The solid which separated from a solution which was relatively rich in one of the components was finely divided; the solid formed from a solution of approximately equimolar proportions was in larger crystals.

Summary

1. The effect of previous treatment of glass surfaces on the properties of propionaldehyde stored in glass vessels has been pointed out.

2. A cryostat has been constructed for use in cryoscopic investigations in solutions of alcohols and aldehydes.

3. The freezing point–composition relationships have been investigated for the systems: (a) *n*-heptanol–*n*-heptaldehyde and (b) methanol–propionaldehyde.

4. The results prove the formation of a compound (hemiacetal) between one molecule of an alcohol and one molecule of an aldehyde.

SEATTLE, WASHINGTON RECEIVED SEPTEMBER 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

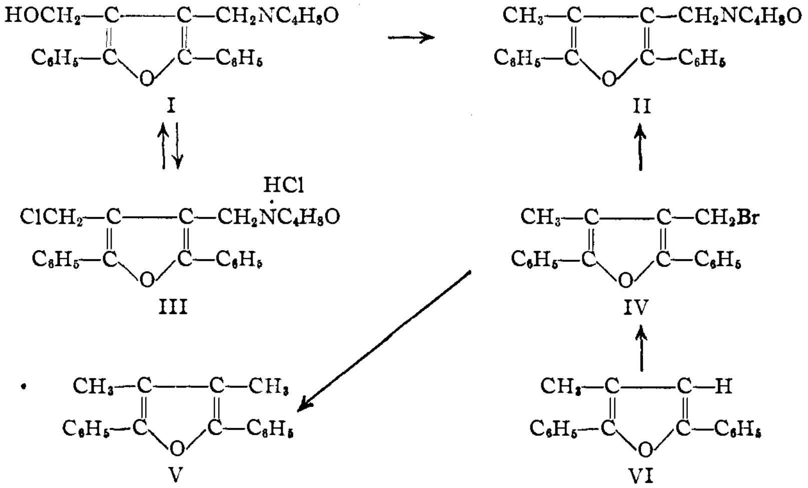
3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran and Some Derivatives[1,2]

BY PHILIP S. BAILEY AND GENE NOWLIN

In an earlier paper[3] was described the isolation of 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I) from a Mannich reaction employing 1,2-dibenzoylethane, paraformaldehyde and morpholine hydrochloride in benzene solution. As stated there, the identity of I was not at first apparent. The present paper deals principally with reactions which led to its identification and some interesting reactions of its derivatives. Improvement in the yield of I is reported. The generality of the reaction leading to I has also been demonstrated by the fact that piperidine hydrochloride gives similar results.

Reduction of I by means of hydriodic acid or by stannous chloride gave II, the structure of which was established by synthesis from 3-methyl-2,5-diphenylfuran (VI). This consisted of the bromomethylation of VI to give IV, followed by treatment of IV with morpholine. Any possible doubt as to the course of the bromomethylation reaction was removed by the catalytic hydrogenolysis of IV to give known 3,4-dimethyl-2,5-diphenylfuran (V). Treatment of I with a chloroform solution of hydrogen chloride gave 3-(chloromethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran hydrochloride (III) which in turn was easily converted back to I. The chloromethyl compound (III) also was made by the chloromethylation of 3-(morpholinylmethyl)-2,5-diphenylfuran. These reactions confirm the structure assigned to I because of reactions reported earlier.[3,4]

The structures of the two products of the Mannich reaction using piperidine hydrochloride (2,5-diphenyl-3-[piperidylmethyl]-furan and 3-[hydroxymethyl]-2,5-diphenyl-4-[piperidylmethyl]-furan) were proven by characteristic syntheses starting from 3-(bromomethyl)-4-chloro-2,5-diphenylfuran, syntheses earlier carried out for the corresponding morpholine compounds.[4]



1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) was prepared by the characteristic nitric acid oxidation[5] of II and was found to give some interesting reactions. Reductive furanization of VII back to II, either directly or stepwise through VIII, establishes the structure of VII. When VII is treated with 6 *N* hydrochloric acid it dissolves, and when the resulting solution is neutralized with sodium carbonate, a product shown to be I crystallizes.

