ORGANIC AND BIOLOGICAL CHEMISTRY

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

The Synthesis of Furoxans from Aryl Methyl Ketones and Nitric Acid[1]

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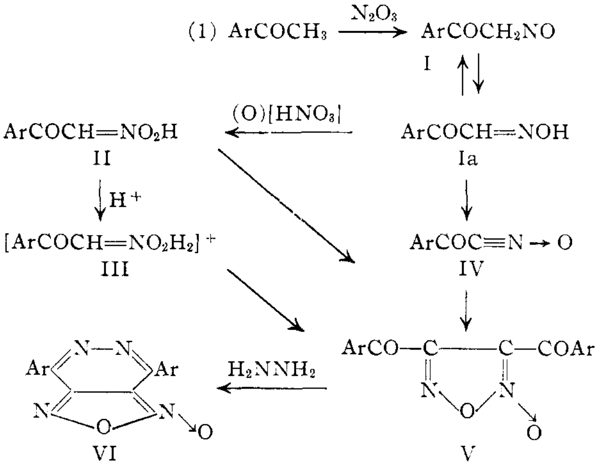
Aryl methyl ketones are smoothly converted to diacylfuroxans by reaction with dilute nitric acid in acetic acid solution, with the addition of a little sodium nitrite as an initiator. Nitrosation of the ketone appears to be followed by oxidation; the nitromethyl ketone probably is not an intermediate, for under the conditions used dibenzoylfuroxan is obtained from ω-nitroacetophenone in poorer yields than from acetophenone. The conversions of ω-nitroacetophenone to dibenoylfuroxan by sulfuric and by nitric acids appear to proceed by different mechanisms. Observations on the reactivity of diacylfuroxans with hydrazine are reported.

In the course of an investigation of the properties of furoxans, which required the preparation of many different members of this class of compounds, it became necessary to consider the conversion of a number of methyl aryl ketones to the corresponding furoxans V by reaction with nitric acid. This transformation is well known, having been used for the synthesis of at least twenty of the substances, but as usually conducted it has not appeared to be attractive for preparative purposes.[2] In preliminary trials with various methyl aryl ketones, the method proved to be quite erratic; induction periods of varying length, occasional violent reactions, nitration of sensitive aromatic rings, and oxidation to the aromatic acids combined to reduce its usefulness.

In a recent study of the action of nitric acid on acetophenone and some of its derivatives, Alexander, Kinter and McCollum[3] observed that dibenzoylfuroxan is not formed by the action of *colorless* nitric acid on acetophenone; Ponzio[2] used sodium nitrite as a catalyst. Alexander, Kinter and McCollum also discovered that ω-nitroacetophenone (II) is converted to the furoxan by the action of nitric acid. These observations led them to suggest that nitrosation of acetophenone, brought about by the oxides of nitrogen in yellow or red nitric acid, is the first step in the transformation of the ketone, and that the nitro compound is an intermediate. In this scheme the nitroso (or oximino) ketone I reduces nitric acid, with the generation of more oxides of nitrogen which attack more of the ketone.

On the basis of the occurrence of nitrosation as the primary process, the induction periods observed could be attributed to the low concentrations of nitrogen oxides and of the nitrosation product in the early stages of the reaction. It should be possible to cause the reaction to start immediately by providing an adequate supply of a nitrosating agent. The addition of a very small amount of sodium nitrite was found to serve this purpose; the reaction started immediately and was controlled easily.



A study of other experimental variables resulted in a procedure which appears to be generally applicable to the conversion of methyl aryl ketones to furoxans in reasonably good yields. The ketone is dissolved in glacial acetic acid and *diluted* (about 20%) nitric acid is added.[4a] This mixture is warmed to a suitable temperature, depending on the substituents present, and a little solid sodium nitrite is added. The reaction starts immediately, but it does not become violent; in fact, continuation of the heating usually is required to maintain the reaction. After about half an hour the mixture is poured into water and the product is isolated. The use of diluted nitric acid was tested first on compounds having sensitive aromatic nuclei (*e.g.*, acetomesitylene), which underwent extensive nitration when concentrated acid was employed, as a measure for suppressing the substitution. The diluted acid proved to be advantageous not only with such compounds, but also with all other methyl aryl ketones studied except those having nitro groups as substituents. The furoxans from *o*- and *p*-nitroacetophenone were obtained in somewhat better yields when the reaction was conducted in concentrated nitric acid (with no other solvent) with the addition of a little sodium nitrite as the initiator. However, these reactions sometimes become quite violent, and the preparation in the presence of acetic acid may be preferred despite the slightly lower yields.

Claus[4b] has reported that the action of a mixture of concentrated nitric acid and sulfuric acid mono-

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[2] Perhaps the best preparative procedure described is that of G. Ponzio, *Gazz. chim. ital.*, **56**, 497 (1926), who carried out the reaction on a number of 10-g. portions of acetophenone and combined the reaction mixtures.

[3] E. R. Alexander, M. R. Kinter and J. D. McCollum, THIS JOURNAL, **72**, 801 (1950).

