Oxidation of Trithioallophanate Esters. A. With Iodine.—While chilling a solution of 2.0 g. (0.012 mole) of methyl trithioallophanate in 50 ml. of absolute ethanol a solution of 3.1 g. (0.012 mole) of iodine in 100 ml. of ethanol was added with shaking over a 10-minute period. After standing at 0° for an hour, the yellow precipitate was filtered, washed with cold ethanol and dried in a vacuum desiccator. The β-hydroxyethyl homolog was prepared in the same fashion, excess iodine being removed from the product with 40–60° petroleum ether washes. The ethyl homolog was prepared by adding solid iodine to a solution of ethyl trithioallophanate. The product was triturated three times with hot chloroform to remove excess iodine.

B. With Bromine.—To a chilled suspension of 4.5 g. (0.027 mole) of methyl trithioallophanate in 100 ml. of chloroform was added with shaking a solution of 4.4 g. (0.027 mole) of bromine in 25 ml. of chloroform over a period of 15 minutes. The dark yellow product was digested in hot ethanol which removed the dark color and left a pale yellow solid. The ethyl homolog was prepared in similar fashion; the reaction product was repeatedly triturated with hot chloroform to remove impurities. The isopropyl and *n*-propyl derivatives were prepared as above. Being soluble in chloroform, they were precipitated as orange oils by the addition of 40–60° petroleum ether. Repeated extractions with petroleum ether gave yellow solids; the isopropyl derivative was recrystallized from chloroform and 40–60° petroleum ether, the *n*-propyl derivative from ethanol. The *n*-butyl homolog was prepared by the method used for the methyl derivative.

C. With Chlorine.—The procedure for the oxidation of *n*-butyl trithioallophanate with chlorine was the same as that for bromine oxidation except that carbon tetrachloride served as solvent. The lumpy yellow product was washed successively with dioxane, ethanol and 40–60° petroleum ether.

D. With Sulfuric Acid.—A paste of 6 ml. of concd. sulfuric acid and 2.0 g. (0.012 mole) of methyl trithioallophanate was stirred five minutes, filtered through Dicalite and diluted with 30 ml. of water, 100 ml. of acetone and 400 ml. of ether. The volume of the aqueous layer was reduced two-thirds by repeated ether extractions, then acetone and ether were added to the remaining aqueous layer until solution was effected. Refrigeration produced pale yellow granular crystals.

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Thiosemicarbazones of *p*-Acetaminocinnamaldehyde and β-2-Thienylacrolein

BY H. CECIL CALDWELL AND W. LEWIS NOBLES

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In pursuing a program dealing with the chemotherapy of tuberculosis, *p*-acetaminocinnamaldehyde and β-2-thienylacrolein thiosemicarbazones have been prepared. The former is a vinylog of *p*-acetaminobenzaldehyde thiosemicarbazone (Tibione)[1]; a compound recognized as an effective tuberculostatic agent. Likewise, 2-thenaldehyde thiosemicarbazone has been reported to have a high order of activity against the tubercle bacillus *in vitro*.[2,3] A later report[4] indicated that this compound afforded weak protection to mice infected with tuberculosis.

As the similarity in physical properties and chemical reactivity of a compound and its vinylog is well known,[5] it would appear that this correlation might be extended to include physiological action. Continued investigations into the pharmacology of vinylogous substances appeared to be warranted on the basis of interesting results previously obtained.[6]

The following points about the chemical work were observed: (1) In the preparation of *p*-acetaminocinnamaldehyde, dilute alcohol was found to be a more convenient solvent for recrystallization than hot water which was used by previous workers.[7] (2) The addition of a small quantity of either hydrochloric or acetic acid facilitated the reaction of thiosemicarbazide with the aldehyde, so that it was complete in 20–30 minutes. This is in contrast to the 6–8 hours reported by others.[3]

The compounds described in this paper have been submitted to Parke, Davis and Company for pharmacological evaluation.

