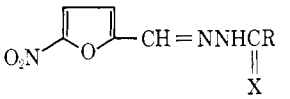
TABLE VI
5-NITRO-2-FURALDEHYDE THIOSEMICARBAZONES AND SEMICARBAZONES



No.	X	R	Method	Yield, %	Solvent of crystn[a]	Mp, °C	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1	S	$N(CH_3)_2$	G	87	A	165	$C_8H_{10}N_4O_3S$	39.67	4.16	23.14	13.24	39.72	4.47	23.09	13.00
2	S	$N(C_2H_5)_2$	G	85	E	145	$C_{10}H_{14}N_4O_3S$	44.44	5.22	20.73		44.39	4.98	20.50	
3	S	$N(C_3H_7)_2$	G	90	E	138	$C_{12}H_{18}N_4O_3S$	48.31	6.08	18.78	10.75	48.05	6.17	19.07	10.79
4	S		G	76	E	198–199	$C_{10}H_{12}N_4O_3S$	44.78	4.51	20.89	11.93	44.51	4.80	21.08	11.56
5	S		G	65	E	150	$C_{11}H_{14}N_4O_3S$	46.81	5.00	19.85	11.33	46.57	5.22	20.00	10.90
6	S		G	91	E	152	$C_{10}H_{12}N_4O_4S$	42.25	4.26	19.71	11.26	42.39	4.40	19.88	11.23
7	S		G[b]	76	I	162–163	$C_{11}H_{16}N_6O_3S$	44.44	5.09	23.56	10.76	44.47	5.29	23.47	10.78
8	O		H	95	E	226–227	$C_{10}H_{12}N_4O_4$	47.24	5.55	22.04		47.33	5.37	21.98	
9	O		H	100	E	177–178	$C_{11}H_{14}N_4O_4$	49.62	5.30	21.04		49.92	5.37	21.07	
10	O		H	80	A	205–206	$C_{10}H_{12}N_4O_5$	44.71	4.51	20.89		44.68	4.71	20.62	
11	O		H[c]	60	A	188	$C_{11}H_{16}N_6O_4$	46.97	5.38	24.90		47.13	5.48	25.05	

[a] A = ethyl acetate, E = ethanol, I = 2-propanol. [b] The reaction was carried out in anhydrous ethanol. [c] The reaction mixture was evaporated to dryness *in vacuo* and the residue was crystallized from ethyl acetate by removing the inorganic salt.

muscle of the opposite leg. The legs were measured at the point of maximal swelling by means of a caliper. The mean of the differences of the leg diameters was plotted daily. Mice were treated by daily oral intubation with the doses indicated in the table.

(d) **Urinary Elimination of the Drug.**—Urinary levels were determined in rats or in mice as follows. The urine of each mouse was collected with a 5-mm filter paper disk at 30, 60, 90, 120, 180, 240, and 300 min after single oral dose of 0.5 mmole of the drugs. The relative drug concentration was estimated evaluating the inhibition zones of the paper disks on agar plates inoculated with *B. subtilis*. For quantitative determinations, urine samples were assayed for drug concentrations by the method of the U. S. Pharmacopeia, Vol. XVII for antibiotics (cylinder cup method). Each drug was used as its own standard.

(e) **Antitrypanosomal Activity.**—The tests were performed with 22–24 g mice, infected with *T. brucei* or *congolense* by the method of Hawking.[8] Groups of five mice were treated by a single subcutaneous dose of $0.5DL_{50}$. When the trypanosomes disappeared from the blood permanently (more than 30 days), the animals were classified as "cured"; when the trypanosomes disappeared and then reappeared within the period of observation, the animals were classified as "suppressed."

(8) F. Hawking, *Exptl. Chemotherapy*, **1**, 137 (1963).

Insect Sex Attractants. VI. 7-Dodecen-1-ol Acetates and Congeners[1]

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cis- and *trans*-7-dodecen-1-ol acetates and several congeners were synthesized. Prior work demonstrating the *cis* isomer to be very attractive to male cabbage looper moths, *Trichoplusia ni* (Hübner), was confirmed. The other compounds were inactive.

