[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTEEN UNIVERSITY, EVANSTON, ILL.]

# Relative Side-Chain Ethylation of 2- and 4-Alkylpyridines[1,2]

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The competitive side-chain ethylation reactions of various pairs of 2- and 4-alkylpyridines were investigated. The results obtained indicate that in the majority of cases the rate of ethylation is a function of the acidity of alkylpyridines. The major component of the ethylated material was in each case derived from the more acidic starting compound. 4-Alkylpyridines undergo ethylation more easily than the corresponding 2-alkylpyridines. The ethylation reaction is hindered by the presence in the side chain of an isobutyl group. The competitive ethylation reactions indicate that solvation of carbanions by the substituted pyridines may play an important role in the ethylation reaction. Certain apparent abnormalities in the ethylation reactions are discussed.

## Introduction

It was previously shown that alkylpyridines containing at least one hydrogen atom on the $\alpha$-carbon atom of the alkyl side chain can undergo side-chain alkylation with ethylene[1,4,5] or propylene[1,4] in the presence of sodium catalyst. In order to gain a better understanding of the mechanism of alkylation, the relative rates of ethylation of various alkylpyridines were determined by means of competitive reactions similar to those used in the study of alkylbenzenes.[6] 2- and 4-alkylpyridines having methyl, ethyl, isopropyl, *n*-propyl, *sec*-butyl, isobutyl and methylisobutyl groups as substituents were used in the present investigation.

The following types of competitive reactions were studied: 1, ethylation of 2-alkylpyridines (Table I); 2, ethylation of 4-alkylpyridines (Table II); 3, ethylation of isomeric 2- and 4-alkylpyridines (Table III).

TABLE I

COMPETITIVE ETHYLATIONS OF 2-ALKYLPYRIDINES

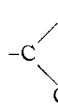
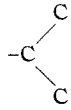
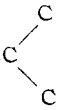
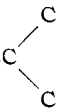
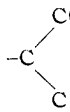
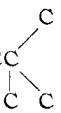
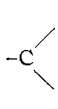
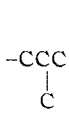
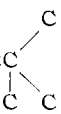
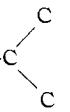
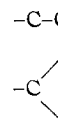
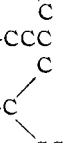
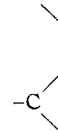
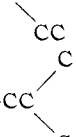
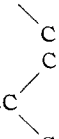
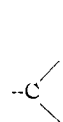
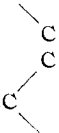
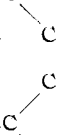
| Expt. | 2-Alkylpyridines used 2-$C_5H_4NR$ R = | 2-$C_5H_4NR'$ R′ = | Temp., °C. | Maximum press., atm. | Extent of reacn., % | Mole ratio R:R′ |
|---|---|---|---|---|---|---|
| 1 | -C | -C-C | 150 | 40 | 20 | 5.5 |
| 2 | -CC |  | 150 | 35 | 15 | >25 |
| 3 | -CC | -CCC | 140 | 29 | 9 | 17 |
| 4 |  |  | 153 | 42 | 10 | >25 |
| 5 |  |  | 150 | 52 | 15 | 15 |
| 6 | -CCC |  | 150 | 35 | 30 | 7 |
| 7 |  |  | 150 | 35 | 9 | 8.5 |
| 8 |  |  | 150 | 35 | 20 | 6.5 |
| 9 |  |  | 150 | 36 | 19 | 13.5 |

TABLE II

COMPETITIVE ETHYLATIONS OF 4-ALKYLPYRIDINES

| Expt. | 4-Alkylpyridines used 4-$C_5H_4NR$ R = | 4-$C_5H_4NR'$ R′ = | Temp., °C. | Maximum press., atm. | Extent of reacn., % | Mole ratio R:R′ |
|---|---|---|---|---|---|---|
| 10 | -C | -C-C | 144 | 74 | 20 | 0.13(1:7.5) |
| 11 | -C-C |  | 165 | 27 | 27 | 1.2 |
| 11a | -C-C |  | 144 | 3 | 15 | 1 |
| 12 | -C-C | -CCC | 160 | 31 | 35 | 1.9 |
| 13 |  |  | 145 | 35 | 19 | 2.3 |
| 14 |  |  | 150 | 51 | 37 | 10 |
| 15 | -CCC |  | 141 | 30 | 15 | 8.3 |
| 16 |  |  | 155 | 29 | 18 | 16 |
| 17 | -C |  | 145 | 36 | 10 | 3 |

(1) Paper XIX of the series "Base-catalyzed Reactions." For paper XVIII, see H. Pines and B. Notari, THIS JOURNAL, **82**, 2209 (1960).

