[CONTRIBUTION NO. 203 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, AND ENZYMOLOGY FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XI. FURTHER REACTIONS OF THENALDEHYDES.[1]

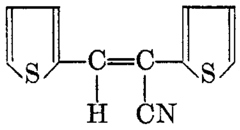
BERNARD F. CROWE AND F. F. NORD

Received April 25, 1950

Hippuric acid and rhodanine have been shown in this laboratory to react readily with 2-thenaldehyde and some monosubstituted 2-thenaldehydes (1). These condensations are demonstrated here to be equally applicable to 3-thianaphthaldehyde and di- and tri-methylsubstituted thenaldehydes. In Table I are listed the products thus obtained.

The study of the effects of substitution of the thiophene nucleus on the ultraviolet absorption of the azlactones (1) was continued and also extended to the rhodanines prepared and to 2-methyl-4-(2-thenal)-5-oxazolone (2). From the spectra presented in Figures 1 and 2, and the data recorded in Table II it can be seen that, with the exception of 2-methyl-4-(2-thenal)-5-oxazolone which has only one peak, both the azlactones and the rhodanines exhibit two absorption peaks in the region 250–430 mμ. The di- and tri-methylsubstituted azlactones possess the lower absorption peak around 272 mμ which was found with the monosubstituted azlactones previously reported (1). Di- and tri-methylsubstitution of 2-phenyl-4-(2-thenal)-5-oxazolone causes a bathochromic shift of the major peak found at the longer wave lengths. This peak is present at shorter wave lengths in the azlactones derived from methylated 3- and 4-thenaldehydes. Furthermore, the shape of the curve of 2-phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone is flatter than those of the other azlactones and the intensity of the absorption at its major peak is considerably lower. The rhodanines display a similar bathochromic shift of their major peaks as a result of substitution of the thiophene ring. In addition the di- and tri-methylrhodanines show a plateau at the lower wave lengths.

α-Phenylcinnamonitrile has been prepared by condensing benzaldehyde and benzyl cyanide in the presence of sodium ethoxide (3). This method was utilized for obtaining a series of substituted α-phenylcinnamonitriles (4). 2-Thenaldehyde (5) and 2-thienylacetonitrile (1), which are easily accessible, when subjected to this procedure gave an 89% yield of α,β-di-(2-thienyl)acrylonitrile (I):



I

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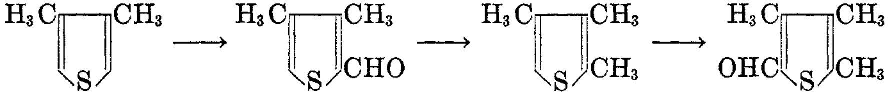
[1] This investigation was carried out under the auspices of the Office of Naval Research.

The reaction was successful if either benzaldehyde or benzyl cyanide was substituted for its thiophene analog, but the yields were lower than those obtained when both components in the condensation possessed a thiophene ring.

Two new thenaldehydes were prepared from 3,4-dimethylthiophene (II) by successive formylation and reduction. It is significant that while all the other thenaldehydes in this series (5, 6) were liquids at room temperature, the two described here are solids. They both exhibit typical aldehyde reactions in condensing with hippuric acid and rhodanine.



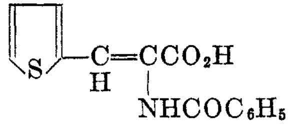
II

TABLE I

AZLACTONES AND RHODANINES PREPARED FROM SUBSTITUTED THENALDEHYDES

COMPOUND	YIELD, %	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone	54	195–196	67.84	4.59	67.78	4.38
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone	61	193.5–194.5	68.68	5.05	68.47	4.79
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone	75	205.2-206	67.84	4.59	67.94	4.36
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone	79	142.5–143.5	67.84	4.59	68.18	4.77
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone	18	101–102.5	68.68	5.05	68.87	4.95
2-Phenyl-4-(3-thianaphthal)-5-oxazolone	69	223–223.5	70.81	3.61	70.70	3.81
3,4-Dimethyl-2-thenalrhodanine	85	263–264	47.06	3.53	47.20	3.48
3,4,5-Trimethyl-2-thenalrhodanine	68	275–276	49.07	4.08	49.07	3.84
3-Thianaphthalrhodanine	90	240–241	51.98	2.52	51.90	2.43

It has been shown (7) that veratralhippuric acid may be decarboxylated to the corresponding styrylamide by heating it in quinoline in the presence of copper chromite. In a similar manner α-benzamido-β-2-thienylacrylic acid (8) (III) was found to undergo decarboxylation, but excessive tar formation accompanied the reaction. When copper powder was substituted for copper chromite, a higher yield was obtained and the amount of tar formed was considerably diminished.