The activity of certain insect attractants has been shown to depend on their stereochemical configuration. For example, the attractancy of *sec*-butyl *trans*-6-methyl-3-cyclohexene-1-carboxylate for the Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann), is greatly superior to that of the *cis* isomer,[2,3] and the four *trans* isomers of trimedlure run the gamut from inactive to highly potent.[4]

When the sex attractant of the cabbage looper, *Trichoplusia ni* (Hübner), was revealed by Berger to be *cis*-7-dodecen-1-ol acetate,[5] we decided to prepare this compound to evaluate its attractancy. The synthesis of several analogs was undertaken in order to explore their attractancy–structure relationships.[6]

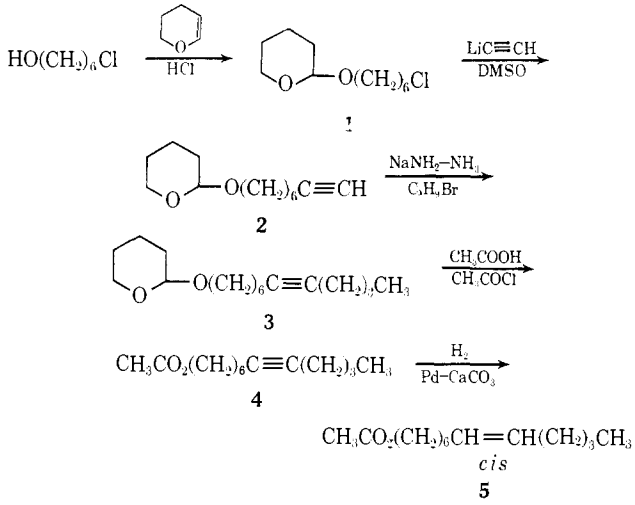
To prepare *cis*-7-dodecen-1-ol acetate, Berger first coupled 1-hexyne with 1-chloro-5-iodopentane in liquid

(1) Part V: W. A. Jones and M. Jacobson, *J. Med. Chem.*, **7**, 373 (1964).
(2) N. Green and M. Beroza, *J. Org. Chem.*, **24**, 761 (1959).
(3) L. F. Steiner, W. C. Mitchell, N. Green, and M. Beroza, *J. Econ. Entomol.*, **51**, 921 (1958).
(4) T. P. McGovern and M. Beroza, *J. Org. Chem.*, **31**, 1472 (1966).
(5) R. S. Berger, *Ann. Entomol. Soc. Am.*, **59**, 767 (1966).
(6) M. Jacobson, "Insect Sex Attractants," Interscience Publishers, Inc., New York, N. Y., 1965, pp 92–101.

NH_3. Reaction of the resulting 1-chloro-6-undecyne with NaCN formed the nitrile, which was then hydrolyzed to 7-dodecynoic acid. This acid was next partially hydrogenated and reduced ($LiAlH_4$) to the alcohol, which was esterified to the acetate.

Our method of preparing *cis*-7-dodecen-1-ol acetate, shown in Chart I, is somewhat more direct. The

