via* 1,2,4,5-Tetrahydro-3*H*-2,4-benzodiazepine-3-thione

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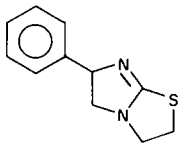
Catalytic reductive scission of phthalazine (II) utilizing a two-stage palladium-Raney nickel procedure afforded *o*-xylene-α,α'-diamine (III) in 97% yield. Treatment of III with carbon disulfide gave [*o*-(aminomethyl)benzyl]dithiocarbamic acid (IV), which upon thermal cyclization furnished 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V). Reaction of V with 1,2-dibromoethane, chloro-2-propanone, ethyl 2-chloroacetoacetate, ethyl chloroacetate, and ethyl 2-bromohexanoate gave 2,3,5,10-tetrahydrothiazolo[3,2-*b*][2,4]benzodiazepine (VII) and substituted 5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepines (VIIIa and b, IX, and X), respectively. Condensation of V with 2-chlorocyclohexanone and 3-bromothiochroman-4-one afforded 1,2,3,4,7,12-hexahydrobenzothiazolo[3,2-*b*][2,4]benzodiazepine (XII) and 9,14-dihydro-6*H*-[1]benzothiopyrano[4',3':4,5]thiazolo[3,2-*b*][2,4]benzodiazepine (XIII). None of the compounds possessed appreciable biological activity.

dl-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride (tetramisole) (I) (1) is a potent, new anthelmintic with broad action against *Ascaris lumbricoides* and *Enterobius vermicularis* in man (2) and against a variety of adult and immature gastrointestinal and pulmonary nematodes in laboratory animals, poultry, and livestock (3). The present communication describes the

