left 1.4 g (75%) of triphenylphosphine oxide. The pentane solution was evaporated. The residue, 2.9 g of orange oil, exhibited a small peak at 4.71 μ in the ir; there was a strong pyridine-like odor apparent. The oil was taken up in benzene and treated with anhydrous hydrogen chloride. Solvent was evaporated and the residue was washed with cold methanol. There remained 1.5 g (52%) of crude **14**, mp 175°. Recrystallization from ethyl acetate raised the melting point to 185–189°; ir NH peak at 2.96 μ, strongest peak at 6.26 μ; nmr multiplet at τ 2.5–3.4 (20) and a broad singlet at 4.7 (0.8).

Anal. Calcd for $C_{28}H_{21}Cl_2N$: C, 76.01; H, 4.79; Cl, 16.03; N, 3.17. Found: C, 76.65; H, 4.97; Cl, 15.68; N, 2.90.

Treatment of 5 with Pyridine. Salt **5**, 250 mg, was dissolved in 5 ml of pyridine. Evaporation of the pyridine resulted in recovery of the starting salt (ir spectrum superimposable on that of starting material).

1,1-Diphenyl-4-*p*-nitrophenylbutatriene (16a). To a cold solution of 0.9 ml of triethylamine in 20 ml of acetonitrile was added 2 g of salt **5**. After 5 min 492 mg of *p*-nitrobenzaldehyde was added. The mixture was allowed to stand at room temperature for several minutes and was then diluted with aqueous methanol. There was collected 1.3 g (69%) of cumulene **16a**. Recrystallization from ethyl acetate afforded orange needles: mp 136–137°; ir ($CHCl_3$) 4.92 μ (m), 6.32 (s), 6.67 (s), 7.51 (s), 8.56 (m), 9.06 (s), 12.68 μ (s); nmr ($CDCl_3$) doublet at τ 2.0, multiplet at 2.6, singlet at 3.64, area ratio 2.1:12.0:0.9.

Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 80.95; H, 4.67, N, 4.42.

To a solution of 250 mg of salt **6**, the allenylphosphonium bromide, in 5 ml of pyridine was added 77 mg of *p*-nitrobenzaldehyde. The mixture was heated 5 min on the steam bath and then diluted with aqueous methanol. There was collected 93 mg (61%) of **16a**, mp 129–132°, mmp (with **16a** prepared from salt **5**) 130–135°.

1,1-Diphenyl-4-(3,4-dichlorophenyl)butatriene (16b). To a cold solution of 0.9 ml of triethylamine in 20 ml of acetonitrile was added 2 g of salt **5**. After 5 min 570 mg of 3,4-dichlorobenzaldehyde was added. The mixture was allowed to come to room temperature and was diluted with aqueous methanol. There was collected 1.1 g of yellow needles, mp 109–111°. Recrystallization from ethyl acetate afforded material with mp 113° dec; ir ($CHCl_3$) 4.94 (w), 6.36 (s), 7.20 (m), 8.88 (s), 9.76 (s), 11.38 (s), 12.12 μ (s); nmr ($CDCl_3$) multiplet at τ 2.7, singlet at 3.71, area ratio 13:1.

Anal. Calcd for $C_{22}H_{14}Cl_2$: C, 75.66; H, 4.04; Cl, 20.30. Found: C, 75.97; H, 4.04; Cl, 20.05.

N-Methyl-4,4-diphenyl-2,3-butadieneamide (18). To a solution of 2 g of salt **5** and 0.25 ml of methyl isocyanate in 15 ml of aceonitrile was added 0.7 ml of triethylamine. The mixture was heated 10 min and diluted with water. There was collected 230 mg (28%) of crude allenamide **18**, mp 189–191°. Repeat recrystallization from chloroform-hexane raised the melting point to 192–193°; ir ($CHCl_3$) 2.96 (w), 3.39 (w), 5.21 (w), 6.06 (s), 6.65 μ (m); nmr ($CDCl_3$) singlet at τ 2.76, singlet at 3.98, broad peak at 4.2, doublet at 7.2 (J = 4.5 cps) area ratios 10:1:0.8:3.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.72; H, 6.24; N, 5.79.

The nmr spectrum in pyridine at 100° and chlorobenzene at 130° continued to exhibit the doublet at τ 7.2; there was no coalescence of the peaks.

Treatment of 5 with Diphenylketene. To a mixture of 2 g of **5** in 15 ml of acetonitrile was added 682 mg of diphenylketene prepared by the method of Staudinger.[14] The solution was cooled to 0° and then 1.5 ml of triethylamine was added. The mixture was was stirred 10 min at 0° and refluxed 5 min. It was then diluted with water and extracted with benzene. The extracts were washed, dried, evaporated, and chromatographed on silica gel and alumina. There was obtained 222 mg (19%) of crude hydrocarbon, mp 205–240°. Recrystallization from benzene-hexane and benzene-methanol raised the melting point to 260–262°; uv 296 (log ϵ 4.56), 370 mμ (log ϵ 3.77). The lit. values[8] are mp 260–262°; uv 297 (log ϵ 4.88), 385 mμ (log ϵ 3.77).

Anal. Calcd for $C_{58}H_{40}$: C, 94.53; H, 5.47; mol wt, 737. Found: C, 94.44; H, 5.46; mol wt, 730.

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(14) H. Staudinger, *Chem. Ber.*, 38, 1735 (1905).

Formation of Pyridinium Ylides and Condensation with Aldehydes

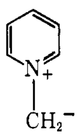
K. W. Ratts, R. K. Howe, and W. G. Phillips

Contribution from the Monsanto Company, Agricultural Division,
Research Department, St. Louis, Missouri 63166. *Received May 10, 1969*

Abstract: Deuterium-exchange studies of N-methylpyridinium salts indicate that the 2 and 6 ring protons exchange more rapidly than the N-methyl protons under basic conditions which give no detectable exchange of the 3, 4, and 5 ring protons. However, under the same conditions condensation of these salts with aldehydes occurs exclusively at the N-methyl position. Discussion of these results is given in terms of formation of intermediate ylides **1** and **2**. Formation of either ylide **1** or **2** by decarboxylative methods in the presence of aldehydes leads to direct condensation to give N-(2-hydroxy-2-arylethyl)pyridinium and 2-(α-hydroxybenzyl)-N-methylpyridinium salts, respectively. These and other data are discussed and the conclusion drawn that the rate ratio of condensation to reprotonation is greater for ylide **1** than for ylide **2**.

