[CONTRIBUTION NO. 238 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XIX. THE APPLICATION OF THE HOFMANN AND CURTIUS REARRANGEMENTS TO THE PREPARATION OF 2-THIENYLACETALDEHYDES[1]

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Received July 31, 1951

Although the application of the Hofmann and Curtius degradations to the preparation of amines has been extensive, the use of these reactions in the formation of aldehydes has been limited. Because of the versatility of aldehydes, their preparation has been the subject of previous study in our laboratories (1–4). In a continuation of this study, the formation of additional aldehydes by means of the above reactions was undertaken.

It was found (5) that when amides of α, β-unsaturated acids are subjected to the conditions of the Hofmann reaction unsaturated urethans are obtained. Hydrolysis of the urethans in an acid medium gives the corresponding aldehydes in excellent yields. However the utilization of these reactions (6) for the preparation of 2-furanacetaldehyde gave only traces of the desired product.

The degradation employed by Weerman was attempted in the thiophene series as outlined in Chart I. Although excellent yields of the unsaturated amides and urethans could be obtained, hydrolysis of the urethans gave poor yields of the aldehydes. Repeated attempts at the hydrolysis utilizing various conditions were never completely successful in overcoming a pronounced tendency towards polymerization.

An interesting feature of Weerman's degradation was the fact that when the amide of cinnamic acid was treated with sodium hypochlorite in the cold, the isocyanate which ensued reacted with the remainder of the amide to give 1 cinnamoyl-3-styrylurea. When 2-thiopheneacrylamide was subjected to the same reaction, a compound was obtained having similar physical characteristics to Weerman's urea. It is believed to be 1-β-(2-thienyl)acrylyl-3-β′-(2-thienyl)-vinyleneurea.

Because of the unsatisfactory yields accompanying the hydrolysis of the 2-thienylvinylurethans to the corresponding aldehydes, an alternate method of preparation was investigated. An attractive approach to aldehydes was reported by Curtius (7), but has not found much synthetic application. It consists in the preparation of monosubstituted malonyl azides from dihydrazides. Treatment of the diazides with alcohol results in the formation of *gem*-diurethans which can be readily hydrolyzed to aldehydes by mineral acid.

The application of the Curtius degradation to the preparation of 2-thiopheneacetaldehyde as outlined in Chart II resulted in excellent yields of the various intermediates and a fair yield of the aldehyde. Thus it demonstrates the superi-

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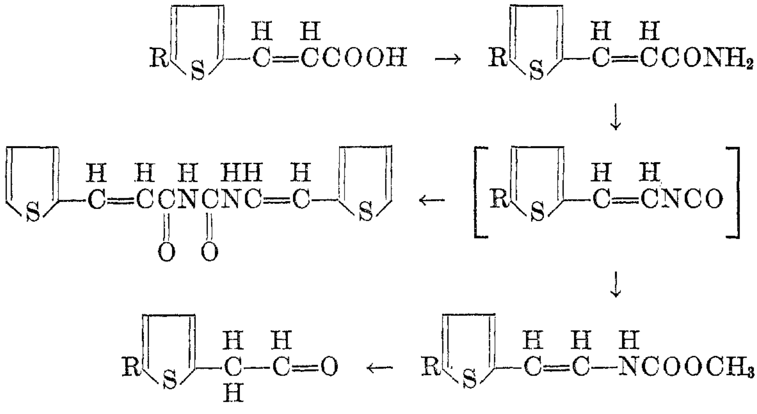
[1] This investigation was aided in part by a grant from the Office of Naval Research. The analyses were conducted by Dr. F. Bühler and A. A. Sirotenko of this department.

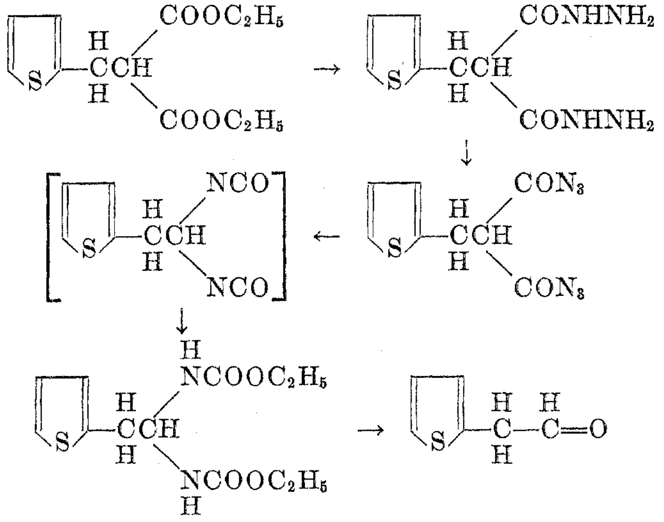
ority of the hydrolysis of the *gem*-diurethan as compared to an unsaturated urethan in the preparation of these aldehydes. This may be due to the rearrangement required on the part of the unsaturated urethan upon hydrolysis. Since both procedures failed to give the aldehyde in yields comparable with those reported by Weerman and Curtius, it appears that the presence of the heterocyclic moiety renders them less stable than the corresponding aldehydes in the benzene series. Possibly the electron-rich thiophene ring gives the hydrogen atoms on the methylene carbon a higher reactivity.

