portion of the vessel. The two pieces were then secured by means of a copper wire and the vessel was degassed on a vacuum manifold. After all samples had been degassed they were placed in an oil bath. At appropriate time intervals a reaction vessel was removed, allowed to cool to room temperature, and was then opened inside a Glove Bag having a nitrogen atmosphere. A 1-ml aliquot of the sample was then diluted to 51 ml with methanol for spectroscopic reading. The progress of the reaction was monitored by following the increase in absorbance at 320 nm using a Cary Model 14 spectrophotometer. Both benzaldehyde and benzoin absorb at this wavelength, but by use of the equation

$$A_t = 28.37([\mathrm{Ald}]_0 - 2X) + 279.80(X)$$

where A_t is absorbance measured at any time, 28.37 is the molar extinction coefficient of benzaldehyde at 320 nm (determined in control experiments), 279.80 is the molar extinction coefficient of benzoin at 320 nm (also determined by us), $[\mathrm{Ald}]_0$ is the initial aldehyde concentration, and X is the concentration of benzoin; the concentration of benzoin can be calculated at any time. The total absorbance and that of both species obeyed Beer's law. The condensation rate constants were calculated on the basis of the free aldehyde concentration as described above.

Yield of Benzoin from the Reaction of Benzaldehyde with Potassium Cyanide in Methanol. Benzaldehyde (5 ml, 49.3 mmol) was added to 100 ml of methanol containing potassium cyanide (0.65 g, 10 mmol) in a 250-ml three-necked round-bottomed flask fitted with a condensor and a gas inlet tube. The reaction was allowed to continue for 30 hr at reflux temperatures under a nitrogen atmosphere. The reaction solution was allowed to cool to room temperature, acidified with concentrated hydrochloric acid, and taken to dryness on the rotatory evaporator. The organic material was taken up in acetone, filtered, and again taken to dryness on a rotatory evaporator. A brownish solid weighing 4.5 g and melting at 121–130° was isolated. A small amount of this recrystallized from glacial acetic acid to give benzoin (crude yield = 21.2 mm, 86%).[36,37]

Acknowledgments. It is a pleasure to thank Professor J. K. Lee for his advice. We are grateful to Professor K. B. Wiberg (Yale University) for his kindness in introducing Dr. Lupes to the rest of us.

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(36) H. Gilman, Ed.-in-Chief, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1942, p 94.

(37) A. Lachman, *J. Amer. Chem. Soc.*, **46**, 709 (1924).

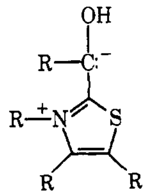
Chemistry of the Active-Aldehyde Intermediate[1]

John P. Kuebrich and Richard L. Schowen*[2]

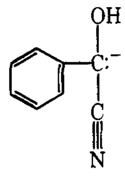
Contribution from the Department of Chemistry,
University of Kansas, Lawrence, Kansas 66044. *Received June 20, 1970*

Abstract: The reaction of benzil with cyanide ion gives an α-benzoyloxycyanocarbanion, a useful model for the α-hydroxycarbanion intermediates ("active aldehyde") of the benzoin condensation and thiamine action in biological systems. As predicted from indications that transition-state binding between these nucleophiles and their electrophilic partners was quite weak, a reasonably unselective behavior and consequently rich chemistry were observed under conditions of varying electrophilicity.

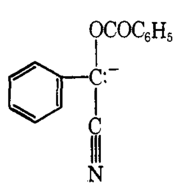
Resonance-stabilized α-hydroxycarbanions (I) are important in biological systems involving thiamine action,[3] where they have acquired the cognomen "active aldehyde" because, if they are formed from aldehydes, the normally electrophilic carbon of the latter becomes activated to a nucleophilic center in I. The cyanocarbanion II is formed in the benzoin condensation[4] and is a good model for studying the chemical behavior of "active aldehyde." Our investigation of the benzoin condensation in methanol led us to the belief that the reactions of II with the two electrophiles of significance in that system, *viz.*, the Brønsted acid methanol and the Lewis acid benzaldehyde, both proceed through "loose" transition states. By this is meant that the transition-state bond between the carbanionic carbon and the electrophile is quite weak, so that the structure of both moieties of the transition state remains little changed from their reactant condition. Among the implications of this proposal are a lack of selectivity of II (and by extension I) in its reactions with electrophiles, since the effects on free energy by structure in the electrophilic portion of the transition state will merely duplicate such effects in the reactant state and thus will be lost from the free energy of activation.



