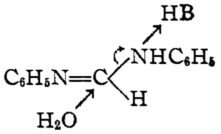
charged molecule is involved in the rate determining step (reference 12, page 128). Diphenylformamidine is known to form a monohydrochloride salt.[17] Two monobasic conjugate acids of diphenylformamidine are possible.

$$\underset{\text{I}}{C_6H_5\overset{+}{N}H{=}CHNHC_6H_5} \qquad \underset{\text{II}}{C_6H_5N{=}CH\overset{+}{N}H_2C_6H_5}$$

Of these two, the one in which the proton is attached to the imino nitrogen atom (I) would be stabilized by resonance to a much greater extent than the other, and probably is the unreactive conjugate acid. The greater stability of I resides in the fact that its resonance hybrid possesses two identical contributing structures

$$C_6H_5\overset{+}{N}H{=}CHNHC_6H_5 \longleftrightarrow C_6H_5NHCH{=}\overset{+}{N}HC_6H_5$$

The acid-catalyzed hydrolysis reaction probably involves attachment of a proton to the amino nitrogen atom of diphenylformamidine to form the conjugate acid II, which reacts with water to form the products. It seems quite likely[18] that the attack of a water molecule may be concerted with the attachment of the proton, the rate-determining step involving III in the transition state


III

where HB is H_3O^+ or HOAc.[19]

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[17] R. M. Roberts, THIS JOURNAL, **72**, 3608 (1950).

[18] See C. G. Swain, *ibid.*, **72**, 4582 (1950), for a suggestion regarding the mechanism of the closely related hydrolysis of ortho esters.

[19] The referee suggested that the experimental observations could be accounted for in an equally satisfactory manner by a second mechanism involving general base-catalyzed hydrolysis of the conjugate acid of diphenylformamidine. This alternate mechanism would explain the observed variation of k_{HA} with buffer ratio in acetic acid buffers, and also the constant rate of hydrolysis in dilute solutions of hydrochloric acid. However, the authors feel that their proposed mechanism is more probable than the base-catalyzed mechanism for the following reason: when the rate constants obtained in *p*-nitrophenol buffers (see Table III) are plotted against *p*-nitrophenol concentration, three separate, parallel straight lines are obtained, one for each buffer ratio. This result is expected if the reaction is general acid-catalyzed hydrolysis of the free base, but cannot be explained on the basis of general base-catalyzed hydrolysis of the conjugate acid of diphenylformamidine. Theoretical considerations indicate that in buffers in which practically all of the substrate is present as the free base, a single straight line should be obtained when k is plotted against [HA], if the reaction involved is general base-catalyzed hydrolysis of the conjugate acid of the substrate.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Cleavage of Heterocycles with Raney Nickel and with Lithium

BY HENRY GILMAN AND DONALD L. ESMAY

RECEIVED JANUARY 5, 1953

Dibenzofuran has been found to be susceptible to cleavage by lithium in dioxane and in ether and dibenzothiophene undergoes a similar cleavage in dioxane. The cleavage of dibenzofuran in dioxane yields only *o*-hydroxybiphenyl after carbonation and hydrolysis while 3,4-benzocoumarin was obtained when the reaction was carried out in ether. The cleavage of dibenzothiophene in dioxane yielded only *o*-mercaptobiphenyl and biphenyl after carbonation and hydrolysis.

The development of methods for the proof of structure of derivatives of various heterocycles has long been of interest in connection with general studies of heterocyclic compounds which have been carried out in this Laboratory. The ideal method of a simple, direct, and one-step reaction has seldom been achieved. The reports by Blicke and Sheets[1] on the successful desulfurization of thianaphthene and several of its derivatives and of dibenzothiophene over Raney nickel presented what appeared to be an approach to the ideal reaction.