The reaction of ylides with aldehydes has proven to be an extremely useful synthetic tool for the preparation of olefins (P ylides) and epoxides (S ylides).[1] Consequently correlation and explanation of ylide reactivity is of considerable interest from the standpoint of synthetic utility.

Pyridinium ylides are of some significance since (1) there exists no possibility for d-orbital stabilization of the carbanion and (2) two possible ylide structures may form (**1** and **2**). Condensation of pyridinium ylides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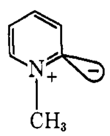
2

with aldehydes, contrary to known reactions of P or S ylides, produces the corresponding alcohols.[2–4]

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[1] A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1967.

(2) R. K. Howe and K. W. Ratts, *Tetrahedron Letters*, 4743 (1967); (b) W. G. Phillips and K. W. Ratts, *ibid.*, 1383 (1969).

(3) M. R. F. Ashworth, R. P. Daffern, and D. L. Hammick, *J. Chem. Soc.*, 809 (1939).

(4) F. Krohnke, *Angew. Chem.*, 65, 605 (1953).

Table I. Deuterium Exchange Studies with N-Methylpyridinium Iodide

Solvent	Substrate concn, *M*	Base (concn, *M*)	Temp, °C	Proton	% exchange[a]	Time, min
CH_3OD	0.7	$NaOCH_3$ (0.08)	35	2,6	54	4.4
				N-CH_3	48	1,240
CH_3OD	0.66	Piperidine (1.0)	*Ca.* 23	2,6	50	1,260
				N-CH_3	≤ 3	11,500
CH_3CH_2OD	0.31	Piperidine (0.19)	78	2,6	44	6.5
				N-CH_3	51	169

[a] Per cent exchange relative to exchange at infinite time, determined by integration over the various proton resonances. The integral of the N-methyl resonance was corrected for overlap with the solvent ^{13}C-H satellite.

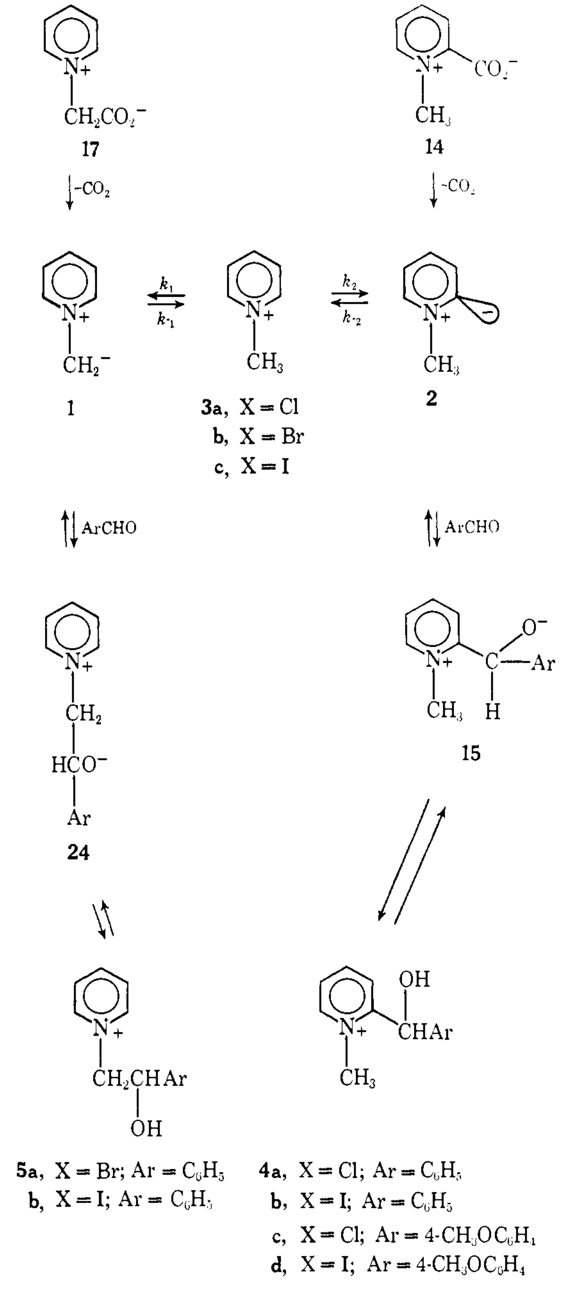
The purpose of this work was to investigate base and decarboxylative pyridinium ylide formation and condensation of these ylides with aldehydes.

Base Method of Pyridinium Ylide Formation. Previously reported studies[5-8] of deuterium exchange at the ring α positions of N-methylpyridinium salts only briefly mention exchange of the N-methyl protons. Kröhnke[4] found that piperidine-catalyzed condensation of N-methylpyridinium salts with aldehydes produces N-(2-hydroxy-2-arylethyl)pyridinium salts in high yield. Products from condensation at the ring α carbon atom were not observed.

In the present work the relative rates of exchange of ring α-protons and the N-methyl protons of N-methylpyridinium iodide (**3c**) were determined under a variety of conditions by nmr analysis. The results are summarized in Table I. The ylides were present only at very low concentrations during the exchange studies as evidenced by lack of any resonances in the nmr spectrum attributable to the ylides **1** and **2**.

Exchange of the 2 and 6 protons is faster than exchange of the N-methyl protons. During the time required for complete equilibration of the N-methyl protons with solvent deuterium atoms in ethanol-*d* at reflux, no detectable exchange of the 3, 4, and 5 protons occurs. The results of the exchange studies prompted further investigation of the piperidine-catalyzed condensation of N-methylpyridinium iodide with benzaldehyde in ethanol at reflux. Several processes are involved in the deuterium exchange and condensation reactions of N-methylpyridinium salts initiated by base. These are summarized in Scheme I. Under the reaction conditions consisting of 0.31 *M* N-methylpyridinium iodide, 1.01 *M* benzaldehyde, and 0.19 *M* piperidine in ethanol, no **4b** (Scheme I) could be detected by nmr during the course of the condensation reaction that gave **5b**, and the pseudo-first-order rate constant for the formation of **5b** was found to be 6×10^{-6} sec^{-1} at 11% conversion of **3c** to **5b**. Authentic **4b** was found to cleave to **3c** in ethanol at reflux containing 0.505 *M* piperidine with a pseudo-first-order rate constant of 8×10^{-6} sec^{-1}; this corresponds to a rate constant of 3×10^{-6} sec^{-1} utilizing 0.19 *M* piperidine. Cleavage of **5b** back to **3c** under conditions of the condensation reaction is negligible since **5b** is formed in good yields.