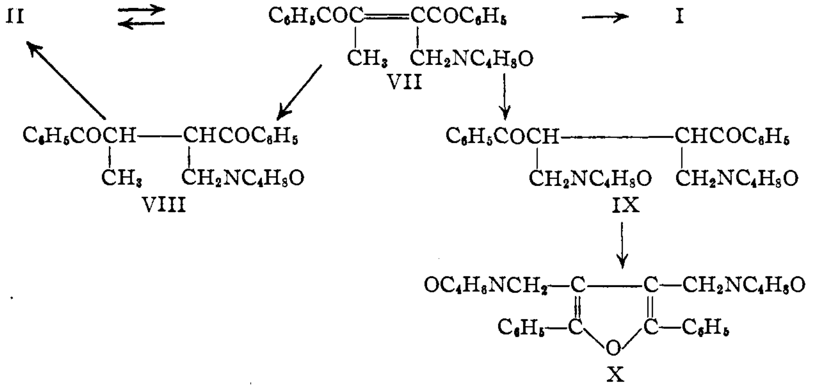
(1) Presented before the Southwest Regional Meeting of the American Chemical Society, Shreveport, Louisiana, December 10, 1948. A small portion was included in a paper presented at the Chicago meeting of the American Chemical Society, April, 1948.

(2) This work was partially supported by a University of Texas Research Institute grant, Project 70, and by a Frederick Gardner Cottrell grant from the Research Corporation, New York, N. Y.

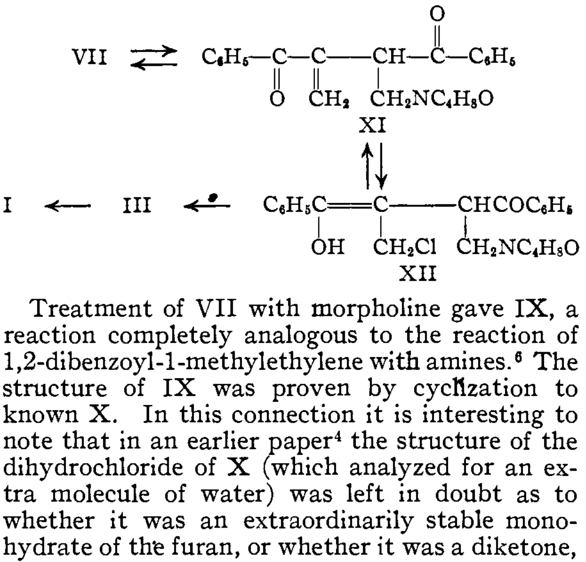
(3) Bailey and Lutz, THIS JOURNAL, **70**, 2412 (1948).

(4) Lutz and Bailey, *ibid.*, **68**, 2002 (1946).

(5) Lutz and Wilder, *ibid.*, **56**, 978 (1934).



This is a reaction similar to that between 1,2-dibenzoyl-1-methylethylene and amines, reported earlier.[6] Probably the reaction occurs through the steps shown below. It differs from the amine reaction[6] in that the acidic medium apparently favors cyclization of intermediate XII to a furan (III) rather than ketonization. It has been shown that III is easily hydrolyzed to I, simply upon treatment with sodium carbonate solution.



Treatment of VII with morpholine gave IX, a reaction completely analogous to the reaction of 1,2-dibenzoyl-1-methylethylene with amines.[6] The structure of IX was proven by cyclization to known X. In this connection it is interesting to note that in an earlier paper[4] the structure of the dihydrochloride of X (which analyzed for an extra molecule of water) was left in doubt as to whether it was an extraordinarily stable monohydrate of the furan, or whether it was a diketone, a dihydrochloride having the same structure as the dihydrochloride of the then unknown IX. The dihydrochlorides of X and IX have been shown to be definitely different, although difficulty was experienced in characterizing the salt of IX because of its great hygroscopic properties (the salt of X is not extremely hygroscopic). Upon neutralization, the dihydrochloride of IX gives back IX, not X; whereas the dihydrochloride in question (that of X) gives back X upon neutralization. Of course it is possible that the dihydrochlorides of IX and X are stereoisomers of one another, one a *meso* and the other a *dl*. However, if a ring opening did occur during the formation of a salt of X, the intermediate formed (probably a dienol) should fall into the more stable configuration of IX. Also the mechanism of formation of IX from VII should cause it to have the more stable configuration. Since the salts of IX and X are different, they must have different structures, and the dihydrochloride of X probably is only an unusually stable monohydrate.

