which on treatment with sodium bicarbonate solution solidified. This was extracted with benzene–ethanol to give white needles of a substance of composition corresponding to S-3-indolyl O-methyl thioimidocarbonate (IV) (5 g., 24%, m.p. 187–188°).

Anal. Calcd. for $C_{10}H_9N_2OS$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.14; H, 4.99; N, 13.60.

Concentration of the mother liquors, followed by recrystallization from aqueous ethanol, gave a solid, m.p. 208°, not depressed on admixture with II (9.6 g., 62% yield of disulfide), whose infrared spectrum is identical with that of II.

The red methylene chloride solution was dried over magnesium sulfate, treated with charcoal, and dry ammonia gas was bubbled through it. A pink solid precipitated (1 g., 9%, m.p. 155–165°) corresponding in composition to the ammonium salt of 3-indolylacetic acid.

Anal. Cacld. for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.39; N. 12.50. Found: C, 54.18; H, 5.36; N, 11.16.

Treatment of thioimidocarbonate IV (1 g.) with a mixture of 20% acetic acid (50 ml.) and concentrated hydrochloric acid (10 ml.) at 0° for two days yielded the corresponding S-3-indolylmethylthiocarbonate (VI), m.p. 119–121° (40%). An analytical sample was recrystallized from benzene–petroleum ether; m.p. 123–124.5°.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 58.00; H, 4.35; N. 6.76. Found: C, 58.22; H, 4.26; N, 6.78.

N-Acetyl-3-thiocyanoindole (IX).—3-Thiocyanoindole (2 g.) was refluxed in 25 ml. of acetic anhydride for 3 hr. On cooling, a crystalline solid separated (2 g., 83%, m.p. 118–120°). Recrystallization from ethanol gave a sample, m.p. 122.5–123.5°, analysis of which corresponds to N-acetyl-3-thiocyanoindole. This structure is assigned on the basis of the elemental analysis, infrared spectrum, which shows no N–H stretching frequency between 3600–3100 cm.$^{-1}$ and the desulfurization product obtained below.

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.11; H, 3.70; N, 12.81.

A portion of IX (1.8 g.) was refluxed with W-2 Raney nickel in 50 ml. absolute ethanol for 24 hr. The residue left after filtration and concentration of the solvent was recrystallized twice from ethanol to give a solid, m.p. 105°, corresponding in properties to N-acetylindoline.[12]

Anal. Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.94; N, 8.56.

Reaction of 3-Thiocyanoindole with Excess Ethylmagnesium Iodide.—A solution of I (5.2 g., 0.03 mole) in 10 ml. of anhydrous ether was slowly added to the Grignard reagent prepared from 2.4 g. of magnesium and 16.2 g. of ethyl iodide (0.09 mole) in 20 ml. of anhydrous ether, the reaction being carried out under an atmosphere of nitrogen. The ether refluxed during the addition of I, and a red solid separated. Stirring was continued for 0.5 hr. and any excess Grignard reagent was decomposed with ice-cold ammonium chloride solution, an odor of hydrogen sulfide being noticed at this stage. The ether layer was separated and the aqueous phase extracted twice with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the ether gave a solid (3.3 g., 75%). m.p. 202–204° not depressed on admixture with II. The infrared spectrum was identical with that of II.

Reaction of 3-Thiocyanoindole with Excess Phenylmagnesium Bromide.—A solution of I (5.2 g., 0.03 mole) in 10 ml. of anhydrous ether was treated with the Grignard reagent prepared from 2.4 g. of magnesium and 13.5 g. of bromobenzene (0.09 mole) in 20 ml. of anhydrous ether, as described in the previous experiment. On evaporation of the ether, an oil with strong odor of bitter almonds was left. This was distilled at reduced pressure to give essentially pure benzonitrile[13] (1.4 g., 50%, b.p. 65° (13 mm.), $n^{30}D$ 1.5249). The infrared spectrum was identical with that of an authentic sample of benzonitrile.

The residue in the distillation flask solidified on cooling (m.p. 198–200°, 3 g.), and appeared from its infrared spectrum to be mainly II.

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[12] G. M. Bennett and M. M. Hafez, *J. Chem. Soc.*, 287 (1941).

[13] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, 1943, gives the b.p. as 69° (10 mm.) and $n^{20}D$ as 1.5289.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Aromatic N-Oxides. II. The Mechanism of the Reaction of 4-Picoline N-Oxide with Acetic Anhydride[1,2]

BY VINCENT J. TRAYNELIS AND ROCCO F. MARTELLO[3]

RECEIVED OCTOBER 9, 1959

The reaction of 4-picoline N-oxide with acetic anhydride gives 4-pyridylmethyl acetate as the major product with some 3-acetoxy-4-methylpyridine. In addition to these esters a number of minor products are found which are best rationalized by the presence of free radicals; however, evidence is offered to exclude a radical chain mechanism. The origin of the esters is explained by an intramolecular rearrangement which proceeds through a common intermediate. Evidence is reported which favors a radical pair process for this intramolecular change.

In the previous report[1] we have confined our comments to the path of the reaction of 2-picoline N-oxide and acetic anhydride. The data collected ruled out a radical chain mechanism and favored an intramolecular rearrangement involving possibilities of a concerted process, radical pairs or ion pairs. With this communication we wish to record our observations with 4-picoline N-oxide and acetic anhydride.