Scheme I



From failure to detect by nmr the presence of N-ylides **1** and **2** in the basic solutions during the exchange studies, it follows that $k_1 \ll k_{-1}$ and $k_2 \ll k_{-2}$. That $k_2 > k_1$ is known from deuterium exchange studies.[9] Since for-

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(5) A. San Pietro, *J. Biol. Chem.*, 217, 589 (1955).

(6) (a) P. Beak and J. Bonham, *J. Am. Chem. Soc.*, 87, 3365 (1965); (b) P. Beak and E. M. Monroe, *J. Org. Chem.*, 34, 589 (1969).

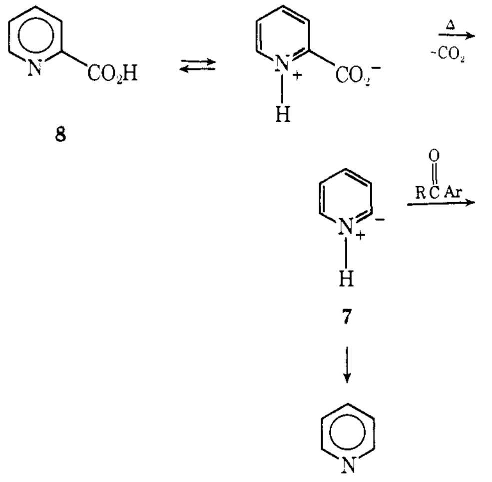
(7) N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *J. Gen. Chem. USSR*, 34, 4124 (1964).

(8) (a) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull. Japan*, 12, 1384 (1964); (b) R. Abramovitch, *Chem. Commun.*, 55 (1967); (c) J. A. Zoltewicz and C. L. Smith, *J. Am. Chem. Soc.*, 89, 3358 (1967).

(9) The greater kinetic acidity of the ring α-protons compared to the N-CH_3 can be attributed to the hydridization differences ($C^{sp^2}H$ *vs.* $C^{sp^3}H$) at carbon. This factor and/or the shorter N^+-C^- bond in **2** than **1** (sp^2-sp^2 *vs.* sp^2-sp^3) apparently override stabilization effects in **1** due to resonance.

mation of **5b** (pseudo-first-order rate constant = 6×10^{-6} sec^{-1}) is faster than cleavage of **4b** (rate constant = 3×10^{-6} sec^{-1} without added benzaldehyde) and since **4b** was not detected during the course of formation of **5b**, the possibility is excluded that **4b** is formed faster than **5b** and is slowly converted through back-reactions to **5b**. Instead, **5b** is formed faster than **4b** even though **2** is formed faster than **1**. *Therefore the rate ratio of product formation to reprotonation is greater for ylide* **1** *than for ylide* **2**.

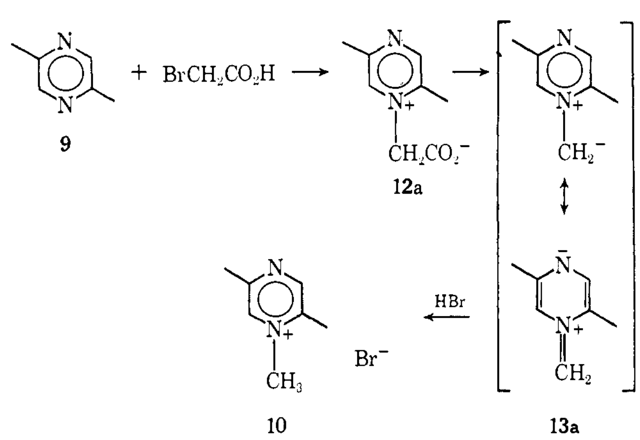
Decarboxylative Method of Ylide Formation. A ring pyridinium ylide (**7**) is intermediate in decarboxylation of picolinic acid (**8**).[3,10] N-Methylation of the pyridine ring has been shown to enhance the rate of decarboxylation (**14** → **2**) by a factor of 720.[10a] However, no instances of reaction of the latter type ylide (**2**) with aldehydes are reported.[3,11-13]

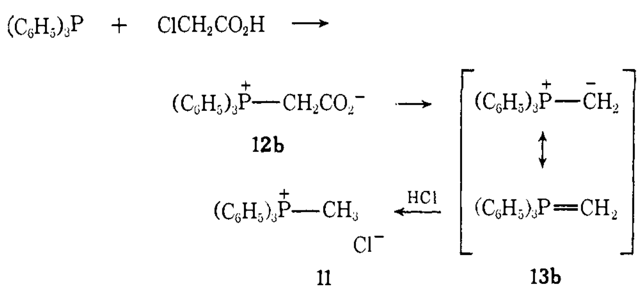


Formation of ylide **1** *via* decarboxylation of **17** has not been reported. Analogy for such decarboxylations does exist, although the supposed intermediate ylides only have been shown to protonate.[14] Treatment of 2,5-dimethylpyrazine (**9**) with α-halo acids gave 1-methyl-2,5-dimethylpyrazinium bromide (**10**).[15] Triphenylphosphine and chloroacetic acid yield a salt which loses carbon dioxide on heating to produce triphenylmethylphosphonium chloride (**11**) in 90% yield.[16] Presumably in both the above cases betaines (**12a** and **b**) form, undergo decarboxylation, and the ylides (**13a** and **b**) protonate.

New decarboxylative methods for the synthesis of 2-(arylhydroxymethyl)-N-methylpyridinium halides (**4**) and N-(2-hydroxy-2-arylethyl)pyridinium halides (**5**) *via* ylides **2** and **1**, respectively, have now been developed as described herein.

Under the proper conditions ylide **2** can be caused to condense with aromatic aldehydes. Decarboxylation of homarine hydrochloride at 114° in excess benzaldehyde (with no other solvent) was complete in 15-20 min, and a mixture of 83% 2-(α-hydroxybenzyl)-N-methylpyridinium chloride and 17% N-methylpyridinium chloride was obtained in quantitative yield. The very large excess of benzaldehyde and the low concentration of proton sources allow trapping of the intermediate ylide by benzaldehyde. Pyridine serves as a catalyst for the reaction by ionizing the carboxyl group, thus facilitating the decarboxylation. With 1 equiv of pyridine the decarboxylation is complete within 1.5 hr at 80°. The product was found to be completely stable (<1% decomposition) under the reaction conditions.





