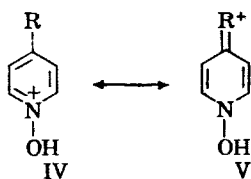


and Katritzky<sup>8</sup> also permit the calculation of  $\sigma^+$ -values for two new groups:  $-\text{NHCH}_3$ ,  $\sigma^+ = -1.59$ ;  $-\text{OCH}_2\text{C}_6\text{H}_5$ ,  $\sigma^+ = -0.616$ .

The basicities of the substituted pyridine-1-oxides are the first reaction series on record which, in the Hammett treatment, require the use of both  $\sigma^+$ - and  $\sigma^-$ -values. A slightly more detailed discussion seems indicated. Although it was originally suggested that  $\sigma^-$ -values were applicable to all reactions of anilines and phenols, evidence now appears to accumulate<sup>9</sup> that the requirement is an appreciable *difference* in conjugation of substituent and reaction site between initial and final (in the case of equilibria) or transition state (in the case of rates). Such a difference in conjugation between initial and final states obviously exists for electron releasing X, since it is impossible to write a plausible quinoid structure analogous to II for the conjugate acids. In the case of electron withdrawing X, however, it is suggested that the resonance  $\text{IV} \leftrightarrow \text{V}$  is sufficiently more important than  $\text{I} \leftrightarrow \text{III}$  to require use of  $\sigma^+$ -values.



In our previous paper<sup>2b</sup> we conclude that the tautomeric equilibria between 4-hydroxypyridine-1-oxide and 1-hydroxy-4-pyridone, and between 4-aminopyridine-1-oxide and 1-hydroxy-4-pyridone imine were overwhelmingly in favor of the pyridine rather than the pyridone structure. This conclusion was based on the estimation of the intrinsic basicities of the two pyridine structures by the Hammett equation, using standard  $\sigma$ -values, which lead to  $pK$ 's for the conjugate acids appreciably *smaller* than the observed values, while in a tautomeric equilibrium of the type under investigation (single acid, tautomeric bases) the observed  $pK$  must be *at least as low* as the *lower* of tautomers. We doubted that the intrinsic  $pK$ 's could have been underestimated by *more* than the discrepancy found.

Gardner and Katritzky<sup>8</sup> have examined the same tautomeric equilibria, and have confirmed our conclusion concerning 4-aminopyridine-1-oxide. They have used the  $pK$ 's of 4-methoxypyridine-1-oxide ( $pK = 2.04$ ) and of 1-methoxy-4-pyridone ( $pK = 2.57$ ) and of the corresponding benzyl derivatives ( $pK = 1.99$  and  $2.58$ , respectively) to estimate the intrinsic basicities of the corresponding hydroxy compounds. These authors found themselves in the same dilemma as we had, since the 4-alkoxy compounds were weaker bases (their conjugate acids stronger acids) by 0.4–0.5 units than the hydroxy compound while the 1-alkoxy-4-pyridones were slightly stronger bases. From these data the

(9) R. W. Taft, Jr., private communication.

authors conclude (rather unconvincingly) that 4-hydroxypyridine-1-oxide must exist as an equilibrium mixture of roughly comparable quantities of the pyridine and pyridone forms. Examination of Fig. 1 shows that the point for 4-hydroxypyridine-1-oxide lies well on the best straight line. Calculations indicate that omission of this datum does not improve the correlation with  $\sigma$ . The inherent accuracy of the Hammett equation is insufficient to accurately evaluate the tautomeric equilibrium constant, or to categorically state that the pyridone form makes no substantial contribution to the tautomeric equilibrium. However, the data lend no support to Gardner and Katritzky's thesis of an *important* contribution from the pyridone structure, but are best interpreted as indicating an equilibrium predominantly in favor of the pyridine form, in agreement with our theoretical calculations.<sup>10</sup>

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(10) H. H. Jaffé, *J. Am. Chem. Soc.*, **77**, 4448 (1955).

