[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Willgerodt Reaction in the Heterocyclic Series. I. 2,5-Dimethyl-3-thienyl Ketones

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The Willgerodt reaction has been successfully applied to a large number of aryl alkyl and dialkyl ketones,[1] but there has been only a limited investigation with heterocyclic compounds. Compounds such as 3-acetylpyridine, 5-acetyl-1-phenyl-4-methylpyrazole and 8-acetylquinoline[2] have been studied, while 2-, 3- and 4-pyridineacetic acids have been prepared from 2-, 3- and 4-methyl pyridyl ketones[3] using sulfur and morpholine. 2-Pyridylacetamide has also been prepared in 31% yield from 2-vinylpyridine.[4] Recently, Turner[5] reported the preparation of the thiomorpholide of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole using the Kindler modification.

In the field of condensed heterocycles, Gilman[6] obtained 2-dibenzofurylacetamide from 2-acetyldibenzofuran, and Buu-Hoï[7] prepared dibenzofuran-2-propionic acid from 2-propionyldibenzofuran. Schwenk and Papa[8] were able to convert 3-pyridyl methyl ketone and 2-phenylquinoline-4 methyl ketone to the corresponding acid by a modified Kindler procedure. They found the reaction unsuitable for α-thienyl methyl ketone as only tarry products were isolated.

Because of this reported failure in the thiophene series, we decided to determine the scope of the Willgerodt reaction in this series. The production of only tarry products from α-thienyl methyl ketone was confirmed by us at the beginning of this study but we have found that amides are obtained from other substituted thienyl ketones in good yields. Thus, the presence of the thiophene nucleus does not presuppose negative results.

As this manuscript was being prepared, a paper by Buu-Hoï and Nguyen-Hoàn[9] was published which indicated some success in the preparation of 3-thienyl aliphatic acids by the Kindler modification. The thiomorpholides were not isolated but were hydrolyzed to the acids. They prepared 2,5-dimethyl-3-thienylacetic acid (m. p. 87°), -propionic acid (m. p. 116°) and -butyric acid (m. p. 56°). The melting points of these acids as obtained in our experiments were 69–70°, 59–60° and 58–59°, respectively.

One group of ketones investigated by us, the 2,5-dimethyl-3-thienyl ketones, is the subject of this paper. Since 2,5-dimethyl-3-thienyl methyl ketone was converted to the amide in good yield, the aliphatic chain was extended to afford a comparison with the phenyl aliphatic ketones. The latter had been studied by DeTar and Carmack.[1,10] Although the conditions used by these authors are not the same as we have used in this study, it is of interest to note the decrease in yield with increased length of aliphatic chain in both series (Table I).

The thienyl ketones used in these experiments were prepared by the method of Johnson and May[11] and the physical constants were found to be in agreement with those of Buu-Hoï.[12]

Two forms of the Willgerodt reaction were studied for each compound: (A) the use of sulfur, concentrated ammonium hydroxide and dioxane in a sealed tube and (B) the use of yellow ammonium polysulfide, sulfur and dioxane in a sealed tube. In addition, sulfur and morpholine[13] at the reflux temperature was used for the Kindler[14] modification. The resulting amides (Table I) and thioamides were hydrolyzed to yield the expected acids. The 2,5-dimethyl-3-thienyl aliphatic acids were unknown with the exception of 2,5-dimethyl-3-thienylbutyric acid.[15] Synthesis of the 2,5-dimethyl-3-thienylacetic, -propionic and -butyric acids by reliable methods for mixed melting point comparisons with the products from the Willgerodt reaction proved the structure of these three compounds. We feel that, by analogy, this makes quite probable the structure of the remaining acid (Table I). The 2,5-dimethyl-3-thienylacetic acid was synthesized from 2,5-dimethyl-3-thienylcarboxylic acid[12,15] by the Arndt–Eistert method using the procedure of Blicke and Zienty.[16] The low yields of the 3-acetic acid made it necessary to investigate another synthesis. We were successful in obtaining satisfactory yields of this acid from 2,5-dimethyl-3-thienylcarboxylic acid by a six step process. The Rosenmund reduction has been reported[17] as giving low yields (trace to 20%) of thiophene aldehydes. We have obtained considerably higher yields since 2,5-dimethyl-3-thenoyl chloride[12] was converted to 2,5-dimethyl-3-thiophene aldehyde

