3차 아민의 4차화반응에 관한 연구 (제 2 보). 치환 브롬화페나실류와 치환 피리딘류와의 반응에 관한 반응속도론적 연구

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Studies on the Quaternization of Tertiary Amines (II).
Kinetics and Mechanism for the Reaction of Substituted
Phenacyl Bromides with Substituted Pyridines

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요 약. 치환 브롬화페나실과 치환 피리딘과의 반응속도를 메탄올과 DMF 용매중, 25~45 °C의 온도범위에서 전기전도도법으로 측정하였다.

그 결과 두 용매 다 같이 치환 피리딘에서는 전자를 주는 기가 치환되었을 경우 반응속도 상수는 컸으며, 반대로 전자를 끄는 치환기일 경우는 반응속도 상수가 작았다.

기질에서의 치환기 효과는 핵에 전자를 끄는기가 치환되었을 경우 반응속도는 증가하였다.

이 사실들은 탄소원자에 아민이 친핵적으로 공격한다는 것을 알 수 있다.

브롬화페나실과 피리딘의 반응에서 보여준 등속온도는 메탄올과 DMF에서 각각 614와 202°K 였고, Brønsted β값은 0.29와 0.36 이었다.

치환 브롬화페나실과 피리딘과의 반응의 경우는 등속온도는 전자를 끄는 치환기일 수록 감소하였으며, β값은 그 반대였다.

위의 결과로부터 p-Cl에서 p-MeO 브롬화페나실로 감에 따라 N···C 결합형성이 점차적으로 줄어들고 있으며 결합 형성은 DMF가 메탄올보다 우세하게 진전함을 추측할 수 있다.

치환 피리딘의 경우 Hammett식의 ρ값은 양 용매에서 모두 부(−)의 값을 가졌다. 핵 치환 브롬화페나실에서의 ρ 값은 0.3의 적은 값이었으며 이는 메틸렌탄소에 피리딘의 질소 원자가 직접적으로 S_N2 공격을 한다고 생각된다.

ABSTRACT. Kinetics and mechanism for the reaction of substituted phenacyl bromides with substituted pyridines have been determined at 25, 35 and 45 °C in methanol and dimethylformamide by the conductivity method. The rate constants for the reaction of various pyridines with phenacyl bromide shown that electron-donating substituents in the pyridine increase the rate, while electron-attracting one decrease in both solvents.

The effect of substituents in substrate, the rate being increased by electron-attracting substituents. This is as expected for nucleophilic attack of amines on the carbon atom.

Isokinetic and Brønsted linear relationship were shown in the reaction of phenacyl bromide with pyridines in both solvent in which isokinetic temperature were obtained 614, 202 °K and β values were 0. 29, 0. 36 in methanol and dimethylformamide respectively.

In the case of the reaction of substituted phenacyl bromide with pyridines, isokinetic temperature decreases with increasing electron-attracting ability of the substituents in the phenacyl bromide, while the β values were reverse.

From the above results, it can be inferred that N⋯C bond formation decreases progressively from p-chloro- to p-methoxyphenacyl bromide and the bond formation predominates in DMF than methanol.

The ρ values of Hammett equation of the reaction of phenacyl bromide with substituted pyridines are negative in both solvent, but its value was larger negative in DMF than methanol and the ρ value of that of substituted substrates with pyridine was 0. 3, the low value is ascribed to direct S_N2 attack of the nitrogen atom in pyridine ring at the methylene carbon.

INTRODUCTION

After a report of Slater and Twiss that α-haloketones easily undergo S_N2 displacement, numerous aspects of such reactions have been actively studied[2,3] Pasto and his co-workers[4] studied the solvolysis of substituted phenacyl halides in various solvents and suggested that the mechanism of the solvolysis of the phenacyl halides is best described as proceeding *via* a highly nucleophilic displacement of halide by the solvent molecules according to low Hammett ρ value (0. 35), no rearranged products and the activation parameters. However nucleophilic displacement for phenacyl bromide with pyridines and substituent effects do not seem to have been made so for. We therefore thought it of interest to investigate kinetic study for nucleophilic displacements for phenacyl bromides.

