Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.60; H, 6.80; N, 17.30.

The **monohydrochloride** of Ic, prepared by addition of 1 equiv of dilute HCl to an ethanolic solution of Ic followed by evaporation to dryness under reduced pressure, was recrystallized from MeOH–EtOAc; pale yellow crystals: mp 232–234°; $\lambda_{max}^{EtOH-H_2O}$ 249, 345 mμ (ε 20,300, 11,800).

Anal. Calcd for $C_{19}H_{22}N_4O \cdot HCl$: C, 63.59; H, 6.46; N, 15.61; Cl^-, 9.88. Found: C, 63.80; H, 6.30; N, 15.30; Cl^-, 9.70.

6-Methoxy-10-hydroxy-2,9-diazaanthracene (IIc, 6-Methoxypyrido[3,4-*b*]quinolin-5(10H)-one).—A mixture of 2.5 g (0.01 mole) of 3-(*p*-anisidino)isonicotinic acid, 40 g of polyphosphoric acid, and 2 ml of $POCl_3$ was heated on a steam bath, with manual stirring, for 7 hr until the evolution of HCl could no longer be detected. The syrup was added to 200 ml of ice–H_2O and the resulting solution was made basic with NH_4OH. The yellow solid was collected, washed with H_2O, and dried in air. On recrystallization from MeOH, 2.0 g (87%) of IIc was obtained as golden yellow leaflets: mp 333–335° dec (uncor); λ_{max}^{EtOH} 242, 279, 309, 322, 408, 425 mμ (ε 28,000, 40,000, 3600, 2500, 8800, 8100); $\lambda_{max}^{pH\ 1}$ 294, 458 mμ (ε 32,000, 6800).

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.29; H, 4.46; N, 12.50.

6-Methoxy-10-chloro-2,9-diazaanthracene (IId).—A mixture of 2.5 g (0.01 mole) of IIc and 60 ml of $POCl_3$ was heated under reflux for 15 hr. After removal of the excess $POCl_3$ (reduced pressure), the mixture was poured onto 200 g of crushed ice and made basic with NH_4OH. The resulting solid product was collected, washed (H_2O), and dried in air. It was recrystallized (Me_2CO) to furnish 2.25 g (83%) of IId as yellow needles: mp 187–188°; λ_{max}^{EtOH} 229, 237, 258, 362 mμ (ε 33,000, 32,000, 74,000, 11,000).

Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.64; H, 3.61; N, 11.48.

6-Methoxy-10-(3-diethylaminomethyl-4-hydroxyanilino)-2,9-diazaanthracene (IIb).—2-Diethylaminomethyl-4-acetamidophenol (3.07 g, 0.013 mole) was boiled with 20 ml of 20% HCl for 3 hr. The solution was allowed to cool and was neutralized with 10% NaOH to pH 6. Compound IId (3.18 g, 0.013 mole) was then introduced. The mixture was heated on a steam bath for 6 hr, cooled, diluted with 50 ml of H_2O, and made basic with NH_4OH. The precipitate was collected, washed (H_2O), and allowed to dry in air. On recrystallization (EtOAc) there was obtained 3.80 g (73%) of IIb as orange-red crystals, mp 189–193°. Further recrystallization raised the melting point to 191–193°; λ_{max}^{EtOH} 252, 290, 445 mμ (ε 41,000, 24,000, 10,000).

Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.53; H, 6.47; N, 14.02.

