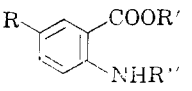
TABLE I
ANTHRANILATE ESTERS



No.	R	R′	R″	% yield	Bp (mm), °C	Formula[a]
I	H	$CH(CH_3)_2$	H	48	152–153 (16)	$C_{10}H_{13}NO_2$
II[b]	H	n-C_4H_9	H	66	173–175 (16)	$C_{11}H_{15}NO_2$
III[b]	H	$CH_2CH(CH_3)_2$	H	78	165–167 (16)	$C_{11}H_{15}NO_2$
IV	H	n-C_6H_{13}	H	64	194–195 (16)	$C_{13}H_{19}NO_2$
V	H	n-C_7H_{15}	H	74	203–204 (16)	$C_{14}H_{21}NO_2$
VI	H	n-$C_{10}H_{21}$	H	58	135–136 (16)	$C_{17}H_{27}NO_2$
VII	Cl	n-C_4H_7	H	63	195–196 (16)	$C_{11}H_{14}ClNO_2$
VIII	Cl	n-C_7H_{15}	H	78	234–235 (20)	$C_{14}H_{20}ClNO_2$
IX	Cl	$CH(CH_3)_2$	CH_3	55	Mp 69–70	$C_{11}H_{14}ClNO_2$

[a] Prepared as the HCl salt and the free base by ester interchange of methyl anthranilate: H. C. Brill, *J. Am. Chem. Soc.*, **43**, 1322 (1921). Brill reported bp 182° which could not be confirmed. [b] Also reported by J. Bredt and H. Hof, *Ber.*, **33**, 29 (1900), who reported bp 156–157° (13.5 mm). [c] All compounds were analyzed for N. Analytical data were within 0.25% of theoretical values.

anthranilates are essentially quantitative (with the exception of the isopropyl esters which experience a competitive formation of isopropyl N-*o*-carboxyphenylcarbamate),[6] the yields expressed in Table I are based on analytically pure material. All esters were purified by distillation except IX which was recrystallized from cyclohexane.

Biological Results.[7]—The anthranilates were screened at a concentration of 250 ppm mixed in melted Difco brain–heart infusion agar in which the test organisms were later cultured. The results are reported in Table II employing a visual rating of amount of colonial growth: 1 = no inhibition, 5 = complete inhibition. It is interesting that none of the esters inhibited *Escherichia coli* growth although anthranilic acid itself is active in this regard.[1,2] The three lower alkyl esters of anthranilic acid, *i.e.*, I, II, and III, showed a slight inhibition of *Aspergillus niger*, but the parent anthranilic acid is more active.[3] Secondary screening at reduced concentration levels, 60 and 15 ppm, demonstrated the esters to be of minimum effectiveness and of no commercial interest.

TABLE II
TESTING RESULTS[a]

Compd	*Staphylococcus aureus*	*E. coli*	*Erwinia amylovora*	*Xanthomonas malvacearum*	*A. niger*
I	1	1	3	3	3
II	3	1	5	5	3
III	5	1	5	5	3
IV	1	1	5	1	1
V	1	1	1	1	1
VI	1	1	1	1	1
VII	5	1	1	1	1
VIII	1	1	1	1	1
IX	1	1	1	1	1

[a] See text for an explanation of data.

Experimental Section[8]

General Procedure.—For the formation of isopropyl and *n*-butyl esters the corresponding alcohols were employed as solvent and reactant. To 50–60 ml of the alcohol[9] in which a chip of freshly cut Na, approximately 0.1 g, had been dissolved, 0.02 mole of the required isatoic anhydride was added and the suspension was stirred at reflux. When the evolution of CO_2 had ceased and a clear solution resulted, the reaction medium was heated for another 0.5 hr and treated cautiously with 2–3 ml of 6 *N* HCl. The contents were filtered through $MgSO_4$, concentrated *in vacuo*, and distilled.