The reaction proceeds with a variety of aldehydes (see Table II). As expected, the yield of condensation product generally increases with the electrophilicity of the aldehyde employed.[17]

Table II. Product Composition from Condensation of Ylide **2** with Aromatic Aldehydes, 2 Hr at 80°

ArCHO Ar	Mole ratio, aldehyde/homarine·HCl[a]	Solvent[b]	Product composn,[c] % **4**	**3a**
C_6H_5	14.7		84	16
4-$CH_3OC_6H_4$	12.5		32	68
3,4-$Cl_2C_6H_3$	6.8	$C_6H_5NO_2$	80	20
2,4-$Cl_2C_6H_3$	6.9	$C_6H_5NO_2$	90	10
4-$O_2NC_6H_4$	6.5	$C_6H_5NO_2$	92	8

[a] One equivalent of pyridine based on homarine·HCl. [b] 30 ml of $C_6H_5NO_2$ per 10 mmoles of homarine·HCl. [c] Determined by nmr integration over the NCH_3 resonances. In each case the combined yield of pyridinium salts was quantitative.

4a was prepared by an independent route to confirm the structure assignment of this material.

The product (**4c**) could not be obtained in pure form from the ylide reaction product mixture when Ar = 4-$CH_3OC_6H_4$. The evidence for the formation of product **4c** in the ylide reaction when Ar = 4-$CH_3OC_6H_4$ is

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(10) (a) P. Haake and J. Mantecon, *J. Am. Chem. Soc.*, **86**, 5230 (1964); (b) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953); (c) B. R. Brown and D. Ll. Hammick, *J. Chem. Soc.*, 659 (1959).

(11) P. Dyson and D. Ll. Hammick, *ibid.*, 1724 (1937).

(12) (a) B. R. Brown, *ibid.*, 2577 (1949); (b) N. H. Cantwell and E. V. Brown, *J. Am. Chem. Soc.*, **69**, 1489 (1947).

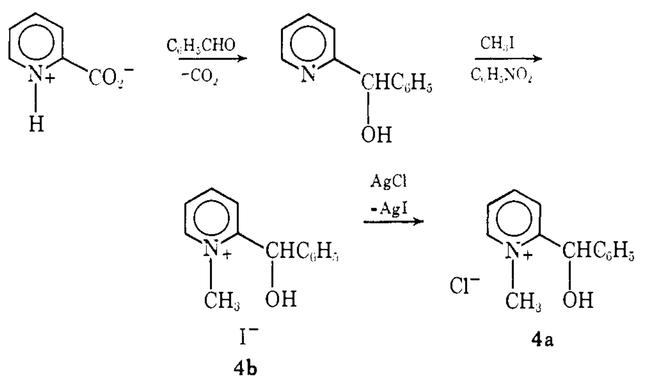
(13) Ylide **2** has, however, been trapped with diazonium salts; H. Quast and E. Frankenfeld, *Angew. Chem. Intern. Ed. Engl.*, **4**, 691 (1965).

(14) T. Cohen and I. H. Song, *J. Am. Chem. Soc.*, **87**, 3780 (1965).

(15) E. V. Hort and P. E. Spoerri, *ibid.*, **77**, 5898 (1955).

(16) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

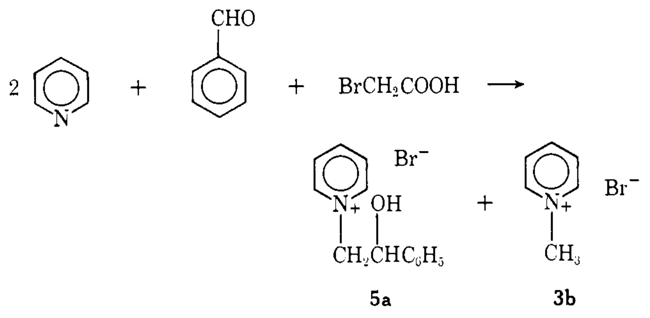
(17) Use of a different ratio of aldehyde to homarine and the solvent difference necessitate correction in comparison of the yields.



based on the nmr spectrum which is identical with a superimposition of the spectra of authentic N-methylpyridinium chloride and iodide **4d** (slightly shifted in τ values).

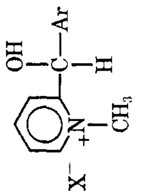
The nmr spectra and elemental analysis confirm the structure assignments (see Table III). In all cases the integrations were in complete accord with theory. The nmr spectrum of 2-(α-hydroxybenzyl)-N-methylpyridinium chloride shows the 2 proton to be absent (only 1 H at lowest field), the 3, 4 and 5 proton resonances are relatively unchanged in comparison with N-methylpyridinium chloride, the NCH_3 resonance (3 H) is present, and in DMSO solution the H_α resonance is a doublet due to splitting with the hydroxyl proton. Coupling of hydroxyl protons with the α protons of alcohols in DMSO solution has been reported by Chapman and King.[18]

A typical procedure for the synthesis of N-(2-hydroxy-2-arylethyl)pyridinium bromides (**5a**) involves addition of 2 equiv of pyridine to a mixture of bromoacetic acid and an excess of benzaldehyde in nitrobenzene. Warming of this solution to 50° results in the formation of a precipitate which gives off carbon dioxide upon further heating to 110°. After carbon dioxide ceases evolution, the product is filtered off.



An examination of Table IV reveals that this synthesis is fairly general. Any combination of aromatic aldehydes and pyridines appears to be satisfactory. A mixture of 2-chloropyridine, bromoacetic acid, and benzaldehyde, however, failed to decarboxylate even at 170°. Presumably, the 2-chloro atom offers enough steric hindrance so that the pyridine cannot displace bromine from bromoacetic acid. Aliphatic aldehydes also yielded no observable adduct, perhaps because of competing aldol condensations. The substitution of chloroacetic acid or ethyl bromoacetate for bromoacetic acid is satisfactory, but higher temperatures are required, and the yields appear to be lower.