The present work was to study the substituent effects for the reaction of phenacyl bromides with pyridines and Brønsted relationship compare with the reaction of w-bromo-1- or 2-acetonaphthones recently reported[5~7].

EXPERIMENTAL

Materials and Instruments. All materials used throughout were commercial products (Ka-Sei Chemical Co, Japan)

Pyridine was a commercial product purified by several distillation over potassium hydroxide before use. Other liquid pyridines were used without further purification, but solid pyridines and phenacyl bromides were recrystallized to constant melting point.

All purified pyridines were stored in brown ampoule or bottle filled with nitrogen gas.

N, N-dimethylformamide (DMF) was purified by distillation under reduced pressure (61°C/30mmHg) after standing with anhydrous magnesium sulfate for three days at room temperature. Methanol was purified by drying over magnesium turnings and then fractionally distillation and had b. p 64. 5~65°C at 760mmHg. IR spectra were recorded on a Hitachi EPI-2G Infrared Grating spectrometer, NMR spectra were recorded on Varian 60 MHZ spectrometer. Conductance measurements were used with a Chemtrix Type 70 conductivity meter(U. S. A).

Preparation of Compounds. Phenacyl bromide was prepared by known procedures and it's melting point agreed with that in the literature.

p-Bromophenacylpyridinium Bromide. A solution of 5.56 g (0.02 mole) of p-bromophenacyl bromide and 2 g(0.072 mole) of pyridine in 50 cc of pure anhydrous ether is placed in dry flask fitted with a reflux condenser on the water bath. The solution was kept refluxing for three hours. After keeping the mixture of crystals and solvent at room temperature, the products were isolated by filteration, washed several times with fresh portions of the ether and dried in vacuum dry oven.

The colorless material is sufficiently pure for many purpose. If higher purity is desired the crude product may be recrystallized from 20~25 cc of methyl ethyl ketone, yielding 4.1g (57 %) of colorless crystals melting at 222 °C (lit.[9] 225~230 °C)

The products obtained were identified by IR, ^{1}H NMR spectra and elementary analysis.

IR(KBr) 1690 cm^{-1}()C=O); H NMR(DMSO-d_6) δ9.2(2H, d, α-H), 9.0(1H, t, γ-H), 8.9 (2H, t, β-H), 7.9(4H, d, phenyl), 6.6(2H, s, —CH$_2$—). Found: Br, 22.30. Calcd. for C$_{13}$H$_{11}$NOBr$_2$: Br, 22.40.

Kinetics. The rate of reaction was measured by means of electric conductivity because the reaction is a kind of formation of salt, in which ions are formed from electrically neutral reagents.

A typical kinetic run is briefly described as follows.[10] The final concentration of phenacyl bromide prepared was made just 0.005 mole/l in 15 ml volumetric flask which was filled with nitrogen gas and solvent. That of pyridine was made just 0.1 mole/l with above same. A kinetic run was initiated by placing 15 ml of pyridine solution in the conductivity cell and adding 15

ml of the phenacyl bromide solution to give a reaction mixture that was 0.05 mole/l in pyridine and 0.0025 mole/l in phenacyl bromide. All measurements were done with pyridines in large excess over phenacyl bromide. Reactions were generally run to ca. 3 to 4 half-lives. Pseudo first-order rate constants were calculated from the slopes obtained from conventional plots of log(C_∞—C_t) against time using the least-squres method.

Second-order rate constants were calculated from the slopes of plots of the observed first-order rate constants against pyridine concentration. Activation energies were calculated from Arrhenius plot and activation entropies were obtained using the theory of absolute reaction rate

$$k=\frac{k_B T}{h}e^{\Delta S^*/R}e^{-\Delta H^*/RT}$$

RESULTS AND DISCUSSION

The second-order rate constants and activation parameters for the reaction of substituted pyridines with phenacyl bromides in methanol and DMF are given in Table 1 and 2.

