after hydrolysis in H_2O^{18} confirms the conclusion reached from 88/86 mass ratio results, *i. e.*, that the one heavy oxygen is in the carbonyl position.

Given that a split of bonds 3 and 5 is relatively probable, one would expect that the ion intensities for masses 29 or 28 would contain contributions from fragments H—C≡O or C=O resulting from the H_2C—O residue left from this bond split. The results discussed above would then lead to a prediction that the 31/29 and 30/28 intensities would show little, if any, increase for the lactones obtained after H_2O^{18} hydrolysis. Actually the results for the γ-butyrolactone, as well as comparisons with those for the β-propio and γ-valerolactones, indicate that the fragments C_2H_5 and C_2H_4 make large contributions to the ion intensities for masses 29 and 28. Even so it is of interest to note in Table III that the 31/29 and 30/28 ratios change rather little for the four lactone samples from the values for the original lactone.

Analysis of the ion intensities for masses in the region 40 to 45 does not permit of any conclusion about the hydrolysis mechanism. The relatively large size of the 43 and 44 peaks makes detection of isotope effects difficult as also does the uncertainty about the magnitude of the carbon dioxide background for the mass 44 peak. Furthermore it is difficult to assess the contribution made to the 41 and 42 peaks by the various possible fragments. However it can be said that none of the effects in this region are inconsistent with the conclusions reached above.

Qualitatively, the experimental results all indicate acyl–oxygen fission for both the acid-catalyzed and basic hydrolysis of γ-butyrolactone but it is not possible to give a quantitative figure to the percentage of reaction by this path. Although the data are best fitted by the assumption that all of the hydrolysis goes by the acyl-oxygen split, the variation in the intensity ratios is such that as much as 10 or 15% might actually go by the path of alkyl–oxygen fission. This uncertainty is probably unavoidable when water with only 1.6% O^{18} is used.

Summary

Samples of γ-butyrolactone have been hydrolyzed in aqueous solutions containing 1.6% H_2O^{18} and either three molar sodium hydroxide or 0.8 molar sulfuric acid and the lactone reformed from the hydrolysis product. These lactone samples have been subjected to mass spectrometric analysis and the ion intensity patterns compared with that obtained from ordinary γ-butyrolactone. On the basis of changes in the ion intensity ratios for masses 88/86 and 58/56 it is concluded that both the acid-catalyzed and basic hydrolysis of this lactone goes by an acyl-oxygen bond split in accord with predictions based on the results for hydrolysis of aliphatic esters and β-lactones.

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[CONTRIBUTION NO. 750 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Condensations Effected by Boron Fluoride Complexes. III. The Acylation of Certain Substituted Thiophenes and Furans[1]

BY MARTIN W. FARRAR AND ROBERT LEVINE

In earlier communications[1,2] from this Laboratory, it was reported that catalytic amounts of the diethyl ether and acetic acid complexes of boron fluoride may be used as condensing agents to give high yields of 2-acylfurans and 2-acylthiophenes when furan and thiophene are acylated with anhydrides. A possible mechanism for these acylations was also presented.

In the present paper, we report the extension of our earlier work to the acylation of a number of substituted furan and thiophene compounds with acetic, propionic and *n*-butyric anhydrides in the presence of boron fluoride etherate as the condensing agent. The ketones which have been prepared in the present study are listed in Table I.

The acylation of 2-methylfuran with acetic anhydride has resulted in a 42% yield of 5-methyl-2-acetylfuran. This yield is considerably higher than that reported by Reichstein[3] who prepared it by the interaction of 2-methylfuran with acetyl chloride in the presence of stannic chloride as the condensing agent. The higher homologs, 5-methyl-2-propionyl and 5-methyl-2-*n*-butyrylfuran, which were prepared in yields of 52% and 62%, respectively, are apparently new compounds. The acylation of 2-methylthiophene in 81% yield compares very favorably with that reported earlier[4] when orthophosphoric acid was used as the condensing agent. Propionylation and *n*-butyrylation of 2-methylthiophene gave 82% and 97% yields of 5-methyl-2-propionyl and 5-methyl-2-*n*-butyrylthiophene, respectively. These ketones have apparently not been reported previously.

