Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: N, 10.29; S, 11.77. Found: N, 10.31; S, 11.44.

Acknowledgments.—The authors wish to thank Mr. E. F. Shelberg of the Micro-analytical Department for the micro-analyses herein reported. The assistance of Messrs. Robert J. Hathaway and Charles J. Strickler in the preparation of some of the products is gratefully acknowledged.

Summary

The preparation and properties of thirty-seven carbamates of varying complexity are described. Moderate antimalarial activity was observed in a number of these, two of the more active ones being *p*-carbobutoxyphenyl *p'*-methoxycarbanilate (SN 1048) and *p*-sulfamylphenyl *p'*-methoxycarbanilate (SN-4178).

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

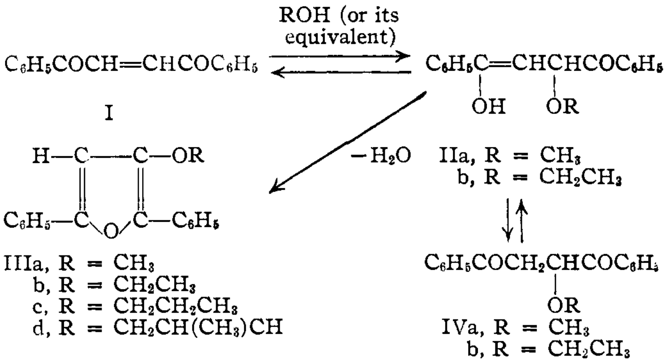
The Reaction of Alcohols with 1,2-Dibenzoylethylene. II.[1,2,3,4]

BY PHILIP S. BAILEY AND JOE T. KELLY[5]

The reaction of alcohols with 1,2-dibenzoylethylene (I) in the presence of an amine hydrochloride and a trace of hydrogen chloride to give 3-alkoxy-2,5-diphenylfurans (III) has been given further study. Previously, the reaction had been carried out with methanol, ethanol and isopropyl alcohol.[4] It has now been found that *n*-propanol and isobutyl alcohol will give the reaction,[6] but the other three isomeric butyl alcohols and *n*-amyl alcohol will not react with dibenzoylethylene to give alkoxyfurans to any appreciable extent. Phenol also failed to give the reaction, an intractable oil being obtained. Apparently the length of the chain as well as the complexity of the alcohol is important in determining whether or not reaction will occur.

In the earlier work on this reaction, the ratio by weight of triethylamine hydrochloride to dibenzoylethylene employed was 1:1.[4] Later work, with the ethanol reaction, has shown that with a 1:10 ratio no decrease in yield of alkoxyfuran is obtained, but with a 1:100 ratio the yield of alkoxyfuran is decreased by about 95%.

One would assume that the alkoxyfurans (III) are obtained from dibenzoylethylene (I) by the equilibrium reactions shown involving structures I, II, III and IV, in which the reaction is probably initiated by the attack of some cation of the reaction mixture upon the oxygen of the diketone. Evidence in favor of this equilibrium was obtained when IVa was placed in a methanolic reaction mixture in place of dibenzoylethylene (I) under identical conditions, and the mixture was refluxed for the usual length of time. The products isolated were dibenzoylethylene (I), the methoxyfuran (IIIa) (in approximately the same yield as obtained from dibenzoylethylene) and an oily material. Where the high melting[4,7] and oily by-products fit into this picture is uncertain, since their structures are as yet undetermined. Alkoxy diketones (IV) have never been isolated from the dibenzoylethylene–alcohol reaction mixtures refluxed for one, five, ten, twenty-four or sixty hours. However, this is not surprising, since the only one of these compounds known, IVa, is extremely hard to crystallize.



Kohler[8] has found that ethanol will add to

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[1] Constructed from the thesis submitted by Mr. Joe T. Kelly to the Graduate Faculty of The University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, January, 1948.

[2] Presented at the Southwest Regional Meeting of the American Chemical Society, Houston, Texas, December 13, 1947.