Attempted Preparation of IIa. Isolation of 6-Methoxy-2,9-diazaanthracene (IIe).—A mixture of 4.90 g (0.02 mole) of IId and 17 ml of 1-diethylamino-4-aminopentane was heated at 145–150° for 5 hr (N_2 atmosphere). The mixture was diluted with 100 ml of H_2O, made basic with NH_4OH, and filtered to remove the precipitated IIc (0.55 g). The filtrate was extracted repeatedly with $CHCl_3$ (total, 250 ml), and the combined extracts were washed (H_2O), dried ($MgSO_4$), and evaporated at atmospheric pressure. After excess dialkylaminoalkylamine was removed (rotary evaporator, steam bath), the tarry substance, which did not solidify on standing, was collected and subjected to short-path distillation (burner, heat source). There was obtained at 220–230° (1 mm) 0.85 g of a yellow solid, mp 136–138°. Recrystallization from EtOAc gave light yellow crystals, mp 139.5–140.5°. Its spectrum ($CDCl_3$) showed aromatic proton signals at τ 3.46 (1 H, doublet), 2.83 (2 H, 2 doublets), 2.27 (1 H, doublet), 2.18 (1 H, singlet), 1.84 (1 H, doublet), and 0.72 (1 H, singlet) and the methoxy singlet at 6.3 (3 H); infrared, 6.13, 6.21, 6.34, 6.68, 7.16, 7.9, 8.5, 8.9, 9.8, 11.0, 12.0, and 12.4 μ; λ_{max}^{EtOH} 226–233, 256, 358 mμ (ε 24,000, 53,000, 14,000).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.17; H, 4.73; N, 13.53.

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1-Substitution in 2-Methyl-4(5)-nitroimidazole. I. Synthesis of Compounds with Potential Antitrichomonal Activity

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In view of the known antitrichomonal activity of some 1-substituted 2-methyl-4(5)-nitroimidazoles, a series of 4-nitro and 5-nitro isomers was synthesized and evaluated for their activity against *Trichomonas vaginalis*. Earlier authors[2-4] have prepared some other series of such compounds and determined[3,5] some structure–activity relationships.

The methods employed and characteristic data for the compounds synthesized are shown in Tables I and II. The starting material for all preparations was 2-methyl-4(5)-nitroimidazole (III).[6] A number of 1-substituted 2-methyl-5-nitroimidazoles was obtained by a general method which consisted of the use of one of the lower carboxylic acids with high polarity, which activates nucleophilic agents and allows the formation of 5-nitro isomers only.[7] The influence of the carboxylic acids is not yet clearly explained,[8] but a greater ratio of these reagents, empirically established, is always necessary to give rise to only 5-nitro isomers (see procedure A). 4-Nitro isomers were obtained when a molar excess of alkylating agents was used without addition of carboxylic acid, or when the solution of the sodium salt of III was employed according to an earlier described procedure.[9] Another synthetic peculiarity is found in procedure E where a supersaturated solution of potassium iodide in methyl isobutyl ketone is found to give significantly better results than the classical Finkelstein method.[10]

In preparing picrates of the compounds listed in Tables I and II, we were able to confirm the observation[11] that only 5-nitro isomers form stable hydrochlorides and picrates (see Table I). This fact could serve to distinguish 5-nitro and 4-nitro isomers if carboxyl functions are absent. Another possibility for such distinction is offered by the nmr spectra of these isomers if there is at least one proton on the α-carbon of the substituting side chain attached to ring nitrogen.

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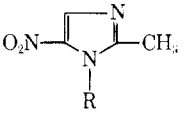
TABLE I