Table III



Ar	X	Mp, °C dec	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % X	Found, % C	Found, % H	Found, % N	Found, % X	Nmr (τ, multiplicity)[a] H_6	H_4	$H_{3,5}$	ArH	H_α[b]	NCH_3	OH	Solvent	Standard
C_6H_5	Cl	171–172	66.24	5.99	5.94	15.04	66.05	6.12	5.79	15.16	0.88 bd, $J = 6$	1.37 bt, $J' + J'' = 15$	1.95 m	2.60 s	3.67 d, $J''' = 5.5$	5.68 s	2.58 d	DMSO	Internal TMS
$4\text{-}CH_3OC_6H_4$	I	137–139	47.07	4.52	3.92	35.53	47.25	4.70	4.02	35.79	1.00 bd, $J = 6$	1.33 bt, $J' + J'' = 15$	1.88 m	2.87 m	3.76 d, $J''' = 5$	5.80 s	3.27 d, $J''' = 5$	DMSO	Internal TMS
$3,4\text{-}Cl_2C_6H_3$	Cl	199–200	51.26	3.97	4.60	34.92	51.49	4.08	4.57	35.11	0.92 bd, $J = 6$	1.43 bt, $J' + J'' = 15$	1.80–2.72 multiplets		3.60 d, $J''' = 6$	5.65 s	2.37 d, $J''' = 6$	DMSO	Internal TMS
											1.20 bd, $J = 6$	1.58 bt, $J' + J'' = 15$	1.90 m	2.53 m	3.62 s	5.78 s	5.33 s	D_2O	Internal DSS[c]
$2,4\text{-}Cl_2C_6H_3$	Cl	195–196	51.26	3.97	4.60	34.92	51.33	3.84	4.50	34.75	1.10 bd, $J = 6$	1.37 bt, $J' + J'' = 16$	1.95 bt	2.57 m	3.40 s	5.68 s	5.33 s	D_2O	Internal DSS[c]
$4\text{-}O_2NC_6H_4$	Cl	209–210	55.62	4.67	9.98	12.63	55.76	4.89	10.13	12.70	1.15 bd	← 1.20–2.45 →			3.47 s	5.73 s	5.33 s	D_2O	Internal DSS[c]

[a] J's are in cycles per second; s = singlet, d = doublet, m = multiplet, bd = doublet broadened by smaller additional couplings, bt = triplet broadened by smaller additional couplings. [b] H_α splitting is caused by coupling with OH. [c] Sodium 2,2-dimethyl-2-silapentane-5-sulfonate.

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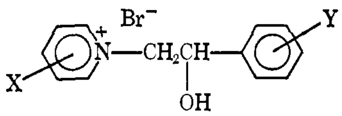
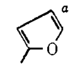
(18) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

Table IV. 1-(2-Hydroxy-2-arylethyl)pyridinium Bromides



X	Y	Yield, %	Mp, °C	Solvent	Calcd, % C	Calcd, % H	Found, % C	Found, % H
H	H	75	237–239	Nitrobenzene	55.71	5.00	55.57	4.97
H	4-CH_3	58	207–209	Excess aldehyde	57.14	5.60	56.91	5.44
4-CN	H	69	234–235	Excess aldehyde	53.24	4.44	53.51	4.52
3-CH_3	H	50	163–165	Excess aldehyde	57.14	5.44	57.30	5.61
4-CH_3	3,4-Cl_2	61	189–192	Nitrobenzene	46.28	3.88	46.52	3.85
4-CH_3	3,4-Methylenedioxy	72	261–262	Nitrobenzene	53.25	4.73	53.08	4.70
4-CH_3	H	29	172–175	Excess aldehyde	57.14	5.44	57.14	5.59
H	3,4-Methylenedioxy	59	232–234	Nitrobenzene	51.85	4.32	51.61	4.40
H	4-NO_2	80	275–276	Nitrobenzene	48.00	4.00	48.15	4.01
4-CN	4-NO_2	14	256–257	Nitrobenzene	48.00	3.43	48.23	3.58
4-CH_3	4-CH_3	64	228–229	Excess aldehyde	56.43	4.70	56.19	4.62
H	CCl_3[a]	20	220–221	Excess aldehyde	29.86	2.80	29.86	2.90
H	 [a]	51	189–192	Excess aldehyde	48.89	4.44	49.08	4.60

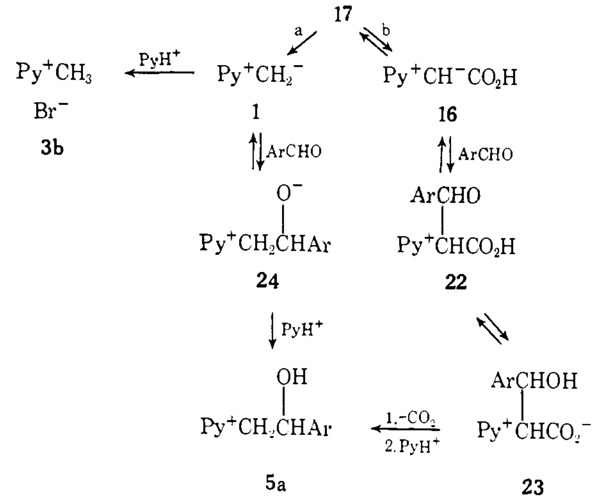
[a] The indicated group replaces the substituted phenyl in the title structure.

The use of 2-bromopropionic or 2-bromobutyric acids resulted in formation of the corresponding condensation products.[19]

The base treatment of N-methylpyridinium salts and the decarboxylation of homarine hydrochloride must involve formation of ylides **1** and **2**, respectively. However, an alternative route must be considered for the formation of **5** from **17**. The two possible routes are illustrated in Scheme II. Pathway a involves decarboxylation of the initial adduct to an ylide followed by condensation. Pathway b is essentially the reverse sequence; the condensation proceeds prior to decarboxylation. The formation of a side product, the N-methylated salt of the starting pyridine, can only result from ylide **1**. Therefore pathway b requires that **1** also be formed concurrently with **16** and that **1** is completely protonated.

Scheme II. Mechanistic Possibilities for Reaction of Bromoacetic Acid, Pyridine, and Benzaldehyde[a]

$$BrCH_2CO_2H + 2Py \longrightarrow Py^+CH_2CO_2^- + PyH^+ \ Br^-$$



[a] Py denotes pyridine

Evidence for the adduct (**17**) formation was obtained when the conjugate acid of **17** was obtained from a mixture of bromoacetic acid and pyridine in bromobenzene. Treatment of this substance with pyridine and benzaldehyde gave the expected adduct **5a** in 72% yield.

Table V. Product Distribution. Reaction of Bromoacetic Acid and Substituted Pyridines with Various Aromatic Aldehydes[a]

Pyridine substituent	Aldehyde substituent	Moles of aldehyde/moles of bromoacetic acid	% **5a**	% **3b**
H	H	10[b]	100	0
H	H	4	97	3
H	H	3	94	6
H	H	2	90	10
H	H	1	65	35
H	4-OCH_3	1	31	69
H	4-NO_2	1	96	4
4-CN	4-NO_2	2.5	23	77

[a] The product distribution was determined by integration of the appropriate peaks in the nmr spectra of the crude products. Controls indicated that the products were stable under the reaction conditions. [b] The solvent here was excess aldehyde. In all other cases cited, the solvent was nitrobenzene.

