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ESTERS OF FUROYLACETIC ACID

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The properties and reactions of furoylacetic ethyl ester, first prepared by Bouveault,[1] were investigated by Torrey and one of us[2] and its close analogy to acetoacetic ester and benzoylacetic ester were pointed out as well as some very decided differences in behavior, particularly in the stability of its oxime. The present paper deals with a further investigation of the methyl, *n*-propyl and *n*-butyl esters of furoylacetic acid.

Method of Preparation.—In the preparation of these esters the method first employed was the condensation of ethyl furoate with methyl, *n*-propyl and *n*-butyl acetates by metallic sodium. This method had to be abandoned owing to the violence of the reaction, which yielded unmanageable, tarry products and very small amounts of the esters. As Claisen[3] has shown, the active catalyst in the acetoacetic ester condensations is sodium ethylate, and when this method was employed the reaction ran smoothly and the yields reached 53% of the theoretical.

Properties of the Esters.—The esters are colorless, oily liquids except the *n*-butyl ester, which is a solid, m. p. 25°. They have pleasant, aromatic odors and show the properties of keto-enol compounds, giving salts as well as oximes and semicarbazones. Attempts to prepare from them phenylhydrazones yielded in all cases the 1-phenyl-3-furyl-5-pyrazolone, which had been investigated by Torrey and one of us[2] in the study of derivatives of furoylacetic ethyl ester.

Behavior of the Oximes.—The fact that the oxime of furoylacetic ester was stable, whereas neither the benzoylacetic ethyl ester nor the acetoacetic ethyl ester gave stable oximes, was brought out and commented on at length by Torrey and one of us.[2] It was shown that the stability of the oxime could be accounted for by the theory of Abegg,[4] since the furfuryl group was more electropositive than either the phenyl or the methyl group and therefore would tend to produce a *syn*-oxime with respect to itself, diminishing the tendency of the compound to split off alcohol and pass into an isoxazolone. It was therefore of interest to determine whether the substituting alcohol group in the furoylacetic ester had any influence on the stability of the various oximes. Oximes with definite melting points were prepared from the methyl, *n*-propyl and *n*-butyl esters. Their melting points (heating rate 4° per minute, starting at room tem-

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[1] Bouveault, *Bull. soc. chim.*, [3] **25**, 440 (1901).

[2] Torrey and Zanetti, *Am. Chem. J.*, **44**, 391 (1910).

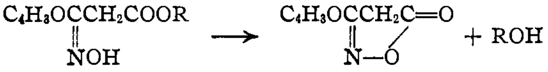
[3] Claisen, *Ann.*, **297**, 92 (1897).

[4] Abegg, *Ber.*, **32**, 291 (1899).

perature) were as follows: furoylacetic methyl ester oxime, 124–125°; furoylacetic ethyl[2] ester oxime, 131–132°; furoylacetic *n*-propyl ester oxime, 120–121°; furoylacetic *n*-butyl ester oxime, 101–102°.

It would be expected that the melting points of the oximes would increase with increasing molecular weight, and consequent rise in the boiling points of the esters, but this was not the case, as the *n*-butyl ester oxime melts nearly 30° below the ethyl ester oxime although the boiling point of the *n*-butyl ester under 3 mm. pressure is nearly 22° above that of the ethyl ester.

This unexpected behavior led to an investigation of what really happened when these oximes melted. Was the "melting point" a real melting point, that is, the passing of the solid oxime to the liquid phase, or a decomposition point where alcohol was split off and an isoxazolone formed? In the first case the liquid phase should solidify on cooling and the same melting point be obtained on remelting; in the second case either solidification should not be obtained or should be only partial and a different and lower melting point should be obtained. Experimental investigation disclosed that once melted, the oximes would only partially solidify and on redetermination of the melting point a much lower value was obtained. The obvious explanation was that alcohol was split off and that the second melting point was really the solution point of the isoxazolone in the alcohol formed according to the reaction



It was then necessary to show that the isoxazolone was really formed at the "melting point." This was easily done by heating the oximes to their melting points in a small test-tube immersed in an oil-bath and lowering the pressure to cause the alcohol to boil off. In all cases needles of the furylisoxazolone sublimed to the cooler parts of the tube just above the level of the oil and showed the correct melting point for that compound, 147–148°. In the case of the methyl ester, the isoxazolone formation began considerably below the melting point, which can be explained by the much greater volatility of the alcohol formed.

In all these cases, then, the "melting points" are not true melting points but decomposition points and the point at which the liquid phase appears is determined by (1) the speed with which the formation of the isoxazolone takes place, and (2) the solution of the isoxazolone as well as of the undecomposed oxime in the alcohol formed.