A brief investigation of the application of Raney nickel desulfurization to the proof of structure of dibenzothiophene and of its derivatives was carried out. The results were rather disappointing. With 2-bromodibenzothiophene only biphenyl was isolated, indicating that debromination occurred along with the desulfurization. No identified product was obtained when an attempt was made to remove the sulfur from dibenzothiophene-5-monoxide and from dibenzothiophene-5-dioxide. Some difficulty was encountered in attempts to repeat the cleavage of dibenzothiophene with Raney nickel,[1] the activity of the Raney nickel was indicated to be a critical factor in the success of the desulfurization.

. Earlier work in this Laboratory[2] showed that when dibenzofuran was treated with lithium in dioxane or ether good yields of *o*-hydroxybiphenyl were obtained. This cleavage reaction was of interest not only from the structure-proof view, but also in connection with the reactions of metals with heterocycles in general since the treatment of dibenzofuran with sodium–potassium alloy yields 4-dibenzofurylpotassium[3] while treatment of dibenzofuran[4] with sodium in ethanol and of dibenzothiophene[5] with sodium in liquid ammonia leads to reduction of the benzenoid ring.

It was found possible to carry out the cleavage of dibenzofuran with lithium in dioxane using an atmosphere of either dry air or nitrogen and terminating the reaction by hydrolysis or by carbonation. A possible mode of reaction would involve the cleavage of an oxygen–carbon bond to form an oxygen–lithium bond and a carbon–lithium bond.

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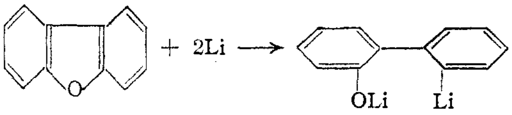
[1] F. F. Blicke and D. G. Sheets, THIS JOURNAL, **70**, 3768 (1948); *ibid.*, **71**, 4010 (1949).

[2] C. W. Bradley, unpublished studies.

[3] H. Gilman and R. V. Young, THIS JOURNAL, **56**, 1415 (1934).

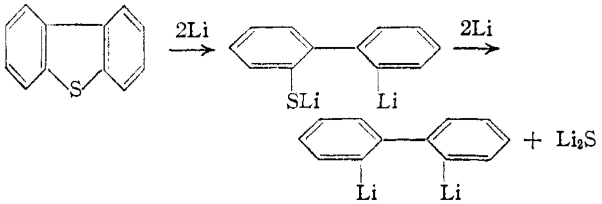
[4] H. Gilman, E. W. Smith and L. C. Cheney, *ibid.*, **57**, 2095 (1935).

[5] H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).



This explanation was made difficult by the observation that at no time was Color Test I[6] positive and that no carboxylic acid product could be isolated when the dioxane reaction mixture was carbonated.

The only product that could be isolated when dibenzothiophene was treated with lithium in dioxane and the reaction mixture hydrolyzed was a small amount of biphenyl. When the reaction was terminated by carbonation, however, biphenyl and *o*-mercaptobiphenyl were obtained in about equal amounts. A two-step cleavage reaction was thus indicated. As with dibenzofuran, though, Color Test I was negative throughout, and no carboxylic acid product could be isolated from the carbonated dioxane reaction mixture.



The earlier[2] reaction of dibenzofuran with lithium in ether had been carried out using a sealed tube and mechanical shaking at room temperature. It appeared of interest to determine what reaction, if any, would occur at the reflux temperature of ether at atmospheric pressure. Somewhat unexpectedly, in view of the above results, Color Test I was positive throughout the reaction and carbonation of the reaction mixture gave a good yield of 3,4-benzocoumarin (the lactone of 2′-hydroxy-2-diphenylcarboxylic acid). On the basis of these results, the above mode of reaction is thought to be satisfactory, although no cleavage could be obtained with lithium and dibenzothiophene in ether. The failure of Color Test I to become positive when the cleavages were carried out in dioxane was thought to be due to an immediate reaction of the carbon–lithium bond of the intermediate compound with the dioxane solvent. Supporting evidence was obtained when it was found that phenyllithium prepared in dioxane gave a positive Color Test I initially but gave a negative test after one hour of stirring at reflux temperature; whereas, over 5 hours were required for the reaction of dioxane with *n*-butyllithium in ether to go to completion at room temperature. That no phenyllithium remained in the first reaction was demonstrated when no benzoic acid could be isolated after carbonation.