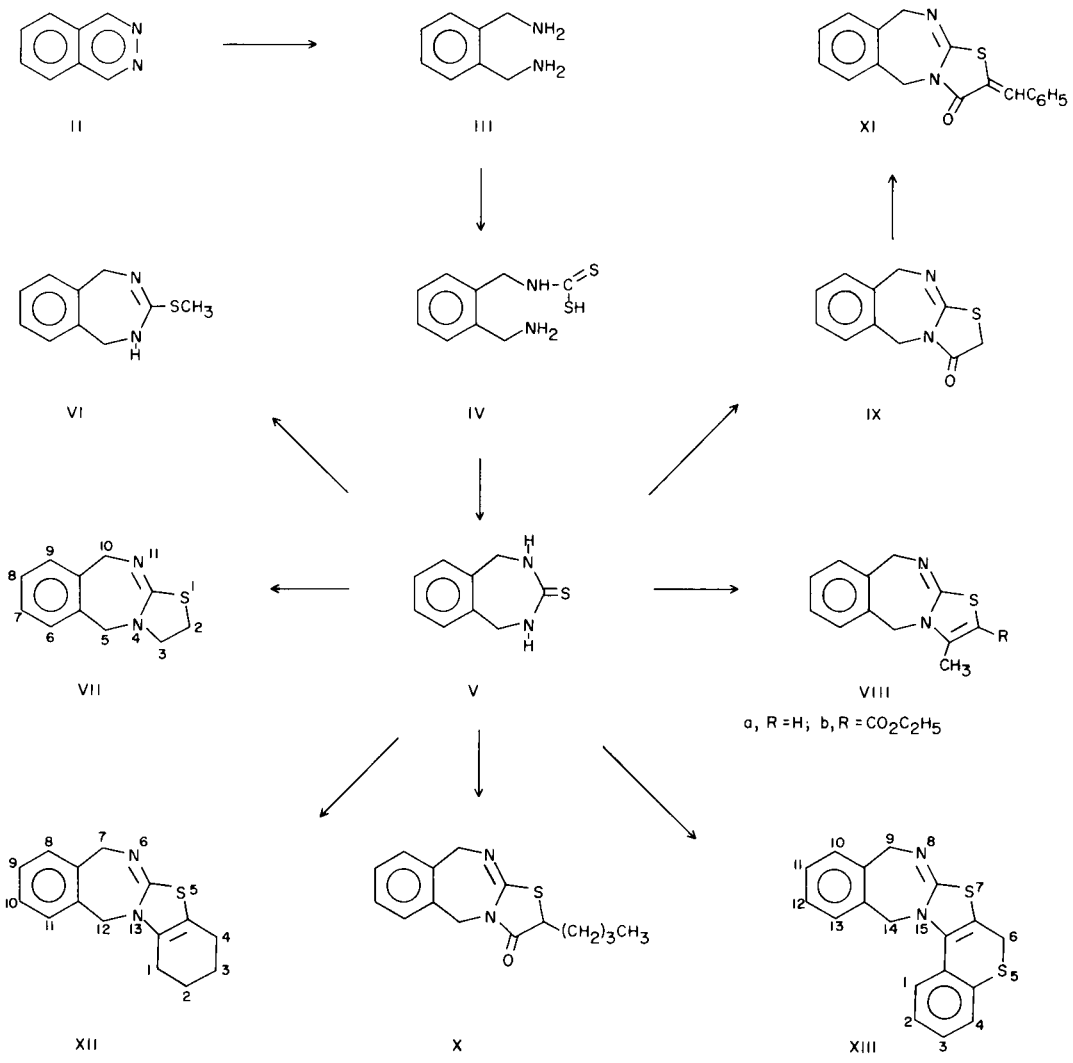


I

synthesis of tetramisole analogs derived from 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V), namely 5,10-dihydro- and 2,3,5,10-tetrahydrothiazolo[3,2-*b*][2,4]-benzodiazepines (VII, VIIIa and b, IX, X, and XI), 1,2,3,4,7,12-hexahydrobenzothiazolo[3,2-*b*][2,4]benzodiazepine (XII), and 9,14-dihydro-6*H*-[1]benzothiopyrano[4',3':4,5]thiazolo[3,2-*b*][2,4]benzodiazepine (XIII). These three ring systems are not listed in *Chemical Abstracts* or "The Ring Index" (4) and appear to be novel heterocyclic types.

The key intermediate for these new heterocyclic compounds is 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V). A cursory review of the literature revealed that few 2,4-benzodiazepine derivatives have been reported (5-7), although considerable attention has been directed to the synthesis of 1,4- and 1,5-benzodiazepines (3,8,9). 1,2,4,5-Tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) was obtained in 69% overall yield by the treating of *o*-xylene-α,α'-diamine (III) with carbon disulfide, followed by thermal cyclization of the intermediate [*o*-(aminomethyl)benzyl]dithiocarbamic acid IV. Alkylation of V with methyl iodide in methanol afforded 2,5-dihydro-3-(methylthio)-1*H*-2,4-benzodiazepine hydriodide (VI) in quantitative yield.

Condensation of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) with 1,2-dibromoethane, chloro-2-propanone, ethyl 2-chloroacetoacetate, ethyl chloroacetate, and ethyl 2-bromohexanoate gave 2,3,5,10-tetrahydrothiazolo[3,2-*b*][2,4]benzodiazepine (VII) (52%), 5,10-dihydro-3-methylthiazolo[3,2-*b*][2,4]benzodiazepine hydrochloride (VIIIa) (41%), ethyl 5,10-dihydro-3-methylthiazolo[3,2-*b*][2,4]benzodiazepine-2-carboxylate (VIIIb) (57%), 5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3(2*H*)-one (IX) (68%), and 2-butyl-5,10-dihydrothiazolo-[3,2-*b*][2,4]benzodiazepine-3(2*H*)-one (X) (16%), respec-



tively. 2-Benzylidene-5,10-dihydrothiazolo[3,2-*b*][2,4]-benzodiazepin-3(2*H*)-one (XI) was obtained from 5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3(2*H*)-one (IX) and benzaldehyde in the presence of piperidine.