Rate Constants and Activation Parameters. The rate constants for the reaction of various pyridines with phenacyl bromide shown shat electron-donating substituents in the pyridine increase the rate, while electron-attracting substituents decrease in both solvents(Table 1).

The effect of substituents in substrate, the rate being increased by electron-attracting substituents in the phenacyl bromides. This is as expected for nucleophilic attack of amines on the carbon atom. Activation parameters for the reaction of phenacyl bromides with pyridines are also noted in Table 1 and 2.

The values of the activation parameters show a regular variation with substituents in the pyridine ring: in methanol, electrondonating groups increase the rate and decrease ΔH^*

Table 1. Second-order rate constants for the reaction of phenacyl bromide with pyridines in MeOH and DMF.

No.	Substituent	$10^2k(l \cdot mol^{-1} \, min^{-1})$ in MeOH			E_a	ΔH^*	$-\Delta S^*$ (e. u)	$10^2k(l \cdot mol^{-1} \, min^{-1})$ in DMF		E_a	ΔH^*	$-\Delta S^*$ (e. u)
		45°C	35°C	25°C	kcal/mol			45°C	35°C	kcal/mol		
1	4-NH₂	148	81.2	45.4	11.7	11.1	25.0	11120.6	5092.0	15.2	14.6	3.8
2	3.5-(CH₃)₂	19.4	9.61	5.2	13.8	13.2	22.7	283.2	138.7	13.9	13.3	14.8
3	3-CH₃	13.2	—					215.5	104.4	14.1	13.5	14.7
4	H	9.38	4.34	1.73	15.0	14.4	20.2	99.3	50.4	13.2	12.6	19.1
5	3-CONH₂	2.34	0.98	0.41	16.9	16.3	16.8	—	—			—
6	3-COC₆H₅	2.05						22.2	11.2	13.9	13.3	21.4
7	3-Br	1.73						11.7	6.5	11.6	11.0	28.5
8	3-CN	0.83						6.9	6.9	11.2	10.6	30.7
9	4-CN	1.54						7.5	4.4	10.4	9.8	33.1

Table 2. Second-order rate constants for the reaction of substituted phenacyl bromides with pyridines methanol.

Sub-pyridine \ Sub-phenacyl bromide	p-Cl phenacylbromide					p-CH₃O phenacylbromide			
	$10^2k(l/mol \cdot min)$			ΔH^* (kcal/mol)	$-\Delta S^*$ (e. u)	$10^2k(l/mol \cdot min)$		ΔH^* (kcal/mol)	$-\Delta S^*$ (e. u)
	45 °C	35 °C	25 °C			45°C	35°C		
(1) 4-NH₂	156	86.0	48.1	11.6	11.0	25.3	14.2	75.9	12.2	11.6	23.6
(2) 3.5-(CH₃)₂	27.6	13.0	6.03	14.7	14.1	19.1	18.3	8.60	14.7	14.1	19.9
(3) 3-CH₃	20.2						12.0			
(4) H	11.0	4.93	2.21	15.6	15.0	17.9	8.77	4.06	15.0	14.4	20.3
(5) 3-CONH₂	2.47	1.04	0.45	14.1	13.5	22.2	1.74	0.74	16.6	16.0	18.4
(6) 3-COC₆H₅	2.21						1.60			
(7) 3-Br	1.82						1.57			
(8) 3-CN	0.70						0.58			
(9) 4-CN	1.67						1.47			

while the reverse is ture for electron-attracting groups, but in DMF, electron-donating groups increase the rate and ΔS^*.

A linear relationship between the enthalpies and the entropies of activation has been realized (*Fig*. 1).

