Preparation and Reactions of 2,6-Di-*t*-butylpyridine and Related Hindered Bases. A Case of Steric Hindrance toward the Proton[1,2]

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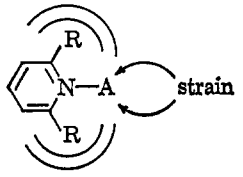
Contribution from the Department of Chemistry, Purdue University, Lafayette, Indiana. *Received September 18, 1965*

Abstract: 2-Ethyl-6-*t*-butyl-, 2-isopropyl-6-*t*-butyl-, and 2,6-di-*t*-butylpyridine were prepared in yields of 50 to 70% by treating 2-*t*-butylpyridine with the appropriate alkyllithium. 2-Methyl-6-*t*-butylpyridine could not be synthesized in this way, the reaction producing a dimeric product tentatively identified as 6,6'-di-*t*-butyl-2,2'-bipyridyl. The desired compound was therefore obtained through a several-step cyclization procedure. 2,6-Diisopropylpyridine was conveniently obtained by the alkylation of 2,6-lutidine. An arithmetical increase in pK_a values is observed in the two series: pyridine, 2-picoline, and 2,6-lutidine, and pyridine, 2-isopropylpyridine, and 2,6-diisopropylpyridine, indicating the absence of any significant steric effects toward the addition of the proton. On the other hand, the series, pyridine, 2-*t*-butylpyridine, and 2,6-di-*t*-butylpyridine, exhibits a marked deviation from linear behavior. 2,6-Di-*t*-butylpyridine is actually 0.8 pK_a unit less basic than pyridine, and is 1.4 pK_a units weaker as a base than the value predicted on the basis of simple additivity, such as is observed in the other series. This decrease in base strength is attributed to steric effects accompanying addition of the proton which are absent in less sterically demanding systems. 2,6-Di-*t*-butylpyridine exhibits unusual chemical characteristics. It fails to react with methyl iodide, even over very long periods of time. It undergoes ready sulfonation to form 2,6-di-*t*-butylpyridine-3-sulfonic acid by treatment with sulfur trioxide in liquid sulfur dioxide (−10°). Under the same conditions, pyridine and 2,6-lutidine form addition compounds but fail to undergo nuclear substitution. Approximate comparison experiments indicate that the reactivity of 2,6-di-*t*-butylpyridine toward such aromatic substitutions is comparable to that of nitrobenzene. It is concluded that the nitrogen atom of the pyridine ring deactivates the ring by an amount comparable to the nitro group in nitrobenzene, but that pyridinium ion formation in the usual electrophilic substitution provides a large additional deactivation.

The effect of steric strain on the relative base strengths of a series of pyridine derivatives was previously investigated by determining the heats of reaction of these bases with a series of reference acids of increasing steric requirements.[5] As is evident from Figure 1, there is observed a regular change in the observed order of base strengths in the series, pyridine, 2-picoline, and 2,6-lutidine, as the steric requirements of the reference acid are increased from H^+ to BH_3 to BF_3 to BMe_3. A similar change in order (Figure 2) has also been observed in the series, pyridine, 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-*t*-butylpyridine.[5] These changes in the apparent base strengths have been attributed to the effect of increasing steric strain accompanying an increase in the steric requirements of the alkyl substituents R and the reference acid A (I).



I

The regular order exhibited by the pK_a values of pyridine (5.17), 2-picoline (5.97), and 2,6-lutidine (6.75) indicates that there is no significant steric effect involving the proton as reference acid.[6] This is supported by the observation that the heats of reaction of these bases with methanesulfonic acid in nitrobenzene solution also increase linearly: ΔH = 17.1, 18.3, and 19.5 kcal/mole, respectively.[7] On the other hand, there is a hint that there may be some steric influence upon the addition of a proton to 2-alkylpyridines in the decreasing pK_a and ΔH values with increasing bulk of the alkyl substituent exhibited by these derivatives (Table I).

Table I. pK_a Values and Heats of Reaction with Methanesulfonic Acid for the 2-Alkylpyridines

Base	pK_a (25°)[a]	$-\Delta H$ (CH_3SO_3H),[b] kcal/mole
2-Picoline	5.97	18.34
2-Ethylpyridine	5.92[c]	18.22
2-Isopropylpyridine	5.83	18.10
2-*t*-Butylpyridine	5.76	18.02

[a] Reference 6. [b] Reference 7. [c] Revised value from the Ph.D. thesis of J. A. Donahue, Purdue University Libraries.

Steric effects accompanying addition of the proton have been suggested as a factor in the ionization constants of *ortho*-substituted aromatic amines and phosphines.[8] For example, in these derivatives it is observed that the introduction of a methyl group into the *meta* and *para* position of aniline (pK_a = 4.58) results in an increase in base strength, in accordance with the inductive influence of the methyl group, while introduction of a methyl group into the *ortho* position has the opposite effect (pK_a = 4.39). Indeed, introduction of a second methyl substituent in the remaining *ortho* position has an even greater effect (pK_a = 3.42).

(1) Chemical Effects of Steric Strains. XVIII.
(2) Based upon a thesis submitted by B. Kanner in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
(3) Research assistant at Purdue University, 1950–1951, on a project supported by the Office of Naval Research.
(4) The Du Pont Company Fellow at Purdue University, 1951–1952.
(5) For a summary with pertinent literature references, see H. C. Brown, D. Gintis, and L. Domash, *J. Am. Chem. Soc.*, 78, 5387 (1956).
(6) H. C. Brown and X. R. Mihm, *ibid.*, 77, 1723 (1955).
(7) H. C. Brown and R. R. Holmes, *ibid.*, 77, 1727 (1955).
(8) H. C. Brown and A. Cahn, *ibid.*, 72, 2939 (1950).

