58, 2192 (1974); (c) U.S. Patent 3 880 840 (1975); (d) L. Fontanella, L. Mariani, and G. Tarzia, *Eur. J. Med. Chem.*, 11, 217 (1976); (e) R. Jaunin, *Helv. Chim. Acta*, **57**, 1934 (1974).
(4) D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **36**, 2542 (1971).
(5) H. A. DeWald and D. E. Butler, U.S. Patent 3 660 425 (1972).
(6) M. D. Coburn, *J. Heterocycl. Chem.*, **7**, 455 (1970); W. D. Emmons, *J. Am. Chem. Soc.*, **76**, 3470 (1954).
(7) G. Chen, C. Ensor, and I. Clark, *AMA Arch. Neurol. Psychiatry*, **66**, 329 (1951); **68**, 498 (1952); G. Chen, R. Porterman, C. Ensor, and A. Bratton, Jr., *J. Pharmacol. Exp. Ther.*, **103**, 54 (1951).
(8) B. P. H. Poschel, *Psychopharmacologia*, **19**, 193 (1971).
(9) B. P. H. Poschel and F. Ninteman, *Life Sci.*, **7**, 317 (1968).
(10) M. M. Bree, B. J. Cohens, and S. E. Rowe, *Lab. Anim. Sci.*, **22** (6), 878 (1972); G. H. Conner, R. W. Coppock, and C. C. Beck, *Vet. Med. Small Anim. Clin.*, **69** (4), 479 (1974).
(11) J. Baukema, R. A. Okerholm, and A. J. Glazko, *Res. Commun. Chem. Pathol. Pharmacol.*, **10**, 227 (1975).
(12) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2456 (1959).

Antischistosomal Effects of 5-(2,4,5-Trichlorophenyl)hydantoin and Related Compounds

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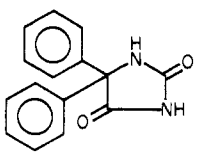
Received May 9, 1977

5-(2,4,5-Trichlorophenyl)hydantoin and several analogues effected an 80–90% reduction of live schistosomes in infected mice at doses ranging from 265 to 329 mg/kg per day when administered orally in the diet for 14 days. The sodium salt of 5-(2,4,5-trichlorophenyl)hydantoin, when given by gavage to rhesus monkeys infected with *Schistosoma mansoni* at 200 mg/kg/day for 5 or 10 days, removed all but a few live worms with no evidence of intolerance.

Although the utility of hydantoin derivatives as anticonvulsant and antiarrhythmic drugs is well recognized, little is known about the antiparasite properties of such substances.

In 1954 it was reported that 5,5-diphenylhydantoin (**1**) and 5-(*p*-chlorophenyl)-5-methylhydantoin (**2**) showed activity against *Schistosoma mansoni* infections in mice.[1] The only other reported interest in hydantoins as schis-



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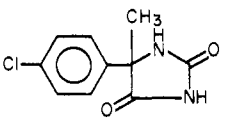

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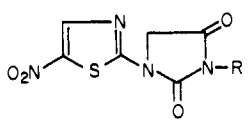
tosomicides has been in the N-substituted derivatives (**3**) related to niridazole.[2]



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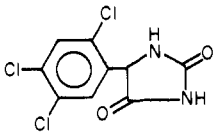
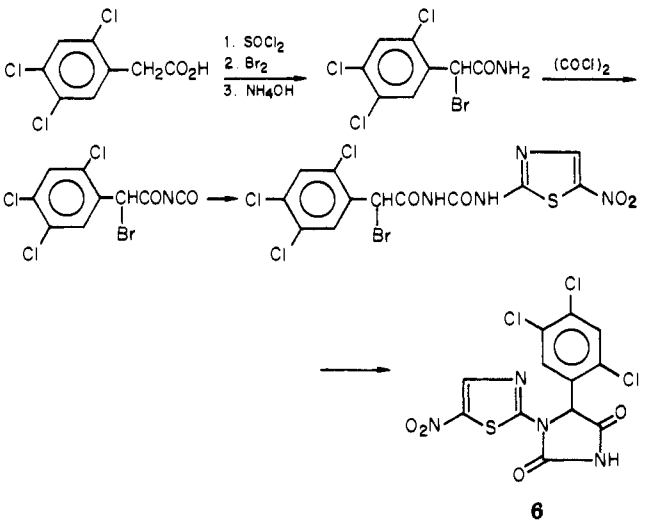


