# The Synthesis of 5,6-Dihydro-6-methylthiazolo-[2,3-*b*][1,3]benzodiazepines, 2,3,10,11-Tetrahydro-10-methyl-1*H*-cyclopenta[4,5]thiazolo[2,3-*b*][1,3]benzodiazepine, and 7,8,9,10,12,13-Hexahydro-13-methylbenzothiazolo[2,3-b][1,3]-benzodiazepine *via* 1,3,4,5-Tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione

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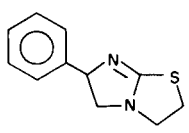
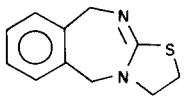
Catalytic reductive scission of 4-methylcinnoline (V) with Raney nickel afforded *o*-amino-β-methylphenethylamine (IV) in 57% yield. Treatment of IV with carbon disulfide followed by thermal cyclization of the product furnished 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III). Reaction of III with ethyl chloroacetate, ethyl 2-bromohexanoate, ethyl 2-chloroacetoacetate, 2-bromo-2′-methoxyacetophenone, and 2-bromoacetophenone provided a series of substituted 5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepines. Condensation of III with 2-chlorocyclopentanone and 2-chlorocyclohexanone gave 2,3,10,11-tetrahydro-10-methyl-1*H*-cyclopenta[4,5]thiazolo[2,3-*b*][1,3]benzodiazepine and 7,8,9,10,12,13-hexahydro-13-methylbenzothiazolo[2,3-*b*][1,3]benzodiazepine, respectively. Structure assignments are discussed. None of the compounds possessed appreciable biological activity.

Tetramisole (*dl*-2,3,5,6-tetrahydro-6-phenylimidazo-[2,1-*b*]thiazole hydrochloride) (I) (1) is a potent anthelmintic with broad action in man (2) and against a variety of adult and immature gastrointestinal and pulmonary nematodes in laboratory animals, poultry, and livestock (3). A previous communication from this laboratory (4) reported the preparation of 2,3,5,10-tetrahydrothiazolo-[3,2-*b*][2,4]benzodiazepine (II) and other related 2,4-benzodiazepine analogs of tetramisole.




