[A CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Di- and Tri-2-furoylmethane

BY GEORGE S. HAMMOND AND FREDERICK S. SCHULTZ

Di- and tri-2-furoylmethane have been identified as by-products in the synthesis of 2-acetylfuran by the reaction of furoyl chloride with dimethylcadmium. The compounds have also been prepared by conventional synthetic procedures. The near ultraviolet absorption spectra of the new ketones indicate that both are highly enolized in ethanol solutions. The spectra of the enolate anions are strikingly similar to those of the enols. This appears to be a general phenomenon and indicates that the bond orbitals of the terminal oxygen atoms of a β-diketone system are essentially unhybridized in the enols as well as in the enolate ions.

In attempting to prepare substantial amounts of 2-acetylfuran by the reaction of dimethylcadmium with 2-furoyl chloride, we found that two other ketones are produced in appreciable yield. The chemical properties and analyses of the compounds indicated that they were di- and trifuroylmethane, henceforth referred to as the di- and triketone, respectively. In the course of the examination of the new ketones their visible and ultraviolet spectra were determined in both neutral and alkaline solutions. These spectra exhibit some interesting and unusual features.

Experimental

Reaction of Dimethylcadmium with 2-Furoyl Chloride.—The cadmium reagent was prepared by adding 130 g. of dry cadmium chloride to a solution of the Grignard reagent from 100 g. of methyl iodide and 17.5 g. of magnesium in 600 ml. of ether. The mixture was stirred until the solution no longer gave the Gilman color test.[1] The ether solution was filtered through a cotton plug and the ether removed by distillation until the vapor temperature reached 40°. The residue was dissolved in 800 ml. of dry benzene. To this benzene solution, 60 g. of furoyl chloride, diluted to 100 ml. with benzene, was added rapidly. During the addition the solution became quite warm. The resulting paste-like mixture was heated under reflux for 30 minutes and allowed to stand overnight. It was then heated at the reflux temperature another hour and allowed to cool. A total of 100 ml. of water was added dropwise to the mixture and the water layer was removed and washed once with benzene. The combined benzene solutions were washed with 10% aqueous potassium hydroxide and a yellowish precipitate formed immediately. Ether was added to aid in separation of the phases and the aqueous layer, with the suspended solid, was removed. The organic layer was washed with a second portion of aqueous potassium hydroxide and with water. Drying the ether–benzene solution over anhydrous sodium sulfate and subsequently distilling through a 44-plate column gave 16.2 g. (32%) of 2-acetylfuran.

The combined aqueous extracts were filtered and the residue was dissolved in ethyl alcohol, acidified with dilute sulfuric acid and cooled in an ice-bath. Filtration gave 2.0 g. of di-2-furoylmethane as fine yellow needles, m.p. 74–77°. The alkaline solution was acidified with 10% sulfuric acid and the resulting precipitate was filtered off and recrystallized from ethyl alcohol. The yield of purified tri-2-furoylmethane was 3 g. (7%), m.p. 191–195°. Dilution of the alcoholic filtrate with water gave a crop of crystals weighing one g. which melted over a wide range. The mixture was extracted with Skellysolve A in a soxhlet apparatus and an additional 0.8 g. of the diketone was obtained from the extract by filtration. The total yield of this product was, therefore, 2.8 g. (6%).

Synthesis of Di-2-furoylmethane.—Ten grams of 2-acetylfuran in 50 ml. of dry ether was added dropwise to a solution of 13 g. of ethyl furoate and 6 g. of sodium methoxide. The solution was stirred and maintained at reflux temperature. The refluxing was continued for two hours. The dark solution was extracted with 100 ml. of 10% potassium hydroxide solution. It was necessary to add an additional 400 ml. of ether to effect good phase separation. A second, 50-ml., alkaline extract was combined with the first and a dark oil separated from the solution on acidification with sulfuric acid. The oil was placed under a water-pump vacuum to remove ether and the residue solidified. Recrystallization from methanol–water gave 10.5 g. (57%) of very fine needles which were further purified by extraction in a Soxhlet apparatus with Skellysolve A. A small amount of brown residue remained in the extraction thimble and the extract deposited 9.0 g., m.p. 70.5–72.0°, which did not depress the melting point of the low melting material from the reaction of dimethylcadmium and furoyl chloride.