CHART I



where R = H or Cl

CHART II



Due to the unstable nature of the aldehyde they were analyzed as semicarbazone derivatives rather than in the uncombined state. A mixture melting point was taken of the semicarbazones of 2-thiopheneacetaldehyde prepared by both the Hofmann and Curtius degradation. There was no depression.

EXPERIMENTAL[2]

2-Thiopheneacrylamide. 2-Thiopheneacrylic acid (3) (44 g., 0.28 mole) was suspended in 300 ml. of anhydrous chloroform and 50 ml. of freshly distilled thionyl chloride was added. The mixture was allowed to stand for 12 hours after which time a clear solution had formed. The solution was then cautiously poured onto 700 ml. of cold ammonium hydroxide containing 35 g. of sodium hydroxide. The amide which separated was filtered and washed thoroughly with water. Additional crystals were obtained by concentrating the chloroform solution. Recrystallization from dilute ethanol gave 40 g. (90%) of white plates, m.p. 152–153°.

Anal. Calc'd for C_7H_7NOS: C, 54.88; H, 4.60.
Found: C, 55.00; H, 4.77.

5-Chloro-2-thiopheneacrylamide was prepared in a similar manner. The yield was 91%; m.p. 148–149°.

Anal. Calc'd for C_7H_6ClNOS: C, 44.92; H, 3.20.
Found: C, 44.89; H, 3.27.

Methyl β-(2-thienyl)vinylcarbamate. To 100 ml. of methanol containing 12 g. (0.08 mole) of 2-thiopheneacrylamide was added 150 ml. of an 0.8 *M* potassium hydroxide solution followed by an 0.8 *M* potassium hypochlorite (8) solution. The temperature was allowed to rise to 55–60° whereupon a thick mass of crystals formed. The flask was rapidly cooled and the crystals filtered. The product was washed with dilute alcohol. Recrystallization from ethanol gave 10 g. (70%) of crystals, m.p. 115–116°.

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.46; H, 4.92.
Found: C, 52.56; H, 4.75.

Methyl β-(5-chloro-2-thienyl)vinylcarbamate was prepared in the same manner, except that the temperature of the solution was not allowed to rise above 50–55°. The yield was 53%; crystals, m.p. 88–89°.

Anal. Calc'd for $C_8H_8ClNO_2S$: C, 44.24; H, 3.68.
Found: C, 44.53; H, 3.82.

1-β-(2-thienyl)acrylyl-3-β'-(2-thienyl)vinyleneurea. 2-Thiopheneacrylamide (7.6 g., 0.08 mole) in 50 ml. of ethanol was added dropwise to 15 ml. of an 0.8 *M* solution of potassium hypochlorite with cooling to 5° and stirring. Stirring was continued for an additional 15 minutes during which time yellow crystals separated. The product was filtered and washed with alcohol and water. After two recrystallizations from acetic acid a small yield of yellow needles, m.p. 225–226°, was obtained.

Anal. Calc'd for $C_{14}H_{12}N_2O_2S_2$: C, 55.25; H, 3.94.
Found: C, 54.96; H, 3.89.

2-Thiopheneacetaldehyde. Methyl β-(2-thienyl)vinylcarbamate (22 g., 0.12 mole) was dissolved in 200 ml. of 50% ethanol and 50 g. of hydrated oxalic acid was added. The solution was heated for 15 minutes on the steam-bath and then vigorously steam-distilled. After all the alcohol had been removed, a yellow oil distilled over. The distillate was extracted with ether and dried over sodium sulfate. After filtration, the ether was removed. Distillation yielded 2.9 g. (19%) of a colorless oil with a rose-like aroma, b.p. 69–74°/8 mm.

A *semicarbazone* prepared according to the usual method (9) gave m.p. 131–132°.

Anal. Calc'd for $C_7H_9N_3OS$: C, 45.90; H, 4.91.
Found: C, 46.22; H, 4.68.

