with **12**. The inactivity of 2-(5-nitro-2-furyl)benzimidazole[18] (**14**) was unexpected since 2-(2-furyl)benzimidazole is reported to have anthelmintic activity.[17]

Compounds **1** and **2** are being studied further in a variety of helminth infections.

Experimental Section[19]

Melting points were determined in open capillary tubes using a Thomas–Hoover Uni-Melt apparatus and are corrected. All final products were homogeneous as determined by thin layer chromatography. Column chromatography was carried out on Woelm neutral alumina, activity grade I. Ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 recording spectrophotometer.

Syntheses of compounds listed in Table I were carried out by two general procedures each of which is illustrated by a detailed procedure. Commercial $Pb(OAc)_4$ was dried *in vacuo* over KOH pellets before use.

Procedure A. 2-(5-Nitro-2-thienyl)benzimidazole.—To a cold (−10°) stirred suspension of *o*-phenylenediamine (3.5 g, 0.033 mole) in 35 ml of absolute alcohol was added a solution of 5-nitro-2-thiophenecarboxaldehyde (5.0 g, 0.033 mole) in 50 ml of 2B alcohol. The resulting deep red mixture was allowed to warm to room temperature over a period of 1 hr, and the precipitated solid was collected and air dried to give 7.0 g (85%) of maroon Schiff base, mp 156–157°.

The Schiff base (6.9 g, 0.028 mole) was suspended in 60 ml of glacial acetic acid, and $Pb(OAc)_4$ (12.4 g, 0.028 mole) dissolved in 150 ml of warm glacial acetic acid was added in one portion. The dark mixture was stirred 15 min at 50–60°, cooled to 25°, and then diluted with 900 ml of water. The precipitate was collected, air dried, and chromatographed on alumina (150 g). Elution with 1:1 ethyl acetate–CH_2Cl_2 gave 1.5 g of material, mp 230–232° dec. An analytical specimen was prepared by recrystallization from isopropyl alcohol, mp 230–232° dec.

Procedure B. 2-(5-Nitro-2-thienyl)benzoxazole.—To a magnetically stirred solution of *o*-aminophenol (2.18 g, 0.02 mole) and 5-nitro-2-thiophenecarboxaldehyde (3.14 g, 0.02 mole) in 70 ml of warm glacial acetic acid was added in one portion a warm (70°) solution of $Pb(OAc)_4$ (8.8 g, 0.02 mole) in 80 ml of glacial acetic acid. The resulting dark solution was stirred at 80° for 5 min, then cooled to 20° and the precipitated brown solid was collected. Dilution of the filtrate with 700 ml of water gave another brown solid. Tlc comparison of the two solids showed similar complex composition. The combined solids (3.2 g) were chromatographed on alumina (100 g) in CH_2Cl_2 to give 1.5 g of lemon yellow solid, mp 200–202°. One recrystallization from toluene gave 1.2 g of product as lemon yellow plates, mp 200.5–201.5°.

2-(5-Nitro-2-thienyl)benzimidazole (1). Imido Ester Method.—To a solution of *o*-phenylenediamine (5.45 g, 0.05 mole) in 60 ml of warm absolute ethanol was added ethyl 5-nitro-2-thiophenecarboximidate hydrochloride[20] (12 g, 0.05 mole). The deep red solution was warmed on a steam bath for 20 min during which time a yellow precipitate formed. The mixture was cooled and diluted with water, and the solid was collected to give 13 g of yellow benzimidazole, mp 228–231°. One recrystallization from aqueous ethyl alcohol gave 11.3 g of **1**, mp 230–232°, identical in every respect with that prepared by method A.

Biological Methods.—*In vitro* trials used *T. foetus* grown in Diamond's medium[21] as the test organism. The procedure was a standard twofold tube dilution assay in which the maximum concentration of test material in the culture medium was 100 μg/ml. Compound activity was described as the minimum inhibitory concentration (MIC), defined as that quantity of compound that completely inhibits growth of the organism after 48 hr of incubation at 37°.

In vivo antitrichomonal trials were carried out in 16–18-g male Charles River Farm mice infected intraperitoneally with 1×10^6 *T. foetus* organisms grown in STS medium.[22] The compounds were administered either subcutaneously or orally for three successive days starting on the day of infection. Percentage survival was the criterion used for evaluation.

The *in vivo* antipinworm evaluation was carried out in 18–20-g male CF_1 mice naturally infected with two species of pinworm (*Syphacia obvelata* and *Aspiculuris tetraptera*). The test compounds were suspended in 0.5% gum tragacanth and administered *per os* for 3 successive days. At 48 hr posttreatment the animals were sacrificed and appropriate helminth counts on pooled samples were made. The criterion for evaluation was the per cent reduction in worm burden as compared with the placebo-treated controls.

(18) We wish to thank Dr. P. M. G. Bavin of Smith Kline and French Laboratories, Ltd., Welwyn Garden City, Hertfordshire, England, for supplying this compound.

(19) We are grateful to Miss M. Carroll and her staff and to Dr. W. Thompson and his staff of our Analytical and Physical Chemistry Section for elemental analyses and ultraviolet spectra, respectively.