(4) (a) After the preparation of the present manuscript, K. Hayes and C. O'Keefe, *J. Org. Chem.*, **19**, 1897 (1954), described the conversion of 2-furyl methyl ketone to the furoxan by reaction with concentrated nitric acid in acetic acid.

(4) (b) A. Claus, *J. prakt. Chem.*, [2] **41**, 483 (1890).

hydrate on 2,4-dimethylacetophenone at room temperature gave bis-(2,4-dimethyl-3,5-dinitrobenzoyl)-furoxan. It was of interest to learn whether the substitution of sulfuric acid for glacial acetic acid in the present process would permit the conversion of ketones containing less active aromatic nuclei directly to nitrofuroxans. It was found that yellow fuming nitric acid gave bis-(*m*-nitrobenzoyl)-furoxan in 50% yield directly from acetophenone. Under the same conditions 2,4-dimethylacetophenone and acetomesitylene were converted directly to bis-(3,5-dinitro-2,4-dimethylbenzoyl)-furoxan and bis-(3,5-dinitro-2,4,6-trimethylbenzoyl)-furoxan in yields of 56 and 47%, respectively; these same products were obtained by nitration of the furoxans in yields of 66 and 81%, respectively.

The synthesis of furoxans from purely aliphatic methyl ketones by the new procedure was not satisfactory. Thus, treatment of acetonylacetone with diluted nitric acid in acetic acid gave only about 10% of bis-(5-methyl-3-isoxazolylcarbonyl)-furoxan, which is prepared better in concentrated nitric acid by the procedure of Quilico.[5] Even poorer yields resulted from attempts to use the procedure with ethyl acetoacetate, and no furoxan could be obtained from pinacolone. However, a great improvement in the synthesis of ethyl furoxan-3,4-dicarboxylate from ethyl acetoacetate was achieved by nitrosating the keto ester and treating the isonitroso derivative with diluted nitric acid.

The observations on the conversion of methyl aryl ketones to furoxans are in general agreement with the mechanism proposed by Alexander, Kinter and McCollum,[3] except with regard to the status of the *ω-nitroacetophenones* as intermediates. These authors observed that ω-nitroacetophenone is converted to the furoxan by nitric or sulfuric acid in glacial acetic acid, but not by hydrochloric or phosphoric acid. As an alternative to their proposal of dimerization of a protonated form of the nitro compound III, the dehydration of the nitro compound to the nitrile oxide, followed by its dimerization, exactly as proposed by Quilico and Speroni[5] for the reaction of methazonic acid, must be considered. Other paths from the nitroso or oximino ketone to the nitrile oxide then are available, and the process can be classified with other conversions of nitroso or oximino compounds, such as simple aldoximes,[6] hydroxamic acids[7] and nitrolic acids[8]; all these transformations can be considered as involving the nitrile oxides.

The question as to whether the ω-nitroacetophenones are intermediates in the present process for converting methyl aryl ketones to furoxans nevertheless remains. To gain information on this point, ω-nitroacetophenone was prepared and treated with diluted nitric acid in acetic acid under the conditions employed with acetophenone. *Dibenzoylfuroxan was formed, but in yields substantially lower than those obtained from acetophenone.* Furthermore, the process was characterized by an induction period, followed by a vigorous reaction accompanied by the evolution of nitrous fumes; the addition of a small amount of sodium nitrite eliminated the induction period, with some improvement in the yield, and the addition of urea lengthened the induction period. These observations point to *nitrosation as the essential step in the reaction of the nitroketone with diluted nitric acid.* If this is true the reason for the failure[3] of hydrochloric acid (containing water) to effect the conversion becomes clear.

Experiments with nitrous acid scavengers also were made in reactions employing the nitroketone and concentrated sulfuric acid with glacial acetic acid as the solvent. When a rather large amount of urea (20% of the weight of the nitroketone) was added portionwise over the entire reaction period, little or no effect was observed and the furoxan was obtained in 57% yield. The addition of a much larger amount of urea (equal to the weight of the nitroketone) at the beginning of the reaction period did prevent the reaction, but the effect probably was merely that of reduction of the acid strength of the medium. In a similar experiment with an equal weight of sulfamic acid instead of urea a moderate yield of the furoxan was isolated. Sulfamic acid in similar amounts proved very effective in inhibiting the reaction with concentrated nitric acid, the nitroketone (85%) being recovered unchanged.

It may be concluded from these experiments that the conversion of methyl aryl ketones to furoxans by the action of diluted nitric acid in acetic acid probably does not involve the intermediate formation of the nitroketones, that the conversion of ω-nitroacetophenone to dibenzoylfuroxan by concentrated nitric acid in acetic acid proceeds by way of nitrosation, and that the most important action of concentrated sulfuric acid in converting ω-nitroacetophenone to the furoxan is that of dehydration.