This compound was dissolved in 50% ethanol and titrated with standard, aqueous sodium hydroxide using a Beckman Model G *p*H meter. Some of the slightly soluble sodium salt precipitated during the titration. As the titration curve did not show a clearly defined point of inflection, the mid-point (apparent *p*H of 10) of the rising portion of the curve was taken as the end-point.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95; neut. equiv., 204. Found: C, 64.57; H, 3.90; neut. equiv., 195.

The diketone is soluble in carbon tetrachloride, chloroform, glacial acetic acid, benzene, ether, alcohol and slightly soluble in Skellysolve A. Ferric chloride in ethanol gives a wine-red color with the compound.

Synthesis of Tri-2-furoylmethane.—To 50 ml. of sodium-dried toluene was added 3.68 g. of the diketone and 0.326 g. of metallic sodium. The solution was stirred and heated under reflux until no more sodium metal could be seen. The suspension was treated with 3.0 g. of furoyl chloride and heated for 30 minutes. Ether was added and the solution was extracted with 10% sodium hydroxide. The basic extract was acidified and the precipitate was filtered off, washed with water and dried *in vacuo*. The dark solid was extracted with Skellysolve A in a soxhlet apparatus and 0.39 g. of unreacted diketone was recovered from the extract. The material remaining in the thimble was extracted with 95% ethanol. A small amount of water was added to the brown extract. The solution was cooled and 2.67 g. of crude tri-2-furoylmethane (55% based on diketone consumed) was removed by filtration. Recrystallization from 95% ethanol gave colorless needles, m.p. 193°. Titration of a suspension of the compound in 50% ethanol with standard alkali with a *p*H meter gave a sharp titration curve with an inflection at an apparent *p*H of 9.5. Titration of potassium acid phthalate in a similar manner gives an end-point at a *p*H of 9.5. The compound is soluble in chloroform, carbon tetrachloride, dioxane and ether and is slightly soluble in ethanol. An alcohol solution gives a deep red color with ferric chloride.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38; neut. equiv., 289. Found: C, 64.22; H, 3.23; neut. equiv., 295.

Reactions of the Di- and Triketones.—Both of the new ketones give the iodoform reaction and both were treated by Goodwin's[2] quantitative procedure. The diketone consumed exactly three moles of iodine but the triketone consumed somewhat less under the conditions employed.

Both compounds gave di-2-furoylmethane dioxime when refluxed overnight with sodium acetate and hydroxylamine hydrochloride.[3] The product was recrystallized from ethanol–water, m.p. 174–178°.

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[1] H. Gilman and F. Schultz, THIS JOURNAL, **47**, 2002 (1925): H. Gilman and L. L. Heck, *ibid.*, **52**, 4949 (1930).

[2] L. F. Goodwin, *ibid.*, **42**, 39 (1920); see also N. H. Furman, "Scott's Standard Methods of Chemical Analysis," 5th Ed., D. Van Nostrand Co., New York, N. Y., 1939, p. 2136.

[3] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 167.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: N, 11.96. Found: N, 11.90.

Similarly, both ketones gave 3,5-di-2-furylisoxazole when treated with hydroxylamine hydrochloride under the conditions used to prepare 3,5-diphenylisoxazole from dibenzoylmethane.[4] The product was dissolved in 95% ethanol, treated with Norite A and precipitated with water. The crystals were washed with 0.1 *N* aqueous sodium hydroxide and recrystallized from alcohol–water, m.p. 112°.

