2-Carbethoxyacetylamino-4-methylpyridine (26).—To an ice-cooled solution of 39 g (0.36 mol) of 2-amino-4-methylpyridine and 36 g (0.36 mol) of triethylamine in 250 ml of toluene was added 54 g (0.36 mol) of carbethoxyacetyl chloride, slowly and with stirring. After standing overnight, the reaction mixture was washed with water and the organic layer was dried and evaporated. The residue was recrystallized from methylcyclohexane to yield 42 g (52%) of **26**, mp 89.5°.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.35; N, 12.61. Found: C, 59.17; H, 6.54; N, 12.70.

***N*-(4-Methyl-2-pyridyl)-2-carbethoxy-3-dimethylaminoacrylamide (12).**—See also Table I; the other compounds in this table were prepared in analogous fashion.

A solution of 40 g (0.172 mol) of **26** and 36 g (0.3 mol) of dimethylformamide dimethyl acetal in 200 ml of 1,2-dimethoxyethane was refluxed for 1.5 hr. The solvent was then removed on a rotatory evaporator and the residue was recrystallized from methylcyclohexane, yield of **12** 33 g.

2-Keto-3-acetyl-2*H*-pyrido[1,2-*a*]pyrimidine (3).—See also Table II; the other compounds in Table II were prepared similarly.

A slurry of 10 g (0.045 mol) of **4** in 70 ml of acetic anhydride was quickly heated to a boil and kept gently boiling for 10 min, during which time the starting material dissolved and, later, the product precipitated. After cooling, the product was separated, washed with 2-propanol, and dried, yield 7.5 g of **3**. All the compounds in Table II were appreciably soluble in water.

1-(2-Pyridyl)-3-acetyl-6-methyl-2-pyridone-5-(5-chloro-2-pyridyl)carboxamide (16).—See also Table III; compounds **2**, **15**, **17**, **18**, and **19** in this table were prepared in analogous fashion.

A mixture of 4.7 g (0.025 mol) of **3**, 10.6 g (0.05 mol) of 2-acetoacetylamino-5-chloropyridine,[1] and 200 mg of $ZnCl_2$ in 150 ml of ethanol was refluxed for 1 hr. The starting materials soon dissolved and the product began to crystallize. The mixture was cooled, and the product was filtered and recrystallized from methylcellosolve, yield 8.6 g of **16**.

***N*-(4,6-Dimethyl-2-pyridyl)-2-acetyl-3-(4,6-dimethyl-2-pyridyl)-aminoacrylamide (13).**—A solution of 3 g (0.014 mol) of **6** and 2.4 g (0.02 mol) of 2-amino-4,6-dimethylpyridine in 100 ml of ethanol was refluxed for 1 hr. The mixture was then cooled, and the product was filtered off and dried, yield 3.5 g (74%) of **13**, mp 226–227°. By mixture melting point and ir spectra, this material was identical with compound **7** of ref 1.

1-(2-Pyridyl)-3-acetyl-5-carbo-*tert*-butoxy-6-methyl-2-pyridone (20).—See also Table III; compound **21** in this table was prepared in the same way.

A slurry of 9.4 g (0.05 mol) of **3**, 16 g (0.1 mol) of *tert*-butyl acetoacetate, and 0.5 g of 1,5-diazabicyclo[4.3.0]-5-nonene in 200 ml of dimethylformamide was stirred at room temperature for 30 min. The starting material had dissolved to form a red solution. The solution was poured into excess water, and the product was filtered off, washed with water, and dried, yield 15.5 g of **20**. Recrystallization from 2-propanol did not raise the melting point.

1-(2-Pyridyl)-3-acetyl-6-methyl-2-pyridone-5-carboxylic Acid Anilide (17). Independent Synthesis.—A solution of 8.0 g (0.024 mol) of **20** in 50 ml of 6 *N* HCl was heated on a steam bath for 15 min and then left standing at room temperature for 1 hr. The solvent was then removed in a rotatory evaporator and the product was dried, yielding 5.5 g (0.02 mol) of the HCl salt of the carboxylic acid corresponding to **20**. This material was slurried in 100 ml of benzene, and 6 g (0.06 mol) of triethylamine was added. Most of the solid dissolved. Then, while applying ice cooling, 2.2 g (0.02 mol) of ethyl chloroformate was added. After 30 min at room temperature, 1.86 g (0.02 mol) of aniline was added and the mixture was refluxed for 30 min. Then water was added, and the benzene layer was separated, dried, and evaporated. The residue was recrystallized from ethanol, yield 3 g (43%), mp 235.1°; on admixture of **17**, the material melted at 235.2°. The ir spectra were identical.