I

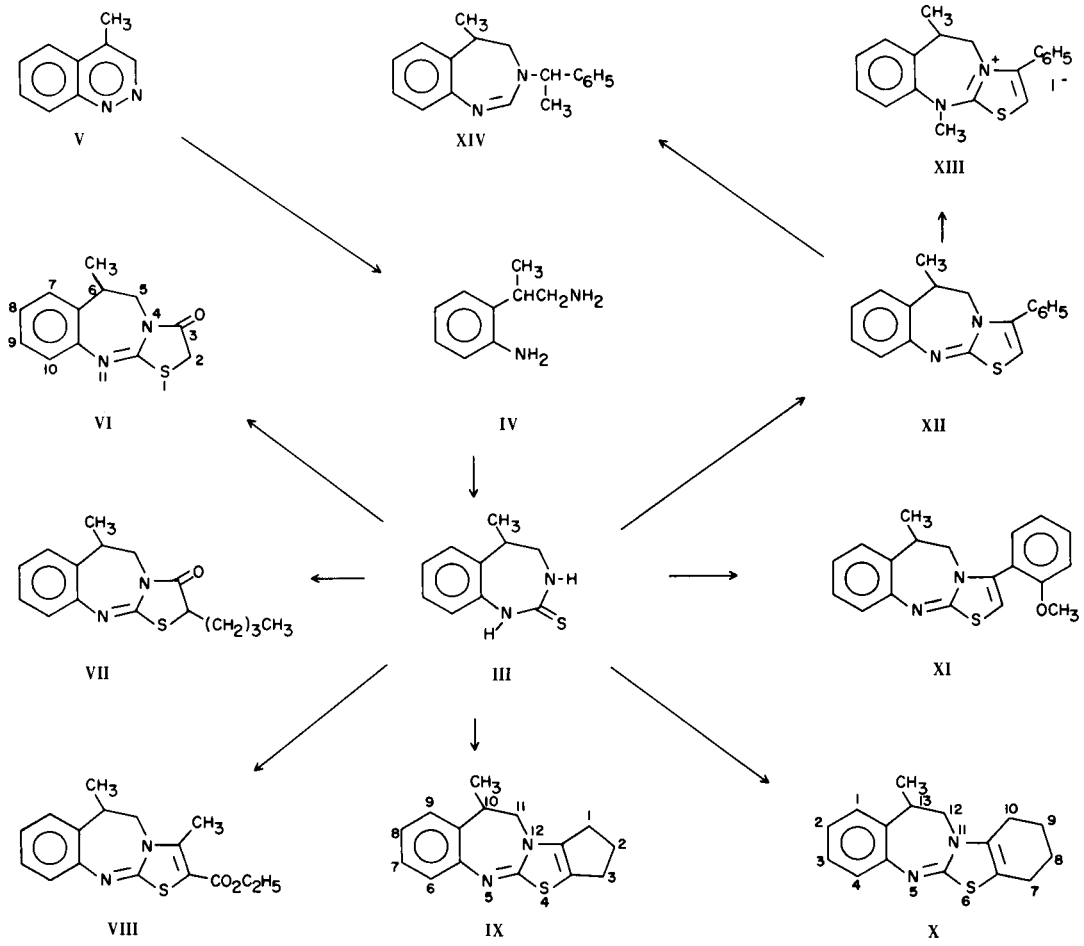



II

The present communication describes the synthesis of a new series of tetramisole analogs derived from 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III), namely, 5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepines (VI, VII, VIII, XI, and XII), 2,3,10,11-tetrahydro-10-methyl-1*H*-cyclopenta[4,5]thiazolo[2,3-*b*][1,3]-benzodiazepine (IX), and 7,8,9,10,12,13-hexahydro-13-methylbenzothiazolo[2,3-*b*][1,3]benzodiazepine (X). These three ring systems are not listed in "The Ring Index" (5) and appear to be novel heterocyclic types.

The key intermediate for these new heterocyclic compounds is 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III). A cursory review of the literature revealed that few 1,3-benzodiazepine derivatives have been reported (5-8), although considerable attention has been directed toward the synthesis of 1,4- and 1,5-benzodiazepines (5,9,10). 1,3,4,5-Tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) was obtained in 65% yield by treatment of *o*-amino-β-methylphenethylamine (IV) with carbon disulfide, followed by thermal cyclization of the intermediate dithiocarbamic acid. *o*-Amino-β-methylphenethylamine (IV) was readily obtained (57%) from the Raney nickel hydrogenation of 4-methylcinnoline (V).

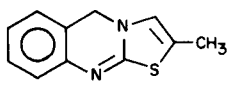
Condensation of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) with ethyl chloroacetate, ethyl 2-bromohexanoate, ethyl 2-chloroacetoacetate, 2-bromo-2′-methoxyacetophenone, and 2-bromoacetophenone gave 5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]-benzodiazepin-3(2*H*)-one (VI) (81%), 2-butyl-5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepin-3(2*H*)-one hydrochloride (VII) (35%), 5,6-dihydro-3,6-dimethylthiazolo[2,3-*b*][1,3]benzodiazepine-2-carboxylic acid ethyl ester (VIII) (64%), 5,6-dihydro-3-(*o*-methoxyphenyl)-



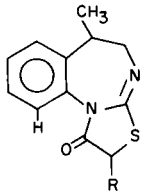

6-methylthiazolo[2,3-*b*][1,3]benzodiazepine (XI) (48%), and 5,6-dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]-benzodiazepine (XII) (26%), respectively. Treatment of 5,6-dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]benzodiazepine (XII) with methyl iodide afforded 6,11-dihydro-6,11-dimethyl-3-phenyl-5*H*-thiazolo[2,3-*b*][1,3]benzodiazepinium iodide (XIII) (68%), while Raney nickel desulfurization of XII gave 4,5-dihydro-5-methyl-3-(α-methylbenzyl)-3*H*-1,3-benzodiazepine (XIV).

2,3,10,11-Tetrahydro-10-methyl-1*H*-cyclopenta[4,5]-thiazolo[2,3-*b*][1,3]benzodiazepine (IX) and 7,8,9,10,12,13-hexahydro-13-methylbenzothiazolo[2,3-*b*][1,3]benzodiazepine (X), which represent the other two novel heterocyclic ring systems investigated, were obtained in a similar manner from 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III), 2-chlorocyclopentanone, and 2-chlorocyclohexanone in yields of 30% and 77%, respectively.

Structure assignments for compounds VI-XII were made assuming preferential attack on sulfur by analogy with the formation of monocyclic thiazoles from *alpha*-halogenated carbonyl compounds (11). It is tentatively assumed that ring-closure of these intermediates occurred on the nitrogen at position 3 of the 1,3-benzodiazepine ring by analogy with previous work, where 2-methyl-5*H*-thiazolo[2,3-*b*]quinazoline (XV) was obtained from reaction of 1,2,3,4-tetrahydro-2-thioquinazoline with 2-chloropropanone (12). Further, it was observed that neither of the 5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepines (VI, VII) containing a carbonyl group showed a large downfield shift of an aromatic proton in close proximity to the carbonyl group. Such a shift would be expected (13) from the corresponding products



(XVIa and b) that would have been obtained if ring-closure had occurred on the nitrogen at position 1.