4a

We have examined through the years a wide variety of hydantoins as potential schistosomicides. Our studies confirmed the modest activity at toxic levels of **1**,[3] and we now wish to report the potent activity of 5-(2,4,5-trichlorophenyl)hydantoin (**4a**) and some related substances.[4]

Chemistry. A standard hydantoin synthesis was used for the most part.[5] Thus a suitably substituted aromatic aldehyde heated in aqueous ethanol with potassium cyanide and ammonium carbonate provided the 5-(substituted phenyl)hydantoins (Table I). Suitably substituted acetophenones were used similarly to prepare the 5-methyl-5-phenylhydantoins (**5a–g**, Table II). The 3-methyl and 3-(dimethylaminopropyl) analogues (compounds **4e** and **4i**, Table I) of **4a** were obtained by alkylation of the parent. Compound **4i** was treated with methyl iodide to provide the quaternary salt (compound **4j**, Table I). Hydroxymethylation of **4a** provided the 3-hydroxymethyl derivative (compound **4g**, Table I). 1-Methyl-5-(2,4,5-trichlorophenyl)hydantoin (compound **4f**, Table I) was obtained by treating 2,4,5-trichlorobenzaldehyde with methylamine and sodium cyanide in the presence of $Na_2S_2O_5$ and allowing the intermediate formed to react with potassium cyanate in hydrochloric acid.[6] Alkylation of this material then provided the 1,3-dimethyl derivative (compound **4h**, Table I).

Scheme I



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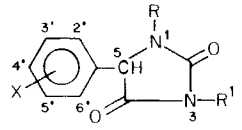
In an attempt to combine the features of the nitrothiazolylhydantoins (**3**) and 5-(2,4,5-trichlorophenyl)hydantoin (**4a**), 1-(5-nitro-2-thiazolyl)-5-(2,4,5-trichlorophenyl)hydantoin (**6**) was prepared (Scheme I). (2,4,5-Trichlorophenyl)acetic acid was converted to 2-bromo-

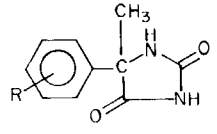
Table I. 5-(Substituted phenyl)hydantoins



No.	X	R	R¹	Mp, °C	Yield purified, %	Recrystn solvent	Effects vs. *S. mansoni* in mice: Drug, Route × days[b]	Drug, mg/kg/day	Live schistosomes, % mice infected	Live schistosomes, % redn
4a	2′,4′,5′-Cl_3	H	H	244–246	59	HOAc	D × 14	329	67	80
							G × 10	400	100	0
4a[d]							D × 14	269	100	65
							G × 5	200	100	86
							G × 10	100	100	76
4b	2′,4′-Cl_2	H	H	179–181	30	EtOH	D × 14	302	100	36
4c	2′,6′-Cl_2	H	H	244–246	50	EtOH	D × 14	347	100	2
4d	3′,4′-Cl_2	H	H	224–226.5	20	Me_2CO–H_2O	D × 14	329	100	0
4e	2′,4′,5′-Cl_3	H	CH_3	233–235	38	HOAc	D × 14	265	33	83
4f	2′,4′,5′-Cl_3	CH_3	H	251–253	25[a]	MeOH	D × 14	396	83	71
4g	2′,4′,5′-Cl_3	H	CH_2OH	237–239	60[a]	MeOH	D × 14	146	100	0
4h	2′,4′,5′-Cl_3	CH_3	CH_3	123–124	29	EtOAc–petr ether	D × 14	336	83	88
4i	2′,4′,5′-Cl_3	H	$(CH_2)_3N(CH_3)_2$	149–151	51	EtOH	D × 14	78[c]	100	0
4j	2′,4′,5′-Cl_3	H	$(CH_2)_3N^+(CH_3)_3I$	141–143	73	MeOH	D × 14	288	100	13
4k	2′,3′,6-Cl_3	H	H				D × 14	305	100	0
Lucanthone hydrochloride							D × 14	140[c]	90	71
Niridazole							D × 14	249	17	99

[a] Crude yield. [b] D represents drug diet; G represents gavage. [c] Maximum tolerated dose. [d] Sodium salt.