Registry No.—**2**, 23600-24-0; **3**, 33068-07-4; **4**, 33015-41-7; **5**, 33015-42-8; **6**, 33015-43-9; **7**, 33015-44-0; **12**, 33068-08-5; **15**, 23600-27-3; **16**, 33015-46-2; **17**, 23600-41-1; **18**, 23646-60-8; **19**, 33015-49-5; **20**, 33015-50-8; **21**, 33015-51-9; **22**, 33015-52-0; **23**, 33068-09-6; **24**, 33015-53-1; **25**, 33015-54-2; **26**, 33015-56-4.

Acknowledgment.—I should like to gratefully acknowledge the encouragement of this work by Dr. C. L. Levesque, Rohm and Haas Company.

Relative Rates of N-Methylation of Ortho-Substituted Pyridines. Steric and Electronic Effects

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Received June 29, 1971

Relative rates of N-methylation of eleven 2-substituted and two 2,6-disubstituted pyridines by methyl iodide in DMSO at 23° were obtained by nmr methods. Rate constants relative to pyridine for the monosubstituted compounds are NH_2, 1.23; CH_3, 0.38; C_2H_5, 0.17; $C_6H_5CH_2$, 0.081; CO_2CH_3, 0.0084; CH_3CONH, 0.0082; Cl, 0.0039; Br, 0.0039; 2-C_5H_4N, 0.0026; and CN, 0.0022. Results for the disubstituted pyridines are CH_3,NH_2, 0.050; and $(CH_3)_2$, 0.023. Kinetic results are only poorly correlated with pK_a values. It is suggested that steric effects are superimposed on electronic effects in the N-methylation reactions and that steric effects can be surprisingly constant.

Our understanding of the effects of ortho substituents on chemical equilibria and reactivity has undergone a recent and profound change. It was long held that steric effects could and often did influence reactions at ortho positions in a nonadditive way. However, in the absence of steric and hydrogen-bonding factors, electronic effects of ortho groups were expected to be proportional to those of para substituents.[2,3]

Charton has challenged this view. He has employed a multiparameter equation to correlate all the known sets of ortho substituent constants.[4] Except for some very bulky groups and those capable of intramolecular hydrogen bonding, previously defined ortho substituent constants have been expressed in terms of inductive and resonance components which often are not related to those for para or even meta groups. Steric effects were said to be absent or constant.[4]

Of the series of compounds statistically examined by Charton, all are monosubstituted and nearly all have the geometry given by I where G is the ortho substituent and Y is a reactive center such as CO_2R, CN, OH, and NH_3^+.

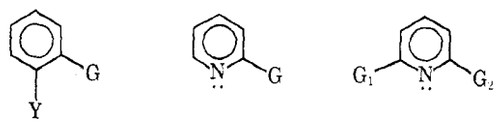
(1) On leave from LaTrobe University, Melbourne, Australia.

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, pp 204–207.

(3) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(4) For a list of references, see M. Charton, *J. Org. Chem.*, **36**, 882 (1971); *Prog. Phys. Org. Chem.*, **8**, 235 (1971).

We felt it desirable to examine structures where the substituent and reactive center have a different geometrical relationship. The relative rates of N-methylation of a series of 2-substituted (II) and 2,6-disubstituted pyridines (III) by methyl iodide in dimethyl sulfoxide (DMSO) were obtained. Our results provide the most extensive set of rate data yet reported for ortho-substituted pyridines.



I II III

The use of II and III as nucleophiles is extensive but G almost always is an alkyl group. It has been said that these nucleophiles exhibit steric effects in their reactions with electrophiles, including hydrogen,[5,6] saturated[3,7-12] and carbonyl carbon,[13] and phosphorus.[14] However, the dissociation constants, K_a, of a wide variety of ortho-substituted pyridines, including many with alkyl groups, are said to be free of the influence of steric effects.[4,7,15] Our purpose was to determine the relative importance of steric and electronic effects on the rates of reaction of II and III with methyl iodide.