This linearity means the substituent is indicative of a single mechanism[11]. From the slopes of the linear plot, the isokinetic temperature are calculated to be 614 and 202 °K in methanol and DMF respectively.

This result agreed with that in methanol, the rate of reaction of phenacyl bromide with pyridines was controlled by ΔH^* and in DMF, its rate controlled by ΔS^*.

Isokinetic relationship was shown in the reaction of substituted phenacyl bromides with pyridines too (*Fig*. 2), in which isokinetic temperatures are calculated to be 818(r=0.985) 614(r=0.991) and 498 °K(r=0.965) in the reaction of p-methoxy, unsubstituted and p-chlorophenacyl bromide respectively in methanol.

It is interesting to note that the reaction was increased in S_N2 mechanism in going from the electron-donating group to the electron-withdrawing.

Br∮nsted Linear Relationship. It was generally accepted that Br∮nsted linear relationship was shown between reaction and
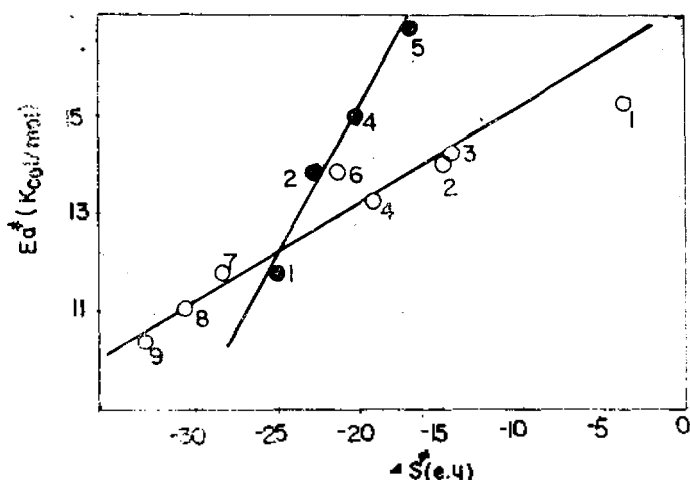
Fig. 1. The isokinetic relationship for the reaction of phenacyl bromide with substituted pyridines in MeOH (●) and DMF (○). The numbers on the curves refer to the series numbers in *Table* 1.
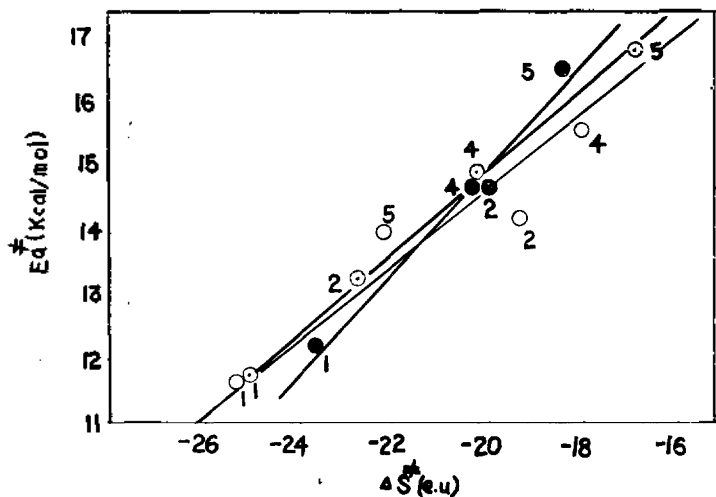

Fig. 2. The isokinetic relationship for the reaction of substituted phenacyl bromide with pyridines in methanol. ⊙ : phenacyl bromide, ○ : *p*-chlorophenacyl bromide, ● : *p*-methoxyphenacyl bromide.

basicities of nucleophiles in which attacking atom is the same in S_N2 reaction.

The direction of the influence of the substituents in the pyridine ring shows that the rate of reaction depends on the electron density on the nitrogen atom.

Good linearity of this relationship has been reported[12] on quarternization of substituted

N, N-dimethylanilines.