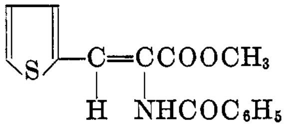
III

The susceptibility of thiophene azlactones to alcoholysis was found to parallel that of the benzene series. This was demonstrated by applying Nicolet's method (9) to 2-phenyl-4-(2-thenal)-5-oxazolone. With a methanol solution of sodium methoxide the azlactone was opened rapidly to the methyl ester (IV). Sodium ethoxide in ethanol acted as readily to produce the ethyl ester.

TABLE II

Absorption Maxima of Azlactones and Rhodanines

COMPOUND	mμ	$\epsilon \times 10^{-3}$	Log ϵ
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone	271–272	11.8	4.07
	411–414	35.2	4.55
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone	273	10.8	4.03
	429	37.6	4.57
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone	272	11.9	4.07
	421–422	39.1	4.59
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone	272	10.0	4.00
	390–391	34.1	4.53
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone	273	10.7	4.03
	387–388	17.3	4.24
2-Phenyl-4-(3-thianaphthal)-5-oxazolone	292	18.3	4.26
	411–412	31.3	4.50
2-Methyl-4-(2-thenal)-5-oxazolone	363	25.6	4.40
2-Thenalrhodanine	287–289	7.3	3.86
	397	34.1	4.53
5-Methyl-2-thenalrhodanine	294	7.5	3.87
	406–408	33.9	4.53
5-Ethyl-2-thenalrhodanine	291	8.0	3.90
	406–407	34.6	4.54
5-Propyl-2-thenalrhodanine	287	7.8	3.89
	407–408	35.1	4.55
3-Methyl-2-thenalrhodanine	292	5.6	3.75
	404–406	27.4	4.43
5-Chloro-2-thenalrhodanine	285	8.5	3.93
	401	33.9	4.53
5-Bromo-2-thenalrhodanine	287	9.3	3.97
	402	36.1	4.56
3-Thianaphthalrhodanine	286	9.3	3.97
	398	30.0	4.48
3,4-Dimethyl-2-thenalrhodanine	292	6.5	3.81
	408–409	33.6	4.52
3,4,5-Trimethyl-2-thenalrhodanine	298–306	7.1	3.85
	423	34.2	4.53



IV

The ease of hydrolysis of the azlactone ring of 2-methyl-4-(2-thenal)-5-oxazolone resembled that of its benzene analog (10). Refluxing with aqueous acetone was sufficient to effect ring opening to α-acetamido-β-2-thienylacrylic acid.

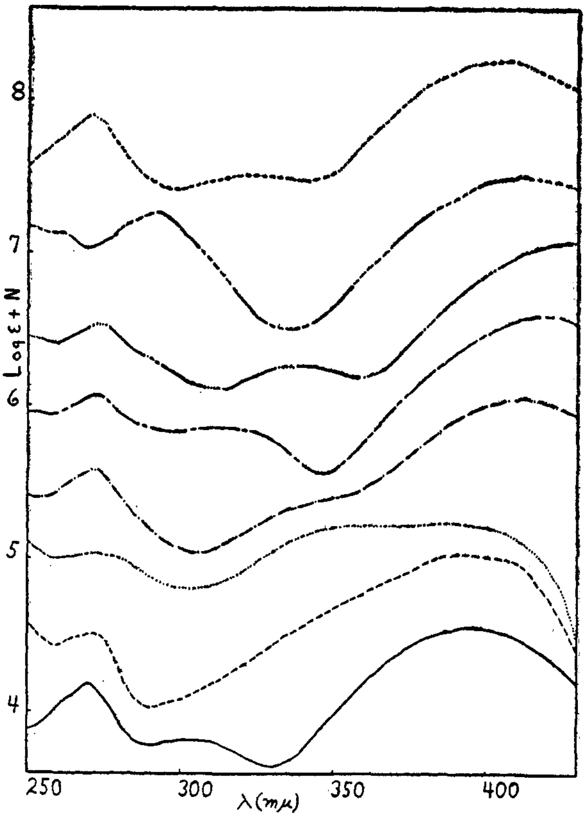


FIGURE 1. ULTRAVIOLET ABSORPTION CURVES OF AZLACTONES.

2-Phenyl-4-(2-thenal)-5-oxazolone ———— N = 0
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone — — — — N = 0.5
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone........ N = 1.0
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone—.—.—.—. N = 1.5
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone—-—-— N = 2.0
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone—.....—..... N = 2.5
2-Phenyl-4-(3-thianaphthal)-5-oxazolone------——------— N = 3.0
2-Phenyl-4-(3-methyl-2-thenal)-5-oxazolone-----.....-----.....----- N = 3.7

EXPERIMENTAL[2]

Azlactones and rhodanines. The procedure described previously for the preparation of other members of these series (1) was followed.