(20) We obtained mp 190–192° in contrast to 152° reported by Bercot-Vatteroni.[14]

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(22) A. B. Kupferberg, G. Johnson, and H. Sprince, *Proc. Soc. Exptl. Biol. Med.*, **67**, 304 (1948).

5,6-Dihydro-4H-1,3,4-oxadiazines. V. Base-Catalyzed Cyclodehydrohalogenation of 2-(β-Chloroalkyl)carboxylic Acid Hydrazides

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The scope of the base-catalyzed cyclodehydrohalogenation of 2-(β-chloroalkyl)carboxylic acid hydrazides into 5,6-dihydro-4H-1,3,4-oxadiazines is discussed. The pharmacological activity of a series of 5,6-dihydro-4H-1,3,4-oxadiazines is presented. Some compounds in this series were found to have anticonvulsant activity in mice.

During a search for new compounds possessing central nervous system activity *via* molecular modification of (−)-ephedrine, we observed that certain 2-(β-hydroxyalkyl)carboxylic acid hydrazides would undergo acid-catalyzed cyclodehydration to give substituted 5,6-dihydro-4H-1,3,4-oxadiazines.[2] Certain of these substituted 5,6-dihydro-4H-1,3,4-oxadiazines exhibited central nervous system activity as shown by their ability to greatly prolong hexobarbital sleep times in mice and to protect mice against maximal electroshock.[3]

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(2) (a) D. L. Trepanier, V. Spranemanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964); (b) D. L. Trepanier and V. Spranemanis, *ibid.*, **29**, 673 (1964); (c) *ibid.*, **29**, 2151 (1964); (d) D. L. Trepanier, V. Spranemanis, D. S. Tharpe, and P. E. Krieger, *J. Heterocyclic Chem.*, **2**, 403 (1965).

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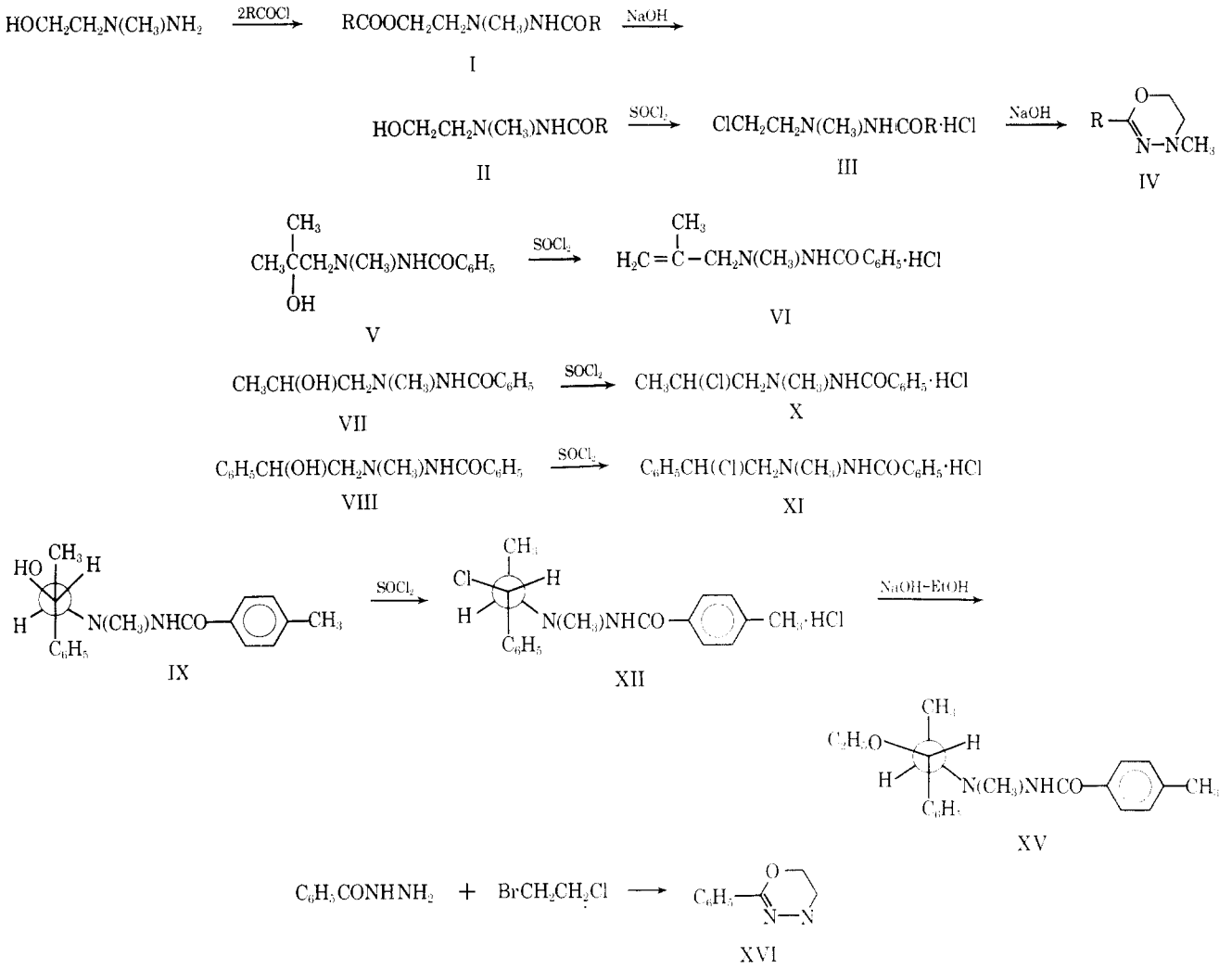
SCHEME I



Certain of these compounds antagonized the effects of injecting tremorine in mice.[3] Because these activities were not confined only to those oxadiazines derived from (−)-ephedrine, we decided to further extend this series of compounds.

