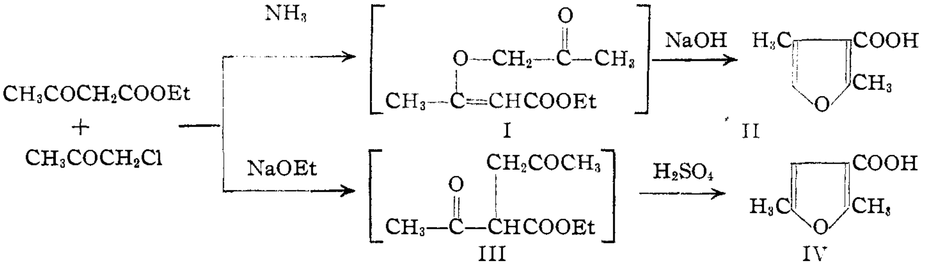
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Preparation of Ethyl 2,4-Dimethyl-3-furoate

BY ELLIOT R. ALEXANDER AND SIDNEY BALDWIN

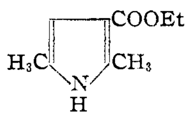
In a recent communication Hurd and Wilkinson[1a] have shown unequivocally that the reaction of chloroacetone with ethyl acetoacetate in the presence of ammonia leads to a *substance* which on alkaline hydrolysis gives 2,4 - dimethyl - 3 - furoic acid (II). From the same study it was demonstrated that the reaction of chloroacetone with the sodio derivative of ethyl acetoacetate gives another *substance* from which 2,5-dimethyl-3-furoic acid (IV) could be obtained by treatment with sulfuric acid. In accordance with the suggestions of a number of earlier workers on condensations of this type,[1a] these investigators interpreted their results on the basis of the intermediate formation of I and III which represent O-alkylation and C-alkylation, respectively (Chart 1).

Chart 1

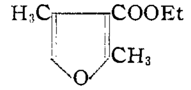


In connection with another study, we have had occasion to investigate the synthesis of 2,4-dimethyl-3-furoic acid in some detail. This paper summarizes some of our experiments.

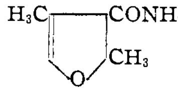
In our hands the reaction of chloroacetone, ethyl acetoacetate and ammonia led principally (41% yield) to the formation of 3-carbethoxy-2,5-dimethylpyrrole (V) as reported by Feist.[1b] In addition to this solid, there is also formed as a by-product an oil from which we were never able to prepare 2,4-dimethyl-3-furoic acid (II) in yields greater than 15%. After repeated distillations of this oil, two fractions were obtained. The more volatile of these was established as ethyl 2,4-dimethyl-3-furoate (VI) by analysis, molecular refractivity, infrared absorption spectrum and saponification to 2,4-dimethyl-3-furoic acid (II). The higher boiling constituent could never be obtained in a state of purity high enough for analysis but all indications are that it was the corresponding amide VII. Thus its infrared absorption spectrum indicated the presence of a furan ring; it contained nitrogen; it gave a specific qualitative test for the amide group[2a]; and on alkaline hydrolysis, it gave ammonia and 2,4-dimethyl-3-furoic acid (II). It is clear, therefore, that the intermediate *substance* in the formation of 2,4-dimethyl-3-furoic acid is not an O-alkylated derivative of acetoacetic ester but rather a mixture of the ethyl ester and the amide of 2,4-dimethyl-3-furoic acid.[2b]



V

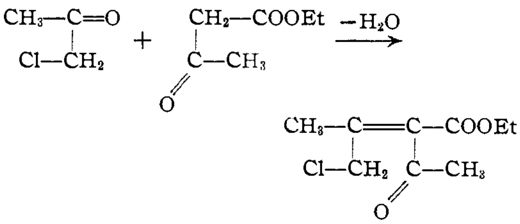


VI

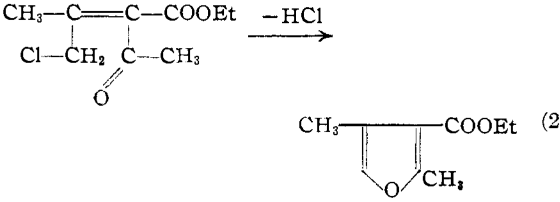


VII

In casting about for ways to improve the synthesis of 2,4-dimethyl-3-furoic acid derivatives, the suggestion of Plancher and Albini[3] concerning the nature of the reaction between chloroacetone, ethyl acetoacetate and ammonia seemed very reasonable. These investigators proposed that the reaction proceeded essentially through a preliminary Knoevenagel condensation between chloroacetone and ethyl acetoacetate (equation 1) followed by cyclization (equation 2).