Experimental[7]

3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).—A mixture of 48 g. of 1,2-dibenzoylethane, 48 g. of morpholine hydrochloride, 28 g. of paraformaldehyde, 2 ml. of concd. hydrochloric acid and 200 ml. of benzene was refluxed with efficient stirring for forty-eight hours, during which time 0.5 g. of paraformaldehyde was added every twelve hours. Two layers were present the entire time. The reaction mixture was worked up by the method described in another paper.[3] Thus was obtained 44.5 g. (65.5% yield) of the hydroxymethyl compound (I) which melted at 169–171°. In a number of different runs of this size the yields varied from 43 to 65%.

Where smaller runs were made, it was necessary to increase the ratio of benzene and hydrochloric acid to dibenzoylethane in order to maintain the above yields. For example, from a reaction mixture consisting of 4.8 g. of dibenzoylethane, 4.8 g. of morpholine hydrochloride, 2.9 g. of paraformaldehyde, 0.2 ml. of hydrochloric acid and 20 ml. of benzene, the yield of I was 7%, while from a similar reaction in which the volumes of benzene and hydrochloric acid were tripled, and everything else remained the same, the yield of I was 43%.

3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) from 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I). A. By Hydriodic Acid Reduction.—A mixture of 15 g. of I and 150 ml. of hydriodic acid (sp. gr., 1.7) was heated at 128° for twenty hours. The precipitate was filtered off and triturated with ethyl acetate; yield, 17.5 g. of brown crystals. A hot methanolic solution of the material was made slightly basic by the dropwise addition of 10% sodium hydroxide solution. After standing overnight the resulting mixture crystallized; 12.2 g. (86% yield), colorless crystals, m. p. 94–96°. Several recrystallizations from methanol raised the melting point to 95–96°.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 79.25; H, 6.95. Found: C, 78.97; H, 6.81.

B. Reduction with Stannous Chloride.—A solution of 1 g. of I in 5 ml. of glacial acetic acid was added to a hot solution of 5 g. of stannous chloride in 7 ml. of glacial acetic acid and 5 ml. of hydrochloric acid. The resulting solution was refluxed for ten minutes, after which it was cooled and poured into 200 ml. of water, where crystallization occurred. Treatment of the resulting crystals (1.1 g.) with methanol and sodium hydroxide, as described in the preceding experiment, yielded 0.7 g. of colorless crystals (m. p. 94–96°); no depression was observed in a mixture melting point with the material obtained from the hydriodic acid reduction.

3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) from 3-Methyl-2,5-diphenylfuran (VI). A. Bromethylation of VI to IV. To a solution of 0.3 g. of paraformaldehyde in 3.2 g. of 30% hydrogen bromide–acetic acid reagent, was added a solution of 1.4 g. of VI in 5 ml. of glacial acetic acid. The resulting mixture was stirred at 15° for two hours. The precipitate, which started to form after ten minutes, was filtered off and washed with

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[6] Lutz and Bailey, THIS JOURNAL, 67, 2229 (1945).

[7] All melting points reported here are corrected. Some of the micro-analyses were performed by the Micro-Tech Laboratories of Skokie, Illinois.

cold acetic acid; 1.4 g., m. p. 81–83°. After several recrystallizations from ligroin (b. p. 90–105°) the melting point was 83–84°. The compound gave a positive Beilstein test.

Anal. Calcd. for $C_{18}H_{15}BrO$: C, 66.07; H, 4.62. Found: C, 66.05; H, 4.67.

Catalytic hydrogenolysis (Raney nickel) of a small sample of IV in the presence of an equivalent amount of potassium hydroxide in methanol solution yielded 3,4-dimethyl-2,5-diphenylfuran (V), which was identified by a mixture melting point with a known sample.[8]

B. Treatment of IV with Morpholine.—A solution of 1 g. of IV and 1 g. of morpholine in 30 ml. of dry ether was allowed to stand overnight, after which the morpholine hydrobromide was filtered off and the filtrate was washed, dried and evaporated. Crystallization of the residual oil from ethanol gave 1.0 g. of II (m. p. 95–96°) which showed no depression in a mixture melting point with the material from the reduction of I.