1-SUBSTITUTED 2-METHYL-5-NITROIMIDAZOLES, THEIR ANTITRICHOMONAL ACTIVITY AND TOXICITY

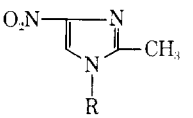


No.	R	Method	Yield,[d] %	Recrystn solvent	Mp, °C	Picrates mp, °C	Formula[g]	Min lethal concn, g/ml × 10^{-3} [f]	LD_{50}, mg/kg × 10^{-2}
1	CH_2CH_2Cl[a]	A[e]	15	H_2O–EtOH (2:1)	78.5–79.5	139–140	$C_6H_8ClN_3O_2$	1:200	10
2	CH_2CH_2Br	A,[c] C	25.5, 65	H_2O–EtOH (2:1)	80–81	145–146	$C_6H_8BrN_3O_2$	1:200	7.3
3	CH_2CH_2I	D	90	H_2O–EtOH (2:1)	103–104	148.5–150	$C_6H_8IN_3O_2$	1:45	3.2
4	$CH_2COOC_2H_5$[b]	A[e]	12	H_2O	72–73	129–130	$C_8H_{11}N_3O_4$	1:400	38
5	CH_2COOH[b]	G	92	H_2O	179–180	...[e]	$C_6H_7N_3O_4$	1:60	6.5
6	CH_2CN[b]	A[e]	14	H_2O	92–93	133–134	$C_6H_6N_4O_2$	1:700	5.0
7	$CH_2CH_2OC_6H_5$	A[e]	39	EtOH	105–106	182–183	$C_{12}H_{13}N_3O_3$	1:250	7.5
8	$CH_2CH_2OCH_2CH_3$	A[e]	72	H_2O	62.5–63.5	134–135	$C_8H_{13}N_3O_3$[h]	1:350	15
9	$CH_2CH_2OCH_2CH_2Cl$	A[e]	55	H_2O–EtOH (1:2)	79–80	114–115	$C_8H_{12}ClN_3O_3$	1:300	6.3
10	$CH_2CH_2OCH_2CH_2I$	D	85	H_2O–MeOH (1:3)	79–81	116–117	$C_8H_{12}IN_3O_3$	1:500	3.5
11	$CH_2CH_2OCH_2CH_2OH$	F	68	MeOH–petr ether (60–80°)	62–63	107–108	$C_8H_{13}N_3O_4$	1:600	9.5

[a] Prepared first by C. Cosar, *et al.*,[2] by a different method. [b] First described by May Co. Baker Ltd., Belgian Patent 639,372 (1964); *Chem. Abstr.*, **62**, 9144*h* (1965), but was obtained *via* CrO_3 oxidation of I. [c] Alkylating agents and carboxylic acids employed: **1**, 43.0 g (25.5 ml, 0.30 mole) of 1-bromo-2-chloroethane, 29.6 g (30 ml) of propionic acid, and 30.0 g (25 ml) of nitrobenzene; **2**, 84.5 g (38.8 ml, 0.45 mole) of 1,2-dibromoethane, 21 g (20.0 ml) of AcOH; **4**, 49.0 g (42.4 ml, 0.40 mole) of ethyl α-chloroacetate, 19.8 g (20.0 ml) of propionic acid; **6**, 90.2 g (25.4 ml, 0.40 mole) of chloroacetonitrile, 19.8 g (20.0 ml) of propionic acid; **7**, 40.0 g (0.18 mole) of β-bromophenetole, 21 g (20.0 ml) of AcOH; **8**, 45.8 g (33.8 ml, 0.3 mole) of β-bromoethyl ethyl ether, 42 ml (43.5 g) of AcOH; **9**, 58.5 g (48 ml, 0.41 mole) of β,β′-dichlorodiethyl ether, 11 g (9 ml) of formic acid. [d] Where several values are indicated, these correspond to the methods mentioned. [e] Picrate cannot be obtained because of the presence of carboxyl group. [f] Minimum lethal concentration for I, 1:1000 (g/ml × 10^{-3}); LD_{50} = 42 (mg/kg × 10^{-2}). [g] Analytical results obtained for C, H, and N were within ±0.4% of the theoretical values unless listed otherwise. [h] *Anal.* C, H; N: calcd, 21.10; found, 20.67.

