224.7°) after one recrystallization from acetone–absolute alcohol. Dr. A. T. Blomquist and Dr. W. C. McCrone of Cornell University showed it to be identical with an authentic specimen[8] by crystallographic measurements.

Treatment of 20 mg. of IV with 2 cc. of 98% nitric acid alone at 40° for ten minutes yielded 7 mg. of V.

Action of Nitrosyl Chloride and Acetic Anhydride on VI.—A suspension of 0.5 g. of 1-acetoxymethyl-3,5,7-trinitro-1,3,5,7-tetrazacycloöctane (VI) (prepared from III and acetic anhydride and nitric acid)[9] in 5 cc. of acetic anhydride at 0° was treated with a chilled solution of 5 cc. of nitrosyl chloride in 5 cc. of acetic anhydride. After the suspension had been stirred for one hour at 0° and for 12 hours at room temperature, 0.25 g. of unchanged VI was removed by filtration; addition of the filtrate to 20 cc. of ice and water precipitated 115 mg. of product (m.p. 192–205°). The **1-nitroso-3,5,7-trinitro-1,3,5,7-tetrazacycloöctane** (VII) crystallized from acetone–absolute alcohol in colorless needles; m.p. 236–237°. The highest m.p. obtained was 243.2–243.3°; the compound decomposed suddenly into gaseous products.

Anal. Calcd. for $C_4H_8N_8O_7$: C, 17.1; H, 2.9; N, 40.0. Found: C, 17.6; H, 3.0; N, 39.9.

Oxidation of VII to HMX (VIII).—Oxidation of 40 mg. of VII by 0.15 cc. of 30% hydrogen peroxide and 2 cc. of 98% nitric acid was carried out as described for the oxidation of IV. The HMX (35 mg.) obtained on drowning the mixture melted at 281° alone and when mixed with an authentic specimen.[6]

ANN ARBOR, MICH. RECEIVED DECEMBER 11, 1950

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Willgerodt Reaction in the Heterocyclic Series. II. Some Compounds of the α- and β-Thienyl Series

BY JOSEPH A. BLANCHETTE AND ELLIS V. BROWN

The Willgerodt reaction in the thiophene series has been extended with a view to determining its scope. Alkyl substituted α-thienyl methyl ketones, β-thienyl methyl ketone, α-formyl-, α-vinyl-, α-acetonyl- and α-(1-hydroxyethyl)-thiophenes have yielded the respective amides. Several new acetamides and acetic acids of the thiophene series are characterized and a method for the preparation of 3-methyl-2-thienyl methyl ketone, which does not involve separation of the 3 and 4 isomers, is described.

We have recently reported[1] a study of the Willgerodt reaction with a series of 2,5-dimethyl-3-thienyl aliphatic ketones. It had previously been shown[1,2] that 2-thienyl methyl ketone does not react under the conditions of the Willgerodt reaction although the introduction of α,α′-methyl groups into thiophene alkyl ketones allowed us to obtain the expected amides. In view of these facts, the effect of substituents and their position seemed to be of major importance in the application of this reaction to thiophene compounds.

This paper deals with the further application of the Willgerodt reaction to thiophene compounds in an attempt to determine the necessary groups and position for a favorable reaction. We have conducted our investigation with the aim of determining the limiting conditions necessary for a successful reaction. As an addition to the previous study both α-methyl groups were replaced by ethyl groups. The 2,5-diethyl-3-thienyl methyl ketone gave the expected 2,5-diethyl-3-thienylacetamide in satisfactory yields.