In this study, a good linear relationship was shown (in *Fig.* 3) between log$k$ against pka of pyridines

$$\log k = 0.29 \ pK_a - 2.47 \quad (r=0.993)$$
$$\text{in MeOH at } 45°C$$
$$\log k = 0.36 \ pK_a - 1.99 (r=0.991)$$
$$\text{in DMF at } 45°C$$

These different β values agreed with that of isokinetic temperature of the reaction of phenacyl bromide with pyridines in methanol and DMF respectively.

The relationship of nucleophilicity to basicity is illustrated in *Fig.* 4 for the *p*-chloro $(\beta=0.296)$ and *p*-methoxy compounds $(\beta=0.282)$.

The other phenacyl bromide $(\beta=0.290)$ gave similar plots.

The β values (*Table* 3.) of these plots, though its value is very similar, decrease with increasing electron-donating ability of the substituents in the phenacyl bromide. Thus β is correlated with σ as shown in *Fig.* 5.

From the β value, it can be inferred that N⋯C bond formation decreases progressively from *p*-chloro to *p*-methoxy phenacyl bromide. This is in agreement with prediction of substituted effects for a simple S_N2 displacement reaction.

A similar conclusion was reached for the reaction of anilines with substituted sulphonyl chloride in methanol[12]

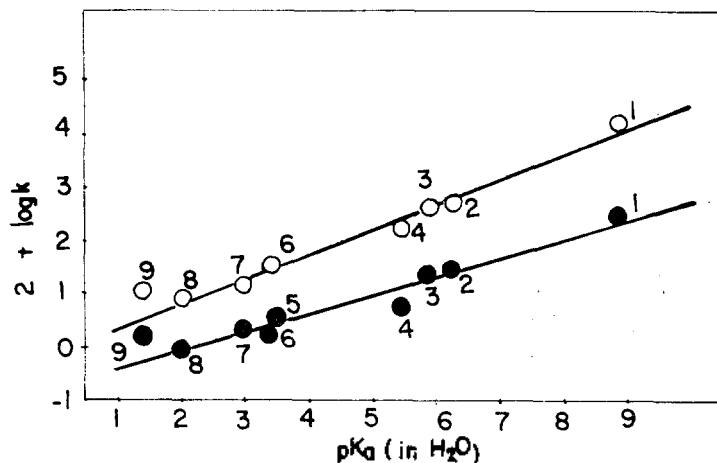In *Fig.* 3, 4-NH₂ and 4-CN groups are deviated from the linearity and was so much

Fig. 3. Correlation between log$k$ and pK_a for the reaction of phe-nacyl bromide with pyridines in MeOH (●) DMF (○) at 45°C.
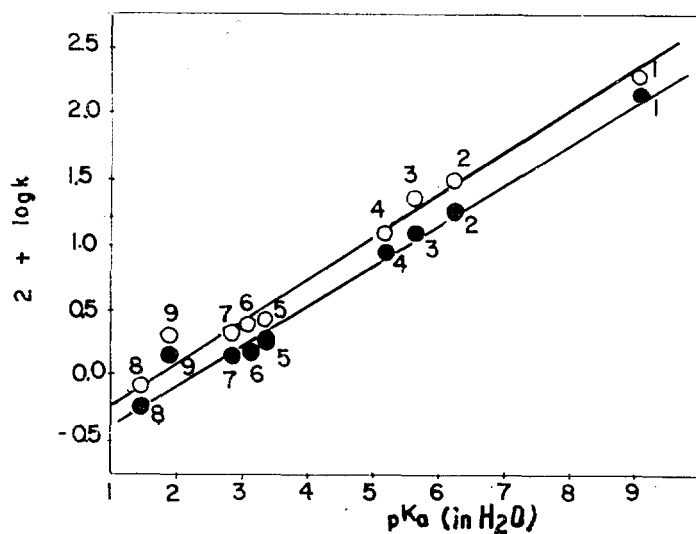

Fig. 4. Relationships of log$k$ to pK_a for the reaction of p-chloro and p-methoxyphenacyl bromide with substituted pyridines in mthanol at 45°C.