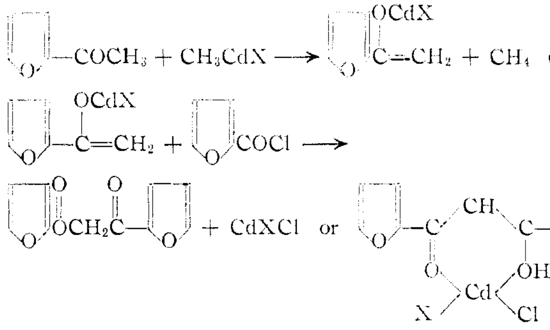
Anal. Calcd. for $C_{11}H_7O_3N$: N, 6.97. Found: N, 6.83.

As is indicated by the above experiments, it was possible to degrade the triketone to the diketone. A 0.5-g. sample of the triketone was heated under the reflux with 10 ml. of pyridine for 10 hours. Furoic acid, m.p. 130°, and the diketone, m.p. 68–69.5°, were isolated in low yield from the resulting solution. Furoic acid was also found in the mother liquors in the preparation of the dioxime and isoxazole from the triketone. However, in the study of the absorption spectrum of the diketone in 1.0 *N* aqueous potassium hydroxide solution it was found that the optical density at 275 mμ decreased rapidly with time. Under similar conditions the triketone was apparently unchanged over the same period of time.

Adsorption spectra were determined with either a Cary recording spectrophotometer or Beckman model DU spectrophotometer. The spectra of the neutral compounds were determined in 95% ethanol and those of the anions were measured in aqueous solutions containing 0.06 *N* sodium hydroxide and 1.0 *N* potassium hydroxide. It was necessary to use the potassium salts at the latter concentration because of the insolubility of the sodium salt of the diketone. The spectra of both compounds were virtually the same at both concentrations of base indicating that conversion to the conjugate bases was essentially quantitative.

Discussion

The isolation of the polyketones, in addition to acetylfuran, from the reaction of dimethylcadmium with furoyl chloride may represent the first instance in which this type of by-product of the familiar ketone syntheses[5,6] has been characterized. It is fairly obvious that the diketone must be produced from acetofuran by the following sequence of reactions.



(1)

(2)

The diketone must be converted to the triketone by a similar process. The product of the reaction (1) is formulated as a cadmium enolate since it is likely that the cadmium–oxygen bond is largely covalent in nature. However, the enolate should be endowed with much the same reactivity as enolate ions which may be produced from ketones in aqueous alkali.[7] Reaction (2) is, therefore, highly reasonable. The occurrence of reaction (1), in the presence of an excess of the acid chloride, is somewhat unexpected, but it is not entirely without analogy. Cason[8] has observed that yields of α-chloro ketones from α-chloro acid chlorides and organocadmium reagents are lower than those obtained from the unsubstituted compounds. He concluded that the cadmium reagent was consumed, in part, in a reaction analogous to (1) and added substance to this view by demonstrating that 70% of the theoretical amount of butane was evolved when 1-chloro-2-hexanone was added to a benzene solution of dibutylcadmium. Since the carbon–chlorine dipole undoubtedly exerts a more pronounced acid strengthening influence at the α-carbon than at the carbonyl group of the acid chloride, the result is entirely reasonable. It has also been shown that diethylcadmium will effect the condensation of benzaldehyde and acetophenone to give benzalacetophenone,[5] indicating that, in the absence of an acid chloride, a single adjacent carbonyl function is sufficient to render proton abstraction by cadmium alkyls measurably rapid.

It is entirely possible that many ketones compete with acid chlorides for reaction with cadmium reagents and that di- and triketones are frequently produced in small yields in the synthesis of ketones by this method. On the other hand, it is also possible that the ability of acetyl furan to form a cyclic cadmium complex by utilizing the oxygen in the ring renders this compound uncommonly susceptible to the active hydrogen reaction. Since a heavy precipitate is formed early in the reaction, it is possible that much of the cadmium reagent may have been in the solid phase and out of contact with the acid chloride. It may be of interest to note that the reaction might be adapted for use as a synthetic method for β-diketones since the conditions are rather mild. In order to obtain such products in higher yields, an acid chloride should be added to a solution of a cadmium enolate prepared by heating a monoketone with dimethylcadmium.