1,2,3,4,7,12-Hexahydrobenzothiazolo[3,2-*b*][2,4]-benzodiazepine hydrochloride (XII) and 9,14-dihydro-6*H*-[1]benzothiopyrano[4′,3′:4,5]thiazolo[3,2-*b*][2,4]benzodiazepine (XIII), which represent the other two novel heterocyclic ring systems investigated, were obtained in a similar manner from 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V), 2-chlorocyclohexanone, and 3-bromothiochroman-4-one in yields of 38% and 16%, respectively.

Structure assignments for compounds VIIIa and b, IX, X, XI, and XIII were made assuming preferential attack on sulfur by analogy with the formation of monocyclic thiazoles from *alpha*-halogenated carbonyl compounds (10) and with earlier structure studies on condensed thiazole systems, such as the imidazothiazoles (11-16), thiazolo[3,2-*a*]pyrimidines (16,17), and thiazolo-[2,3-*b*]quinazolines (16,18). Spectral data (Experimental Section) were in accord with the structures assigned.

The intermediate *o*-xylene-α,α′-diamine (III) has been synthesized previously by several different routes. The first synthesis was devised by H. Strassmann (19) who condensed α,α′-dibromo-*o*-xylene with potassium phthalimide to give α,α′-diphthalimido-*o*-xylene, followed by hydrolysis in a heated tube. A recent modification of the hydrolysis procedure utilizing hydrazine and hydrochloric acid in 1-butanol (6) afforded *o*-xylene-α,α′-diamine in 85% yield, and enabled large-scale preparation under normal laboratory conditions. Other workers have prepared the diamine *via* α,α′-dibromo-*o*-xylene and urea (20) or *t*-butyl imidodicarboxylate (7,21).

The catalytic reductive scission of phthalazine represents an alternative, simple approach to the preparation of *o*-xylene-α,α'-diamine in laboratory quantities, and was utilized in the current work. Initially, Raney nickel was used as the catalyst; although the yields were acceptable (75%), large quantities of catalyst were required and the hydrogenation was slow. In subsequent preparations, a two-stage reduction was used. For the first stage, in which two equivalents of hydrogen were absorbed and which presumably involves reduction to 1,2,3,4-tetrahydrophthalazine, 20% palladium on carbon was employed. In the second stage, which involved the absorption of one equivalent of hydrogen and presumably the scission of the cyclic hydrazine bond, Raney nickel was used. The overall yield was 97%. *o*-Xylene-α,α'-diamine has also been prepared by the reduction of phthalazine with zinc and hydrochloric acid (22).

The compounds described in the present communication were tested against a broad spectrum of helminths in mice, including *Syphacia obvelata*, *Nematospiroides dubius*, *Hymenolepis nana*, and *Amplicaecum robertsi*. The effects of the compounds on the central nervous system of mice and on the inhibition of ADP-induced thrombocyte aggregation *in vitro* were also evaluated. None of the compounds possessed appreciable biological activity in these test systems.

EXPERIMENTAL (23)

o-Xylene-α,α'-diamine Dihydrochloride (III).

Raney Nickel Method.

A solution of 130 g. (1.00 mole) of phthalazine (II) (Aldrich) in 1 l. of methanol was treated with 50 g. of Raney nickel, and the mixture was hydrogenated on a Parr shaker at an initial hydrogen pressure of 50 p.s.i.g. After heating at 55-59° for 17 hours, the hydrogenation became sluggish and only 72% of the theoretical amount of hydrogen had been taken up. A second 50 g. batch of Raney nickel was then added, and heating was continued for an additional 20 hours, when 92% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and excess hydrogen chloride was bubbled into the filtrate. The mixture was cooled to give a first crop of 129 g. (60%) of colorless product; the filtrate was concentrated and cooled to give 32 g. (15%) of a second crop. Both crops melted above 300° and gave infrared curves identical to that of a sample obtained from an earlier, smaller scale preparation which was analyzed. The product contained water of hydration as reported previously by Strassmann (19).

