[CONTRIBUTION NO. 187 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. VII.¹ THE APPLICATION OF THE REFORMATSKY REACTION TO THIOPHENE ALDEHYDES AND KETONES

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Although the use of the Reformatsky reaction has been widespread in the aliphatic and aromatic series, only few attempts have been recorded with heterocyclic aldehydes or ketones (1, 2, 3). Since recent work in this laboratory (4) led to the development of a direct, one-step procedure for the preparation of various substituted thenaldehydes, it was desired to test the applicability of the Reformatsky reaction with these compounds.

The Reformatsky reaction involves the interaction of a carbonyl compound, such as an aldehyde, a ketone, or an ester with an α -haloester in the presence of zinc. With aldehydes or ketones, a β -hydroxyester is produced, although simultaneous dehydration during the reaction may produce an unsaturated ester. These syntheses involve the formation of an organozinc halide as an intermediate (5), which then adds to the carbonyl compound to form an addition complex analogous to those involving the Grignard reagent and carbonyl compounds. The intermediate complex is decomposed with dilute acid to yield the final product:

The Reformatsky reaction not only offers a convenient method for producing β -hydroxy esters and the corresponding unsaturated esters and acids, but also constitutes a method for lengthening the carbon chain. By the proper choice of reactants it is possible to branch the chain on the α -, β -, or α - and β -carbon atoms. It is one of the most suitable synthetic methods for obtaining an unsaturated acid with branching on the β -carbon atom. It also offers a direct method for branching the chain on both the α - and β -carbon atoms.

First, the reaction of the carbonyl compounds with ethyl α -chloroacetate was attempted. 2-Acetothienone reacted with this ester slowly and gave only low yields of the desired product. This was not unexpected since the reactivity of the α -haloacetates is of the order ICH₂COOC₂H₅ > BrCH₂COOC₂H₅ > ClCH₂-COOC₂H₅. The side reaction, the coupling of the haloester by the zinc, to form diethyl succinate did not occur even when the reaction time was increased. The modification described by Nieuwland and Daly (6), in which copper powder is added to the reaction mixture containing the chloroester was also applied, but without avail. This observation corroborates the findings of Kon and Nargund

¹ For paper No. VI of this series see J. Org. Chem., preceding paper.

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Ethyl α -methyl- β - hydroxy- β -(5-chloro-	2-thienyl)propionate Ethyl β -(5-bromo-2-thienvl)acrylate	Ethyl α -methyl- β -hvdroxy- β -(5-chloro-	2-thienyl)propionate Ethyl β-methyl-β-(3- thianaphthyl)acryl- ate	
Ethyl α-bromo- propionate	Ethyl bromoace-	Ethyl α -bromo- propionate	Ethyl bromoace- tate	110-116°/3.5. 121-126°/3.
5-Chloro-2-then- aldehyde	5-Bromo-2-then- aldehvde	5-Bromo-2-then- aldehyde	3-Acetothianaph- thone	^a Ref. (19) gives ^b Ref. (19) gives

^e Ref. (20) gives 138°; Ref. (19, 21) each give 143-144°.
^d Ref. (19) gives 172-173°.
^e Ref. (19) gives 201-203°.

" M.p. 37.5-38". ^A Yields based on the amount of the aldehyde or ketone used. ^A All melting points taken on a Fisher-Johns apparatus.

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(7), who were unable to duplicate the results of Nieuwland and Daly, and who failed to observe a condensation between acetophenone and chloroacetic ester.

However, by utilizing various α -bromoesters, the reaction was successfully carried out with four thenaldehydes, 2-acetothienone, and 3-acetothianaphthone. The yields of the Reformatsky ester obtained in these cases ranged from 45–63%. In two instances, where the bromoester consisted of a highly branched chain, namely ethyl α -bromoisovalerate and ethyl bromomalonate, the yields amounted to 10–20%. The collected data on the Reformatsky esters prepared are recorded in Table I.