Esters of other alcohols were prepared by reaction of a 1:1 ratio of the alcohol, in which a chip of Na had been dissolved, and the isatoic anhydride in anhydrous dioxane. Typically, 0.02 mole of alcohol containing alkoxide, 0.02 mole of anhydride, and 35–50 ml of dioxane would be employed. The former procedure was utilized for isolation of product. All ir spectra were as expected.

(9) Because considerable foaming (CO_2) results on decomposition of isatoic anhydrides, it is desirable to employ a larger than normal reaction vessel.

(7) We are grateful to the Union Carbide Corp., Agricultural Research Station, Clayton, N. C., for providing the testing data.

(8) Combustion analyses were performed by V. B. F. in these laboratories. Infrared spectra were obtained neat on a Perkin-Elmer 257 spectrophotometer. Isatoic anhydride, 5-chloroisatoic anhydride, and N-methyl-5-chloroisatoic anhydride were provided as generous samples by Mannee Chemical Co., Toledo, Ohio.

The Preparation and Histomonastatic Activity of Some Haloethylimidazoles

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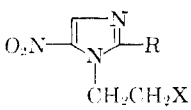
In a study of the synthesis and biological activity of nitroimidazoles we were led to investigate the haloethylimidazoles (I–III). These compounds were of interest because of the reported activity of the corresponding hydroxyethyl derivatives (Ia, IIIa[1]) against certain protozoans.[2–4] During the late stages of this investigation a report appeared which described the *in vitro* activity of I and II against *Trichomonas vagin-*



I, R = H; X = Cl
Ia, R = H; X = OH
II, R = CH_3; X = Cl
III, R = CH_3; X = Br
IIIa, R = CH_3; X = OH

(1) Flagyl®.

(2) M. Bock, *Arzneimittel-Forsch.*, **11**, 587 (1961).

(3) R. Mandoul, R. Dargelos, and J. Millan, *Bull. Soc. Pathol. Exotique*, **54**, 12 (1961).

(4) D. Boff and J. Bennett, U. S. Patent 3,107,201 (Oct 15, 1963).

TABLE I: ACTIVITY AGAINST *Histomonas meleagridis*

Compd	Concn in feed, %	No. of expts	Total no. of turkeys	Efficacy: % without[a] blackhead	Efficacy: % survival
I	0.015–0.05[b]	9	31	100	100
I	0.0125	1	5	80	100
I	0.0075	4	15	13	27
I	0.005	3	11	0	27
II	0.05	4	10	100	100
II	0.03	3	10	80	80
II	0.025	1	5	60	80
II	0.015	3	10	0	40
II	0.0038–0.0125	8	33	0	0
1,2-Dimethyl-5-nitroimidazole	0.0125–0.025	5	18	100	100
	0.0075	2	9	44	56
Infected controls	...	9	25	All died of blackhead	
Uninfected controls	...	9	25	No blackhead infections	

[a] Total absence of cecal or liver lesions at postmortem examination. [b] At 0.05% the birds demonstrated slight neurological disturbances as evidenced by movements characteristic of intoxication.

alis.[5] Because certain compounds have shown activity against both *Trichomonas* sp. and *Histomonas meleagridis*, the causative organism of blackhead (histomoniasis) in poultry, the investigation of I and II for histomonastatic activity *in vivo* was particularly significant.[6,7]

The synthesis of I–III was accomplished by treating 4(5)-nitroimidazole or 2-methyl-4(5)-nitroimidazole with ethylene oxide to form the hydroxyethylimidazoles (Ia, IIIa). Subsequent treatment of Ia or IIIa with thionyl chloride or thionyl bromide gave the desired haloethylimidazole.

The efficacies of I–III were determined against the protozoan *H. meleagridis* in Broad Breasted Bronze or Broad Breasted White turkeys. Poults which were reared in wire-bottom cages were orally inoculated with approximately 1000 embryonated cecal worm (*Heterakis gallinarum*) ova per bird at approximately 6 weeks of age. Prior experimentation had confirmed the presence of *Histomonas* organisms in these ova.

All tests were 28 days in duration. Turkeys were infected on the first day of the test. Medicated feed was given the first 21 days and nonmedicated the final 7 days of each experiment.

