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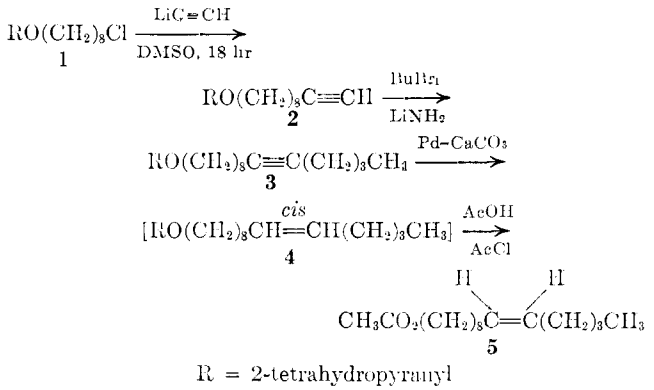
During the course of an investigation of potential insect sex attractants,[1] the four possible geometric iso-

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

mers of 5,9-tridecadien-1-ol acetate were synthesized. The *cis*-5,*cis*-9 and *trans*-5,*cis*-9 isomers elicited sexual excitement in male fall armyworm moths, *Spodoptera frugiperda* (J. E. Smith), in laboratory tests, but the *cis*-5,*trans*-9 and *trans*-5,*trans*-9 isomers did not. Therefore, it was hypothesized that, for activity, the *cis* configuration in the 9 position was essential, whereas the configuration in the 5 position was not. A number of examples supporting such a hypothesis for an effective structure–attractancy relationship are given in the literature.[2] Since acids and acetates with an odd number of carbon atoms rarely occur in nature,[3–6] the active isomers of tridecadien-1-ol acetate appeared to be analogs of the natural sex pheromone of the fall armyworm moth.[7] It was, therefore, decided to prepare the even-numbered fourteen-carbon acetate having a *cis* configuration at the C-9 double bond and saturation at the C-5 position.

The method used to prepare *cis*-9-tetradecen-1-ol acetate is shown in Chart I. The tetrahydropyranyl

CHART I



ether (**1**) of 8-chloro-1-octanol was allowed to react with lithium acetylide. The resultant tetrahydropyranyl ether of 9-decyn-1-ol (**2**) was alkylated with butyl bromide. Reduction of the tetrahydropyranyl ether of 9-tetradecyn-1-ol (**3**) by hydrogenation over poisoned Pd–$CaCO_3$ yielded almost exclusively the *cis* intermediate,[8] tetrahydro-2-(*cis*-9-tetradecenyloxy)pyran (**4**). Subsequent refluxing with acetic acid–acetyl chloride cleaved the tetrahydropyran group to form the desired *cis*-9-tetradecen-1-ol acetate (**5**).

Shortly before the synthesis of this compound was completed, Sekul and Sparks[9] identified the natural sex pheromone of the female fall armyworm moth as *cis*-9-tetradecen-1-ol acetate. These investigators also succeeded in synthesizing a very small amount of this compound by reducing the extremely rare methyl myristoleate with lithium aluminum hydride and acetylating the resulting *cis*-9-tetradecen-1-ol. The synthetic procedure described here therefore represents a considerable improvement in cost of the attractant over that of Sekul and Sparks.[9]

Experimental Section[10]

2-[(8-Chlorooctyl)oxy]tetrahydropyran (1).—Dihydropyran (21.0 g, 0.25 mole) was added to 33.9 g (0.21 mole) of 8-chloro-1-octanol and 4 drops of concentrated HCl, with stirring. The solution was cooled to below 40° and then stirred at room temperature for 3 hr. Excess Na_2CO_3 was added to the solution, and stirring was continued for an additional 1 hr. After filtration, the filtrate was distilled to yield, after a small forerun, 47.2 g (91%) of colorless liquid: bp 85–90° (0.03 mm); $n^{23}D$ 1.4612; ir, 2930 (broad CH) and 1200–1040 cm^{-1} (tetrahydropyranyl); gas chromatography, single sharp peak, retention time 132 sec at 180° and 30 cc of N_2/min.

Anal. Calcd for $C_{13}H_{25}ClO_2$: C, 62.76; H, 10.13; Cl, 14.25. Found: C, 62.90; H, 10.28; Cl, 14.45.