The benzoylation of 3-methylthiophene using aluminum chloride as the catalyst has resulted in the formation of two isomeric ketones, 3-methyl-2-benzoylthiophene and 4-methyl-2-benzoylthiophene.[5] The acetylation of this alkylated thiophene using aluminum chloride as the condensing

(1) For paper II in this series, see Levine, Heid and Farrar, THIS JOURNAL, **71**, 1207 (1949).

(2) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

(3) Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).

(4) Hartough and Kosak, THIS JOURNAL, **69**, 3093 (1947).

(5) Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).

TABLE I

KETONES DERIVED FROM SUBSTITUTED FURANS AND THIOPHENES[a]

Ketone	Yield, %	B. p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
5-Methyl-2-acetylfuran[b,c]	42	71–73	8							
5-Methyl-2-propionylfuran[c,d]	52	69.5–70	4.5	$C_8H_{10}O_2$	69.54	69.22	7.30	7.23		
5-Methyl-2-butyrylfuran[c,e]	62	80–81	4	$C_9H_{12}O_2$	71.02	70.86	7.94	8.06		
5-Methyl-2-acetylthiophene[f,g]	81	98–100	8							
5-Methyl-2-propionylthiophene[g,h]	82	93–94	4.5	$C_8H_{10}OS$	62.28	62.42	6.54	6.53	20.77	20.68
5-Methyl-2-butyrylthiophene[g,i]	97	105–106	4.5	$C_9H_{12}OS$	64.25	64.37	7.19	7.12	19.06	19.03
3-Methyl-2-acetylthiophene[j,k,l]	71	74–74.5	4							
4-Methyl-2-acetylthiophene[j,m,n]	12	85–85.5	4							
3-Methyl-2-propionylthiophene[o,p,l]	80	85–86	4	$C_8H_{10}OS$	62.28	62.30	6.54	6.71	20.77	20.60
4-Methyl-2-propionylthiophene[o,q,n]	11	98–99	5			62.41		6.52		20.55
3-Methyl-2-butyrylthiophene[o,r,l]	59	98–99	5	$C_9H_{12}OS$	64.25	64.31	7.19	7.18	19.06	19.27
4-Methyl-2-butyrylthiophene[o,s,n]	38	108.5–109	5			64.42		7.45		18.84
5-Chloro-2-acetylthiophene[t,u]	70	88–89 (45.5–46 (m. p.))	4.5							
5-Chloro-2-propionylthiophene[v,u]	78	96–97 (46.5–47.5 (m. p.))	4.5	C_7H_7OSCl	48.13	47.83	4.04	3.78		
5-Chloro-2-butyrylthiophene[w,u]	83	106–107 (38–39 (m. p.))	4.5	C_8H_9OSCl	50.92	51.30	4.81	5.07		
5-Bromo-2-acetylthiophene[x,y]	66	105–107 (94–95 (m. p.))	4.5							
5-Bromo-2-propionylthiophene[z,y]	71	112–113 (52–53 (m. p.))	5	C_7H_7OSBr	38.37	38.20	3.22	2.99		
5-Bromo-2-butyrylthiophene[aa,y]	83	124–125 (34–35 (m. p.))	5	C_8H_9OSBr	41.21	41.29	3.89	3.78		

