Anal. Calcd. for $C_{10}H_{12}O_7N_4$: C, 40.00; H, 4.03; N, 18.66. Found: C, 40.17; H, 4.05; N, 18.62.

N-*cis*-Crotyl-N'-phenylurea, prepared from the amine and phenyl isocyanate and crystallized from 40% ethanol, melted at 112–112.5°.

Anal. Calcd. for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.54; H, 7.69; N, 14.91.

N-*cis*-Crotyl-N'-phenylthiourea, prepared from the pure amine and crystallized as silky plates from 70% ethanol, melted at 85.5–86°.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.81; H, 6.80; N, 13.60.

The absorption spectrum of an oil mull had characteristic bands at 9.4, 10.53, 11.3, 11.93, 12.43, 13.45, 14.18 and 14.58 μ.

cis-**Crotyl isothiocyanate**, b.p. 83° at 30 mm., $n^{27.5}_D$ 1.5265, was obtained from the amine (5 g.) in 70% yield.

Anal. Calcd. for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.49; H, 6.36; N, 12.58.

The infrared absorption spectrum of the liquid had maxima at 3.43 and 7.0 μ of carbon–hydrogen, 4.75 μ of the isothiocyanate group, 6.05 μ of the double bond, 7.3 μ of the methyl group, and others at 7.58, 7.97, 8.97, 9.3, 10.47, 11.25 and 13.4 (broad) μ.

cis-Crotyl isothiocyanate was allowed to react with aqueous-alcoholic ammonia at 0° during three days. The crude product, m.p. 71.5–75°, was crystallized repeatedly from benzene to give *cis*-**crotylthiourea**, m.p. 88–89°.

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.12; H, 7.74; N, 21.52; S, 24.63. Found: C, 46.13; H, 7.70; N, 20.95; S, 24.84.

In an oil mull the substance absorbed at 7.65, 8.03, 8.15, 8.92, 9.85 and 13.0 μ. On chromatography on paper in water-saturated chloroform,[64] *cis*-crotylthiourea migrated at a rate 0.94 of that of the *trans*-isomer, corresponding to a R_{Ph} of 0.73.

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(64) A. Kjaer and K. Rubinstein, *Acta Chem. Scand.*, **7**, 528 (1953).

HOUSTON, TEXAS

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

Carbonyl Derivatives of Thiophene. I. The Reformatsky Reaction with α-Bromoesters

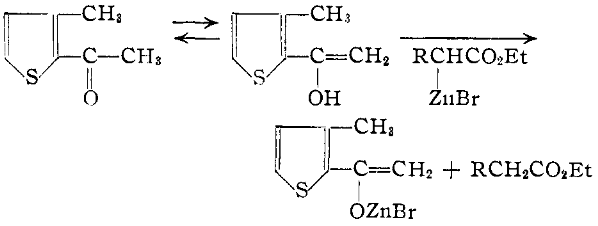
BY ROBERT D. SCHUETZ AND WM. H. HOUFF[1]

RECEIVED JUNE 16, 1954

The Reformatsky reaction between 2- and 3-thienyl aldehydes, and the 2- and 3-thienyl alkyl ketones with α-bromoesters was carried out in an effort to correlate yields with steric factors, reaction solvents and inductive effects.

The Reformatsky reaction[2] involves the interaction of a carbonyl compound with an active organic halogen compound in the presence of zinc under anhydrous conditions, followed by hydrolysis with dilute acid to yield a hydroxy compound. Previous studies of the Reformatsky reaction with carbonyl derivatives of thiophene[3–5] have been restricted to the two substituted isomers. Moreover, only the aldehyde and methyl ketone were investigated. It was the purpose of the work described here to investigate more fully the Reformatsky reaction of 2-thienyl aldehyde, the 2-thienyl methyl, ethyl and *n*-propyl ketones as well as 3-thenal and 3-acetylthiophene with the ethyl esters of bromoacetic, α-bromopropionic and α-bromoisobutyric acids in an effort to determine possible correlations between yields, steric factors, solvent effects and inductive effects.