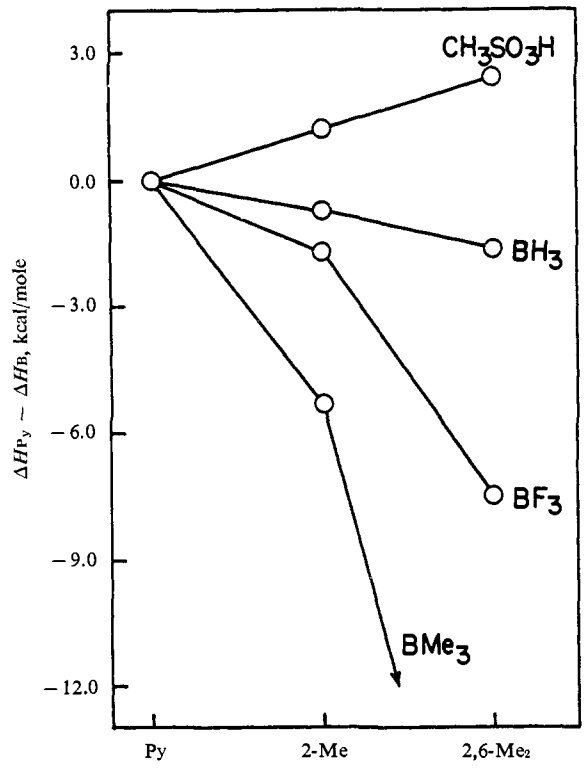


Figure 1. Relative strengths of pyridine, 2-picoline, and 2,6-lutidine with reference acids of increasing steric requirements.

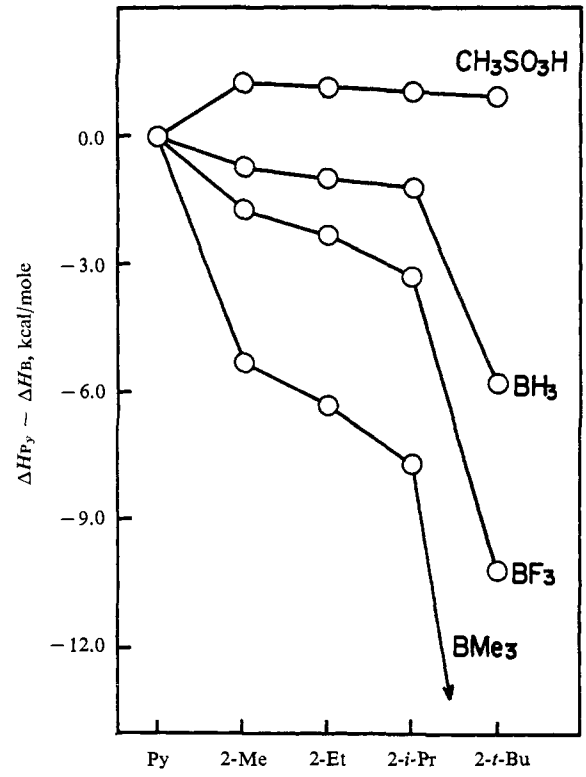
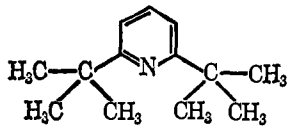


Figure 2. Relative strengths of pyridine and the 2-alkylpyridines with reference acids of increasing steric requirements.

It appeared of interest, therefore, to undertake the synthesis and study of the properties of 2,6-di-*t*-butylpyridine and related bases containing bulky alkyl substituents in the 2,6-positions in order to explore the possibility that such compounds might exhibit in enhanced form the phenomenon of steric hindrance toward addition of the proton to the basic center[9] (II).



II

Results and Discussion

Syntheses. The preparation of 2-*t*-butylpyridine from 2-picoline *via* alkylation with methyl chloride and sodium amide in liquid ammonia[10] suggested that 2,6-di-*t*-butylpyridine might be prepared by the exhaustive alkylation of 2,6-lutidine. Accordingly, 2,6-lutidine was subjected to the alkylation procedure. After four successive alkylations, with large excesses of methyl chloride and sodium amide, the predominant product was a base with a neutralization equivalent of 163. This corresponded either to 2,6-diisopropylpyridine or its isomer, 2-ethyl-6-*t*-butylpyridine. Further alkylation was exceedingly difficult—after three consecutive alkylations less than 5% of the product was converted into 2-isopropyl-6-*t*-butylpyridine (neut equiv 177). Based on the earlier observation[10] that 2-isopropylpyridine undergoes alkylation much more slowly than the corresponding methyl or ethyl derivatives, it appeared reasonable to assign the structure of 2,6-diisopropylpyridine to this relatively inert product.

In a one-step reaction, 2,6-lutidine was converted into this 2,6-diisopropylpyridine in 55% yield by alkylating 2,6-lutidine with a 4:1 mole ratio of methyl chloride and sodium amide to base.

2-Ethyl-6-*t*-butylpyridine was prepared in 46% yield by the reaction of ethyllithium with 2-*t*-butylpyridine. A comparison of the properties (Table II) establishes the nonidentity of the two products and confirms the structural assignment for 2,6-diisopropylpyridine.

The relatively high melting point, 2.5°, may be considered to provide confirmatory evidence. Thus, symmetrical 2,6-dialkylpyridines tend to have much higher melting points (2,6-lutidine, −6.05°; 2,6-di-*t*-butylpyridine, 2.2°) than the unsymmetrical derivatives (2-isopropyl-6-*t*-butylpyridine, −66.0°).

An attempt was made to synthesize 2,6-di-*t*-butylpyridine by treating 2,6-diisopropylpyridine with ethyllithium in ether, to form the carbanion, followed by methyl iodide. However, only a low yield of impure 2-isopropyl-6-*t*-butylpyridine was obtained, so this route was abandoned.

2,6-Di-*t*-butylpyridine was successfully synthesized, finally, by the reaction of *t*-butyllithium[11] with 2-*t*-butylpyridine at −78°. A 67% yield was realized. Although we generally utilized 2-*t*-butylpyridine from the alkylation of 2-picoline, we demonstrated the feasibility of the synthesis through a two-stage, successive alkylation of pyridine[12] (eq 1).

(9) A preliminary communication dealing with this study was published earlier: H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, 75, 3865 (1953).