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[1] M. Carmack and M. A. Spielman, "Organic Reactions," Vol. III, Wiley and Sons, New York, N. Y., 1947, pp. 83–107.

[2] British Patent 558,774; *Brit. C. A.*, **B11**, 102 (1944).

[3] Malan and Dean, THIS JOURNAL, **69**, 1797 (1947).

[4] Carmack and DeTar, *ibid.*, **68**, 2033 (1946).

[5] D. L. Turner, *ibid.*, **70**, 3961 (1948).

[6] H. Gilman, *ibid.*, **68**, 2104 (1946).

[7] Buu-Hoï, *Rec. trav. chim.*, **67**, 175–190 (1948).

[8] Schwenk and Papa, *J. Org. Chem.*, **11**, 798–802 (1946).

[9] Buu-Hoï and Nguyen-Hoàn, *Rec. trav. chim.*, **68**, 5–33 (1949).

[10] DeTar and Carmack, THIS JOURNAL, **68**, 2025 (1946).

[11] J. R. Johnson and C. E. May, "Organic Syntheses, Coll. Vol. II, Wiley and Sons, New York, N. Y., 1944, p. 8.

[12] Buu-Hoï and Nguyen-Hoàn, *Rec. trav. chim.*, **67**, 309–327 (1948).

[13] Schwenk and Block, THIS JOURNAL, **64**, 3051 (1942).

[14] Kindler, *Ann.*, **431**, 193, 222 (1923).

[15] Steinkopf, Foulsson and Herdey, *Ann.*, **536**, 128 (1938).

[16] Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941).

[17] Barger and Easson, *J. Chem. Soc.*, 2100 (1938); Rojahn and Schulten, *Arch. Pharm. Ber. deut. pharm. Ges.*, **264**, 348 (1926).

TABLE I

ω-(2,5-DIMETHYL-3-THIENYL)-ALKANOIC AMIDES BY WILLGERODT REACTION

2,5-Dimethyl-3-thienyl ketones			Methyl	Ethyl	Propyl	Butyl
Amine[a]			Acet-	*n*-Propion-	*n*-Butyr-	*n*-Valer-
Yield,[b] %	A		69	48	22	7.8
	B		95	80	27	6.5
M. p.,[c] °C.			153.5	144	100.5	104.5
Formula			$C_8H_{11}NOS$	$C_9H_{13}NOS$	$C_{10}H_{15}NOS$	$C_{11}H_{17}NOS$
Nitrogen,[d] %	Calcd.		8.28	7.65	7.11	6.64
	Found		8.45	7.65	7.18	6.81
Acids by hydrolysis of amides	2,5-dimethyl-3-thienyl[e]		3-acetic	3-propionic	3-butyric	3-valeric[f]
	M. p.,[c] °C.		69.5	59.5	58	43.5
	Carbon, %	Calcd.	56.47	58.69	60.61	62.26
		Found	56.82	58.7	60.3	62.0
	Hydrogen, %	Calcd.	5.88	6.52	7.07	7.55
		Found	5.87	6.68	6.89	7.36
Thiomorpholides	Yield, %		66	40	[g]	....
	M. p., °C.		76.5	86.5	....	....
	Nitrogen, %	Calcd.	5.49	5.20	....	....
		Found	5.72	5.16	....	....
Phenyl aliph., yield, %[h]	A		86[i]	82	42	29
	B		63[j]	50	37	....