Our studies[2] of the acid-catalyzed cyclodehydration of 2-(β-hydroxyalkyl)carboxylic acid hydrazides into 5,6-dihydro-4H-1,3,4-oxadiazines indicated that this cyclodehydration could not be effected with 2-(β-hydroxyalkyl)carboxylic acid hydrazides possessing a primary hydroxyl group. Therefore, we investigated the base-catalyzed cyclodehydrohalogenation of 2-(β-chloroalkyl)carboxylic acid hydrazides as a possible alternate synthetic route.

Various 2-methyl-2-(β-acyloxyethyl)carboxylic acid hydrazides (I) were prepared by treating β-(1-methylhydrazino)ethanol with 2 molar equiv of an acid chloride in methylene chloride in the presence of triethylamine. The hydrazides (I) were converted to 2-(β-hydroxyethyl)-carboxylic acid hydrazides (II) by saponification with 2 *N* sodium hydroxide solution (Scheme I). Treatment of II with thionyl chloride yielded 2-(β-chloroethyl)carboxylic acid hydrazide hydrochlorides (III). These salts were cyclodehydrohalogenated into the desired 5,6-dihydro-4H-1,3,4-oxadiazines (IV) by treatment with alcoholic sodium hydroxide. The cyclodehydrohalogenation of III into IV was successful when III contained a primary halide and a variety of different acyl moieties, such as benzoyl, variously substituted benzoyl, 2-furoyl, and isonicotinoyl.

In order to further delineate the scope of this base-catalyzed cyclodehydrohalogenation reaction, we attempted the preparation, and subsequent dehydrohalogenation, of various 2-(β-chloroalkyl)carboxylic acid hydrazides possessing either secondary aliphatic, tertiary aliphatic, or secondary benzyl halide. Treatment of 2-methyl-2-(β-hydroxyisobutyl)benzoic acid hydrazide (V) with thionyl chloride at ambient temperature yielded 2-methyl-2-methylallylbenzoic acid hydrazide (VI). Repeated attempts to prepare *threo*-2-methyl-2-(α-methyl-β-chlorophenethyl)benzoic acid hydrazide hydrochloride by treatment of *threo*-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide with either thionyl chloride or hydrogen chloride were unsuccessful.

Treatment of 2-methyl-2-(β-hydroxypropyl)benzoic acid hydrazide (VII), 2-methyl-2-(β-hydroxyphenethyl)benzoic acid hydrazide (VIII), and *erythro*-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*p*-toluic acid hydrazide (IX) with thionyl chloride yielded 2-methyl-2-(β-chloropropyl)benzoic acid hydrazide hydrochloride (X), 2-methyl-2-(β-chlorophenethyl)benzoic acid hy-

Table I

2-Methyl-2-(β-acyloxyethyl)carboxylic Acid Hydrazides

$RCONHN(CH_3)CH_2CH_2OOCR \cdot yHCl$

No.	R	y	Mp, °C[a]	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	0	112–113	56	68.44	6.08	9.39	68.03	5.96	9.39
2	4-ClC_6H_4	0	121–122	67	55.60	4.39	7.63	55.66	4.67	7.70
3	4-$CH_3OC_6H_4$	0	124–125	68	63.67	6.19	7.82	63.63	6.32	7.40
4	3-BrC_6H_4	0	139–141	71	44.71	3.52	35.05[b]	45.58	3.09	37.34[b]
5	2-ClC_6H_4	1	134–138	64	50.57	4.25	26.35[c]	50.73	4.51	26.27[c]
6	2-C_4H_3O	1	189–191 dec	36	49.61	4.80	8.90	49.73	5.19	8.94

[a] Compound **1** was recrystallized from 2-butanone, **2** from ethyl acetate, **3** and **4** from isopropyl alcohol, **5** from methanol–ether, and **6** from methanol. [b] Bromine. [c] Chlorine.