(1)



(2)

In support of their proposal, they showed that the product obtained from the reaction of chloroacetaldehyde, ethyl acetoacetate and dry hydrogen chloride could be converted to 2-methyl-3-furoic acid by the action of ethanolic ammonia in a sealed tube. Although it was not possible to obtain the condensation product pure, they believed it to be ethyl 2-chloroethylideneacetoacetate (VIII) on the basis of its method of preparation.[4] Accordingly

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[1a] Hurd and Wilkinson, THIS JOURNAL, **70**, 739 (1948).

[1b] Feist, *Ber.*, **35**, 1539 (1902).

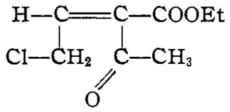
[2a] Davidson, *J. Chem. Education*, **17**, 84 (1940).

[2b] It is interesting that A. P. Dunlop and C. D. Hurd (*J. Org. Chem.*, in press) have recently reached the same general conclusions.

[3] Plancher and Albini, *Atti Accad. Naz. Lincei*, [5] **13**, I, 39 (1904). See also Gilman and Wright, *Ind. Eng. Chem.*, **40**, 1519 (1948).

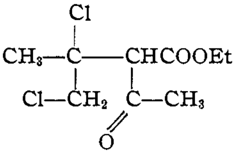
[4] Ethyl*i*sopropylideneacetoacetate, for example, can be prepared by a similar reaction with acetone. See (a) Pauly, *Ber.*, **30**, 482 (1897); and (b) Merling and Welde, *Ann.*, **366**, 131 (1909).

our attention was directed toward modifying, if possible, the reaction of Plancher and Albini for the synthesis of derivatives of 2,4-dimethyl-3-furoic acid (II).



VIII

It was found that ethyl acetoacetate condensed readily with chloroacetone in the presence of dry hydrogen chloride to give an unstable compound which was probably ethyl α-(1,2-dichloroisopropyl)-acetoacetate (IX). This material rapidly lost hydrogen chloride on standing at room temperature and partially cyclized to ethyl 2,4-dimethyl-3-furoate (VI) on attempted distillation. There can be no doubt as to the carbon skeleton of this molecule, since hydrogenolysis with Raney nickel gave ethyl α-isopropylacetoacetate. This material was characterized by the formation of a pyrazolone (which showed no melting point depression with an authentic sample) and by hydrolysis to methyl isobutyl ketone.



IX

Treatment of the crude dichloro compound with triethylamine in ether gave pure ethyl 2,4-dimethyl-3-furoate (VI) in 54% yield. This appears to be a better route to derivatives of 2,4-dimethyl-3-furoic acid than the ammonia-catalyzed reaction of ethyl acetoacetate and chloroacetone or the three step method of Blomquist and Stevenson[5] based upon acetonedicarboxylic ester.

## Experimental[6]

**Reaction of Chloroacetone, Ethyl Acetoacetate and Ammonia.**—Following the procedure of Hurd and Wilkinson,[1a] 195 g. (1.5 moles) of ethyl acetoacetate, 139 g. (1.5 moles) of chloroacetone and 500 ml. of dry ether were treated with excess ammonia. Initially there was no heat effect but as the addition of ammonia continued, enough heat was liberated to warrant cooling the reaction mixture in an ice-bath.