3-(Chloromethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran Hydrochloride (III). A. From 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).—A solution of 1 g. of I in 25 ml. of chloroform, saturated with hydrogen chloride, was set aside for two months, after which time it was evaporated. Several recrystallizations of the residue (1.3 g., m. p., 185–189°) from acetone raised the melting point to 232–233°.[9]

Anal. Calcd. for $C_{22}H_{23}Cl_2NO_2$: C, 65.35; H, 5.73. Found: C, 65.52; H, 5.97.

B. From 3-(Morpholinylmethyl)-2,5-diphenylfuran.—Into a solution of 2 g. of 3-(morpholinylmethyl)-2,5-diphenylfuran hydrochloride and 0.2 g. of paraformaldehyde in 14 ml. of glacial acetic acid, was passed hydrogen chloride for twenty-four hours. The solution was evaporated under reduced pressure and the residue was recrystallized several times from acetone; yield 1.6 g., m. p. 231–233°, no depression in a mixture melting point with the material obtained in part (A).

In another run the reaction mixture was worked up by dilution with water and neutralization with sodium carbonate. The product was I. Also, when crystalline III was shaken with sodium carbonate solution and ether it was converted to I.

The Mannich Reaction in Benzene Solution Using Piperidine Hydrochloride. A. 3-(Hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan.—A reaction mixture consisting of 4.8 g. of 1,2-dibenzoylethane, 4.3 g. of piperidine hydrochloride, 3.0 g. of paraformaldehyde, 60 ml. of benzene and 0.6 ml. of concd. hydrochloric acid was refluxed with stirring for forty-eight hours, during which time 0.1 g. of paraformaldehyde was added every twelve hours. The mixture was treated with 50 ml. of 6 *N* hydrochloric acid and extracted with ether. When the hydrochloric acid layer was worked up as described in the morpholine experiment[3] there was obtained 3.0 g. (46% yield) of crystals which melted at 161–165°. Several recrystallizations from ethanol raised the melting point to 169–170°.

Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25. Found: C, 79.28; H, 7.36.

B. 2,5-Diphenyl-3-(piperidylmethyl)-furan.—When the above reaction was repeated and worked up in precisely the same way with the exception that only 30 ml. of benzene and 0.3 ml. of hydrochloric acid was used, there was obtained 4.7 g. of material (m. p., 201–205°) which did not dissolve in either the hydrochloric acid or the ether layer. From the hydrochloric acid layer was obtained 0.5 g. of 3-(hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan. The 4.7-g. batch of crystals was dissolved in hot water, the solution was neutralized with sodium carbonate, and the resulting mixture was extracted with ether. From the ether extract was obtained 2.5 g. of colorless crystals which after recrystallization from ethanol melted at 83–84°.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.25; H, 7.30. Found: C, 83.13; H, 7.26.

2,5-Diphenyl-3-(piperidylmethyl)-furan from 3-(Bromomethyl)-4-chloro-2,5-diphenylfuran. A. 3-Chloro-2,5-diphenyl-4-(piperidylmethyl)-furan.—To a solution of 1 g. of 3-(bromomethyl)-4-chloro-2,5-diphenylfuran[4] in 20 ml. of ether was added 0.7 g. of piperidine. After twelve hours the reaction mixture was filtered and the filtrate was washed, dried and evaporated. Thus was obtained 0.9 g. of colorless crystals which melted at 76–77°, after purification by recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{22}ClNO$: C, 75.09; H, 6.30. Found: C, 75.00; H, 6.48.

B. Catalytic Hydrogenolysis of 3-Chloro-2,5-diphenyl-4-(piperidylmethyl)-furan (0.8 g.) was carried out in a solution also containing 0.13 g. of potassium hydroxide and 40 ml. of methanol. The catalyst was Raney nickel (0.2 g.); 59 ml. of hydrogen was absorbed, after which the mixture was filtered, the filtrate was evaporated, and the residue was crystallized from isopropyl alcohol. The product was 0.6 g. of 2,5-diphenyl-3-(piperidylmethyl)-furan (m. p. 83–85°; no depression in a mixture melting point with a sample obtained from the Mannich reaction).