Table II

2-(β-Hydroxyalkyl)carboxylic Acid Hydrazides

$RCONHN(CH_3)CH_2CR_1R_2OH$

No.	R	R_1	R_2	Mp, °C[a]	Yield, %	Method	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	H	H	120–120.5	93	A	61.83	7.26	14.43	61.62	7.16	15.17
2	4-ClC_6H_4	H	H	126–128	77	A	52.52	5.73	12.25	52.59	6.01	12.38
3	4-$CH_3OC_6H_4$	H	H	124–125	36	A	58.91	7.19	12.49	59.06	7.53	12.72
4	3-BrC_6H_4	H	H	84–85	62	A	43.97	4.80	29.26[b]	44.31	5.05	29.27[b]
5	2-ClC_6H_4	H	H	87–90	41	A	52.52	5.73	12.25	53.10	6.02	12.21
6	2-C_4H_3O	H	H	87–89	25	A	52.16	6.57	15.21	52.55	6.64	15.14
7	4-NC_5H_4	H	H	112–113 dec	29	B	55.37	6.71	21.53	54.86	7.40	21.53
8	C_6H_5	CH_3	CH_3	109–111	26	C	64.84	8.16		64.75	8.15	

[a] Compound **1** was recrystallized from benzene, **2** from toluene, **3, 4, 5,** and **8** from ethyl acetate, **6** from ethyl acetate–ether, and **7** from methanol–ether. [b] Bromine.

drazide hydrochloride (XI), and *erythro*-2-methyl-2-(α-methyl-β-chlorophenethyl)-*p*-toluic acid hydrazide hydrochloride (XII), respectively.

Treatment of X with sodium hydroxide in ethanol–water gave an oil which by gas–liquid partition chromatography was shown to be a mixture of four components. Component 1, which represented 35% of the mixture, was collected and, on the basis of infrared and ultraviolet spectral data, tentatively identified as 4,6-dimethyl-2-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine (XIII).

Treatment of XI with sodium hydroxide in ethanol–water gave 4-methyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine (XIV) (23%) and benzoic acid (31%).

Treatment of XII with sodium hydroxide in ethanol–water gave *erythro*-(−)-2-methyl-2-(α-methyl-β-ethoxyphenethyl)-*p*-toluic acid hydrazide (XV). That the conversions IX → XII → XV proceed with retention of configuration is evidenced by the results of nmr analysis. These showed that $J_{\alpha-\beta}$ for L-(−)-ephedrine, IX, XII, and XV were 3.0, 2.4, 1.6–2.0, and 2.4 cps, respectively, whereas $J_{\alpha-\beta}$ for D-(+)-pseudoephedrine was 8.1–8.2 cps. Because the replacement of hydroxyl by chlorine or ethoxyl abolishes the hydrogen-bonding effects on the nmr spectra, this assignment cannot be considered positive until the nmr analyses of the diastereomers of IX, XII, and XV have been obtained.

2-Phenyl-5,6-dihydro-4H-1,3,4-oxadiazine (XVI) was obtained in 29% yield from the condensation of benzoic acid hydrazide and 1-bromo-2-chloroethane in refluxing ethanol in the presence of sodium hydroxide.

The foregoing data clearly indicate that the behavior of halide in this base-catalyzed cyclodehydrohalogenation is analogous to that exhibited by simple alkyl halides. 2-(β-Chloroalkyl)carboxylic acid hydrazides possessing primary chloride, which has a high order of SN2 activity, are readily cyclodehydrohalogenated, in good yield, into 5,6-dihydro-4H-1,3,4-oxadiazines. Those possessing secondary aliphatic and secondary benzyl chloride, in which SN1 solvolysis of halide becomes important, give mixtures. *erythro*-2-Methyl-2-(α-methyl-β-chlorophenethyl)carboxylic acid hydrazide hydrochloride, which possesses besides a benzyl-type chloride an α-methyl group that sterically retards SN2 displacement of chloride, reacted *via* SN1 solvolysis exclusively to give 92% yield of *erythro*-2-methyl-2-(α-methyl-β-ethoxyphenethyl)carboxylic acid hydrazide.

Experimental Section

Pharmacology. Hexobarbital Sleeping Times.—Adult male mice in groups of ten were injected intraperitoneally with the test compound 1 hr before they were injected intraperitoneally with 100 mg/kg of hexobarbital. The time in minutes between injection of the hexobarbital and the regain of the righting reflex was taken as the duration of sleeping times. The mean results are presented as a ratio with the mean sleeping times of a control group tested simultaneously.

In another series of hexobarbital sleeping time tests, the mice were injected intraperitoneally with the test compounds 48, 24, and 1 hr before the hexobarbital challenge. These results are given in Table IV under the appropriate heading.

Strychnine Lethality. Chronic Dosing.—Adult male mice in groups of ten were injected intraperitoneally with test compound at hours 0, 24, and 48. At hour 49 they were injected intraperitoneally with 2 mg/kg of strychnine and observed for death within the following 30 min. The results are presented as a ratio of number of survivors to the number tested.

Acute Dosing.—The compounds showing antagonism to strychnine (**6, 8,** and **10** in Table IV) in these chronic tests were tried again in an acute test. They were injected intraperitoneally (200 mg/kg) 1 hr before the strychnine challenge. In contrast to the results in the chronic dosing tests, there was no protection under these experimental conditions.