5-Chloro-2-thiopheneacetaldehyde was prepared in a similar manner. Distillation gave a colorless oil (24%) with a faint aroma of roses, b.p. 55–60°/5 mm.

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[2] The thiophene used in this study was obtained through the courtesy of Dr. G. A. Harrington of Socony-Vacuum Oil Company.

The *semicarbazone* prepared had m.p. 147–147.5°.

Anal. Calc'd for $C_7H_8ClN_3OS$: C, 38.70; H, 3.68.
Found: C, 39.00; H, 3.74.

2-Thenylmalonodihydrazide. A mixture of 30 g. (0.17 mole) of ethyl 2-thenylmalonate (9, 10), 20 g. (0.39 mole) of hydrazine hydrate, and 5 ml. of ethanol was refluxed for six hours. The dihydrazide which crystallized after cooling was filtered and washed with cold alcohol. After drying *in vacuo* 25.1 g. (94%) of the crude product was obtained. A small portion was recrystallized from ethanol, m.p. 165–166°.

Anal. Calc'd for $C_8H_{12}N_4O_2S$: C, 42.10; H, 5.26.
Found: C, 42.16; H, 4.88.

Ethyl 2-thenylmethylenedicarbamate. 2-Thenylmalonodihydrazide (22.8 g., 0.1 mole) was dissolved in 88 ml. of water containing 19.6 g. of conc'd sulfuric acid. The solution was covered with 100 ml. of ether. The contents were stirred and cooled to −7°, after which time 42 ml. of water containing 21.1 g. of sodium nitrite was added dropwise. The temperature was never allowed to rise above −5°. After all the nitrite solution had been added, stirring was continued for an additional five minutes. The ethereal solution containing the diazide was decanted into a flask and the remaining solution extracted with 50 ml. of ether. The combined ethereal solution was dried over sodium sulfate for one hour at −5° to 0°.

After filtration, the ether solution was added to 200 ml. of absolute ethanol and the mixture refluxed for three hours, during which time most of the ether was allowed to escape. After the removal of the alcohol, a brown oil was obtained which eventually solidified. The solid was dried *in vacuo* to give 23 g. (80%) of the diurethan. Recrystallization of a portion from petroleum ether gave white crystals, m.p. 125–126°.

Anal. Calc'd for $C_{12}H_{18}N_2O_4S$: C, 50.35; H, 6.29; N, 9.79.
Found: C, 49.94; H, 5.79; N, 9.72.

2-Thiopheneacetaldehyde. Ethyl 2-thenylmethylenedicarbamate (20 g., 0.07 mole) was added to 200 g. of 2% sulfuric acid and the mixture heated for a half hour on the steam-bath with occasional swirling. The yellow oil which separated was rapidly steam-distilled. After extraction and drying over sodium sulfate, the aldehyde (4.9 g., 55%) distilled as a colorless oil, b.p. 52–54°/4 mm.; n_D^{20} 1.5167.

A *semicarbazone* was prepared according to Ref. (9); m.p. 131–131.5°. A mixture melting point with a sample of the semicarbazone of the aldehyde from the alternate procedure showed no depression.

The *2,4-dinitrophenylhydrazone* (9) had m.p. 100–101°.

Anal. Calc'd for $C_{12}H_{10}N_4O_4S$: N, 18.34. Found: N, 18.36.

SUMMARY

1. The applicability of the Hofmann and Curtius degradation to the preparation of 2-thiopheneacetaldehydes has been demonstrated and evaluated.

NEW YORK 58, N. Y.

REFERENCES

(1) KING AND NORD, *J. Org. Chem.*, **13**, 635 (1948).
(2) KING AND NORD, *J. Org. Chem.*, **14**, 405 (1949).
(3) KING AND NORD, *J. Org. Chem.*, **14**, 638 (1949).
(4) CROWE AND NORD, *J. Org. Chem.*, **15**, 1177 (1950).
(5) (a) WEERMAN, *Ann.*, **401**, 1 (1913); (b) *Rec. trav. chim.*, **37**, 2 (1918).
(6) RINKES, *Rec. trav. chim.*, **39**, 200 (1920).
(7) CURTIUS AND MOTT, *J. prakt. Chem.*, **94**, 323 (1916).
(8) NEWMAN AND HOLMES, *Org. Syntheses*, Coll. Vol. II, 428 (1943).
(9) SHRINER AND FUSON, *The Systematic Identification of Organic Compounds*, 3rd edition, John Wiley and Sons, New York, 1948, p. 170.
(10) OWEN AND NORD, *J. Org. Chem.*, **15**, 988 (1950).
(11) BLICKE AND LEONARD, *J. Am. Chem. Soc.*, **68**, 1934 (1946).