[a] All melting points are corrected. [b] Semicarbazone, m. p. 190.5–191.5° (ref. 3). [c] Hypochlorite oxidation (ref. 9 and 10) gave 5-methyl-2-furoic acid, m. p. 108.8–109.8° (Runde, Scott and Johnson, THIS JOURNAL, **52**, 1284 (1930)). [d] Semicarbazone, m. p. 156–157° (recrystallized from a mixture of benzene and ethanol). *Anal.* Calcd. for $C_9H_{13}O_2N_3$: N, 21.52. Found: N, 21.48. [e] Semicarbazone, m. p. 149–150° (recrystallized from dilute ethanol). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: N, 20.48. Found: N, 20.39. [f] Semicarbazone, m. p. 223–224° (Steinkopf, *Ann.*, **424**, 16 (1920)). [g] Hypochlorite oxidation (ref. 9 and 10) gave 5-methyl-2-thenoic acid, m. p. 137–138° (Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947)). [h] Semicarbazone, m. p. 203–204° (recrystallized from a mixture of benzene and ethanol). *Anal.* Calcd. for $C_9H_{13}ON_3S$: N, 19.89; S, 15.19. Found: N, 20.16; S, 15.10. [i] Semicarbazone, m. p. 199–200° (recrystallized from a mixture of benzene and ethanol). *Anal.* Calcd. for $C_{10}H_{15}ON_3S$: N, 18.68; S, 14.25. Found: N, 18.54; S, 14.47. [j] In this run, 3 moles of 3-methylthiophene, 3.45 moles of acetic anhydride and 28 g. of boron fluoride etherate were used. [k] Semicarbazone, m. p. 206–207° (see ref. in note *g*). [l] Hypochlorite oxidation (ref. 10 and 11) gave 3-methyl-2-thenoic acid, m. p. 146–147° (see ref. in note *g*). [m] Semicarbazone, m. p. 219–220° (see ref. in note *g*). [n] Hypochlorite oxidation (ref. 10 and 11) gave 4-methyl-2-thenoic acid, m. p. 122–122.5° (see ref. in note *g*). [o] In this run, 1.5 moles of 3-methylthiophene, 1.72 moles of acetic anhydride and 21 g. of boron fluoride etherate were used. [p] Semicarbazone, m. p. 189–190° (recrystallized from ethanol). *Anal.* Calcd. for $C_9H_{13}ON_3S$: N, 19.89; S, 15.19. Found: N, 19.65; S, 15.04. [q] Semicarbazone, m. p. 204–205° (recrystallized from ethanol). *Anal.* Calcd. for $C_9H_{13}ON_3S$: N, 19.89; S, 15.19. Found: N, 20.12; S, 15.37. [r] Semicarbazone, m. p. 147–148° (recrystallized from a mixture of benzene and ethanol). *Anal.* Calcd. for $C_{10}H_{15}ON_3S$: N, 18.68; S, 14.25. Found: N, 18.52; S, 14.01. [s] Semicarbazone, m. p. 192–193° (recrystallized from a mixture of benzene and ethanol). *Anal.* Calcd. for $C_{10}H_{15}ON_3S$: N, 18.68; S, 14.25. Found: N, 18.85; S, 14.09. [t] Semicarbazone, m. p. 233–234° (see ref. in note *g*). [u] Hypochlorite oxidation (ref. 10 and 11) gave 5-chloro-2-thenoic acid, m. p. 153–154° (see ref. in note *g*). [v] Semicarbazone, m. p. 217–218° (recrystallized from ethanol). *Anal.* Calcd. for $C_8H_{10}ON_3SCl$: N, 18.13. Found: N, 18.36. [w] Semicarbazone, m. p. 210.5–211.5° (recrystallized from ethanol). *Anal.* Calcd. for $C_9H_{12}ON_3SCl$: N, 17.10. Found: N, 17.26. [x] Semicarbazone, m. p. 234–235° (see ref. in note *g*). [y] Hypochlorite oxidation (ref. 10 and 11) gave 5-bromo-2-thenoic acid, m. p. 141–142° (see ref. in note *g*). [z] Semicarbazone, m. p. 215–216° (recrystallized from ethanol). *Anal.* Calcd. for $C_8H_{10}ON_3SBr$: N, 15.22. Found: N, 15.29. [aa] Semicarbazone, m. p. 208–209° (recrystallized from ethanol). *Anal.* Calcd. for $C_9H_{12}ON_3SBr$: N, 14.48. Found: N, 14.32.

agent has also been studied.[6,7a,7b] While Demuth[6] and Gerlach[7a] isolated only one ketone, 3-methyl-2-acetylthiophene, Linstead and coworkers[7b] apparently obtained a mixture of 3-methyl-2-acetyl and 4-methyl-2-acetylthiophene since they isolated the isomeric carboxylic acids after oxidation of the ketonic mixture. Recently, Hartough and Kosak[4] have studied this reaction using orthophosphoric acid as the condensing agent and have isolated a 92% yield of mixed ketones, which consisted of 80% of the 3-methyl-2-acetyl and 20% of the 4-methyl-2-acetyl derivatives.