[a] All these amides were recrystallized from water. [b] Yields by Method A and B as described in experimental part. [c] Melting points corrected; ±0.5°. [d] All microanalysis performed by F. A. Buhler of this laboratory. [e] These acids were recrystallized from water. [f] This acid was recrystallized from alcohol–water. [g] Not obtained crystalline. Hydrolysis of the oil gave 18% over-all yield of the acid. [h] This yield refers to the sum of the yields of amides and free acids. [i] Ammonium hydroxide, sulfur and pyridine–water. [j] Ammonium polysulfide in water (original Willgerodt).

in yields of 55–80% by this reaction. We did not attempt to obtain maximum yields, and further investigation may show that these are not the highest possible for this reduction. This aldehyde was converted to the alcohol by a Meerwein–Ponndorf reduction and the alcohol gave the chloride on treatment with thionyl chloride. This was then treated with potassium cyanide followed by hydrolysis to yield the 2,5-dimethyl-3-thienylacetic acid. Starting again with 2,5-dimethyl-3-thiophene aldehyde and treating it with malonic acid, an excellent yield of 2,5-dimethyl-3-thienylacrylic acid was obtained. This acid was then reduced with sodium amalgam to give 2,5-dimethyl-3-thienylpropionic acid according to the method used by Barger and Easson[17] for 2-thienylpropionic acid. 2,5-Dimethyl-3-thienylbutyric acid was prepared according to the procedure of Steinkopf[15] with some modification.

Subsequent experiments have indicated that properly substituted α-thienyl methyl ketones will also undergo the Willgerodt reaction and this work will be the subject of future reports.

Experimental

2,5-Dimethyl-3-thienylacetamide. Method A.—2,5-Dimethyl-3-acetothienone (10 g.), 25 g. of sulfur, 20 ml. of concentrated ammonium hydroxide and 20 ml. of dioxane were sealed in a glass combustion tube and heated for 11–12 hours at 155–160°. The contents (black liquid, sulfur crust, and long needles) were evaporated to dryness and the residue extracted several times with boiling water. The water extracts were cooled and the crude product crystallized as long needles which melted at 149–150°. Recrystallization from water gave 7.5 g. (69%) of white needles, m. p. 153–154°.

2,5-Dimethyl-3-thienylacetamide. Method B.—2,5-Dimethyl-3-acetothienone (5 g.), 25 g. of yellow ammonium polysulfide, 2.5 g. of sulfur and 20 ml. of dioxane were sealed in a glass combustion tube and heated for 12 hours at 155–160°. The contents were evaporated to dryness and the residue extracted with boiling water. The crude product melted at 151–152°. Recrystallization from water gave 5.2 g. (95%) of white needles, m. p. 153–154°. A mixed melting point with the product from Method A showed no depression.

Hydrolysis of the Amide.—The above product (3 g.) was refluxed with 100 ml. of 10% aqueous potassium hydroxide for 5 hours, acidified with 20% hydrochloric acid and filtered. 2,5-Dimethyl-3-thienylacetic acid crystallized from water as white plates, m. p. 69–70°.

2,5-Dimethyl-3-thienylacetic Acid by the Arndt–Eistert Method.—2,5-Dimethyl-3-thienyl diazomethyl ketone was prepared from 2,5-dimethyl-3-thenoyl chloride, b. p. 113–114° (10 mm.), 135° (42 mm.),[18] according to the procedure of Blicke and Zienty[16] and recrystallized from absolute ether, m. p. 52–53°.

Anal. Calcd. for $C_8H_8N_2OS$: C, 53.33; H, 4.44; N, 15.55. Found: C, 53.53; H, 4.37; N, 15.48.