Several papers have appeared defining the scope of the reaction of 4-alkylpyridine N-oxide[4–9] and 4-methylquinoline N-oxide[10] with acetic anhydride. The report by Berson and Cohen[6] described the isolation and identification of a by-product, 3-hydroxy-4-methylpyridine, in addition to the major product, 4-pyridylmethyl acetate. These authors reviewed several possible mechanisms for the origin of both substances which would be consistent with the data available. One path involves the intermediate anhydrobase II which can undergo nucleophilic attack by acetate anion at the exocyclic

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[1] For paper I in this series see, V. J. Traynelis and R. F. Martello, THIS JOURNAL, **80**, 6590 (1958).

[2] Presented at the 136th Meeting of the American Chemical Society at Atlantic City, N. J., in September, 1959.

[3] Peter C. Reilly Fellow 1957–1958. Abstracted from the Ph.D. dissertation of R. F. Martello, May, 1959.

[4] V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).

[5] O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

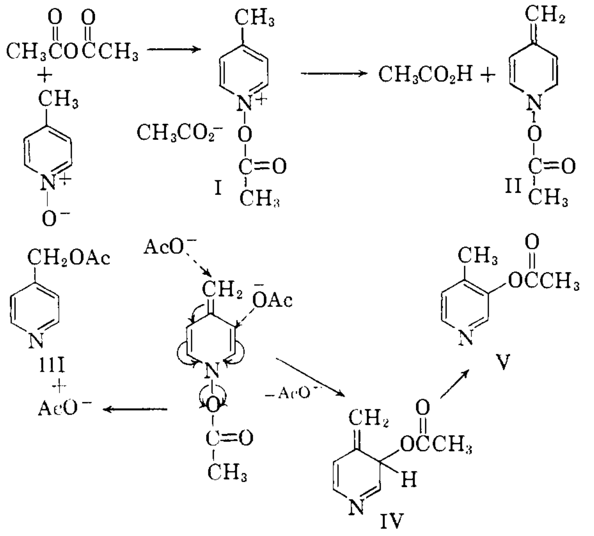
[6] J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).

[7] S. Furukawa, *Pharm. Bull.* (*Japan*), **3**, 413 (1955); *C. A.*, **50**, 13926a (1956).

[8] T. Kato, *J. Pharm. Soc. Japan*, **75**, 1233 (1955); *C. A.*, **50**, 8664i (1956).

[9] F. Cislak, U. S. Patent 2,748,141, May 29, 1956; *C. A.*, **51**, 2878c (1957).

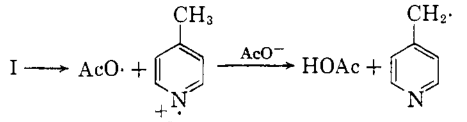
[10] G. Kobayashi, S. Furukawa, Y. Akimoto and T. Hoshi, *J. Pharm. Soc. Japan*, **74**, 791 (1954); *C. A.*, **49**, 11659b (1955).



methylene position with elimination of the acetate group attached to nitrogen to give 4-pyridylmethyl acetate (III); or attack by acetate anion at the C-3 position of the ring with expulsion of acetate ions and the generation of IV. An allylic shift of the C-3 hydrogen leads to 3-acetoxy-4-methylpyridine (V) which accounts for the by-product reported. Secondly, the possibility of an internal rearrangement was offered whereby II gave the products, presumably by rearrangement to IV which can undergo the allylic shift to give V or can undergo a second migration[11] of the acetate group to generate the major product III. Thirdly, these authors admit that a radical mechanism cannot be ruled out.

Our experimental approach to collect data about this process was comparable to the reactions involving 2-picoline N-oxide; first determine if radicals are present and then if they are involved in the formation of the ester products. When 21.8 g. (0.200 mole) of 4-picoline N-oxide was allowed to react with 21.0 g. (0.206 mole) of acetic anhydride, the following products were found: a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine (65%) which contained 88–89% 4-pyridylmethyl acetate (the ester composition was analyzed by the application of infrared spectroscopy the details of which are described in the Experimental section); methyl acetate (2.6%), identified by comparison of its infrared spectrum with that of an authentic sample; a mixture of amines which contained 4-picoline (2.9%), 2,4-dimethylpyridine (0.2%) and 4-ethylpyridine (0.6%) (these three pyridine bases were separated by vapor phase chromatography and were identified by comparison of retention times and infrared spectra with those of authentic samples): and 370 ml. of a gas which was analyzed by mass spectrometry (Table I) and contained carbon dioxide (4.7%), methane (1.0%), methyl acetate (0.15%), acetic acid (0.15%), nitrogen and air. Chemical evidence for carbon dioxide was established when a white precipitate resulted upon passage of the gas into a solution of barium hydroxide. Methane was identified by its mass spectrum pattern after subtraction of the contributions of carbon dioxide and nitrogen (present since the reaction was performed in this atmosphere). The percentage composition based on these six compounds was calculated by the usual method[12] and either small or no residuals were found for all mass numbers.