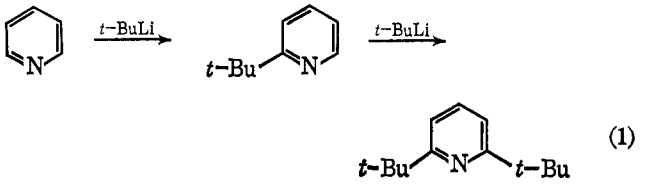
(10) H. C. Brown and W. A. Murphey, *ibid.*, 73, 3308 (1951).

(11) P. D. Bartlett and E. B. Lefferts, *ibid.*, 77, 2805 (1955).

(12) This procedure has since been utilized to prepare 2,6-di-*t*-butyl-4-ethoxypyridine: H. C. van der Plas and H. J. den Hertog, *Rec. Trav. Chim.*, 81, 841 (1962).

Table II. Physical Properties of 2-Ethyl-6-*t*-butylpyridine and 2,6-Diisopropylpyridine

Pyridine	Bp, °C (mm)	$n^{22}D$	Fp, °C	Mp of chloroaurate, °C
2-Ethyl-6-*t*-butyl-	193.6–193.9 (745)	1.4818	−62.0	117.5–118.3
2,6-Diisopropyl-	194.1–194.5 (746)	1.4801	+2.5	138.7–139.5

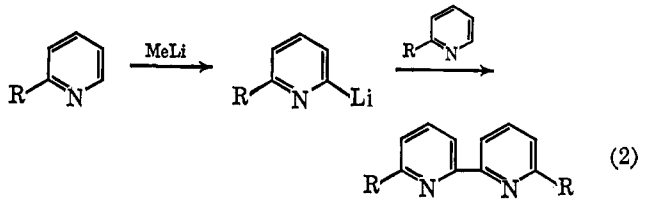


(1)

2-Isopropyl-6-*t*-butylpyridine was prepared in 70% yield by the same general procedure, treating 2-*t*-butylpyridine with isopropyllithium.

Attempts to extend the reaction to the synthesis of 2-methyl-6-*t*-butylpyridine were unsuccessful. 2-*t*-Butylpyridine was largely recovered in its original form (80%) after treatment with methyllithium under conditions which had been entirely satisfactory for the synthesis of 2-ethyl-6-*t*-butylpyridine. Approximately 10 to 20% of the base was converted into a solid product, mp 122.3–122.8°, of low volatility. No 2-methyl-6-*t*-butylpyridine was detected, and it was noted qualitatively that the yield of this solid product increased with increasing reaction temperature. The molecular weight, 269, and the analysis yielded the molecular formula, $C_{18}H_{24}N_2$. No color was observed with ferrous chloride, in contrast to 2,2′-bipyridyl. However, comparison of the ultraviolet spectra in 95% alcohol revealed a close similarity. Moreover, the compound neutralized only 1 mole of acid, yielding a neut equiv of 260, another similarity to 2,2′-bipyridyl. Accordingly, the reaction product was assigned the structure, 6,6′-di-*t*-butyl-2,2′-bipyridyl.

It is probable that methyllithium, instead of alkylating the pyridine base in the usual manner, metalates the base, and the resulting 2-lithio-6-*t*-butylpyridine reacts with a second molecule of base to produce the product (eq 2).

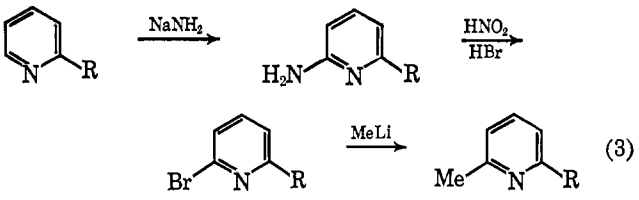


(2)

The formation of small amounts of a solid by-product has been previously observed in the reactions of ethyl-, isopropyl-, and *t*-butyllithium and 2-*t*-butyllithium. The solids were isolated from the rectification residues and recrystallized from alcohol. In each case the melting point and mixture melting point established the identity of the materials. The yield was 30% from methyllithium, 15% from ethyllithium, and 1–2% from *t*-butyllithium.

It was of interest to examine the reaction of methyllithium with pyridine in order to determine whether alkylation or bipyridyl formation would predominate. Rectification of the reaction product indicated the formation of approximately 20% of 2-picoline and less than 10% of crude 2,2′-bipyridyl, identified by its characteristic red color test with ferrous chloride.

As a possible route to 2-methyl-6-*t*-butylpyridine, we considered the sequence shown in eq 3. Indeed, in a



(3)

preliminary experiment, treatment of 2-bromopyridine with methyllithium yielded 2-picoline in a 42% yield. However, attempts to aminate 2-*t*-butylpyridine with sodium amide in dimethylaniline were unsuccessful.

2-Methyl-6-*t*-butylpyridine was finally prepared by the multistep cyclization procedure of Mumm and his co-workers.[13,14]

Base Strengths. The base dissociation constants for pyridine, the 2-alkylpyridines, and the 2,6-dialkylpyridines were determined in 50% aqueous ethanol, using the ultraviolet absorption spectra method.[6,15,16] The results are summarized in Table III.

Table III. Dissociation Constants of Pyridine Bases in 50% Ethanol–Water

Pyridine	pK_a[a]	Pyridine	pK_a[a]
Pyridine	4.38	2,6-Lutidine	5.77
2-Picoline	5.05	2-Methyl-6-*t*-butyl-	5.52
2-Ethyl-	4.93	2-Ethyl-6-*t*-butyl-	5.36
2-Isopropyl-	4.82	2-Isopropyl-6-*t*-butyl	5.13
2-*t*-Butyl-	4.68	2,6-Di-*t*-butyl-	3.58
		2,6-Diisopropyl-	5.34

[a] The measurements were made at room temperature (27 ± 2°).

As was earlier observed for water solutions, there is a regular increase in strength in the present mixed solvent[17] for pyridine, 2-picoline, and 2,6-lutidine (Figure 3). A similar linear increase in base strength is observed for the series pyridine, 2-isopropyl- and 2,6-diisopropylpyridine. However, in the case of the *t*-butyl derivatives, following the usual increase for the first alkyl group there is observed a sharp *decrease* with the second (Figure 3).