Table II. 5-Methyl-5-(substituted phenyl)hydantoins

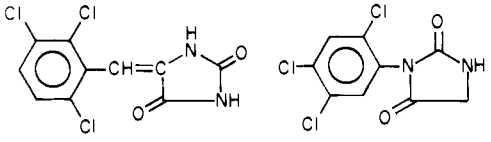


No.	R	Mp, °C	Yield purified, %	Recrystn solvent	Effects vs. *S. mansoni* in mice: Drug, Route × days	Drug, mg/kg/day	Live schistosomes, % mice infected	Live schistosomes, % redn
5a	2′,4′,5′-Cl_3	191–193	20	HOAc	D × 14	297	66	90
5b	2′,4′-Cl_2	212.5–213.5	35	EtOH–H_2O	D × 14	301	100	8
5c	3′,4′-Cl_2	203–204	74	EtOH–H_2O	D × 14	376	100	38
5d	3′-NO_2	194–197[a]			D × 14	298	100	0
5e	4′-NO_2	228–231[a]			D × 14	314	100	0
5f	2′,4′-Cl_2,3′-Me	232–233	51	95% EtOH	D × 14	332	100	26
5g	4′,5′-Cl_2,2′-Me	208.5–210.5	65	2-PrOH	D × 14	349	100	48

[a] T. A. Connors, W. C. J. Ross, and J. G. Wilson, *J. Chem. Soc.*, 2994 (1960).

2-(2,4,5-trichlorophenyl)acetamide and treated with oxalyl chloride to provide bromo(2,4,5-trichlorophenyl)acetyl isocyanate. This was allowed to react with 2-amino-5-nitrothiazole to yield 1-[bromo(2,4,5-trichlorophenyl)-acetyl]-3-(5-nitro-2-thiazolyl)urea which was cyclized with sodium hydride in *N,N*-dimethylformamide to give the hydantoin **6**.

Biology. The hydantoins were examined against a Puerto Rican strain of *S. mansoni* in mice by Dr. Paul E. Thompson and co-workers of these laboratories.[7] Drugs were given in a powdered diet for 14 days. Several of the compounds (**4a**,**e**,**h** and **5a**) exhibited significant antischistosome activity in mice (Tables I and II). Thus 5-(2,4,5-trichlorophenyl)hydantoin (compound **4a**), 3-methyl(2,4,5-trichlorophenyl)hydantoin (compound **4e**), 1,3-dimethyl-5-(2,4,5-trichlorophenyl)hydantoin (compound **4h**), and 5-methyl-5-(2,4,5-trichlorophenyl)hydantoin (compound **5a**) effected an 80–90% reduction of live schistosomes in infected mice at doses ranging from 265 to 329 mg/kg per day when administered orally in the diet for 14 days. With the exception of 1-methyl-5-(2,4,5-trichlorophenyl)hydantoin (compound **4f**) which also had fair activity, the remainder of the variants prepared had little or no activity. 5-(2,3,6-Trichlorophenyl)hydantoin (compound **4k**, Table I)[8] and the related benzylidene derivative **7**[8] were also devoid of activity as was the N-substituted analogue **8**[9] and the nitrothiazole derivative **6**. The active members of the series are seen to be more effective at well-tolerated doses than lucanthone and to approach the potency range of niridazole. In an effort to solubilize these materials with the hope of achieving increased potency through more efficient absorption, the sodium salt of 5-(2,4,5-trichlorophenyl)hydantoin was prepared. This material, although no more



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effective than **4a** upon administration in the diet, can be seen (Table I) to be considerably more effective by gavage. The soluble salt also proved to have a distinct advantage in the monkey. Thus against *S. mansoni* infections in rhesus monkeys 5-(2,4,5-trichlorophenyl)hydantoin, when administered at gavage doses of 200 mg/kg per day for 10 days, produced only a slight to moderate temporary egg suppression. Daily gavage doses of 400 mg/kg for 5 days left five live and two dead worms in the treated animal. By contrast, the sodium salt, given by gavage at 200 mg/kg per day for 5 or 10 days, removed all but a few (three to four) live worms with no evidence of intolerance. The hydantoins represent a novel structural type with good activity against experimental *S. mansoni* infections. Since, however, more recently available agents such as Hycanthone[14] and Oxamniquine[15] are clinically effective in a single dose, it was not felt that the potency of the hydantoins warranted further investigation.