XVI

a, R = H

b, R = $(CH_2)_3CH_3$

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 (14)

*o*-Amino-β-methylphenethylamine Dihydrochloride (IV).

To a solution of 54 g. (0.38 mole) of 4-methylcinnoline (Aldrich Chemical Co.) in 600 ml. of methanol was added 20 g. of Raney nickel, and the mixture was hydrogenated on a Parr shaker at an initial pressure of 52 p.s.i.g. After heating at 56-58° for 21 hours, the hydrogenation became sluggish. The pressure change indicated that 88% of the theoretical amount of hydrogen had been absorbed. A second 20 g. of Raney nickel was added, and heating was continued for an additional 16 hours, when 91% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was concentrated to 500 ml. Excess hydrogen chloride was bubbled into the solution. Addition of ether gave 48 g. (57%) of beige crystals, m.p. 236° dec.; UV λ max (methanol containing excess sodium hydroxide), 287 mμ (ε, 2,060), 235 mμ (ε, 7,030).

*Anal.* Calcd. for $C_9H_{14}N_2 \cdot 2HCl$: C, 48.44; H, 7.23; N, 12.56. Found: C, 48.32; H, 7.03; N, 12.46.

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

An aqueous solution of 50 g. (0.22 mole) of *o*-amino-β-methylphenethylamine dihydrochloride (IV) was treated with excess sodium hydroxide solution, and the mixture was extracted with chloroform. After washing the chloroform extracts with water and drying over potassium carbonate, the solvent was removed by rotatory evaporation. The oily residue was dissolved in 200 ml. of ethanol and added dropwise over 1 hour to a solution of 30 ml. (0.50 mole) of carbon disulfide in 300 ml. of ethanol. The slightly exothermic reaction produced a maximum temperature of 28°. After standing for 3 days, the reaction solution was heated under reflux until hydrogen sulfide evolution ceased. After cooling, the precipitate which formed was collected by filtration, washed with ethanol, and was used as an intermediate without further purification, yield, 28 g. (65%), m.p. 171-181°. This material gave an infrared absorption curve essentially identical to that obtained from a previously prepared analytical sample of m.p. 180-182°; infrared (carbon tetrachloride) $cm^{-1}$, 3430(m), 3390(m), 1610(m), 1560(s), 1490(s); NMR (dimethylsulfoxide-$d_6$), broad 1 proton singlets at 9.83 and 8.82, 1.16 (3 proton doublet).

*Anal.* Calcd. for $C_{10}H_{12}N_2S$: C, 62.47; H, 6.29; S, 16.67. Found: C, 62.37; H, 6.22; S, 16.79.

5,6-Dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepin-3(2*H*)-one (VI).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 6.4 g. (0.052 mole) of ethyl chloroacetate in 25 ml. of toluene was heated with stirring to 100° when a vigorous reaction took place. After heating an additional hour at 100-110°, the hot mixture was filtered to obtain a crude hydrochloride salt, m.p. 236° dec. This was slurried with dilute, excess ammonium hydroxide, and the mixture was extracted with chloroform. The combined extracts were washed with water and dried over potassium carbonate. Rotatory evaporation gave a solid which upon recrystallization from 2-propanol yielded 4.9 g. (81%) of pale yellow solid, m.p. 115-116°; NMR 7.0-7.4 (4 proton multiplet), 1.22 (3 proton doublet); infrared (carbon tetrachloride) $cm^{-1}$, 1730(s), 1680(w), 1640(s).

*Anal.* Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 61.95; H, 5.32; N, 12.27.

2-Butyl-5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepin-3(2*H*)-one Hydrochloride (VII).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 6.25 g. (0.028 mole) of ethyl 2-bromohexanoate in 25 ml. of toluene was heated under reflux for 2 hours. The mixture was filtered hot to obtain a crude hydrobromide. This was treated with excess, aqueous sodium hydroxide, and the mixture was extracted with chloroform. After drying over potassium carbonate, the extracts were concentrated to a tan oil. Upon treatment with 2-propanol containing excess hydrogen chloride there was obtained a precipitate which was collected by filtration, washed with 2-propanol, and dried to give 3.0 g. (35%) of colorless crystals, m.p. 163-166°; infrared $cm^{-1}$, 1770(s), 1640(s). A 50 mg. sample of the hydrochloride was converted to the oily base. The carbonyl region of the infrared curve (carbon tetrachloride) was very similar to the curve obtained from VI, with absorption at 1730(s), 1680(w), and 1640(s) $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{20}N_2OS \cdot HCl$: C, 59.15; H, 6.52; N, 8.62; S, 9.87; Cl, 10.92. Found: C, 59.01; H, 6.59; N, 8.21; S, 9.83; Cl, 11.10.

