lized from absolute ethanol to give the spirobarbituric acid XVI (0.19 g., 14%), m.p. 222–223°.

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 63.35; H, 5.88; N, 12.12.

λ_{max}^{nujol}: 5.6 μ (strong), 5.66 μ (strong), 5.9 μ (strong). The n.m.r. spectrum was satisfactory.

Acknowledgment.—This research was supported in part by a grant (MY-3930) from the National Institutes of Health, U. S. Public Health Service. We are thankful to Dr. E. R. Malinowski and Paul H. Weiner[1] for the n.m.r. data.

The Synthesis of 5-Diphenylmethylene-2(5*H*)-thiophenone and Related Compounds[1,2]

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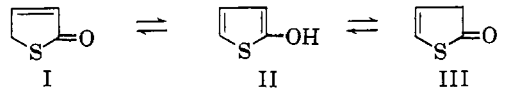
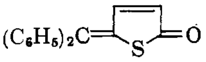
A general reaction leading to 5-substituted methylene-2(5*H*)-thiophenones is described. The mechanism, scope, and limitations of the reaction are discussed.

A number of 2(5*H*)-thiophenone derivatives have been reported[4]; they have been produced, for the most part, by ring closure methods leading to substituted thiolactone–thienol systems,[5] although two compounds possessing this structure have been reported as stemming from reactions involving 2-methoxythiophene.[6] The related compound, 2-thienol, II, has been prepared and characterized by Hurd and Kreuz[7]; evidence was also obtained indicating the existence of the tautomer 2(5*H*)-thiophenone, I, and possibly 2(3*H*)-thiophenone, III.



I II III

During the course of some work directed toward the preparation of potential antimetabolites of the estrogens, an attempt was made to prepare a 2-methoxythienyl analog of triphenyl carbinol through the reaction of benzophenone with 5-methoxy-2-thienyllithium. Instead of the expected carbinol, 5-diphenylmethylene-2(5*H*)-thiophenone, IV, was obtained in 72% yield.



IV

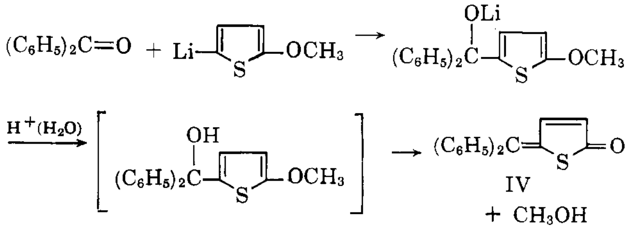
It was found on further study that the reaction is general and leads to 5-diarylmethylene-2(5*H*)-thiophenones in good yield; the corresponding 5-dialkylmethylene and 5-alkarylmethylene derivatives are also accessible but in poorer yield.

The key reactant in our procedure was 2-methoxythiophene which was first characterized by Hurd and Kreuz[7]; it was not until the work of Sicé, however, that this thiophene derivative became readily available.[8] Using the latter method with minor modifications, it was possible to convert thiophene by way of 2-iodothiophene to 2-methoxythiophene in 69% yield. The reaction of 2-methoxythiophene with either phenyl or, more conveniently, with *n*-butyllithium produced the reagent, 5-methoxy-2-thienyllithium.

When benzophenone was treated with the lithium reagent followed by hydrolysis, a bright yellow crystalline product melting at 112° was obtained. This compound failed to show either the expected hydroxyl absorption in the vicinity of 3560 cm.$^{-1}$ or absorption at 1205 cm.$^{-1}$ which is characteristic of the 2-methoxythienyl group; it did absorb strongly, however, at 1675 cm.$^{-1}$ which is consistent with an α,β-unsaturated thiolactone structure.[7] The ultraviolet spectrum was consistent with a highly conjugated carbonyl system, exhibiting bands at 251.5 and 358 mμ (Fig. 1). An analysis of the compound indicated the formula, $C_{17}H_{12}OS$, and oxidation of the compound with potassium permanganate in acetone produced benzophenone. All of the experimental observations are consistent with the structure of 5-diphenylmethylene-2(5*H*)-thiophenone, IV.