It should be mentioned that the cleavage of dibenzofuran with lithium in diethyl ether followed by carbonation is probably the method of choice for the preparation of 3,4-benzocoumarin. Cahn[7] reported that the condensation of phenol with the diazonium sulfate of anthranilic acid gave yields of only a little over 20% of 3,4-benzocoumarin, but that even these relatively low yields were better than those that could be obtained by any of the other procedures tried. The yield of 47.0% obtained during the present investigation with the lithium cleavage of dibenzofuran is consequently over twice as high as any previously reported.

The cleavage of heterocyclic carbon–oxygen and carbon–sulfur bonds with lithium appears to offer a method of structure proof superior in some respects to the Raney nickel cleavage procedure. First, the reaction is much easier and simpler to carry out with lithium since it does not involve an initial activation of the metal. Second, it seems reasonable that the hydrogen present in the Raney nickel catalyst might react with certain functional groups which would be stable toward lithium. The lithium cleavage reaction is being extended to other heterocycles in order to determine the scope of the reaction.

Experimental[8]

The cleavage reactions with Raney nickel were carried out in accordance with the procedure reported by Blicke and Sheets[1] for the reaction of dibenzothiophene with Raney nickel to yield biphenyl. The Raney nickel was activated by the procedure of Mozingo,[9] using some of the slight modifications suggested by Mozingo and co-workers,[10] and incorporating ideas presented by Covert and Adkins.[11]

Raney Nickel Cleavage of 2-Bromodibenzothiophene.—A mixture of 1.3 g. (0.005 mole) of 2-bromodibenzothiophene, about 18 g. of freshly prepared Raney nickel and 250 ml. of ethanol was refluxed for 0.5 hour, cooled, and filtered. Vacuum distillation of the filtrate gave an oily emulsion which partially solidified on standing overnight in the refrigerator. Filtration yielded 0.3 g. of white, shiny flakes melting at 67–70°. Recrystallization from dilute ethanol yielded 0.25 g. (31.2%) of pure diphenyl; m.p. and mixed m.p. 70–71°.

Raney Nickel Cleavage of Dibenzothiophene-5-oxide and 5-dioxide (Attempted).—No identified product was obtained from the reaction of Raney nickel with dibenzothiophene-5-oxide. The small amount of oil that was isolated could not be crystallized or sublimed. A sample of the purest fraction had an index of refraction of 1.5286. This value does not correspond to that of any of the normally expected products. The reaction of Raney nickel with dibenzothiophene-5-dioxide also yielded only a small amount of an unidentified oil.

Lithium Cleavage of Dibenzofuran. Run I.—One-tenth of a mole (16.8 g.) of dibenzofuran which had been well-desiccated over sulfuric acid, 0.22 g. atom (1.5 g.) of lithium and 200 ml. of purified and sodium-dried dioxane were heated to slow reflux while maintaining rapid stirring. The reaction mixture turned brick red immediately. After stirring and refluxing for 12 hours, the mixture was filtered hot through a plug of glass wool to remove a few particles of unreacted lithium. The cooled solution was hydrolyzed by carefully adding a water–dioxane mixture, then most of the solvent was removed by distillation under a water-pump vacuum. The still-pot residue was acidified with 3 *N* hydrochloric acid and extracted with ether. Removal of the solvent from the dried ether layer gave a residual oil which was vacuum distilled to yield a total of 12.9 g. (77.2%) of *o*-hydroxydiphenyl; m.p. 54–56° and mixed m.p. with authentic material (m.p. 57–58°) 55–57°.