Obviously these "melting points" are meaningless as criteria of purity unless the speed and time of heating are made constant. For example, the *n*-butyl ester oxime which melts at 102° when heated at the rate of 4 degrees per minute, starting at room temperature, will "melt" at 96° when held at that temperature for seven minutes, and when "dipped" at 98° will melt at 103°.

In explaining the fact that the oximes of these esters are stable, the position assigned by Hantzsch to the furyl group in his list of order for attraction for the OH group is inadequate if that order is followed in explaining the stability of the oximes of the acetoacetic ester homologs. It explains well enough why the benzoylacetic ester oxime should be unstable but falls down in the case of the furoylacetic ester oxime which according to him should be even less stable than that of the benzoylacetic ester. On the other hand, Abegg's theory explains the stability of the furoylacetic ester oximes but when his theory is applied to the higher esters it fails completely. According to him the *n*-propyl and *n*-butyl ester oximes should be *more* stable than the methyl and ethyl ester oximes, whereas the reverse has been shown to be the case, the *n*-propyl and *n*-butyl oximes splitting off the corresponding alcohols at *lower* temperatures than the methyl and ethyl oximes. There must be, therefore, some other factor than the electrostatic attraction for the OH group which comes into play in determining the stability of these oximes. It is not possible at present to decide on this matter.

TABLE I

DERIVATIVES OF THE ESTERS OF FUROYLACETIC ACID

	Sodium salt, Na, %		Potassium salt, K, %		Copper salt, Cu, %		Oxime			Semicarbazone		
Ester	Calcd.	Found	Calcd.	Found	Calcd.	Found	M. p. °C.	N, % Calcd.	N, % Found	M. p. °C.	N, % Calcd.	N, % Found
Methyl	12.10	12.00	18.97	18.64	16.00	16.14	....	7.65	7.78	....	18.66	18.43
	...	12.28	...	18.68	...	15.80	124–5[a]	..	7.48	141–2[a]	...	18.73
***n*-Propyl**	10.55	10.19	...	...	14.02	14.33	....	6.63	6.60	....	16.60	16.80
	...	...	...	...	...	14.14	120–1[a]	..	6.76	137–8[a]	..	16.34
***n*-Butyl**	...	...	...	...	13.20	13.35	102[a]	6.22	6.21		15.73	15.49
	...	...	...	...	...	...	....	..	6.13	127–8[a]	...	16.01

[a] With decomposition.

Experimental

Methyl Ester of Furoylacetic Acid.—About 30 g. of sodium was placed in 500 cc. of dry xylene contained in a liter flask. To this was added the requisite amount of absolute alcohol to dissolve the sodium. The excess xylene was distilled off in a stream of hydrogen. The flask was then connected with a reflux condenser and a mixture of 75 g. of ethyl furoate and 140 g. of dry methyl acetate was added. The reaction mixture was heated on the water-bath for four to five hours. More dry methyl acetate was then added to keep the mixture liquid. The heating was continued for ten to twelve hours. The mixture was acidified with dilute acetic acid to liberate the ester, extracted with ether and dried with anhydrous sodium sulfate; the ether and the unchanged esters were distilled off and the ketonic ester was distilled under vacuum.

The ester is a colorless oil with a pleasant odor. It turns yellow on standing; b. p. 96–98° at 1 mm., 144–145° at 20 mm.; yield, 45–50% of the theoretical.

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.76. Found: C, 57.37, 57.26; H, 4.93, 4.76.

***n*-Propyl Ester of Furoylacetic Acid.**—The condensation of *n*-propyl acetate and ethyl furoate was carried out in the same manner as described for the methyl ester.

The ester is a colorless oil which turns yellow upon standing. It has a pleasant odor; b. p. 110–112° at 1 mm.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 60.50, 60.67; H, 6.25, 6.13.

***n*-Butyl Ester of Furoylacetic Acid.**—The condensation of *n*-butyl acetate and ethyl furoate was carried out in the same manner as described for the methyl ester. The ester is a colorless oil which turns yellow upon standing. It has a pleasant odor; b. p. 136–138° at 3 mm. On cooling it solidifies to white needles, m. p. 25.2°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.66. Found: C, 62.80, 62.52; H, 6.66, 6.75.