Maximal Electroshock Test.—Groups of ten mice were given the test compounds intraperitoneally 1 hr prior to being subjected to supramaximal electroshock delivered through corneal

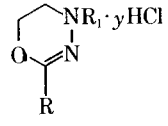
TABLE III: 2-(β-CHLOROALKYL)CARBOXYLIC ACID HYDRAZIDE HYDROCHLORIDES

$RCONHN(CH_3)CHR_1CHR_2Cl \cdot HCl$

No.	R	R_1	R_2	Mp, °C[a] dec	Yield, %	Caled, % C	Caled, % H	Caled, % Cl	Found, % C	Found, % H	Found, % Cl
1	C_6H_5	H	H	183–184	78	48.23	5.66	28.42	48.56	5.82	28.23
2	4-ClC_6H_4	H	H	197–198	57	42.35	4.62	37.51	42.91	4.79	37.53
3	4-$CH_3OC_6H_4$	H	H	163–164	79	47.32	5.78	25.40	47.15	6.20	25.57
4	3-BrC_6H_4	H	H	158–160	75	36.61	3.99		37.27	4.18	
5	4-$CH_3C_6H_4$[b]	CH_3	C_6H_5	153–155	94	61.20	6.28		61.15	6.43	
6	C_6H_5	H	C_6H_5	145–148	42	59.08	5.58	8.58[c]	58.85	5.83	8.58[c]
7	C_6H_5	H	CH_3	149–152	34	50.21	6.13	10.65[c]	51.31	6.32	10.90[c]
8	4-$CH_3C_6H_4$	H	H	191–193	65	50.21	6.13	26.95	50.17	6.30	28.03
9	3,4,5-$(CH_3O)_3C_6H_2$	H	H	191–192	65	46.03	5.94	20.90	46.42	6.14	20.50

[a] Compounds **1** and **8** were recrystallized from methanol, **2** and **9** from ethanol, **3** and **6** from isopropyl alcohol, and **4, 5,** and **7** from methanol–ether. [b] *erythro* isomer. [c] Nitrogen.

TABLE IV: 2-SUBSTITUTED 5,6-DIHYDRO-4H-1,3,4-OXADIAZINES



No.	R	R_1	y	Mp, °C[a]	Yield, %	Method	Caled, % C	Caled, % H	Caled, % N	Found, % C	Found, % H	Found, % N	Dose,[d] mg/kg	Strychnine 3-day test[d]	Hexobarbital sleep time 3-day test[d]	Hexobarbital sleep time 1-hr test[d]	Max electric shock test[d]
1	C_6H_5	CH_3	1	145–146 dec	80	A	56.47	6.16	13.17	56.26	6.20	12.72	100	1/8	58/35		
													200			79/26	9/10
2	4-ClC_6H_4	CH_3	0	48–49	80	A	57.01	5.26	13.24	56.66	5.37	13.24	100	0/10	45/35	89/32	5/10
													200				10/10
3	4-$CH_3OC_6H_4$	CH_3	1	156–157 dec	72	A	54.43	6.23	11.54	54.67	6.56	11.58	100	1/10	89/35	83/32	
													200				3/10
4	3-BrC_6H_4	CH_3	1	185–187 dec	63	A	41.19	4.15	24.16[b]	41.65	4.33	24.21[b]	100	0/9	71/35	93/30	0/10
5	2-ClC_6H_4	CH_3	1	179–180 dec	48	B	48.60	4.89	28.69[c]	48.88	5.01	28.91[c]	100	0/10	198/35	217/32	1/10
													200				10/10
6	2-C_4H_3O	CH_3	1	171–172 dec	27	B	47.42	5.47	17.50[c]	47.24	5.67	17.30[c]	100	9/10	74/35	65/32	
													200				0/10
7	C_6H_5	H	1	173–174 dec	29	C	54.41	5.58	14.10	54.64	5.33	13.80	100	4/10	65/35	52/32	
													200				0/10
8	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	1	169–170 dec	81	A	51.57	6.33	9.25	51.92	6.67	8.83	100	9/10	19/39	80/26	0/10
													200	10/10	20/44		4/10
9	4-$CH_3C_6H_4$	CH_3	1	175–176 dec	80	A	58.28	6.67	12.36	58.08	6.80	12.18	100	1/10	96/35	84/32	
													200				0/10
10	3,4-$Cl_2C_6H_3$	H	0	48–49	76	C	49.00	4.11	28.93[c]	48.93	4.47	29.13[c]	100	5/10	104/35	158/32	
													200	9/10			1/10
11	4-$CH_3C_6H_4$	H	1	188–189 dec	11	C	56.47	6.16	16.67[c]	56.82	6.34	16.48[c]	100	0/9	54/35	57/32	
													200				1/10

[a] Compounds **1, 2, 4, 5, 6, 8, 9,** and **11** were recrystallized from methanol–ether, **3** from isopropyl alcohol and **10** from ethanol. [b] Total halogen as chlorine. [c] Chlorine. [d] See Pharmacology.

electrodes.[4] The results are expressed as a ratio of the number of mice protected from the hind limb extensor phase of the seizure to the number shocked.