Results

Relative rates of N-methylation of 2-substituted and 2,6-disubstituted pyridines as well as a few quinolines were obtained by competition methods. Pairs of heterocycles were allowed to compete for methyl iodide in dimethyl sulfoxide (DMSO) at 23°. Relative rate constants were obtained from the product ratios, as determined by nmr analysis of the *N*-methyl product peaks. Three different methods of analysis were employed.

In the first a deficiency of methyl iodide was utilized and the product ratio was determined when all of this reactant had been consumed.[16] This method was not employed with the less reactive pyridines, owing to side reactions.

When the substrates were about 100 times less reactive than pyridine, a significant amount of the methyl iodide reacted with the DMSO.[17] Two variations of the competition method then were followed. The second method involved determining the product ratio after small amounts of the heterocycles had reacted. The rate constant ratio was calculated from a knowledge of the initial concentration ratio of the heterocyclic reactants, $[Het]_0$, and the product ratio (eq 1). This essentially is the initial rate method. Whereas

$$\frac{k_1}{k_2} \cdot \frac{[Het_1]_0}{[Het_2]_0} \approx \frac{[CH_3Het_1]}{[CH_3Het_2]} \quad (1)$$

in the initial rate method often only 1–2% of a product is allowed to form before a product analysis is made, larger amounts of product were allowed to form in our experiments in order to provide strong nmr signals. In the results reported here, the error introduced by conversions as large as 25% is only on the order of the error in the nmr measurements, ~4%.

A third variation involved determining the product concentration as a function of time. Rate constant ratios then were calculated using a standard, integrated rate expression (eq 2). This method was

$$\frac{k_1}{k_2} = \frac{\log ([Het_1]/[Het_2]_0)}{\log ([Het_2]/[Het_2]_0)} \quad (2)$$

employed in a competition involving 2-chloro- and 2-carboxymethylpyridine where >50% product was formed. The rate constant ratio determined at various stages of the reaction agreed to ±10% and this average value agreed with that given by the product ratio early in the reaction to ±10%. Note that for the latter two methods, unlike the first, a knowledge of the methyl iodide concentration is not necessary. Equation 2 is an exact solution and applies generally.

Rate constant ratios for 13 pyridines and 2 quinolines are given in Table I. These values are based on the several competition standards indicated. Using these data and eliminating the comparison heterocycle, rate constant ratios, k^G/k^H, with pyridine as the standard are obtained. The uncertainty in k^G/k^H is estimated to be about 6–10%. No results were obtained for 2-methoxypyridine, owing to product instability.[18]

A control experiment showed that only a negligible amount of hydrolysis of N-methylated 2-bromopyridine to *N*-methylpyridone took place under the conditions of the competition experiment. A small amount of water added to a reaction mixture following N-methylation was without effect over 24 hr. The ring protons of *N*-methylpyridone served as a sensitive test for this material. Thus, residual water in the DMSO has no influence on the competition constant.

Since oxotrimethylsulfonium iodide (methylated DMSO, τ 6.0) is present in some of the reactions, a check was made to determine whether this material would compete with methyl iodide as an N-methylating agent. The methylated DMSO failed to give a significant amount of N-methylated methyl 2-pyridinecarboxylate. It seems likely that other pyridines are not N-methylated by this reagent in the presence of the more reactive methyl iodide.

Our k^{Br}/k^H value of 0.0039 for 2-bromopyridine is similar to the value of 0.0031 (25°, nitrobenzene) derived from other studies[7,12] where rate constants rather than rate constant ratios were obtained. However, our results indicate that 2-chloro- and 2-bromopyridine have about the same reactivity and the earlier report indicated that the chloro is about twice as reactive as the bromo compound.[12] However, the chloro to ester rate constant ratio we obtained indirectly using 3-

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Table I

Relative Rate Constants for Reactions of Substituted Pyridines with Methyl Iodide in DMSO at 23° [a]