Experimental Section

Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

2,4,5-Trichlorobenzaldehyde.[11] A mixture of 49.2 g (0.25 mol) of 2,4,5-trichloroaniline in 150 mL of concentrated HCl and 100 mL of H_2O was heated to the boiling point, cooled, and treated at 0 °C with a solution of 17.5 g (0.25 mol) of $NaNO_2$ in 50 mL of H_2O. After about 10 min the solid present dissolved and the solution was neutralized to congo red with NaOAc solution. The diazonium solution was added dropwise to a stirred freshly prepared solution of formaldoxime (from 11.5 g of paraformaldehyde, 26.3 g of $NH_2OH{\cdot}HCl$, and 170 mL of H_2O, warmed at 100 °C until solution occurred and then heated under reflux for 15 min with 51 g of $NaOAc{\cdot}3H_2O$) containing 6.3 g of $CuSO_4{\cdot}5H_2O$, 1.0 g of Na_2SO_3, and 165 g of $NaOAc{\cdot}3H_2O$ in 180 mL of H_2O at 0–5 °C. After 10 min the mixture was acidified (to congo red) with concentrated HCl, treated with additional (230 mL) concentrated HCl, and heated under reflux for 2 h. The mixture was cooled and extracted with EtOAc. The extracts were dried and the solvent was removed in vacuo to give 48 g of a brown oil which was dissolved in a small amount of EtOH and added to a stirred concentrated aqueous solution of 43.8 g of $Na_2S_2O_5$. The mixture was allowed to stand overnight and the solid was collected, washed with ether, and added to a stirred mixture of 2 N Na_2CO_3 solution and EtOAc. The organic layer was separated, dried, and concentrated, and the residue was recrystallized from EtOH to give 12 g (24%) of the product, mp 110–111.5 °C.

5-(2,4,5-Trichlorophenyl)hydantoin (4a). A mixture of 23.3 g (0.11 mol) of 2,4,5-trichlorobenzaldehyde,[10] 14.5 g (0.22 mol) of KCN, and 70.5 g (0.74 mol) of $(NH_4)_2CO_3$ in 500 mL of 50% EtOH was heated for 7 h at 60–80 °C. Additional $(NH_4)_2CO_3$ (~1-g portions) was added at 0.5-h intervals. Most of the EtOH was removed in vacuo, H_2O was added (to ~500 mL), and the mixture was allowed to remain overnight at 0 °C. The solid that formed was collected and dissolved in 2 N NaOH. The solution was filtered, treated with charcoal, acidified, and recrystallized from HOAc to afford 18.4 g (59%) of the product, mp 244–246 °C.

5-Methyl-5-(2,4,5-trichlorophenyl)hydantoin (5a, Table II). The 5-methyl derivatives were prepared similarly to 4 described above. Thus, 2,4,5-trichloroacetophenone (9.4 g)[12] provided 2.5 g (20%) of 11, mp 191–193 °C, after recrystallization from HOAc.

3-Methyl-5-(2,4,5-trichlorophenyl)hydantoin (4e, Table I). To a solution of 2.8 g (0.01 mol) of 5-(2,4,5-trichlorophenyl)-hydantoin in 10 mL of 1 N NaOH was added 0.47 mL (0.005 mol) of Me_2SO_4. The mixture was shaken for a few minutes and the solid that formed was collected to provide 1.1 g (38%) of the product after recrystallization from HOAc, mp 233–235 °C.

3-[3-(Dimethylamino)propyl]-5-(2,4,5-trichlorophenyl)-hydantoin (4i, Table I). To a solution of 2.8 g (0.01 mol) of 5-(2,4,5-trichlorophenyl)hydantoin in 50 mL of EtOH containing 0.23 g (0.01 mol) of Na was added 1.4 g (0.012 mol) of 3-chloro-*N,N*-dimethylpropylamine, and the mixture was heated for 4 h at 100 °C and then concentrated to dryness. The residue was dissolved in EtOAc and washed with 2 N NaOH and then with H_2O, and the organic layer was removed in vacuo. The residue gave 1.9 g (51%) of the product after recrystallization from EtOH, mp 149–151 °C.

[3-[2,5-Dioxo-4-(2,4,5-trichlorophenyl)-1-imidazolidinyl]propyl]trimethylammonium Iodide (4j, Table I). A solution of 2.0 g (0.0055 mol) of 3-[3-(dimethylamino)propyl]-5-(2,4,5-trichlorophenyl)hydantoin in 50 mL of MeOH containing 4.0 mL of MeI was allowed to remain at room temperature for 18 h and concentrated to dryness. Recrystallization from MeOH gave 2.0 g of the product (73%), mp 141–143 °C.