I



II



III

To explore this proposition for validity, we desired to examine the reactions of II under conditions of variable electrophilicity. The mobility of its hydroxyl proton introduced such practical difficulty, however, that we decided instead on the employment of the acyl derivative III. This species can be generated from benzil under a wide variety of conditions.[5–9] Kwart and Baevsky[6] have made plausible the mechanism of eq 1 for its generation.

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[1] This research was supported by the National Science Foundation and the National Institutes of Health. Further details may be found in J. P. Kuebrich, Ph.D. Thesis in Chemistry, University of Kansas, 1968.

[2] Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(3) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

(4) J. P. Kuebrich, R. L. Schowen, M.-s. Wang, and M. E. Lupes, *J. Amer. Chem. Soc.*, **93**, 1214 (1971).

(5) F. Jourdan, *Ber.*, **16**, 659 (1883).

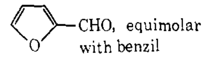
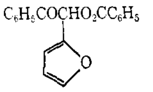
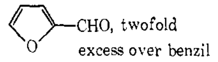
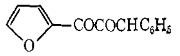
(6) H. Kwart and M. Baevsky, *J. Amer. Chem. Soc.*, **80**, 580 (1958).

(7) W. Dilthey and P. Scheidt, *J. Prakt. Chem.*, **142**, 125 (1935).

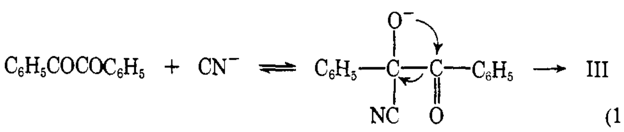
(8) H. D. Darking and C. R. Harrington, *J. Biol. Chem.*, **55**, 485 (1923).

(9) J. C. Trisler and J. L. Frye, *J. Org. Chem.*, 30, 306 (1965).

Table I. Reactions of 0.4–1.6 *M* Benzil and 0.1–0.8 *M* Potassium Cyanide under Various Conditions

Reaction	Solvent system	Added substances	Products	Remarks
1	DMSO or DMF	None	C_6H_5 $O_2CC_6H_5$ $>C{=}C<$ $C_6H_5CO_2$ C_6H_5	The only electrophile present is benzil
2	DMF	C_6H_5CHO, equimolar with benzil	$C_6H_5COCH(C_6H_5)O_2CC_6H_5$	Aldehydic electrophiles compete effectively with benzil
3	DMF	 CHO, equimolar with benzil	 $C_6H_5COCHO_2CC_6H_5$	
4	DMF	CH_3CHO, equimolar with benzil	$C_6H_5COCH(CH_3)O_2CC_6H_5$	
5	DMF-C_2H_5OH (70:30, v/v)	None	$C_6H_5COCH(C_6H_5)O_2CC_6H_5$, $C_2H_5O_2CC_6H_5$ (1:1)	*Not* formed by ethanolysis of stilbenediol dibenzoate
6	DMF-C_2H_5OH (70:30, v/v)	C_6H_5CHO, equimolar with benzil	$C_6H_5COCH(C_6H_5)O_2CC_6H_5$, small amount of $C_2H_5O_2CC_6H_5$	
7	DMF-C_2H_5OH (70:30, v/v)	CH_3CHO, equimolar with benzil	$C_6H_5COCH(C_6H_5)O_2CC_6H_5$, $C_2H_5O_2CC_6H_5$, small amount of $C_6H_5COCH(CH_3)O_2CC_6H_5$	
8	DMF-C_2H_5OH (70:30, v/v)	CH_3CHO, fivefold excess over benzil	$C_6H_5COCH(CH_3)O_2CC_6H_5$	
9	CH_3OH-H_2O (70:30, v/v)	None, initial concentration of benzil 1.2 *M*	$C_6H_5COCHOHC_6H_5$, C_6H_5CHO, $CH_3O_2CC_6H_5$	Benzoin *not* formed by benzoin condensation
10	CH_3OH, CH_3CH_2OH, or $CH_3CH_2CH_2OH$	None, initial concentration of benzil 8–40 × 10^{-4} *M*	C_6H_5CHO, $RO_2CC_6H_5$	a
11	CH_3OH	 CHO, twofold excess over benzil	 $COCOCHC_6H_5$	