3-(Hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan from 2,5-Diphenyl-3-(piperidylmethyl)-furan.—A solution of 0.6 g. of paraformaldehyde in 12 g. of 30% hydrogen bromide–acetic acid reagent was added to a solution of 2.5 g. of 2,5-diphenyl-3-(piperidylmethyl)-furan in 8 ml. of glacial acetic acid. After twelve hours the mixture was poured into 200 ml. of water. Neutralization with sodium carbonate gave an oil which crystallized when treated with ether. Recrystallization yielded 0.86 g. of colorless crystals which melted at 167–170° and showed no depression in a mixture melting point with the product obtained from the Mannich reaction.

1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII).—To a solution of 6 g. of 3-methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) in 40 ml. of propionic acid, cooled to 0°, was added a cold solution of 12 ml. of nitric acid in 24 ml. of propionic acid. After twenty minutes the solution was poured into water and neutralized with sodium carbonate. The resulting mixture was extracted with ether and the ether extract was washed dried and evaporated. Thus was obtained 6 g. of crude yellow crystals, which after several recrystallizations from ethanol melted at 104–105°.

Anal. Calcd. for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.64. Found: C, 75.86, 75.76; H, 6.50, 6.59.

Conversion to the picrate, by treating an ethanolic solution of VII with an ethanolic picric acid solution, gave a yellow solid which melted at 163–165° after several recrystallizations from an isopropyl alcohol–acetone mixture.

Anal. Calcd. for $C_{28}H_{26}N_4O_{10}$: C, 58.13; H, 4.53. Found: C, 58.10, 58 15; H, 4.42, 4.35.

Reduction of 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII). A. To 3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II).—To a solution of 5 g. of stannous chloride, 5 ml. of hydrochloric acid and 7 ml. of acetic acid was added a solution of 0.6 g. of VII in 5 ml. of acetic acid. The mixture was heated over a steam-bath, with stirring, for five minutes, after which it was diluted with water and neutralized with sodium carbonate. Extraction with ether and evaporation of the ether extract gave an oil which was crystallized from ethanol (0.4 g., m.p. 99–100°) and identified as II by a mixture melting point with an authentic sample.

B. To 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethane (VIII).—A porcelain spatulaful of zinc dust was added to a solution of 2 g. of VII in 40 ml of glacial acetic acid. The reaction mixture was stirred and warmed over a steam-bath for nine minutes, after which it was filtered. The filtrate was neutralized with sodium carbonate and extracted with ether. Evaporation of the ether solution and crystallization of the residue from

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[8] Lutz and Taylor, THIS JOURNAL, 55, 1593 (1933).

[9] If the melting point tube is placed in a bath preheated to 200°, the compound immediately melts, then resolidifies and melts again at 232–233°.

ethanol gave 1.2 g. of colorless crystals which melted at 112–113°. The melting point did not change upon recrystallization.

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17. Found: C, 75.20; H, 7.39.

Furanization of VIII to II was accomplished by treating a solution of 1 g. of VIII in 5 ml. of acetic anhydride with 0.17 ml. of sulfuric acid (to bring about salt formation) followed by five drops excess. After twenty minutes the mixture was poured into water, where it was neutralized with sodium carbonate and extracted with ether. Evaporation of the ether extract and crystallization of the residue from ethanol gave colorless crystals (melting at 98–100°) which were shown to be II by a mixture melting point with an authentic sample.

Conversion of 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) to 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).—Five-tenths gram of VII was dissolved in 100 ml. of 6 *N* hydrochloric acid and the solution was extracted with ether. Neutralization of the acid layer with sodium carbonate gave 0.48 g. of material which melted at 168–172° after recrystallization from ethanol; it showed no depression in a mixture melting point with known 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).

1,2-Dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX).—A solution of 1 g. of 1,2-dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) in 10 ml. of morpholine was warmed at 75–80° for twenty-four hours. The solution was then poured into water and extracted with ether. Evaporation yielded 0.98 g. of crystals which melted at 135–140°. Several recrystallizations from ethanol raised the melting point to 141–142°. A mixture melting point with 3,4-di-(morpholinylmethyl)-2,5-diphenylfuran (X)[4] (m. p. 143–144°) was depressed to 125–131°.