Table 3. Slopes (β) and correlation coefficients (r) of the Brφnsted plots (*Fig.* 4) for the reaction of pyridines with phenacyl bromides.

Phenacyl bromide	α	β	r
p-Cl	0.227	0.296	0.986
H	0.000	0.290	0.993
p-MeO	−0.268	0.282	0.970

faster than any other compounds.

Perhaps this fact was resulted from solvent effect: pK_a values of pyridines were determined in water, but these reaction were carried out in DMF and MeOH.

Amino and cyano groups have hydrogen bonds in water, but these bonds become weaker in methanol and disappear entirely in DMF, so amino group indicated stronger electron donating power, but cyano group weaker electron attracting power.

Thus both groups accelerlated the rates of reactions. These solvent effects agreed with Tsuruta's work[14].

Hammett Relationship. In the case of a heterocyclic compound, it was reported[15] that Hammett plot was not well correlated with σ value. The reason was that hetero atoms caused larger electro-negativity especially in nitrogen atom than carbon in alicyclic compounds, but nucleophilic reaction with pyridines in S_N2 reaction was reported[16] to good linearity in some case.

These rate constants in substi-tuted pyridines are also correlated by the σ constants[17] giving a Hammett plot with $\rho = -1.32$ and -1.73 in methanol and DMF (*Fig.* 6) res-pectively.

In *Fig.* 6, 4-amino and 4-cyano groups in pyridine were deviated from linearity, the reason is considered to be difference between pyridine and benzene ring in which the reac-tion center of one is carbon and the other
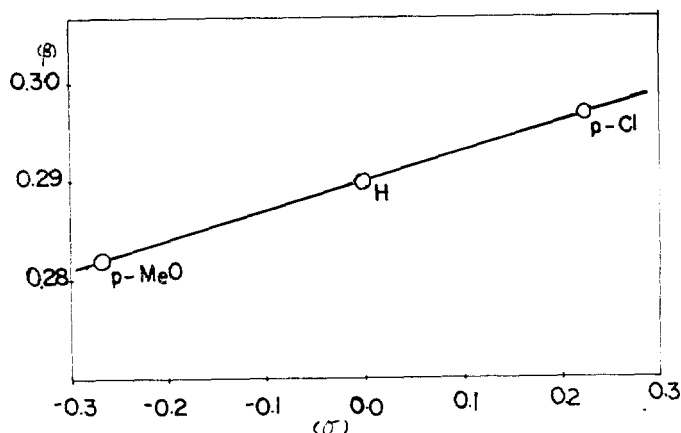
Fig. 5. Dependence of the Brönsted slopes, β (*Table* 3) upon the σ values for the phenacyl bromide substituents.
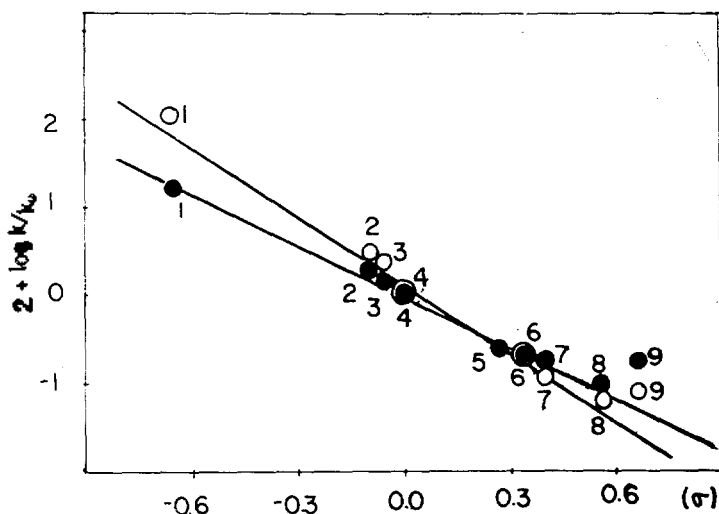

Fig. 6. Hammett plot for the reaction of phenacyl bromide with (substituted) pyridine in methanol and DMF at 45°C

is nitrogen. π-electron densities are localized at direction of nitrogen atom because electronegativity of nitrogen is larger than carbon.