Most of the diacylfuroxans prepared in the present study were treated with hydrazine for conversion to the cyclic azines VI. Dibenzoylfuroxan and its derivatives having only electron-withdrawing groups, such as nitro or chloro, as substituents in the aromatic rings, could be converted to the azines by reaction with a hydrazine salt in acid solution. Electron-donating substituents reduced the reactivity, but the dibenzoylfuroxans having both rings substituted in the *para* position with methoxyl or with phenyl evidently did yield the cyclic azines, although only in alkaline medium. However, it has not been possible to obtain these azines in analytically pure state. Bis-(2,4-dimethylbenzoyl)-furoxan evidently reacts to a slight extent, for its reaction mixtures with hydrazine develop the orange color characteristic of the azines, but attempts to isolate the product resulted only in the recovery of the original furoxan. As expected, the compounds in which each benzene ring bears two electron-donating *o*-substituents, such as bis-(2,4,6-trimethylbenzoyl)- and bis-(2,4,6-triisopropylbenzoyl)-furoxans, proved entirely inert to hydrazine. That steric factors outweigh the electronic influ-

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(5) A. Quilico, *Gazz. chim. ital.*, **61**, 265 (1931); A. Quilico and G. Speroni, *ibid.*, **76**, 153 (1946).

(6) For an example, see H. Franzen and F. Zimmermann, *J. prakt. Chem.*, [2] **73**, 255 (1906); R. Ciusa and E. Parisi, *Gazz. chim. ital.*, **53**, 143 (1923).

(7) A. Werner, *Ber.*, **27**, 2848 (1894); A. Werner and W. Skiba, *ibid.*, **32**, 1662 (1899).

(8) H. Wieland and L. Semper, *ibid.*, **39**, 2522 (1906).

ences of the substituents is indicated by the fact that the compounds in which the 2,4,6-trimethylbenzoyl group was further substituted by a bromine in the 3- position or by two nitro groups in the 3,5-positions likewise were unreactive. In fact, the further substitution of nitro groups (in the 3,5-positions) into bis-(2,4-dimethylbenzoyl)-furoxan evidently *decreased* the reactivity toward hydrazine.

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Experimental

Furoxans from Methyl Ketones and Concentrated Nitric Acid. Bis-(*p*-nitrobenzoyl)-furoxan (VII).—To 20 g. of *p*-nitroacetophenone was added 160 g. of concentrated nitric acid (d. 1.42). The ketone dissolved readily at room temperature. The solution was warmed cautiously to about 55°, at which point gas bubbles started to develop in the solution. The flask was removed quickly from the steam-bath; the temperature of the mixture continued to rise and nitrogen oxides were evolved copiously. After about 20 minutes the white crystals were separated by filtration; an additional amount could be recovered by pouring the filtrate into 500 g. of ice-water.

The white crystals obtained were washed with water, then aqueous ethanol, dried, and recrystallized from 2-nitropropane, m.p. 154°, yield 19 g. (82%).

Anal. Calcd. for $C_{16}H_8O_8N_4$: C, 50.01; H, 2.10; N, 14.58. Found: C, 49.89; H, 2.40; N, 14.54.

From ethanolic washings, a small amount of white crystals was recovered. Recrystallized from absolute ethanol, the side product was identified as *p*-nitrobenzoic acid by its m.p. (243°) and by analysis.

In another similar experiment, the solution of *p*-nitroacetophenone in concentrated nitric acid was warmed to 40°, and a small crystal of sodium nitrite was added. The reaction, involving a vigorous development of nitrogen dioxide, started at once.

Bis-(*m*-nitrobenzoyl)-furoxan (VIII).—By a similar procedure bis-(*m*-nitrobenzoyl)-furoxan was prepared from *m*-nitroacetophenone and concentrated nitric acid (d. 1.42) in 74% yield; the addition of a small amount of sodium nitrite at 35° in order to start the reaction was found to be useful. In the absence of sodium nitrite, the reaction started immediately at 50–60°, while at 20–30° induction periods of from several hours to four days were observed.

Bis-(*m*-nitrobenzoyl)-furoxan is a white crystalline substance, m.p. 150°; the samples from two preparations were analyzed.

Anal. Calcd. for $C_{16}H_8O_8N_4$: C, 50.01; H, 2.10; N, 14.58. Found: C, 50.42, 50.55; H, 2.53, 2.28; N, 14.04, 15.02.

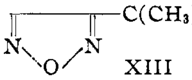
Other Furoxans.—By similar procedures the furoxans listed (in the order of decreasing yields obtained) in Table I were prepared. Especially in the preparations of X, XI and XII, the reactions proceeded with unusual violence, and certain precautions were necessary, such as the use of only small amounts of the reactants, immediate external cooling after the reactions had started, and good ventilation for removal of the rapidly evolved nitrogen oxides. For XI, the method of Quilico[5] gave the optimum yields. For XII, the procedure suggested by Claus[4b] (addition of reactants at 65°) was found to be inadequate; a yellow oil resulted containing 2,4-dimethylbenzoic acid and several derivatives of 2,4-dimethylacetophenone with nitrated benzenoid nuclei. From this oil, XII could be isolated in 9.2% yield. Even by mixing the reactants in the cold, warming cautiously, and adding a crystal of sodium nitrite at 40°, with subsequent external cooling, only a 15% yield of XII was obtained.