Had the usual linearity been followed, the predicted pK_a value for 2,6-di-*t*-butylpyridine would have been

(13) O. Mumm and R. Bohme, *Ber.*, **54**, 734 (1921); O. Mumm and R. Neumann, *ibid.*, **59**, 1616 (1926).

(14) We have since developed a one-step synthesis involving the methylation of 2-*t*-butylpyridine with lead tetraacetate: M. H. Howie, Ph.D. Thesis, Purdue University Libraries.

(15) W. Stenstrom and N. Goldsmith, *J. Phys. Chem.*, 30, 1683 (1926).

(16) E. B. Hughes, H. H. Jellinek, and B. A. Ambrose, *ibid.*, **53**, 410 (1949).

(17) It was necessary to shift to a mixed solvent because of the exceedingly low solubility of the higher pyridine bases in water.

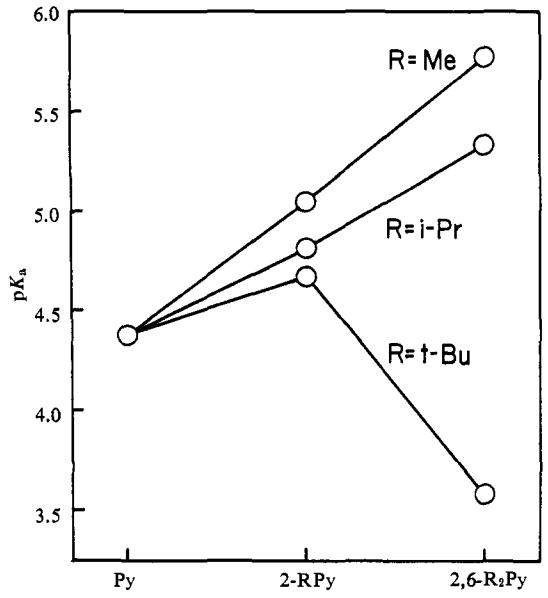


Figure 3. Effect of increasing steric requirements of the alkyl groups in the 2,6 positions on the strengths of pyridine bases (in 50% ethanol).

4.98 (4.38 + 0.30 + 0.30). The observed value of 3.58 therefore represents a discrepancy of 1.4 pK_a units.

The effect apparently requires a minimum of two *t*-butyl groups; it is absent in 2-isopropyl-6-*t*-butylpyridine. In this compound the predicted pK_a value, assuming additivity, is 5.12 (4.38 + 0.44 + 0.30). The observed value is 5.13.

The suddenness and magnitude of the effect is further illustrated by a comparison of the behavior of the 2-alkylpyridines with the 2-alkyl-6-*t*-butylpyridines (Figure 4).

Similar large decreases in the base strength of 2-*t*-butyl- and 2,6-di-*t*-butylaniline have been observed.[18] Moreover, 2,6-di-*t*-butylphenol is a relatively weak acid.[19]

In the case of *ortho*-substituted aniline bases we suggested that the steric requirements of the amino group, $-NH_2$, should be less than that of the ammonium group, $-NH_3^+$.[8] Consequently, there would be an increase in strain accompanying the addition of a proton to the lone pair. In effect, this postulates that the steric requirements of a lone pair on the nitrogen atom are less than the steric requirements of a lone pair bonding a proton to the nitrogen atom.

This concept can readily be extended to the 2,6-dialkylpyridine bases. An ethyl or isopropyl group is capable of rotating in such a manner as to minimize its steric interactions with the group associated with the nitrogen atom. Consequently, the behavior of 2-ethyl- and 2-isopropyl-6-*t*-butylpyridine is not significantly different from that of 2-methyl-6-*t*-butylpyridine. The presence of two *t*-butyl groups in 2,6-di-*t*-butylpyridine, however, with their incapability for rotation to minimize the strain, results in steric interactions with the nitrogen–hydrogen bond and an enhanced tendency for ionization (eq 4).

(18) B. M. Wepster, *Rec. Trav. Chim.*, 76, 357 (1957).
(19) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.* 76, 2349 (1954).

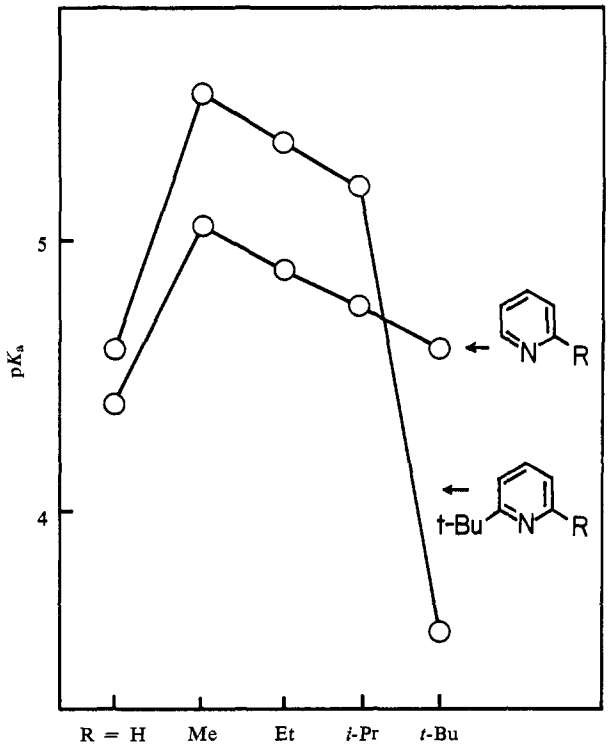
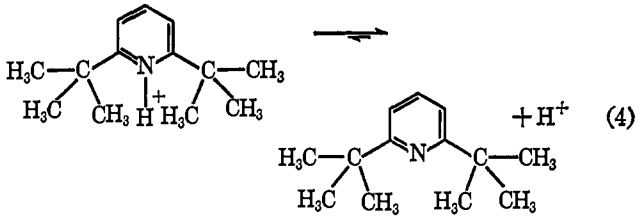
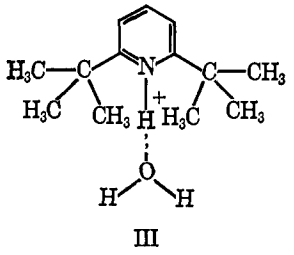


Figure 4. Effect of increasing steric requirements of an alkyl group in the 2 position on the strengths of pyridine bases (in 50% ethanol).