Although spectral evidence was never obtained for an intermediate carbinol stage in the case of the benzophenone reaction, even when the hydrolysis step was carried out in cold water, hydroxyl absorption was observed in subsequent runs with other carbonyl compounds, and it seems probable that the initial reaction of the lithium reagent occurs normally to first form the lithium salt of the carbinol.

The over-all reaction with benzophenone may be represented by the following equation.



Although a study of the demethylation rearrangement mechanism is still under way, it now seems probable that a resonance stabilized carbonium ion, V, is in-

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[1] This investigation was supported by a research grant, T-114, from the American Cancer Society and a grant, A-3388, from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

[2] Presented in part at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

[3] Department of Chemistry, University of Washington, Seattle, Wash.

[4] Although compounds of this type are indexed by *Chemical Abstracts* as thiolactones of the corresponding acids, they are cross indexed as 2(5*H*)-thiophenones; for convenience, the latter names are used here. These compounds may also be named as substituted 3-thiolen-2-ones and 3-thiacyclopenten-5-ones, although these two methods of naming have not gained general acceptance.

[5] P. Friedlander and V. Kielbasinski, *Ber.*, **45**, 3389 (1912); H. Paal, *ibid.*, **19**, 556 (1886). For a general discussion of thiolactone–thienol tautomerism see H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 292.

[6] W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **77**, 3529 (1955).

[7] C. D. Hurd and K. L. Kreuz, *ibid.*, **72**, 5543 (1950).

[8] J. Sicé, *ibid.*, **75**, 3697 (1953).

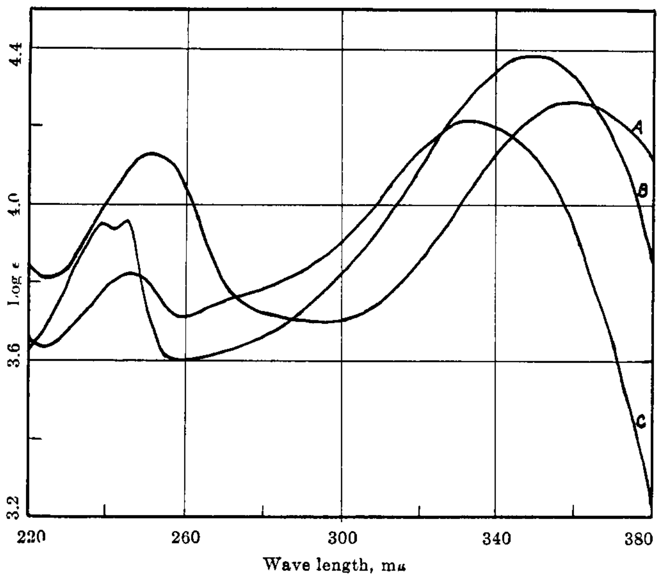
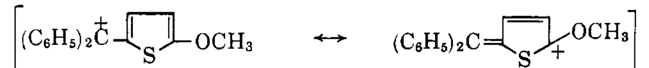


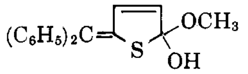
Fig. 1.—Ultraviolet absorption spectra: A, 5-diphenylmethylene-2(5*H*)-thiophenone, IV; B, 5-benzylidene-2(5*H*)-thiophenone, IX; C, 5-(1-phenyl-1-ethylidene)-2(5*H*)-thiophenone, VIII. All spectra determined in 95% ethanol.



V

volved which arises from the carbinol after coördination with a proton and loss of water.