After rearrangement[16] to the ethyl ester and alcoholic hydrolysis, 2,5-dimethyl-3-thienylacetic acid was isolated, in small quantity, 1–2%, from the resinous mass obtained after filtration of the reaction mixture and removal of the alcohol. This substance was treated with sodium carbonate solution and filtered. The filtrate was acidified yielding a brown hard mass which was removed by filtration. This second filtrate was placed in the ice-box overnight and yielded a small crop of white crystals. The procedure was repeated several times on the original precipitate, the second crops of white crystals were combined and melted at 69° after recrystallization from water. A mixed melting point with a sample from the Willgerodt reaction showed no depression.

Anal. Calcd. for $C_8H_{10}O_2S$: C, 56.47; H, 5.88. Found: C, 56.25; H, 5.86.

2,5-Dimethyl-3-thiophene Aldehyde (Rosenmund Reduction).—A three-necked 1-liter flask was equipped with an efficient mechanical stirrer, a reflux condenser and a

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(18) Ref. 12 described this compound as distilling at 144–145° (13 mm.).

hydrogen inlet tube reaching to within one-half inch of the bottom of the flask. The inlet tube was attached to a calcium chloride drying tube, sulfuric acid trap and to the hydrogen source. An outlet tube was attached to the top of the reflux condenser and passed through a trap into standard sodium hydroxide. Dry xylene (500 ml.) and 7 g. of 5% Pd on carbon were introduced into the flask, hydrogen was passed through the mixture with stirring and 30-50 ml. of the xylene was distilled. 2,5-Dimethyl-3-thenoyl chloride (59 g.) was then introduced. A vigorous stream of hydrogen, efficient stirring and reflux temperature were maintained throughout the reduction. After two hours the reaction was 80% completed and after three hours approximately 90% completed as shown by titration. The catalyst was filtered, xylene was removed in a nitrogen atmosphere at reduced pressure and the aldehyde was vacuum distilled under nitrogen, b. p. 99-101° (10 mm., 55-65%.

Semicarbazone recrystallized from 50% alcohol-water decomposed 234-236°.

Anal. Calcd. for $C_8H_{11}N_3OS$: N, 21.32. Found: N, 21.1.

2,5-Dimethyl-3-thenyl Alcohol.—The above aldehyde (25 g.), 30 g. of aluminum isopropoxide and 450 ml. of dry isopropyl alcohol were heated on a steam-bath for fourteen hours until the test for acetone was negative. The alcohol was removed by distillation, and the residue decomposed with hydrochloric acid and extracted with benzene. The extracts were dried over anhydrous sodium sulfate, the benzene distilled under reduced pressure and the product which weighed 16.5 g. (65%) was obtained as a viscous oil, b. p. 118-121° (15 mm.). Urethane: recrystallized from petrol ether (60-80°), m. p. 77-78°.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.37; H, 5.75; N, 5.37. Found: C, 64.7; H, 5.64; N, 5.56.

2,5-Dimethyl-3-thienylacetic Acid.—2,5-Dimethyl-3-thenyl alcohol (16 g.), 17 g. of dimethylaniline and 20 g. of thionyl chloride in 50 ml. of dry chloroform yielded 9 g. (50%) of the chloride, b. p. 105-107° (20 mm.). The chloride was dissolved in 100 ml. of ethyl alcohol, treated with 7 g. of potassium cyanide in 12 ml. of water and refluxed for twenty hours. To this reaction mixture was added 40 ml. of 5 *N* potassium hydroxide and it was refluxed for eight hours. The alcohol was removed by distillation, the dark brown solution filtered, extracted with ether and acidified with 1:1 hydrochloric acid. The expected acid, 2,5-dimethyl-3-thienylacetic acid, weighed 2.6 g. (26%) and melted at 69-70°. A mixed melting point with a sample from the Willgerodt reaction showed no depression.

Anal. Calcd. for $C_8H_{10}C_2S$: C, 56.47; H, 5.88. Found: C, 56.6; H, 5.61.