2-(9-Decynyloxy)tetrahydropyran (2).—To 5.0 g (0.055 mole) of lithium acetylide stabilized with ethylenediamine in 25 ml of freshly distilled DMSO (dried over CaH_2) was added, at ice-bath temperature, 11.0 g (0.044 mole) of **1** in 25 ml of DMSO under N_2. The reaction mixture was stirred for 0.5 hr at ice-bath temperature and then 18 hr at room temperature (below 30°). The mixture was chilled, and H_2O (100 ml) was added with stirring. The aqueous phase was extracted four times with ether; the combined ether layers were washed twice with NaCl solution, dried (Na_2SO_4), and distilled to give, after a small forerun, 7.3 g (69%) of colorless liquid: bp 88–91° (0.05 mm); $n^{26}D$ 1.4590; ir, 3300 cm^{-1} (terminal C≡C); gas chromatography, single sharp peak, retention time 234 sec at 155° and 30 cc of N_2/min.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.81; H, 11.24.

Tetrahydro-2-(9-tetradecynyloxy)pyran (3).—Compound **2** (7.3 g, 0.031 mole) was added with stirring to a mixture of 1.0 g (0.043 mole) of $LiNH_2$ and 50 ml of dry purified dioxane under N_2. The reaction mixture was refluxed for 3.5 hr and cooled, and 4.5 g (0.033 mole) of BuBr was added dropwise. Refluxing was continued for 17 hr; then H_2O (57 ml) was added to the mixture. The solution was extracted three times with ether, and the ether extracts were washed (NaCl solution). The combined ether extracts were dried (Na_2SO_4) and distilled to give, after a small forerun, 3.3 g of **2**, bp 85–92° (0.05 mm), and 3.2 g (36%) of a colorless liquid, bp 120–127° (0.03 mm), $n^{26}D$ 1.4630. The ir spectrum of the product showed no absorption at 3300 cm^{-1} (terminal C≡C); gas chromatographic analyses, single sharp peaks with retention times of 210 and 841 sec at 190 and 180° with flow rates of 25 and 20 cc of N_2/min, respectively.

Anal. Calcd for $C_{25}H_{34}O_2$: C, 77.49; H, 11.64. Found: C, 77.30; H, 11.55.

***cis*-9-Tetradecen-1-ol Acetate (4).**—A solution of 3.0 g (0.010 mole) of **3** in 20 ml of absolute EtOH was hydrogenated at room temperature, by using 0.10 g of 5% Pd–$CaCO_3$ and 1 drop of quinoline. When the required amount of H_2 for one double bond had been absorbed (247 ml at 27° and 760 mm), the reaction was interrupted. The mixture was filtered, and freed of solvent. Gas chromatographic analysis showed a single sharp peak, retention time 552 sec at 180° and 20 cc of N_2/min.

A solution of the reduced product, 12 ml of AcOH, and 3 ml (0.042 mole) of AcCl was refluxed for 7 hr and then allowed to stand overnight. The solution was poured onto ice, diluted to about 100 ml with saturated NaCl, and extracted three times with ether. The combined ether layers were washed (three times with water and three times with 5% Na_2CO_3 and twice with NaCl solution) and the ether extract was dried (Na_2SO_4) and distilled to yield 1.8 g (71%) of colorless liquid, bp 89–95° (0.06 mm), $n^{25}D$ 1.4450. The ir spectrum showed absorption at 2925 (CH), 1740 and 1230 (primary acetate) and 720 cm^{-1} (*cis*-CH=CH). A small peak at 965 cm^{-1} represented *trans*

(2) M. Jacobson, "Insect Sex Attractants," Interscience Publishers, Inc., New York, N. Y., 1965, pp 92–101.

(3) G. Doby, "Plant Biochemistry," Interscience Publishers, Inc., New York, N. Y., 1965, p 286.

(4) I. Wolff, *Science*, **154**, 1140 (1966).

(5) R. Berger, *Ann. Entomol. Soc. Am.*, **59**, 767 (1966).

(6) W. A. Jones, M. Jacobson, and D. F. Martin, *Science*, **152**, 1516 (1966).

(7) A. A. Sekul and H. C. Cox, *Bull. Entomol. Soc. Am.*, **10**, 167 (1964); *Bioscience*, **15**, 670 (1965).