[3] This work was supported in part by grants from The University Research Institute, Project No. 70.

[4] Paper I, Bailey and Lutz, THIS JOURNAL, **69**, 498 (1947).

[5] Present address: Pan-American Refining Co., Texas City, Texas.

[6] Attempts to prove the structures of the products, 2,5-diphenyl-3-*n*-propoxyfuran and 3-*i*-butoxy-2,5-diphenylfuran by the same general method used in proving the structure of the ethoxyfuran (IIIb) (ref. 4, *i. e.*, treatment of 1,2-dibenzoyl-1,2-dibromoethane with the desired sodium alkoxide, followed by reductive furanization of the resulting 1-alkoxy-1,2-dibenzoylethylene) failed in the first step, from which a resinous material was obtained. Likewise, 2,5-diphenyl-3-*i*-propoxyfuran could not be made by this method (ref. 4). There can be little doubt of the structures of these compounds, however, since they were obtained from reactions identical with those which yielded the corresponding methoxy and ethoxyfurans. Also, the melting points of the alkoxyfurans (Me, 114–115°; Et, 94–95°; Pr, 86–87°, *i*-Pr, 87–88°; *i*-Bu, 71–72°) are in harmony with the proposed structure.

[7] The fact that the high melting by-products (ref. 4) were not isolated in the last experiment described is probably not significant in view of the small amount of methoxydiketone (IVa) employed and the small amounts of dibenzoylethylene (I) and the methoxyfuran (IIIa) produced.

[8] Kohler, *Am. Chem. J.*, **42**, 375 (1909).

phenyl vinyl ketone in the presence of a trace of hydrochloric acid to give β-ethoxypropiophenone, but that alkylated phenyl vinyl ketones (1-phenyl-2-buten-1-one and 3-methyl-1-phenyl-2-buten-1-one) will not give the reaction. We have found that benzalacetophenone, likewise, will not add alcohols under the conditions of the dibenzoylethylene reactions. It is noteworthy that in these cases no such cyclization as II to III is possible. This cyclization apparently is the driving force of our reaction. It is perhaps this step that the amine hydrochloride catalyzes, since hydrochloric acid only is necessary for the addition to phenyl vinyl ketone.

Methoxydibenzoylethane (IVa) was also allowed to react with ethanol under conditions identical with those of the dibenzoylethylene reaction. The crystalline products obtained were the ethoxyfuran (IIIb) and dibenzoylethylene (I). Since it was surprising that no methoxyfuran (IIIa) was obtained (conversion IIa to IIIa), the methoxyfuran (IIIa) was allowed to react with ethanol under conditions identical with those of the dibenzoylethylene reaction. After the usual reflux period, the ethoxyfuran (IIIb) was obtained in good yield. Thus, from methoxydibenzoylethane (IVa), the ethoxyfuran (IIIb) probably was obtained by means of two paths (a and b) as shown in the accompanying diagram. The conversion of IIIa to IIIb is believed not to involve structures IIa, I or IIb, since dibenzoylethylene (I) was not isolated from reaction mixtures refluxed for ten or twenty-four hours.

Path (a), ethanol solution

$$\begin{tikzcd}
\text{IVa} \arrow[r, shift left] & \text{IIa} \arrow[l, shift left] \arrow[r, shift left] \arrow[d, "\substack{\text{Path (b)}\\ \text{ethanol}\\ \text{solution}}"', "-H_2O"] & \text{I} \arrow[l, shift left] \arrow[r, shift left] & \text{IIb} \arrow[l, shift left] \arrow[r, shift left] \arrow[d, "-H_2O"', "\substack{\text{Path (a)}\\ \text{ethanol}\\ \text{solution}}"] & \text{IVb} \arrow[l, shift left] \\
& \text{IIIa} \arrow[rr, shift right] & & \text{IIIb} \arrow[ll, shift right] &
\end{tikzcd}$$

Path (b), ethanol solution

This unusual conversion of one stable ether into another is being given further study. Besides the conversion of IIIa to IIIb in ethanol solution, the reverse has been carried out in methanol solution.