(2) This research was supported by a Grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of the fund.

(3) Petroleum Research Fund Postdoctoral Fellow, 1958–1959. On leave of absence from Ente Nazionale Idrocarburi, San Donato Milanese, Milano, Italy.

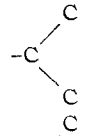
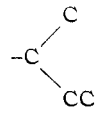
(4) H. Pines and D. Wunderlich, THIS JOURNAL, **81**, 2568 (1958).

(5) E. Profft and F. Schneider, *Arch. Pharm.*, **289**, 99 (1956).

(6) H. Pines and L. Schaap, THIS JOURNAL, **80**, 3076 (1958).

TABLE III

COMPETITIVE ETHYLATION OF ISOMERIC 2- AND 4-ALKYLPYRIDINES

| Expt. | 2- and 4-Alkylpyridines $C_5H_4NR$, R = | Temp., °C. | Maximum press., atm. | Extent of reacn., % | Mole ratio 4-:2- |
|---|---|---|---|---|---|
| 18 | -C | 150 | 38 | 15 | 3.5 |
| 19 | -CC | 134 | 67 | 20 | 4 |
| 20 | -CC | 110 | 77 | 20 | 6.1 |
| 21 |  | 150 | 31 | 21 | 6.7 |
| 22 |  | 150 | 46 | 19 | 7 |

In the study of the relative rates of side-chain ethylation in aromatic hydrocarbons it was found that the substitution of a benzylic hydrogen by an alkyl group greatly influences the rate of ethylation. With such a substitution two factors were changed simultaneously—the acidity of the alkylbenzene and the steric requirements of the intermediate benzylic carbanions participating in the reaction. In the pyridine series, barring solvation effects, it should therefore be possible to separate these two factors. It was observed by us that 4-alkylpyridines are more acidic than the corresponding 2-isomers; their steric requirements for ethylation should, however, be the same. For this reason it was thought possible to determine the effect of alkylpyridine acidity on the side-chain ethylation reaction.

## Results

The experimental results are summarized in Tables I III. The structure of the ethylated product from each of the listed alkylpyridines resulted from the replacement of a hydrogen atom on the $\alpha$-carbon of the alkyl group by an ethyl group. In carrying out the experiments, equimolar ratios of the different pairs of alkylpyridines were used and the reaction was planned in such a way as to permit in most cases only about 20% of the alkylpyridines to undergo ethylation. This was necessary in order not to disturb to any considerable extent the ratio of the original alkylpyridines subjected to ethylation.

From Table I it is seen that the extent of ethylation of 2-picoline is over five times as great as that for 2-ethylpyridine (expt. 1). The ratio of ethylation for 2-ethyl- and 2-isopropylpyridine as compared with its next higher homolog is much higher: 17:1 to >25:1 (expt. 2, 3, and 4).

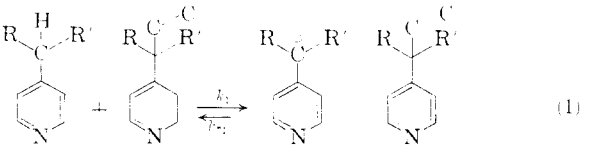
In the 4-alkylpyridine series the ratio of 4-picoline to 4-ethylpyridine is 1:7.5 (Table II, expt. 10) which is the reverse of what was found in the 2-series. The ratio of ethylation of 4-ethyl- as compared with 4-propylpyridines and that of 4-isopropyl- as compared with 4-*sec*-butylpyridine is of the order of 1.2:1 to 2.3:1 (expt. 11–13). The ratio is, however, greatly increased (8.3:1 to 16:1) when an alkylpyridine is compared with its higher homolog containing an isobutyl group in the side chain (expt. 14–16, Table II).

The competitive reactions show that the 4-alkylpyridines undergo ethylation much more easily than the corresponding 2-isomers; for the picolines the ratio of 4- to 2- was 3.5:1 and for the *sec*-butylpyridines the ratio was 7:1 (Table III).