During the reaction a white solid separated. This was removed by filtration and the oily reddish-brown filtrate was washed with 10% hydrochloric acid, with water and then dried over anhydrous magnesium sulfate. Upon evaporation of the ether under reduced pressure, a copious precipitate separated from solution. Filtration gave 103 g. (41%) of 3-carbethoxy-2,5-dimethylpyrrole (V) which after two recrystallizations from 95% ethanol melted at 116–117°.[7]

The filtrate was then distilled through a modified Claisen flask. The fraction boiling at 106–112° (16 mm.) amounted to 26.9 g.[8] In order to separate this material into pure components, the products so obtained from three runs were combined and fractionally distilled at 0.2–1.0 mm. through an electrically heated 17.5 × 1.6 cm. column packed with glass helices. After eight redistillations there was obtained fraction I, 13.3 g., b.p. 48–51° (0.4 mm.), $n^{20}\text{D}$ 1.4680, $d^{20}_{20}$ 1.0646 and fraction II, 3.6 g., b.p. 48–50° (0.2 mm.), $n^{20}\text{D}$ 1.4992. Prior to the final distillation, the fractions were washed twice with 2% sodium hydroxide, twice with 5% hydrochloric acid, twice with water and then dried over anhydrous magnesium sulfate.

Fraction I we believe to be ethyl 2,4-dimethyl-3-furoate (VI).

*Anal.* Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19; $M^{20}\text{D}$, 43.93. Found: C, 64.08; H, 7.26; $M^{20}\text{D}$, 43.92.[9]

This material showed infrared absorption bands characteristic of the furan ring (1564 and 1612 cm.$^{-1}$) and of a conjugated ester (1712 cm.$^{-1}$).[10] Saponification of 2.0 g. (0.0119 mole) of fraction I with excess 5% sodium hydroxide gave 1.5 g. (90%) of 2,4-dimethyl-3-furoic acid, m.p. 122°.[1a]

In spite of repeated distillations, fraction II could never be obtained pure enough for analysis. However, we believe that it consisted principally of 2,4-dimethyl-3-furoamide. Thus, its infrared absorption spectrum showed bands at 1564 and 1620 cm.$^{-1}$ characteristic of a furan ring substituted in this manner and further bands at 3450, 3333 and 1666 cm.$^{-1}$ characteristic of an unsubstituted amide. Nitrogen was present[11] and it showed a positive ferric hydroxamate test,[2a] which is reported to be specific for amides. Hydrolysis of 1.0 g. of fraction II with 5% sodium hydroxide gave a strong odor of ammonia and 0.9 g. (90%) of 2,4-dimethyl-3-furoic acid, m.p. 122°. This material showed no melting point depression on admixture with the acid prepared from hydrolysis of the ester described above.

**Ethyl α-(1,2-Dichloroisopropyl)-acetoacetate** (IX).—Dry hydrogen chloride gas was passed for 24 hours into a well-stirred mixture of 1.5 molar quantities of ethyl acetoacetate and chloroacetone contained in a 500-ml., three-necked flask immersed in an ice–salt mixture (0 to −5°). The flask was then fitted with a calcium chloride tube to permit the escape of excess hydrogen chloride and the yellow reaction mixture was allowed to stand in the hood at −5 to 0° for an additional 48 hours. The oil was next poured onto cracked ice and 40 g. of sodium carbonate was added in 10-g. portions. It was extracted with ether and washed with 10% sodium carbonate. Distillation through a modified Claisen flask gave 66.5 g. (27.6%) of a colorless liquid, b.p. 85° (0.5 mm.), $n^{20}\text{D}$ 1.4649, $d^{20}_{20}$ 1.2031. This material we believe to be principally ethyl α-(1,2-dichloroisopropyl)-acetoacetate (IX).

*Anal.* Calcd. for $C_9H_{14}O_3Cl_2$: C, 44.83; H, 5.85; Cl, 29.41; $M^{20}\text{D}$, 55.16. Found: C, 45.86; H, 6.14; Cl, 28.13; $M^{20}\text{D}$, 55.40.

This liquid was unstable at room temperature. It lost hydrogen chloride spontaneously and became discolored. Redistillation gave a forerun, b.p. 57–60° (1 mm.), $n^{20}\text{D}$ 1.4679 and a main fraction of ethyl α-(1,2-dichloroisopropyl)-acetoacetate, whose analysis was not improved. The forerun was identified by infrared analysis as ethyl 2,4-dimethyl-3-furoate (VI). Saponification by the usual procedure gave 2,4-dimethyl-3-furoic acid (II), m.p. 122°, which showed no melting point depression on admixture with the acid prepared from hydrolysis of the ester described above.