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[2] The 3,4-dimethylthiophene used in these experiments was obtained through the courtesy of Dr. H. D. Hartough of the Socony-Vacuum Oil Company, Paulsboro, N. J. The analyses were performed by A. A. Sirotenko of this laboratory.

α,β-Di-(2-thienyl)acrylonitrile. 2-Thenaldehyde (5.0 g., 0.045 mole) and 5.5 g. (0.045 mole) of 2-thienylacetonitrile were dissolved in 68 cc. of ethanol contained in a 500-cc. round-bottom flask. One gram of sodium was dissolved in 90 cc. of ethanol and added to the above solution. Yellow crystals began to precipitate at once. The flask was fitted with a reflux condenser and heated over a low flame until the solution began to boil. After chilling in an ice-bath the contents of the flask were filtered, yielding 7.93 g. of yellow crystals. The filtrate was diluted with a little water and left in a refrigerator overnight. An additional 0.75 g. of product was thus obtained, giving a total yield of 8.68 g. (89%). After recrystallization from ethanol the m.p. was 129.5–130.5°.

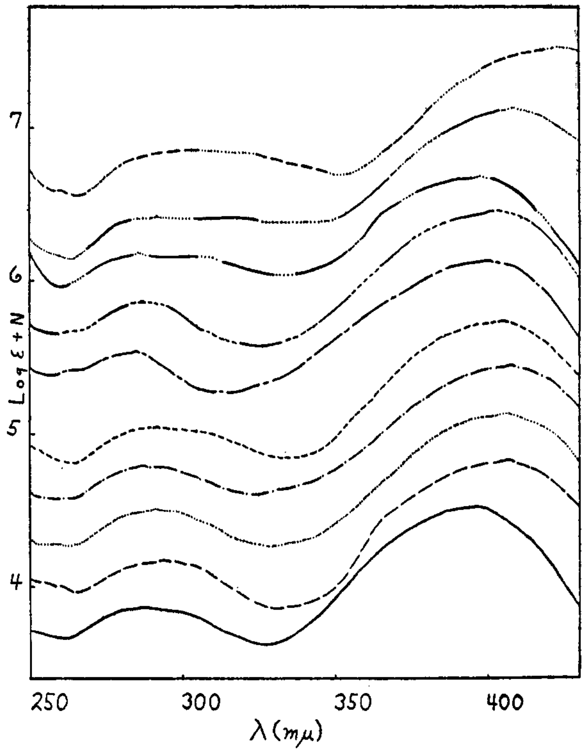

FIGURE 2. ULTRAVIOLET ABSORPTION SPECTRA OF RHODANINES.

2-Thenalrhodanine ———	N = 0
5-Methyl-2-thenalrhodanine — — — —	N = 0.3
5-Ethyl-2-thenalrhodanine........	N = 0.6
5-Propyl-2-thenalrhodanine—.—.—.—.—.—.—.	N = 0.9
3-Methyl-2-thenalrhodanine---------	N = 1.3
5-Chloro-2-thenalrhodanine— — — — — — — -	N = 1.6
5-Bromo-2-thenalrhodanine— - - - - - — - - - - -	N = 1.9
3-Thianaphthalrhodanine—.....—.....—.....	N = 2.2
3,4-Dimethyl-2-thenalrhodanine—.............—	N = 2.6
3,4,5-Trimethyl-2-thenalrhodanine — — — — —............	N = 3.0

Anal. Calc'd for $C_{11}H_7NS_2$: C, 60.82; H, 3.22.
Found: C, 60.83; H, 3.15.

α-Phenyl-β-(2-thienyl)acrylonitrile. Applying the above method a yield of 82% of yellow crystals was obtained, m.p. 89.5–90.5°, from 2-thenaldehyde and benzyl cyanide.

Anal. Calc'd for $C_{13}H_9NS$: C, 73.93; H, 4.26.
Found: C, 73.90; H, 4.04.

α-(2-Thienyl)-β-phenylacrylonitrile. Using the above procedure a yield of 77% of yellow crystals was obtained, m.p. 75.5–76.5°, from benzaldehyde and 2-thienylacetonitrile.

Anal. Calc'd for $C_{13}H_9NS$: C, 73.93; H, 4.26.
Found: C, 73.88; H, 4.13.

3,4-Dimethyl-2-thenaldehyde. The N-methylformanilide synthesis (5) was applied to 3,4-dimethylthiophene and gave an 83% yield. White needles were obtained from ethanol (Norit), m.p. 69–70°.

