

THE NITRATION OF 2-FURYL METHYL KETONE: METHYL  
5-NITRO-2-FURYL KETONE AND 3,4-DI-(2-FUROYL)-  
FUROXAN

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As part of a program of investigation requiring the use of methyl 5-nitro-2-furyl ketone (I) we have investigated the action of mixed-acid on 2-furyl methyl ketone for the preparation of I. It has not been possible to duplicate the 32% yield of I, obtained by a Marquis type nitration, reported by Rinkes (1). By operating at 0°, or below, with a mixture of nitric and sulfuric acids, consistent yields of 12–15% of I could be obtained on a relatively small scale. Nitrations on a larger scale were difficult to control because of the high viscosity and poor heat transfer characteristics of the cold mixed-acid.

When acetic acid was employed as a diluent to reduce the viscosity of the mixed-acid no reaction was apparent until the temperature was increased to 15–20°. Dilution of this nitration reaction mixture with water produced a solid (II) of melting point 108° (m.p. of I, 78°) in excellent yield. The ultraviolet absorption curve was very similar to that of I, but analysis indicated that II differed from I by the loss of one molecule of water. A Rast molecular weight determination showed the molecular formula of II to be C<sub>12</sub>H<sub>6</sub>N<sub>2</sub>O<sub>6</sub>.

The structure of II was investigated because it was thought that the nitration might be directed to the desired product, I, if the nature of the reaction leading to II was known.

The substance II exploded with a luminous flame when heated above 225°. It reacted vigorously with aqueous alkali to yield furoic acid after acidification. When catalyzed with iodine it formed a derivative with two moles of 2,4-dinitrophenylhydrazine. However, it did not decolorize bromine in water or chloroform.

These characteristics are reminiscent in part of the products obtained by Hollemann (2) by the action of concentrated nitric acid on acetophenone at slightly elevated temperatures. This reaction has been studied in much detail by Ponzio and his students (3–5), and recently by Alexander, *et al.* (6). The major product derived from acetophenone, of melting point 87° (III), has been shown to be 3,4-dibenzoylfuroxan.

The structure of 3,4-dibenzoylfuroxan (III) has been established, in part, by the nature of the hydrolytic degradation products. Ponzio (5) has obtained benzoylmethazonic acid (V), along with 3-hydroxy-5-benzoyl- and 5-hydroxy-3-benzoyl-1,2,4-oxadiazole, by a prolonged hydrolysis at pH 4.5. The isomeric hydroxyoxadiazoles may be differentiated since the 3-isomers produce diarylureas where heated with arylamines and the 5-isomers do not (5). Durio (4) has also obtained V from III by the action of dilute sodium hydroxide. These reactions are outlined in Flowsheet I.





Erlenmeyer (7) and Scholl (8) have observed that aldoximes can be oxidized with nitrogen dioxide to produce furoxans.

This postulated mechanism seems plausible in our case for lower oxides of nitrogen are visibly present in the reaction.

#### EXPERIMENTAL<sup>2</sup>

*Mixed-Acid nitration of 2-furyl methyl ketone, to give I.* 2-Furyl methyl ketone (technical,<sup>3</sup> three moles, 300 g.) was added slowly with stirring to 900 cc. of concentrated sulfuric acid while cooling to maintain  $-5$  to  $+5^\circ$ . The brown solution was further cooled to  $-10^\circ$  and 315 cc. of concentrated nitric acid (*d.*1.42) was added during  $2\frac{1}{2}$  hours. Vigorous agitation and strong cooling were employed so that the temperature did not exceed  $-4^\circ$  during the addition and for one hour thereafter. The viscous, orange mixture was poured into 5 l. of water containing 2 kg. of chopped ice. The organic material was then extracted with benzene ( $1 \times 3$  l.,  $3 \times 1$  l.). The combined benzene extracts were washed with 20% sodium acetate solution ( $1 \times 700$  cc.), and water until neutral. After drying with Drierite the benzene was distilled off on the steam-bath. The brown residue (100 g.) was vacuum-distilled to remove unnitrated furyl methyl ketone (40 g.,  $40-95^\circ$  at 1.5 mm.). The residue of crude I was not distilled because of the tendency of by-products therein to explode but was cooled to give tan crystals, 58.5 g., 14.3% yield based on ketone consumed, m.p.  $66-71^\circ$ . This was of adequate purity for some uses but may be purified by recrystallization from ligroin with a recovery of 85% yielding a product of m.p.  $74-75^\circ$ ;  $E_{1\%}^{1\text{cm.}}$  = 808 at  $3080\text{\AA}$  in water.