Substituent(s)	Registry no.	Competition std: Pyridine[b]	2-Cyanopyridine	2-Carboxymethylpyridine	3-Bromoquinoline	1,10-Phenanthroline
H	110-86-1	(1.0)			(0.016[c,d])	(0.047[d,f])
2-NH_2	504-29-0	1.23 (1.23)				
2-CH_3	109-06-8	0.38 (0.38)				
2-C_2H_5	100-71-0	(0.17[e])				
2-$NHCOCH_3$	5231-96-9	(0.0082)		0.97		
2-CO_2CH_3	2459-07-6	(0.0084)			0.52	
2-Cl	109-09-1	(0.0039)	1.8	0.50	0.24	
2-Br	109-04-6	(0.0039)	1.8			
2-$CH_2C_6H_5$	101-82-6	(0.081)				1.7[f]
2-CN	100-70-9	(0.0022)				
2-(2-Pyridyl)	366-18-7	(0.0029[f])	1.2[f]		0.21[f]	
2,6-$(CH_3)_2$	108-48-5	(0.023)			1.4	
2-CH_3-6-NH_2	1824-81-3	(0.050)				1.05[f]
2-CH_3Q[g]	91-63-4	(0.0062)		0.74		

[a] Comparison of substituted pyridine to standard compound. [b] Values in parentheses are relative rate constants using pyridine as a standard; see text. [c] Reference 16. [d] Reference 20. [e] 2-Ethylpyridine–pyridazine = 0.667 and pyridine–pyridazine = 4.0. [f] Statistically corrected for reaction of two equivalent nitrogen atoms. [g] 2-Methylquinoline.

bromoquinoline and the ratio obtained directly agreed to ±4%.

Our relative rate constants for quinoline and 2-methyl-, 2-ethyl-, and 2,6-dimethylpyridines are very similar to those reported.[10] Our relative rate constant for 2-methylquinoline is about one-half that reported; nitrobenzene was the solvent.[10] Some small variation in this ratio with solvent change is to be expected.

2-Methyl-6-aminopyridine underwent methylation at both the annular and amino nitrogen atoms; 1,2-dimethyl-6-aminopyridinium and 2-methyl-6-trimethylammoniopyridine iodides were isolated from a reaction mixture. The rate constant ratio given in Table I reflects reaction at just the annular nitrogen atom and results from the use of eq 1. Although the *N*-methyl peaks of both of the isolated products overlapped in DMSO-d_6, the addition of KOD to a mixture resulted in signal separation. The *N*-methyl peak of the aminopyridinium salt shifted upfield by about 25 Hz.

A Brønsted plot of log k^G/k^H *vs.* pK_a for pyridines and quinolines is given in Figure 1. The k^G/k^H values cover a range of $\sim 5 \times 10^2$ while the K_a[19] values range over a factor of $\sim 5 \times 10^7$. Thus, the nucleophilicity of the heterocycles toward methyl iodide is only moderately dependent on basicity. Results for quinoline are taken from ref 20. The pK_a and log k^G/k^H values for the pyridyl group in 2,2′-bipyridyl are statistically corrected by −0.30.

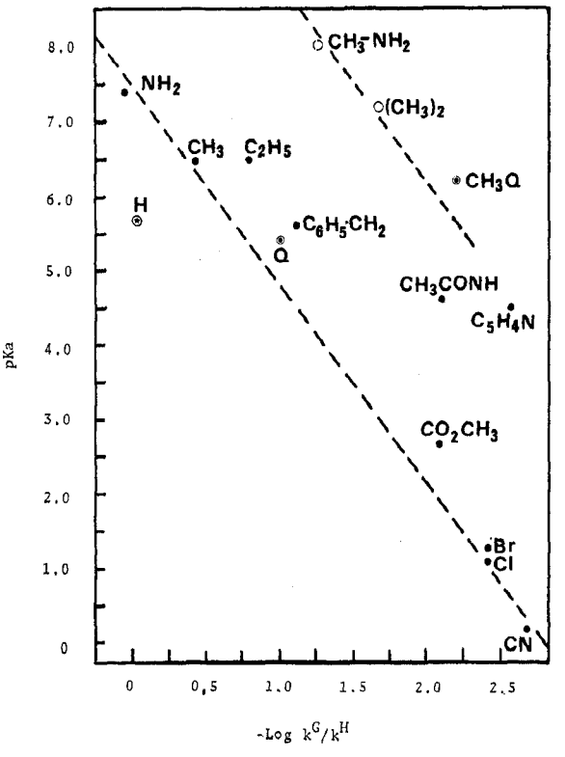

Figure 1.—Brønsted plot of the relative rates of N-methylation of 2-substituted (filled circles) and 2,6-disubstituted pyridines (open circles) and quinoline (Q) and 2-methylquinoline (CH_3Q) *vs.* the dissociation constants of the heterocyclic conjugate acids in water. Rate studies employ DMSO solvent at 23°. Pyridine (H) is the rate standard.