TABLE I

DIACYLFUROXANS FROM METHYL KETONES AND CONCENTRATED (70%) NITRIC ACID

Furoxan deriv.	Product, furoxan	M.p., °C.	Yield, %
VII	Bis-(*p*-nitrobenzoyl)-	154	82
VIII	Bis-(*m*-nitrobenzoyl)-	150	74
IX	Dibenzoyl-[9]	87	72
X	Dimesitoyl-[10]	145	70
XI	Bis-(5-methyl-3-isoxazolylcarbonyl)-[5]	128	70
XII	Bis-(2,4-dimethylbenzoyl)-[4b]	108	15

When pinacolone was treated with concentrated nitric acid in the presence of a little sodium nitrite a vigorous reaction occurred, but bis-(*t*-butylcarbonyl)-furoxan (XIV) could not be isolated from the liquid products. Analysis of some fractions showed a nitrogen content higher than that of XIV, possibly as a result of the presence of *t*-butylfurazan (XIII).


XIII

Furoxans from Methyl Ketones and Diluted Nitric Acid in Acetic Acid. Bis-(*p*-chlorobenzoyl)-furoxan (XX).—Eighty grams of concentrated (70%) nitric acid (d. 1.42) was mixed with 170 g. of water, and added to the solution of 50 g. of *p*-chloroacetophenone in 250 ml. of glacial acetic acid. After heating the mixture to 60°, a crystal (0.2 g.) of sodium nitrite was added. The reaction proceeded with a slow development of nitrogen oxides. The mixture was stirred and kept at 60° for 30 minutes by moderate warming on a steam-bath. A white precipitate was isolated by filtration, and an additional amount was obtained by pouring the filtrate into 2 l. of ice-water. The white crystals were washed with water, dried, washed with a small amount of cold ether, and fractionally recrystallized from chloroform. The most soluble portion in chloroform yielded, upon repeated crystallization, bis-(*p*-chlorobenzoyl)-furoxan as white crystals, m.p. 124° (50%).

Anal. Calcd. for $C_{16}H_8O_4N_2Cl_2$: C, 52.91; H, 2.22; N, 7.72. Found: C, 52.97; H, 2.28; N, 7.55.

The least soluble fraction was found by melting point and analysis to be *p*-chlorobenzoic acid, m.p. 237°.

Other Acyl Furoxans by the Acetic Acid–Dilute Nitric Acid Procedure.—All aryl methyl ketones subjected to the reaction in the course of this investigation gave diaroyl furoxans. The procedure employed was essentially that just given; results are shown in Table II, in which the products are listed in the order of decreasing yields. Certain compounds prepared for the first time are described herewith.

Bis-(2,4,6-trimethyl-3-bromobenzoyl)-furoxan (XVI) is a white solid, m.p. 158° (after four recrystallizations from chloroform).

Anal. Calcd. for $C_{22}H_{20}O_4N_2Br_2$: C, 49.27; H, 3.76; N, 5.22. Found: C, 49.30; H, 3.77; N, 5.13.

Bis-(*p*-phenylbenzoyl)-furoxan (XVII) was obtained in the form of a white, crystalline powder, m.p. 183°, after several recrystallizations from ether and then from benzene.

Anal. Calcd. for $C_{28}H_{18}O_4N_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.94; H, 4.60; N, 5.56.

The analysis is not entirely satisfactory, probably as a result of incomplete removal of the last traces of a side product, *p*-phenylbenzoic acid, m.p. 224°. Attempts to wash the product with a basic aqueous solution in order to remove the side product resulted in decomposition of the furoxan derivative. From an experiment in which a solution of *p*-phenylacetophenone and diluted nitric acid in acetic acid was heated for two hours (instead of 30 minutes, as usual), only *p*-phenylbenzoic acid could be isolated.

Bis-(2,4,6-triisopropylbenzoyl)-furoxan (XVIII) was made from 2,4,6-triisopropylacetophenone by the standard method, and recrystallized several times from ether as the least soluble fraction; a yellow, oily impurity is the most soluble phase. The compound XVIII forms white crystals, m.p. 128° dec.

Anal. Calcd. for $C_{34}H_{46}O_4N_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.61; H, 8.51; N, 4.55.

Bis-(2,4,6-trimethyl-3,5-dinitrobenzoyl)-furoxan is a white powder, m.p. 235°, after three recrystallizations from chloroform; acetone, nitrobenzene and 2-nitropropane proved to be less satisfactory solvents.

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(9) A. F. Holleman, *Ber.*, **20**, 3360 (1887); **21**, 2838 (1888).

(10) F. Baum, *ibid.*, **28**, 3211 (1895).

Anal. Calcd. for $C_{22}H_{18}N_6O_{12}$: C, 47.32; H, 3.25; N, 15.05. Found: C, 47.59; H, 3.18; N, 14.93.