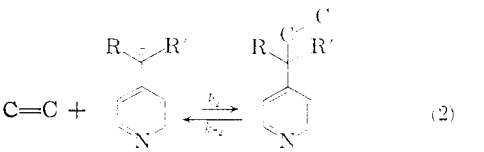
The temperature has an effect on the ratio of the ethylated products, lower temperature favoring the formation of reaction products from the more acidic compounds (expt. 19 *vs.* 20, Table III).

## Discussion

The mechanism proposed for the addition reaction to ethylene is



(1)



(2)

The initiation step is here not considered since, as soon as the steady state is reached, it no longer influences the reaction.

The path of the ethylation reaction depends on the relative values of the rate constants and upon the pressure of ethylene.[1] The mechanism of ethylation of alkylpyridine is very similar to that of alkylbenzenes.[1,4,7,8] For that reason the information regarding the ethylation of alkylbenzenes could be used in elucidating the mechanism of alkylpyridines alkylation.

It has been reported[9] that (−)-2-phenylpentane reacts with ethylene at elevated pressure to form optically inactive 3-methyl-3-phenylhexane. The recovered 2-phenylpentane had the same optical activity as the starting material. This would indicate that metalation is the rate-determining step and that the addition to ethylene is a relatively fast subsequent reaction. Had the rate-determining step been the addition of carbanions to ethylene, then the carbanions present would have a chance to racemize the starting material by prototropic transfer. It has been shown[10] that carbanions undergo racemization readily.

In light of the above findings the rate of formation of ethylated alkylpyridines should be a function of the rate of metalation. In many instances this was found to be the case. In expt. 2–4 it was found that the more acidic alkylpyridines[11] give the major amounts of the ethylated material. The effect of the acidity of alkylpyridines on the rate of ethylation was also demonstrated in competitive reactions between the isomeric 2- and 4-

(7) H. Pines, J. A. Vesely and V. N. Ipatieff, THIS JOURNAL, **77**, 554 (1955).

(8) H. Pines and V. Mark, *ibid.*, **78**, 4216 (1956).

(9) H. Hart, *ibid.*, **78**, 2619 (1956).

(10) R. L. Letsinger, *ibid.*, **72**, 4842 (1959).

(11) The relative acidity of alkylpyridines was not reported. It is fair, however, to assume that the relative acidities of the alkylpyridines follow the same pattern as that of alkylbenzenes.[12]

(12) H. Hart and R. E. Crocker, THIS JOURNAL, **82**, 418 (1960).

alkylpyridines. The 4-alkylpyridines, being more acidic underwent ethylation more readily (Table III).

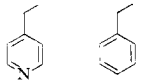
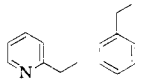
The effect of acidity on the rate of ethylation was further indicated by competitive reactions in which 2- and 4-ethylpyridine, respectively, were ethylated in the presence of ethylbenzene (Table IV). As expected[13] only a trace of *sec*-butylbenzene was formed when 2- and none when the more acidic 4-ethylpyridine was used.

Metalation, however, is not always the rate-determining steps; kinetic studies had revealed that at lower pressures the pressure of ethylene may determine the rate of ethylation.[1]

The competitive ethylation carried out with 2-alkylpyridines (Table I) show surprising results. The ratios of ethylated products obtained from 2-ethyl- *vs.* 2-isopropyl and *vs.* *n*-propyl- and from 2-isopropyl- *vs.* 2-*sec*-butylpyridine were over 17 to 1. These ratios are much higher than those obtained from the corresponding competitive ethylation reactions of 4-alkylpyridines (Table II) and of alkylbenzenes.[6] If the acidity of the compounds undergoing ethylation were the rate-determining factor, then the ratios of the ethylated products obtained from 2-alkylpyridines should have values intermediate between those obtained for the corresponding 4-alkylpyridines and alkylbenzenes. It is tentatively proposed that the solvation of the carbanions might be responsible for the observed results. If the nitrogen of the pyridine nucleus is involved in the solvation, either in the solvated carbanion and/or in the solvating molecule, then the alkyl group in the 2-position will interfere with the solvation. The carbanion with the smaller side chain will be more effectively solvated, its concentration increased, and its ethylated product favored. This would fall in line with the gradual decrease in reaction ratio observed with increasing size of the alkyl group. Preliminary experiments indicate that when competitive reactions are performed in the presence of a third compound with good solvating power, *e.g.*, tetrahydrofuran, a lower ratio is obtained.