As depicted in Table V, increasing amounts of aldehyde gave more adduct (**5a**) at the expense of the N-methylated pyridine (**3b**). More electrophilic aldehydes favor the adduct over the N-methylated pyridine (see Table V). A 4-cyano group which stabilizes the pyridinium ylide decreases the ratio of condensation to protonation (23/77) relative to the ratio for the unsubstituted ylide (96/4) even though the aldehyde concentration is increased. Although other explanations are possible, a simple competition between a proton and an aldehyde molecule for ylide **1** seems most reasonable.

Further evidence favoring pathway a was obtained when aliquots were taken from a heated mixture of N-carboxymethylpyridinium bromide, pyridine, and

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(19) When the latter two acids were employed, *erythro* and *threo* isomers were formed as indicated by the nmr spectrum of the crude product. Krohnke [F. Krohnke, *Chem. Ber.*, 67, 656 (1934)] found similar results in condensation reactions of N-ethylpyridinium bromide.

benzaldehyde. The nmr spectrum of these aliquots indicated only starting material and **5a** were present. No evidence was found for the presence of a structure corresponding to **22** or **23**. One can only conclude that pathway b is not operative or that **22** and **23** decompose much faster than they form. While the evidence is not conclusive, we believe the evidence favors pathway a over pathway b.

Decarboxylation of homarine proceeds *via* ylide **2** which reacts with a rate ratio of condensation to protonation of 26/74 = 0.35 in nitrobenzene with equivalent amounts of homarine hydrochloride, pyridine, and aldehyde. Under identical conditions reaction of bromoacetic acid, pyridine, and benzaldehyde gave a ratio of 65/35 = 1.86 *via* ylide **1**.[20] The results are qualitatively consistent with the deuterium-exchange studies and base-catalyzed condensation studies in that this ratio for ylide **1** is greater than for ylide **2**. The factors which affect condensation to protonation ratios in ylides **1** and **2** are not well defined. One major factor must be the comparative basicity–nucleophilicity[21] although rate of betaine decomposition and conditions of reversibility may also be important.

In any event, ylides formed by decarboxylation may be effectively induced to react as nucleophiles in the presence of strong proton donors. In situations where two highly reactive ylides may be formed with comparative ease, basic methods tend to give products derived from the ylide which has the higher ratio of condensation to reprotonation.

Experimental Section

Melting points were determined in open capillary tubes with a Mel-Temp apparatus and are uncorrected. Boiling points are uncorrected. Nmr spectra were determined with a Varian A-60. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Deuterium-Exchange Studies in Methanol-*d*. The nmr spectrum of N-methylpyridinium iodide in CH_3OD (chemical shifts are downfield from the solvent methyl resonance) displays the 2 and 6 proton resonance as a doublet, $J = 6$ cps, slightly broadened by additional smaller couplings, 2 H, at δ 343 cps; the 4 proton resonance as a triplet, $J' = 7$ cps, slightly broadened, 1 H, at 321 cps; the 3 and 5 proton resonance as a broadened triplet, $J + J' = 12$ cps, 2 H, at 290 cps; and the NCH_3 resonance as a singlet, 3 H, at 72 cps, slightly overlapping the ^{13}C satellite (at 69 cps) of the solvent methyl resonance.

A solution of $NaOCH_3$ in CH_3OD was prepared from fresh sodium and CH_3OD in a glove bag under nitrogen. Titration of an aliquot with 0.1 *N* HCl indicated the $NaOCH_3$ concentration to be 0.080 *N*. In a glove bag under nitrogen was added 0.70 ml of the $NaOCH_3$ solution to 111.2 mg of N-methylpyridinium iodide, the solution was transferred to an nmr tube, and the tube was tightly capped. The sample was placed in an nmr probe at 35° within 2 min of the preparation The spectrum was repeatedly integrated. The integral of the nonexchanging protons 3 and 5 was taken as 2.00 protons. At 4.4 min after the sample was placed in the probe at 35°, the exchange of protons 2 and 6 was determined to be 48%. After 73 min ("infinite" time for this exchange), 89% exchange had occurred. Thus, at 4.4 min the 2 and 6 protons had undergone 54% of the exchange at "infinite" time. The integral of the NCH_3 resonance was determined by substraction of the integral of the ^{13}C satellite on the high-field side of the solvent methyl resonance from the sum of the integrals of the NCH_3 resonance integral and the low-field ^{13}C satellite, which slightly overlapped with the NCH_3 resonance. After 1240 min, 40% of the NCH_3 protons had exchanged. An infinity value for NCH_3 exchange of 83.6% was calculated from the total number of exchangeable protons (protons 2 and 6, NCH_3 protons, and 2.5% OH originally present in the CH_3OD). Thus, at 1240 min, the NCH_3 exchange was 48% relative to the exchange at infinite time.

Nmr analysis of a solution prepared from 72.7 mg of N-methylpyridinium iodide and 0.50 ml of CH_3OD that was 1.0 *M* in piperidine revealed the extent of deuteration after various time intervals at room temperature, *ca.* 23°. The exchange of the 2 and 6 protons was 50% complete in 21 hr at *ca.* 23°. After 8 days at room temperature, 14% of the 2 and 6 hydrogens remained (calculated 11% for complete equilibration), and less than 3% of the NCH_3 protons had exchanged.

Deuterium Exchange Studies in Ethanol-*d*. A solution of 3.45 g (0.0156 mol) of N-methylpyridinium iodide in 50 ml of ethanol-*d* was brought rapidly to reflux under nitrogen, and 0.95 ml (0.0096 mol) of piperidine was added. After various time intervals 0.5-ml aliquots were removed and analyzed by nmr. The spectrum of N-methylpyridinium iodide in CH_3CH_2OD displays a slightly broadened doublet (2 H), $J = 6$ cps, δ 330 cps (chemical shifts are in cycles per second downfield from the center of the solvent methylene quartet), due to the 2 and 6 protons; a triplet (1 H), $J + J' = 15$ cps, δ 305 cps, due to the 4 proton; and unresolved multiplet (2 H), δ 275 cps, due to the 3 and 5 protons; and a singlet (3 H), δ 56 cps, due to the NCH_3 protons. As the exchange proceeded the singlet OH signal at 84 cps became larger, the lowest field doublet rapidly decreased in area, and the singlet at 56 cps slowly decreased in area. Integration over the various resonances at different times was performed. The extent of deuteration at the various sites was determined by comparison of the various integrals with the integral of the 3 and 5 protons. The high-field line of the solvent methylene ^{13}C satellite quartet overlapped with the NCH_3 resonance. One-third of the integral of one of the inner lines of the ^{13}C satellite quartet was subtracted from the integral of the signal at 56 cps to obtain the integral of the NCH_3 signal.