Alternatively, it has been argued that the effect of *ortho* substituents is predominantly the result of their interference with the solvation of the ionic charge in the protonated species.[18,19] This appears compatible with the small regular decreases observed in the 2-alkylpyridines and for the first three members of the 2-alkyl-6-*t*-butylpyridines (Figure 3). However, the sudden large drop for 2,6-di-*t*-butylpyridine appears more suggestive of a direct steric interaction than a secondary steric influence on the general solvation of the ion.

Such a direct steric interaction could be the steric compression of the nitrogen–hydrogen bond, as indicated in eq 4, or it could involve steric interference with a water molecule which is normally hydrogen bonded to the protonated base (III).

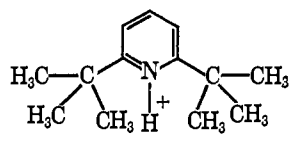


III

(The importance of such hydrogen bonding is indicated by the results described later in this paper on the in-

teraction of 2,6-di-*t*-butylpyridine with hydrogen chloride.) Unfortunately, there does not appear to be any means available at this time to decide how much each factor may contribute to the observed effect.[19a]

At one time we had hoped to apply the concept of homomorphs[20] to resolve the question. If the effect is really due to a direct steric interaction of the two neighboring *t*-butyl groups on the intervening nitrogen–hydrogen bond, we should expect to find similar strains in *m*-di-*t*-butylbenzene (IV) and in 3-*t*-butylpyridine–trimethylboron (V), and the strains could be detected by the usual thermochemical approaches.[20]



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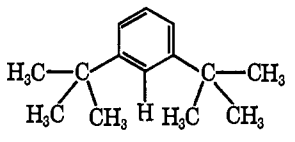

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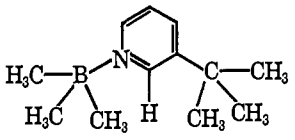


V

Unfortunately, we have been distracted into other areas of research, so that this test of our suggestion of a direct steric compression of the protonated center still remains to be completed.

Properties. Attempts to prepare the picrates of the 2,6-dialkylpyridines met with only partial success. The picrates of 2,6-diisopropylpyridine and of 2-ethyl-6-*t*-butylpyridine were obtained in small yield, but the picrates of 2-isopropyl-6-*t*-butylpyridine and 2,6-di-*t*-butylpyridine did not form. It was previously noted that the picrates of the 2-alkylpyridines formed considerably less readily than the 3- or 4-alkylpyridines. For this reason, we sought another suitable derivative, and the chloroaurates proved satisfactory. These derivatives were easily prepared and readily recrystallizable from water or aqueous ethanol.

The decoloration of a solution of bromine in carbon tetrachloride by pyridine with the formation of the perbromide is a well-known reaction.[21] Qualitative tests were run on pyridine, 2-picoline, 2,6-lutidine, 2-*t*-butylpyridine, and 2,6-di-*t*-butylpyridine. Only the last failed to decolorize at least the first few drops of the bromine solution. Apparently, the steric requirements of the two *t*-butyl groups prevent bonding of the bromine with the nitrogen atom.

An acetonitrile solution of methyl iodide, 1.00 *M*, and 2,6-di-*t*-butylpyridine, 0.101 *M*, was allowed to stand at room temperature for 30 days. No reaction was observed.[22]

Boron trifluoride, which reacts readily with pyridine, 2,6-lutidine, and 2-*t*-butylpyridine,[23] failed to react with 2,6-di-*t*-butylpyridine. On the other hand, the base does react with hydrogen chloride. Unexpectedly, it does not form a simple hydrochloride. Treatment of 1 mole of 2,6-di-*t*-butylpyridine with 1 mole of hydrogen chloride results in the formation of 0.5 mole of the dihydrochloride, mp 147°, and 0.5 mole of free base. Under the same conditions pyridine readily forms both a mono- and a dihydrochloride.[24,25]

Thus the base can be used to separate a mixture of hydrogen chloride and boron trifluoride. It should also be useful in situations where it is desired to have a base present which can neutralize acid but is itself incapable of forming acid through elimination reactions.

Sulfonation. While benzene is readily nitrated at room temperature by a mixture of nitric and sulfuric acid, pyridine requires fuming sulfuric acid and potassium nitrate at 300°. This remarkable inertness of the pyridine nucleus has been attributed to a combination of two factors: the inductive effect of the nitrogen atom and the greatly enhanced electron-withdrawing effect of the positive pole in the pyridinium ion, the form in which pyridine must exist in these nitrating mixtures.[26]

Similar inertness of the pyridine nucleus has been observed in other electrophilic substitutions. It is apparent that the electrophilic species will find the lone pair on the nitrogen atom far more accessible than the electrons of the ring. Consequently, even in an aprotic system, the reaction will not involve the free base but a deactivated derivative of the base.

The tremendous hindrance toward coordination at the nitrogen atom, shown by 2,6-di-*t*-butylpyridine, suggested its possible utility for exploring the true reactivity of the pyridine ring in the free base itself. Aprotic sulfonation with sulfur trioxide in liquid sulfur dioxide[27] appeared to be a suitable test reaction. Accordingly, this procedure was applied to pyridine, 2,6-lutidine, 2,6-di-*t*-butylpyridine, benzene, and nitrobenzene. The results are summarized in Table IV.