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Experimental[8]

Intermediate Carbonyl Compounds.—*p*-Acetaminocinnamaldehyde was prepared according to the procedure of Russell, Todd and Waring,[7] modifying the procedure only in regard to the solvent used in recrystallization as reported above. These authors did not report a yield; the crude yields obtained in the present work ranged from 15–20%.

β-2-Thienylacrolein was prepared according to the method of Keskin, Miller and Nord.[9]

Thiosemicarbazones.—The thiosemicarbazones were prepared by the general procedure as described by Nobles and Burckhalter,[10] using either hydrochloric or acetic acid to augment the reaction. Both of the products were recrystallized from 50% ethanol.

***p*-Acetaminocinnamaldehyde Thiosemicarbazone.**—By the foregoing procedure, a 92% yield of light orange solid was obtained, m.p. 207°. *Anal.* Calcd. for $C_{12}H_{14}ON_4S$: C, 54.94; H, 5.39. Found: C, 55.25; H, 5.54.

β-2-Thienylacrolein Thiosemicarbazone.—By the same general procedure, a 90% yield of orange solid was obtained, m.p. 102°. *Anal.* Calcd. for $C_8H_9N_3S_2$: C, 45.48; H, 4.29. Found: C, 45.00; H, 4.47.

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Vinylidene Cyanide. IV. A Dienophile in the Diels–Alder Reaction[1]

BY S. J. AVERILL AND H. L. TRUMBULL

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When vinylidene cyanide (I) became available as a result of the synthetic methods described in the earlier papers of this series,[2] it became of

(1) Presented before the Division of Organic Chemistry of the American Chemical Society 124th Meeting, Chicago, Ill., September, 1953.

(2a) A. E. Ardis, *et al.*, THIS JOURNAL, **72**, 1305 (1950); (b) A. E. Ardis, *et al.*, *ibid.*, **72**, 3127 (1950).

TABLE I

ADDUCTS OF VINYLIDENE CYANIDE

Work on the anthracene adduct was carried out in coöperation with W. P. Tyler and D. W. Beesing.

Diene	Yield, %	Physical properties	Analyses	Carbon	Hydrogen	Nitrogen
2-Phenylbutadiene-1,3	45	M.p. 138–140°	Calcd. for $C_{14}H_{12}N_2$	80.72	5.82	13.45
			Found	80.45	5.92	13.39
2-Methylbutadiene-1,3	97	B.p. 108° (4.8 mm.)	Calcd. for $C_9H_{10}N_2$	73.95	6.90	19.23
			Found	74.06	6.99	19.05
trans-Pentadiene-1,3	67	B.p. 67° (0.3 mm.), m.p. 30.6°	Calcd. for $C_9H_{10}N_2$	73.95	6.90	19.23
			Found	74.03	6.97	19.17
2-Chlorobutadiene-1,3	66	B.p. 105–110° (0.4 mm.), m.p. 59–60°	Calcd. for $C_8H_7N_2Cl$	57.68	4.21	16.82
			Found	57.55	4.13	16.75
2,3-Dimethylbutadiene-1,3	56	B.p. 136° (18 mm.)	Calcd. for $C_{10}H_{12}N_2$	74.95	7.55	17.49
			Found	75.11	7.68	17.43
2-(2,2-Dimethylpropyl)-butadiene-1,3	56	B.p. 108–111° (1.4 mm.)	Calcd. for $C_{13}H_{18}N_2$	77.18	8.97	13.85
			Found	77.46	8.99	13.71
Methyl sorbate	65	M.p. 75–76°	Calcd. for $C_{11}H_{12}N_2O_2$	64.69	5.92	13.72
			Found	64.89	5.93	13.74
Anthracene[a]	77	M.p. 188–189°	Calcd. for $C_{18}H_{12}N_2$	84.35	4.72	10.93
			Found	84.57	4.64	10.96

[a] This adduct upon crystallizing from benzene has one-half molecule of benzene of crystallization, m.p. 133–135° with gas evolution. Calcd. for $C_{21}H_{15}N_2$: C, 85.43; H, 5.12; N, 9.49. Found: C, 85.76; H, 5.11; N, 9.64.

interest to explore some of its chemical reactions. The Diels–Alder adduct with cyclopentadiene[1] and that with butadiene-1,3[2] have been prepared as derivatives of I. A study of its reaction with various other dienes has shown it to be a very versatile dienophile. Table I presents the properties of various adducts prepared.