TABLE IV

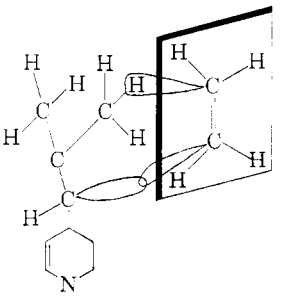
COMPETITIVE ETHYLATION OF ALKYLPYRIDINES AND ALKYLBENZENES

| Expt. | Starting material A | B | Extent of reacn., % | Temp., °C. | Maximum press., atm. | Mole ratio A:B |
|---|---|---|---|---|---|---|
| 1 |  |  | 20 | 146 | 69 | >25[a] |
| 2 |  |  | 30 | 150 | 79 | 25[b] |

[a] No reaction product from ethylbenzene detectable. [b] Only a trace of *sec*-butylbenzene was found in the reaction mixture.

When 4-alkylpyridines are compared with higher homologs containing an isobutyl group in the side chain (*e.g.*, iso- and *n*-propyl- *vs.* isobutyl- or *sec*-butyl- *vs.* sec-isoamylpyridine, expt. 14–16, Table III), a much greater molar ratio of the corresponding ethylated product results than would be expected on the basis of the assumed acidities of the respective compounds.[14]

The above observation could be accounted for if the steric effects involved in the addition of carbanions to ethylene are considered. The ethylation reaction could be visualized as an approach of the carbanion to the plane of the ethylene molecule so as to polarize the $\pi$-electron system and then form the final $sp^3$-hybrid. Inspection of molecular models shows that under these conditions there will be steric hindrance to the approach to the ethylene molecule when the side-chain contains $\beta$-methyl group. This effect would be expected to increase with the increase in the number of $\beta$-methyl groups.



In the cases of toluene *vs.* ethylbenzene[6] and of 4-methyl- *vs.* 4-ethylpyridine (expt. 11, Table II) the acidity cannot be the only controlling factor, since the ethyl derivatives react faster. It may be that, owing to a greater loss of resonance energy in the activation process of the primary carbanion, the free energy difference between the transition states is smaller than that between the carbanions. This effect could more than compensate for the effect of acidity and therefore favors the ethylation of the ethyl derivatives.

## Experimental Part

The ethylation reactions were carried out in a 100-ml. capacity agitated autoclave, Magne-Dash,[16] which was charged with 0.2–0.5 mole of each alkylpyridine, 0.3–0.5 g. (0.013–0.026 g. at.) of sodium and 0.05 g. of anthracene. The autoclave was sealed and after flushing with nitrogen it was charged with about 18–23 atm. of ethylene and heated to the desired temperature, generally to 150° unless otherwise indicated. When this was reached stirring was begun. After 0.5–1.5 hours the desired amount of reaction occurred as judged by pressure drop. The stirring was then stopped and the autoclave was removed from the heating jacket and allowed to cool. After the pressure was released, a few ml. of methanol was added to the reaction mixture in order to decompose the organosodium compounds.

The crude reaction mixture was then analyzed by vapor phase chromatography[17] on a 20-foot column packed with 40% of monohydroxyethyltrihydroxypropylethylenedi-

(13) Ethylpyridines are much more acidic than ethylbenzene since only the former undergo metalation by sodium amide in liquid ammonia.

(14) The relative acidities *e.g.* of isopropyl- and isobutylbenzene were not measured. Experimental data reported in the literature,[12,15] however, leads one to expect not too great a difference in the acidities of these two compounds since the inductive effect of one isopropyl groups should be comparable to the inductive effect of two methyl groups. Similar reasons could be applied to the relative acidities of 4-isopropyl- and 4-isobutylpyridine.

(15) D. Bryce-Smith, V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 2743 (1954).

(16) Autoclave Engineers, Inc., Erie, Pa.

(17) Podbielniak, Inc., Chicago, Ill.

amine[18] on Chromosorb.[19] The retention times of some alkylpyridines on this substrate have been determined[20] and it was observed that the values of 2- and 4-isomers differ greatly, the 4-isomers having longer retention times. It is interesting to note that 2-ethylpyridine has a smaller retention time than 4-picoline. This could be ascribed to the hindrance to solvation of the 2-substituted pyridines on the polar solvent. A complete separation of the starting material and the reaction product was in such cases achieved. The column was kept at 150°. Helium was used as a carrier gas. In the case of 4-alkylpyridines homologs, a shorter column—about 10 feet—could be used, since the separation is quite large; for the lower 2-alkylpyridine homologs, an additional 10-foot column improved the separation. The pressure of the carrier gas was changed from 10 to 30 lb./sq. inch according to the increase in length of the column.