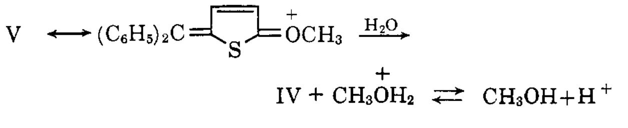
Evidence has been obtained which indicates that the reaction does not necessarily proceed by way of an intermediate of type VI,



VI

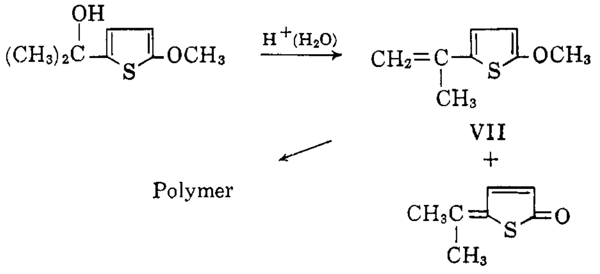
although this route was at first attractive; hydrolysis of the lithium complex in O^{18} enriched water followed by mass spectrometric analysis of the resulting 2-thiophenone failed to show any significant increase in O^{18} content of the product. An enrichment of O^{18} might be expected to result upon elimination of methanol from intermediate VI formed in O^{18} enriched water.

An alternate mechanism, consistent with accepted views on cleavage of ether,[9] would involve displacement of the methyl group by a water molecule and formation of the carbonyl group.[10]

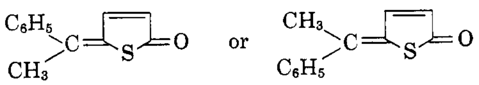


When 9-fluorenone was treated with 5-methoxy-2-thienyllithium followed by hydrolysis with dilute acid, a crystalline thiophenone was obtained in 57% yield. Attempts to carry out the reaction with *p,p'*-dimethoxybenzophenone failed however, perhaps because of the inhibitory resonance effect of the methoxyl groups coupled with the insolubility of the ketone in the ether medium. The desired reaction did occur with 9-anthrone, as shown by the infrared spectrum; however, efforts to obtain a crystalline product were unsuccessful.

The reaction of acetone with the lithium reagent followed by acid hydrolysis led to an acetone-free reaction product, which exhibited two strong absorption bands, one at 1725 cm.$^{-1}$ and the other in the thiophenone region of 1675 cm.$^{-1}$. Distillation of the reaction mixture under reduced pressure led to only a trace of the thiolactone; the nonvolatile residue was a viscous polymeric substance. From our observations it seems probable that normal dehydration of the intermediate carbinol occurred to a greater degree than demethylation and rearrangement, which would result in the thiophenone. The absorption in the 1725 cm.$^{-1}$ region may be caused by the dehydration product, VII, which upon heating readily polymerizes.



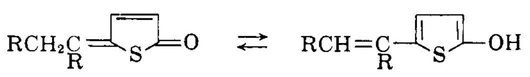
The reaction of acetophenone with 5-methoxy-2-thienyllithium followed by acid hydrolysis led to a product resembling the acetone reaction product, and again it is probable that normal dehydration of the intermediate carbinol occurred to an appreciable degree. Extensive chromatographic analysis of the acetophenone product on silica did finally produce the crystalline 5-(1-phenyl-1-ethylidene)-2(5*H*)-thiophenone, VIII, in 11% yield. Since this product resulted from an unsymmetrical ketone, it should exist in two geometrical forms:



VIII

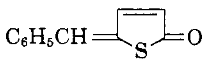
Although samples with two different melting points have been observed, it has not been conclusively shown that they are the predicted isomers.

It may be noted that a 2-(5*H*)-thiophenone resulting from a ketone possessing an α-hydrogen might conceivably exist in tautomeric equilibrium with an enol form.

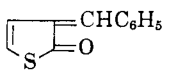


In the work done so far, no spectral or chemical evidence of a 2-thienol component was obtained.

A characteristic reaction of a thiophenone possessing an active methylene group is condensation with benzaldehyde to form a benzylidene derivative.[5] Hurd and Kreuz isolated a benzylidene derivative, either IX



IX



X

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[9] R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954).