The optimum temperature for the reaction was found to be $90-95^{\circ}$, which can best be maintained through the use of a solvent consisting of a mixture of equal amounts of anhydrous benzene and toluene (8). Raising the temperature to $105-110^{\circ}$ did not improve the yields.

Ethyl β -bromopropionate did not yield a Reformatsky ester (9) when reacted with 2-acetothienone even after prolonged heating (10 hours) at a higher temperature (110–115°). The addition of copper powder was also without effect.

The nature of the product seems to depend on the degree of branching of the α -bromoester. In only one case where ethyl bromoacetate was used, was a hydroxy ester obtained. However, when the carbon atom adjacent to the carbethoxy group was substituted, the product usually contained a β -hydroxyl group. That the compounds obtained with ethyl α -bromoisovalerate and ethyl bromomalonate do not appear to follow this generalization can be easily accounted for by the high temperatures required for distillation, which cause a mole of water to split out.

The fact that β -hydroxy esters and their derivatives tend to lose water during distillation or saponification often makes it difficult to isolate the pure compounds. As a matter of fact, every saponification of a β -hydroxy ester resulted in the formation of the unsaturated acid. This proved useful in the isolation of a product from the reaction of 3-acetothianaphthone with ethyl α -bromopropionate. The expected ester, ethyl α,β -dimethyl- β -hydroxy- β -(3-thianaphthyl)propionate, did not give a correct analysis after repeated distillations. The product was therefore saponified and the crystalline unsaturated acid, α,β -dimethyl- β -(3-thianaphthyl)acrylic acid, so obtained analyzed correctly.

In the following, the effect of a dehydrating agent which could be applied to the hydroxy esters without attacking the sensitive thiophene nucleus was investigated. Reagents of a strongly acidic nature, especially on heating, caused the formation of tarry by-products when attempts were made to dehydrate various hydroxy esters with thionyl chloride and pyridine (7, 10, 11) or phosphorus oxychloride (7, 12, 13). The use of aqueous oxalic acid (14, 15, 16) however, resulted in a nearly quantitative conversion to the unsaturated ester. These data are recorded in Table II.

3-Acetothianaphthone did not react with the α -bromoesters under the conditions previously employed. The reaction was effected, however, by employing the method of Newman (17), with modifications; the compound was hydrolyzed and distilled in the usual manner.

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TABLE	

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ESTER	REACTION	BEAGENT	PRODUCT	B.P. OF M.P., °C.	n _D 30°	Calc'	р	Four	p
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Ethyl α, β -dimethyl- β -hy- droxy- β -(2-thienyl)pro- pionate	Dehydration	6% aqueous Ox- alic Acid	Ethyl α, β -dimethyl- β -(2-thienyl)acrylate	104-105/2	. 5246	62.83	6.71	62.70	6.85
Ethyl α -methyl- β -hydroxy- β -(2-thienyl)propionate	29	6% aqueous Ox- alic Acid	Ethyl α-methyl-β-(2-thi- enyl)acrylate	111-113/2	1.5779	61.23	6.16	60.96	6.03
Ethyl α -methyl- β -hydroxy- β -(3-methyl-2-thienyl)- propionate	1 6	6% aqueous Ox- alic Acid	Ethyl <i>a</i> -methyl- <i>β</i> -(3- methyl-2-thienyl)acty- late	108-110/1	. 5738	62.82	6.71	63.09	6.96
Ethyl β-methyl-β-(2-thi- enyl)acrylate	Reduction	Sodium Amalgam	Ethyl β-methyl-β-(2-thi- enyl)propionate	106-107/3	. 4993	60.60	7.12	60.49	6.88
* Ethyl α, β -dimethyl- β -hy- droxy- β -(3 thianaph- thyl)propionate	Saponification	6% aq. Potassium Hydroxide	α, β -Dimethyl- β -(3-thia- naphthyl)acrylic acid	52-53	1	67.24	5.21	67.05	5.20

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* This was the expected product; it did not analyze correctly after repeated distillations, however. • The low melting point may be an indication that this is the *cis* isomer.