Chemistry.—The melting points were obtained in a capillary tube with a Thomas–Hoover Uni-Melt and are corrected. The elemental analyses were done by Midwest Microlaboratories, Inc., Indianapolis, Ind. The nmr spectra were obtained at 60 Mc, with a Varian A-60 spectrometer, for 10% $CDCl_3$ solutions containing a trace of tetramethylsilane (TMS) as internal standard. Infrared absorption spectra were obtained on a Beckman IR5 recording spectrophotometer. β-(1-Methylhydrazino)-ethanol, 1-(1-methylhydrazino)-2-propanol, 1-methylhydrazino-*t*-butyl alcohol, N-amino-L-(−)-ephedrine, N-amino-D-(+)-pseudoephedrine, *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*p*-toluic acid hydrazide, *threo*-(−)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide, and 2-methyl-2-(β-hydroxy-*n*-propyl)benzoic acid hydrazide have been reported.[3]

2-Methyl-2-(β-acyloxyethyl)carboxylic Acid Hydrazides (Table I). General Procedure.—To a stirred mixture of 0.2 mole of β-(1-methylhydrazino)ethanol, 0.4 mole of triethylamine, and 300 ml of methylene chloride was added, dropwise, a solution of 0.4 mole of acid chloride in 150 ml of CH_2Cl_2. The mixture was stirred and refluxed for 4 hr. The cooled mixture was washed (water, Na_2CO_3 solution, water), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was either crystallized from an appropriate solvent or, if not readily crystallizable, converted to its hydrochloride using ethereal HCl.

2-(β-Hydroxyalkyl)carboxylic Acid Hydrazides (Table II). Method A.—A mixture of 0.2 mole of a 2-methyl-2-(β-acyloxyethyl)carboxylic acid hydrazide, 300 ml of ethanol, and 300 ml of 2 *N* aqueous NaOH solution was heated on a steam bath for 2 hr. Most of the ethanol was removed by distillation *in vacuo*. The cooled mixture was diluted with water until cloudy and extracted five times with 200-ml portions of chloroform. The $CHCl_3$ extracts were evaporated *in vacuo* and the residue was crystallized from an appropriate solvent.

Method B.—To a stirred mixture of 0.4 mole of β-(1-methylhydrazino)ethanol and 300 ml of methylene chloride was added, dropwise, a solution of 0.4 mole of isonicotinic acid anhydride in 600 ml of CH_2Cl_2. The mixture was stirred and refluxed for 1 hr and then allowed to stand at room temperature overnight. The mixture was suction filtered to remove the isonicotinic acid, and the filtrate was evaporated *in vacuo*. The residue was crystallized.

Method C.—To a stirred mixture of 0.2 mole of 1-methylhydrazino-*t*-butyl alcohol, 0.2 mole of triethylamine, and 300 ml of methylene chloride there was added, dropwise, over a period of 2 hr, a solution of 0.2 mole of acid chloride in 100 ml of CH_2Cl_2. The mixture was stirred and refluxed for 3 hr. The cooled mixture was diluted with 300 ml of chloroform, washed (Na_2CO_3 solution, water), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized from ethyl acetate.

2-(β-Chloroalkyl)carboxylic Acid Hydrazide Hydrochlorides (Table III). General Procedure.—To 300 ml of stirred $SOCl_2$ was added, portionwise, 0.3 mole of a 2-(β-hydroxyalkyl)carboxylic acid hydrazide. The mixture was stirred and heated at 40–50° for 2 hr. The cooled mixture was treated with dry ether until the precipitation of the 2-(β-chloroalkyl)carboxylic acid hydrazide hydrochloride was completed. The hydrochloride was removed by suction filtration, washed with dry ether, and recrystallized from an appropriate solvent.

5,6-Dihydro-4H-1,3,4-oxadiazines (Table IV). Method A.—To a hot solution of 0.2 mole of a 2-(β-chloroalkyl)carboxylic acid hydrazide hydrochloride in 400 ml of ethanol was added a solution of 0.5 mole of NaOH in 300 ml of 75% ethanol. The mixture was heated on a steam bath for 2 min and then poured into 1200 ml of cold water. The mixture was extracted five times with 300-ml portions of ether. The dried ($MgSO_4$) ether solution was either evaporated to dryness and the residue was crystallized with an appropriate solvent or treated with ethereal HCl until the precipitation of the hydrochloride was completed. The hydrochloride was removed by suction filtration, washed with dry ether, and recrystallized from an appropriate solvent.

Method B.—To 300 ml of stirred $SOCl_2$ was added, portionwise, 0.3 mole of a 2-(β-hydroxyalkyl)carboxylic acid hydrazide. The mixture was stirred and heated at 40–50° for 2 hr. The $SOCl_2$ was removed by distillation *in vacuo* and the residue was dissolved in 600 ml of hot ethanol. To this hot ethanol solution was added a solution of 0.7 mole of NaOH in 500 ml of 75% ethanol. The mixture was heated on a steam bath for 2 min and then poured into 1500 ml of cold water. The mixture was extracted five times with 300-ml portions of ether. The dried ($MgSO_4$) ether solution was treated with ethereal HCl until the precipitation of the hydrochloride was complete. The hydrochloride was removed by suction filtration, washed with dry ether, and recrystallized from an appropriate solvent.