*Mixed-Acid nitration of 2-furyl methyl ketone with acetic acid as diluent, to give II.* A solution of mixed-acid was prepared by adding 26 cc. of concentrated nitric acid (*d.*1.42), with stirring and cooling, to 75 cc. of concentrated sulfuric acid. To this was added 150 cc. of glacial acetic acid while maintaining the temperature below  $25^\circ$ . A solution of 28.0 g. (0.225 mole) of furyl methyl ketone in 50 cc. of glacial acetic acid was added during seven minutes with stirring and cooling to maintain the temperature at  $10-15^\circ$ .

The approximate rate of reaction was determined by periodic sampling. A 25-cc. sample was withdrawn by pipet and added to 75 cc. of ice-water. After standing one hour at  $0^\circ$  the mixture was extracted with two 25-cc. portions of chloroform. An aliquot of the chloroform solution was diluted stepwise  $1 \rightarrow 5000$  with isopropyl alcohol and assayed for II by determination of the optical density at  $2950\text{\AA}$  employing a Beckman spectrophotometer (Quartz Model DU). A blank of acetic acid in chloroform (1:19) diluted  $1 \rightarrow 5000$  with isopropyl alcohol was used. The observed absorption coefficient for pure II was observed to be  $E_{1\%}^{1\text{cm.}}$  = 899 at  $2950\text{\AA}$  in this medium. The ultraviolet absorption at  $2700\text{\AA}$  was also observed to estimate the disappearance of furyl methyl ketone,  $E_{1\%}^{1\text{cm.}}$  = 1160 at  $2700\text{\AA}$ .

Time—at $10-15^\circ$ After Mixing	15 Min.	45	75	165	240	375	72 Hours
Yield of II, by U.V. absorption at $2950\text{\AA}$ , %.	7.3	8.5	10.1	31.3	44.1	55.6	52.5

The furyl methyl ketone was not entirely consumed after 375 minutes but was absent after 72 hours. II was actually isolated from one-fourth of the reaction mixture after 72 hours by pouring into 225 cc. of ice-water and stirring for one hour. The solid was filtered and dried at  $50^\circ$ . Yield 4.13 g., 47.2%, of m.p.  $106-107^\circ$ .

Purification of II was effected by recrystallization from isopropyl alcohol (10 cc. per gram) using Darco, giving nearly white material of m.p.  $107-108^\circ$ . Two subsequent re-

<sup>2</sup> We are indebted to Joseph Corrado for all the micro-analyses. All melting points were determined on a calibrated Fisher-Johns apparatus.

<sup>3</sup> The 2-furyl methyl ketone was purchased from Cliffs-Dow Co., Marquette, Mich. The melting point was  $>28^\circ$  and thus of sufficient purity for use.

crystallizations from the same solvent did not alter the melting point. The slight yellow color was most effectively removed by warming in pyridine at 50° for 30 minutes, followed by dilution with a large volume of water and recrystallization of the solid from isopropyl alcohol using Darco. The melting point was unchanged. The material inflames when rapidly heated above 225°.

*Anal.* Calc'd for  $(C_6H_3NO_2)_x$ : C, 52.56; H, 2.20; N, 10.21.

Found: C, 52.79, 52.54; H, 2.04, 2.21; N, 10.16.

A Rast molecular weight estimation in camphor gave 266, under conditions where I as a standard gave 153, calc'd 155. Thus II has the composition  $C_{12}H_3N_2O_6$ , molecular weight calc'd 274. The solubility in water at room temperature was 39 mg. per l.  $E_{1\%}^{1cm} = 830$  at 3050Å in water.

Attempts to condense II with 2,4-dinitrophenylhydrazine were unsuccessful until iodine was added to serve as a catalyst. A mixture of 3.0 g. of II, several small crystals of iodine, and 4.0 g. of 2,4-dinitrophenylhydrazine in 100 ml. of alcohol, acidified with 5 cc. of concentrated hydrochloric acid was heated at reflux for one hour, from which 4.96 g. of an orange crystalline product was obtained. After recrystallization from a mixture of nitromethane and isopropyl alcohol this material had m.p. 218–219° d. Analysis showed that II had combined with two equivalents of 2,4-dinitrophenylhydrazine.

*Anal.* Calc'd for  $C_{24}H_{14}N_{10}O_{12}$ : C, 45.5; H, 2.22.

Found: C, 45.5, 45.7; H, 2.00, 2.18.

II did not decolorize bromine in water or carbon tetrachloride, nor did it yield a silver or copper salt with ammoniacal silver oxide or cuprous chloride. A sulfuric acid-sodium dichromate oxidation for two hours at 100° had little effect, 75% of II being recovered. Catalytic hydrogenation in alcohol with palladium on charcoal produced a hydrogen uptake of 5.5 moles but only tars could be isolated.