α-Thienyl ketones which react to give the respective amides are 5-methyl-2-thienyl methyl ketone, 5-ethyl-2-thienyl methyl ketone and 2,3-dimethyl-5-thienyl methyl ketone. Recently Ford, Prescott and Colingsworth[2b] applied the Kindler modification to 5-*t*-butyl-2-thienyl methyl ketone obtaining a derivative of 5-*t*-butyl-2-thienylacetic acid and, in view of the failure of 2-acetothienone to react, speculated that the reactive hydrogen in the 5-position must be replaced by an alkyl group before the Willgerodt reaction can take place. This does not seem to be the case as we have converted both 3,4-dimethyl-2-thienyl methyl ketone and 3-methyl-2-thienyl methyl ketone to the corresponding acetamides. To circumvent the isomeric mixture obtained from direct acetylation of 3-methylthiophene, the latter ketone was prepared by a five-step process. 3-Methylthiophene was converted to 2-bromo-3-methylthiophene by the action of N-bromosuccinimide. 2-Bromo-3-methylthiophene was treated with magnesium and then carbonated to yield 3-methyl-2-thienylcarboxylic acid. This acid was treated with thionyl chloride and then converted to the ketone with dimethylcadmium by the method of Gilman and Nelson[3] in 85% yield. The melting point of the 3-methyl-2-thienylcarboxylic acid was in agreement with that reported in the literature.[4]

At this point it seemed plausible to assume that at least one ring position, either α or β, must contain an alkyl substituent for reaction to occur. However, 2-vinylthiophene was found to give 2-thienylacetamide in yields of 25–30% despite an otherwise completely unsubstituted ring. The failure of 2-acetothienone to react may therefore be due to some peculiarity of this particular molecule rather than to the unsubstituted character of the ring. Further support for this assumption was sought from other monosubstituted thiophenes with different functional groups at the 2-position.

2-Thienylcarboxaldehyde[5] gave 2-thienylcarboxamide[6] in excellent yields and a mixed melting point with an authentic sample of this amide, prepared from 2-cyanothiophene, showed no de-

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[1] E. V. Brown and J. A. Blanchette, THIS JOURNAL, **72**, 3414 (1950).

[2] (a) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946); (b) J. H. Ford, G. C. Prescott and D. R. Colingsworth, THIS JOURNAL, **72**, 2109 (1950).

[3] H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[4] W. Steinkopf and H. Jacob, *Ann.*, **515**, 273 (1935); L. E Levi, *Ber.*, **19**, 657 (1886); L. Gattermann, *Ann.*, **244**, 58 (1888); I. J. Rinkes, *Rec. trav. chim.*, **52**, 1052 (1933).

[5] K. Wiberg, "Organic Syntheses," Vol. 29, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 87.

[6] W. Steinkopf, "Chemie Des Thiophens," J. W. Edwards, Ann Arbor, Mich., 1944, p. 85.

TABLE I

THIENYLALKANOIC AMIDES

Thienyl compound	Amide	M.p., °C.	Yield, % A	B	Formula	Nitrogen,[g] % Calcd.	Found
2,5-Diethyl-3-methyl ketone	3-Acetamide	116–117	52	40	$C_{10}H_{15}NOS$	7.11	6.99
5-Ethyl-2-methyl ketone	2-Acetamide	148	42	55	$C_8H_{11}NOS$	8.28	8.17
5-Methyl-2-methyl ketone	2-Acetamide	143–144	41	54	C_7H_9NOS	9.03	8.98
3,4-Dimethyl-2-methyl ketone	2-Acetamide	152	34	24	$C_8H_{11}NOS$	8.28	8.16
3-Methyl-2-methyl ketone	2-Acetamide	142	27	29	C_7H_9NOS	9.03	8.98
2,3-Dimethyl-5-methyl ketone	5-Acetamide	165–166	40	55	$C_8H_{11}NOS$	8.28	8.27
3-Methyl ketone	3-Acetamide	154–155	5	13	C_6H_7NOS	9.94	10.25
2-Acetone[a]	2-Propionamide	99–100[d]	20	28			
2-Vinyl[b]	2-Acetamide	147–148[e]	25	30	C_6H_7NOS	9.93	9.94
2-Carboxaldehyde[c]	2-Carboxamide	179–180[f]	63	70			
2-Methylcarbinol	2-Acetamide	147–148[e]	22	35			