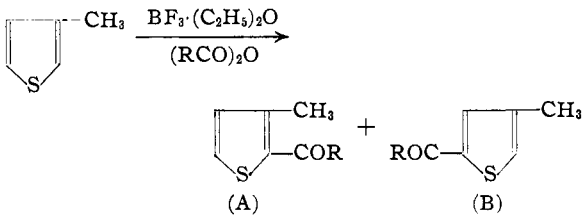
In the present study, we have found that with boron fluoride etherate as the condensing agent, the acylation of 3-methylthiophene also gives rise to the formation of isomeric ketones. The over-all reactions are summarized in Chart I.

It may be seen that 3-methylthiophene is acylated predominantly at the 2-position of the thiophene ring. These results are in agreement

(6) Demuth, *Ber.*, **18**, 3024 (1885).

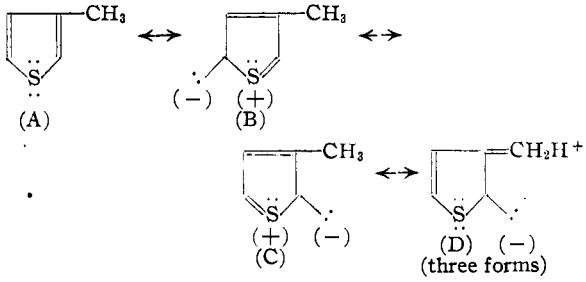
(7) (a) Gerlach, *Ann.*, **267**, 153 (1892); (b) Linstead, Noble and Wright, *J. Chem. Soc.*, 911 (1937).

CHART I



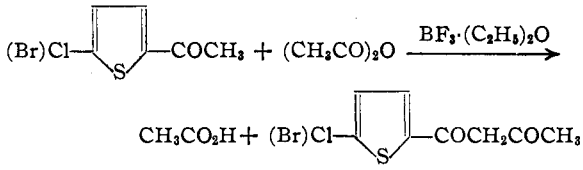
R	Mixed ketones, %	A, %	B, %
CH_3–	83	86	14
C_2H_5–	91	88	12
n-C_3H_7–	97	61	39

with the assumption that in an electrophilic substitution reaction only the following resonance forms make important contributions to the structure of the molecule. Since these acylation



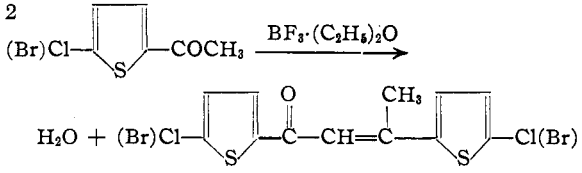
reactions are of the Friedel–Crafts type and since the mechanism of such acylations is believed to involve an electrophilic attack of a carbonium ion at an electron rich spot of the ring[1,2,8] equal amounts of the 2,3 and the 2,4 isomers should be formed if structures (B) and (C) contributed equally to the structure of the 3-methylthiophene molecule in the absence of other resonance forms. However, superimposed upon the resonance within the thiophene ring, there is the possibility of the added activating effect at the 2-position due to the hyperconjugation of the hydrogen atoms of the methyl group which is located on the 3-carbon atom of the thiophene ring. As a result of the added activation at the 2-position over that at the 5-position of the ring, it is reasonable that the predominant isomer formed in the acylations is the 2-acyl-3-methyl derivative. The reason for the sharp drop in the ratio of the 2,3 to the 2,4-isomers from six to one in the case of the methyl ketones to approximately one and one-half to one with the n-propyl ketones is not apparent, although a steric factor may be increasingly operative as the size of the acylating group is increased.