At 6.5 min 41% exchange of the 2 and 6 protons had occurred. At 169 min (*ca.* 22 half-lives) there was 93.1% exchange of the 2 and 6 protons, which corresponds to the infinity value for this exchange. Thus, at 6.5 min 44% of the exchange at "infinite" time had taken place. Similarly, after 169 min 46.1% of the NCH_3 protons had exchanged, and at "infinite" time (2810 min) 90.1% exchange had occurred. Thus, at 169 min the relative exchange was 51%.

N-(2-Hydroxy-2-phenylethyl)pyridinium Iodide (5b). A solution of 6.4 g (0.31 *M*) of N-methylpyridinium iodide, 10 g (1.01 *M*) of benzaldehyde, and 1.75 ml (0.19 *M*) of piperidine in 93 ml of ethanol was held at reflux. Aliquots (2 ml) were withdrawn after 2.5, 5, and 18.3 hr. Each aliquot was immediately concentrated under vacuum to a solid, the solid was dissolved in DMSO, and the solution was examined by nmr. No **4b** was detected in any of the aliquots. The solid from the aliquot taken after 5 hr was found to consist of 11% **5b** and 89% **3c**.

In a preparative run, the procedure described by Kröhnke[4] for condensation of N-methylpyridinium bromide was employed. A solution of 25.4 g (0.115 mol) of N-methylpyridinium iodide, 6.6 ml of piperidine, and 13.2 g (0.124 mol) of benzaldehyde in 350 ml of ethanol was held at reflux. After 12 hr the precipitated light tan solid, 6.24 g, mp 256–258° dec, was collected. To the filtrate was added 4.4 ml of benzaldehyde and 3 ml of piperidine, and the solution was held at reflux another 24 hr. The solid that formed, 6.88 g, mp 251–258° dec, was collected. Addition of 4.4 ml of benzaldehyde and 3 ml of piperidine to the filtrate followed by another 24-hr period of reflux of the solution gave an additional 4.3 g of product, mp 254–258° dec. The total yield was 72%. One crystallization of the product from methanol–ether (charcoal) gave white solid, mp 256–258° dec.

Anal. Calcd for $C_{13}H_{14}INO$: C, 47.72; H, 4.31; I, 38.79; N, 4.28. Found: C, 47.88; H, 4.36; I, 39.02; N, 4.17.

Cleavage of 2-(α-Hydroxybenzyl)-N-methylpyridinium Iodide. A solution of 1.00 g (0.31 *M*) of **3c** and 0.50 ml (0.505 *M*) of piperidine in 10 ml of ethanol was held 18 hr at reflux (dark purple solution). The solution was cooled, and ether was added to precipitate

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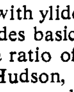
[20] Surprisingly, this ratio is greater than one for ylide **1**, suggesting the ylide preferentially reacts with the aldehyde rather than a proton. This may be due to the fact that the pyridinium ion



may be hydrogen bonded to the solvent thereby reducing proton availability and the extent of reaction with ylide.

[21] In simple phosphorus ylides basicity is linearly correlated with nucleophilicity although the rate ratio of condensation to protonation is not known [S. Fliszar, R. F. Hudson, and F. Salvadori, *Helv. Chim. Acta*, 1580 (1963)]. In other cases this relationship appears not to hold [A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **85**, 2790 (1963)].

0.81 g (94% yield) of a solid mixture that consisted of 42% **3c** and 58% **4b** (no detectable amount of **5b** was present). Based on this composition, a pseudo-first-order rate constant of 8×10^{-6} sec^{-1} is calculated for cleavage of **4b** to **3c** under these conditions.

A grape color formed immediately upon addition of 9.30 g of 2-(α-hydroxybenzyl)-N-methylpyridinium iodide to a solution of 4.0 ml of piperidine in 90 ml of ethanol. Swirling of the solution in the presence of air resulted in disappearance of the color. Upon standing the solution again acquired a grape color. The solution was held at reflux 93 hr. The solvent was removed under vacuum with a rotary evaporator. The distillate was caught in a Dry Ice-acetone trap; distillation through a spinning band column gave 82 ml of ethanol, bp 77°, a trace of piperidine, and just a trace of pot residue. Ether was added to the residue obtained upon concentration of the reaction mixture; 7.13 g of dark solid remained undissolved. Distillation of the ether extract gave 2.02 g (47%) of clear liquid, bp 42–45° (0.30 mm). The ir and nmr spectra were identical with that of authentic ethyl benzoate.[22] Nmr analysis of the dark solid revealed an 85:15 mixture of N-methylpyridinium iodide and starting material.

2-(α-Hydroxybenzyl)-N-methylpyridinium Chloride (4a). A mixture of 1.747 g (10.05 mmol) of homarine hydrochloride (Aldrich Chemical Co.) and 0.843 g (10.7 mmol) of pyridine in 15 ml (15.75 g, 148 mmol) of benzaldehyde (distilled just prior to use) was stirred at 81°. Evolution of CO_2 had nearly ceased after 1.5 hr. After another 0.5 hr the mixture was cooled, and ether was added. The solid was collected and washed with ether. The 2.07 g of solid was analyzed by nmr in DMSO solution and was found to consist of 84% 2-(α-hydroxybenzyl)-N-methylpyridinium chloride and 16% N-methylpyridinium chloride. Crystallization from methanol-ether gave pure **4a**, mp 171–172° dec, 1.22 g.

The general procedure employed for condensation of the ylide with aromatic aldehydes was identical with that given for 2-(α-hydroxybenzyl)-N-methylpyridinium chloride except that 30 ml of nitrobenzene per 10 mmoles of homarine was used when the aldehyde was solid at room temperature (Table III).

Stability of 2-(α-Hydroxybenzyl)-N-methylpyridinium Chloride in Benzaldehyde Containing Pyridine. A mixture of 0.50 g of the chloride, 0.20 g of pyridine, and 3.3 ml of benzaldehyde (distilled just prior to use) was held 3.5 hr at 80° under N_2. The solvent was removed under vacuum. Nmr analysis of the solid residue, 0.50 g, revealed it to be starting material with <1% N-methylpyridinium chloride.