[a] This compound was prepared by the method of Cagniant (ref. 7), The semicarbazone was recrystallized from 50% alcohol–water and melted at 193–194° (ref. 7). [b] This compound was prepared by the method of Schick and Hartough, THIS JOURNAL, **70**, 1646 (1948), from 2-iodothiophene. [c] This compound was prepared from 2-chloromethylthiophene (ref. 8) by the method of Wiberg (ref. 5). [d] This compound was described by Barger and Easson, *J. Chem. Soc.*, 2100 (1938). [e] This compound was described by ref. 2b, 7, Crowe and Nord, *J. Org. Chem.*, **15**, 81 (1950). [f] A mixed melting point with an authentic sample of this compound showed no depression. [g] All microanalyses performed by A. Sirotenko of this Laboratory.

pression. Hydrolysis of the 2-thienylcarboxamide from the Willgerodt reaction yielded the known 2-thienylcarboxylic acid and a mixed melting point with an authentic sample of this acid showed no depression.

Attempts to prepare 2-thienylacetone from dimethylcadmium and 2-thienylacetyl chloride[7] resulted in a resinous mass, whereas the reaction between 2-thienylacetonitrile[8] and methylmagnesium bromide gave a compound which has not been identified. This ketone was prepared from ethyl α-methyl-2-thiopheneglycidate by the method of Cagniant[7] and was converted to 2-thienylpropionamide under the conditions of the Willgerodt reaction.

Methyl-α-thienylcarbinol,[9] prepared from 2-thienylcarboxaldehyde and methylmagnesium bromide in yields of 85%, was also successfully converted to 2-thienylacetamide by the Willgerodt reaction.

The ability of these thiophene compounds to give a successful Willgerodt reaction and the failure of 2-acetothienone to react properly made it of considerable interest to investigate 3-thienyl methyl ketone.[10] Attempts to prepare this ketone directly from 3-methylthiophene were unsuccessful. Using the commercial samples of N-bromosuccinimide at our disposal, we were unable to obtain the 3-bromomethylthiophene which had previously been reported.[10] 3-Thienyl methyl ketone was synthesized from 2,5-dichlorothiophene by a five-step process. 2,5-Dichlorothiophene was acetylated and sodium hypochlorite oxidation of the resulting methyl ketone gave 2,5-dichloro-3-thienylcarboxylic acid. Dehalogenation of 2,5-dichloro-3-thienylcarboxylic acid was accomplished by the method of Folkers[11] with 5% Pd-on-carbon to yield the known 3-thienylcarboxylic acid.[6,10] Treatment of the acid chloride with dimethylcadmium gave the 3-acetothienone which was found to undergo a Willgerodt reaction to the amide in yields of 5–15%.

These results seem to indicate that the thiophene nucleus of the ketone does not require the presence of alkyl substituents to produce the respective amide by the Willgerodt reaction and that 2-acetothienone is unique in its failure to undergo this reaction. The yields of amides obtained from the various compounds are given in Table I.

TABLE II

THIENYL ACIDS

Thienyl acid	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
2-Acetic[a]	54–55	$C_7H_8O_2S$	53.85	54.18	5.13	4.84
2-Acetic	67–68	$C_8H_{10}O_2S$	56.47	56.80	5.88	5.81
2-Acetic[a]	89–90	$C_7H_8O_2S$	53.85	54.12	5.13	4.96
5-Acetic[a]	97–98	$C_8H_{10}O_2S$	56.47	56.66	5.88	5.73
3-Acetic[a]	79–80[b]					
2-Propionic[a]	44–45[c]					
2-Acetic[a]	62–63[d]	$C_6H_6O_2S$	50.70	50.93	4.23	4.35
2-Carboxylic	128[e]					
2-Acetic[a]	62–63[d]					

[a] These acids were recrystallized from petroleum ether (30–60°); the others from water. [b] This compound is described by ref. 10. [c] This compound was described by Barger and Easson, *J. Chem. Soc.*, 2100 (1938). [d] This compound was described by ref. 2b, 7, Crowe and Nord, *J. Org. Chem.*, **15**, 81 (1950). [e] A mixed melting point with an authentic sample of this compound showed no depression.