Table IV. Sulfonation of 2,6-Di-*t*-butylpyridine and Representative Model Compounds by Sulfur Trioxide in Liquid Sulfur Dioxide

Compound	Time, hr	Reaction product yield, % Addition	Substitution
Benzene	4	0	100
Nitrobenzene	4	0	70
Pyridine	1	100	0
2,6-Lutidine	4	100	0
2,6-Di-*t*-butyl-pyridine	4	0	37
	20	0	45

(19a) NOTE ADDED IN PROOF. For a recent discussion of the influence of hydration on the base strength of 2,6-di-*t*-butylpyridine and similar sterically hindered bases, see F. E. Condon, *J. Am. Chem. Soc.*, 87, 4494 (1965).

(20) H. C. Brown, G. K. Barbaras, H. L. Berneis, W. H. Bonner, R. F. Johannesen, M. Grayson, and K. L. Nelson, *ibid.*, 75, 1 (1953).

(21) R. Shriner and R. Fuson, "Identification of Organic Compounds," 2nd, ed, John Wiley and Sons Inc., New York, N. Y., 1947, p 37.

(22) Dr. Y. Okamoto of New York University has informed us that he has been able to achieve a reaction between these two compounds by the use of enormous pressures.

(23) H. C. Brown and R. H. Horowitz, *J. Am. Chem. Soc.*, 77, 1733 (1955).

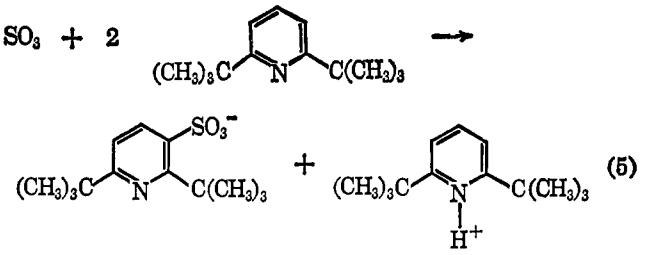
(24) A detailed study of the higher hydrochlorides of a number of pyridine bases is contained in the Ph.D. thesis of C. W. McGary, Jr., Purdue University Libraries.

(25) The monohydrochlorides of simple pyridine bases appear to be stabilized by hydrogen bonding between the protonated base and the chloride ion. This does not appear possible in the present case, where the two large alkyl groups must prevent approach of the chloride ion to within hydrogen bonding distance of the proton. For example, it has been observed that in contrast to 3- and 4-pyridinesulfonic acids and 2,6-lutidine-3- and -4-sulfonic acids, which exhibit such hydrogen bonding (the acids exist as the zwitterions), the infrared spectrum of 2,6-di-*t*-butylpyridine-3-sulfonic acid reveals its complete absence: R. F. Evans and W. Kynaston, *J. Chem. Soc.*, 1005 (1962).

(26) R. C. Elderfield, Ed., "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p 403.

(27) L. Leiserson, R. W. Bost, and R. LeBaron, *Ind. Eng. Chem.*, 40, 508 (1948).

2,6-Di-*t*-butylpyridine was sulfonated in 37 to 45% yields, although pyridine and 2,6-lutidine formed only the addition compounds. A possible explanation for the relatively minor difference in yield for the 4-hr and 20-hr reactions may be that the sulfonic acid formed protonates the free base, thus limiting the yield under these conditions to a maximum of 50% (eq 5).



(5)

The sulfonic acid was isolated by recrystallization of the crude material from methanol. The white crystalline sulfonic acid was insoluble in water but soluble in aqueous sodium hydroxide and had a neut equiv of 272.5 (calcd 271). Originally, we considered the possibility that the compound might be the 4 derivative, because of the steric difficulties involved in placing the bulky sulfo group in the 3 position, adjacent to the *t*-butyl group. Attempts to establish the structure by comparing the pK_a value with those of model compounds led to ambiguous results.[28] However, it has now been definitely established that the sulfo group is in the 3 position by reactivity studies,[29] synthesis,[12] and the nmr spectrum.[30]

Assuming that the maximum yield is 50%, as discussed above, the reaction in 4 hr has proceeded approximately 74% toward completion. Under these conditions, benzene is entirely converted, but the sulfonation of nitrobenzene is only 70% complete. It follows that the reactivity of the nucleus of the free pyridine base must be comparable to that of nitrobenzene.

Experimental Section

Exhaustive Alkylation of 2,6-Lutidine. Methyl chloride (112 g, 2.15 moles) was added over 1.5 hr to a mixture of 107 g (1.0 mole) of 2,6-lutidine and 2.1 moles of sodium amide in 750 ml of liquid ammonia. The crude base recovered was subjected to the alkylation procedure three more times, using successively lower rates of addition of the methyl chloride. The dried product was then distilled in a 12-mm × 30 cm column packed with 1/16-in. stainless steel helices. A product, bp 191.5–192.5°, 49 g (30%), was collected and identified as 2,6-diisopropylpyridine.

2,6-Diisopropylpyridine. The procedure followed was similar to that previously described.[10] 2,6-Lutidine was alkylated in liquid ammonia with a 4:1 ratio of sodium amide and methyl chloride to the base. From the distillation curve, the yield of the product, bp 192.3–193.0°, was estimated to be 55%.

Anal. Calcd for $C_{11}H_{17}N$: C, 81.0; H, 10.4; N, 8.6. Found: C, 81.0; H, 10.1; N, 8.8.

2-Ethyl-6-*t*-butylpyridine.[31] Ethyllithium was prepared from 54 g (0.5 mole) of dry ethyl bromide and 7.0 g (1.0 g-atom) of cut lithium wire in 250 ml of anhydrous ether at −10 to −20°. The solution was filtered and transferred under nitrogen pressure into a solution of 45 g (0.33 mole) of 2-*t*-butylpyridine[10] in 250 ml of purified, anhydrous petroleum ether (bp 90–100°), contained in a 1-l. flask fitted with a sealed Hershberg stirrer, a dropping funnel, and a condenser. The bright red solution that resulted was heated to reflux and stripped of low-boiling solvent until the reflux temperature was 70°. Heating at this reflux temperature was continued for 8 hr. Then 25 ml of water was cautiously added, the organic layer was decanted, dried over pellets of potassium hydroxide, and distilled in the previously described column. The yield was 25 g, 46%. Approximately 5 g (0.019 mole) of crude bipyridyl separated out from the pot residue (12% yield).