Discussion

The kinetic results found for the N-methylation of II and III differ substantially from those for N-alkylation of meta- and para-substituted pyridines.[11,16,20,21] For example, while the *o*-amino group is just slightly activating, the *p*-amino group activates strongly. *o*-Alkyl groups deactivate while *m*- and *p*-alkyl groups activate. In general, meta- and para-substituted pyridines give a good Brønsted plot with both groups lying on the same line.

That the results for ortho and para N-methylation are not simply related is to be anticipated from a knowledge of the effects of substituents on pK_a values. The pK_a values of II show a good correlation with meta σ values and not with para σ values.[15] Inductive effects are relatively more important in the ortho series.

In an attempt to correct for the special nature of the electronic effects of ortho substituents, we have compared the relative rates of N-methylation with experi-

(19) K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Plenum Press, New York, N. Y., 1967, pp 146–149; D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

(20) J. A. Zoltewicz and L. W. Deady, unpublished results.

(21) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3596 (1964).

mental K_a values for the same bases. It is clear from Figure 1 that there is considerable scatter in this Brønsted plot. All of the kinetic data cannot be incorporated into a single, satisfactory correlation. Some of the scatter is larger than the 25% commonly found in linear free-energy relationships.[22] For example, the effect of a methyl group is not additive. 2-Methyl- is 2.6 times and 2,6-dimethylpyridine is 43 times less reactive than pyridine. 2-Ethyl- is about 2 times less reactive than 2-methylpyridine. 2-Acetylamino- negatively deviates by a factor of about 10 and 2-(2-pyridyl)pyridine by about 25 from the Brønsted line drawn for monosubstituted compounds.

The results in Figure 1 suggest that separate correlation lines are required for 2-substituted and 2,6-disubstituted pyridines, not including pyridine, the parent compound. The line for the monosubstituted compounds is drawn so as to favor the smaller groups. Both lines are drawn with the same slope. Even with two lines, there is scatter. That the results for the 2,6-disubstituted compounds show a Brønsted correlation is only a suggestion because of our limited study. It is interesting that the quinoline and 2-methylquinoline results fit the Brønsted lines for mono- and disubstituted pyridines, respectively, about as well as any pyridine. The effect of the fused benzene ring appears to be much like that of an ortho substituent. By comparison, isoquinoline lies on a Brønsted line which includes pyridine and meta- and para-substituted pyridines.[20,21] The slope of the line we have drawn for ortho-substituted pyridines is 0.4, the same as that found for meta-substituted pyridines reacting with methyl iodide in DMSO.[20]

Proton transfer reactions involving II and III are expected to be good models for the alkylation reaction. These proton transfer reactions reflect the electronic effects of the substituents on the rates of attack of the pyridines on water molecules. This follows because (1) $pK_w = pK_a + pK_b$ where K_b is the equilibrium constant for the reaction $B + H_2O \rightleftarrows BH^+ + OH^-$ and (2) the rate constant for the reaction of BH^+ and OH^- is expected to be that for a diffusion-controlled reaction.[23] That is, changes in K_b with pyridine structure reflect changes in the rate of reaction of pyridine B with H_2O. Steric factors are not important because of the small size of the proton which is being transferred. Thus, the results in Figure 1 indicate that ortho substituents do not influence the rates of reaction of pyridine nucleophiles with methyl iodide and with water in exactly the same way.

Consider now the question of the cause of the scatter in the Brønsted plot. It may be suggested that the scatter is a consequence of the use of different solvents. The rate data were derived using DMSO but the pK_a values result from studies using aqueous solutions. While this suggestion can not be ruled out rigorously, it does not seem likely that this is the primary cause of the scatter. (1) No such scatter results in the case of N-methylation of meta-substituted pyridines; again data are derived using DMSO and water solvents.[20,24] (2) The same reactivity order, H > 2-CH_3 > 2-C_2H_5, is consistently reported for a variety of alkylating agents in a variety of solvents, including water.[7-9,11]

We can think of two possible reasons for the poor fit of the data in Figure 1. (1) The K_a values do not correctly express the nature of the electronic effects in the alkylation reactions and/or (2) steric factors are important.

It is to be expected that our data could be better fit by a multiparameter equation,[25] but the following conclusion is still expected to hold. Steric effects influence the rates of N-methylation of II and III.