Experimental[9]

2,5-Diphenyl-3-*n*-propoxyfuran (IIIc).—The procedure followed here is similar to the procedure followed in the reactions of dibenzoylethylene with methanol, ethanol and isopropyl alcohol.[4] To a solution of 5 g. of dibenzoylethylene, 5 g. of triethylamine hydrochloride and 70 ml. of anhydrous *n*-propanol was added enough propanolic hydrogen chloride solution to give an indicated *p*H of 2–3 (*p*Hydrion paper). The reaction mixture was refluxed with stirring for forty hours. The solvent was evaporated by a stream of air, the residue dissolved in ether and the resulting solution extracted with water to remove the triethylamine hydrochloride. After evaporation of the ether the residue was allowed to fractionally crystallize from methanol. Thus was obtained 0.9 g. (15% yield) of crude 2,5-diphenyl-3-*n*-propoxyfuran (m. p. 84–86°), 0.03 g. of high melting material (m. p. 184–186°, shown by a mixture melting point to be identical with one of the by-products reported earlier[4]), 0.12 g. of dibenzoylethylene and an oily residue. From a similar reaction, carried out at 90°, a 22% yield of IIIc was obtained. Several recrystallizations of the furan (IIIc) from ethanol raised the melting point to 86–87°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.25; H, 6.58.

An attempt to confirm the structure of IIIc by synthesis from 1,2-dibenzoyl-1,2-dibromoethane failed. Treatment of an absolute propanolic suspension of the latter with a propanolic solution containing two mole-equivalents of sodium propoxide led to an intractable oil which upon reduction with zinc and acetic acid also gave an oil. This same synthetic method was successful in the earlier proof of structure of the ethoxyfuran (IIIb).

3-*i*-Butoxy-2,5-diphenylfuran (IIId) was prepared from dibenzoylethylene and isobutyl alcohol by essentially the same method described in the *n*-propanol reaction. The yield of crude IIId was 23% (m. p. 55–60°). Several recrystallizations from ethanol raised the melting point to 71–72°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.24; H, 6.85.

An attempt to prepare IIId from 1,2-dibenzoyl-1,2-dibromoethane failed. The results were comparable to those described above concerning the attempt to prepare IIIc by this method.

Attempts to prepare alkoxyfurans by the reactions of dibenzoylethylene with *n*-butyl alcohol, *s*-butyl alcohol, *t*-butyl alcohol and *n*-amyl alcohol, using the same procedure described in the propoxyfuran (IIIc) experiment, failed. From the reactions with *n*-amyl alcohol and *s*-butyl alcohol only intractable oils were obtained. From the *t*-butyl alcohol reaction mixture was recovered a high yield of starting material and a few crystals of what might be the corresponding alkoxyfuran (m. p. 91–92°; there was not enough material to purify and analyze). In the case of *n*-butyl alcohol there was obtained some crystals which melted at 164–165° after several recrystallizations from ethanol. The substance was analyzed but not given further study.

Anal. Found: C, 83.86; H, 4.74.

Reactions of Dibenzoylethylene with Ethanol to Determine the Minimum Amount of Triethylamine Hydrochloride Necessary for the Formation of the Alkoxyfuran.—A solution of 5.0 g. of dibenzoylethylene, 0.5 g. of triethylamine hydrochloride (one-tenth of the amount used in previous reactions) and 70 ml. of absolute ethanolic hydrogen chloride (indicated *p*H, *p*Hydrion paper, 2–3) was allowed to reflux for twenty-four hours. It was worked up as described in the *n*-propanol reaction. Thus was obtained 0.9 g. (16% yield) of IIIb, 1.0 g. of recovered dibenzoylethylene, 0.2 g. of material melting at 144–148° and an oil. Identifications were by mixture melting points.