Anal. Calcd. for $C_8H_{12}N_2 \cdot 2HCl \cdot 0.25H_2O$: C, 44.98; H, 6.87; N, 13.12. Found: C, 44.95; H, 6.89; N, 13.06.

Raney Nickel-Palladium Method.

A solution of 65 g. (0.65 mole) of phthalazine (II) in 400 ml. of methanol containing 2 g. of 20% palladium on carbon was placed on a Parr shaker at an initial hydrogen pressure of 51 p.s.i.g. After 18 hours at room temperature 2 equivalents of hydrogen had been absorbed. Raney nickel (20 g.) was added and the bottle was repressurized to 51 p.s.i.g. After 5 hours at 50°, the theoretical amount of hydrogen had been absorbed. The reaction mixture was worked up in the manner described above to give 101 g. (97%) of *o*-xylene-α,α'-diamine dihydrochloride.

[*o*-(Aminomethyl)benzyl]dithiocarbamic Acid (IV).

o-Xylene-α,α'-diamine dihydrochloride (III) (59.5 g., 0.284 mole) in 300 ml. of water was treated with excess 50% sodium hydroxide and the mixture was extracted with chloroform. After drying over anhydrous potassium carbonate, the chloroform was removed by rotatory evaporation. The residue was dissolved in 500 ml. of ethanol and added dropwise to a stirred solution of 43.2 g. (0.568 mole) of carbon disulfide in 150 ml. of ethanol while the temperature was maintained at 25-30° through occasional cooling with an ice bath. After stirring overnight at room temperature, the precipitate was collected and dried to give 58 g. (96%) of a cream solid, m.p. >300°. This material was used without further purification.

Anal. Calcd. for $C_9H_{12}N_2S_2$: C, 50.91; H, 5.70; N, 13.20; S, 30.20. Found: C, 50.44; H, 5.59; N, 13.22; S, 29.34.

1,2,4,5-Tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V).

[*o*-(Aminomethyl)benzyl]dithiocarbamic acid (IV) (180 g., 0.85 mole) in 500 ml. of 2-methoxyethanol was boiled under reflux for 1 hour. After cooling to room temperature, the precipitate was collected by filtration, washed with ether, and dried to give 108 g. (72%) of a colorless solid, m.p. 290° dec. This material was used without further purification. Infrared cm^{-1}, 3220 (s), 2900 (s), 1570 (s), 1550 (s), 770 (s), 740 (m).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72; S, 17.99. Found: C, 60.78; H, 5.87; N, 15.84; S, 18.35.

2,5-Dihydro-3-(methylthio)-1*H*-2,4-benzodiazepine Hydriodide (VI).

A mixture of 10 g. (0.056 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) and 10 g. (0.071 mole) of methyl iodide in 1.6 l. of methanol was heated under reflux for 4 hours. A small amount of insoluble material was removed by filtration, and the filtrate was concentrated to 500 ml. Addition of ether and cooling gave a precipitate which was collected and dried to give 18 g. (100%) of a cream powder, m.p. 226° dec.; infrared cm^{-1}, 3160 (s), 3100 (s), 2960 (s), 1600 (s), 1560 (m), 780 (m), 730 (m).

Anal. Calcd. for $C_{10}H_{12}N_2S \cdot HI$: C, 37.51; H, 4.09; N, 8.75; I, 39.64. Found: C, 37.71; H, 4.27; N, 8.65; I, 39.47.

2,3,5,10-Tetrahydrothiazolo[3,2-*b*][2,4]benzodiazepine (VII).

A mixture of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) and 5.6 g. (0.030 mole) of 1,2-dibromoethane in 500 ml. of 2-methoxyethanol was boiled under reflux for 96 hours. The solvent was removed by rotatory evaporation, and the residue triturated with ether. Excess 1 *N* sodium hydroxide was added and the mixture was extracted with chloroform. After drying over anhydrous potassium carbonate, the chloroform was removed by evaporation and the residue triturated repeatedly with ether until solidification occurred. Crystallization from xylene afforded 3.0 g. (52%) of beige crystals, m.p. 151-153°; infrared cm^{-1} (chloroform), 3020 (m), 2960 (m), 2860 (m), 1630 (s); NMR spectrum (deuteriochloroform), 7.3-7.5, 4.8 (singlet), 4.6 (singlet), 3.8 (triplet), 3.1 (triplet).

Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.72. Found: C, 65.05; H, 6.03; N, 14.05.

5,10-Dihydro-3-methylthiazolo[3,2-*b*][2,4]benzodiazepine hydrochloride (VIIIa).

A solution of 3.1 g. (0.034 mole) of chloro-2-propanone in 50 ml. of 2-methoxyethanol was added dropwise to a solution of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) in 500 ml. of 2-methoxyethanol. After heating under reflux for 3 hours, the solvent was removed by rotatory evaporation. The residue was crystallized from ethanol, then 2-propanol to give 2.9 g. (41%) of colorless crystals, m.p. 250-252°; infrared cm^{-1}, 1620 (m), 1590 (s).

Anal. Calcd. for $C_{12}H_{12}N_2S$·HCl: C, 57.01; H, 5.18; N, 11.08; Cl, 14.02. Found: C, 56.83; H, 5.26; N, 11.04; Cl, 13.96.

Ethyl 5,10-Dihydro-3-methylthiazolo[3,2-*b*][2,4]benzodiazepine-2-carboxylate (VIIIb).

A mixture of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) and 9.2 g. (0.056 mole) of ethyl 2-chloroacetoacetate in 25 ml. of toluene was heated under reflux for 1.5 hours. The mixture was filtered while hot. The insoluble hydrochloride salt was treated with excess dilute ammonium hydroxide. The base was extracted with chloroform, and the combined chloroform extracts were dried over anhydrous potassium carbonate. The chloroform solution was concentrated yielding a tan solid which was recrystallized from acetonitrile to give 4.6 g. (57%) of beige needles, m.p. 152-154°; infrared cm^{-1}, 2980 (m), 1700 (s), 1640 (s), 760 (m), 740 (s); NMR spectrum (deuteriochloroform), 7.2-7.5, 5.0 (singlet), 4.8 (singlet), 4.2 (quadruplet), 2.5 (singlet), 1.3 (triplet).

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.47; H, 5.59; N, 9.72. Found: C, 62.44; H, 5.49; N, 9.76.

5,10-Dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3(2*H*)-one (IX).

A mixture of 6.9 g. (0.056 mole) of ethyl chloroacetate and 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) was heated slowly to 90° when vigorous foaming and then solidification took place. The mixture was diluted with 20 ml. of Dowtherm A and heated to 100° where foaming again occurred. Heating was continued over 2 more hours to a maximum of 140°. The reaction mixture was then cooled, diluted with ether, and the precipitate collected by filtration. Recrystallization from water gave 4.9 g. (68%) of pale yellow crystals, m.p. 277° dec.; infrared cm^{-1}, 3400 (s), 2800 (s), 1760 (s), 1620 (s).

Anal. Calcd. for $C_{11}H_{10}N_2OS$·HCl·0.75H_2O: C, 49.25; H, 4.70; N, 10.45; Cl, 13.22; H_2O, 5.03. Found: C, 49.21; H, 4.79; N, 10.41; Cl, 13.30; H_2O, 4.96.

A 0.8 g. sample of this material was treated with excess dilute ammonium hydroxide and extracted with chloroform. The chloroform was removed on a rotary evaporator, and the residue recrystallized from 2-propanol to give 0.5 g. of free base, m.p. 165-167°; infrared cm^{-1}, 1720 (s), 1640 (s); NMR spectrum (deuteriochloroform), 7.3 (4 proton singlet), 5.0 (2 proton singlet), 4.8 (2 proton singlet), 3.8 (2 proton singlet).

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.84. Found: C, 60.64; H, 4.47; N, 12.88.

2-Butyl-5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepine-3(2*H*)-one (X).