The reactions were carried out using the reactants in equimolar quantities under anhydrous conditions. The solvent employed was benzene since no reaction was found to have occurred in ethyl ether and excessive decomposition took place in toluene. The use of a benzene–toluene mixture gave no improvement in yields. With ethyl bromoacetate and ethyl α-bromopropionate yields ranging from 54–68% were obtained except in the instances where 2-acetyl-3-methylthiophene served as the carbonyl component. The low yields, 20–25%, with this reagent presumably are due to the blocking effect of the 3-methyl group which is analogous to the observation made by Newman[6] for acetylmesitylene. Approximately half of the 2-acetyl-3-methylthiophene was recovered from the reaction mixture and its recovery may be ascribed to enolization of the ketone by the organometallic intermediate.



On hydrolysis of the reaction mixture the ketone is regenerated. The amount of enolization has been found to be a function of the type of solvent, the halogen derivative employed and the steric blocking, of groups, in the ketone.[7,8] Usually the enolization reaction proceeds at a slower rate than the normal reaction except in those cases where steric factors hinder the formation of the normal product. As a measure of the amount of enolization, the percentages of recovered ketones are listed in Tables I and II. The interaction of 2-thenal and 3-thenal with the highly branched ethyl α-bromoisobutyrate resulted in yields of 64 and 63%, respectively, of the expected products. However, the use of the same bromoester with 2- and 3-acetylthiophene gave yields of only 15 and

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(1) Abstracted, in part, from the thesis submitted by Wm. H. Houff in partial fulfillment of the requirements for the degree Doctor of Philosophy at Michigan State College.

(2) Roger Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 1–38.

(3) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **15**, 89 (1950).

(4) R. E. Miller and F. F. Nord, *ibid.*, **16**, 728, 1380, 1720 (1951).

(5) H. Keskin, R. E. Miller and F. F. Nord, *ibid.*, **16**, 199 (1951).

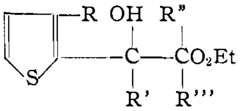
(6) M. S. Newman, THIS JOURNAL, **64**, 2131 (1942).

(7) M. S. Newman, *ibid.*, **64**, 2131 (1942).

(8) A. S. Hussey and M. S. Newman, *ibid.*, **70**, 3024 (1948).

TABLE I

ETHYL 3-(2-THIENYL)-3-HYDROXYALKANOATES

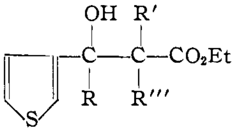


R	R'	R″	R'''	Formula	B.p., °C.	Mm.	$n^{25}D$	Yield, %	Carbonyl recovd., %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	H	H	$C_9H_{12}O_2S$	113–114	0.2	1.5220	62	8	54.0	54.1	6.0	6.2
H	H	H	CH_3	$C_{10}H_{14}O_3S$[a]	108–110	.5	1.5129	57	6				
H	H	CH_3	CH_3	$C_{11}H_{16}O_3S$	113–114	.1	1.5112	64	9	57.9	57.9	7.0	6.4
H	CH_3	H	H	$C_{10}H_{14}O_3S$	93–94	.2	1.5084	66(42)[b]	16	56.1	55.9	6.5	6.6
H	CH_3	H	CH_3	$C_{11}H_{16}O_3S$[a]	102–103	.1	1.5122	63(53)[b]	17				
H	CH_3	CH_3	CH_3	$C_{12}H_{18}O_3S$	100–101	.1	1.5534	15	56	59.5	59.8	7.4	7.3
H	C_2H_5	H	H	$C_{11}H_{16}O_3S$	95–96	.2	1.5105	65(43)[b]	15	57.9	58.2	7.0	6.9
H	C_2H_5	H	CH_3	$C_{12}H_{18}O_3S$	103–104	.1	1.5018	62(55)[b]	13	59.5	59.6	7.4	7.4
H	n-C_3H_7	H	H	$C_{12}H_{18}O_3S$	97–98	.2	1.5048	58(43)[b]	16	59.5	59.9	7.4	7.4
H	n-C_3H_7	H	CH_3	$C_{13}H_{20}O_3S$	112–113	.1	1.4970	54(46)[b]	14	60.9	60.7	7.8	8.0
CH_3	CH_3	H	H	$C_{11}H_{16}O_3S$	114–116	.5	1.5137	25	48	57.9	58.0	7.0	7.0
CH_3	CH_3	H	CH_3	$C_{12}H_{18}O_3S$	117–118	.2	1.5038	20	57	59.5	59.4	7.4	7.3