TABLE II

1-SUBSTITUTED 2-METHYL-4-NITROIMIDAZOLES, THEIR ANTITRICHOMONAL ACTIVITY AND TOXICITY



No.	R	Method	Yield,[d] %	Recrystn solvent	Mp, °C	Formula[g]	Min lethal concn, g/ml × 10^{-3} [f]	LD_{50}, mg/kg × 10^{-2}
12	CH_2CH_2Cl	E[a]	65	H_2O–EtOH (2:1)	97–98	$C_6H_8ClN_3O_2$	1:1.5	8.5
13	CH_2CH_2Br	C, E[a]	65, 70	H_2O–EtOH (2:1)	100–101	$C_6H_8BrN_3O_2$	1:1	3.5
14	CH_2CH_2I	D	90	H_2O–EtOH (2:1)	121–122	$C_6H_8IN_3O_2$[h]	1:1.5	2.8
15	$CH_2COOC_2H_5$[b]	B, from 16[c]	63,[b] 92	H_2O	111–112	$C_8H_{11}N_3O_4$	1:1	65
16	CH_2COOH	B, G	25, 92	H_2O	247–248[e]	$C_6H_7N_3O_4$	1:1	25
17	CH_2CN	B, E[a]	28, 38	H_2O	125–126	$C_6H_6N_4O_2$	0	8.0
18	$CH_2CH_2OC_6H_5$	E[a]	60	EtOH	136–137	$C_{12}H_{13}N_3O_3$	1:1.2	30
19	$CH_2CH_2OCH_2CH_3$	B, E[a]	14, 70	H_2O	100–101	$C_8H_{13}N_3O_3$[i]	1:2	18
20	$CH_2CH_2OCH_2CH_2Cl$	B, E[a]	40, 65	H_2O–EtOH (1:2)	101–102	$C_8H_{12}ClN_3O_3$	1:1	7.5
21	$CH_2CH_2OCH_2CH_2I$	D	85	H_2O–EtOH (1:3)	67–68	$C_8H_{12}IN_3O_3$	1:1	3.5
22	$CH_2CH_2OCH_2CH_2OH$	F	68	H_2O	93–94	$C_8H_{13}N_3O_4$	1:1.6	23

[a] Alkylating agents: **12**, 1-bromo-2-chloroethane; **13**, 1,2-dibromoethane; **17**, α-chloroacetonitrile; **18**, β-bromophenetole; **19**, β-bromoethyl ethyl ether; **20**, β,β′-dichlorodiethyl ether. [b] Prepared by method B by Cosar, *et al.*[2] [c] Esterification of **16** in HCl-ethanol. [d] Where several values are indicated, these correspond to the methods mentioned. [e] Slow decomposition above 240°. [f] Minimum lethal concentration for II, 1:1 (g/ml × 10^{-3}); LD_{50} = 58 mg/kg × 10^{-2}. [g] C, H, N analyses; see Table I, footnote *g*. [h] *Anal.* C: calcd, 25.63; found, 26.13. [i] *Anal.* H: calcd, 6.58; found, 6.01.

δ values of 5-nitro isomers are about 0.45 ppm greater than those of the corresponding 4-nitro isomers,[12] because of the greater deshielding effect of the 5-nitro group as compared with that in position 4. The polarographic measurements served as the third analytical method for the differentiation of the isomeric compounds. It was found that half-wave potentials were dependent only upon the position of the nitro group.[13] Ir spectra of the isomeric compounds showed a characteristic difference for 4(5)-CH out-of-plane bending vibration. The difference between characteristic frequencies was about 11 cm^{-1}. The frequency of the C–H band of the 4-nitro isomers lies at 754–755 cm^{-1}, and of the 5-nitro isomers at 743–744 cm^{-1}.

Pharmacology. Methods.—Acute toxicities were determined in mice weighing 15–20 g. The viscous suspension containing 1 g of the substance in 5 ml of water was administered orally. All deaths occurring during the following 24 hr after administration of the drug were recorded for the estimation of LD_{50} values. *In vitro* trichomonacidal activity was determined by test-

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ing the inhibitory effect of the different concentrations of the compound against *Trichomonas vaginalis* in vaginal secretion. Compounds I and II served as the reference substances. I is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, a well-known antitrichomonal agent,[2,14] II is its 4-nitro isomer, the relative activity of which has been established.[5,6] Compounds I, II, and **1–22** were dissolved in saline in different concentrations and the minimum concentration which suppressed completely the growth of trichomonads at 24 and 37° was determined. The end points were ascertained by microscopic examination of the culture, death being indicated by the characteristic morphological change of the cells and complete cessation of motility. The assays were carried out in Löefler's nutrient medium at 24 and 37°.

Results (see Tables I and II).—Preliminary investigations confirmed the observation that the 5-nitro isomers regularly had higher activity than the corresponding 4-nitro isomers.[2] However, the difference in the activities of the isomeric compounds was found to be far greater in favor of 5-nitro isomers than noticed earlier.[3a,15,16] In addition, the exchange of the functional group in the side chain on N^1 led to a noteworthy alteration of the activity. This effect was particularly noticeable for the 5-nitro isomers. The compounds containing nitrile, ester, or ether groups (**4**, **6**, **7**, **9–11**) showed distinctly increased activity as compared with I.