**Determination of the Carbon Skeleton** of (IX).—With 150 ml. of 95% ethanol as solvent, 36.0 g. (0.15 mole) of ethyl α-(1,2-dichloroisopropyl)-acetoacetate ($n^{20}\text{D}$ 1.4649) was hydrogenated for 21 hours at 3 atmospheres pressure in the presence of about 60 g. of Raney nickel. The solution became warm during the beginning of the reduction, but after about 2 hours it returned to room temperature where it remained for the rest of the hydrogenation.

The green reaction mixture was then diluted with about 300 ml. of ether, the dark green layer which separated drawn off and the ether–alcohol solution dried over anhydrous magnesium sulfate. After removal of the excess solvent, fractionation of the residue through an electrically heated 17.5 × 1.6 cm. column packed with glass helices

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[5] Blomquist and Stevenson, THIS JOURNAL, **56**, 146 (1934).

[6] All melting points and boiling points are uncorrected.

[7] Hantzsch, *Ber.*, **23**, 1474 (1890).

[8] 11% yield based on a molecular weight corresponding to ethyl 2,4-dimethyl-3-furoate. The best yield of this fraction obtained from six runs was 15%. The average yield was about 10%.

[9] Although ethyl 2,4-dimethyl-3-furoate is known (see ref. 5), no refractive index or density has been reported.

[10] We are indebted to Mrs. J. R. Johnson and Miss Elizabeth Petersen for the determination and interpretation of the infrared data.

[11] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 52.

gave 10.2 g. (40%) of ethyl α-isopropylacetoacetate, b.p. 42–43° (0.2 mm.), $n^{20}\text{D}$ 1.4240.[12]

*Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.60; H, 9.67.

This ester was characterized by the formation of a pyrazolone and hydrolysis to methyl isobutyl ketone. Thus from 5.0 g. (0.028 mole) of ethyl α-isopropylacetoacetate was prepared 5.5 g. (88%) of 1-phenyl-3-methyl-4-isopropylpyrazolone, m.p. 115–117°,[13] using the method of Pauly.[4a] A mixed melting point of this material and the corresponding pyrazolone obtained from ethyl α-isopropylacetoacetate prepared through the alkylation of ethyl acetoacetate with isopropyl iodide,[14] showed no depression.

Similarly the hydrolysis of 10.0 g. (0.056 mole) of ethyl α-isopropylacetoacetate by the method of Hauser and Breslow[15] gave 3.8 g. (66%) of methyl isobutyl ketone, b.p. 110–120°. This material was identified by conversion to a semicarbazone, m.p. 133–135°. The melting point of a mixture of this semicarbazone with that prepared from authentic methyl isobutyl ketone was 132–134°.

**Preferred Preparation of Ethyl 2,4-Dimethyl-3-furoate (VI).**—A mixture of ethyl acetoacetate (195 g., 1.5 moles) and chloroacetone (277 g., 3.0 moles) was treated with dry hydrogen chloride in the manner already described for the preparation of ethyl α-(1,2-dichloroisopropyl)-acetoacetate. As before, the reaction mixture was poured onto ice, treated with sodium carbonate, extracted with ether and washed with 10% sodium carbonate solution. Since excess chloroacetone was employed, these operations were carried out in a good hood. The ether solution was then transferred to a one liter three-necked flask equipped with a dropping funnel, a reflux condenser and a mechanically driven paddle stirrer. The flask was then immersed in an ice-bath and 600 ml. (437 g., 4.32 moles) of triethylamine was added as rapidly as possible. Almost immediately heat was evolved and triethylamine hydrochloride separated from solution. After addition was complete, the reaction mixture was stirred 8 hours at 0° and 35 hours longer at room temperature.