The term steric effects is used in a broad sense and includes the common notion of steric compressions as well as steric hindrance to solvation, resonance, and motion (a conformational factor).[15,26]

Since steric effects are expected to be more important for the reactions of III, the central question raised by our results is whether steric effects influence the rates of N-methylation of less bulky II. That steric effects do operate throughout the monosubstituted pyridine series is indicated by the positive deviation of the hydrogen "substituent" from the Brønsted correlation line.[27]

Superimposed on the electronic effect of an ortho substituent is a steric effect which is nearly constant for those substituents lying close about the Brønsted line for monosubstituted pyridines. It is surprising how insensitive the rates of N-methylation are to small changes in substituent size. However, for groups such as 2′-pyridyl, steric effects dominate reactivity.

The N-alkylation reaction is especially suited to probing subtle changes in steric requirements at the reaction site. It would be of interest to determine how the size of other alkylating agents would influence the scatter in Brønsted plots for ortho-substituted pyridines.

Experimental Section

Materials.—All compounds were obtained from Aldrich Chemical Co. except 2-acetylaminopyridine, mp 68–69° (lit.[28] mp 71°), which was prepared from the amine. All but one of the methiodides reported in this study have been prepared.[7,10,12,28,29]

From the reaction of 2-amino-6-methylpyridine and methyl iodide in DMSO, two products were isolated. Addition of ethyl acetate to a reaction mixture resulted in the formation of an oily precipitate. This material on fractional crystallization from ethanol gave two iodides: 1,6-dimethyl-2-aminopyridinium iodide, mp 191–193° (*Anal.* Calcd for $C_7H_{11}IN_2$: C, 33.6; H, 4.4; N, 11.2. Found: C, 33.6; H, 4.5; N, 11.1.); 2-methyl-6-trimethylammoniopyridine iodide, mp 182.5–183.5° dec (*Anal.* Calcd for $C_9H_{15}IN_2$: C, 38.8; H, 5.4; N, 10.1. Found: C, 38.6; H, 5.3; N, 9.9).

DMSO was dried over molecular sieves. DMSO-d_6 was obtained from Stohler Isotope Chemicals.

Relative Rates of Methylation with Methyl Iodide in DMSO.—Three methods were employed but the preparations of reaction mixtures were essentially the same and have been reported.[15] Various compounds served as internal standards; they are listed in Table I. Analyses were made using nmr at 60 MHz.

(22) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(23) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); E. E. Grunwald and E. K. Ralph, *Accounts Chem. Res.*, **4**, 107 (1971).

(24) The data in ref 16 may be employed to give such a Brønsted plot.

(25) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 7.

(26) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, Chapter 4.

(27) It has been noted that the value for a hydrogen "substituent" often deviates from correlation lines established by other substituents.[15,22]

(28) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

(29) E. Koenigs, K. Köhler, and K. Blindow, *Chem. Ber.*, **58**, 933 (1925); A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *ibid.*, **54**, 814 (1921); O. Magidson and G. Menschikow, *ibid.*, **59**, 1209 (1926); F. H. Westheimer and O. T. Benfey, *J. Amer. Chem. Soc.*, **78**, 5309 (1956).

TABLE II

CHEMICAL SHIFTS OF THE *N*-METHYL GROUPS OF 2-SUBSTITUTED AND 2,6-DISUBSTITUTED *N*-METHYLPYRIDINIUM IODIDES IN DMSO[a,b]

Substituent	τ	Substituent	τ
H	5.51	Cl	5.55
CH_3	5.63	Br	5.50
C_2H_5	5.58	CN	5.33
NH_2	6.13	2′-C_5H_4N	5.63
$NHCOCH_3$	5.70	$C_6H_5CH_2$	5.55
CO_2CH_3	5.35	2,6-diCH_3	5.88
		2-CH_3-6-NH_2	6.31

[a] The DMSO satellite peak at τ 6.23 served as a reference standard. [b] Value for 2-methylquinoline is τ 5.50.

Results for pyridine, 2-aminopyridine, and all alkylated compounds except 2-methylquinoline were obtained by a method reported earlier.[16] This method is based upon a determination of the relative amounts of N-methylated products after all the methyl iodide limiting reagent had been consumed.