Experimental Section[17]

Syntheses of the compounds in Tables I and II were carried out by procedures A–G, which are illustrated below.

Procedure A.—Compound III (6.3 g, 0.05 mole), 0.45 mole of alkylating agent, and the particular carboxylic acid (see Table I, footnote *c*) were heated at reflux temperature for 12–18 hr. Minimum reflux temperature should be about 120–125°; therefore, in the preparation of 1 nitrobenzene was added to the reaction mixture. After removing the liquid components *in vacuo*, the residue was dissolved in hot H_2O, filtered (charcoal), and cooled to precipitate unchanged III. The filtrate was basified, and the crude product which separated was collected and dried. Further recrystallizations were carried out in the solvents listed in Table I.

Procedure B.—A mixture of 6.3 g (0.05 mole) of III and 0.3–0.5 mole of alkylating agent (Table II, footnote *b*) was heated at reflux temperature for 12–20 hr. Excess reagent was evaporated *in vacuo* and the residue was recrystallized from hot H_2O (charcoal) giving the crude product. Specific separation of **16** from unreacted III consisted in dissolving the mixture obtained in a fivefold amount of cold H_2O and changing the pH from 3 to 7.3 to dissolve **16** in the form of its Na salt. Undissolved III was filtered, and the filtrate was acidified again to give crude **16**.

Procedure C.—Compound **9** (10.0 g, 0.0428 mole) and 145 g (100 ml, 1.78 moles) of 48% HBr were heated at reflux temperature for 14 hr. 1-Bromo-2-chloroethane formed by cleavage of **9** was continuously separated by drawing it off the bottom of the flask. The crude by-product was washed (H_2O), dried (Na_2SO_4), and redistilled to give 2.2 ml (3.72 g) of material, $n^{20}D$ 1.5250–1.5300. After the reaction was finished HBr was evaporated *in vacuo* and the residue recrystallized from 100 ml of hot H_2O (charcoal). The filtrate was basified to pH 10 and the precipitate was collected to furnish the crude product. Compound **13** was prepared by the same procedure from **20**.

Procedure D.—The substance to be iodinated and KI were slurried in a molar ratio of 2:1 with about the tenfold amount of methyl isobutyl ketone. The reaction mixture was stirred vigorously to prevent sedimentation of the inorganic salt, and heated at reflux temperature. To prepare **3** and **14** heating was carried out for 8 hr, and to prepare **10** and **21**, for 18 hr. When the reaction was finished, the solvent was evaporated *in vacuo*, inorganic salts and product were filtered and washed with cold H_2O, and the remaining crude product was recrystallized (see Tables I and II).

Procedure E.—Sodium ethoxide (2.77 g, 0.05 mole) in 50 ml of absolute EtOH and 6.3 g (0.05 mole) of III were heated to complete solution. The solution of the sodium salt of III thus obtained was cooled and 0.05 mole of the particular alkylating agent was added (see Table II, footnote *a*). The reaction mixture was refluxed for 24 hr and then evaporated to dryness. The residue was treated in one of the following ways. (a) To isolate **12**, **13**, and **20** the residue was slurried with $CHCl_3$, undissolved III and inorganic salts were altered, and the filtrate was concentrated to dryness. The crude products thus obtained were recrystallized according to the Table II. (b) Compound **17** was extracted from the residue with MeCN. (c) Compounds **18** and **19** were obtained recrystallizing the residue from H_2O.

Procedure F.—A solution of 0.05 mole of a substance which was to be hydrolyzed (**9** or **20**) in 35 ml (39.5 g) of formamide and 4.75 ml (5 g) of 46% formic acid was heated at 140–150° for 4 hr. When the reaction was finished formamide was evaporated at 80–90° (0.5 mm) and the residue recrystallized.

Procedure G.—Compounds **4** or **15** (4.2 g, 0.02 mole) were dissolved in 50 ml of 5% NaOH, shaken, and heated on a steam bath until a slightly red color appeared. Heating was discontinued, the solution was cooled immediately and acidified with concentrated HCl to pH 1, and the product was filtered and dried.

(14) Flagyl®, Clont®, Efloran®.