TABLE II

FUROXANS FROM METHYL KETONES[a] AND DILUTED NITRIC ACID IN ACETIC ACID

Furoxan deriv.	Product, furoxan	M.p., °C.	Yield, %
XV	Dianisoyl-[11]	139	81
X	Dimesitoyl-[10]	145	80
IX	Dibenzoyl-[9]	87	75
XVI	Bis-(2,4,6-trimethyl-3-bromobenzoyl)-	158	70
VIII	Bis-(*m*-nitrobenzoyl)-	150	70
VII	Bis-(*p*-nitrobenzoyl)-	154	65
XVII	Bis-(*p*-phenylbenzoyl)-	183	60
XVIII	Bis-(2,4,6-triisopropylbenzoyl)-	128	60
XIX	Bis-(2,4-dimethyl-3,5-dinitrobenzoyl)-[4b]	209	50
XX	Bis-(*p*-chlorobenzoyl)-	124	50
XII	Bis-(2,4-dimethylbenzoyl)-[4b]	108	48
XXI	Bis-(2,4,6-trimethyl-3,5-dinitrobenzoyl)-	235	40
XI	Bis-(5-methyl-3-isoxazolylcarbonyl)-	128	10
XXII	Diethyl furoxandicarboxylate[12]	[b]	3

[a] All the furoxans were prepared from the corresponding methyl ketones except XI and XXII, which were prepared from acetonylacetone and ethyl acetoacetate, respectively. [b] B.p. 120° (5 mm.).

Diarylfuroxans by Yellow, Fuming Nitric Acid in Sulfuric Acid. Bis-(2,4,6-trimethyl-3,5-dinitrobenzoyl)-furoxan (XXI).—A sulfuric acid–water solution of the concentration to correspond approximately to sulfuric acid monohydrate was prepared by pouring 105 g. of concentrated (97%) sulfuric acid into 15 g. of water; the solution was cooled to 5° before use in the reaction.

Twenty grams of dimesitoylfuroxan (X) was dissolved, with adequate cooling, in 60 g. of yellow, fuming nitric acid (d. 1.52); care was taken to avoid violent development of nitrous gases and rise of temperature. This was accomplished best by cooling the furoxan to −20° or below in a 2-l. flask resting on crushed Dry Ice, cooling the fuming nitric acid in a beaker to about −15°, and adding it to the furoxan in small portions, so that the temperature remained at about −15° or lower.

The materials were mixed thoroughly during the addition of nitric acid; when the addition was complete, the mixture was allowed to warm slowly to about 0°, at which point solution was complete.

The solution of X in fuming nitric acid was cooled again on Dry Ice, with stirring, while the cold sulfuric acid monohydrate was added dropwise to the flask from a separatory funnel. During the addition, the temperature was kept below 0°; the optimum temperature, established by several experiments, is around −5°. When the operation was finished, the solution was allowed to stand for a few minutes at 0 to +5°.

After the reaction had been thus completed, the liquid, containing yellowish clumps of crystals, was poured into ice-water (800 g.); fine white crystals appeared in the solution and were separated by filtration, washed free of acids and dried. The dry material was washed with 50 ml. of boiling glacial acetic acid and then with 100 ml. of cold ether; some of the impurities (such as unreacted X and mesitoic acid) were dissolved, but only very little of XXI was lost. The undissolved material was recrystallized from acetone; at this stage of purification the melting point was 205–207°.

The best solvent for the final recrystallizations proved to be chloroform, although XXI is only moderately soluble in this solvent. The yield of bis-(2,4,6-trimethyl-3,5-dinitrobenzoyl)-furoxan was 81%, m.p. 235°.

The compound XXI also was prepared by a similar procedure from acetomesitylene; in this case, the temperature was allowed to rise considerably above the room temperature, and a vigorous development of nitrogen dioxide resulted. This procedure is not recommended as a preparative method, since at the temperature at which both nitration and furoxan formation occur the reaction tends to become uncontrollably violent. The yield was only 47%.

Using similar amounts of reactants and procedures, **bis-(2,4-dimethyl-3,5-dinitrobenzoyl)-furoxan (XIX)**[4b] was prepared from bis-(2,4-dimethylbenzoyl)-furoxan (XII) in 66% yield, as well as directly from 2,4-dimethylacetophenone in 56% yield. In this case, too, the direct method is not recommended, for similar reasons.

By the same method, **dianisoylfuroxan (XV)**[11] was prepared from *p*-methoxyacetophenone in 55% yield. Better yields (70%) were obtained employing concentrated nitric acid (d. 1.4) instead of fuming nitric acid.[2,11] The most attractive procedure for this compound (XV), too, is the diluted nitric acid–acetic acid method (yield 81%).

Bis-(*m*-nitrobenzoyl)-furoxan (VIII) was obtained from dibenzoylfuroxan (IX) and fuming nitric acid by a similar procedure as outlined for XXI; the yield was 50% and, among impurities, unreacted IX was found and separated by its greater solubility in ether. These results indicate that the carbonylfuroxan group is predominantly *meta* directing, as it is to be expected from its electron-withdrawing character.

Diethyl Furoxandicarboxylate (XXII).—Freshly distilled ethyl acetoacetate (50 g.) and 60 g. of glacial acetic acid were mixed and cooled to −10°. With mechanical stirring a concentrated aqueous solution of 30 g. of sodium nitrite was added dropwise. The temperature of the mixture was held at about −5°. The resulting colorless or nearly colorless solution was poured into 200 ml. of distilled water at 10° and allowed to stand at this temperature. Seven other 50-ml. portions of ethyl acetoacetate were successively subjected to the same treatment as rapidly as possible, about two hours being required for all eight preparations. The diluted aqueous solutions were combined as they were produced, and the collected lot was allowed to stand at 20° for one hour after the addition of the last portion. If gas evolution started in the solution during this period, small amounts of cold water or ice were added to reduce the temperature.