Rate constant ratios for all other compounds were calculated from product ratios using eq 1 or from product concentrations using eq 2. In order to determine product concentrations, mesitylene (ring signals) was employed as an internal standard. Chemical shifts for the *N*-methyl peaks are listed in Table II.

Registry No.—Methyl iodide, 74-88-4; 1,6-dimethyl-2-aminopyridinium iodide, 32654-50-5; 2-methyl-6-trimethylammoniopyridine iodide, 34314-77-7.

Acknowledgment.—This work was supported in part by the the National Science Foundation (GP 25500).

Formation of Triazabenzacephenanthrylium Salts. Their Solvolysis and Borohydride Reduction

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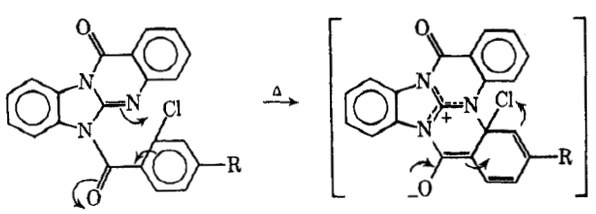
Received January 12, 1971

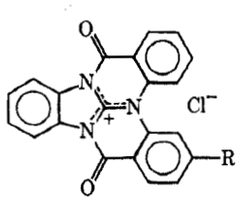
The preparation[1] of a series of benzimidazo[2,1-*b*]quinazolin-12-ones possessing potent immunosuppressive activity[2] has been described. A novel rearrangement of 6-(2-chlorobenzoyl)benzimidazo[2,1-*b*]quinazolin-12-ones is now discussed, together with the solvolytic cleavage of the resulting ionic pentacyclic salts. Borohydride reduction of this type of salt leads to unusual products containing the $CH(N<)_3$ unit.

The chlorobenzoyl compound **1** undergoes pyrolytic rearrangement which, we suggest, involves intermediate **2**. The initial rearrangement product **3** was not identified directly but by means of the derivatives described later. Similarly, the corresponding 2,4-dichlorobenzoyl derivative **4** gives the ionic chloride **5**.



1, R = H
4, R = Cl

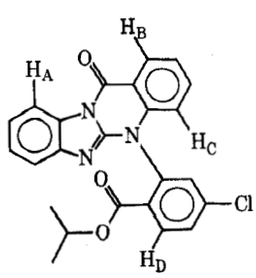
2



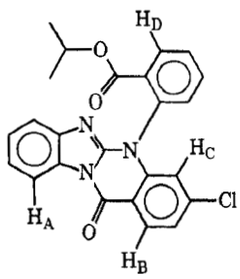
3, R = H
5, R = Cl

The solvolysis of **5** on refluxing with isopropyl alcohol will be discussed first since this is the only case in which *both* of the two possible isomeric products were actually isolated in the pure state.

These isomers analyzed as $C_{24}H_{18}N_3O_3Cl$; and this, together with the infrared and nmr spectra, is consistent for the isopropyl esters **6** and **7**.



6



7

Inspection of Dreiding models of structures of type **8** (Figure 1) reveals that the likely conformation is as shown. The plane of the aroyl benzene ring is approximately at right angles to the plane of the tetracyclic system, while the position of the aroyl carbonyl group is, as will be seen later, dependent on the nature of R.

The nmr spectra of **6** and **7** each exhibit signals integrating for three protons between 8.9 and 8.4 ppm. These are due to H_A, H_B,[3] and presumably H_D in the deshielding zones of the two carbonyl groups, with the aroyl carbonyl function in the position shown in the diagram. Also, both spectra contain a single proton signal, in the vicinity of 7 ppm; this arises from H_C which is shielded by the aroyl benzene ring. In the case of **6** this signal is in the form of a broad doublet (J = 7.5 cps) centered at 6.99 ppm; each of the peaks was widened by m and p coupling. In the spectrum of **7**, however, a narrowly spaced doublet (J = 1.7 cps) is evident (very small p coupling accounts for the sharpness of the doublet).

It was hoped that mass spectroscopy might confirm these assignments, but the mass spectra of **6** and **7**

(1) W. H. W. Lunn and R. W. Harper, *J. Heterocycl. Chem.*, **8**, 141 (1971).
(2) W. H. W. Lunn and R. W. Harper, *J. Med. Chem.*, **14**, 1069 (1971).
(3) W. H. W. Lunn and R. W. Harper, *Tetrahedron*, **27**, 2079 (1971).