[a] Reference 6.



(1)

Results

The model carbanion III was exposed to conditions representing a great range of electrophilic opportunity and choice, and its reactions were quite diverse, as shown in Table I. The formation of III by a 1,2 C-O shift of the benzoyl group, as in eq 1, must be exceedingly rapid since no evidence was found under any of the conditions which could not be understood in terms of an initial generation of III.

The results of Table I can be explained by the general mechanistic hypothesis of Scheme I. The numbers shown along the reaction routes in this scheme correspond to the numbered reactions of the table. We may consider the results in order of increasingly electrophilic media, roughly the order of reactions in the table.

In reaction 1, III is produced in nonelectrophilic media and therefore attacks the reactant benzil to generate the adduct IV. This species contains an oxyanion center (strongly nucleophilic in DMF and DMSO) and two electrophilic carbonyl groups. Only the adjacent ketone is attacked rather than the ester function, since none of the α,α′-dibenzoylbenzyl benzoate expected from attack at the ester is found among the products. Only *trans*-α,α′-stilbenediol dibenzoate (V) is isolated, in agreement with earlier work by Trisler and Frye.[9] Attack on the ketone in preference to the ester group is reasonable in view of the known smaller electrophilicity of the latter.[10] The reason for the trans stereochemistry is unclear; it was not established whether the cis compound is stable under these conditions.

Reactions 2, 3, and 4 provide opportunities for III to choose another electrophile in preference to benzil and in each case it does so. The adduct VI now lacks any occasion for intramolecular nucleophilic attack except at the ester function which was formerly shunned; now it is attacked to yield the benzoin ester VII.

The Brønsted acid ethanol takes the role of electrophile in reaction 5. The product here is benzoin benzoate, but with an equal amount of ethyl benzoate also formed. One's first thought might be that stilbenediol dibenzoate is the true primary product but is ethanolyzed in the medium (which is made basic by cyanide ion) to give the two esters observed. A control experiment showed, however, that the stilbene derivative is stable in this solution. The actual route of formation appears to begin with neutralization of III by ethanol to form the mandelonitrile benzoate VIII, which is then ethanolyzed to ethyl benzoate and benzaldehyde. III then reacts with the product aldehyde to generate VI. In DMF-rich media, such as in reaction 5, VI reacts intramolecularly as before to give benzoin benzoate (VII). This sequence is confirmed by the experiment of reaction 6, in which benzaldehyde is introduced directly at the