The yellow aqueous solution was extracted twice with ether, then saturated with salt and extracted a third time. The combined ether solutions were washed with cold sodium carbonate solution until neutral and then with water. The combined carbonate wash liquors were extracted with ether, and the extract, after washing with water, was added to the ether solution. The combined ether solution was dried over sodium sulfate and the ether was distilled. The greenish-yellow liquid residue of ethyl isonitrosoacetoacetate was poured into a 5-l. flask and a salt–ice-bath was made ready to accommodate it.

In a separate container 280 g. of concentrated (70%) nitric acid was dissolved in 455 g. of water and the solution cooled to about 20°. This solution was added to the isonitroso ester in five equal portions, with intervals of about two minutes between successive additions (not more than 12 minutes for the entire addition). Reaction occurred with the evolution of heat; as the temperature of the solution approached the boiling point it was reduced, but not below 35°, by immersion of the flask in the cooling bath. The temperature of the solution was observed after removal of the cooling bath, and it was reduced a second time if it threatened to approach the boiling point. Thirty minutes after the completion of the addition, the heavy oil was separated and the aqueous layer was heated to 80° for 20 minutes to ensure complete reaction. The cooled mixture was twice extracted with ether and the extracts were combined with the oil, dried (sodium sulfate) and concentrated. The residual yellow oil was warmed to 75° *in an open flask* over a steam-bath and held at this temperature for three minutes to ensure the decomposition of any remaining ethyl nitroöximinoacetoacetate, the presence of which would render distillation hazardous. The liquid then was distilled; the fraction boiling at 136 to 168° (14 mm.) was collected and redistilled to give diethyl furoxandicarboxylate boiling at 120° (5 mm.) in 75% yield based on ethyl acetoacetate. The ester was of an amber color and a characteristic odor; it was a strong skin irritant. When freshly prepared it

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(11) A. F. Holleman, *Rec. trav. chim.*, **10**, 216 (1891).

(12) L. Bouveault and A. Bongert, *Bull. soc. chim. France*, [3] **27**, 1166 (1902).

TABLE III

REACTIONS OF ω-NITROACETOPHENONE IN THE PRESENCE OF ACIDS

Expt.	C_6H_5CO-CH_2NO_2, g.	CH_3-CO_2H, ml.	HNO_3, g.	H_2SO_4, ml.	H_2O, g.	Inhibitor, g.	$NaNO_2$, g.	Induction per min.	Reacn. time, min. at 95°	NO_2 evolution	C_6H_5CO-CH_2NO_2, g. (%)	Dibenzoylfuroxan, g. (%)	Other
1	20.0	100	32		68			15	30	+	0	8.1(45)	I,[a] 2 g.
2	20.0	100	32		68		0.2	0	15	+	0	9.2(52)	I,[a] 1 g.
3	16.1	100	32		68	U,[b] 1		22	10	+	0	3.1(22)	I,[a] trace
4	3.0	100	32		68	U,[b] 6		>75	[c]	−	1.7(58)	0	
5	3.0	65		3		U,[b] 3		>20	[c]	−	1.8(60)	0	
6	2.0	20		2					20	−	0	0.83(47)	
7	0.91	10		1.5			0.2		20	−	0	0.2(25)	
8	10.0	100		10		U,[b] 2[d]			20	−	0	5.0(57)	I,[a] trace
9	9.0	100		10		R,[e] 3.5			10	−	0	0	[f]
10	5.0	25	8						25	+	0	1.08(24.4)	B,[g] 0.1
11	10.0	100	32		68	U,[b] 4		120	30	+	1.12(11.2)	1.44(16.3)	B,[g] 3.68
12	3.0	65		3		S,[h] 3			20	−	0	0.9(33.8)	
13	2.0	20	3			S,[h] 2		>20	[c]	−	1.71(85.5)	0	
14	1.5	100	32		68	S,[h] 4		>20	[c]	−	1.15(76.7)	0	
15	0.57	10		1.5	10			>20	[c]	−	0.44(77.2)	0	

[a] I = The isomer of dibenzoylfuroxan, m.p. 179°, described by A. F. Holleman, *Ber.*, **20,** 3360 (1887); **21,** 2840 (1888). [b] U = urea. [c] No evidence of reaction was noted. [d] Added in ten equal portions at 2-minute intervals. [e] R = resorcinol. [f] Highly colored products, which were not isolated, were formed. [g] B = benzoic acid. [h] S = sulfamic acid.

could be converted to the amide (m.p. 232°) in 92% yield by the action of diluted aqueous ammonia.[12] Upon standing it gradually developed a red color; a dark red sample stored for several months gave only 50% yield of the amide. Decomposition of the ester to carbon dioxide, hydrogen cyanide and other products under the action of mineral acids or upon steam distillation of the crude product has been recorded[13]; a similar decomposition may have occurred in the samples stored at room temperature.