3-(Hydroxymethyl)-5-(2,4,5-trichlorophenyl)hydantoin (4g, Table I). To a suspension of 2.3 g (0.0082 mol) of 5-(2,4,5-trichlorophenyl)hydantoin and 1.4 mL of 40% HCHO in 60 mL of EtOH at 40 °C were added 0.7 g (0.0082 mol) of $NaHCO_3$ and then a few drops of 2 N NaOH. The mixture was stirred for 0.5 h at 35 °C and made acidic with HOAc, and the EtOH was removed in vacuo. The residue was triturated with dilute NaOH and extracted with EtOAc. The extract upon standing overnight deposited the product, 1.5 g (60%), mp 237–239 °C (slow heating), after recrystallization from MeOH.

1-Methyl-5-(2,4,5-trichlorophenyl)hydantoin (4f, Table I). To a mixture of 8.9 g (0.042 mol) of 2,4,5-trichlorobenzaldehyde, 4.5 g (0.024 mol) of $Na_2S_2O_5$, and 9 mL of H_2O was added 4.2 g (0.086 mol) of NaCN and 5.2 mL of 33% $MeNH_2$ in EtOH at 0 °C. This mixture was diluted with 60 mL of 50% EtOH, 6 mL of 22% $MeNH_2$ in EtOH was added, and the reaction mixture was stirred at 0 °C for 0.75 h and allowed to come to room temperature overnight. The EtOH was removed; the residue was diluted with H_2O and extracted with EtOAc. Removal of the

solvent from the extract gave 10 g of a residue which was treated with 42 mL of 1 N HCl and 7.7 g (0.095 mol) of KCNO and maintained at 0 °C during the portionwise addition of 16.3 mL of concentrated HCl. The mixture was heated at 100 °C for 1.5 h, cooled, and extracted with EtOAc. Isolation of acidic material from the extract gave 3.1 g (25%) of the product. A sample from HOAc had mp 251–253 °C.

1,3-Dimethyl-5-(2,4,5-trichlorophenyl)hydantoin (4j, Table I). This was prepared from **4f** with Me_2SO_4, similar to the preparation of **4e** described above.

5-(2,4,5-Trichlorophenyl)hydantoin Sodium Salt. To a suspension of 13.9 g (0.05 mol) of 5-(2,4,5-trichlorophenyl)hydantoin in 150 mL of H_2O was added 50 mL of 1.0 N NaOH. After stirring for several hours at room temperature all but a trace of the solid had dissolved. The mixture was filtered and then concentrated to dryness in vacuo. The residue was recrystallized from EtOH to give 5.1 g of the product (34%) as a white solid which sinters at 288 °C, gradually shrinks, and melts with decomposition at 294–297 °C. Anal. ($C_9H_4Cl_3N_2O_2Na$) C, H, N. This procedure is not completely reproducible. From run to run salts containing varying degrees of hydration were obtained.

1-(5-Nitro-2-thiazolyl)-5-(2,4,5-trichlorophenyl)hydantoin (6). A solution of 3 g (0.0061 mol) of 1-[bromo(2,4,5-trichlorophenyl)acetyl]-3-(5-nitro-2-thiazolyl)urea in 5 mL of DMF containing 0.3 g of NaH (45% dispersion in mineral oil) was stirred at room temperature for 0.5 h and poured onto ice. Acidification with AcOH provided the product which was recrystallized from 2-PrOH to give 0.7 g (30%), mp 203–205 °C dec (after drying for 3 days at 100 °C under high vacuum). Anal. ($C_{12}H_5Cl_3N_4O_4S$) C, H, N.

2-Bromo-2-(2,4,5-trichlorophenyl)acetamide. A mixture of 29 g (0.12 mol) of (2,4,5-trichlorophenyl)acetic acid[13] in 24.6 mL of $SOCl_2$ was heated under reflux for 2 h, and the $SOCl_2$ was then removed in vacuo. The residue was treated with 22.4 g (0.14 mol) of Br_2 and a trace of red P and heated for 2 h at 130–150 °C under illumination. Excess Br_2 and HBr were removed by passing air through the reaction mixture for 1 h, and the contents of the flask was then dissolved in Me_2CO and added dropwise to concentrated NH_4OH. The solid that formed was recrystallized from C_6H_6 to give 24 g of the product (62%), mp 132–134 °C. Anal. ($C_8H_5BrCl_3NO$) C, H, N.

Bromo(2,4,5-trichlorophenyl)acetyl Isocyanate. A suspension of 6.3 g (0.0265 mol) of 2-bromo-2-(2,4,5-trichlorophenyl)acetamide in 30 mL of 1,2-dichloroethane containing 2.2 mL of oxalyl chloride was heated under reflux for 17 h. Distillation furnished the product as an oil (3.0 g, 43%), bp 130 °C (0.7 mm). The material absorbs moisture readily and was not analyzed but used as is in the next step.