[a] Previously reported.[3] [b] Dioxane used as reaction solvent, in all other cases benzene was used.

TABLE II

ETHYL 3-(3-THIENYL)-3-HYDROXYALKANOATES

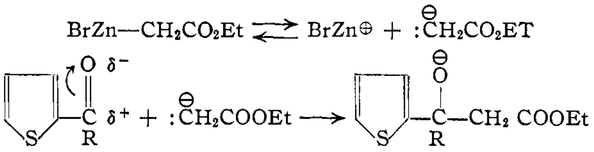


R	R'	R″	Formula	B.p., °C.	Mm.	$n^{25}D$	Yield, %	Carbonyl recovd., %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	H	$C_9H_{12}O_3S$	114–116	0.5	1.5202	65	9	54.0	54.2	6.0	5.9
H	H	CH_3	$C_{10}H_{14}O_3S$	114–115	.5	1.5110	58	5	56.1	56.1	6.5	6.8
H	CH_3	CH_3	$C_{11}H_{16}O_3S$	116–118	.5	1.5098	63	7	57.9	58.0	7.0	7.2
CH_3	H	H	$C_{10}H_{14}O_3S$	93–94	.1	1.5067	68	14	56.1	56.4	6.5	6.8
CH_3	H	CH_3	$C_{11}H_{16}O_3S$	104–106	.5	1.5114	56	22	57.9	58.0	7.0	7.0
CH_3	CH_3	CH_3	$C_{12}H_{18}O_3S$	105–107	.5	1.5521	26	56	59.5	59.3	7.4	7.5

26%, respectively, while with 2-propionyl- and 2-*n*-butyrylthiophene, no Reformatsky product could be detected. In those instances where the acetylthiophenes were used, 56% of recovered ketone resulted while for the cases in which no reaction occurred, about 65% recovery was possible. Increasing the reaction time and temperature resulted in excessive decomposition and no improvement in yields.

The small quantity (5–10%) of unreacted aldehyde and a comparable amount of reduced ester recovered in the Reformatsky reactions involving thiophene aldehydes, which are incapable of enolization, may be explained on a basis similar to that used to account for the recovery of benzaldehyde[9] in the same type of reactions.

Some slight improvement in yields was noted for those cases where the 3-thienyl derivatives were employed in comparison with the corresponding 2-thienyl compounds. This difference may have been greater in view of the fact that the mole quantities utilized for the reactions of the 3-thienyl derivatives were only one-half of the amounts used for the 2-thienylcarbonyl derivatives. The percentage due to mechanical loss was certainly larger for the 3-thienyl compounds which were used in smaller quantities, due to the much greater difficulties involved in their preparation. The difference in yields between the two groups of isomers may be due to the increased electronegativity of the 2-position of the thiophene ring as compared to that of the 3-position resulting in a slightly decreased tendency for the negative species to attack the carbonyl carbon. Thus, according to the possible mechanism



$$BrZn{-}CH_2CO_2Et \rightleftharpoons BrZn^{\oplus} + :\overset{\ominus}{C}H_2CO_2ET$$

the carbonyl carbon of the 2-thienyl ketones would be slightly less positive than would that of the 3-thienyl isomer.

It is noteworthy that in all cases, it was possible to isolate the products as the hydroxy ester. This is in contrast with Nord's observation[3] that only the dehydrated esters could be obtained from the reactions of 2-acetylthiophene and 2-thenal with ethyl bromoacetate. The use of a lower boiling solvent as a reaction medium and lower distillation pressures probably accounts for the success in isolating the hydroxy esters.