Anal. Calc'd for C_7H_8OS: C, 59.99; H, 5.71; M.W., 140.
Found: C, 59.82; H, 5.56; M.W., 156.

2,3,4-Trimethylthiophene. The Wolff-Kishner reduction was applied to 3,4-dimethyl-2-thenaldehyde as described for other members in these studies (6). The yield of the water-clear liquid was 81%, b.p. 47–49°/5 mm.; 162–165°/763 mm.; n_D^{20} 1.5213. Reference (11) lists b.p. 160–163° at normal pressure.

Anal. Calc'd for $C_7H_{10}S$: C, 66.67; H, 7.93.
Found: C, 66.33; H, 7.58.

3,4,5-Trimethyl-2-thenaldehyde. The N-methylformanilide synthesis (5) was applied to 2,3,4-trimethylthiophene. The yield of white needles after recrystallization from ethanol (Norit) was 79%, m.p. 46–47°; b.p. 116–117°/5 mm.

Anal. Calc'd for $C_8H_{10}OS$: C, 62.34; H, 6.49.
Found: C, 62.36; H, 6.34.

ω-Benzamido-2-vinylthiophene. α-Benzamido-β-2-thienylacrylic acid (8.2 g., 0.03 mole), 40 cc. of freshly distilled quinoline, and 1 g. of copper powder were heated in an oil-bath slowly to 180° and kept there for 20 minutes. The reaction mixture was cooled and decanted into dilute hydrochloric acid, whereupon a dirty yellow solid precipitated. The solid was filtered and washed successively with dilute hydrochloric acid and water. It was then boiled with dilute sodium carbonate solution for 15 minutes and filtered again. Upon recrystallization from aqueous ethanol (Norit) 1.2 g. of white plates was obtained which sintered at 135° and had m.p. 144.5–145.5°.

Anal. Calc'd for $C_{14}H_{11}NO_3S$: C, 68.12; H, 4.80.
Found: C, 67.83; H, 4.42.

Ethyl α-benzamido-β-(2-thienyl)acrylate. 2-Phenyl-4-(2-thenal)-5-oxazolone (3.48 g., 0.014 mole) was suspended in 14 cc. of benzene and 1.7 cc. of 1 *N* sodium ethoxide was added. The azlactone rapidly dissolved and the ester began to precipitate. After 3 minutes an excess of dilute hydrochloric acid was added and the mixture shaken. The white precipitate was filtered and washed with water. The yield after recrystallization from aqueous ethanol amounted to 3.55 g. (86%) of white needles, m.p. 177.5–178°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: C, 63.79; H, 4.98.
Found: C, 63.41; H, 4.59.

Methyl α-benzamido-β-(2-thienyl)acrylate. When the above procedure was repeated with 1 *N* sodium methoxide, the methyl ester was obtained in a yield of 75%, m.p. 185.5–186.5°.

Anal. Calc'd for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.52.
Found: C, 62.82; H, 4.23.

α-Acetamido-β-2-thienylacrylic acid. To a mixture of 328 cc. of acetone and 127 cc. of water was added 35.2 g. (0.18 mole) of 2-methyl-4-(2-thenal)-5-oxazolone. The mixture was refluxed for 4 hours and the acetone removed on the steam-bath. After addition of 290 cc. of water the solution was boiled for 5 minutes and filtered. The residue was again boiled with 250 cc. of water, filtered, and the combined filtrates left in a refrigerator overnight. The acid which had precipitated was filtered and dried *in vacuo* over P_2O_5 and KOH. After recrystallization from hot water (Norit) there was obtained 27.4 g. (71%) of white crystals, m.p. 227.5–228.5°d.

Anal. Calc'd for $C_9H_9NO_3S$: C, 51.18; H, 4.26.
Found: C, 51.13; H, 4.19.

Ultraviolet absorption spectra. The spectra were obtained with a Beckman quartz spectrophotometer, Model DU, using chloroform as the solvent for the azlactones and absolute alcohol for the rhodanines.

SUMMARY

1. Several azlactones and rhodanines were prepared from 3-thianaphthaldehyde and some di- and tri-methylsubstituted thenaldehydes and their ultraviolet absorption spectra were compared.

2. The condensation of aldehydes with arylacetonitriles was shown to take place in the thiophene series.

3. Two new thenaldehydes were synthesized from 3,4-dimethylthiophene by successive formylation and reduction.

4. The decarboxylation of α-benzamido-β-2-thienylacrylic acid to the corresponding styrylamide was effected by heating with quinoline and copper powder.

5. Alcoholysis of 2-phenyl-4-(2-thenal)-5-oxazolone proceeded readily with either methanol or ethanol.

6. Hydrolysis of 2-methyl-4-(2-thenal)-5-oxazolone was achieved in a 71% yield.

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