2-(α-Hydroxybenzyl)-N-methylpyridinium Iodide (4b). Phenyl-2-pyridylcarbinol, mp 75.5–77.5° (lit.[3] mp 78°), was prepared by decarboxylation of picolinic acid in benzaldehyde at reflux. A solution of 10.0 g (0.0573 mol) of the carbinol and 8.95 g (0.063 mol) of methyl iodide in 30 ml of nitrobenzene was held 18 hr at 50° with stirring. The resultant solid was collected and washed with ether to yield 12.2 g of very pale yellow solid. Crystallization from methanol-ether gave 9.5 g of product, mp 164–166°.

Anal. Calcd for $C_{13}H_{14}INO$: C, 47.72; H, 4.31; I, 38.79; N, 4.28. Found: C, 47.64; H, 4.46; I, 39.02; N, 4.12.

2-(α-Hydroxybenzyl)-N-methylpyridinium Chloride from the Iodide. A 1.5-g sample of 2-(α-hydroxybenzyl)-N-methylpyridinium iodide was stirred overnight in the absence of light with 20 g of AgCl in 75 ml of water. The mixture was filtered. Removal of the solvent from the filtrate under vacuum gave an oil. Ethanol was added, and the solvent was removed under vacuum. This operation was repeated once with ethanol and three times with benzene. The resultant solid was crystallized from methanol–ether to give 1.0 g of white solid, mp 170–171° dec.

Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04; N, 5.94. Found: C, 66.05; H, 6.12; Cl, 15.16; N, 5.79.

N-Methylpyridinium Chloride (3c). A 2.0-g sample of N-methylpyridinium iodide was stirred overnight in the absence of light with 20 g of AgCl in 50 ml of water. The mixture was filtered. The filtrate was concentrated under vacuum to an oil. Benzene was added, and the mixture was evaporated to dryness. This drying procedure was repeated several times. The residue was then crystallized from ethanol–tetrahydrofuran. The resultant white solid, after drying under vacuum, weighed 0.90 g, had mp 135–137° (lit.[23] mp 136–138°), and was very hygroscopic.

General Procedure for the Preparation of N-(2-Hydroxy-2-arylethyl)pyridinium Bromides (Table IV). To 0.10 mol (13.1 g) of bromoacetic acid in a three-necked flask equipped with a condenser, nitrogen, and stirrer, was added 0.2 mol of a pyridine and at least 0.1 mol (see Discussion) of an aromatic aldehyde. Excess aldehyde, nitrobenzene, or dimethylformamide may be employed as the solvent. The solution was heated to 130° until carbon dioxide evolution ceased (usually 1 hr or less). After cooling, the solid which formed was filtered off and washed with ether. The products were purified by recrystallization from water or alcohol. In cases where mixtures were obtained, the crude product was analyzed by nmr in sulfur dioxide solution. In general the nmr spectra gave a multiplet at τ 1.25–1.75 (pyridinium), a seven- or eight-line multiplet at 5.0–5.15 (methylene), a quartet at 4.16–4.62 (methine), a singlet or multiplet at 2.05–2.95 (phenyl), and a singlet at 5.5–6.5 (hydroxyl). The methylene protons are nonequivalent since they are next to an asymmetric carbon.

Treatment of N-Methylpyridinium Bromide with Pyridine and Benzaldehyde. To 17.4 g (0.1 mol) of N-methylpyridinium bromide was added 7.4 g (0.1 mol) of pyridine and 159 g (1.5 mol) of benzaldehyde. The mixture was heated to 135° for 2 hr, cooled, and filtered. The solid was washed with ether and recrystallized from a methanol-ether mixture. The nmr spectrum was identical with that of starting material. The recovery was 98%.

N-Carboxymethylpyridinium Bromide. To 39.3 g (0.3 mol) of methyl bromoacetate and 300 ml of bromobenzene in an erlenmeyer flask was added 47.4 g (0.6 mol) of pyridine. After heating to 80° for 30 min, the mixture was cooled and filtered. The solid was washed with ether and recrystallized from methanol alcohol to give product, mp 210–212°, in 44% yield. The product gave a positive bromide ion test with silver nitrate.

Anal. Calcd for $C_7H_8BrNO_2$: C, 38.53; H, 3.67; N, 6.42; Br, 36.70. Found: C, 38.78; H, 3.75; N, 6.40; Br, 36.64.

Reaction of Ethyl Bromoacetate with Pyridine and Benzaldehyde. To 16.7 g (0.10 mol) of ethyl bromoacetate and 159 g (1.5 mol) of benzaldehyde in a three-necked flask equipped with nitrogen, condenser, and stirrer, was added 7.9 g (0.10 mol) of pyridine. The solution was heated at 160° (carbon dioxide evolution) for 4 hr, cooled, and filtered. The product, N-(2-hydroxy-2-phenylethyl)pyridinium bromide, was recrystallized from water and obtained in 34% yield, mp 237–239° (lit.[3] mp 230.5°). The nmr was identical with that of authentic material.

When the mixture was heated only to 100°, N-carbethoxymethylpyridinium bromide was obtained in 78% yield. The nmr (SO_2) showed a multiplet at τ 1.30 (5 H), a singlet at 4.48 (2 H), a quartet centered at 5.62 (2 H), and a triplet at 8.70 (3 H).

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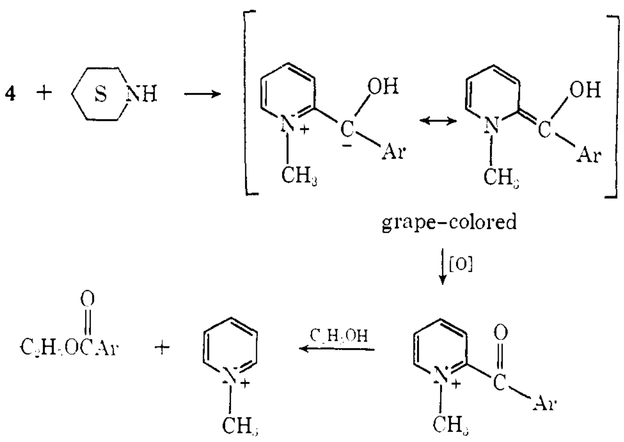
[22] The ethyl benzoate may arise from air oxidation of a grape colored intermediate in turn formed by proton removal from the benzylic carbon of **4**.



[23] M. S. Rozhdestvenskii and L. M. Broude, *J. Appl. Chem. (USSR)*, **10**, 722 (1937).