The presence of free radicals nicely explains the origin of carbon dioxide, methane and the alkylpyridines. The homolytic cleavage of the nitrogen oxygen bond in II would generate acetoxy and γ-picolyl radicals. An alternate formation of these radicals as suggested by Boekelheide[13] for the 2-picoline N-oxide system involves a comparable homolytic cleavage of I to form acetoxy radicals and the radical ion VI which upon loss of a proton to acetate ions leads to a picolyl radical. The acetoxy radicals decompose into carbon dioxide and methyl radicals which may abstract a hydrogen atom from either reactants or products to give methane. The production of 4-picoline from the 4-picolyl radical could be explained in a similar manner; while the union of a methyl and 4-picolyl radicals would form 4-ethylpyridine and the combination of a methyl radial and 4-picoline would give 2,4-dimethylpyridine. Thus the isolation of these products suggests the presence of free radicals in solution but leaves unanswered the question whether they are involved in the formation of the major products.



VI

TABLE I

MASS SPECTRUM ANALYSIS OF GASES PRODUCED IN THE REACTION OF 4-PICOLINE N-OXIDE AND ACETIC ANHYDRIDE

Gas	m/e[b]	H[c]	H'[d]	P[e]	Mole %[a]
Methane	16	324.0	185.0	2.81	0.95
Carbon dioxide	44	1350.0	1349.5	14.49	4.71
Methyl acetate	43	8.1	7.1	0.45	0.15
Acetic acid	60	1.0	1.0	0.46	0.15
Nitrogen	28	276.0	137.2	1.59	
Air	32	2.0	1.9	0.14	
	$P_{\text{calcd.}}$ 19.50 μ		$P_{\text{obsd.}}$ 19.93 μ		

[a] Calculations were based on the volume corrected to standard temperature. [b] m/e = mass number of "100" peak for the pure compound. [c] H = peak height for mixture. [d] H' = contribution of pure component to peak height. [e] P = partial pressure for each component.

Radical acceptors were introduced into the reaction to observe their effect on the yield of methane, carbon dioxide and the mixture of esters 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine. Two reactions, under conditions identical to those which gave the products listed above, were studied in the presence of 10 and 20% *m*-dinitrobenzene. These results appear in Table II. First, the addi-

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(11) This rearrangement would be reminiscent of the Claisen type involving a six-atom transition in going from I to IV and also in converting IV to III.

(12) H. W. Washburn, in W. G. Berl, "Physical Methods in Chemical Analysis," Vol. I, Academic Press, Inc., New York, N. Y., 1950, pp. 612–618.

(13) V. Boekelheide and D. L. Harrington, *Chemistry & Industry*, 1423 (1955).

TABLE II

EFFECT OF *m*-DINITROBENZENE ON THE REACTION OF 4-PICOLINE N-OXIDE AND ACETIC ANHYDRIDE

Product	Yield, % with *m*-dinitrobenzene 0%	10%	20%
Methane	0.95	0.56	0.36
Carbon dioxide	4.71	3.97	2.34
Ester mixture	65	67	38
(4-Pyridylmethyl acetate, %)	88	86	88
(3-Acetoxy-4-methylpyridine, %)	12	14	12
Decrease in methane, %		41	62
Decrease in carbon dioxide, %		15	50
Decrease in ester mixture, %			42

tion of 10% *m*-dinitrobenzene caused a 41% decrease in the production of methane, 15% decrease in the liberation of carbon dioxide and essentially no change in either the yield or composition of the ester mixture. One set of conclusions drawn from these results is that free radicals in solution leading to methane are removed to a reasonable extent by *m*-dinitrobenzene and thus if radicals in solution were intermediates in the formation of esters, then the ester yield should also decrease like methane. Therefore these data cannot be rationalized by a free radical chain mechanism. When the concentration of *m*-dinitrobenzene was increased to 20%, the following data were obtained: 62% decrease of methane, 50% decrease in carbon dioxide and 42% decrease in the yield of ester mixture but no change in the composition of this mixture. The reduction of methane was expected; however, the decrease in carbon dioxide begins to suggest capture of acetoxy radicals before they decompose and perhaps before they get too far away from the species that generates them. The reduction in ester yield was somewhat surprising. One rationalization involves a reaction between *m*-dinitrobenzene and 4-picoline N-oxide or the ester mixture (III and V). These possibilities have been excluded by subjecting *m*-dinitrobenzene plus 4-picoline N-oxide and *m*-dinitrobenzene plus an ester mixture (III and V) to the reaction conditions. In each case good yields of unreacted starting materials were recovered and no new products were found. Thus the *m*-dinitrobenzene must influence some intermediates in this process; and since the ester composition showed no change, the same intermediate must be responsible for the origin of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine. An explanation which would account for all the results thus far is an intramolecular rearrangement of II which involves the homolytic cleavage of the nitrogen–oxygen bond with the formation of a radical pair. This pair may recombine to give the two ester products thus satisfying the common intermediate requirement. Also some acetoxy radicals and picolyl radicals may separate from the pair and form the gaseous products and alkylpyridines reported in the initial experiment. The reduction in the percentage yield of carbon dioxide and the mixture of esters can be rationalized in the following manner; as the amount of radical acceptor (*m*-dinitrobenzene) is increased, its concentration in the sphere of molecules surrounding the intermediate increases and when this concentration reaches a certain value, these radical acceptors may begin to remove the radical pairs before they recombine or separate thus causing a decrease in the yields of ester, methane and carbon dioxide.