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EXPERIMENTAL²

Materials. 2-Acetothienone and 3-acetothianaphthone were obtained through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company.

Reformatsky reactions. The general procedure for all thenaldehydes and 2-acetothienone was as follows: In a clean, dry 250-cc. three-necked flask fitted with a mechanical stirrer, a 250-cc. separatory funnel, and a reflux condenser protected from moisture was placed 20 gm. (0.31 mole) of 20-mesh zinc granules. A solution of approximately 0.25 mole of the ethyl α -bromoester and 0.31 mole of the aldehyde or ketone in 40 cc. of dry benzene and 40 cc. of dry toluene was placed in the separatory funnel. A few cc. of this solution was added to the zinc and a crystal of iodine was introduced. The flask was warmed until a vigorous reaction set in. The mixture was stirred and the rest of the solution introduced at such a rate that gentle refluxing occurred. This required one-half to three-quarters of an hour. As the mixture was refluxed, the iodine color faded and the solution became cloudy. Refluxing and stirring were continued for one hour after addition was complete. Not all the zinc was used up. The flask was then cooled, and the contents poured into 200 cc. of ice-cold 10% hydrochloric acid with vigorous stirring. The acid layer was drawn off and the benzene layer was washed twice with 100-cc. portions of water, then neutralized with 20% aqueous sodium carbonate solution, and again washed with 25-cc. portions of water. The acid extracts were washed with ether and the combined benzene and ether extracts were dried over Drierite. After filtration, the solvent was removed on a steam-bath and the residue fractionated in vacuo.

The following modification was applied to 3-acetothianaphthone reactions. The ketone (20 g.), zinc (20 g.), and 30 g. of the α -bromoester were added to 100-cc. of dry benzene in a flask. A crystal of iodine was introduced and the mixture was heated to boiling. The reaction commenced and the heat of reaction was sufficient to reflux the solvent for a short time. When the reaction moderated, the mixture was stirred and refluxed over a free flame for ten hours. The product was hydrolyzed and distilled in the usual manner.

Dehydration of the hydroxyesters. The ester (10 cc.) was refluxed with 100 cc. of 6% aqueous oxalic acid for 3-6 hours. The aqueous layer was drawn off and the acrylic ester was washed thoroughly with two 25-cc. portions of water, dried (Drierite) and distilled.

Reduction of double bonds (18). The ester (10 cc.) was dissolved in 100 cc. ot ethyl alcohol and freshly prepared sodium amalgam (5%) was added with continual shaking. To complete the reaction, the mixture was warmed on a steam-bath until all the mercury had collected in liquid form. When the solution had cooled the metal was separated, the solvent removed, and the ester distilled.

Saponification of the esters was accomplished by refluxing 10 cc. of the ester with 120 cc. of 20% aqueous potassium hydroxide for 2-3 hours, or until the ester layer had disappeared. The solution was cooled and then acidified with ice-cold dilute hydrochloric acid. The acid was recrystallized from ethyl alcohol.

SUMMARY

1. The Reformatsky reaction was shown to be applicable to four thenaldehydes, 2-acetothienone, and 3-acetothianaphthone.

2. Seven β -hydroxy esters, eight acrylic esters, α,β -dimethyl- β -(3-thianaphthyl)acrylic acid, and ethyl β -methyl- β -(2-thienyl)propionate heretofore not listed in the literature, were prepared. The acids of both types of esters were unsaturated.

² The analyses recorded in this paper were carried out by Dr. F. Bühler of this Department. This investigation was carried out under the auspices of the Office of Naval Research.

3. Aqueous oxalic acid was found to be an excellent dehydrating agent for thiophenehydracrylic acids.

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