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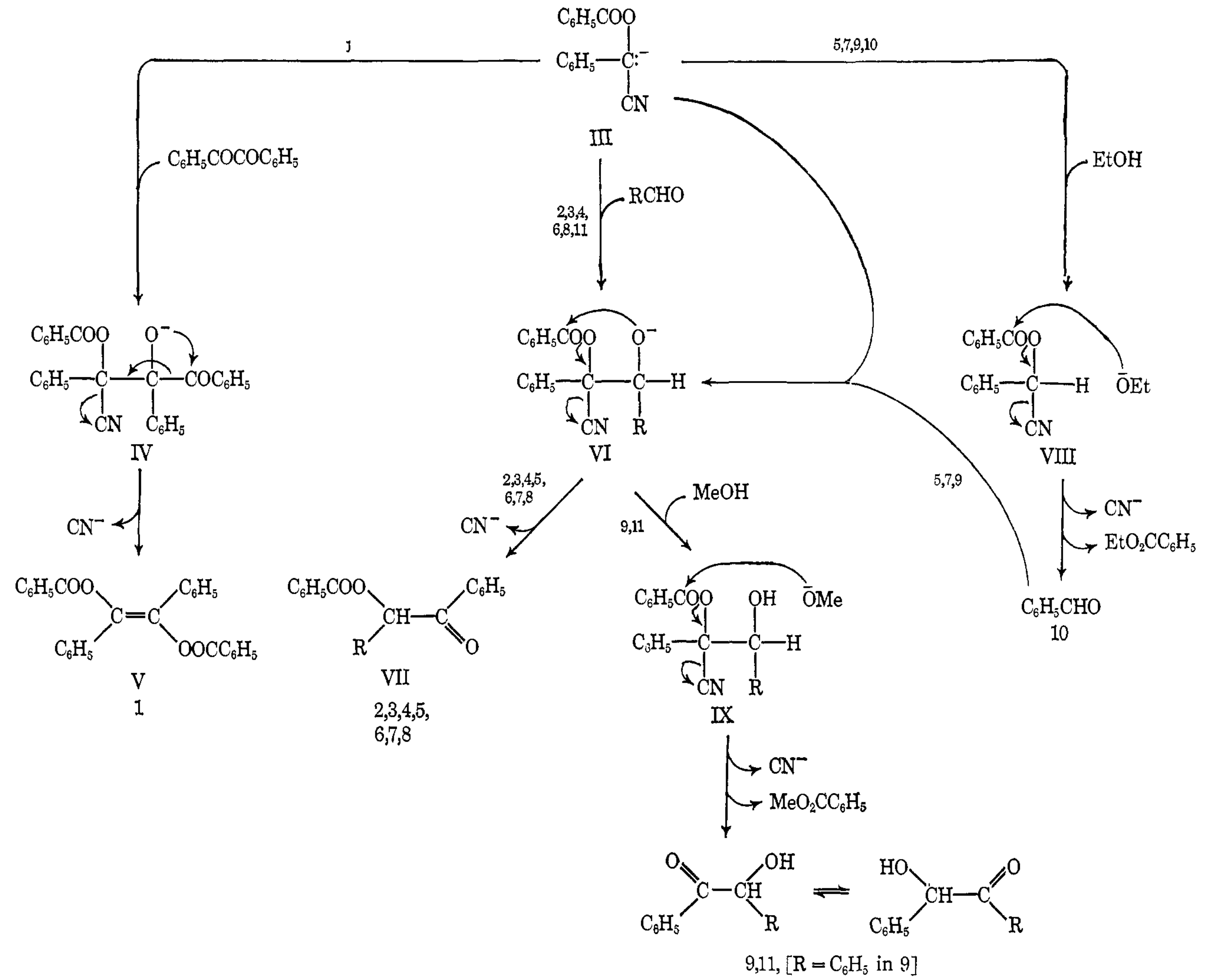
(10) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, Chapters 11 and 12. Of course, other factors may enter, such as ring size in the transition state for attack or for decomposition of the carbonyl adduct, or orbital-overlap considerations concerned with the geometrical differences. Leaving group differences favor the ester reaction and are apparently outweighed.

Scheme I



beginning. It now competes effectively with ethanol for III, leading *via* VI to benzoin benzoate, the observed product. Only a small quantity of ethyl benzoate is found, representing the material diverted through VIII and then VI to the same product VII. Further evidence for the intermediacy of VIII is offered by the demonstration 48 years ago by Greene and Robinson[11] that mandelonitrile benzoate (VIII), independently synthesized, produces benzoin benzoate by formation of III and benzaldehyde and their subsequent reaction.