Experiments with ω-Nitroacetophenone.—ω-Nitroacetophenone was prepared from benzil and nitromethane in 55% yield by modifications of the procedure of Jakubowitsch.[14] The fifteen experiments on its conversion to dibenzoylfuroxan carried out are summarized in Table III. Various mineral acids in acetic acid with and without added water, with and without sodium nitrite as an initiator, and with and without urea or sulfamic acid as an inhibitor, were tested at various temperatures and reaction times. An attempt to employ resorcinol as an inhibitor (experiment 9) gave highly colored products which were not identified. The procedure employed in experiment 11 is described. The principal variations of procedure in the other experiments are shown in Table III.

Dibenzoylfuroxan (IX) from ω-Nitroacetophenone (Experiment 11, Table III).—A mixture of 32 g. of concentrated (70%) nitric acid and 68 g. of water was freed of nitrous acid by refluxing with 1 g. of urea for five minutes and cooling to room temperature while a stream of nitrogen was bubbled through. To the solution were added 2.5 g. of urea, 100 ml. of glacial acetic acid and 10.0 g. of ω-nitroacetophenone and the mixture was refluxed. After one hour 0.5 g. more of urea was added and refluxing was continued. About one hour later nitrogen dioxide began to appear, coloring the gas phase above the solution yellow, indicating that the urea had been hydrolyzed completely. Refluxing was continued for one-half hour, and the solution was poured onto 300 g. of ice and stirred until crystallization appeared complete.

The light yellow solid was collected, dried and recrystallized twice from ether and petroleum ether, yielding 1.44 g. (16.3%) of pure dibenzoylfuroxan (m.p. 87°) identified by mixed melting point. Ether extracts of the aqueous phase were combined and extracted with aqueous sodium carbonate; acidification of the alkaline extract gave benzoic acid, identified by mixed melting point, amounting to 3.68 g. (m.p. 122°, 49.7%) after crystallization from ether and petroleum ether. The ether solution gave a yellow oily solid upon evaporation. Recrystallization from ether gave 1.12 g. (11.2%) of ω-nitroacetophenone, identified by mixed melting point.

Although some of the benzoic acid formed in this experiment may have resulted from the hydrolysis of dibenzoylfuroxan (an independent experiment established that benzoic acid is formed from it on long boiling with water), the inhibitory effect of urea is demonstrated by the recovery of part of the ω-nitroacetophenone, none of which was recovered in experiments 1 and 2 conducted without any inhibitor (see also experiment 4).

Azines of Diaroylfuroxans.—The preparation of the **azine of bis-(*m*-nitrobenzoyl)-furoxan** is given as an example.

A mixture of 21 g. of the furoxan VIII and 200 ml. of methanol was heated to reflux while a solution of 7 g. of hydrazine dihydrochloride in 100 ml. of hot methanol was prepared. Shortly after the solutions were combined a yellow precipitate began to form; refluxing was continued for an hour, and the mixture was cooled. The azine was washed on a filter with water, dried in the air, and extracted with 50 ml. of boiling benzene to remove unchanged furoxan. It then was recrystallized from 2-nitropropane as small bright yellow crystals, m.p. 251°, yield 18 g. (86%).

Anal. Calcd. for $C_{16}H_8N_6O_6$: C, 50.53; H, 2.12; N, 22.10. Found: C, 50.39; H, 2.11; N, 21.90.

The orange-yellow **azine** of the isomeric **bis-(*p*-nitrobenzoyl)-furoxan** prepared similarly (80% yield) melted at 252°.

Anal. Calcd. for $C_{16}H_8N_6O_6$: N, 22.10. Found: N, 22.23.

The known[15] **azine of dibenzoylfuroxan** was prepared in 70% yield in the same way; twice recrystallized from 2-nitropropane, it melted at 210° instead of 207° as reported by Widman and Virgin for the crude product.

The bright red **azine of bis-(*p*-chlorobenzoyl)-furoxan,** prepared similarly (85% yield) except that ethanol was used as the reaction solvent and chloroform as the recrystallization solvent, melted at 235°.

Anal. Calcd. for $C_{16}H_8O_2N_4Cl_2$: C, 53.51; H, 2.24; N, 15.60. Found: C, 53.61; H, 2.21; N, 15.67.

Bis-(2,4-dimethylbenzoyl)-furoxan was recovered when subjected to the above procedure in ethanol. In an experiment in which a concentrated aqueous solution of 7 g. of sodium carbonate was added to a solution of 500 ml. of ethanol, 14 g. of the furoxan and 7 g. of hydrazine dihydrochloride, and the whole was refluxed for 30 minutes, the solution developed an orange color indicative of azine formation. However, the only substance isolated was the original furoxan. A similar treatment of dianisoylfuroxan XV gave a bright red solution, from which deep red crystals separated; however, these evidently contained much unchanged XV. Bis-(*p*-phenylbenzoyl)-furoxan similarly

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[13] C. Cramer, *Ber.*, **25,** 713 (1892); H. Wieland, L. Semper and E. Gmelin, *Ann.*, **367,** 63 (1909).

[14] A. J. Jakubowitsch, *J. prakt. Chem.*, [2] **142,** 37 (1935).