Results shown in Table I demonstrate that I has greater histomonastatic activity at lower concentrations than II. This is in accordance with the efficacy reported for the corresponding hydroxyethyl compounds Ia and IIIa against blackhead.[4] In contrast, I and Ia are reported to be less effective than II and IIIa against *Trichomonas*.[5]

The corresponding bromoethyl derivative (III)[8] at a concentration of 0.05% provided 100% blackhead preventive efficacy in two experiments. It was only little effective at 0.025%, and no efficacy was provided at concentrations of 0.015 and 0.005%. All concentrations were palatable and nontoxic to the poults.

A comparison of the efficacy of I–III with that of 1,2-dimethyl-5-nitroimidazole,[9] a well-known antiblackhead product, shows that I compared favorably with the standard drug while II and III did not.

(5) C. Cosar, C. Crisan, R. Horlois, R. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupre, *Arzneimittel-Forsch.*, **16**, 23 (1966).
(6) R. M. Stabler and R. W. Mellentin, *J. Parasitol.*, **39**, 637 (1953).
(7) D. K. McLoughlin, *Avian Diseases*, **10**, 288 (1966).
(8) G. Karmas, U. S. Patent 3,244,726 (April 5, 1966).
(9) Emtryl®, Emtrymix®.

Experimental Section[10]

1-(2-Chloroethyl)-5-nitroimidazole (I).—Ethylene oxide (100 g, 2.27 moles) was slowly added over a period of 6 hr to 98 g (0.29 mole) of 4(5)-nitroimidazole[11] in 850 ml of 88% formic acid at 35°. The mixture was then filtered to give a yellow filtrate and a white residue of unreacted 4(5)-nitroimidazole. The formic acid was distilled from the filtrate under vacuum, 50 ml of H_2O was added to the residue, and the mixture was made basic with 50% NaOH. The basic solution was then extracted (EtOAc). The EtOAc extracts were dried (Na_2SO_4) and concentrated to an oily residue under vacuum. The oil was dissolved in anhydrous $CHCl_3$ and heated at reflux for 4 hr with $SOCl_2$. The mixture was then distilled under vacuum to give a solid residue which was dissolved in H_2O and made basic with NaOH while chilling in an ice bath. The crude product precipitated, was collected, and dried to give 21.5 g (42%) of yellow solid, mp 49–51°. Recrystallization ($CHCl_3$) gave a pale yellow solid with mp 49–51°, lit.[5] mp 51°.

Anal. Calcd for $C_5H_6ClN_3O_2$: C, 34.20; H, 3.45; N, 23.93; Cl, 20.20. Found: C, 34.10; H, 3.79; N, 23.98; Cl, 20.03.

1-(2-Chloroethyl)-2-methyl-5-nitroimidazole (III).—1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole[12] (20 g, 0.117 mole) was added to 100 ml of $SOCl_2$ and the resulting mixture was heated at reflux for 3.5 hr. The reaction mixture was then treated as described for I to give 17 g (76.6%) of cream-colored solid with mp 77–79°. Recrystallization from Et_2O gave a white solid, mp 78–80°, lit.[5] mp 78°.

Anal. Calcd for $C_6H_8ClN_3O_2$: C, 38.01; H, 4.26; N, 22.16; Cl, 18.70. Found: C, 38.29; H, 4.43; N, 21.91; Cl, 18.98.

Acknowledgment.—The authors are indebted to Mr. Marvin Carr for assistance with some of the experiments.

(10) Melting points were determined in open glass capillaries with a Mel-Temp heated block and are corrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(11) R. G. Fragher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).
(12) From extraction of Flagyl® tablets with CH_2Cl_2 or by hydroxyethylation of 2-methyl-4(5)-nitroimidazole; mp 158–160°.

Synthesis of *cis*-9-Tetradecen-1-ol Acetate, the Sex Pheromone of the Fall Armyworm

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During the course of an investigation of potential insect sex attractants,[1] the four possible geometric iso-

(1) D. Warthen and M. Jacobson, *J. Med. Chem.*, **10**, 1190 (1967).