When the reaction was repeated exactly with the exception that only 0.05 g. of triethylamine hydrochloride was used, there was obtained only 0.06 g. (1% yield) of IIIb, 0.4 g. of dibenzoylethylene, 0.1 g. of material melting at 179–186° and an oily residue. Identifications were by mixture melting points.

Reaction of Dibenzoylethylene with Ethanol for Different Time Intervals.—Reactions between dibenzoylethylene and ethanol were carried out for time intervals of one, five, ten, twenty-four and sixty hours under the same conditions described in the *n*-propanol reaction. In the first three cases mixtures of dibenzoylethylene and the ethoxyfuran (IIIb) were obtained, which consisted principally of the former. Residual oils were also obtained after all crystalline materials were removed. The sixty hour run gave a 22% yield of IIIb and considerable amounts of the high melting products reported earlier.[4] Only a few drops of residual oil was obtained. No substance which could be IVb ever crystallized. The residual oils from these reactions, upon attempted furanization

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[9] All melting points reported here are corrected. The microanalyses were carried out by the Micro-Tech Laboratories of Skokie, Illinois.

with acetic anhydride and sulfuric acid, gave either noncrystalline materials or high melting materials different from those reported previously. This should not be interpreted as IVb being absent, however, since Lutz has found that known IVa under these conditions does not give IIIa, as expected, but instead gives a high melting material.[10]

The reaction of dibenzoylethylene with 95% ethanol for twenty-four hours, all other conditions being as described in the *n*-propanol experiment, gave a few crystals of high melting material and a residual oil. No IIIb was obtained.

Attempted reaction of ethanol and methanol with benzalacetophenone under precisely the same conditions described in the reaction of dibenzoylethylene with *n*-propanol failed. An 80% recovery of benzalacetophenone was obtained in each case.

Reaction of Dibenzoylmethoxyethane (IVa) in Methanol in the Presence of Triethylamine Hydrochloride and Hydrogen Chloride.—A solution of 0.9 g. of crystalline dibenzoylmethoxyethane (IVa),[10] 1.0 g. of triethylamine hydrochloride and 35 ml. of methanolic hydrogen chloride solution (indicated *p*H, *p*Hydrion paper, 2–3) was refluxed for twenty-six hours. The reaction mixture was worked up precisely as described in the reaction between dibenzoylethylene and *n*-propanol. Thus was obtained 0.15 g. of 3-methoxy-2,5-diphenylfuran (IIIa), 0.02 g. of dibenzoylethylene and an oily material (identifications by mixture melting points).

In a similar experiment using oily dibenzoylmethoxyethane, there was obtained 0.1 g. of the methoxyfuran (IIIa) and 0.2 g. of dibenzoylethylene (identifications by mixture melting points).

Reaction of dibenzoylmethoxyethane (0.9 g.) with ethanol in the presence of triethylamine hydrochloride and hydrogen chloride under precisely the same conditions described in the preceding experiment yielded 0.07 g. of 3-ethoxy-2,5-diphenylfuran (IIIb), 0.02 g. of dibenzoylethylene (I) and an oil. No 3-methoxy-2,5-diphenylfuran (IIIa) was isolated. Identifications were made by mixture melting points.

Reaction of 3-Methoxy-2,5-diphenylfuran (IIIa) with Ethanol.—To a solution of 1 g. of 3-methoxy-2,5-diphenylfuran (IIIa), 1 g. of triethylamine hydrochloride and 30 ml. of absolute ethanol was added enough ethanolic hydrogen chloride to give the solution an indicated *p*H of 2–3 (*p*Hydrion paper). This solution (*p*H kept constant at 2–3) was refluxed for twenty-four hours, after which the reaction mixture was worked up as described in the reaction between dibenzoylethylene and *n*-propanol. Thus was obtained 0.8 g. of the ethoxyfuran (IIIb), 0.1 g. of the methoxyfuran (IIIa) and a small amount of oil.