Method C.—To a stirred mixture of 50 g (0.37 mole) of benzoic acid hydrazide, 53 g (0.37 mole) of 1-bromo-2-chloroethane, and 200 ml of ethanol was added a solution of 32 g (0.81 mole) of NaOH in 200 ml of water. The mixture was stirred and refluxed for 1.5 hr, cooled, diluted with 300 ml of water, and extracted thoroughly with ether. The dried ($MgSO_4$) ether solution was evaporated *in vacuo*. The residual tan oil (18 g) was dissolved in methanol–ether and treated with ethereal HCl until the precipitation of the hydrochloride was complete. The hydrochloride was recrystallized from ethanol.

Treatment of 2-Methyl-2-(β-hydroxyisobutyl)benzoic Acid Hydrazide with Thionyl Chloride.—To 70 ml of stirred $SOCl_2$ was added, portionwise, 19.0 g of 2-methyl-2-(β-hydroxyisobutyl)-benzoic acid hydrazide. The mixture was stirred for 1 hr. The mixture was treated with dry ether until the precipitation of the hydrochloride was completed. The hydrochloride was removed by suction filtration, washed with ether, and recrystallized from isopropyl alcohol–ether. There was obtained 7.8 g (45%) of 2-methyl-2-methallylbenzoic acid hydrazide hydrochloride, mp 171–172° dec. Mixture melting point with authentic 2-methyl-2-methallylbenzoic acid hydrazide hydrochloride, prepared from 2-methyl-2-methallylhydrazine and benzoyl chloride, was 171–172° dec.

Anal. Calcd for $C_{12}H_{16}N_2O \cdot HCl$: C, 59.87; H, 7.12; Cl, 14.73; N, 11.64. Found: C, 59.89; H, 7.35; Cl, 15.07; N, 11.84.

Treatment of 2-Methyl-2-(β-chloropropyl)benzoic Acid Hydrazide Hydrochloride with NaOH.—To a solution of 3.0 g (0.011 mole) of 2-methyl-2-(β-chloropropyl)benzoic acid hydrazide hydrochloride in 50 ml of hot 95% ethanol was added a solution of 1.4 g (0.034 mole) of NaOH in 30 ml of 75% ethanol. The mixture was heated on a steam bath for 5 min, cooled, diluted with 200 ml of water, and extracted thoroughly with ether. The dried ($MgSO_4$) ether extract was evaporated *in vacuo* leaving 1.9 g of tan oil. Examination of the tan oil by gas–liquid partition chromatography on a 1.524 m × 9.65 cm, 15% SE-30, 60–80 AW/Chromosorb W column at a temperature of 200° and a He flow of 200 cc/min indicated that it was a mixture of four components. The retention times and amounts of four components were I = 110 sec, 35%; II = 130 sec, 27%; III = 208 sec, 20%; and IV = 275 sec, 17%. Component I was collected and on the basis of infrared and ultraviolet spectral data designated as 4,6-dimethyl-2-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine; ν_{max} (film) 1625 (OC=N) cm^{-1}, and OH, NH, and hydrazide carbonyl absent; ν_{max}^{EtOH} 225 and 274 mμ.

Base-Catalyzed Dehydrohalogenation of 2-Methyl-2-(β-chlorophenethyl)benzoic Acid Hydrazide Hydrochloride.—To a solution of 10.0 g of 2-methyl-2-(β-chlorophenethyl)benzoic acid hydrazide hydrochloride in 75 ml of ethanol was added a solution of 3.1 g of NaOH in 60 ml of 75% ethanol. The mixture was heated on a steam bath for 5 min and then poured into 250 ml of cold water. The mixture was extracted four times with 100-ml portions of ether. The ether solution was washed (water), dried ($MgSO_4$), and evaporated *in vacuo* to yield 1.8 g (23%) of 4-methyl-2,6-diphenyl-5,6-dihydro-4H,1,3,4-oxadiazine, mp 72–74°. This material was identified by comparison of its infrared spectrum and melting point with an authentic sample.[3d]

Acidification of the alkaline mixture gave 1.1 g (31%) of benzoic acid, mp 121–122.

Treatment of *erythro*-2-Methyl-2-(α-methyl-β-chloro-β-phenethyl)-*p*-toluic Acid Hydrazide Hydrochloride with Sodium Hydroxide.—To a solution of 10.5 g (0.031 mole) of *erythro*-2-methyl-2-(α-methyl-β-chloro-β-phenethyl)-*p*-toluic acid hydrazide hydrochloride in 100 ml of hot ethanol was added a solution ot 3.7 g (0.093 mole) of NaOH in 75 ml of 75% ethanol. The mixture was heated for 2 min on a steam bath, poured into 450 ml of ice water, and extracted with ether. The dried ($MgSO_4$) ether extract was evaporated *in vacuo* and residual oil crystal-

(4) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

lized with isopropyl ether. Recrystallization of the solid from isopropyl ether gave 6.8 g (92%) of *erythro*-(−)-2-methyl-2-(α-methyl-β-ethoxyphenethyl)-*p*-toluic acid hydrazide: mp 124–125; ν_{max} (mull) 3240 sharp (NH), 1645 (hydrazide carbonyl), and 1085, 1075 (ether) cm^{-1}; nmr, $J_{\alpha-\beta}$ 2.4 cps, C_2H_5O shown as triplet at −1.3 ppm and quartet at −3.5 ppm; $[\alpha]^{27}D$ −50.63° (*c* 2.5, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03. Found: C, 73.59; H, 7.86.