The properties of ten previously unreported ethyl 3-(2-thienyl)-3-hydroxyalkanoates are listed in Table I, while those of six previously unreported

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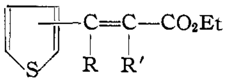
(9) E. H. R. Jones, D. G. Sullivan and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949).

TABLE III

ETHYL β-(THIENYL)-ACRYLATES



Thienyl deriv.	R	R'	Formula	B.p., °C.	Mm.	n^{25}D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2	H	H	$C_9H_{10}O_2S^a$	115–116	1	1.5588				
2	H	CH_3	$C_{10}H_{12}O_2S^a$	109–110	0.5	1.5769				
2	CH_3	H	$C_{10}H_{12}O_2S^a$	104–106	1	1.5588				
2	CH_3	CH_3	$C_{11}H_{14}O_2S^a$	110–112	3	1.5263				
2	C_2H_5	H	$C_{11}H_{14}O_2S$	116–117	1	1.5529	62.8	62.2	6.8	6.7
2	C_2H_5	CH_3	$C_{12}H_{16}O_2S$	111–112	1	1.5448	64.3	64.5	7.1	7.1
2	*n*-C_3H_7	H	$C_{12}H_{16}O_2S$	117–119	1	1.5501	64.3	64.3	7.1	7.3
2	*n*-C_3H_7	CH_3	$C_{13}H_{18}O_2S$	114–115	1	1.5422	65.6	65.7	7.6	7.5
3	H	H	$C_9H_{10}O_2S$	114–115	1	1.5562	59.3	59.4	5.5	5.6
3	H	CH_3	$C_{10}H_{12}O_2S$	112–113	1	1.5760	61.2	60.7	6.1	6.3
3	CH_3	H	$C_{10}H_{12}O_2S$	99–100	1	1.5571	61.2	61.0	6.1	6.3
3	CH_3	CH_3	$C_{11}H_{14}O_2S$	103–105	1.5	1.5248	62.8	62.5	6.8	6.8

[a] Previously reported.[3]

ethyl 3-(3-thienyl)-3-hydroxyalkanoates are summarized in Table II.

The use of dioxane as a reaction solvent was studied to determine if yields were decreased because of the promotion of enolization as was found in the benzene series.[8] While with phenyl ketones yields were reduced by as much as 40%, the effects upon the thienyl derivatives were of the order of only a 10–20% decrease. Correspondingly greater reductions were obtained with ethyl bromoacetate than with ethyl α-bromopropionate. The results of these studies are shown in Table I.

The β-hydroxy esters were dehydrated by refluxing them for a period of eight hours in a 6% oxalic acid solution.[3] The use of acetic anhydride, 85% formic acid,[10] zinc chloride in acetic acid[11] or benzene solutions of iodine[12] resulted in the formation of tars and highly colored reaction mixtures. The unsaturated products are presumed to be α,β-unsaturated, but there is the possibility that in certain instances β,γ-unsaturated esters may have been produced.[13] In no case, however, were two isomeric unsaturated esters isolated. The physical properties of the unsaturated esters prepared are summarized in Table III, eight of which are previously unreported.

Experimental

Intermediates.—A generous sample of 3-methylthiophene was supplied by the Socony-Vacuum Oil Company. It was purified by drying over anhydrous sodium sulfate followed by distillation from sodium metal; b.p. 111–113°. The preparation of ethyl α-bromoisobutyrate was effected by treating isobutyric acid with bromine in the presence of phosphorus pentachloride, followed by conversion of the α-bromoacid to its acid chloride with thionyl chloride and then interaction of the acid chloride with ethanol. An overall yield of 77% resulted; b.p. 50–51° (10 mm.).