The reactions of the new ketones are much as would be anticipated. They are both acidic with the triketone having about the same acid strength in 50% ethanol–water as the acid phthalate ion. The ionization constant of the diketone is about one power of ten smaller than that of the triketone. Since the absorption spectrum of neither compound is changed appreciably by increasing the concentration of aqueous base from 0.06 to 1.0 *N*, it follows that both are at least 95% ionized in the less basic solution. Both ionization constants, therefore, are greater than about 10^{-11} in aqueous solution.

The triketone is degraded when it is treated with hydroxylamine and yields only the dioxime or isoxazole of the diketone. However, the diketone was cleaved much the more rapidly of the two in one normal potassium hydroxide. We do not know whether this apparent reversal in the relative reactivities of the two compounds is due to the trapping of the diketone by hydroxylamine in the former experiments or to a change in the mechanism of the cleavage reaction.

The ultraviolet absorption spectra of the two

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(4) J. Wislicenus, *Ann.*, **308**, 219 (1898).

(5) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(6) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Co., New York, N. Y., 1940, p. 229.

(8) J. Cason, THIS JOURNAL, **68**, 2078 (1946).

new ketones, the dioxime and the isoxazole were determined in alcoholic solution. The positions and molar extinction coefficients of the maxima are given in Table I along with the corresponding data for acetylfuran and its oxime. The spectra of the acidic polyketones were also determined in aqueous alkali. It will be noted that the spectrum of acetylfuran has maxima at 226 and 270 mμ with the latter being the more intense. As has been previously shown by Raffauf,[9] such a spectrum is rather characteristic of furans bearing an electron withdrawing substituent in the 2-position. The triketone has maxima of comparable intensity at 225 and 281 mμ and, in addition, has a broad band with a maximum at 370 mμ and an inflection at 382 mμ. The short wave length maximum is missing entirely in the spectrum of the diketone and the 284 mμ transition occurs with considerably reduced intensity. The long wave length band, which again appears to be a poorly resolved doublet, is characterized by a rather large extinction coefficient.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF FUROYL KETONES AND THEIR DERIVATIVES

Compounds	λ_{max} in mμ[a]	Molar extinction coefficient
2-Acetylfuran	226	2,400
	270	14,000
Di-2-furoylmethane	284	8,300
	365	30,500
	380[b]	24,900
Tri-2-furoylmethane	225	8,500
	281	33,000
	370	10,800
	382[b]	10,100
Di-2-furoylcarbanion	276	15,300
	375	23,600
Tri-2-furoylcarbanion	225	7,520
	282	23,600
	370	18,200
2-Acetyfuranoxime	265	27,600
Di-2-furoylmethane dioxime	264	27,600
3,5-Di-2-furylisoxazole	253	15,300
	292	23,600

[a] All spectra except those of the ions determined in 95% ethanol. The anions were run in 0.06 and 1.0 *N* aqueous base (see experimental). [b] Point of inflection.