[10] The synthesis of α,β-unsaturated ketones from enol ethers has been reported by H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953); R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950); and J. P. Blanchard and H. L. Goering, *ibid.*, **73**, 5863 (1951).

or X, m.p. 97°, from their tautomeric 2-thienol—2(5*H*)-thiophenone—2(3*H*)-thiophenone system.[7]

Utilization of the demethylation–rearrangement reaction has now established the structure of their benzylidene derivative and has at the same time lent support to the α,β-unsaturated thiolactone structure of the compounds prepared by our method.

When benzaldehyde was treated with 5-methoxy-2-thienyllithium, followed by acidic hydrolysis, a benzylidene derivative was obtained which was identical in every respect with the condensation product of Hurd and Kreuz, thus establishing the structure of their product to be the 5-benzylidene derivative, IX, rather than the 3-benzylidene derivative, X.

It is of interest to note that although hydroxyl absorption was never observed in the case of the benzophenone reaction product, and thiolactone formation occurred readily even when water was used in the hydrolysis–demethylation step, the products from dialkyl or alkaryl ketones gave absorption evidence of relatively stable carbinol intermediates. Retreatment with dilute acid was usually required to effect complete demethylation and conversion to the thiolactone structure. The benzaldehyde reaction product in particular was stable toward acidic hydrolysis, and because of the relatively drastic conditions required for rearrangement, considerable amounts of resinous by-product resulted and the yield of benzylidene derivative was correspondingly low.

Experimental[11,12]

2-Iodothiophene.—The procedure of Lew and Noller[13] was modified in one important respect. Several milliliters of nitric acid was first added to the reaction flask before adding thiophene and iodine. The remainder of the nitric acid was then added according to the described procedure. When nitric acid was initially added, the iodination proceeded smoothly, even on a large scale, in 85% yield; failure to add nitric acid first resulted in uncontrolled reactions on several occasions and the formation of resinous material.

5-Diphenylmethylene-2(5*H*)-thiophenone (IV).—To a dry 125-ml. three-necked flask fitted with a mechanical stirrer, dropping funnel, and drying tube was added 25 ml. of 0.61 *N* (0.0152 mole) freshly prepared phenyllithium ether solution. Through the dropping funnel was rapidly added 1.81 g. (0.0159 mole) of 2-methoxythiophene (obtained in 65–80% yield[8]), and the solution was stirred for 45 min. at room temperature; after *ca.* 20 min. the solution turned yellow. A solution of 2.76 g. (0.0152 mole) of benzophenone in 15 ml. of anhydrous ether was then added slowly with stirring. A white precipitate began to form immediately. After the addition of the benzophenone solution was complete, the mixture was stirred for 0.5 hr. at room temperature, after which time it was hydrolyzed with ice-cold 1 *N* hydrochloric acid and then extracted with three portions of ether. The ether solution was washed with several portions of water and then dried over anhydrous sodium sulfate. Removal of the ether left an oil which crystallized from methanol to give in a single crop 3.20 g. (72.0%), m.p. 100–107°, of the yellow thiolactone. Several recrystallizations from methanol produced an analytical sample, m.p. 111.5–112.0°.

Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.24; H, 4.58. Found: C, 77.14; H, 4.34.

In a subsequent run *n*-butyllithium in hexane[14] was used instead of phenyllithium and the resulting lithium complex was hydrolyzed with cold water. The thiolactone was obtained directly in 69.0% yield; infrared absorption at 1675 cm.$^{-1}$ (α,β-unsaturated thiolactone), none at 3560 cm.$^{-1}$ (hydroxyl) or 1205 cm.$^{-1}$ (2-methoxythienyl); $\lambda_{\max}$ (Fig. 1) 251.5 mμ (log ϵ 4.13) and 358 mμ (log ϵ 4.26).