When this reaction was repeated, cutting the reflux time to ten hours, 0.6 g. of the ethoxyfuran, 0.1 g. of the methoxyfuran, 0.1 g. of the 186°-melting by-product,[4] and an oil were obtained. All of the above identifications were by mixture melting points.

Reaction of 3-ethoxy-2,5-diphenylfuran (IIIb) **with methanol** using 0.6 g. of the ethoxyfuran, 0.6 g. of triethylamine hydrochloride and 25 ml. of methanolic hydrogen chloride (indicated *p*H of 2–3) for twenty-four hours under the same conditions described in the preceding experiment yielded 0.3 g. of the methoxyfuran (IIIa) and 0.2 g. of material believed to be a mixture of the methoxy and ethoxyfurans (m.p. 85–110°). Identifications were by mixture melting points.

Attempted reaction of 3-chloro-2,5-diphenylfuran with ethanol under precisely the same conditions described in the methoxyfuran reactions gave a 92% recovery of starting material.

Summary

The reaction between dibenzoylethylene and alcohols in the presence of amine hydrochlorides and a trace of hydrogen chloride has been found to occur also with *n*-propanol and isobutyl alcohol, but not with more complex alcohols. The mechanism of the reaction has been given some study. 3-Methoxy-2,5-diphenylfuran under the conditions of this reaction in ethanol solution has been converted to the corresponding ethoxyfuran and the reverse has been carried out in methanol solution.

AUSTIN, TEXAS RECEIVED MAY 5, 1948

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[10] Lutz, THIS JOURNAL, **51**, 3008 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Kinetics of the Reactions of Thiosulfate Ion with Ethyl, Propyl and Isopropyl Bromides[1]

BY THOMAS I. CROWELL AND LOUIS P. HAMMETT

The reactivity of the saturated alkyl halides in bimolecular displacement reactions always decreases when alpha or beta hydrogen atoms are replaced by methyl groups. The rates of reactions of the type

$$\mathrm{B{:}} + \mathrm{RX} \longrightarrow \mathrm{BR} + \mathrm{{:}X} \qquad (1)$$

have been studied[2] in cases where :B, the nucleophilic displacing group, is bromide, iodide, hydroxyl, ethoxide, phenolate, benzyloxide and thiosulfate ion. In each of the second-order reactions, the rates for different R groups are in the relation Me > Et > *i*-Pr > *t*-Bu and Et > *n*-Pr > *i*-Bu > neopentyl. This effect of structure on reactivity has been explained in two ways: first, by the tendency of an accumulation of electrons around the reaction center to repel the entering group[3,2g]; second, by increased steric hindrance in the transition state in the higher members of both series.[4,5] An increase in the potential energy change accompanying formation of the transition state would be expected in either case. These explanations

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[1] Dissertation submitted by Thomas Irving Crowell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

[2] (a) Conant and Hussey, THIS JOURNAL, **47**, 476 (1925); (b) Le Roux, Lu, Sugden and Thomson, *J. Chem. Soc.*, 586 (1945); (c) Seelig and Hull, THIS JOURNAL, **64**, 940 (1942); (d) McKay, *ibid.*, **65**, 702 (1943); (e) Bartlett and Rosen, *ibid.*, **64**, 543 (1942); (f) Bateman, Cooper, Hughes and Ingold, *J. Chem. Soc.*, 931 (1940); (g) Dostrovsky and Hughes, *ibid.*, 157 (1946); (h) Segaller, *ibid.*, **105**, 106 (1914); (i) Haywood, *ibid.*, **121**, 1904 (1922); (j) Slator and Twiss, *ibid.*, **95**, 93 (1909).

[3] Hughes, Ingold and Patel, *ibid.*, 529 (1933).

[4] Ogg and Polanyi, *Trans. Faraday Soc.*, **31**, 604 (1935); Evans, "The Reactions of Organic Halides in Solution," Manchester University Press, Manchester, 1946.

[5] Dostrovsky and Hughes, *J. Chem. Soc.*, 173 (1946).