Experimental

Preparation of Thienyl Methyl Ketones.—With the exception of 3-methyl-2-thienyl methyl ketone, 3-thienyl methyl ketone and 2-thienylacetone, the ketones used in this investigation were prepared by acetylation of the corresponding alkyl thiophenes by the method of Johnson and May[12] for the preparation of 2-acetothienone.

3-Methyl-2-thienyl Methyl Ketone.—A mixture of 55 g. (0.56 mole) of 3-methylthiophene,[13] 95 g. (0.53 mole) of N-bromosuccinimide and 150 ml. of carbon tetrachloride was refluxed for 5 hours on the steam-bath. The reaction was quite vigorous during the initial 15 minutes and required cooling with a water-bath. The reaction mixture was cooled and the succinimide removed by filtration. The solvent was removed at reduced pressure and fractionation of

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[7] P. Cagniant, *Bull. soc. chim.*, 847 (1949).

[8] F. F. Blicke and F. Leonard, THIS JOURNAL, **68**, 1934 (1946).

[9] R. Kuhn and O. Dann, *Ann.*, **547**, 293 (1941); D. T. Mowry, M. Renoll and W. F. Huber, THIS JOURNAL, **68**, 1105 (1946).

[10] E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

[11] K. Folkers, *et al.*, *ibid.*, **67**, 2092 (1945).

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

[13] 3-Methylthiophene was obtained through the courtesy of the Socony-Vacuum Oil Company.

the residue yielded 70 g. (40–50%) of 3-methyl-2-bromothiophene,[14] b.p. 61–63° (13 mm.), 68–70° (16 mm.).

3-Methyl-2-bromothiophene (0.64 mole) was converted to the Grignard reagent in the usual manner. The reaction flask was then fitted with an inlet tube and a capillary outlet and cooled to −7°. A stream of dry carbon dioxide was passed into the mixture with continuous stirring for 3 hours after which time no temperature rise was noted on increasing the flow of gas. The temperature was allowed to rise to 4° after the first 1.5 hours. The reaction mixture was decomposed with dilute sulfuric acid and the ether layer washed with water several times, after which it was extracted with three 100-ml. portions of 10% sodium hydroxide. The solutions were well cooled during this extraction. The aqueous solution was then acidified and the acid removed by filtration. Recrystallization from water yielded 59 g., 64%, of 3-methyl-2-thienylcarboxylic acid, m.p. 147–148°.

3-Methyl-2-thienylcarboxylic acid (50 g.) (0.36 mole) was refluxed with 200 ml. of thionyl chloride for 3 hours and the excess thionyl chloride removed by distillation. The acid chloride, without further purification, was dissolved in 100 ml. of anhydrous ether and added slowly to 0.36 mole of an ethereal solution of dimethylcadmium[3] prepared from 0.36 mole of cadmium chloride and 0.7 *M* of methylmagnesium bromide. During the addition of the acid chloride, the reaction mixture was mechanically stirred and cooled in an ice-bath after which it was warmed to the reflux temperature for an additional 0.5 hour. The mixture was again cooled in an ice-bath and decomposed with dilute sulfuric acid. The ether layer was separated, washed successively with water, dilute sodium hydroxide and water, after which it was dried over anhydrous sodium sulfate. The product, 3-methyl-2-thienyl methyl ketone,[15] distilled at 98–99° (14 mm.), 43 g., 86%.