Run II.—This reaction was carried out in a manner identical to run I except that an atmosphere of nitrogen was used. The results were essentially the same.

Run III.—This experiment was the same as run II except that the reaction was terminated by carbonation in the usual manner. Color Test I[6] was negative throughout. Hydrolysis and removal of most of the dioxane solvent were

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[6] H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

[7] R. S. Cahn, *J. Chem. Soc.*, 1400 (1933).

[8] All melting points are uncorrected.

[9] R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

[10] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

[11] L. W. Covert and H. Adkins, *ibid.*, **54**, 4116 (1932).

carried out as above. The remaining residue was treated with 200 ml. of 1% sodium hydroxide, then extracted with three 150-ml. portions of ether. The combined ether layer was washed twice with 100-ml. portions of 4% sodium hydroxide.[12] Removal of the solvent from the dried ether layer yielded 11.1 g. (65.2%) of slightly impure *o*-hydroxybiphenyl melting at 53–55° which gave a mixed melting point with authentic material (m.p. 57–58°) of 55–57°. The combined alkaline layer was warmed on a steam-bath, filtered hot, cooled in an ice-bath, and acidified with 6 *N* hydrochloric acid. Filtration gave 2.6 g. (15.3%) of nearly pure *o*-hydroxybiphenyl; m.p. and mixed m.p. 56–57°. The total yield of *o*-hydroxybiphenyl was 80.5%.

Run IV.—This run was the same as run III except that the dioxane was replaced with 200 ml. of ether and the total reaction time was 22 hours. Color Test I was positive at the end of 8, 18 and 22 hours. An additional 150 ml. of ether was added at the end of 18 hours to replace the solvent which had been carried off in the slow stream of nitrogen. Carbonation, hydrolysis and isolation of products were carried out as in run III. From the alkaline solution there was obtained 12.6 g. (64.3%) of impure 3,4-benzocoumarin (the lactone of 2′-hydroxy-2-diphenylcarboxylic acid) melting from 80–86°. The product was recrystallized from 150 ml. of dilute ethanol to yield a total of 8.3 g. (47.0%) of 3,4-benzocoumarin; m.p. and mixed m.p. 95–96°.[13] Removal of the solvent from the dried ether layer from the reaction mixture gave 2.5 g. (14.9% recovery) of dibenzofuran melting at 78–81°, identified by the method of mixed melting points. The yield of 3,4-benzocoumarin based on the amount of dibenzofuran which actually reacted was 75.7% crude and 55.2% pure.

Lithium Cleavage of Dibenzothiophene. Run I.—A mixture of 0.1 mole of dibenzothiophene (18.4 g.) which had been well-desiccated over sulfuric acid, 0.22 g. atom (1.5 g.) of lithium and 200 ml. of purified and sodium-dried dioxane was refluxed and stirred vigorously for 12 hours. The reaction flask was closed with a calcium chloride tube. Most of the lithium had disappeared by the end of 8 hours. After cooling overnight a few particles of unreacted lithium were removed mechanically, and the suspension was carefully hydrolyzed with a water–dioxane mixture. Isolation and purification of products as in the dibenzofuran runs above gave a 30.5% yield of biphenyl melting at 69–70° and a 33.2% recovery of dibenzothiophene melting at 98–99°.

Run II.—The same amounts of reagents and conditions of reaction were used in this experiment as in Run I, except that the reaction was conducted under an atmosphere of nitrogen. Color Test I was negative at the end of 4, 8 and 12 hours. Carbonation, hydrolysis and treatment by customary procedures yielded 3.4 g. (18.3%) of *o*-mercaptobiphenyl melting at 38–40°. Purification through the sodium salt gave 3.0 g. (16.1%) of pure material melting at 40–41°.

Anal. Calcd. for $C_{12}H_{10}S$: S, 17.21. Found: S, 17.12, 17.05.