[15] O. Widman and E. Virgin, *Ber.*, **42,** 2799 (1908).

gave bright red crystals which resisted purification; the best sample had a nitrogen content indicating a mixture of about equal parts of the furoxan and the azine. As indicated above, more heavily substituted diaroylfuroxans gave no indication of reaction even in the presence of alkali.

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

The Infrared Absorption Spectra of Furoxans[1]

BY N. E. BOYER, GLORIA M. CZERNIAK, H. S. GUTOWSKY AND H. R. SNYDER

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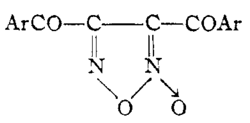
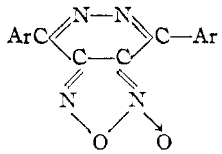
The infrared absorption spectra of a number of diacylfuroxans, of some bicyclic azines obtained from such diacylfuroxans and hydrazine, and of some more simply substituted furoxans have several unique regions of absorption in the range of 1800–800 cm.$^{-1}$. Certain of the absorption bands are assigned to particular vibrations of the furoxan structure. The use of the spectra in the identification of furoxans is discussed.

As a part of a general study of the properties of furoxans,[2] we have investigated the infrared absorption spectra of a number of diacylfuroxans (I), of some of the bicyclic azines (II) obtained from them by reaction with hydrazine, and of several more simply substituted furoxans. The interest in these spectra was twofold. They should provide data for the empirical assignment of the characteristic absorption frequencies of the furoxan ring and thus be of use in structure determination, and the characteristic frequencies and their variations upon substitution should eventually permit a better understanding of the electronic nature of the furoxan system and of its interaction with substituents. At the time these studies were made no infrared absorption data for furoxans had been published, although the spectra of some furazans, azoximes and oxadiazoles were available.[3] Recently, the spectra of benzfuroxan and some of its derivatives were reported.[4]


I


II

In the present work, the spectra of the various compounds exhibited no absorption bands characteristic of the furoxan group within the ranges 4000–1800 cm.$^{-1}$ and 800–625 cm.$^{-1}$. However, several regions of absorption in the range 1800–800 cm.$^{-1}$ are peculiar to the furoxan ring. These regions are listed in Table I with tentative vibrational assignments. Each of these regions is discussed in some detail below.

The spectra of all the furoxans as well as of the benzfuroxans,[4] have a consistently strong absorption band in the 1625–1600 cm.$^{-1}$ region. This is the double bond stretching region and since the only double bonds in dimethylfuroxan are C=N, this assignment is made. One might expect different frequencies for the $\mathrm{C{=}N}\overset{\nearrow O}{\diagup}$ and C=N—O sides of the ring; however, the evidence on this point is not conclusive. An appreciable fraction of the spectra have a weak to strong band in the 1600–1500 cm.$^{-1}$ region which could be a second C=N stretching frequency. A comparison of the spectra of the furoxans with those of the furazans[4] suggests that the 1625–1600 cm.$^{-1}$ band is associated with the presence of the $\mathrm{C{=}N}\overset{\nearrow O}{\diagup}$ group. This view is supported by the relative insensitivity of the band to substituents, which contrasts with the wide ranges found for C=N bands in other compounds.[5]

The absorption occurring as a doublet in the 1475–1410 cm.$^{-1}$ region is easily discernible in compounds without methyl groups, which absorb in the same region. In some compounds, such as bis-(*m*-nitrobenzoyl)-furoxan, the azine of bis-(5-methyl-3-isoxazolecarbonyl)-furoxan and furoxandicarboxamide, interference by Nujol resulted in the occurrence of one broad band when samples were examined as mulls. However, even in most such instances the lower vibration of the doublet could be detected. A characteristic band in the 1360–1300 cm.$^{-1}$ region, of medium to very strong intensity, is masked by the absorption of nitro groups in compounds which bear this group as a substituent. In some instances, such as bis-(*m*-nitrobenzoyl)-furoxan and bis-(*p*-nitrobenzoyl)-furoxan, the composite band is split as the absorption by the nitro group shifts to higher frequencies. In only one spectrum, that of the azine of bis-(*p*-chlorobenzoyl)-furoxan was there no indication of absorption in this range; all the bands in this spectrum were weak. Since neither Nujol nor chloroform interferes in the 1360–1300 cm.$^{-1}$ region, the strong absorption here should be useful in the identification of furoxans which do not bear nitro groups as substituents.

A summary of the absorption bands in the 1475–1410 cm.$^{-1}$ and 1360–1310 cm.$^{-1}$ regions is given in Table II. This table includes all the samples having no conflicting methyl or nitro groups, and is based on spectra determined in chloroform solution to avoid interference by Nujol. The similarity of these absorption bands to those of the nitro

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[2] H. R. Snyder and N. E. Boyer, THIS JOURNAL, **77**, 4233 (1955).

[3] M. Milone and E. Borello, *Gazz. chim. ital.*, **81**, 368 (1951).

[4] R. J. Gaughran, J. P. Picard and J. V. R. Kaufman, THIS JOURNAL, **76**, 2233 (1954).

[5] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 226.