When 100 mg. of benzophenone was treated in the previously described manner with the 5-methoxy-2-thienyllithium reagent and the intermediate lithium salt hydrolyzed with 2 ml. of 1.7% O^{18} enriched 1 *N* hydrochloric acid, a sample of the α,β-unsaturated thiolactone obtained was subjected to *mass spectrometric* analysis.[15] Ionization of the sample at 8 volts avoided fragmentation, leaving a group of peaks representing the different isotopic species in the parent molecule. The most abundant ion (M/e 264) was $C_{17}{}^{12}H_{12}{}^{1}O^{16}S^{32}$; the peak at 266 was due primarily to $C_{17}{}^{12}H_{12}{}^{1}O^{16}S^{34}$ but also, in part, to the ion, $C_{17}{}^{12}H_{12}{}^{1}O^{18}S^{32}$. No significant increase in the height of the 266 peak was observed for the thiolactone, IV, prepared in the presence of O^{18}-enriched water, when compared with the same peak produced by the untreated thiolactone.

Oxidation of 5-Diphenylmethylene-2(5*H*)-thiophenone.—To a 250-ml. three-necked flask fitted with a mechanical stirrer, reflux condenser, and dropping funnel was added 1.00 g., of the thiolactone in 50 ml. of acetone. Through the dropping funnel was slowly added 30 ml. of 10% potassium permanganate solution, while the mixture was cooled in an ice bath. After the addition was complete, the reaction was stirred for 15 hr. at room temperature. The excess potassium permanganate was then reduced by adding portions of 10% sodium bisulfite solution until the purple color no longer persisted. After removal of the acetone and dilution with water, the mixture was acidified and extracted with two portions of ether. The ether solution was successively washed with water, 5% potassium hydroxide solution, and water, and then dried over anhydrous sodium sulphate. Removal of the ether left a semisolid product which was recrystallized from petroleum ether–ethanol to give 0.138 g. (20%) of benzophenone, m.p. 47–47.5°. A mixed melting point determination with an authentic sample of benzophenone gave no depression.

5-(9-Fluorenylidene)-2(5*H*)-thiophenone.—The 5-methoxy-2-thienyllithium reagent prepared from 2.09 g. (0.0183 mole) of 2-methoxythiophene in 15 ml. of anhydrous ether and 10.0 ml. of *n*-butyllithium-hexane solution (0.0166 mole) was added dropwise with rapid stirring to a solution of 3.00 g. (0.0166 mole) of 9-fluorenone dissolved in 125 ml. of anhydrous ether and 50 ml. of benzene. Stirring was continued for 1 hr. after the addition was completed, and the resulting fluorescent yellow suspension was poured into water and allowed to stand overnight. After separation of the ether solution and further extraction of the water layer, the combined ether extract was dried and the ether removed. An infrared examination indicated the presence of unrearranged carbinol, absorption at 3560 cm.$^{-1}$ (hydroxyl) and 1205 cm.$^{-1}$ (2-methoxythienyl), as well as starting ketone, 1715 cm.$^{-1}$, and some α,β-unsaturated thiolactone, 1675 cm.$^{-1}$. The product was then dissolved in enough methanol–ether to preserve homogeneity, and 20 ml. of 1 *N* hydrochloric acid was added; the solution was warmed on the steam bath for 10 min. and the solution cooled, extracted with ether, and the ether layer washed successively with water, dilute sodium bicarbonate solution, and water. After drying, the ether was removed. Absorption in the infrared region, 1675 cm.$^{-1}$, indicated that the α,β-unsaturated thiolactone was the principal component although evidence of starting ketone remained. The thiolactone crystallized from benzene–petroleum ether in three crops as yellow needles, 2.52 g. (57.7%), m.p. 165–169°. Several recrystallizations produced an analytical sample, m.p. 169.2–169.7°.

Anal. Calcd. for $C_{17}H_{10}OS$: C, 77.83; H, 3.84. Found: C, 77.51; H, 3.92.

In another run the lithium reagent was added to the ketone at reflux temperature, but no improvement in the yield was observed.

5-(1-Phenyl-1-ethylidene)-2(5*H*)-thiophenone, VIII.—To the 5-methoxy-2-thienyllithium reagent, prepared from 0.0158 mole (25 ml., 0.632 *N*) of phenyllithium and 1.89 g. (0.0166 mole) of 2-methoxythiophene, was added slowly with stirring 1.90 g. (0.0150 mole) of redistilled acetophenone in 15 ml. of dry ether. The mixture remained homogeneous but became bright orange in

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(11) Melting points of analytical samples were determined by means of the Hershberg apparatus; Anschütz total immersion thermometers were used.