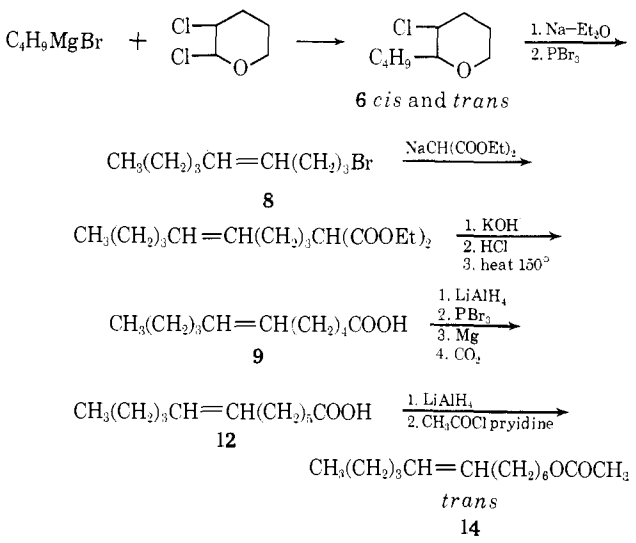
CHART I



hydroxyl group of 6-chloro-1-hexanol was protected by conversion to the tetrahydropyranyl ether **1**, which was then treated with lithium acetylide–ethylenediamine *complex in dimethyl sulfoxide (DMSO) to form* 2-(7-octynyloxy)tetrahydropyran (**2**). Alkylation of **2** with butyl bromide in liquid ammonia, followed by prolonged refluxing with acetic acid–acetyl chloride, simultaneously cleaved off the tetrahydropyran group and formed the desired 7-dodecyn-1-ol acetate **4**. Partial hydrogenation with quinoline-poisoned palladium catalyst converted the triple bond to a *cis* double bond to give **5**.

We wished to prepare the *trans* isomer by a completely different method so that the product would be entirely free of *cis* isomer. The scheme used (Chart II) was based on the finding of Crombie and Harper[7] that ring scission of 2-alkyl-3-chlorotetrahydropyrans produced only the *trans* form of 4-alken-1-ols. Reaction of butylmagnesium bromide with 2,3-dichlorotetrahydropyran[8] gave the *cis* and *trans* isomers of 4-butyl-3-chlorotetrahydropyran (**6**). Ring cleavage of both isomers with granulated sodium yielded the same product, *trans*-4-nonen-1-ol (**7**). The chain was extended by two methylene groups by using diethyl malonate, and an additional methylene group was added by carbonylation of the Grignard reagent prepared from **11**. $LiAlH_4$ reduction of the acid **12** yielded *trans*-7-dodecen-1-ol, which was then esterified by reaction with acetyl chloride and pyridine.

CHART II



The 7-dodecenol acetates were colorless liquids with mild, fruity odors, that of the *trans* isomer being reminiscent of fresh cucumbers. Their infrared spectra were very similar to that of Berger's *cis*-7-dodecenol acetate except that the *trans* isomer exhibited a strong characteristic band at 965 cm^{-1}. A weak band at the same frequency in the spectrum of the *cis* isomer indicated the presence of a small amount of *trans* isomer; Berger's product showed a similar *trans* band.

The *cis*- and *trans*-7-dodecenol acetates could not be separated by gas chromatography on columns of 10% DEGS, 5% SE-30, or 20 M Carbowax,[9] but preliminary tests indicated that the isomers were separable by thin layer chromatography on silica gel containing 25% silver nitrate by using $CHCl_3$ to elute the spots and a solution of $KMnO_4$ to make them visible. This separation was not further investigated.

Attractancy Tests.—All the available esters, **4**, **5**, **14**, 7-octyn-1-ol acetate, 7-octen-1-ol acetate, and dodecyl acetate, were evaluated as attractants for cabbage loopers. *cis*-7-Dodecen-1-ol was very attractive to the males in both laboratory and field tests; a formulation containing 0.1 ml was more attractive than 100 live virgin females. Field tests indicated that the attractant has a marked effect for 400 feet downwind. No tests were conducted to determine the minimum effective dose, but the results seemed comparable to those of Berger who found that male moths were stimulated by concentrations of 0.1 μg/ml.

The other congeners were completely inactive.

Experimental Section

2-[(6-Chlorohexyl)oxy]tetrahydropyran (1).—Dihydropyran (40 g) was slowly dripped into a stirred mixture of 55 g of 6-chloro-1-hexanol (Aldrich C-4500) and 0.3 ml of concentrated HCl, which was cooled to keep the temperature below 40°. After the mixture was stirred for 3 hr at 25°, 2 g of $NaHCO_3$ was added, and the mixture was stirred for 1 hr, filtered, and distilled to give 76.4 g (87%) of **1**, bp 84–87° (0.13 mm), $n^{25}D$ 1.4599.

Anal. Calcd for $C_{11}H_{21}ClO_2$: C, 59.85; H, 9.59; Cl, 16.06. Found: C, 60.32; H, 9.55; Cl, 15.70.