3-Thienyl Methyl Ketone.—2,5-Dichlorothiophene was acetylated according to Bachman and Heisey.[16] 2,5-Dichloro-3-thienyl methyl ketone[16,17] was oxidized with potassium hypochlorite to the known 2,5-dichloro-3-thienylcarboxylic acid[14,17b] which was then dehalogenated[11] with 5% Pd-on-carbon in the Parr apparatus in yields of 75%. The ratio of the catalyst to ketone used was 2:1 by weight. When the dehalogenation was carried out on fairly large amounts of the dichloro acid, 10–15 g., the melting point of the 3-thienylcarboxylic acid was somewhat depressed probably due to the presence of a small quantity of monochloro acid. The impurity was removed either by a rerun with fresh catalyst or by distillation after preparation of the ketone. A mixed melting point of the resulting 3-thienylcarboxylic acid[6,10] with a sample prepared by the alkaline permanganate oxidation of 3-methylthiophene[18] showed no depression. As the latter preparation of 3-thienylcarboxylic acid gives very low yields it was not a satisfactory method for our work.

3-Thienylcarboxylic acid (30 g.) was converted to 3-thienyl methyl ketone,[10] b.p. 117° (21 mm.), 12 g. (41%), by the procedure described above for 3-methyl-2-thienyl methyl ketone. The semicarbazone was recrystallized from 33% alcohol-water and melted at 173–174°.[10]

2-Thienylcarboxamide.—2-Cyanothiophene[19] (6 g.) was dissolved in 20 ml. of concentrated sulfuric acid with cooling. After 15 minutes the mixture was poured onto cracked ice whereupon the amide separated as white crystals. Filtration and recrystallization from water gave 4 g. of 2-thienylcarboxamide, m.p. 179–180°. A mixed melting point with a sample obtained from the Willgerodt reaction showed no depression.

Methyl-α-thienylcarbinol.—Methylmagnesium bromide (0.73 mole) was prepared in the manner previously described. 2-Thiophenecarboxaldehyde, 82 g. (0.73 *M*) in 50 ml. of anhydrous ether was added dropwise while the reaction mixture was cooled in an ice-bath with mechanical stirring. After the addition, the flask was brought to reflux for 0.5 hour, cooled and poured onto ice and dilute sulfuric acid. The ether layer was separated, washed successively with water, 2% sodium bicarbonate solution, water and dried over anhydrous calcium chloride. The ether was removed and the alcohol distilled at 80–83° (5 mm.), 79 g., 85%. The urethan was recrystallized from petroleum ether (60–80°) and melted at 85–86°.[9]

Willgerodt Reaction. Method A.—The thiophene derivative (10 g.), 25 g. of sulfur, 25 ml. of concentrated ammonium hydroxide and 30 ml. of dioxane were sealed in a Carius tube and heated for 11–12 hours at 150–160°. The contents of the tube were evaporated to dryness and the residue extracted several times with boiling water. The water extracts were cooled and the crude amides removed by filtration.

Willgerodt Reaction. Method B.—The thiophene compound (5 g.), 25 g. of yellow ammonium polysulfide, 3.5 g. of sulfur and 25 ml. of dioxane were sealed in a Carius tube and heated for 11–12 hours at 150–160°. The contents were evaporated to dryness and the residue extracted several times with boiling water. The water extracts were cooled and the crude amides removed by filtration.

With the exception of 2-thienylpropionamide, the amides were purified by treating with Norit and recrystallization from water. 2-Thienylpropionamide was recrystallized from benzene–petroleum ether. The amides were somewhat soluble in ether and crystallized from water as white plates or needles.

Hydrolysis of the Amides.—The amides from the Willgerodt reaction (1–2 g.) were refluxed with 70–100 ml. of 25% aqueous potassium hydroxide until the evolution of ammonia was slight, usually 2 to 3 hours. The cooled solutions were acidified with 20% hydrochloric acid and filtered. In those cases where the acids separated as oils the acidic solutions were extracted with ether, the ether evaporated and the oil solidified by cooling. The acids were purified by recrystallization from water or petroleum ether (30–60°).

NEW YORK, N. Y. RECEIVED NOVEMBER 20, 1950

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