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The Chemical, Spectral, and Biological Properties of Monomethine Cyanine Dyes Containing 1,3-Benzoxazine and Quinazoline Nuclei

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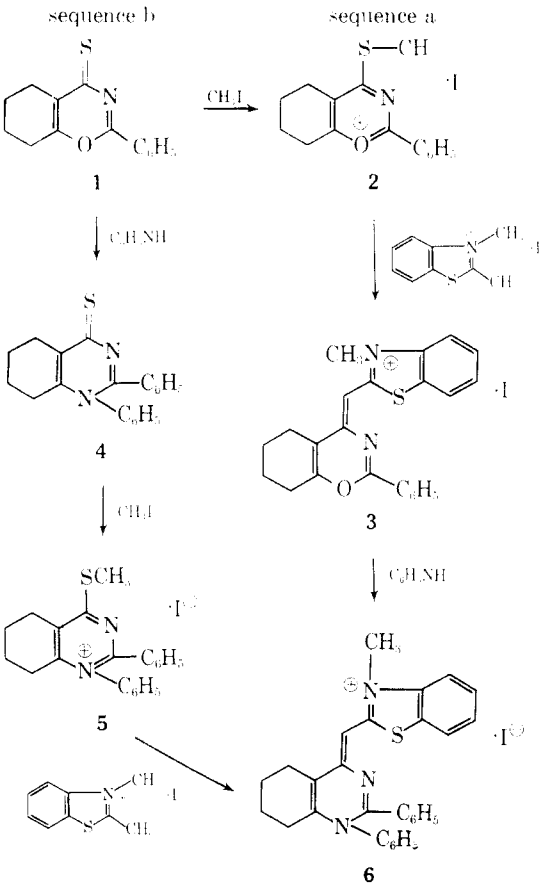
The quaternary salts, 5,6,7,8-tetrahydro-4-methylthio-2-phenylbenzoxazin-1-ium iodide and 5,6,7,8-tetrahydro-1,2-disubstituted 4-methylthioquinazolin-1-ium iodides readily interact with the alkyl iodide salts of 2-methylbenzoxazole, 2-methylbenzothiazole, and 2-methylquinoline to yield monomethine cyanine dyes. The chemical, spectral, and biological properties of these substances are discussed.

The principal use of quaternary nitrogen containing heterocycles has been in the synthesis of cyanine dyes.[1] Although virtually all such heterocyclic compounds have been studied extensively in this regard, the quinazoline group has received relatively little attention.[2-4] This is particularly evident in the case of the quaternary salts of 4-methylthioquinazoline since it has remained undetermined whether the 1- or the 3-nitrogen becomes quaternarized in the reaction of the heterocyclic base with the alkyl halide.[5] It appeared to us that this difficulty could be easily circumvented if the N-1 of the heterocyclic base were already substituted.

In a previous communication from our laboratory, we reported on the synthesis of 5,6,7,8-tetrahydro-1,2-disubstituted quinazoline-4-thiones *via* condensation of morpholinocyclohexene with aroyl isothiocyanates or interaction of 5,6,7,8-tetrahydro-2-substituted 1,3-benzoxazine-4-thione with primary amines.[6] Another aspect of this study has shown that such tetrahydroquinazolines can be readily formed through condensation of morpholinocyclohexene with N-substituted-imidoyl isothiocyanates.[7,8] Consequently, the resulting heterocycles readily lent themselves to quaternarization to form reactive intermediates which could be employed in cyanine dye synthesis. In Scheme I are shown two sequences whereby the desired dyes were prepared.

In sequence a, 5,6,7,8-tetrahydro-2-phenyl-1,3-benzoxazine-4-thione (**1**) was quaternarized according to the method of Hünig and Hübner[9] to 5,6,7,8-tetrahydro-4-methylthio-2-phenyl-1,3-benzoxazin-1-ium iodide (**2**).

SCHEME I



The latter substance was then allowed to react with the appropriate heterocyclic intermediate containing an activated methyl group (*e.g.*, 2-methylbenzothiazole methiodide). In this way, for example, there was formed a 40% yield of 2-[(5,6,7,8-tetrahydro-2-phenyl-4H-1,3-benzoxazin-4-ylidene)methyl]-3-methylbenzothiazolium iodide (**3**). Compound **3** was dissolved in aniline[10] and the resulting solution was heated under

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(2) W. König, German Patent 410,487 (June 4, 1922).
(3) F. M. Hamer, I. M. Heilbron, J. H. Reade, and H. M. Walls, *J. Chem. Soc.*, 251 (1932).
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(5) J. D. Kendall, British Patent 425,609 (Sept 12, 1933).
(6) R. W. J. Carney, J. Wojtkunski, and G. deStevens, *J. Org. Chem.*, **29**, 2887 (1964).
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(8) G. deStevens, H. M. Blatter, and R. W. J. Carney, *Angew. Chem.*, **78**, 125 (1966).
(9) S. Hünig and K. Hübner, *Chem. Ber.*, **95**, 937 (1962).
(10) In sequence a and b aniline has been used for illustrative and brevity purposes. However, it is emphasized that most primary amines can be used in these reactions.