2,5-Dimethyl-3-thienylpropionic Acid.—2,5-Dimethyl-3-thiophenealdehyde was prepared according to the procedure previously described. The yield of aldehyde from this particular run was 80%. The above aldehyde (22.4 g., 0.16 *M*), 34 g. (0.32 *M*) of malonic acid, 80 ml. of dry pyridine and 1 ml. of piperidine were warmed on a steam bath for two and one-half hours and then boiled for fifteen minutes. After cooling, the solution was poured into water and treated with excess hydrochloric acid. Filtration and recrystallization from alcohol-water mixture yielded 27 g., 90%, of 2,5-dimethyl-3-thienylacrylic acid, m. p. 165-166°.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.34; H, 5.49. Found: C, 59,41; H, 5.37.

2,5-Dimethyl-3-thienylacrylic acid (7 g.), was just neutralized with 5% sodium hydroxide solution and 200 g. of 2% sodium amalgam was added. The mixture was left overnight at 15° and then warmed on a steam-bath until all of the amalgam was decomposed. The solution was decanted from the mercury, filtered and treated with Norite. After filtration and cooling the solution was acidified to yield an oil which solidified immediately. Filtration and recrystallization from water yielded 3.5 g., 50%, of 2,5-dimethyl-3-propionic acid, m. p. 59-60°. A mixed melting point with a sample from the Willgerodt reaction showed no depression.

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.69; H, 6.52. Found: C, 58.61; H, 6.34.

2,5-Dimethyl-3-thienylbutyric Acid.—The procedure used was essentially that of Steinkopf[15] except that the steam distillation in the preparation of β-(2,5-dimethyl-3-thenoyl)-propionic acid was eliminated. Instead, the entire reaction mixture was made strongly alkaline, diluted with water and extracted with ether to remove the nitrobenzene. The water layer was filtered, made strongly acidic to retain aluminum hydroxide in solution and filtered. Recrystallization from water yielded 78% of the product. Reduction with zinc amalgam and hydrochloric acid yielded the 3-butyric acid, m. p. 58-59°.[19] A mixed melting point with a sample from the Willgerodt reaction showed no depression.

2,5-Dimethylthiophene-3-thioacetmorpholide.—2,5-Dimethyl-3-acetothienone (10 g.), 13 g. of morpholide and 3.5 g. of sulfur were refluxed for twelve hours. The heavy black oil was poured into 150 ml. of warm water and ethyl alcohol was added until solution was complete (about 50 ml.). The resulting mixture was allowed to stand for two days. The solid was filtered and recrystallized from alcohol. Further product was recovered by addition of water to the alcohol filtrate. Recrystallization from alcohol–water gave 11 g. (66%), m. p. 76-77°.

Experimental procedures for the other amides and thiomorpholides reported are essentially the same. Thiomorpholides of the longer chain ketones required longer periods of standing before crystallization occurred.

Hydrolysis of the Thiomorpholide.—A portion of the above thiomorpholide (3 g.) was refluxed for six hours in 50 ml. of 10% aqueous potassium hydroxide. Acidification of the cooled filtrate yielded an acid which melted 69-70° after recrystallization from water. A mixed melting point with 2,5-dimethyl-3-thienyl-acetic acid showed no depression.

Summary

1. The Willgerodt reaction has been successfully extended to a group of ketones in the thiophene series.

2. 2,5-Dimethyl-3-thienylalkanoic amides are reported from two forms of the Willgerodt reaction. The first four amides of this series have been prepared and hydrolyzed to the corresponding acids.

3. The Kindler modification using morpholine and sulfur has been applied to the first three members of the 2,5-dimethyl-3-thienyl alkyl ketone series. Crystalline thiomorpholides have been prepared from the first two members. All three thiomorpholides have been hydrolyzed to the corresponding acids.

4. The structures of three of the products, 2,5-dimethyl-3-thienylacetic, -propionic and -butyric acids, have been established by independent syntheses involving the Rosenmund and Arndt–Eistert reactions.

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[19] Ref. 15 described this compound as melting at 55-56°.