The long wave length bands in the spectra of the di- and tri-ketones are attributed to the enol forms of these ketones. It should not be concluded that the similarity of the spectra in the region 200–300 mμ to that of acetylfuran indicates that there are any appreciable amounts of the diketonic forms of the former compounds in solution. Morton, Hassan and Calloway[10] have shown that the spectra of both benzoylacetone and dibenzoylmethane have maxima at a wave length close to the position of the principal band of acetophenone even in solvents in which the diketones are more than 99% enolized. These workers also noted that the spectra of the diketones in alkaline solution were rather similar to the spectra in neutral media. We have observed the same striking similarity in the spectra of the furoyl ketones and their anions, so the correspondence appears to be a rather general phenomenon indicating a similarity of the electronic configurations of the enols of β-diketones and their conjugate bases, the enolate anions. Furthermore, this similarity persists in the first few excited states. It is highly unlikely that the number of observed near coincidences in transition energies can be due to an "accidental" similarity in the spacing of the energy levels in the enols and their anions. As an *ad hoc* interpretation the following seems to provide a satisfactory analysis of the situation and points out an interesting electronic formulation of the enols of acyclic β-diketones. In the enolate ion the three carbon atoms must be in the plane trigonal state of hybridization and each terminal oxygen atom must use one p_x orbital to form a σ bond to an adjacent carbon atom and each should also have a p_z orbital normal to the plane of the molecule. The latter will combine with the carbon p_z orbitals to form a set of five π molecular orbitals. The remaining p_y and s orbitals of each oxygen will not be used in bond formation and will each accommodate two unshared pairs of electrons. This will leave a total of six electrons to be placed in the three lowest π-orbitals leaving two vacant. The near ultraviolet spectrum should be due to transitions between the filled and vacant π-orbitals. If we now examine the enol, we find that the cyclic, hydrogen-bonded molecule[11] bears a considerable resemblance to the anion. The carbon atoms will certainly again be adequately described as trigonal. If we anticipate the result of the discussion and assume that the end carbon atoms are nearly equivalent, a model of the enol can be constructed. If both of the carbon–carbon distances are taken as 1.39 Å., the distance in benzene, the 120° bond angles require that the oxygen atoms are separated by a distance of 2.43 Å. irrespective of the length of the carbon–oxygen bonds as long as both are assumed to be of the same length. This distance is only slightly shorter than the oxygen–oxygen distance (2.67 Å.) in formic acid dimer[12] which may be considered to be "ideal" for the O–H–O hydrogen bond since other structural features of the molecule probably have little influence on the length of the bond. Therefore, the hydrogen of the enol can be placed on the line between the two oxygen atoms, thus achieving the linear arrangement which is usually observed with all strong hydrogen bonds.[13] If this is done, the C–O–H bond angle is 90°. The only state of the oxygen atom which will give a "natural" 90° bond angle is the same trigonal pyramid hybridization as was used in the description of the enolate anion. Since the carbonyl oxygen will be similarly unhybridized, it develops that the only difference between the enol and its anion is that in the former,

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(9) R. F. Raffauf, THIS JOURNAL, **72**, 753 (1950).

(10) R. A. Morton, A. Hassan and T. C. Calloway, *J. Chem. Soc.*, 883 (1934).

(11) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 599.

(12) L. Pauling and L. O. Brockway, *Proc. Natl. Acad. Sci.*, **20**, 336 (1934).

(13) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 248 ff.

one oxygen p_y orbital is used to form a σ bond to hydrogen, whereas, in the latter, it holds an unshared pair. The only difference in the π orbitals will arise from distortion of this system by the charge on the oxygens in the anion and from symmetry differences arising from the probable tendency of the oxygens of the ion to assume a "*trans*" rather that a "*cis*" orientation with respect to each other. The first of these factors may be expected to have relatively little influence on the separation of the first few energy levels which are reached by promotion of electrons from one π-orbital to another. Sklar[14] has pointed out that in the anilinium ion, a strong, local field does not distort the benzene 265 mμ band to any great extent. The change in the symmetry of the molecule would not be expected to affect the positions of the maxima but might alter intensities appreciably. No evidence for the latter effect is apparent in our data.

The spectra of both the enols show evidence that the long wave length band is actually an unresolved doublet. This feature disappears in the anions. Such a change is usually associated with some operation which creates a new symmetry element in some slightly unsymmetrical structure. That this is the case with the triketone is immediately obvious. In the case of the diketone it may indicate that even though the hydrogen bond is compressed slightly, the hydrogen does not assume a symmetrical position with respect to the two oxygens, but is, as we have assumed, bound to one oxygen by a covalent linkage.