1-[Bromo(2,4,5-trichlorophenyl)acetyl]-3-(5-nitro-2-thiazolyl)urea. The above isocyanate (3.0 g, 0.007 mol) in about 5 mL of THF was added dropwise to a solution of 1.0 g (0.0072 mol) of 2-amino-5-nitrothiazole in 25 mL of THF, and the mixture was allowed to remain at room temperature overnight. The mixture was filtered, and solvent was removed from the filtrate in vacuo. The residue was recrystallized from EtOH to give 1.3 g (38%) of the product, mp 176–177 °C. Anal. Calcd for $C_{12}H_6BrCl_3N_4O_4S$: C, 29.5; H, 1.2; N, 11.5. Found: C, 30.7; H, 1.4; N, 11.7. This material appears to lose HBr upon further crystallization and satisfactory analytical values could not be obtained. The product is adequate for use in the cyclization step.

Acknowledgment. The authors express their appreciation to Dr. Paul E. Thompson and co-workers for the antischistosome testing, Mr. C. E. Childs and Mr. F. H. Oliver and associates for the microanalyses, and Mrs. Zoe Gavrillis, Mr. Nickolas Jenesel, and Mr. Harvey Troutman for preparation of several of the compounds described herein.

References and Notes

(1) G. W. Luttermoser and H. W. Bond, *J. Parasitol.*, **40**, 33 (1954).
(2) Netherlands Patent 6 505 226 (Oct 25, 1965) (Ciba Ltd.).
(3) The compound was toxic at 0.25 and 0.125% in the diet. At 0.0625% (66 mg/kg) for 14 days no more than a 50% reduction of worm burden could be obtained. The compound was also inactive when given by gavage. P. E. Thompson, unpublished data, Parke, Davis and Co.
(4) The initial sample of **4** was provided by the Dow Chemical Co.
(5) For a review see E. Ware, *Chem. Rev.*, **46**, 403 (1950).
(6) This represents a slight modification of the method of L. M. Long, C. A. Miller, and H. D. Troutman, *J. Am. Chem. Soc.*, **70**, 900 (1948).
(7) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, 11, 31 (1962).
(8) Supplied by Dow Chemical Co.
(9) Supplied by U.S. Borax Co.
(10) E. Seelig, *Justus Liebigs Ann. Chem.*, **237**, 147 (1887).
(11) This is a modification of the procedure of W. F. Beech, *J. Chem. Soc.*, 1297 (1954).
(12) G. G. Yakobson, L. I. Denisova, and L. B. Krasnova, *J. Gen. Chem.*, **32**, 3078 (1962).
(13) British Patent 573 377 (Nov 19, 1945) (Imperial Chemical Industries Ltd.).
(14) J. A. Cook, P. Jordan, and P. Armitage, *Am. J. Trop. Med. Hyg.*, **25**, 602 (1976).
(15) N. Katz, F. Zicker, and J. P. Pereira, *Am. J. Trop. Med. Hyg.*, **26**, 234 (1977).

Synthesis and Hypoglycemic Activity of 4-Substituted 3-Mercaptopicolinic Acids[1]

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3-Mercapto-4-methylpicolinic acid was one of very few compounds derived from 3-mercaptopicolinic acid (3-MPA) to have hypoglycemic activity. In an effort to find compounds with greater potency than 3-MPA, several 4-substituted 3-mercaptopicolinic acids (4-OMe, OC_6H_5, SMe, SH, Cl, NH_2, Et; **1–7**) were prepared and tested in 48-h fasted rats. None was hypoglycemic in this test system after oral dosing of 150 mg/kg.

3-Mercaptopicolinic acid (3-MPA) is a potent inhibitor of gluconeogenesis[2] in several animal models primarily by virtue of its ability to inhibit the enzyme phosphoenolpyruvate carboxykinase (PEPCK).[3-6] Since this enzyme is one of the key regulatory enzymes in the de novo synthesis of glucose, inhibition of PEPCK should result in a lowering of blood glucose levels in fasted and diabetic animals. Although the concept of lowering blood sugar levels in diabetics by inhibiting their elevated rates of gluconeogenesis has been an idea of long standing,[7] 3-MPA has been the first agent potent enough to lower blood glucose levels in a number of animal models by this