5,6-Dihydro-3,6-dimethylthiazolo[2,3-*b*][1,3]benzodiazepine-2-carboxylic Acid Ethyl Ester (VIII).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 8.6 g. (0.052 mole) of ethyl 2-chloroacetoacetate in 25 ml. of toluene was heated under reflux for 3 hours while water was removed in a Dean-Stark trap. After cooling to room temperature, a crude hydrochloride (m.p. 203-205° dec.) was collected by filtration. This was stirred into a mixture of excess ammonium hydroxide and chloroform. The aqueous layer was separated and washed with chloroform. The combined chloroform extracts were dried over potassium hydroxide and concentrated by rotatory evaporation to an oil which crystallized on scratching. Recrystallization from acetonitrile gave 5.0 g. (64%) of pale yellow prisms, m.p. 142-144°; NMR 6.8-7.3 (4 proton multiplet), 2.47 (3 proton singlet), 1.23 (3 proton

doublet), 1.30 (3 proton triplet); infrared $cm^{-1}$, 1710(s), 1630(s).

*Anal.* Calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.27. Found: C, 63.77; H, 5.96; N, 9.34.

2,3,10,11-Tetrahydro-10-methyl-1*H*-cyclopenta[4,5]thiazolo-[2,3-*b*][1,3]benzodiazepine (IX).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 6.2 g. (0.052 mole) of 2-chlorocyclopentanone (Aldrich Chemical Co.) was heated under reflux for 2 hours in 25 ml. of toluene while water was removed in a Dean-Stark trap. After cooling to room temperature, the supernatent liquid was decanted, and the tarry residue was triturated with 2-propanol to give the crude hydrochloride salt as a tan solid, m.p. 236° dec. This was treated with excess, dilute sodium hydroxide, and the mixture was extracted with chloroform. After drying over potassium carbonate, and treatment with charcoal, the chloroform was removed leaving an oil which crystallized on scratching. Two recrystallizations from acetonitrile gave 2.0 g. (30%) of light tan solid, m.p. 131-133°; infrared $cm^{-1}$, 2860(m), 1640(s), 1570(s), 760(s).

*Anal.* Calcd. for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.34; H, 6.31; N, 10.96.

7,8,9,10,12,13-Hexahydro-13-methylbenzothiazolo[2,3-*b*][1,3]-benzodiazepine (X).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 6.9 g. (0.052 mole) of 2-chlorocyclohexanone in 50 ml. of toluene was heated to 100° when melting, foaming, and then resolidification occurred. After heating an additional hour under reflux, the insoluble hydrochloride was collected by filtration. This was treated with excess dilute sodium hydroxide, and the mixture was extracted with chloroform. The extracts were washed with water, dried over potassium carbonate, and concentrated. Recrystallization of the residue from acetonitrile gave 5.4 g. (77%), m.p. 158-159°; infrared $cm^{-1}$, 2840(m), 1640(s), 1570(s), 760(s).

*Anal.* Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36. Found: C, 71.01; H, 6.51; N, 10.21.

5,6-Dihydro-3-(*o*-methoxyphenyl)-6-methylthiazolo[2,3-*b*][1,3]-benzodiazepine (XI).

A mixture of 2.4 g. (0.012 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 3.2 g. (0.014 mole) of 2-bromo-2′-methoxyacetophenone in 100 ml. of 2-methoxyethanol was heated under reflux for 3 hours. The solvent was removed on a rotary evaporator, and the residue was triturated with 2-propanol to obtain a solid which upon recrystallization from 2-propanol gave 2.4 g. (48%) of a pale yellow solid, m.p. 241-243°; NMR 6.89 (1 proton singlet), 3.85 (3 proton singlet), 1.18 (3 proton doublet); infrared $cm^{-1}$, 1630(s).

*Anal.* Calcd. for $C_{19}H_{18}N_2OS\cdot HBr$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.43; H, 4.85; N, 6.95.

5,6-Dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]benzodiaze-pine (XII).