Additional support for these conclusions was found when the reaction of 4-picoline N-oxide in acetic anhydride was carried out in nitrobenzene and in styrene, both radical acceptors. In the nitrobenzene experiment the yield of the ester mixture (89% 4-pyridylmethyl acetate, 11% 3-acetoxy-4-methylpyridine) was 30%; while the styrene experiment produced 42% of ester mixture (89% 4-pyridylmethyl acetate, 11% 3-acetoxy-4-methylpyridine), 10% unreacted styrene and 30% polystyrene.[14] Although the experimental conditions in these two reactions varied from those of the experiments with *m*-dinitrobenzene, the yield of esters without change in composition clearly indicates a sharp reduction from the expected amount and is consistent with the explanation offered earlier.

Evidence for the intramolecular rearrangement was obtained from the study of the reaction of 4-picoline N-oxide with butyric anhydride in the presence of sodium acetate.[15] When 4-picoline N-oxide was allowed to react with butyric anhydride, the following fractions were obtained: a mixture of butyrate esters (38%), 4.4 g. of alkylpyridines and 2750 ml. of gas. The identity of the ester mixture was established by saponification which gave butyric acid, 4-pyridylmethanol and 3-hydroxy-4-methylpyridine, each identified by comparison of the respective infrared spectrum with that of an authentic sample. Analysis of the mixture by infrared spectroscopy showed the composition to be 79–85% 4-pyridylmethyl butyrate and 15–21% 3-butyroxy-4-methylpyridine. The amine fraction was separated and analyzed by vapor phase chromatography and contained 4-picoline (6.7%), 2-*n*-propyl-4-methylpyridine (1.9%) and 4 *n*-butylpyridine (9.9%). These compounds were identified by comparison of retention times in gas chromatography and infrared spectra with authentic samples. In addition the picrate of 4-butylpyridine was prepared and the boiling point of 4-picoline determined. The gas was analyzed by mass spectrometry (Table III) and contained carbon dioxide (42.5%), propane (16.7%) and propylene (1.8%) in addition to other products. Chemical evidence for carbon dioxide was obtained by precipitation of barium carbonate when the gas was passed through a solution of barium hydroxide. The gas also decolorized bromine in a solution of carbon tetrachloride which can be attributed to the propylene present. An interesting observation in this experiment is the high yield of carbon dioxide (42%) compared to the amount (4.7%) evolved when acetic anhydride was used. Apparently the pair of 4-picolyl radicals and butyroxy radicals have a greater tendency to decompose as free radicals than combine to give butyrate esters.

When a second experiment was performed using the same quantities and conditions with the addi-

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(14) In a separate control experiment it was shown that 4-picoline N-oxide alone was not responsible for the polymerization of styrene. Thus additional evidence is available for the presence of radicals in the reaction mixture.

(15) The reasons for the choice of butyric anhydride and sodium acetate were described before, ref. 1.

Table III

Mass Spectrum Analysis of Gases Produced in the Reaction of 4-Picoline N-Oxide and Butyric Anhydride

Gas	m/e^a	H	H'	P	Mole %
Propylene	41	55.8	15.9	0.30	1.82
Propane	29	288.0	283.0	2.75	16.73
Carbon dioxide	44	804.0	728.0	7.01	42.5
Nitrogen	28	942.0	70.0	0.72	
Air	32	133.0	133.0	8.67	

Pressure (calcd.) 19.68 μ. Pressure (exp.) 19.45 μ.

[a] Symbols were defined in Table I.

tion of an equimolar amount of sodium acetate, the only esters isolated, 37% yield, were a mixture of 4-pyridylmethyl butyrate (95%) and 3-butyroxy-4-methylpyridine (5%). Thus the explanation involving attack of anions on the anhydro base II appears to be unfavorable.

In conclusion, the data presented in this report are consistent with (1) the exclusion of a free radical chain mechanism, (2) the exclusion of nucleophilic attack of acid anions on the anhydro base II, (3) the proposal of an intramolecular rearrangement. This rearrangement may proceed *via* an ion pair or radical pair, which result from a heterolytic or homolytic cleavage, respectively, of the nitrogen–oxygen bond in II; or the internal cyclic rearrangement described earlier. On the basis of the experiments with radical acceptors the radical pair intermediate is favored; although the evidence does not exclude the cyclic rearrangement. There is a possibility that structure IV may react in some way with nitrobenzene, *m*-dinitrobenzene and styrene.

Experimental[16]

3-Hydroxy-4-methylpyridine.[17]—The sulfonation of 4-picoline (42.0 g., 0.451 mole) was carried out according to the procedure of McElvain and Goese[18] with a minor modification in the isolation procedure. The excess sulfuric acid was removed as barium sulfate and the residue after evaporation, barium 4-methyl-3-pyridinesulfonate, was dissolved in water and treated with an equivalent quantity of potassium sulfate. After the barium sulfate was separated, the filtrate was evaporated and gave 24 g. of crude potassium 4-methyl-3-pyridinesulfonate.

The fusion of the above potassium salt with potassium hydroxide by the procedure in the literature gave after recrystallization from benzene 4.0 g. (8% based on 4-picoline) of 3-hydroxy-4-methylpyridine, m.p. 120–122° (lit.[17] m.p. 120°).

3-Acetoxy-4-methylpyridine.—After a solution of 3-hydroxy-4-methylpyridine (2.0 g., 0.018 mole) and acetic anhydride (4.0 g., 0.039 mole) was warmed on a steam-bath for 4 hours, acetic acid and acetic anhydride were removed by distillation through a metroware Vigreux column at atmospheric pressure. Distillation of the residue gave 2.3 g. (82%) of colorless 3-acetoxy-4-methylpyridine, b.p. 97–98° (4.5 mm.), $n^{20}\text{D}$ 1.4999.