Derivatives of the Esters of Furoylacetic Acid

Sodium Salts.—The sodium salts of the methyl and *n*-propyl esters were prepared by dissolving 1 g. of sodium in 25 cc. of absolute alcohol and adding the corresponding amount of the ester. In the case of the methyl ester the salt was so insoluble that it precipitated out in a few minutes. In the case of the *n*-propyl ester about one-half the alcohol had to be evaporated before crystallization occurred. The sodium salt of the butyl ester is evidently so soluble that we were unable to prepare it in a pure condition.

The sodium salts were recrystallized from alcohol and analyzed (see Table I). They are white, crystalline solids.

Potassium Salt.—An alcoholic KOH solution was added to the methyl ester. Upon standing for 3 to 4 hours, long white needles of the potassium salt separated out. They were filtered off and recrystallized from alcohol. They were soluble in water and hot alcohol and slightly soluble in ether. The potassium salts of the other esters could not be prepared in a pure condition owing to their much greater solubilities.

Copper Salts.—The copper salts were prepared by shaking an ether solution of the ester with a concentrated water solution of copper acetate. In the case of the butyl ester a benzene solution of the ester had to be used as the copper salt dissolves in ether and even slightly in benzene. The copper salts crystallized out in the form of small green needles. These were repeatedly washed with ether or benzene, dried and analyzed.

Oximes.—The oximes were prepared by mixing the theoretical amounts of hydroxylamine hydrochloride, sodium acetate and the esters in dilute alcohol, using just enough water to dissolve the hydroxylamine and just enough alcohol to dissolve the ester. The mixture was allowed to stand for four hours, when the oxime began to crystallize. About 4 to 5 volumes of water were then added, when a voluminous precipitate of the oxime would come out upon standing for another hour. The crystals were filtered, washed with water, dried and recrystallized from benzene. The oximes are white, fluffy crystals, soluble in alcohol, ether and hot benzene but insoluble in water. For melting points and analyses see Table I.

Semicarbazone.—The semicarbazones were prepared by mixing theoretical proportions of the esters, semicarbazide hydrochloride and sodium acetate. The rest of the procedure was the same as for the oxime. The semicarbazones were purified by recrystallization from a benzene-alcohol (3:1) mixture. The products were white, crystalline solids, soluble in alcohol, hot benzene and ether but insoluble in water. For melting points and analyses see Table I.

Summary

1. The methyl, *n*-propyl and *n*-butyl esters of furoylacetic acid, their typical salts, oximes and semicarbazones have been synthesized and their properties reported.

2. The stability of the oximes is discussed and shown to be contrary to Hantzsch's theory and not fully explained by Abegg's theory.

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[CONTRIBUTION FROM BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

PREPARATION AND PROPERTIES OF THE 2-METHYL-5-ISOPROPYL PHENYL AMIDES OF SOME HIGHER FATTY ACIDS

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The use of amides as a means of identification of acids is too generally recognized to require more than a passing mention. It is noteworthy, however, that the amides[3] of the higher fatty acids differ so slightly in melting point that it is questionable if the identification by this method is positive enough to be of much value. Phenyl amides and substituted phenyl amides show a greater increment between melting points of closely following members of the saturated series, but even here much is to be desired. Phenylene diamides have been prepared by De Conno,[4] and the differences in melting point between neighboring members of the series are of such magnitude as to be of use for differentiation.

It seemed possible that weighting of the phenyl nucleus and corresponding increase in the molecular weight would lead to some useful results. Accordingly cymidine (2 methyl-5-*iso*propylaniline) was prepared and coupled with the higher fatty acid chlorides. The resulting substituted phenyl amides were purified and their physical constants were determined. It was observed that up to arachidic acid the melting point of the amides increased with the molecular weight, but that arachidic and lignoceric cymidines are lower in melting point than myristyl cymidine. This condition finds an analogy in the behavior of the toluides, since palmitic toluide melts at 66, or 27° lower than myristic toluide, whereas in the phenylene diamides it has been observed that both stearic and arachidic *p*-phenylene diamides melt at lower temperatures than palmitic *p*-phenylene diamide.

Experimental

Cymidine was prepared from cymene by nitration according to Phillips'[5] modification of Andrews'[6] procedure and subsequent reduction by tin and

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[2] Chemist in charge, Oil, Fat and Wax Laboratory, Bureau of Chemistry and Soils, U. S. Department of Agriculture.

[3] Lewkowitsch and Warburton, sixth edition, Vol. I, p. 150.

[4] De Conno, *Gazz. chim. ital.*, **47**, I, 93 (1917).

[5] Phillips, THIS JOURNAL, **44**, 1777 (1922).

[6] Andrews, *J. Ind. Eng. Chem.*, **10**, 453 (1918).