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(17) All melting points were determined using a Bötius Mikrobeiztisch apparatus and are corrected. Elemental microanalyses were carried out by microanalytical laboratory, Department of Organic Chemistry, Faculty of Pharmacy and Biology, University of Zagreb. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Resolution and Racemization of *dl*-Tetramisole, *dl*-6-Phenyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazole

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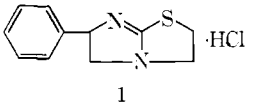
dl-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride (tetramisole) (**1**) has been found to be a broad-spectrum anthelmintic compound extremely effective for the treatment of helminthiases in domestic animals. Methods for the preparation of this *dl* compound and reports of useful biological activity have been published.[1]



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(1) (a) A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. V. Ottenwert, and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966); (b) D. C. I. Thienpont, O. F. J. Vanporijs, A. H. M. Raeymaekers, J. Vandenberk, P. J. A. Demoen, F. T. N. Allewijn, R. P. H. Marsboom, C. J. E. Niemegueers, K. H. L. Schellekens, and P. A. J. Janssen, *Nature*, **209**, 1084 (1966); (c) J. W. Pankhurst and D. O. Sutton, *Vet. Record*, **79**, 166 (1966); (d) J. S. Remders, *Neth. J. Vet. Sci.*, **91**, 967 (1966); (e) J. K. Walley, *Vet. Record*, **78**, 406 (1966); (f) L. D. Spicer, M. W. Bullock, M. Garber, W. Groth, J. J. Hand, D. W. Long, J. L. Sawyer, and R. S. Wayne, submitted for publication.

The *dl* compound was resolved with *d*-10-camphorsulfonic acid when chloroform was used as the solvent. The *d*-(+)-6-phenyl-1,2,3,5,6-tetrahydroimidazothiazole *d*-10-camphorsulfonate crystallized as a trisolvate in 90% yield. When the mother liquor containing the soluble *l*-amine salt was concentrated and treated with hot acetone, a racemic salt crystallized which contained the balance of the *d*-amine salt and left in solution essentially pure *l*-amine salt. The *l*-amine salt crystallized on cooling.

A novel procedure for effecting the resolution took advantage of the fact that in solvents other than chloroform the *dl* base crystallized with *d*-10-camphorsulfonic acid as a racemic compound which is less soluble than the resolved salts. When the *dl* base was added to a chloroform solution of either the *d*- or *l*-amine *d*-10-camphorsulfonates, *which need not be optically pure*, and toluene was added, racemic amine *d*-10-camphorsulfonate crystallizes leaving only optically pure amine in solution. The optimum amount of racemic amine to add is slightly less than equimolar to compensate for the cocrystallization of a small amount of the resolved salt with the racemic salt. This method yielded both the *d* and the *l* bases in high yield and in high optical purity, and simultaneously recovered the resolving acid as the racemic amine salt which can be recycled.

This general method can be employed to precipitate the *dl* component as the camphorsulfonate from an optically impure amine and leave only optically pure amine in solution from which it is easily precipitated as the hydrochloride.

dl-10-Camphorsulfonic acid can be resolved by the optically active amines. The general method of Corrodi and Hardegger[2] is applicable although not as convenient as using both forms of the amine which are now readily available.

We have found that the *d* and *l* forms of tetramisole are approximately equal in acute toxicity and that the activity toward those nematodes tested predominated in the levo isomer. Tables I and II illustrate these toxicity and activity relationships.

Raeymaekers and collaborators[3] have synthesized the isomers from optically active phenylethylenediamine and established that the levo form is sinistral. Racemization of the uninteresting dextrorotatory isomer would be important in converting it to a more anthelmintically active form. The asymmetric center of **1** is the benzylic carbon in position 6. The 6-hydrogen would appear to be the most acidic hydrogen in the molecule and formation of an anion at this position would be predicted to racemize the compound. Since tetramisole is hydrolyzed in basic solutions[1] the use of strong bases in solvents that have no ionizable hydrogen would be essential. The free base was found to be racemized when heated neat at 100° in the presence of potassium *t*-butoxide. The amine is racemized immediately when a solution in dimethyl sulfoxide is treated with the sodium salt of dimethyl sulfoxide. Racemizations with sodium methoxide in dimethyl sulfoxide, potassium *t*-butoxide in dimethylformamide, and *n*-butyllithium in benzene were less satisfactory as more by-products were formed.