This result occurred that the points for groups of potential (-I-R) type in the 4-position fall off the line in a direction which implies a increment or reduction in their electron-donating and electron-withdrawing capacity as indicated by their σ values. Thus

the apparent σ values from *Fig.* 6 for 4-NH$_2$ and 4-CN are -1.2 (σ^+) ad 0.50, rather than -0.66 and 0.66 respectively.

In additional remark, this seems rational when it is considered that resonance withdrawal of electrons by CN groups will be far more difficult from a nucleus containing an electronegative atom than from benzene nucleus. But this argument leads to the deduction that the correlation with resonance donors should be with σ^+ rather than σ values, because in such case there will be, apparently, greater rsesonance with the pyridinium ion than with the uncharged pyridine nucleus.

The Hammett ρ value of pyridines in DMF is large than methanol and this result fits in with expectation of β value.

According to these results, S_N2 reaction of phenacyl bromide with pyridine in DMF is more predominate than methanol.

Hammett σ plots of this work showed negative slopes in both solvents ($\rho = -1.32$ in methanol, -1.73 in DMF).

Compared with ρ values for the reaction of pyridines with ethyl iodide[18] ($\rho = -2.94$), allyl bromide ($\rho = -1.42$) and β-phenylethyl tosylate ($\rho = -1.33$), the ρ values of this work in methanol and DMF were lower values than that of ethyl iodide, but about same value of latter two compounds.

This fact suggested that this reaction in methanol is very similar to that of allyl bromide and β-phenylethyl tosylate in S_N2 mechanism.

Table 4. Second-order rate constants ($k_2 \times 10^2$, $l \cdot mol^{-1}min^{-1}$ and ρ values for the reactions of substituted phenacyl bromide with pyridines at 45°C in methanol.

Pyridines phenacyl bromides	4-NH$_2$	3,5-(CH$_3$)$_2$	3-CH$_3$	H	3-CONH$_2$	3-COC$_6$H$_5$	3-Br	3-CN	4-CN	Hammett ρ
p-MeO	142	18.3	12.0	8.77	1.74	1.60	1.57	0.58	1.47	1.3
H	148	19.4	13.2	9.38	2.34	2.05	1.73	0.83	1.54	1.3
p-Cl	156	27.6	20.2	11.0	2.47	2.21	1.82	0.70	1.67	1.5
p-Br	—	—	—	11.01	—	—	—	—	—	—

Though solvents were changed from methanol to DMF and the rate constants were different in both solvents(pyridine: $9.4 \times 10^{-2} l/mol \cdot$
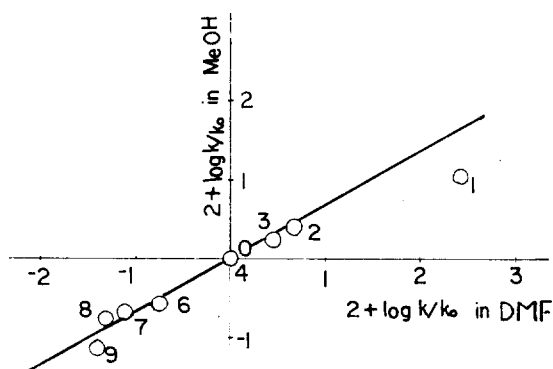