Reformatsky Reaction.—In a typical experiment, 12.6 g. (0.10 mole) of 2-acetylthiophene, 16.7 g. (0.10 mole) of ethyl bromoacetate and 100 ml. of dry benzene were placed in a 500-ml. three-necked flask equipped with an efficient stirrer and a reflux condenser which was fitted with a drying tube. To the mixture in the flask was added 6.5 g. (0.10 mole) of dry, acid-washed zinc dust and a small crystal of iodine. After starting the stirrer, the reaction flask was heated lightly to initiate the reaction and once commenced it was necessary to moderate the vigorous reaction by a brief immersion of the reaction vessel in an ice-bath. After the initial exothermic reaction had subsided, the mixture was heated, with stirring, at its reflux temperature for an hour. The reaction mixture, after cooling to room temperature was hydrolyzed by the addition, with rapid stirring, of 75 ml. of ice cold 10% sulfuric acid. The non-aqueous layer was separated and combined with a subsequent ether extract of the aqueous portion. The combined solutions were given consecutive treatments with 100 ml. of water, 100 ml. of 10% sodium carbonate and 100 ml. of water followed by drying over anhydrous sodium sulfate. The ether and benzene were removed at reduced pressure and the residue was distilled under vacuum. At 86–88° (2 mm.), 2.0 g. of 2-acetylthiophene were recovered followed by 14.2 g. (66%) of a clear, colorless product boiling at 93–94° (0.2 mm.), n^{25}D 1.5083.

Anal. Calcd. for $C_{10}H_{14}O_3S$: C, 56.1; H, 6.5. Found: C, 55.9; H, 6.6.

Dehydration of the β-Hydroxy Esters.—To 5 g. of the β-hydroxy ester was added 50 ml. of a 6% oxalic acid solution and the mixture was heated for 8 hours at its reflux temperature. After cooling, the mixture was extracted twice with 50-ml. portions of ethyl ether and the combined extracts were washed once with water and dried over anhydrous sodium sulfate. After removal of the ether on a water-bath the ethyl β-thienylacrylate was distilled under reduced pressure.

2-Thenal.—The preparation of 2-thenal was effected by two different procedures. The method described by Campaigne and Archer,[14] involving the interaction of thiophene with dimethylformamide and phosphorus oxychloride was found superior to the procedure reported by Hartough and Dickert[15] since higher yields are obtained and less involved experimental manipulations are required. The latter procedure employs the reaction of thiophene with formaldehyde and ammonium chloride.

2-Acylthiophenes.—The compounds, 2-acetyl-, 2-propionyl- and 2-butyrylthiophenes as well as the 2-acetyl-3- and 4-methylthiophenes were prepared in good yields by the acylation of thiophene or its 3-methyl derivative with the appropriate acid anhydride in the presence of 85% phosphoric acid.[16]

3-Thenal.—The aldehyde was prepared from 3-methylthiophene by reaction with N-bromosuccinimide to yield 3-thenyl bromide,[17] which was converted to 3-thenal through the Sommelet reaction by treatment with hexamethylenetetramine and hydrolysis of the subsequent salt.[18]

3-Acetylthiophene.—The oxidation of 3-thenal with silver oxide to the acid, and its conversion to the acid chloride with thionyl chloride, followed by the reaction of the latter with dimethylcadmium gave a good yield of 3-acetylthiophene.[17]

EAST LANSING, MICHIGAN

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(10) H. Rupe, *Ann.*, **369**, 321 (1909).

(11) M. L. Tetry, *Bull. soc. chim.*, [3] **27**, 600 (1902).

(12) H. Hibbert, THIS JOURNAL, **37**, 1748 (1915).

(13) G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932).

(14) E. Campaigne and W. L. Archer, THIS JOURNAL, **75**, 989 (1953).

(15) H. D. Hartough and J. J. Dickert, Jr., *ibid.*, **71**, 3922 (1949).

(16) H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3093 (1947).

(17) K. Kittmer, R. B. Martin, W. Herz and S. J. Cristol, *ibid.*, **71**, 1201 (1949).

(18) E. Campaigne and W. M. Lesoeur, *ibid.*, **70**, 1557 (1948).