2-(7-Octynyloxy)tetrahydropyran (2).—A solution of 115 g (0.52 mole) of 1 in 50 ml of DMSO was slowly added, over 1 hr, to a stirred slurry of 53.4 g of lithium acetylide–ethylenediamine complex[10] in 200 ml of dry DMSO, cooled to 15°. The mixture was stirred an additional 3 hr, during which the temperature rose to 30°. It was then diluted with 400 ml of ice and water, the layers were separated, and the aqueous phase was extracted three times with ether. The combined organic phase was washed four times with saturated NaCl and distilled to give a main

(7) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950).

(8) M. Jacobson, *J. Am. Chem. Soc.*, **72**, 1489 (1950).

(9) Company and trade names are given for identification purposes only and do not constitute endorsement by U. S. Department of Agriculture.

(10) Obtained from Foote Mineral Co., Exton, Pa.

fraction, 78.8 g (72.3%), bp 83–84° (0.3 mm), $n^{25}D$ 1.4590. Analysis of the adjacent distillation fractions by gas chromatography showed them to contain an additional 17.3 g (15.9%) of **2**.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.40; H, 10.60.

2-(7-Dodecynyloxy)tetrahydropyran (3).—To a solution of 15 g of sodamide in 1.5 l. of liquid NH_3 was added, dropwise with, stirring, 66.6 g (0.317 mole) of **2**. After the solution was stirred for an additional 1.5 hr, 85 g (0.62 mole) of *n*-butyl bromide was dripped in, and the mixture was stirred 3 hr more and then allowed to stand overnight while the NH_3 evaporated. The mixture was worked up by cautious addition of 500 ml of ice–water and extraction with three portions of ether, which were then washed with H_2O, and saturated NaCl solution. Distillation gave 29.3 g of impure starting material **2** and 47.2 g (56.9%) of product **3**, bp 114–127° (0.08 mm), $n^{25}D$ 1.4632.

7-Dodecyn-1-ol Acetate (4).—A mixture of 47.2 g of **3**, 150 ml of glacial acetic acid, and 35 ml of acetyl chloride was refluxed for 7 hr. After 110 ml was distilled off at 760 mm, the residue was poured into a water–ice slurry, and the product was extracted with ether and washed repeatedly with H_2O, $NaHCO_3$, and NaCl solutions. A virtually quantitative yield, 39.4 g, of **4** was obtained, bp 87–97° (0.07 mm), $n^{25}D$ 1.4491.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.76.

***cis*-7-Dodecen-1-ol Acetate (5).**—A solution of 8.7 g of **4** in 40 ml of absolute ethanol was hydrogenated at 30° by using 1.0 g of 5% Pd–$CaCO_3$ to which three drops of quinoline had been added. Absorption ceased after 925 ml of H_2 had been absorbed, the theoretical volume for 1 mole being about 960 ml. The catalyst was filtered off, the solvent was evaporated, and the residue was distilled at 85–90° (0.08–0.09 mm) to give 7.3 g (84%) of **5**, $n^{25}D$ 1.4420. [Berger's product[5] boiled at 98–100° (0.05 mm).]

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.22; H, 11.74.

7-Octyn-1-ol Acetate.—Treatment of **2** with acetic acid and acetyl chloride in the manner previously described gave the desired product, bp 108–110° (15 mm), $n^{25}D$ 1.4401.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.74; H, 10.32.

7-Octen-1-ol Acetate.—Semihydrogenation of the octynyl acetate gave the desired compound, bp 101–104° (14.5 mm), $n^{25}D$ 1.4317.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.64; H, 10.83.

2-Butyl-3-chlorotetrahydropyran (6).—2,3-Dichlorotetrahydropyran[6] (310 g, 2.0 moles) was dripped during 4 hr into a cooled, well-stirred, ether solution of 3.0 moles of butylmagnesium bromide. After it stood 16 hr, the mixture was worked up by cautious addition of 250 ml of saturated NH_4Cl solution and 200 ml of HCl (1:1), and the organic layer was separated and cleaned up. Distillation gave 269 g (76%) of the *cis* and *trans* isomers of **6**, bp 90–112° (15.5 mm).