Anal. Calcd for $C_{11}H_{17}N$: C, 81.0; H, 10.4; N, 8.6. Found: C, 80.8; H, 10.4; N, 8.3.

2-Isopropyl-6-*t*-butylpyridine. Isopropyllithium, from 0.5 mole of isopropyl chloride and 1.0 g-atom of lithium sand, in ether, was filtered as above into 27 g (0.20 mole) of 2-*t*-butylpyridine in 200 ml of purified petroleum ether (bp 90–100°). The flask and its contents were kept at −78° for several hours and slowly allowed to warm up to room temperature overnight. The solution was milky white in color. The solution was heated, the low-boiling solvent removed, and the reaction mixture maintained at reflux (70°) for 8 hr. The work-up was as above. Distillation yielded 24.7 g (0.14 mole), yield 70%, bp 94° (23 mm).

Anal. Calcd for $C_{12}H_{19}N$: C, 81.4; H, 10.7; N, 7.9. Found: C, 81.5; H, 10.5; N, 7.8.

2,6-Di-*t*-butylpyridine. *t*-Butyllithium was prepared from 46 g (0.5 mole) of freshly distilled *t*-butyl chloride and 7 g (1.0 g-atom) of lithium sand in 200 ml of anhydrous ether.[11,32] The cold solution (−45°) was transferred under nitrogen to 27 g (0.2 mole) of 2-*t*-butylpyridine in petroleum ether at −78°. After several hours, the reaction mixture was allowed to warm up to room temperature, and the procedure was then the same as above. The yield was 18.8 g (67%) of 2,6-di-*t*-butylpyridine, bp 100–101° (23 mm).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.6; H, 11.0; N, 7.3. Found: C, 81.4; H, 10.9; N, 7.5.

Reaction of Methyllithium with 2-*t*-Butylpyridine. Methyllithium in ethyl ether (0.136 mole by titration) was added without cooling to 0.2 mole of 2-*t*-butylpyridine in 100 ml of purified petroleum ether. The mixture was heated under reflux for 9 hr, and the work-up then followed above procedures. Distillation yielded 18 g (0.13 mole, 67%) of 2-*t*-butylpyridine. From the pot residue, 8 g (30%) of solid bipyridyl was isolated by filtration.

The dark solid was treated with charcoal and recrystallized from 95% ethanol, mp 122.3–122.8°.

Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 8.95; N, 10.47 Found: C, 80.56; H, 9.06; N, 10.58.

The neut equiv was 260, compared to a calculated value of 268, assuming that only 1 mole of acid is neutralized. The molecular weight, measured in refluxing pyridine, was 269.

A second reaction with methyllithium was carried out, keeping the reactants at 0° for 6 hr, room temperature for 12 hr, followed by refluxing for 5 hr. However, there was obtained 75% of recovered 2-*t*-butylpyridine and 15% of the solid bipyridyl.

Reaction of Methyllithium with Pyridine. The procedure was the same as above. When the reaction mixture (methyllithium from 0.5 mole of methyl iodide, 1.0 g-atom of lithium wire, and 0.35 mole of pyridine) was heated to reflux, gas was evolved in copious quantities. At the end of 6 hr, a total of 2 l. (0.082 mole) was measured. Addition of another 28 g of pyridine gave 300 ml of gas, but further addition had no effect. There was isolated 8.5 g of 2-picoline and somewhat less than 5 g of 2,2′-bipyridyl which gave the strong red color test with ferrous chloride.

Reaction of Methyllithium with 2-Bromopyridine. Methyllithium (as above) was added to 24 g (0.15 mole) of 2-bromopyridine in 200 ml of petroleum ether. After 5 hr of reflux (70°) there was isolated 6 g of 2-picoline, a yield of 42%.

2-Methyl-6-*t*-butylpyridine. The procedure of Mumm and coworkers was followed with minor modifications.[13] The yield of diethyl 2-methyl-6-*t*-butylcinchomeronate was 32%. After decarboxylation and distillation of the crude product, 3.5 g of 2-methyl-6-*t*-butylpyridine, bp 174–179° (lit.[13] 179–180°), was isolated.

Preparation of the Chloroaurates. Approximately 0.2 g of the pyridine base was added to 5 ml of water and 1 ml of dilute hydrochloric acid (sufficient to dissolve all of the pyridine base). A 25% excess of chloroauric acid was added as a 10% aqueous solution. The precipitate was washed with 4 ml of cold water and recrystallized to constant melting point (usually twice was sufficient) from water, dilute ethanol, or ethanol.

(28) R. F. Evans and H. C. Brown, *J. Org. Chem.*, **27**, 3127 (1962).
(29) H. C. van der Plas and H. J. den Hertog, *Chem. Weekblad*, **53**, 560 (1957).
(30) N. Muller and W. J. Wallace, *J. Org. Chem.*, **24**, 1151 (1959).
(31) This synthetic route was based on the synthesis of 2,6-di-*n*-butylpyridine: K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931).
(32) See ref 12 for a detailed procedure for the preparation of *t*-butyllithium.

Table V. Physical Properties and Chloroaurates of the 2,6-Dialkylpyridines

Pyridne	Bp, °C (mm)	$n^{20}D$	Fp, °C	Chloroaurates: Mp, °C	Calcd Au	Found Au	Calcd C	Found C
2-Methyl-6-*t*-butyl-	174.0–179.0 (746)	1.4870		140.5–141.0	40.3	40.8	24.6	24.5
2-Ethyl-6-*t*-butyl-	193.6–193.9 (745)	1.4818	−62.0	117.5–118.3	39.1	39.3	26.3	26.2
2-Isopropyl-6-*t*-butyl-	94 (23)	1.4753	−66.0	167.0–167.2	38.0	38.3	27.7	27.8
2,6-Di-*t*-butyl-	101 (23)	1.4733	2.2	184.2–184.5	37.1	36.9	29.4	29.7
2,6-Diisopropyl-	194.1–194.5 (746)	1.4801	2.5	138.7–139.5	39.1	39.5	26.3	26.3

The data, along with pertinent physical constants for the parent bases, are summarized in Table V.