The picrate was prepared in the usual manner[19] and after recrystallization from ethanol gave yellow needles, m.p. 172–174°.

Anal. Calcd. for $C_{14}H_{12}N_4O_9$: C, 44.22; H, 3.18. Found: C, 44.23; H, 3.37.

3-Butyroxy-4-methylpyridine.—Using the procedure described above, 3-hydroxy-4-methylpyridine (2.0 g., 0.018 mole) and butyric anhydride (4.2 g., 0.026 mole) gave after two distillations 2.0 g. (60%) of colorless 3-butyroxy-4-methylpyridine, b.p. 109–110° (2.5 mm.), $n^{20}\text{D}$ 1.4936.

The picrate was prepared in the usual manner[19] and, after recrystallization from ethanol, gave yellow needles, m.p. 111–114°.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95. Found: C, 47.02; H, 4.01.

4-Pyridylmethyl Acetate.—By the above procedure 2.4 g. (55%) of 4-pyridylmethyl acetate, b.p. 110–112° (12 mm.), $n^{20}\text{D}$ 1.5035 (lit.[20] b.p. 126–127° (16 mm.)) was isolated by distillation from the reaction of acetic anhydride (4.0 g., 0.039 mole) and 4-pyridylmethanol (3.0 g., 0.027 mole, obtained from the hydrolysis of the ester mixture described below).

4-Pyridylmethyl Butyrate.—According to the above directions the reaction of 4-pyridylmethanol (3.0 g., 0.027 mole) and butyric anhydride (4.2 g., 0.026 mole) gave upon distillation 2.0 g. (43%) of 4-pyridylmethyl butyrate, b.p. 120° (5 mm.), $n^{21}\text{D}$ 1.4940.

The picrate was prepared in the usual manner[19] and after crystallization from ethanol gave yellow needles, m.p. 122–125°.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95. Found: C, 47.35; H, 4.04.

The Reaction of 4-Picoline N-Oxide and Acetic Anhydride. (A) Without *m*-Dinitrobenzene.—The apparatus described in the previous report[1] was charged with acetic anhydride (21.0 g., 0.206 mole) and the system flushed thoroughly with dry nitrogen. A solution of 4-picoline N-oxide (21.8 g., 0.200 mole) in glacial acetic acid (35 ml.) was added dropwise over a period of 40 minutes to gently refluxing acetic anhydride, oil-bath temperature 140–150°. The mixture became dark brown and heating was continued for 1.5 hours after the addition was completed. The gas produced during the reaction was collected in the gas buret over mercury at pressures slightly greater than atmospheric and measured 290 ml.[21] After the reaction was completed, a gas sample was taken for mass spectrometric analysis (Table I) and when a portion of the gas was bubbled through a solution of barium hydroxide, a white precipitate resulted.

The reaction mixture was initially distilled through an 0.8 × 25 cm. column packed with 1/16 inch glass helices and equipped with a variable take-off head and gave 0.36 g. (2.4%) of crude methyl acetate, b.p. up to 70°. The infrared spectrum of this product was identical with that of authentic methyl acetate.

The acetic acid was removed at atmospheric pressure and distillation at reduced pressure gave 4.5 g. of a liquid, b.p. 60–70° (19 mm.). This material was added to water (10 ml.), neutralized with sodium hydroxide (50%), extracted with ether and the ether solution was dried over sodium sulfate. After the ether was removed, the residue of amines (0.75 g.) was analyzed by vapor phase chromatography. The conditions for efficient separation of the mixture into three components were: column, mineral oil on 30–60 mesh fire brick; temperature, 120°; and rate of helium flow, 56 ml./min. The compounds, identified by collection of fractions from several chromatography runs and comparison of their infrared spectra with authentic samples,[22] were 4-picoline (2.9%, retention time 20 min.), 2,4-dimethylpyridine

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[16] All melting points and boiling points are uncorrected. The microanalysis were carried out by Midwest Microlab Inc., Indianapolis, Ind., and Gailbraith Laboratories, Knoxville, Tenn. Mass spectra were recorded by Mr. George Young on a Consolidated 21-103 A analytical mass spectrometer, Radiation Project, University of Notre Dame. Infrared spectra were determined with a Perkin-Elmer model 21 or a Baird Associates infrared spectrophotometer by Mr. R. F. Love and Mr. A. Saraceno. All vapor phase chromatography was carried out using the Aerograph model A-90 instrument.

[17] I. G. Farbenind., French Patent 685,583, November 18, 1929; *C. A.*, **24**, 5766 (1930).

[18] S. M. McElvain and M. A. Goese, This Journal, **65**, 2233 (1943).

[19] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," third edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

[20] M. Simonetta and G. Fauini, *Gazz. chim. ital.*, **84**, 566 (1954).

[21] The volume was measured at 25° and was corrected to standard temperature for the calculations.

[22] These compound were kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Co., and were distilled prior to use: 4 picoline, b.p. 140°, $n^{20}\text{D}$ 1.5022; 4-ethylpyridine, b.p. 84° (49 mm.), $n^{20}\text{D}$ 1.5019; and 2,4-lutidine, b.p. 92° (49 mm.), $n^{20}\text{D}$ 1.5053. Each compound was passed individually under the conditions cited above through the vapor phase chromatograph and the pure samples collected.