### Metalation of 1-Methylbenzimidazole with *n*-Butyllithium

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The reaction of 1-methyl-2-*t*-butylbenzimidazole with organolithium reagents has been reported<sup>1</sup> to involve addition across the azomethine linkage. Benzothiazole undergoes either metalation in the 2-position or addition across the azomethine linkage, depending upon the reaction temperature.<sup>2,3</sup> Benzoxazole apparently gives no metalation product with *n*-butyllithium.<sup>3</sup>

Treatment of 1-methylbenzimidazole with *n*-butyllithium at  $-60^\circ$ , followed by carbonation, gave 1-methyl-2-benzimidazolecarboxylic acid in 45% yield. The high water solubility of the acid product, prepared previously from the reaction of glyoxylic acid and *N*-methyl-*o*-phenylenediamine,<sup>4</sup> prevented the quantitative isolation of the acid by precipitation with mineral acid from the aqueous layer of the carbonation mixture. A portion of the product was isolated in this manner, but the remainder was obtained as its water insoluble copper (II) complex. This complex is similar to the one

(1) R. C. Elderfield and V. B. Meyer, *J. Am. Chem. Soc.*, **76**, 1891 (1954).

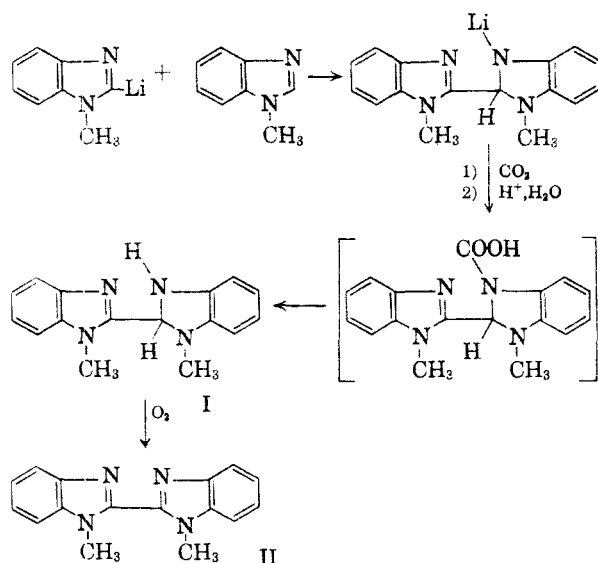
(2) H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, **71**, 2328 (1949).

(3) J. A. Beel, Doctoral Dissertation, Iowa State College, 1949; *Iowa State Coll. J. of Sci.*, **25**, 161 (1951).

(4) E. H. Usherwood and M. A. Whitely, *J. Chem. Soc.*, 123, 1069 (1923).

formed by 1-methyl-2-imidazolecarboxylic acid.<sup>5</sup> 1-Methyl-2-benzimidazolecarboxylic acid melts with decomposition and evolution of carbon dioxide forming 1-methylbenzimidazole.

When 1-methylbenzimidazole was metalated at room temperature with an excess of *n*-butyllithium, only a trace of acid product was isolated following carbonation. Instead, a mixture of 1,1'-dimethyl-2,3-dihydro-2,2'-bibenzimidazole, I, (m.p. 139–140°) and 1,1'-dimethyl-2,2'-bibenzimidazole, II (m.p. 213–214°), was obtained in total yield of 53.5%. The lower melting material could be converted to the higher by air oxidation. These products apparently arose by initial metalation of 1-methylbenzimidazole followed by addition of 1-methyl-2-lithiobenzimidazole to another molecule of 1-methylbenzimidazole. On acidification, the carbamic acid type decarboxylated to the products as shown in the figure.



#### EXPERIMENTAL<sup>6</sup>

The following procedure for the preparation of 1-methylbenzimidazole was better in our hands than the reported methods of methylation of benzimidazole.<sup>7,8</sup>

**1-Methylbenzimidazole.** Benzimidazole (17.5 g., 0.15 mole) moistened with 20 ml. of dry ether was cautiously added to a stirred solution of 3.8 g. of sodium and 0.15 g. of ferric nitrate in 200 ml. of liquid ammonia. The resulting solution was stirred for 15 min. and methyl iodide (24 g.) was added dropwise. The ammonia was allowed to evaporate and 50 ml. of water was added to the residue. The aqueous solution was extracted continuously overnight with ether. The ether was evaporated and the residue dried by distilling benzene from it. The product was fractionally distilled twice *in vacuo*, and 1-methylbenzimidazole was obtained as a colorless solid, b.p. 99–102°/0.5 mm., m.p. 60–61°. The

yield of product was 8.0 g. or 40.5%. 1-Methylbenzimidazole is reported to melt at 66°.<sup>9</sup>