Removal of the solvent from the dried ether layer yielded 13.3 g. of liquid which solidified on standing; m.p. 55–70°. Steam distillation and purification of the materials by customary procedures gave a total yield of biphenyl melting at 66–68° of 3.3 g. (21.4%) and a total recovery of dibenzothiophene melting at 96–98° of 9.0 g. (48.8%). Based on the amount of bibenzothiophene which actually reacted, the yield of *o*-mercaptobiphenyl was 35.8%, and the yield of biphenyl was 41.8%.

Run III.—A stirred suspension of 18.4 g. (0.1 mole) of dibenzothiophene in 150 ml. of ether and 1.75 g. (0.25 g. atom) of lithium was refluxed for 36 hours. Color Test I was negative throughout. Carbonation, hydrolysis and acidification yielded no acidic material. Removal of the solvent from the dried ether layer resulted in a 95.1% recovery of dibenzothiophene; m.p. and mixed 98–99°. A check run gave essentially the same results.

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[12] Mr. K. Oita has observed that 1% sodium hydroxide is apparently more effective than a 5% solution for extracting 2-chloro-4-(or 6-) hydroxydibenzofuran.

[13] An authentic sample of 3,4-benzocoumarin was prepared in 18.7% yield by the procedure of reference 7. Cahn reports a m.p. of 94–95° and yields of 20–22%.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND CHEMISTRY, VANDERBILT UNIVERSITY]

Alkylated Derivatives of Ethyl *t*-Butylmalonate and the Corresponding Barbituric Acids[1,2]

BY MILTON T. BUSH AND WM. DUDLEY BEAUCHAMP[3]

RECEIVED APRIL 14, 1952

Methyl, ethyl and allyl groups have been introduced into ethyl *t*-butylmalonate. The 5-methyl-5-*t*-butyl- and 5-allyl-5-*t*-butylbarbituric acids were prepared from these esters in small yields by condensation with urea. The latter barbituric acid was prepared also (in much better yield) from *t*-butylbarbituric acid and allyl bromide. 5-Ethyl-5-*t*-butylbarbituric acid was obtained in impure form. The anesthetic activities were compared with a known standard (amytal).

The 5,5-dialkyl barbituric acids in which one of the substituents is a *t*-butyl or other tertiary group have apparently not been described in pure form. This is due primarily to the difficulty of synthesis of the corresponding disubstituted malonic esters, which previously has been accomplished, if at all, in yields too small to allow satisfactory characterization of the products.[4,5] Secondarily, certain of the pure *t*-butyl-alkyl-malonic esters condense with urea only very slowly (as we have found), which makes the preparation of the barbituric acids still more difficult.

After the synthesis in relatively good yields of *t*-butylmalonic acid[6] it was hoped that substitution of a second alkyl group, despite the marked hindrance, could be made satisfactorily in the corresponding ester. The preparation in moderately good yields of the allyl, ethyl and methyl derivatives has now been carried out by appropriate modifications of the usual methods. It is the purpose of this report to describe these preparations, and also those of the corresponding barbituric acids.

The condensation of the esters with urea by the usual procedure has yielded minute amounts of 5-allyl-5-*t*-butyl- and of 5-ethyl-5-*t*-butylbarbituric acid, and considerably larger amounts of the 5-methyl derivative. Only the first and last of these have been obtained pure, but the ethyl deriva-

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[1] Supported in large part by the Mallinckrodt Chemical Works.

[2] Presented at the XIIth International Congress of Pure and Applied Chemistry, New York, New York, September 10 to 13, 1951.

[3] Taken in part from the Ph.D. thesis of Wm. Dudley Beauchamp, August, 1952.

[4] A. W. Dox and W. G. Bywater, THIS JOURNAL, **58**, 731 (1936).

[5] F. C. Whitmore, private communication (1938).

[6] M. T. Bush, THIS JOURNAL, **61**, 637 (1939); U. S. Patent 2,260,800.