(0.2%, retention time 32 min.) and 4-ethylpyridine (0.6%, retention time 37 min.). The composition of the mixture was determined from the individual peak areas which were measured with a planimeter. A mixture of authentic compounds was prepared and analyzed by vapor phase chromatography using the above conditions. The retention times of these components were identical to those listed above and the area under each peak was proportional to the molar concentration of the component.

Distillation of the remaining reaction residue gave 19.7 g. (65%) of a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine, b.p. 100–101° (5 mm.), $n^{20}\text{D}$ 1.5021 (lit.[4] b.p. 50–53° (0.3 mm.), $n^{20}\text{D}$ 1.5023). The percentage composition of components was determined by infrared spectra analysis of chloroform solutions utilizing the peak ratio–percentage composition plot.[23] The intense absorption bands at 11.10 μ for 3-acetoxy-4-methylpyridine and 6.37 and 9.15 μ for 4-pyridylmethyl acetate were used in these calculations. The mixture contained 88–89% 4-pyridylmethyl acetate and 11–12% 3-acetoxy-4-methylpyridine.

(B) **With *m*-Dinitrobenzene.**—Using the above quantities of reactants and identical reaction conditions two experiments were carried out in the presence of *m*-dinitrobenzene (2.2 g., 0.013 mole, 10% by weight of 4-picoline N-oxide and 4.4 g., 0.026 mole, 20% by weight). By the procedure described distillation gave crude methyl acetate, 0.38 g. (2.4%) and 0.1 g. (0.6%), respectively. Each experiment gave 0.6 g. of an amine fraction, which was analyzed by vapor phase chromatography and contained 4-picoline (1.5%), 2,4-dimethylpyridine (0.5%), 4-ethylpyridine (1.2%) and 4-picoline (2.7%), 2,4-dimethylpyridine (0.2%), 4-ethylpyridine (0.5%), respectively. Distillation of the residue from the 10% *m*-dinitrobenzene reaction gave 20.7 g. (68%) of a mixture of acetate esters, b.p. 100–102° (5 mm.), $n^{20}\text{D}$ 1.5018. Infrared analysis as described above showed 85–87% 4-pyridylmethyl acetate and 13–15% 3-acetoxy-4-methylpyridine. The 20% *m*-dinitrobenzene experiment gave 11.6 g. (38%) of acetate esters, b.p. 100–102° (5 mm.), $n^{20}\text{D}$ 1.5018; 4-pyridylmethyl acetate (88–89%) and 3-acetoxy-4-methylpyridine (11–12%). The volume of gas for each experiment was 245 and 172 ml., respectively. The analysis was by mass spectrometry (Table II).

Control Experiments. *m*-Dinitrobenzene plus 4-Picoline N-Oxide.—A solution of 4-picoline N-oxide (9.0 g., 0.083 mole), *m*-dinitrobenzene (1.8 g., 0.011 mole) and 20 ml. of glacial acetic acid was refluxed for 2 hours, pot temperature 140°. After most of the acetic acid was removed under reduced pressure, the residue was diluted with ether and gave upon filtration 4.4 g. of 4-picoline N-oxide, m.p. 183–186°. Removal of the ether from the filtrate and dilution of the residue with water gave 1.6 g. of *m*-dinitrobenzene, m.p. 89.5–91°. The remaining aqueous solution was made strongly alkaline with sodium hydroxide, saturated with sodium chloride and then exhaustively extracted with chloroform. The first 210 ml. of chloroform solution was evaporated and gave 1.6 g. of a solid which after triturating with ether left 1.1 g. of 4-picoline N-oxide, m.p. 184–186°. After the ether was removed, the residue upon treatment with water gave 0.17 g. of *m*-dinitrobenzene, m.p. 89–91°. The remainder of the chloroform extractions yielded 2.6 g. of 4-picoline N-oxide, m.p. 183–186°. Each fraction of 4-picoline N-oxide and *m*-dinitrobenzene showed no depression in mixed melting points with authentic samples. The total yield of 4-picoline N-oxide, m.p. 183–186°, was 8.1 g. (90%) and of *m*-dinitrobenzene, m.p. 89–91°, 1.75 g. (97%).

***m*-Dinitrobenzene plus a Mixture of 4-Pyridylmethyl Acetate and 3-Acetoxy-4-methylpyridine.**—A solution of *m*-dinitrobenzene (4.0 g., 0.023 mole) and pyridine ester mixture (10.0 g., 0.065 mole) in 25 ml. of glacial acetic acid was refluxed for 2 hours. After removal of the acetic acid, distillation gave 8.2 g. (82%) of a mixture of 4-pyridylmethyl acetate and 3-acetoxy-4-methylpyridine, b.p. 120–122° (20 mm.), $n^{20}\text{D}$ 1.5040.

In a separate experiment under comparable conditions *m*-dinitrobenzene was recovered quantitatively from the reaction mixture by dilution with water, acidification with hydrochloric acid and extraction with ether. After the aqueous layer was made alkaline and extracted with ether, distillation gave a 65% yield of the pyridine–ester mixture.