(12) Infrared spectra were determined on a Beckman IR-5 spectrophotometer using carbon disulfide as solvent. Ultraviolet spectra were obtained by means of a Beckman DK-2 spectrophotometer; 95% ethanol was the solvent.

(13) H. Y. Lew and C. R. Noller, *Org. Syntheses*, **30**, 53 (1950).

(14) A 15% solution of *n*-butyllithium in hexane was obtained from the Foote Mineral Co., Philadelphia 44, Pa.

(15) The mass spectrometric analysis was conducted in the laboratories of the California Research Corporation by Dr. R. M. Teeter.

color as stirring was continued for 0.5 hr. at room temperature. The reaction mixture was hydrolyzed by pouring into cold 1 *N* hydrochloric acid solution. Extraction of the product with ether followed by washing with water and then drying the ether layer led, upon evaporation of the ether, to a brown oily product which was only partially rearranged to the thiolactone; absorption at 1675 cm.$^{-1}$ (α,β-unsaturated thiolactone), 1205 cm.$^{-1}$ (2-methoxythienyl), and 3560 cm.$^{-1}$ (hydroxyl). Retreatment of the product with 2 ml. of 1 *N* hydrochloric acid and enough methanol to maintain homogeneity, followed by warming led to a product which lacked methoxyl and hydroxyl absorption but exhibited a strong band at 1675 cm.$^{-1}$ characteristic of the α,β-unsaturated thiolactone.

Chromatographic separation on silica using petroleum ether (30–60°), benzene, and ether for elution produced several fractions (benzene eluate) which crystallized from methanol in several crops to give 0.33 g. (11%) of the yellow thiolactone, m.p. 78–86°. Several recrystallizations from methanol produced an analytical sample, m.p. 87–88°.

Anal. Calcd. for $C_{12}H_{10}OS$: C, 71.26; H, 4.98. Found: C, 71.11; H, 5.08.

In addition to absorption in the infrared region at 1675 cm.$^{-1}$ the compound absorbed in the ultraviolet at 246 mμ (log ϵ 3.82) and 333 mμ (log ϵ 4.21).

One of the last fractions from the column produced a trace of crystalline material which melted at 108–114°; further characterization of this product was not attempted.

5-Benzylidene-2(5*H*)-thiophenone, IX.—To 5.00 g. (0.047 mole) of redistilled benzaldehyde in 30 ml. of anhydrous ether was added dropwise with stirring 70 ml. of a solution of 5-methoxy-2-thienyllithium prepared from 5.91 g. (0.0518 mole) of 2-methoxythiophene and 0.047 mole of phenyllithium by the method previously described. The mixture was stirred for 1 hr. after the addition was complete and then poured into 1 *N* hydrochloric acid and vigorously stirred. The product was extracted with several portions of ether, and the combined ether layer was then washed successively with water, dilute sodium bicarbonate solution, and water and dried over anhydrous sodium sulfate. Removal of the ether left an oily product; infrared absorption at 3560 cm.$^{-1}$ (hydroxyl), 1205 cm.$^{-1}$ (2-methoxythienyl), and 1675 cm.$^{-1}$ (α,β-unsaturated thiolactone). The oil was diluted with 50 ml. of methanol and 10 ml. of 1 *N* hydrochloric acid, and the solution was then warmed on the steam bath for 5 min. The product obtained partially crystallized from ethanol to give 1.50 g. (17%) of the yellow benzylidene derivative, m.p. 94–97°. Further recrystallization from ethanol produced an analytical sample, m.p. 97.5–98.5°.

Anal. Calcd. for $C_{11}H_8OS$: C, 70.18; H, 4.28. Found: C, 70.21; H, 4.19.