Anal. Calcd. for $C_{28}H_{32}N_2O_4$: C, 71.53; H, 7.39. Found: C, 71.56; H, 7.55.

Treatment of this material with 6 *N* hydrochloric acid, followed by neutralization with sodium carbonate, produced no change.

Conversion of 1,2-Dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX) to 3,4-Di-(morpholinylmethyl)-2,5-diphenylfuran (X).—To a solution of 0.5 g. of IX in 5 ml. of acetyl chloride was added, dropwise, 0.53 ml. of concd. sulfuric acid. After twenty minutes the dark green solution was poured into water and the resulting solution was neutralized with sodium carbonate. Extraction with ether and evaporation of the ether extract gave 0.41 g. of crystals which melted at 115–122°. Several recrystallizations from ethanol raised the melting point to 143–144°. The material showed no depression in a mixture melting point with known 3,4-di-(morpholinylmethyl)-2,5-diphenylfuran (X),[4] but showed a twenty degree depression in a mixture melting point with starting material (IX).

The Dihydrochloride of IX was made by treating an ether solution of IX with excess ethereal hydrogen chloride. It proved to be difficult to purify because of its great hygroscopic properties; for this same reason, a carbon and hydrogen analysis was not made. Several recrystallizations from acetone by the addition of dry ether gave colorless crystals melting at 120–123°.

Anal. Calcd. for $C_{28}H_{34}Cl_2N_2O_4$: Cl^-, 13.92. Found: Cl^-, 13.75.

The dihydrochloride was converted back to IX by neutralizing an aqueous solution of it with sodium carbonate. The yield was 70% and the melting point after one recrystallization from ethanol was 139–141°. There was no depression in a mixture melting point with known 1,2-dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX), but a twenty degree depression was observed with known X.

Summary

A rigorous proof of structure for 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran is presented. 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene has been made and found to undergo some interesting reactions. Treatment of the latter with hydrochloric acid, followed by neutralization with sodium carbonate, gives 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran, while treatment with morpholine gives 1,2-dibenzoyl-1,2-di-(morpholinylmethyl)-ethane. Mechanisms are discussed.

AUSTIN, TEXAS RECEIVED OCTOBER 15, 1948

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Hydrogenation Products from Furfuralacetofuran

BY KLIEM ALEXANDER AND GEORGE H. SMITH, JR.

The chalcone-like compound, furfuralacetofuran,[2] represents a little known type of furfural condensation product. It is readily obtainable by condensing furfural with 2-acetylfuran. The latter intermediate is conveniently available by the preparative procedure of Hartough and Kosak.[3] Total hydrogenation of furfural and difurfural ketone and aldehyde condensation products, in which all of the ethylenic, carbonyl and furyl groups were saturated, has been reported by several authors.[4,5] Intermediates prepared by selective hydrogenation of the alkene and carbonyl groups have, however, received much less attention. Adkins and associates[4,6] have shown that by suitable choice of catalyst and other reaction conditions, the alkene, carbonyl, and furan ring groups of β-furylacrolein can be selectively hydrogenated in that order. In this instance they also observed a complicating side reaction involving ring closure of an intermediate, probably β-furylpropionaldehyde, and leading to the bicyclic structure 1,9-dioxa-5-spirononane. More drastic conditions of hydrogenation gave various ring cleavage and other hydrogenolysis products.

In this study procedures were developed for the conversion of furfuralacetofuran (I) to 1,3-di-

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(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Previously reported by Weygand and Strobelt, *Ber.*, **68**, 1839 (1935).

(3) H. D. Hartough and A. I. Kosak, THIS JOURNAL, **69**, 3093 (1947).

(4) H. Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937.

(5) A. Hinz, G. Meyer and G. Schücking, *Ber.*, **76B**, 676 (1943).

(6) (a) H. E. Burdick and H. Adkins, THIS JOURNAL, **56**, 438 (1934); (b) M. Farlow, H. E. Burdick and H. Adkins, *ibid.*, **56**, 2498 (1934).