(C) **With Nitrobenzene as Solvent.**—Acetic anhydride (22.0 g., 0.215 mole) was added dropwise, over a period of 30 minutes, to a gently refluxing solution of 4-picoline N-oxide (21.8 g., 0.20 mole) and nitrobenzene (50 ml.) in a three-neck flask fitted with a reflux condenser, a mechanical stirrer and an additional funnel. The reddish-brown mixture was allowed to reflux for 1.5 hours after the addition was completed. The reaction mixture was flashed over at 15 mm. pressure through a metroware Vigreux column. The pale yellow distillate was extracted with hydrochloric acid (20%), the aqueous layer was neutralized with potassium carbonate, extracted with ether and the ethereal solution dried over potassium carbonate. After the ether was removed, distillation gave 9.2 g. (30.2%) of a mixture of acetate esters, b.p. 112–116° (15 mm.), $n^{20}\text{D}$ 1.5040. Composition analysis of these esters by infrared spectra as described above showed 91% of 4-pyridylmethyl acetate and 9% 3-acetoxy-4-methylpyridine.

(D) **In the Presence of Styrene.**—Using the same quantities of reactants and conditions as described in part C, the reaction of 4-picoline N-oxide and acetic anhydride was carried out in the presence of inhibitor-free styrene (14.0 g., 0.134 mole). After the reaction mixture was heated for 65 minutes, the red-brown liquid was distilled through a 10-inch Vigreux column. A colorless fraction, b.p. 40–60° (30 mm.), was collected and added to water (20 ml.). The resulting solution was neutralized with potassium carbonate, extracted with ether and the ethereal extract was dried over potassium carbonate. After the ether was removed, 1.5 g. (11%) of styrene remained.

The residue from the initial distillation was added to methanol (350 ml.) and 4.2 g. (30%) of a gummy polymeric material separated. After filtration, the solid was dried and had an infrared spectrum identical with polystyrene.

The methanol was removed and distillation gave a liquid, b.p. 40–70° (10.5 mm.), from which 0.2 g. of amines was obtained. Analysis of these amines by vapor phase chromatography under the conditions described above gave the following results: 4-picoline (0.69%), 2,4-dimethylpyridine (0.03%) and 4-ethylpyridine (0.30%). Further distillation gave 13.0 g. (42%) of esters, b.p. 100–102° (4 mm.), $n^{20}\text{D}$ 1.5030, which by infrared analysis had the composition of 88–89% 4-pyridylmethyl acetate and 11–12% 3-acetoxy-4-methylpyridine.

Polymerization Control Experiments.[24] Styrene and 4-Picoline N-Oxide.—A solution of 4-picoline N-oxide (10.0 g., 0.092 mole), inhibitor free styrene (14.0 g., 0.134 mole) and glacial acetic acid (25 ml.) was refluxed with stirring for 2 hours under an atmosphere of nitrogen. Distillation gave a fraction, b.p. 35–50° (30 mm.), which was added to water, neutralized with potassium carbonate and extracted with ether. After the ether solution was dried and the ether removed, distillation gave 11.5 g. (82%) of styrene, b.p. 50–55° (30 mm.).

Crude 4-picoline N-oxide, m.p. 168–174° (7.0 g., 70%), was obtained from the residue of the initial distillation and no polymeric material was precipitated when the remaining residue was treated with methanol.[25]

Hydrolysis of a Mixture of 4-Pyridylmethyl Acetate and 3-Acetoxy-4-methylpyridine.—A solution of 20% potassium hydroxide (25 ml.) and the mixture 4-pyridylmethyl acetate–3-acetoxy-4-methylpyridine (12.0 g., 0.08 mole) was heated at 120° for 20 hours. After the reaction mixture was cooled to room temperature, the alkaline solution was extracted with ether continuously for 83 hours. The ether layer was dried over potassium carbonate and after removal of the ether, distillation gave 6.2 g. (71%) 4-pyridylmethanol, b.p. 148° (13 mm.), which solidified upon standing, m.p. 44–47° [lit.[26] m.p. 47–50°, b.p. 140–142° (12 mm.)].

The residue was recrystallized from benzene and gave 0.5 g. (5.7%) of crude 3-hydroxy-4-methylpyridine, m.p. 106–110° (lit. m.p. 120°). The impure product gave a red color with ferric chloride and an infrared spectrum which was identical with that of an authentic sample.

The Reaction of 4-Picoline N-Oxide and Butyric Anhydride.—A three-necked cone-shaped flask, fitted with an addition funnel, a gas inlet tube and a reflux condenser connected to a

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[23] C. A. Stewart and C. A. VanderWerf, THIS JOURNAL, **76**, 1259 (1954).

[24] In the previous report[1] when styrene was refluxed for two hours in acetic anhydride only a 4% yield of polystyrene resulted.

[25] 2-Picoline N-oxide and styrene gave 0.2% polystyrene.

[26] P. Rabe, O. Sprecheli and L. Wilhelm, *J. prakt. Chem.*, **151**, 65 (1938).

graduated gas cylinder (2000 ml.) filled with distilled water and equipped with a pressure equalizer bell-jar, was charged with butyric anhydride (37.0 g., 0.23 mole). After the system was thoroughly flushed with dry nitrogen, a solution of 4-picoline N-oxide (21.8 g., 0.20 mole) in butyric acid (28.0 g., 0.32 mole) was added dropwise over a period of 1.5 hours to the pre-heated butyric anhydride (oil-bath temperature 145–155°). The gases evolved displaced 2750 ml. of water, gave a white precipitate when bubbled through an aqueous solution of barium hydroxide and decolorized a dilute solution of bromine in carbon tetrachloride. A gas sample was obtained for mass spectrometric analysis after passing the gases through a column of calcium chloride into an evacuated bulb. The results are given in Table III. Titration of an aliquot of the displaced water in the gas cylinder for carbon dioxide showed less than 0.1% was in solution and thus was disregarded in the calculations.