***trans*-4-Nonen-1-ol (7).**—Compound **6** (269 g, 1.52 moles) was dripped onto 74 g (3.2 g-atoms) of powdered Na in 1 l. of ether at a rate which caused the ether to reflux gently. After the mixture stood overnight, the excess Na was treated with aqueous ethanol. The mass was diluted with water, the layers separated, and the aqueous phase was extracted with ether. Washing, drying, and distillation gave 204.3 g (94%) of the desired compound, bp 103–107° (15 mm).

***trans*-1-Bromo-4-nonene (8).**—A solution of 204 g of **7** in 400 ml of hexane was stirred at −20°, and 266 g of PBr_3 was slowly drippped in while the flask was swept out with a stream of N_2. After it stood 18 hr at 25°, the mixture was poured onto 500 g of ice and diluted with water; then the product was separated and washed with saturated NaCl solution. Two distillations were required to obtain 164 g (55%) of satisfactory product **8**,[11] bp 96–104° (16.5 mm), $n^{25}D$ 1.4630.

***trans*-6-Undecenoic Acid (9).**—Compound **8** (163 g) was combined with 131 g of diethyl malonate in 600 ml of anhydrous ethanol. A solution of 12.5 g of KOH in 250 ml of H_2O was added to the crude mixture, and the mixture was refluxed 5 hr, diluted with 700 ml of H_2O, and distilled to remove about 800 ml of aqueous ethanol. Extraction with ether yielded 8.0 g of unsaponified material, which was rejected. The aqueous layer was acidified (congo red) with H_2SO_4 (1:1) and extracted with ether which was then washed and evaporated to give the dicarboxylic acid. The acid was decarboxylated by heating at 140–150° until CO_2 evolution ceased. Distillation gave 89.3 g (61%) of the product, bp 127–131° (0.73 mm), $n^{25}D$ 1.4500.

***trans*-6-Undecenol (10).**—Reduction of **9** in the usual way with $LiAlH_4$ gave a 95% yield of **10**, bp 89–92° (0.44 mm), $n^{25}D$ 1.4493.

***trans*-6-Undecenyl Bromide (11).**—Treatment of **10** with PBr_3 in the manner described previously gave a 48% yield of **11**, bp 81–96° (0.4 mm), $n^{25}D$ 1.4649.

***trans*-7-Dodecenoic Acid (12).**—An ether solution of 6-undecenylmagnesium bromide prepared from 55 g of **11** was slowly poured, with stirring, onto 400 g of crushed Dry Ice. When the Dry Ice had evaporated, the mixture was worked up by adding 200 ml of HCl (1:4) and extracting with ether, which was then shaken with aqueous NaOH to separate neutral impurities. Acidification of the aqueous phase and extraction with ether yielded 20.4 g (44%) of **12**, bp 105–114° (0.04–0.05 mm), $n^{25}D$ 1.4502.

***trans*-7-Dodecen-1-ol (13).**—Reduction of the acid **12** with $LiAlH_4$ gave an 88% yield of **13**, bp 78–81° (0.06 mm), $n^{25}D$ 1.4521.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.13. Found: C, 78.25; H, 13.10.

***trans*-7-Dodecen-1-ol Acetate (14).**—Compound **13** was converted to the acetate in 95% yield by reaction with acetyl chloride and pyridine in anhydrous benzene, bp 78–82° (0.05 mm), $n^{25}D$ 1.4410.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.17; H, 11.71.

***n*-Dodecyl acetate**, bp 84–88° (0.04 mm), $n^{25}D$ 1.4311, was prepared from redistilled dodecyl alcohol by the method used to prepare **14**.

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.42; H, 12.39.

Acknowledgment.—Initial samples of **1** and **2** were supplied by Dr. Meyer Schwarz, of the Entomology Research Division. Attractancy tests were conducted under the supervision of Mr. E. A. Taylor at various laboratories of the Entomology Research Division, including those at Riverside, Calif., Mesa, Ariz., Quincy, Fla., and Brownsville, Texas. Elemental analyses were done by Galbraith Laboratories Inc., Knoxville, Tenn. Thin layer chromatography of *cis–trans* mixtures was done by Mr. Stanley Blacker.

(11) E. Truscheit and D. Eiter, *Ann.*, **658**, 65 (1962).