(8) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, p 71.

(9) A. A. Sekul and A. N. Sparks, *J. Econ. Entomol.*, **60**, 1270 (1967).

(10) Boiling points are uncorrected. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer 521 spectrophotometer. Gas chromatographic analyses were performed on an Aerograph Model 204-1B gas chromatograph with a flame ionization detector by using a column of 5% Carbowax 20M on 60–80 mesh base-washed Chromosorb W (152.4 × 0.03 cm) and nitrogen as the carrier gas. Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.

double bond impurity. Gas chromatography revealed a single sharp peak, retention time 282 sec at 170° and 30 cc of N_2/min.

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.37; H, 12.02.

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Insect Sex Attractants. X. 5-Dodecen-1-ol Acetates, Analogs of the Cabbage Looper Sex Attractant[1]

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In a continuing investigation of sex attractants for the control of insect pests,[2] the *cis* and *trans* isomers of 5-dodecen-1-ol acetate were synthesized. These compounds are analogs of *cis*-7-dodecen-1-ol acetate, the sex attractant produced by the female cabbage looper, *Trichoplusia ni* (Hübner), and synthesized by Berger and Green, *et al.*[3,4]

The method used to prepare the 5-dodecen-1-ol acetates is shown in Chart I. The tetrahydropyranyl

CHART I

$$\underset{\mathbf{1}}{RO(CH_2)_4C{\equiv}CH} \xrightarrow[\text{dioxane}]{C_6H_{13}Br,\ LiNH_2} \underset{\mathbf{2}}{RO(CH_2)_4C{\equiv}C(CH_2)_5CH_3} \xrightarrow[H_2,\ Pd\text{-}CaCO_3]{Na\text{–}NH_3\ or} RO(CH_2)_4CH{=}CH(CH_2)_5CH_3 \xrightarrow{AcOH\text{–}AcCl}$$

3a, *cis*-5
b, *trans*-5

$$CH_3CO_2(CH_2)_4CH{=}CH(CH_2)_5CH_3$$

4a, *cis*-5
b, *trans*-5

R = 2-tetrahydropyranyl

ether of 5-hexyn-1-ol was alkylated with hexyl bromide. Reduction of **2** in sodium–liquid ammonia or in the presence of poisoned Pd–$CaCO_3$ yielded almost exclusively the *trans* or *cis* isomer,[5-7] respectively, of the tetrahydropyranyl ethers of 5-dodecen-1-ol (**3**). Subsequent refluxing with acetic acid–acetyl chloride cleaved the tetrahydropyranyl group to form the desired 5-dodecen-1-ol acetates (**4**).

The acetates **4a** and **4b** were evaluated as attractants for male and female Mexican fruit flies, *Anastrepha ludens* (Loew); Mediterranean fruit flies, *Ceratitis capitata* (Wiedemann); oriental fruit flies, *Dacus dorsalis* (Hendel); melon flies, *Dacus cucurbitae* (Coquillet); male fall armyworm, *Spodoptera frugiperda* (J. E. Smith); codling moths, *Carpocapsa pomonella* L.; gypsy moths, *Porthetria dispar* L.; cabbage loopers and pink bollworm moths, *Pectinophora gossypiella* (Saunders). The *cis* and *trans* isomers of 5-dodecen-1-ol acetate were found in laboratory tests to be less attractive to cabbage loopers than *cis*-7-dodecen-1-ol acetate. All other test results were negative.

Experimental Section[8,9]

2-(5-Hexynyloxy)tetrahydropyran (1).—Dihydropyran (25.2 g, 0.30 mole) was added to 24.5 g (0.25 mole) of 5-hexyn-1-ol and 5 drops of concentrated HCl, with stirring. The solution was cooled to keep the temperature below 40° and then stirred at room temperature for 3 hr. Excess $NaHCO_3$ was added to the solution, and stirring was continued for an additional 1 hr. After filtration, the filtrate was distilled to yield, after a small forerun, 42.6 g (93%) of colorless liquid, bp 52–57° (0.03 mm), $n^{25}D$ 1.4579 (lit.[10] bp 70–80° (0.3 mm), $n^{25}D$ 1.4556).