Our study was then extended to the acylation of 2-chloro and 2-bromothiophene and it may be seen in Table I that the 5-halo-2-acylthiophenes were prepared in high yields. In the acetylation of these halogenated thiophenes two products were isolated in small amounts in addition to the 5-chloro(bromo)-2-acetylthiophene. These products were a β-diketone, acetyl-(5-chloro(bromo)-2-thenoyl)-methane and an α,β-unsaturated ketone, 1,3-bis-(5-chloro(bromo)-2-thienyl)-buten-2-one-1. The β-diketones were probably formed by an acid catalyzed Claisen condensation in which the ketone was acylated to a small extent by acetic anhydride in the presence of the boron fluoride etherate as the condensing agent. The method of formation of these β-diketones is indicated by the following equation and finds support in the work of Adams and Hauser[9] who



have shown that boron fluoride is a very effective reagent for the acylation of ketones with anhydrides.

The α,β-unsaturated ketones were probably formed by an aldol condensation between two molecules of the halogenated ketone followed by the elimination of a mole of water. The formation of these compounds is indicated by the



equation. That the α,β-unsaturated ketone was probably formed in this way was shown by treating a sample of the chloroketone with boron fluoride etherate under the same conditions as those used to acylate 2-chlorothiophene and isolating the aldol product.

Experimental

General Procedure for Acylations.—The apparatus used in these acylations consisted of a 500-ml. three-necked round-bottom flask equipped with a mercury sealed stirrer, a reflux condenser (protected from atmospheric moisture by a drying tube filled with Drierite) and a thermometer dipping into the reaction mixture. One-half mole of the appropriately substituted thiophene or furan and 0.58 mole of the appropriate anhydride were placed in the flask. (In the acylations of 3-methylthiophene, larger amounts of the reactants were used. See notes *j* and *o* to Table I.) To the rapidly stirred mixture at room temperature (the acetylation of 2-methylfuran was started at 0°, see below) 7 g. of boron fluoride etherate was added all at once. Except in the experiments with 2-chloro and 2-bromothiophene (see below), the temperature of the reaction mixture rose rapidly to 90–115° upon the addition of the catalyst. Stirring was continued for thirty minutes longer, by which time the mixture had cooled to room temperature. After approximately 200 ml. of water had been added to hydrolyze the reaction mixture, the contents of the flask was extracted with several portions of ether. The combined ether extracts were shaken with a saturated solution of sodium carbonate to remove any acid and then

(8) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., p. 309.

(9) Hauser and Adams, THIS JOURNAL, **66**, 345 (1944).

dried over Drierite. The solvent was distilled at atmospheric pressure and the residue fractionated in vacuum. The yields of the ketones prepared are found in Table I. In the case of the new ketones, samples of both the ketone and its semicarbazone were analyzed. Samples of all the ketones prepared were subjected to hypochlorite oxidation[10,11] in order to establish with certainty the positions occupied by the acyl groups in the heterocyclic rings.

In the acetylation of 2-methylfuran, the mixture of 2-methylfuran and acetic anhydride was cooled to 0° in an ice-bath before the addition of the catalyst. Upon its addition, the temperature of the mixture rose to 105–110° and then rapidly dropped to room temperature. The ice-bath was removed and the stirring continued for fifteen minutes longer. The reaction mixture was then worked up as described above.

In the acylations of 2-chloro and 2-bromothiophene, a very small temperature rise was observed upon the addition of the catalyst. Therefore, the reaction mixture was heated to and stirred at 100° for thirty minutes, cooled to room temperature and worked up in the regular way. If this heating period was omitted, the yields of the desired ketones were greatly decreased.

The three pairs of isomeric ketones derived from the acylations of 3-methylthiophene were of greater than 97% purity as shown by infrared absorption analysis.