TABLE I

BIOLOGICAL ACTIVITY OF *l*-(−), *d*-(+), AND *dl*-TETRAMISOLE AGAINST *Nematospiroides dubius* IN MICE

Oral dose, mg/kg	% efficacy		
	levo	dextro–levo	dextro
2	0	..	..
4	47	..	..
6	69	10	..
8	79	31	..
12	97	61	..
16	..	83	0
32	..	..	22
48	..	..	36

TABLE II

ACUTE ORAL TOXICITY OF *l*-(−), *d*-(+), AND *dl*-TETRAMISOLE IN MICE

Dose, mg/kg	Dead/total mice		
	levo	dextro–levo	dextro
100	0/10	1/10	1/10
150	16/30	8/30	8/10
200	16/20	15/20	8/10
300	9/10	10/10	9/10

(2) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **40**, 193 (1957).

Experimental Section

Melting points are corrected. The optical rotations were measured with a manually operated polarimeter in 2-dm tubes. Evaporations, unless otherwise specified, were done with a rotary evaporator.

DL-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole *d*-10-Camphorsulfonate.—A suspension of 227 g (0.938 mole) of *dl*-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride in 400 ml of water and 400 ml of CH_2Cl_2 was treated with a solution of 45 g (1.09 moles) of 97% NaOH in 200 ml of water and ice. The organic layer was separated and dried (K_2CO_3), filtered, and treated with 217.9 g (0.938 mole) of *d*-10-camphorsulfonic acid in portions which dissolved rapidly with the liberation of heat. Toluene (800 ml) was added, the CH_2Cl_2 was distilled, and the salt was recovered by filtration and washed with toluene and with hexane. The yield was 408 g (0.935 mole, 99%), mp 195–197°, $[\alpha]^{25}D$ +14.0° (*c* 11, H_2O).

Anal. Calcd for $C_{29}H_{38}N_2O_8S_2$: N, 6.42; S, 14.66. Found: N, 6.13; S, 14.36.

***d*-(+)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole *d*-10-Camphorsulfonate.**—A warm solution of 204.3 g (1 mole) of *dl*-1 (**1a**) and 232.3 g (1 mole) of *d*-10-camphorsulfonic acid in 1750 ml of $CHCl_3$ was allowed to crystallize overnight at −28°. The $CHCl_3$ solvate was recovered by filtration and washed with 400 ml of ice-cold $CHCl_3$. The solvate (somewhat hygroscopic) was dried several hours in dry N_2 and then in air overnight. The yield of nonsolvated material was 202.5 g (92.8%), mp 139–140°, $[\alpha]^{25}D$ +82.6° (*c* 16, H_2O). Material recrystallized from $CHCl_3$ had mp 140–141° and $[\alpha]^{25}D$ +83.0° (*c* 15, H_2O).

Anal. Calcd for $C_{29}H_{38}N_2O_8S_2$: N, 6.42; S, 14.66. Found: N, 6.23; S, 14.28.

The $CHCl_3$ solvate is unstable in air. The composition was estimated to be that of a trisolvate by nmr spectroscopy on freshly prepared samples.

***l*-(−)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole *d*-10-Camphorsulfonate.**—The mother liquor from the above preparation (containing *ca.* 10% of *d*) was evaporated to a syrup which was approximately one-half $CHCl_3$ by weight and treated with 1500 ml of hot Me_2CO. When maintained near the boiling point for about 10 min a solid crystallized. The crystals (*dl*-salt enriched with *l*-salt) were collected by filtration of the hot acetone mixture and washed with 200 ml of hot acetone. The optically impure salt weighed 24.2 g (0.055 mole), mp 186–192°, $[\alpha]^{25}D$ −14.7° (*c* 16, H_2O). It can be resolved by recrystallization ($CHCl_3$). Refrigeration of the acetone filtrate at −15° overnight

(3) A. H. M. Raeymaekers, L. F. C. Roevens, and R. A. J. Janssen, *Tetrahedron Letters*, 1467 (1967).