According to Alder[3] ethylenes, which are substituted in such a way as to produce conjugation and/or polarity in the molecule, should be highly reactive in the diene synthesis. The mechanism of the Diels–Alder reaction as presented in a review of the reaction by Kloetzel[4] would indicate that a highly polar dienophile should aid in the formation of an intermediate ionic complex. A consideration of the structure of I shows that it should fulfill the requirements of both a conjugated and polar molecule. I reacts very readily with most dienes to form an adduct. Its reactivity in the Diels–Alder reaction may be shown in a qualitative manner by comparing the conditions required for formation of an adduct with those of other dienophiles of related structure. To form an adduct from 2-methylbutadiene-1,3 with I, it is necessary to use a diluent to slow the reaction to a controllable rate at room temperature. To prepare the 2-methylbutadiene-1,3:maleic anhydride adduct,[5,6] it is necessary to heat the reaction mixture. Maleic anhydride is a highly conjugated dienophile but not polar. To prepare the 2-methylbutadiene-1,3:acrylonitrile adduct,[7] it is also necessary to heat the reaction mixture. Acrylonitrile is both highly conjugated and polar but not as markedly as is I. The adducts of I are stable and there does not appear to be any reverse reaction in solution at room temperature. The reaction may be reversed with some of the adducts by heating to relatively high temperatures.[1]

There are a few dienes from which it has not been possible to prepare an adduct at room temperature or above. *cis*-Pentadiene-1,3, furan and hexachlorobutadiene-1,3 did not react with I even upon refluxing in the absence of solvent.

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(4) M. C. Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 8.

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Experimental

All the adducts with the exception of those of anthracene, methyl sorbate and 2-chlorobutadiene-1,3 were prepared as follows. The vinylidene cyanide was dissolved in five times its weight of benzene. An excess of the diene was then added with stirring and allowed to stand at room temperature for 24 hours. The benzene was removed by distillation and the adduct recovered from the residue by distillation at reduced pressure. The involatile adduct of 2-phenylbutadiene-1,3 was recrystallized from chloroform as it did not lend itself to distillation.

Anthracene Adduct.—Nine grams of anthracene was suspended in 50 ml. of benzene. Vinylidene cyanide (3.9 g.) was added whereupon a yellow color developed. The mixture was heated under reflux for 1.5 hours during which time the yellow color disappeared. The reaction mixture was cooled and the solid product collected on a filter. The product was recrystallized from acetonitrile and washed with benzene (wt. 10 g.).

Chloroprene Adduct.—Eight grams of vinylidene cyanide and 9 g. of 2-chlorobutadiene-1,3 and 127 ml. of benzene were mixed together in a 250-ml. erlenmeyer flask, and allowed to stand for 40 hours in a 40° bath. The liquid in the flask was then decanted from a small amount of polymer in the flask. The liquid was distilled to remove the benzene and the residue distilled at reduced pressure.

Methyl Sorbate Adduct.—Forty grams of benzene, 25.2 g. of methyl sorbate and 15.6 g. of vinylidene cyanide were placed in a 250-ml. round-bottom flask. The flask was fitted with a condenser and the mixture heated in an oil-bath at 110° for two hours. Four grams of methyl sorbate was added to the reaction mixture which was then allowed to stand overnight at room temperature. The reaction mixture was cooled in ice-water to cause crystallization. The crystals were filtered off, dried at room temperature, and found to weigh 24.2 g. These were recrystallized from a mixture of two volumes of hexane and one volume of benzene.

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