*Alkaline hydrolysis of II.* A suspension of 4.0 g. of II in 50cc. of 10% aqueous sodium hydroxide was heated producing a vigorous reaction. After boiling the brown solution for 20 minutes it was cooled by adding ice and was extracted with 10 cc. of ether. The aqueous solution was acidified with 10% sulfuric acid and extracted with ether (5 × 25 cc.). The combined ether extracts were dried with Drierite, then the solvent was removed by evaporation leaving 1.15 g. of white crystals. This product was purified by sublimation at one atmosphere, m.p. 130°; ultraviolet absorption coefficient in water,  $E_{1\%}^{1cm} = 935$  at 2460Å; neutral equivalent 115; no nitrogen was present.

*Anal.* Found: C, 53.74; H, 3.47.

These data fit 2-furoic acid; m.p. 132°; neutral equivalent 112; ultraviolet absorption  $E_{1\%}^{1cm} = 955$  at 2460Å; Calc'd for  $C_6H_4O_3$ : C, 53.6; H, 3.57.

*Mild acid hydrolysis of II.* A suspension of 10 g. of II in a solution of 30 g. of anhydrous sodium acetate, 75 cc. of glacial acetic acid, 75 cc. of water, and 75 cc. of methanol was kept at 25–35° for six days. At this time the II had dissolved and the solution had the odor of methyl furoate. The yellow solution was cooled in an ice-bath and was neutralized by addition of 20% sodium hydroxide solution. At about the neutral point yellow platelets separated and after refrigeration for two hours these were filtered. Yield 1.0 g., m.p. 185–190° dec.

This first product (a sodium salt) was stirred with a mixture of 10 cc. of 10% sulfuric acid and 1 cc. of ethanol for 15 minutes. The solid was filtered, washed with water and air-dried, 0.73 g. This acid was purified by sublimation at 125–140° and 1 mm. pressure, followed by recrystallization from methanol. Yield 0.55 g., m.p. 157–159° with strong sublimation above 120°. Dried *in vacuo* at 56°.

*Anal.* Calc'd for  $C_7H_4N_2O_4$ : C, 46.68; H, 2.24; N, 15.55.

Found: C, 46.91; H, 2.28; N, 15.43.

Since this material did not produce diphenylurea on boiling in aniline it is assumed to be 3-(2-furoyl)-5-hydroxy-1,2,4-oxadiazole (VI) rather than the isomeric 5-(2-furoyl)-3-hydroxy-1,2,4-oxadiazole.

The filtrate from the neutralized hydrolysis mixture of II was treated with 100 cc. of

10% aqueous cupric acetate. Filter-Cel was added and the gelatinous, blue-green, copper complex was filtered. The filter cake was slurried with 150 cc. of 10% sulfuric acid which dissolved the copper complex. The Filter-Cel was removed by filtration and washed with 25 cc. of 10% sulfuric acid. On scratching the combined filtrates a white solid precipitated, which was removed by filtration. Yield 1.1 g., m.p. 99-104°, resolidified at 120-125° and remelted at 148-150°. By analogy to Ponzio (5) this should be the isomeric 1,2,4-oxadiazole derivative but this proved not to be the case. The green filtrate was treated with saturated sodium acetate solution to reprecipitate the copper complex. This was isolated by centrifugation, washed with water, and the solid was redissolved in the minimum of 10% sulfuric acid (35 cc.). On standing a short time this gave a light tan precipitate, yield 0.5 g., m.p. 99-104°, 148-150°. This procedure was carried through again to yield 0.1 g. of similar material. The acid filtrate then was extracted with ether to isolate the substituted methazonic acid following the procedure of Ponzio (5). A small amount of crystalline material, which melted at 99-104°, resolidified at 120-125°, and remelted at 148-150°, was obtained on evaporation of the ether. All this material was combined and recrystallized three times from water using Norit to give pure white needles. The needles melted at 100-105°, resolidified at 120-125° and remelted sharply at 149-150°; they were dried *in vacuo* at room temperature.

*Anal.* Calc'd for  $C_7H_5N_2O_5 \cdot H_2O$ : C, 38.93; H, 3.47; N, 13.08;  $H_2O$ , 8.34.

Found: C, 38.81; H, 3.72; N, 12.95;  $H_2O$ , 8.56.

The water content was determined by drying at 100° *in vacuo* to constant weight.

#### SUMMARY

The action of mixed-acid on 2-furyl methyl ketone at low temperatures yields methyl 5-nitro-2-furyl ketone conveniently but in low yield.

The action of mixed-acid on 2-furyl methyl ketone, under certain conditions, has led to a substance that has been shown to be 3,4-di-(2-furoyl)furoxan. This was demonstrated by degradation to 2-furoylmethazonic acid and 2-furoic acid and by formation of a bis-2,4-dinitrophenylhydrazone.

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