Enough water was then added to dissolve the amine salt which formed, the organic layer separated and the aqueous portion extracted with ether. The ether extracts and the organic layer were combined and washed cautiously with dilute hydrochloric acid until the washings were acid to congo red paper, then with water and finally dried by adding about 15 ml. of benzene and evaporating the excess solvents *in vacuo.* Distillation through an electrically heated 33 × 2.4 cm. column packed with glass helices gave 135.5 g. (54%) of ethyl 2,4-dimethyl-3-furoate, b.p. 52° (0.8 mm.), $n^{20}\text{D}$ 1.4681. The infrared absorption curve of this product was identical to that prepared from the reaction of chloroacetone, ethyl acetoacetate and ammonia.

Several other bases were investigated for the dehydrohalogenation step, but none gave as good results as triethylamine. Ammonia led to a mixture of the ester and the amide in 49% yield based on the molecular weight of the ester. Aqueous and anhydrous pyridine gave the ester in yields of 2.5 and 4.3%, respectively. Direct treatment of the crude ethyl α-(1,2-dichloroisopropyl)-acetoacetate with 10% sodium hydroxide gave only traces of 2,4-dimethyl-3-furoic acid.

## Summary

The *substance* obtained in the reaction of chloroacetone, ethyl acetoacetate and ammonia from which it is possible to prepare 2,4-dimethyl-3-furoic acid by alkaline hydrolysis has been found to be a mixture of ethyl 2,4-dimethyl-3-furoate and 2,4-dimethyl-3-furoamide. An improved synthesis for ethyl 2,4-dimethyl-3-furoate has been developed based upon a hydrochloric acid-catalyzed aldol-type condensation of chloroacetone and ethyl acetoacetate followed by cyclization with triethylamine.

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(12) Ethyl α-isopropylacetoacetate is known [see Adams, Levine and Hauser, *Org. Syntheses,* **27**, 35 (1947)] but apparently no refractive index has been reported.

(13) v. Auwers and Dersch, *Ann.*, **462**, 116 (1928).

(14) We are indebted to Roger Adams and Kenneth Schowalter for this sample.

(15) Hauser and Breslow, THIS JOURNAL, **62**, 2392 (1940).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE DEFENSE RESEARCH LABORATORY, THE UNIVERSITY OF TEXAS]

# Allylic Chlorides. XIII. Relative Reactivities of *cis*- and *trans*-Crotyl Chloride[1,2]

BY LEWIS F. HATCH AND STUART S. NESBITT

Both isomers of crotyl chloride have been studied in respect to their relative reactivities toward potassium iodide in acetone, sodium ethoxide in ethanol and in their cuprous chloride catalyzed acid hydrolysis. This investigation was made to extend our knowledge of the influence of various groups and atoms on the number one carbon atom of allyl chloride and also to learn more about the effect of geometrical configuration on these reactions. The rates of reaction of both isomers with these three reagents are greater than for allyl chloride. This general increase in reactivity is not surprising in view of the greatly increased reactivity of 1-chloro-3-methyl-2-butene over allyl chloride.[3]

In the reaction with potassium iodide the rate of *cis*-crotyl chloride was more than five times that for the *trans* isomer. The *cis* isomer, however, shows a definite drift in the specific reaction rate constant after 70 per cent. reaction while the *trans* isomer shows only a slight drift. A possible explanation for this drift is the slow rearrangement of some of the crotyl chloride to 3-chloro-1-butene which reacts very slowly with potassium iodide under these conditions. It is also quite possible that there is a slow rearrangement of the *cis* isomer to the slower reacting *trans* isomer. A similar drift in specific reaction rate constant was not noted for the reaction with sodium ethoxide.

The difference in the reactivity of the two isomers was much less pronounced for the reaction with sodium ethoxide with the rate of reaction of the *cis* isomer being only 1.16 times that for the *trans* isomer. Young and Andrews[4] have noted that crotyl chloride obtained by chlorination of a butene mixture had a rate of reaction with sodium ethoxide which was higher than for crotyl chloride obtained by other methods. This was interpreted

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(1) For number XII of this series see Hatch and Alexander, THIS JOURNAL, **72**, 5643 (1950).

(2) Presented in part at the Southwest Regional Meeting of the American Chemical Society, Oklahoma City, Okla., December 9, 1949.

(3) Hatch and Gerhardt, THIS JOURNAL, **71**, 1679 (1949).

(4) Young and Andrews, *ibid.*, **66**, 421 (1944).