(18) Visco Products Co., Inc., Houston, Texas.

(19) Johns-Manville Corporation.

(20) A. W. Decora and G. V. Dinneen, Paper presented before the Analytical Division, American Chemical Society Meeting, September, 1958, Chicago, Ill.

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EVANSTON, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

# Diaryliodonium Salts. XIV. Reactions of Organometallic Compounds with Iodosobenzene Dichlorides and with Iodonium Salts[1,2]

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At low temperatures aryllithium compounds react with aryliodoso dichlorides in ether, tetrahydrofuran or toluene to give 20–50% of diaryliodonium salts. More aryllithium compound or arylmagnesium halide converts the iodonium salt to a triaryliodine, from which the iodonium salt can be recovered in good yield by cleavage with acid. A triaryliodine or an alkyldiaryliodine allowed to warm to 0° or above in ether gives products formed by decomposition to iodo compounds and free radicals, which may react with each other or with solvent.

**Introduction.**—Three steps may be considered in the reactions of organometallic compounds (RM) with iodine(III) chlorides.

$$RM + ICl_3 \longrightarrow RICl_2 + MCl \quad (A)$$

$$RM + RICl_2 \longrightarrow R_2ICl + MCl \quad (B)$$

$$RM + R_2ICl \longrightarrow R_3I + MCl \quad (C)$$

Reaction A is exemplified by the formation of *trans*-2-chlorovinyliodoso dichloride from the corresponding mercuric chloride by treatment with iodine trichloride.[4] There are few examples of reaction A alone, as in most cases it is followed by reaction B to give an iodonium salt; *e.g.*, bis-(*trans*-2-chlorovinyl)-mercury with iodine trichloride gave bis-(*trans*-2-chlorovinyl)-iodonium chloride[4] while both diphenylmercury and phenylstannic chloride with iodine trichloride gave diphenyliodonium chloride.[5]

Reaction B has been run with organometallic compounds of mercury,[5,6] silver,[7] tin[5] and magnesium.[8] Reactions with phenylstannic chloride[5] were convenient and successful while those with Grignard reagents[8] gave iodonium salts in only trace amounts. For example, iodosobenzene dichloride with ethylmagnesium bromide gave ethylbenzene and iodobenzene and with phenylmagnesium bromide gave biphenyl, iodobenzene and a trace of a diphenyliodonium salt.

The appearance of ethylbenzene, biphenyl and iodobenzene suggests the further reaction of the Grignard reagent with the iodonium salt formed in the initial reaction. Examples of reaction C are the formation at low temperature of triphenyliodine[9,10] from diphenyliodonium iodide and phenyllithium and of phenyl-2,2′-biphenylyliodine[11] from 2,2′-biphenylyliodonium iodide and phenyllithium. Both trisubstituted iodines are yellow. The latter cyclic trisubstituted iodine was relatively stable to 100°, while triphenyliodine decomposed above 0° to give, as one product, biphenyl.

In 1953, it was reported[12] from these laboratories that ethereal methylmagnesium iodide, ethylmagnesium bromide, phenylmagnesium bromide and phenyllithium at 0° or above gave with diphenyliodonium bromide toluene (59%), ethylbenzene (37%) and biphenyl (33 and 46%). At that time it was thought that these products probably arose from nucleophilic attack of the organometallic compound on the 1-carbon of the diphenyliodonium ion. The alternative route of formation *via* trisubstituted iodines was not explicitly considered.

The first aim of the present work was to investigate the synthesis of diaryliodonium salts from aryliodoso dichlorides and organolithium or magnesium compounds at low temperatures. The second aim was to investigate further the products of the reaction of diphenyliodonium chloride in ether with Grignard reagents.

(1) This paper is taken from the M.S. thesis of Murray Winicov and the Ph.D. dissertation of Joseph W. Dehn, Jr., and was presented in part at the New York City Meeting of the American Chemical Society in September, 1957 (Abstracts of Papers, p. 36P).

(2) Preceding paper: F. M. Beringer and I. Lillien, THIS JOURNAL, **82**, 725 (1960).

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