A mixture of 5.0 g. (0.026 mole) of 1,3,4,5-tetrahydro-5-methyl-2*H*-1,3-benzodiazepine-2-thione (III) and 10.3 g. (0.052 mole) of 2-bromoacetophenone in 50 ml. of toluene was heated under reflux for 1 hour while water was collected in a trap. The mixture was filtered while hot to obtain the crude hydrobromide. Treatment with excess, aqueous sodium hydroxide and extraction of the mixture with chloroform, followed by drying over potassium carbonate and concentration on a rotary evaporator, gave a brown solid. Recrystallization from 2-propanol and then acetonitrile gave 2.0 g. (26%) of pale yellow crystals, m.p. 137-140°; NMR 6.8-7.6 (9 proton multiplet), 5.92 (1 proton singlet), 1.25 (3 proton doublet).

*Anal.* Calcd. for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 74.08; H, 5.54; N, 9.53.

6,11-Dihydro-6,11-dimethyl-3-phenyl-5*H*-thiazolo[2,3-*b*][1,3]-benzodiazepinium Iodide (XIII).

A solution of 0.50 g. (0.0017 mole) of 5,6-dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]benzodiazepine (XII) in 15 ml. of methyl iodide was heated under reflux for 2 hours. Upon cooling the yellow precipitate was collected by filtration and recrystallized twice from ethanol to give 0.50 g. (68%) of pale yellow needles, m.p. 225-226° dec.; NMR 7.2-7.6 (10 proton multiplet), 1.38 (3 proton doublet); infrared $cm^{-1}$, 1590(m), 1540(s), 1490(s).

*Anal.* Calcd. for $C_{19}H_{19}IN_2S$: C, 52.54; H, 4.41; N, 6.45. Found: C, 52.57; H, 4.42; N, 6.24.

4,5-Dihydro-5-methyl-3-(α-methylbenzyl)-3*H*-1,3-benzodiazepine (XIV).

To a solution of 0.50 g. (0.0017 mole) of 5,6-dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]benzodiazepine (XII) in 200 ml. of ethanol was added 12 g. of a 50% slurry of Raney nickel in water (W. R. Grace) and the mixture was heated under reflux for 6 hours. After cooling to room temperature the catalyst was removed by filtration and the filtrate was concentrated to an oil. Treatment of an ether solution of this oil with excess hydrogen chloride in 2-propanol gave a precipitate which on crystallization from acetone yielded 0.05 g. of colorless crystals, m.p. 269-272°.

*Anal.* Calcd. for $C_{18}H_{20}N_2\cdot HCl$: C, 71.86; H, 7.04; N, 9.31. Found: C, 71.54; H, 7.01; N, 9.17.

Acknowledgment.

The authors are indebted to Dr. Paul E. Thompson, Dr. Graham Chen, Dr. J. R. McLean, and co-workers of these laboratories for the biological evaluation of the compounds described herein. We also thank Mr. William Pearlman for carrying out the catalytic hydrogenations, Mr. Charles E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and co-workers for determination of the spectral data.

## REFERENCES

(1) A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. Van Offenwert, and P. A. J. Janssen, *J. Med. Chem.*, 9, 545 (1966).

(2) For a brief review, see E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p. 146; *ibid.*, 1967, p. 141.

(3) For a brief review, see D. R. Hoff in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p. 150; *ibid.*, 1967, p. 149.

(4) E. F. Elslager, D. F. Worth, N. F. Haley, and S. C. Perricone, *J. Heterocyclic Chem.*, 5, 609 (1968).

(5) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed., American Chemical Society, Washington, D. C., 1960 and Supplements I (1963), II (1964), and III (1965).

(6a) J. A. Moore and E. Mitchell in "Heterocyclic Compounds," Vol. 9, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, pp. 224-361; (b) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 68, 747 (1968).

(7) G. deStevens and M. Dughi, *J. Am. Chem. Soc.*, 83, 3087 (1961).

(8) H. R. Rodriguez, B. Zitko, and G. deStevens, *J. Org. Chem.*, 33, 670 (1968).

(9) L. H. Sternbach in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press, Inc., New York, N. Y., 1965, pp. 158-161.

(10) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, 53, 577 (1964).

(11) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 484.

(12) P. Sykes, *J. Chem. Soc.*, 2390 (1955).

(13) S. C. Bell and G. Conklin, *J. Heterocyclic Chem.*, 5, 179 (1968), and references cited therein.

(14) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. The infrared spectra were determined with a Beckman IR-9 Spectrophotometer in potassium bromide discs unless otherwise indicated. The Nuclear Magnetic Resonance Spectra were taken with a Varian A60 Spectrophotometer. Results are reported in ppm downfield from tetramethylsilane in deuteriochloroform unless otherwise noted. Ultraviolet spectra were determined on a Cary Model A recording spectrophotometer.

Received February 24, 1969 Ann Arbor, Michigan 48106