Isolation of By-products in the Acetylation of 2-Chlorothiophene.—After vacuum distilling the 5-chloro-2-acetylthiophene, the tarry residue was extracted with 150 ml. of hot 95% ethanol. The alcoholic extract was cooled to room temperature and then an excess of saturated aqueous copper acetate solution was added. A mixture of the aldol product and the copper salt of the β-diketone, acetyl-(5-chloro-2-thenoyl)-methane (I) precipitated and was filtered. This mixture was dissolved in hot benzene and allowed to cool. The copper salt (1.3 g., m. p. 250–251°), which precipitated, was separated by filtration from the aldol product which remained in solution. The filtrate was concentrated and there was obtained, 5.1 g. of 1,3-bis-(5-chloro-2-thienyl)-buten-2-one-1, m. p. 95–96° (from 95% ethanol). *Anal.* Calcd. for $C_{12}H_8S_2Cl_2O$: C, 47.53; H, 2.65. Found: C, 47.73; H, 2.43. Using the method described in the literature,[12] the copper salt was decomposed with 15% sulfuric acid to give the β-diketone (I), m. p. 99.5–100° (from 60–90° petroleum ether). *Anal.* Calcd. for $C_8H_7SClO_2$: C, 47.41; H, 3.48. Found: C, 47.49; H, 3.27.

Isolation of By-products in the Acetylation of 2-Bromothiophene.—After vacuum distilling the 5-bromo-2-acetylthiophene, the residue was extracted with hot 95% ethanol. From this solution there precipitated on cooling to room temperature, 5.0 g. of 1,3-bis-(5-bromo-2-thienyl)-buten-2-one-1, m. p. 107–108° (from 95% ethanol). *Anal.* Calcd. for $C_{12}H_8S_2Br_2O$: C, 36.77; H, 2.06. Found: C, 37.14; H, 2.30. The filtrate obtained after removing the above solid was treated with saturated copper acetate and 0.4 g. of a copper salt m. p. 242–243° was obtained. It was decomposed with 15% sulfuric acid[12] to give the β-diketone, acetyl-(5-bromo-2-thenoyl)-methane, m. p. 125.5–126.5° (from 60–90° petroleum ether). *Anal.* Calcd. for $C_8H_7SBrO_2$: C, 38.88; H, 2.85. Found: C, 38.87; H, 2.54.

Synthesis of 1,3-Bis-(5-chloro-2-thienyl)-buten-2-one-1.—Two and eight-tenths grams of boron fluoride etherate was added to 0.20 mole (32.1 g.) of 5-chloro-2-acetylthiophene contained in a 200-ml. round-bottom three-necked flask equipped as described above in the general acylation procedure. The rapidly stirred mixture was heated to 100°, stirred at that temperature for thirty minutes, and then worked up as described above for the acylations. After removing the solvent, the residue was distilled in vacuum to give 23.0 g. of recovered 5-chloro-2-acetylthiophene, b. p. 87–88° at 4.5 mm. The contents of the distilling flask was then extracted with hot 95% ethanol. When the extracts were cooled to room temperature, there precipitated 3.6 g. of 1,3-bis-(5-chloro-2-thienyl)-buten-2-one-1, m. p. 95–96°. A mixed melting point of this compound with the aldol product isolated in the acetylation of 2-chlorothiophene showed no depression.

Acknowledgment.—The authors gratefully acknowledge the financial support of the United States Atomic Energy Commission during the course of this investigation. We also wish to thank Dr. Robert Friedel of the U. S. Bureau of Mines, Bruceton, Pa., for his assistance with the infrared absorption analyses.

Summary

The boron fluoride method for the synthesis of heterocyclic ketones has been extended to the acylation of 2-methylfuran, 2-methylthiophene, 3-methylthiophene, 2-chlorothiophene and 2-bromothiophene with acetic, propionic and butyric anhydrides.

The acylations of 3-methylthiophene give rise to the formation of isomeric ketones, the 3-methyl-2-acyl and the 4-methyl-2-acyl derivatives. The former compounds are always produced in much higher yield than the latter. An explanation is offered to account for these results.

In the acetylation of 2-chloro- and 2-bromothiophene two by-products are produced in each case, a β-diketone, formed by the acylation of the ketone produced with acetic anhydride, and an aldol product, formed by the self-condensation of the ketone.

PITTSBURGH 13, PA. RECEIVED JANUARY 9, 1950

(10) Newman and Holmes, "Organic Syntheses," 2nd Coll. Vol., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

(11) Farrar and Levine, THIS JOURNAL, **71**, 1496 (1949).

(12) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).