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[14] A. L. Sklar, *J. Chem. Phys.*, **7**, 987 (1939).

[CONTRIBUTION FROM THE MORLEY CHEMISTRY LABORATORY, WESTERN RESERVE UNIVERSITY]

Free Radical Aromatic Substitution. I. The Reaction of Benzoyl Peroxide with Naphthalene Derivatives[1,2]

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The thermal decomposition of benzoyl peroxide in α-chloro-, α-bromo- and α-nitronaphthalene has been found to result in monosubstitution by a benzoyloxy group in the 2-, 4- or 5-positions of the naphthalene derivative. The yields of isomeric esters were determined semiquantitatively and the ratio of yields of homonuclear to heteronuclear substitution products indicated that toward attack by the benzoyloxy radical, the substituents had the following relative activating influences: $NO_2 > Br > Cl > H$.

A number of reactions of aromatic substitution proceed by free radical mechanisms. Such reactions (*e.g.*, the preparation of biaryls by the Hey and Gomberg–Bachmann methods) are characterized by universal ortho–para substitution. In the reaction of a free radical with an aromatic derivative, the substituent in the ring undoubtedly exerts not only a directive but also an activating or deactivating influence upon the attack by the entering radical. Such influences may be determined by means of competition reactions but very few experiments of this type have been reported.

One possible type of competition reaction would consist of the attack of a free radical upon a benzene derivative in which two substituents have opposing directive influences. Thus Grieve and Hey[3] decomposed sodium benzenediazotate in *o*-nitrotoluene and found an 8.7% yield of 4-nitro-3-methylbiphenyl and no trace of 3-nitro-4-methylbiphenyl. By applying the law of invariable ortho–para orientation, the substitution of the phenyl radical para to the nitro group (meta to the methyl group) must mean that the nitro group has a greater directive influence than the methyl group.

A second type of competitive reaction involves the decomposition of a free radical reagent in a mixture of two monosubstituted benzenes to determine which will be preferentially attacked. Grieve and Hey[3] heated an alkaline solution of benzenediazonium chloride (1.00 mole) with an equimolecular mixture of toluene and nitrobenzene to give 0.12 mole of nitrobiphenyls and 0.032 mole of methylbiphenyls. These relative yields indicate that the nitro group has an activating influence roughly four times that of the methyl group. This technique of decomposition of a free radical reagent in an equimolecular mixture of solvents has also been applied by De Tar and Scheifele[4] to the thermal decomposition of 0.12 mole of N-nitrosoacetanilide in a mixture of benzene and chlorobenzene to give 0.021 mole of biphenyl and 0.040 mole of chlorobiphenyl (determined by halogen analysis). These yields show that chlorobenzene is about twice as reactive as benzene toward substitution by phenyl free radicals.

A third possible type of competitive reaction had not been attempted until the present work. In the reaction of a free radical with a substance such as chloronaphthalene, the relative amount of substitution in the two rings would be a measure of the activating or deactivating influence of the chlorine atom. Huisgen and Sorge[5] have shown that substitution of the naphthalene nucleus by free radicals is possible for they obtained α-phenylnaphthalene from the thermal decomposition of N-nitrosoacetanilide in naphthalene.

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[1] From a thesis submitted by Morris Gippin to the Graduate School, Western Reserve University, in partial fulfillment of the requirements for the Doctor's degree, 1951.

[2] Presented at the Cleveland Meeting of the American Association for the Advancement of Science, December 27, 1950.

[3] W. S. M. Grieve and D. H. Hey, *J. Chem. Soc.*, 1797 (1934).

[4] D. F. De Tar and H. J. Scheifele, THIS JOURNAL, **73**, 1442 (1951).

[5] R. Huisgen and G. Sorge, *Ann.*, **566**, 162 (1950).