**Low temperature metalation of 1-methylbenzimidazole.** To a solution of 1-methylbenzimidazole (4.3 g., 0.0325 mole) in 130 ml. of dry ether was added at –60° a solution of 0.036 mole of *n*-butyllithium in 40 ml. of ether. The resulting solution was stirred with continued cooling for 3 hr., and the resulting colorless solution was carbonated. The carbonation mixture was hydrolyzed with 50 ml. of water. The ether layer was separated and washed with additional water. The combined aqueous layers were cooled in an ice salt bath and carefully acidified with concentrated hydrochloric acid. The white solid which formed was collected by filtration and dried. The product weighed 1.3 g. A sample of the acid product, after recrystallization from a small amount of water, melted at 93° (dec.). Usherwood and Whitely<sup>4</sup> report the melting point of 1-methyl-2-benzimidazolecarboxylic acid as 98–99° (dec.).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.36; H, 4.58; N, 15.90; Neut. eq. 176. Found: C, 60.94, 61.01; H, 4.64, 4.62; N, 16.30, 16.30; Neut. eq. 182.

The filtrate from the 1.3 g. of crude acid product was treated with a concentrated solution of copper sulfate. A light blue water-insoluble powder separated which, after careful washing and drying, weighed 1.70 g.

*Anal.* Calcd. for C<sub>18</sub>H<sub>14</sub>CuN<sub>4</sub>O<sub>4</sub>: C, 52.32; H, 3.41; N, 13.54. Found: C, 52.30; H, 3.27; N, 13.50.

The yield of 1-methyl-2-benzimidazolecarboxylic acid from the acid precipitation and the copper (II) complex was 45%.

**Room temperature metalation of 1-methylbenzimidazole.** 1-Methylbenzimidazole (10.9 g., 0.0825 mole) in 50 ml. of dry ether was placed in a flask, and a solution of *n*-butyllithium [prepared from 18.5 g. (0.2 mole) of *n*-butyl chloride and 3.0 g. (0.43 g.-atom) of lithium<sup>9</sup>] was added in a dropwise fashion to the stirred solution. The resulting solution was stirred at room temperature for 2.5 hr. At the end of this period the solution was red and a copious amount of greenish yellow solid was present. This mixture was carbonated with solid carbon dioxide and then hydrolyzed with 50 ml. of water. The yellow ether layer was separated and extracted with three 30-ml. portions of water. The basic aqueous extracts were combined with the aqueous layer and the solution was neutralized. At the neutral point a copious amount of precipitate was present, and acidification was stopped when the solution was only faintly acid. The solid was collected by filtration and dried over phosphorous pentoxide *in vacuo*. The product weighed 5.63 g. and melted from 140° to 210°. By fractional crystallization of a portion of this material from absolute ethanol, two products were obtained. The first fraction was the lower melting material, which after recrystallization from acetone melted at 139–140°. Elemental analysis and molecular weight determination indicated an empirical formula of C<sub>8</sub>H<sub>6</sub>N and a molecular formula of C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>: C, 72.70; H, 6.10; mol. wt. 264. Found: C, 72.80, 72.64; H, 6.13, 5.93; mol. wt. 240 by Rast camphor method.

Elemental analysis of the second fraction, m.p. 213–214°, indicated an empirical formula of C<sub>8</sub>H<sub>7</sub>N<sub>2</sub>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.26; H, 5.16; N, 21.32.

The molar ratio of the lower melting material to the higher melting material was approximately 3:1. Passing oxygen through an acetone solution of the lower melting compound converted it into the higher melting material. The ether layer from the metalation reaction was evaporated and the residue sublimed to produce an additional 0.18 g. of the higher melting product. The lower melting product was assigned structure I, 1,1'-dimethyl-2,3-dihydro-2,2'-bibenzi-

(5) D. A. Shirley and P. W. Alley, *J. Am. Chem. Soc.*, **79**, 4922 (1957).

(6) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Weiler and Strauss, Oxford, England. All melting points are uncorrected.

(7) E. Bamberger and J. Lorenzen, *Ann.* **273**, 269 (1893).

(8) M. A. Phillips, *J. Chem. Soc.*, 1931, 1143.

(9) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932).

midazole, and the higher melting material (II) was designated 1,1'-dimethyl-2,2'-bibenzimidazole. Formation of the bibenzimidazole derivatives occurred in 53.5% yield.

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### Acetylation of Imides with Ketene

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Previous studies, in our laboratories, have involved an extension of the acetylation of alcohols, mercaptans, carboxylic acids, glycols, polyhydroxy compounds, amides, hydrocarbons, nitroparaffins, and carbohydrates, with ketene. All of the above classes of compounds are similar in that they contain activated or readily replaceable hydrogen. Ketene is characterized by its ability to form combinations with such organic substances. Although somewhat toxic and difficult to prepare, it ranks first in reactivity among the common acetylating reagents. The predominating advantage of ketene, as compared to acetic acid, acetyl halides, and acetic anhydride, is the fact that it theoretically produces no objectionable by-products.