It was striking that benzaldehyde could compete so well with ethanol for III (as in reaction 6); the corresponding ability of acetaldehyde was examined in reactions 7 and 8. In reaction 7, where equimolar quantities of benzil and acetaldehyde were used, little of the product corresponding to trapping of III by acetaldehyde was found, perhaps in part because some of the aldehyde was present in hemiacetal form. When the initial ratio of aldehyde to benzil was made five, however, the only product was the benzoate of methyl benzoyl carbinol (reaction 8). The aldehydes are clearly good competitors, although the reversibility of protonation of III by ethanol may be a factor.

Finally, in reactions 9–11, completely protic media are introduced. At high initial concentrations of benzil (reaction 9), the benzaldehyde product is still trapped by III to yield VI. The latter does not undergo an intramolecular reaction in the electrophilic aqueous methanol solvent; instead it is neutralized by solvent to IX, which in turn solvolyzed to yield benzoin. The benzoin is *not* formed merely by benzoin condensation of the original benzaldehyde product, as was shown in a control experiment. At the low concentrations used by Kwart and Baevsky[6] for spectrophotometric kinetic studies, the secondary trapping by III does not occur and benzaldehyde and ethyl benzoate are the observed products.

When furfural is added in high initial concentrations, it appears directly to drain away III to VI. The latter again does not react intramolecularly in the electrophilic methanol solvent; instead it is neutralized to IX, which is then methanolyzed. Presumably the first-formed product is 2-furylbenzoylcarbinol (the mixed benzoin with the hydroxyl next to the furan ring), but interconversion of mixed benzoins occurs rapidly under these conditions[12–14] so that furobenzoin was isolated.

The rich chemistry observed for III in electrophilic media is in complete accord with the prediction based on the "loose" structure proposed[4] for the transition states of its reactions with electrophiles. The lack of

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[11] H. Greene and R. Robinson, *J. Chem. Soc.*, **121**, 2182 (1922).

[12] M. Tiffeneau and M. J. Levy, *Bull. Soc. Chim. Fr.*, **49**, 725 (1931).

[13] H. Greene, *J. Chem. Soc.*, 332 (1926).

[14] J. S. Buck and W. S. Ide, *Org. React.*, **4**, 269 (1948).

selectivity and the resulting variety of reactions available to the species III under mild conditions constitute a property of the reaction directly deducible from the transition-state structure. The success of this deduction here does not, of course, "prove" the utility of transition-state structures in this kind of application but does represent, we believe, encouraging progress toward predictive mechanism chemistry.[15]

Experimental Section[16]

Materials. Benzoin (Matheson Coleman and Bell, practical grade), cupric sulfate (Allied Chemical reagent grade "copper sulfate"), pyridine (Fisher reagent), potassium cyanide (Baker analyzed reagent), *N,N*-dimethylformamide (DMF, Baker analyzed reagent), nitrogen (Linde dry), acetic anhydride (Fisher certified), potassium nitrate (Baker analyzed reagent), sodium bicarbonate (Baker analyzed reagent), absolute methanol (Baker and Adamson reagent), deuterium oxide (Bio-Rad, 99.88 mol % D_2O), dimethyl carbonate (Eastman White Label), dimethyl sulfate (Mallinckrodt), and dimethyl sulfoxide (DMSO, Baker analyzed reagent) were used as obtained. Benzaldehyde was purified as previously outlined.[4] Acetaldehyde (Matheson Coleman and Bell practical grade) and furfural (Matheson Coleman and Bell practical grade) were distilled immediately prior to use. Benzil was either obtained commercially (Aldrich) and used without further purification, or was recrystallized from methanol or ethanol, or was prepared[17] by the oxidation of benzoin with copper sulfate.