2-(5-Dodecynyloxy)tetrahydropyran (2).—Compound 1 (40.0 g, 0.22 mole) was added with stirring to a mixture of 5.1 g (0.22 mole) of $LiNH_2$ and 250 ml of dry dioxane (purified by refluxing over Na and then distilling) under N_2. The reaction mixture was refluxed for 3.5 hr and cooled, and 36.3 g (0.22 mole) of hexyl bromide was added dropwise. Refluxing was continued for 17 hr; then H_2O (250 ml) was added to the mixture. The solution was extracted three times with ether, and the ether extracts were washed (NaCl solution). The combined ether extracts were dried (Na_2SO_4) and distilled to give, after a small forerun, 27.2 g (47%) of colorless liquid: bp 105–108° (0.06 mm); $n^{24}D$ 1.4630; ir, 2930 (broad CH) and 1200–1040 cm^{-1} (tetrahydropyranyl); gas chromatography, single sharp peak, retention time 336 sec at 150° and 40 cc of N_2/min.

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.50; H, 11.41.

2-(*cis*-5-Dodecenyloxy)tetrahydropyran (3a).—A solution of 10.0 g (0.038 mole) of **2** in 40 ml of absolute EtOH was hydrogenated at room temperature, by using 300 mg of 5% Pd–$CaCO_3$ and 2 drops of quinoline. When the required amount of H_2 for one double bond had been absorbed (920 ml at 26° and 760 mm), the reaction was interrupted. The mixture was filtered, freed of solvent, and distilled to yield 8.8 g (87%) of colorless liquid, bp 96–99° (0.04 mm), $n^{25}D$ 1.4578. The ir spectrum showed absorption at 720 cm^{-1} (*cis* CH=CH) and a very weak bond at 965 cm^{-1} representing *trans* double bond impurity. Gas chromatography showed a single sharp peak, retention time 102 sec at 150° and 40 cc of N_2/min.

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.86; H, 12.04.

2-(*trans*-5-Dodecenyloxy)tetrahydropyran (3b).—To a mixture of 4.0 g (0.18 g-atom) of Na in about 400 ml of liquid NH_3 was added dropwise, with stirring, 10.0 g (0.038 mole) of **2** at −76°. Ether (20 ml) was added, and the NH_3 was allowed to reflux for 5 hr. The reaction mixture was again cooled to −76°, and excess NH_4Cl and 40 ml of ether were added. After the mixture stood overnight, 100 ml of ether and H_2O (50 ml) were added under N_2. The aqueous phase was extracted twice with ether; the combined ether layers were washed (cold H_2O, cold 5% HCl, 5% Na_2CO_3, and NaCl solution). The ether solution was dried (Na_2SO_4) and distilled to give 9.2 g (91%) of colorless liquid, bp 94–96° (0.03 mm), $n^{25}D$ 1.4569, ir absorption at 965 (*trans* CH=CH) and a very weak bond at 720 cm^{-1} representing *cis* double bond impurity. Gas chromatographic analyses showed single sharp peaks, retention times 114 and 108 sec at 150° and 40 and 55 cc of N_2/min, respectively.

(1) Part IX: M. Jacobson and C. Harding, *J. Econ. Entomol.*, in press.
(2) M. Jacobson and M. Beroza, *Science*, **140**, 1367 (1963); *Sci. Am.*, **211** (2), 20 (1964).
(3) R. S. Berger, *Ann. Entomol. Soc. Am.*, **59**, 767 (1966).
(4) N. Green, M. Jacobson, T. J. Henneberry, and A. N. Kishaba, *J. Med. Chem.*, **10**, 533 (1967).
(5) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 71.
(6) K. N. Campbell and L. T. Eby, *J. Am. Chem. Soc.*, **63**, 216 (1941).
(7) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, p 71.
(8) Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer 521 spectrophotometer. Gas chromatographic analyses were performed on a Varian Aerograph Autoprep 700 gas chromatograph with a thermal conductivity detector by using a column of 5% Carbowax 20M on 60–80 mesh base-washed Chromosorb W (60.9 × 0.03 cm) and helium as the carrier gas.
(9) Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.
(10) W. A. Jones, M. Jacobson, and D. F. Martin, *Science*, **152**, 1516 (1966).