Since amides have been found to be readily acetylated with ketene to form monoacetyl derivatives,<sup>1</sup> it seemed highly probable, by analogy, that imides could be similarly acetylated to the corresponding *N*-acetyl derivatives. In addition, several similar reactions have been observed during recent years. Rice and coworkers,<sup>2</sup> for instance, prepared *N*-phenyldiacetylimide by passing ketene into acetanilide at 140°. They suggested that *N*-acetylbenzamide was formed similarly from benzamide at 180°, but that it decomposed into benzonitrile as the reaction progressed. Later, Padgham and Polya<sup>3</sup> isolated *N*-acetylbenzamide and diacetylimide by passing ketene into molten benzamide and acetamide, respectively. The use of sulfuric acid in the production of *N*-phenyldiacetylimide from ketene and molten acetanilide was reported by Smirnova<sup>4</sup> and others, who also reported the preparation of *N*-formyldiacetylimide, and described it as a liquid. Our findings, however, indicate that this triacylated ammonia is a crystalline product.<sup>1</sup> For these reasons it seemed desirable to conduct an extended study of the reaction of ketene with any and all available imides.

The first difficulty encountered in this study was

(1) R. E. Dunbar and Gerald C. White, *J. Org. Chem.*, **23**, 915 (1958).

(2) F. O. Rice, J. Greenberg, C. E. Waters, and R. E. Vollrath, *J. Am. Chem. Soc.*, **56**, 1760 (1934).

(3) D. N. Padgham and J. B. Polya, *Australian J. Sci.*, **13**, 113 (1951).

(4) N. V. Smirnova, A. P. Skoldinov, and K. A. Kocheshkov, *Doklady Akad. Nauk S.S.S.R.*, **84**, 737 (1952).

the selection of a suitable inert solvent. Among those employed were carbon tetrachloride, benzene, ether, ligroin, dioxane, and chloroform. Hot benzene seemed to be the most efficient solvent for the imides, but it also induced excessive polymerization. Dioxane appeared to be a better solvent but could not be readily removed without causing the acetylated imide to decompose. This was probably due to the formation of peroxides while the dioxane was exposed to air. Also, acetylation was extremely slow when this solvent was employed. A suspension of the imide in carbon tetrachloride yielded maximum acetylation with little or no polymerization.

It was found that the imides could not be acetylated when treated with ketene alone. A catalyst was therefore necessary. Concentrated sulfuric acid has been found, by other investigators, to be a very satisfactory catalyst in similar reactions. When concentrated sulfuric acid was used with the imides, however, no acetylation took place. There was no change in the melting point from that of the parent compound, either before or after the attempted acetylation. Fused sodium acetate produced positive results. The compounds which were unaffected by the ketene in previous attempts, acetylated readily with no noticeable by-products when sodium acetate was used. This catalyst was found to be satisfactory with every imide treated.

This work could be valuable from the standpoint of the organic analytical student, because derivatives of imides are as yet little known. The literature is very sketchy concerning imide derivatives, and they are difficult to prepare. The acetyl derivatives of imides have previously been prepared by reaction with acetic anhydride followed by long hours of refluxing to affect a reaction. The yields are low. Attempts to acetylate imides using acetic acid or acetyl halides have been unsuccessful. Ketene will react readily with the imides producing satisfactory yields in a matter of minutes. The gas can be produced satisfactorily on a laboratory scale. Seven imides, namely naphthalimides, 4-nitrophthalimide, pyromellitic diimide, tetrahydrophthalimide, phthalimide, saccharin, and succinimide; and one anilide, namely acetanilide, have been successfully acetylated with ketene for the first time. Of these, the first four were acetylated for the first time by any means. The other four compounds involved in the study have been previously acetylated by using acetic anhydride. The results are summarized in Table I.

### EXPERIMENTAL

The ketene for this study was prepared by the use of a Hurd type "lamp."<sup>5</sup> It was prepared by the pyrolysis of purified acetone. The acetone was vaporized by boiling, and the vapors were passed over an electrically heated wire. It

(5) W. E. Hanford and J. C. Sauer, *Org. Reactions*, **III**, 108 (1946).