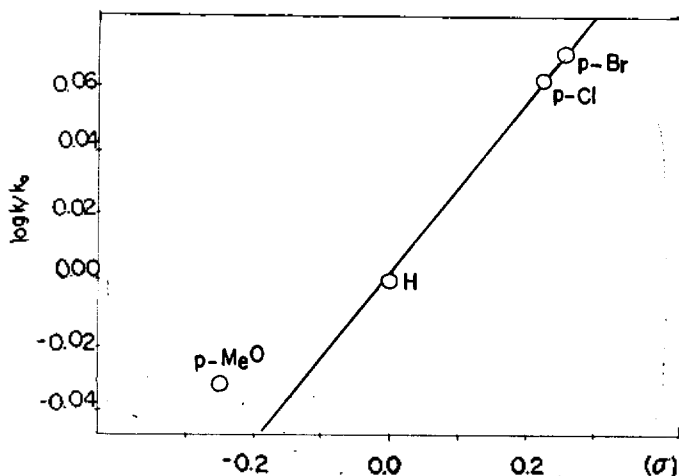*Fig.* 7. Plot of rate constant for the reaction of phenacyl bromide with pyridines in MeOH *vs.* DMF at 45 °C.

Fig. 8. Hammett plot for the reaction of substituted phenacyl bromides with pyridine in methanol at 45 °C.

min in MeOH, $99.3 \times 10^{-2}l/mol$, min in DMF at 45 °C), The mechanism in both solvents were not changed only sensitivity to substituents was larger in DMF as shown graphically in *Fig.* 7, *i.e.* log-log plots of rate constant of the reaction of phenacyl bromide with pyridine in methanol and DMF at 45 °C [$\log k/k_0$ MeOH $=0.77 \log k/k_0$ DMF $(r=0.999)$].

The ρ values for the reaction of *p*-methoxy, unsubstituted and *p*-chlorophenacyl bromide with pyridines are obtained 1.5, 1.3 and 1.3 respectively except 4-CN and 4-NH$_2$ (*Table* 4).

The ρ values depend on the substrate reactivity: the more (less) reactive is the substituted phenacyl bromide, the lower (higher) is the reaction tensitivity to substituent effects in the pyridines, though its ρ values of latter two compounds are same within experimental error, in agreement with the Hammond postulate and the selectivity principle[19].

The validity of the Hammett equation was examined in the reaction of substituted phenacyl bromides with pyridine in methanol at 45 °C (*Fig.* 8.) The reaction conforms with the Hammett equation at four substituents. The ρ values observed by us is 0.30 at 45 °C in methanol except methoxy phenacyl bromide $(r=0.9999)$.

This low value is very similar

to those obtained by others in direct S_N2 displacement reactions of phenacyl bromide with nucleophiles.

The products formed under the condition of our kinetic study are phenacylpyridinium bromide only and there was no detectable trace of rearranged products. This shows that these is no participation of phenyl group and carbonyl oxygen in the transition state. The low ρ value rules out intermediate of addition of pyridine to carbonyl carbon: for its formation would require a high ρ value in view of the values of 2.0, 3.2 and 2.76 (2.24) found for the addition reactions of methanol, methoxide ion, and hydroxide ion, respectively, to substituted benzaldehyde[20~22]. The low ρ value of observed by us in the reaction of p-substituted phenacyl bromide with pyridine is ascribed as *Sheme* 1 to direct S_N2 attack of the nitrogen atom in pyridine ring at the methylene carbon. Similar conclusion has been reached by Pasto and his coworkers in the solvolysis of phenacyl bromides.
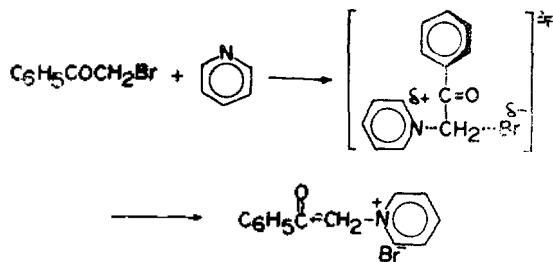
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