A mixture of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) and 12.6 g. (0.056 mole) of ethyl 2-bromohexanoate in 25 ml. of toluene was boiled under reflux for 3 hours. The mixture was filtered while still hot, and the insoluble material was treated with excess ammonium hydroxide and extracted with chloroform. After drying over anhydrous potassium carbonate, the chloroform was removed on a rotary evaporator, and the residue recrystallized to give 1.2 g. (16%) of a cream solid, m.p. 89-91°; infrared cm^{-1}, 1720 (s), 1640 (s); NMR spectrum (deuteriochloroform), 7.3 (4 proton singlet), 5.0 (2 proton singlet), 4.8 (2 proton singlet), 3.8-4.2 (1 proton multiplet), 0.6-2.6 (9 proton multiplet).

Anal. Calcd. for $C_{15}H_{18}N_2OS$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.47; H, 6.48; N, 10.19.

2-Benzylidene-5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3(2*H*)-one (XI).

A mixture of 0.40 g. (0.0018 mole) of 5,10-dihydrothiazolo-[3,2-*b*][2,4]benzodiazepin-3(2*H*)-one (IX), 0.29 g. (0.0028 mole) of benzaldehyde, and 0.16 g. (0.0018 mole) of piperidine in 10 ml. of 1-butanol was heated under reflux for 2 hours. After cooling to room temperature, the precipitate was collected and recrystallized from methanol to give 0.24 g. (43%) of beige crystals, m.p. 179-183°. Infrared cm^{-1}, 1705 (s), 1650 (s); NMR spectrum (deuteriochloroform), 7.1-7.8 (10 proton multiplet), 5.1 (2 proton singlet), 4.9 (2 proton singlet).

Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61; N, 9.15. Found: C, 70.54; H, 4.67; N, 9.08.

1,2,3,4,7,12-Hexahydrobenzothiazolo[3,2-*b*][2,4]benzodiazepine Hydrochloride (XII).

A solution of 4.1 g. (0.031 mole) of 2-chlorocyclohexanone in 50 ml. of 2-methoxyethanol was added to a boiling solution of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) in 500 ml. of 2-methoxyethanol. After boiling under reflux for 2 hours, thin layer chromatography (alumina, ethyl acetate) indicated little reaction had occurred. An additional 2.0 g. of 2-chlorocyclohexanone was added, and heating was continued for an additional 7 hours when thin layer chromatography indicated substantial reaction had occurred. The solvent was removed on a rotary evaporator. Trituration of the residue with ether followed by crystallization from an ethanol-ethyl acetate mixture gave 3.1 g. (38%) of a grey solid, m.p. 267-270°; infrared cm^{-1}, 1640 (m), 1590 (s).

Anal. Calcd. for $C_{15}H_{16}N_2S$·HCl: C, 61.52; H, 5.85; N, 9.57; Cl, 12.11. Found: C, 61.03; H, 5.91; N, 9.20; Cl, 12.40.

9,14-Dihydro-6*H*-[1]benzothiopyrano[4′,3′:4,5]thiazolo[3,2-*b*]-[2,4]benzodiazepine (XIII).

A mixture of 5.0 g. (0.028 mole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (V) and 13.7 g. (0.056 mole) of 3-bromothiochroman-4-one (Eastman) was heated under reflux for 1 hour in 100 ml. of *N,N*-dimethylformamide. After cooling, the dark solution was diluted with water, and the precipitate was collected and crystallized from an acetonitrile-water mixture to yield 1.4 g. (16%) of product, m.p. 138-140°. Infrared cm^{-1}, 1600 (m), 1570 (s), 1540 (m); NMR spectrum (deuteriochloroform), 6.9-8.1 (8 proton multiplet), 4.7 (4 proton singlet), 4.0 (2 proton singlet).

Anal. Calcd. for $C_{18}H_{14}N_2S_2$: C, 67.05; H, 4.38; N, 8.69; S, 19.88. Found: C, 67.20; H, 4.36; N, 8.58; S, 19.98.

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