Upon distillation of the reaction mixture, the first fraction, b.p. 60–94° (16 mm.), was collected and added to ether (50 ml.). This ethereal solution was extracted with hydrochloric acid (20%) and the acid layer neutralized with potassium carbonate. After extraction of the alkaline solution with ether, the ether was dried, removed and gave a residue of 4.4 g. of an amine mixture, which was analyzed by vapor phase chromatography. The conditions for separation of the amine mixture were: column, mineral oil on 30–60 mesh fire brick; temperature, 160°; and rate of helium flow 56 cc./min. The compounds were 4-picoline (6.7%, retention time 4.5 min.), 2-propyl-4-methylpyridine (1.9%, retention time 19.0 min.) and 4-*n*-butylpyridine (9.9%, retention time 25 min.); and were identified by comparison of infrared spectra with authentic samples.[27] In addition to the spectra 4-*n*-butylpyridine was converted to a picrate, m.p. 112° (lit.[28] m.p. 112–113°). A mixture of authentic compounds was prepared and analyzed by vapor phase chromatography using the above conditions. The retention times of these components were identical to those listed above and the area under each peak was proportional to the molar concentration of the component.

The second fraction of the distillation was 17.0 g. of a pale yellow liquid, b.p. 114–123° (3 mm.). Careful redistillation through a metroware Vigreux column gave 13.4 g. (37.5%) of a mixture of butyrate esters, b.p. 121–123° (3 mm.), $n^{20.6}\text{D}$ 1.4927. The percentage composition of components was determined by infrared spectral analysis as described previously and utilized the absorption bands 6.37 and 10.05 μ of 4-pyridylmethyl butyrate and 6.69 μ of 3-butyroxy-4-methylpyridine. The mixture contained 77–84% 4-pyridylmethyl butyrate and 16–23% 3-butyroxy-4-methylpyridine.

In a separate experiment using only 4-picoline N-oxide and butyric anhydride, 4-picoline, b.p. 140–144°, and a mixture of 4-*n*-butylpyridine and 2-*n*-propyl-4-methylpyridine, b.p. 195–204°, were isolated. Also a 91% yield of butyric acid was found.

The Reaction of 4-Picoline N-Oxide and Butyric Anhydride in the Presence of Sodium Acetate.—Using the same procedure described above, 4-picoline N-oxide (10.9 g., 0.10 mole) in butyric acid (15.0 g.) was added to a solution of sodium acetate (8.2 g., 0.10 mole) and butyric anhydride (18.0 g., 0.114 mole) at 100–105° over a period of 25 minutes. After the addition was completed, the mixture was heated for 2 hours. The low boiling amine mixture was 0.2 g. and vapor phase chromatography under the above conditions showed the presence of 4-picoline (0.44%), 2,4-dimethylpyridine (0.14%), 4-ethylpyridine (0.16%), 2-*n*-propyl-4-methylpyridine (0.26%) and 4-*n*-butylpyridine (0.96%). These were identified by their retention times. The yield of butyrate esters, b.p. 119–122° (4 mm.), $n^{20}\text{D}$ 1.4943, was 6.5 g. (36.5%). Analysis was by infrared spectra and showed 4-pyridylmethyl butyrate was about 95% of the product mixture.

Hydrolysis of a Mixture of 4-Pyridylmethyl Butyrate and 3-Butyroxy-4-methylpyridine.—A solution of 20% potassium hydroxide (20 ml.) and the mixture 4-pyridylmethyl butyrate–3-butyroxy-4-methylpyridine (10.0 g., 0.066 mole) was heated at 110–120° for 22 hours. After cooling, the alkaline solution was extracted continuously with ether for 24 hours. The ether layer was dried over sodium sulfate and after the ether was removed, distillation gave 1.3 g. (21.3%) of 4-pyridylmethanol, b.p. 120–121° (3.5 mm.), which solidified upon standing; m.p. 40–42°.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The organic layer was dried over sodium sulfate and after removal of the ether, 2.3 g. (40%) of a pale yellow liquid was obtained which gave an infrared spectrum identical with that of an authentic sample of butyric acid.

The aqueous layer was neutralized with potassium carbonate and after standing overnight a solid precipitated which was filtered, dried and extracted with ether. Removal of the ether gave 0.9 g. (13%) of a white solid, m.p. 112–116°, the infrared spectrum of which was identical with that of an authentic sample of 3-hydroxy-4-methylpyridine.

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Notre Dame, Ind.

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[27] These compounds were kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Co., and were distilled prior to use: 4-picoline, b.p. 140°, $n^{20}\text{D}$ 1.5022; 4-*n*-butylpyridine, b.p. 101–102° (28 mm.), $n^{20}\text{D}$ 1.4940; and 2-propyl-4-methylpyridine, b.p. 90–91° (18 mm.), n^{20} 1.4942. Each compound was passed individually under the conditions cited above through the vapor phase chromatography and the pure samples collected.

[28] F. E. Frey and H. J. Hepp, This Journal, **55**, 3357 (1933).