Sulfonation Experiments. Gaseous sulfur dioxide was drawn from a cylinder, dried by passing through phosphorus pentoxide coated glass beads, and collected in a 50-ml flask fitted with a modified Claisen head to which a graduated dropping funnel and a Dry Ice condenser were attached. Liquid sulfur trioxide (Sulfan) was distilled into the top of the dropping funnel from an all-glass distillation apparatus. In this manner 2.0 ml or 4.0 g (0.05 mole) was collected and added to the flask containing about 20 ml of sulfur dioxide. Then the material to be treated (benzene, nitrobenzene, pyridine, 2,6-lutidine, and 2,6-di-*t*-butylpyridine) was placed in the dropping funnel and added to the reaction mixture over a period of 10 min. Where a rapid exothermic reaction occurred (benzene, pyridine, and 2,6-lutidine), vigorous refluxing was observed during the addition.

At the end of 4 hr, the sulfur dioxide was removed and the flask brought to constant weight by pumping at 1 mm. The reaction products were dissolved in water and analyzed for total acidity (neutralization equivalent) and for sulfuric acid by sulfate determination. The sulfur trioxide addition compounds readily decomposed in water to give the base and sulfuric acid. The yield of sulfonic acid was then calculated as the difference between the total acidity and the acidity due to sulfuric acid. As sulfonic acids do not give a precipitate with barium chloride, it was easily possible to distinguish between sulfur trioxide addition compounds and sulfonic acids.

2,6-Di-*t*-butylpyridine-3-sulfonic Acid. Following the above general procedure, 3.6 g (0.045 mole) of sulfur trioxide and 8.0 g (0.042 mole) of 2,6-di-*t*-butylpyridine were allowed to react in about 20 ml of liquid sulfur dioxide at approximately −10° for 4 hr. The liquid sulfur dioxide was evaporated off and 11.6 g (quantitative) of solid was recovered from the flask. The neutralization equivalent was then run on a sample: 141.5. Analysis for sulfate indicated the presence of 2.7 g of sulfur trioxide. Since the crude solid had a neut equiv of 141.5, and 11.6 g of solid had 2.7 g of sulfur trioxide with a neut equiv of 40, the amount of sulfonic acid is calculated to be 4.1 g, 37%. Addition of the crude solid to hot methanol yielded white crystals on cooling, 2.0 g. The recrystallized product decomposed at 310° (lit.[12] mp 333–334 dec).

Anal. Calcd for $C_{13}H_{21}NSO_3$: C, 57.6; H, 7.8; N, 5.2. Found: C, 57.5; H, 7.8; N, 5.1.

The S-benzylthiuronium derivative was prepared, mp 216.0–216.5° (lit.[12] 215–216°).

Anal. Calcd for $C_{21}H_{31}N_3S_2O_3$: N, 9.6. Found: N, 9.6.

Base Dissociation Constants. A Cary recording spectrophotometer was used for all ultraviolet absorption measurements. All pH measurements were made on a Beckman Model G pH meter. The pH meter was calibrated with standard buffers before each series of measurements.

The solvent was 50:50 ethanol–water (by volume). The density of the solvent was 0.92960 at 25° and corresponded to 40.9 wt % ethanol. The estimated dielectric constant of the solvent was 50 at 25°.

The spectra of the pyridine bases in 0.1 *M* sodium hydroxide, 0.1 *M* hydrochloric acid, and two acetate buffers, all made up in the 50% ethanol, were obtained for the range 220–300 mμ. The temperature of the measurements was 27 ± 2°. The pH of the buffered solutions was measured immediately following the absorbancy measurements. The pK_a' values were obtained from the expression

$$pK_a' = pH + \log \frac{A_B - A_{NaOH}}{A_{HCl} - A_B}$$

where A_B, A_{NaOH}, and A_{HCl} represent the absorbancy in the buffer, 0.1 *M* sodium hydroxide, and 0.1 *M* hydrochloric acid, respectively.

For each pyridine base an average pK_a' for at least four different wavelengths was determined. The pK_a' values were corrected for the activity of the pyridinium ion at 25°. The average deviation of the pK_a' values was ±0.03. The average deviation of the pK_a' values was ±0.03. The average deviation of the readings taken on the pH meter was ±0.02. (The thesis should be consulted for the spectral data.)

Reaction with Methyl Iodide. A solution in acetonitrile was prepared, 1.0 *M* in methyl iodide and 0.101 *M* in 2,6-di-*t*-butylpyridine. Aliquots, 10.0 ml, were sealed in capsules and allowed to remain at room temperature for varying lengths of time. They were then opened and titrated for iodide with 0.1045 *M* $AgNO_3$ by the usual kinetic technique: 1.5 hr, −0.04 ml; 12.0 hr, −0.01 ml, 11.5 days, 0.04 ml; 30 days, 0.04 ml. It can be concluded that there is no reaction within the limits of experimental uncertainty.

Reaction with Boron Trifluoride and Hydrogen Chloride. The reactions were carried out in the usual high-vacuum line. A sample of 0.1871 g (9.8 mmoles) of 2,6-di-*t*-butylpyridine was treated with 23.5 mmoles of boron trifluoride at room temperature. There was no drop in pressure corresponding to absorption of gas. Condensation with liquid nitrogen in another section of the apparatus resulted in the recovery of 23.0 mmoles of the gas.

A mixture of 23.0 mmoles of boron trifluoride and 34.2 mmoles of hydrogen chloride was contacted with 0.510 g (26.7 mmoles) of 2,6-di-*t*-butylpyridine for 30 min at room temperature. There was observed a rapid decrease in pressure. Condensation in another section of the apparatus recovered 23.0 mmoles of gas, presumably boron trifluoride since it corresponded exactly with the amount of this gas used.

Reaction with Hydrogen Chloride. Treatment of 2,6-di-*t*-butylpyridine with hydrogen chloride at room temperature rapidly results in the absorption of 2 moles of hydrogen chloride per mole of base. The product melted at 147° and proved to be quite stable, with a dissociation pressure of 2.7 mm at 37°.