The melting point was not depressed when the compound was mixed with a sample of the benzylidene derivative prepared by Hurd and Kreuz.[7,16] The infrared spectrum exhibited a band at 1675 cm.$^{-1}$ (α,β-unsaturated thiolactone) and none at 3560 cm.$^{-1}$ and 1250 cm.$^{-1}$ (hydroxyl and 2-methoxythienyl groups, respectively); λ_{max} (Fig. 1) 238 mμ (log ϵ 3.95), 245 mμ (log ϵ 3.96) and 350 mμ (log ϵ 4.39).

Acknowledgment.—The authors wish to thank Henri Arzoumanian and Curtis Diebert for their help in the preparative work. We are especially grateful to Dr. R. M. Teeter for his interpretation of the mass spectrometric analysis and to Dr. Donald S. Noyce for helpful correspondence concerning the mechanism of the reaction.

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[16] The sample was generously furnished by Dr. C. D. Hurd of Northwestern University.

Preparation of 1-Aminobenzimidazoles

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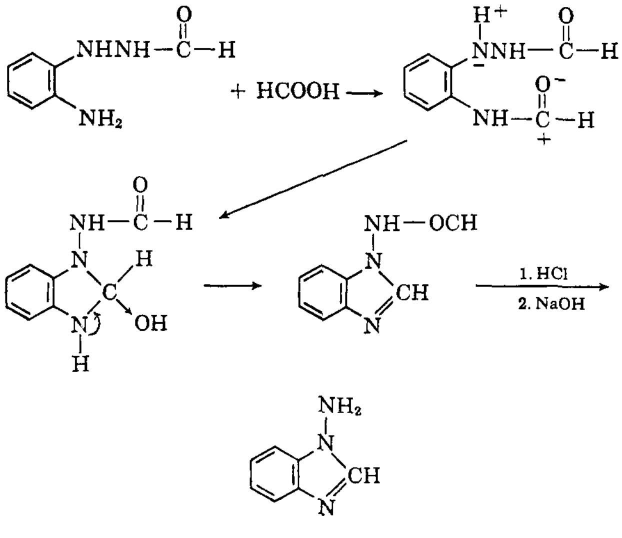
Received February 21, 1962

A method has been developed for the syntheses of a number of 1-aminobenzimidazoles. Some of the characteristic reactions of 1-aminobenzimidazole are reported.

The first attempt to prepare 1-aminobenzimidazoles was reported by Ried and Urlass.[1] They prepared 1-nitrosobenzimidazole and 1-nitroso-2-methylbenzimidazole. The compounds were isolated only as their dihydrates. They attempted to reduce these compounds with zinc and acetic acid in methanol solution but recovered only benzimidazole and 3-methylbenzimidazole as products. The reduction of a number of N-nitroso compounds, with lithium aluminum hydride, to the corresponding hydrazines has been reported.[2] In the current work, attempts to reduce 1-nitrosobenzimidazole and 1-nitroso-2-methylbenzimidazole, with lithium aluminum hydride, gave only the hydrogenolysis products.

Abramovitch and Schofield[3] reported that *o*-formhydrazidoaniline was converted to 1-aminobenzimidazole when refluxed with a slightly acidified aqueous solution of sodium *m*-nitrobenzenesulfonate. However, when the formhydrazidoaniline was heated with 4 *N* hydrochloric acid, 1,2,4-benzotriazine was formed (10–20% yields) after oxidation with potassium ferricyanide.[3] In the present study, attempts to repeat the preparation of 1-aminobenzimidazole gave only low yields. A modified method was finally found which gave good results. When the formyl derivative was refluxed in 98% formic acid, an almost quantitative yield of 1-formamidobenzimidazole was obtained. The latter was then converted to 1-aminobenzimidazole



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[1] W. Ried and G. Urlass, *Ber.*, **86**, 1101 (1953).

[2] C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Am. Chem. Soc.*, **79**, 6430 (1957); C. Hanna and F. W. Schueler, *ibid.*, **74**, 3693 (1952).

[3] R. A. Abramovitch and K. Schofield, *J. Chem. Soc.*, 2326 (1955).