***trans*-α,α′-Stilbenediol dibenzoate** was prepared from the reaction of benzil with potassium cyanide in either DMSO or DMF according to the procedure of Trisler and Frye.[9] Benzil (2 g, 10 mmol) was added to a stirred mixture of potassium cyanide (0.4 g, 6 mmol) and solvent (25 ml) under a nitrogen atmosphere. The reaction was accompanied by color formation (brown in DMSO and orange fading to brown in DMF) and heat evolution. After 15 min the reaction mixture was poured over crushed ice. The white precipitate formed was filtered and air-dried. Recrystallization from ethanol gave *trans*-α,α′-stilbenediol dibenzoate as the only product: mp 190–191° (lit.[9] mp 190–191°); ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 8.5 (4 H multiplet), 7.8 (16 H multiplet).

Benzoin benzoate was prepared by the same method as used in preparing *trans*-α,α′-stilbenediol dibenzoate with the exception that 25 ml of a mixture of DMF and ethanol (70:30 v/v) was used as the solvent. A short-lived green color formed on the addition of benzil. Ethyl benzoate was formed in a roughly equimolar ratio with benzoin benzoate. The white benzoin benzoate was recrystallized from ethanol: mp 124–125° (lit.[18] mp 124–125°); ir ($CHCl_3$) 1715, 1690 cm^{-1}; nmr ($CDCl_3$) δ 8.05 (4 H multiplet), 7.4 (11 H, multiplet), 7.16 (1 H, singlet). On mixing with an authentic sample, prepared according to the method of Wren[18] from benzoin and benzoyl chloride, no depression in melting point was observed. A nitrogen atmosphere was not found necessary for the reaction. On changing the solvent to DMF–ethanol–water (70:14:7, v/v/v), more cyanide was required to drive the reaction to completion than was the case when no water was present.

Role of *trans*-α,α′-Stilbenediol Dibenzoate in the Formation of Benzoin Benzoates. When *trans*-α,α′-stilbenediol dibenzoate was added to potassium cyanide in DMF–ethanol (70:30, v/v) or DMF–ethanol–water (70:14:7, v/v/v), in either the presence or absence of a nitrogen atmosphere, and was heated for 20 min on a steam bath, only unreacted starting material was recovered. When a mixture of benzil and the stilbenediol diester was submitted to the above reaction conditions, benzoin benzoate and ethyl benzoate were isolated in nearly theoretical yield with almost total recovery of the unreacted stilbene diester.

Trapping Experiment to Form Benzoin Benzoate. Benzil (10 g, 47 mmol) and benzaldehyde (5 g, 47 mmol) were dissolved together in 25 ml of DMF and added to a stirred solution of potassium cyanide (1 g, 15 mmol in 25 ml of DMF) under nitrogen. An orange color formed on addition of the benzil-benzaldehyde solution to the cyanide solution. After 30 min the reaction mixture was poured into cold water. The resulting precipitate was filtered off and recrystallized from ethanol yielding 13 g (41 mmol) of benzoin benzoate. When DMF–ethanol (70:30, v/v) was used, 1 g (9 mmol) of benzaldehyde and 2 g (9 mmol) of benzil produced 2.4 g (8 mmol) of benzoin benzoate along with a small amount of ethyl benzoate.

Trapping Experiment to Form the Benzoate of Methylbenzoylcarbinol. Benzil (5 g, 24 mmol) and acetaldehyde (1.34 ml, 24 mmol) were dissolved in 20 ml of DMF. The reaction with potassium cyanide was carried out in the same manner as described above. The product, a white crystalline solid which was recrystallized from ethanol, proved to be the benzoate of methylbenzoylcarbinol: mp 108–109° (lit.[19] mp 108–109°); ir ($CHCl_3$) 1692, 1715 cm^{-1}; nmr ($CDCl_3$) δ 8.1 (4 H, multiplet), 7.5 (6 H, multiplet), 6.25 (1 H, quartet), 1.75 (3 H, doublet).

When the same reaction was run in DMF–ethanol (70:30, v/v) with the same ratio of benzil to acetaldehyde, the crude solid reaction product was found to be almost entirely benzoin benzoate with a small amount of the benzoate of methylbenzoylcarbinol. Some ethyl benzoate was also formed. However, when the reaction was repeated with a 5:1 molar ratio of acetaldehyde to benzil, the only product that could be isolated was the benzoate of methylbenzoyl carbinol.

Trapping Experiment to Form the Benzoate of 2-Furylbenzoylcarbinol. Benzil (25.4 g, 120 mmol) and furfural (10 ml, 120 mmol) were dissolved in 50 ml of DMF and treated in the manner described above. A white crystalline solid was obtained on recrystallization from ethanol: mp 91–92°; ir ($CHCl_3$) 1685, 1720, 882 cm^{-1}; nmr ($CDCl_3$) δ 8.15 (2 H, multiplet), 7.50 (10 H, multiplet), 6.95 (1 H, singlet), 6.45 (1 H, multiplet). The infrared absorption at 870–885 cm^{-1} is characteristic of a furan ring.[20] No previous report of this compound could be found in the literature.

Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.55; H, 4.60. Found: C, 74.61; H, 4.34.

Benzoin Condensation Not Operative in Benzoin Formation from Benzil and Cyanide Ion. Potassium cyanide (1 g, 15 mmol) was added to 20 ml of a methanol–water solution (5:2, v/v) containing benzil (5 g, 24 mmol). The exothermic reaction was allowed to proceed for 15 min and the mixture was then poured over crushed ice. An oily phase gradually separated which partially crystallized on standing. The crystals were filtered off and air-dried yielding 0.5 g (2 mmol) of benzoin. An nmr spectrum of the oily phase of the filtrate confirmed the presence of benzaldehyde and methyl benzoate.

Benzaldehyde (2.5 g, 24 mmol) was allowed to react with potassium cyanide (0.2 g, 3 mmol) in 25 ml of methanol–water (5:2, v/v) for 10 min at 40° (conditions approximately equivalent to those in the above experiment). Five milliliters of 10% aqueous hydrochloric acid was then added to quench the reaction. The reaction mixture was poured into 25 ml of cold water and allowed to sit overnight in the refrigerator. When the solution was filtered the following day no evidence of any benzoin formation was noted. Simultaneous with this reaction but at room temperature, a reaction of 5 g (24 mmol) of benzil, which would be expected to form 2.5 g (24 mmol) of benzaldehyde by cleavage, yielded 0.15 g (0.7 mmol) of benzoin.

Furobenzoin (2-Furyl α-Hydroxybenzyl Ketone). Benzil (5 g, 24 mmol) and furfural (5 g, 52 mmol), were added to 15 ml of methanol. Water (4 ml) containing potassium cyanide (1 g, 15 mmol) was added to the methanol solution. The exothermic reaction was accompanied by the formation of a nearly black solution. After 5 min the reaction solution was poured into cold water, causing an oily layer to separate. This partially solidified on standing. The solid was filtered off and recrystallized from CCl_4 to give as a light yellow solid, furobenzoin: mp 137–138.5° (lit.[14] mp 139°); ir ($CHCl_3$) 1662, 885 cm^{-1}.

Acknowledgments. We are happy to thank Professor R. G. Carlson for his interest and help with this study.

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[15] See pertinent comments of G. L. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967); S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968); and E. M. Arnett, "An Explainer's Guide to the Effects of Physical Organic Chemistry."

[16] Melting points were taken on a Mel-Temp apparatus and are uncorrected; nmr spectra were taken on a Varian A-60 instrument with tetramethylsilane (TMS) as an internal reference; infrared spectra were taken on a Beckman IR8 infrared spectrophotometer.

[17] H. Gilman, Ed., "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 80.

[18] H. Wren, *J. Chem. Soc.*, **95**, 1601 (1909).

[19] K. Auwers, H. Ludewug, and A. Muller, *Justus Liebigs Ann. Chem.*, **526**, 163 (1936).

[20] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 213.