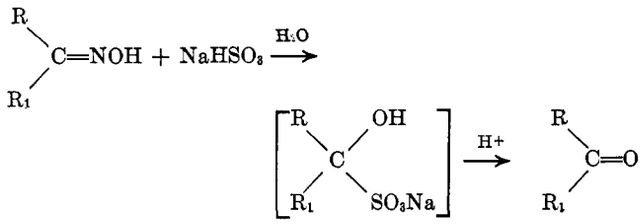
ried out under neutral, nonreversible conditions; brief exposure to acid (in the cold) is required only for the isolation of the product.



The reaction was first described by von Pechmann[2] in 1887 at which time he characterized a crystalline intermediate in the case of benzaldoxime.[3,4] The failure to find references to this excellent procedure in the modern literature, coupled with our finding of its general utility prompt us to report the results of the hydrolysis of several representative oximes.

Our results are tabulated in Table I. Reaction times are not necessarily optimized; thin layer chromatography was used extensively to assess the progress of the hydrolysis.

TABLE I

BISULFITE CLEAVAGE OF OXIMES

Oxo compd[a,b]	Reaction time, hr	Yield, %[c]
3,4-Diphenyl-2-butanone (1)	2	84
Acetophenone (2)	6	83
Benzophenone (3)	24	98
2′,3′-α-Tetrahydrofuran-2′-spiro-17-(4-androsten-3-one)[d] (4)	16	86
Heptaldehyde (5)	2	87
5-Chlorosalicylaldehyde (6)	6	77

[a] Oximes corresponding to **2**, **3**, **5**, and **6** were purchased from Eastman Chemicals. [b] Thin layer chromatography was run on silica gel G plates (Analtech, Inc.). Benzene was used as solvent in all cases; with the oxime of **4**, 5% ether was added to enhance mobility. Approximate R_f values (oximes): **1**, 0.2; **2**, 0.3; **3**, 0.2; **4**, 0.15; **5**, 0.15; **6**, 0.25. The corresponding oxo compounds showed greater mobility. The developed spots were visualized by exposure to iodine vapor. [c] Yields are of purified products: liquids by distillation and solids by crystallization from appropriate solvents. [d] G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, 6, 617 (1963). The oxime was made in the usual fashion.

Experimental Section

The oxime, dissolved in 10 to 12 vol. of 50% aqueous ethanol, was refluxed with 3.5 molar equiv of sodium bisulfite until thin layer chromatography indicated complete reaction. After removal of the ethanol by distillation, the residue was admixed with chloroform and an excess of dilute hydrochloric acid, and the ketone or aldehyde was extracted into the organic layer. In the case of the aldehydes, hydrolysis of the bisulfite adduct required stirring with acid for up to 30 min to obtain two clear layers.

The extracts gave near-quantitative yields of "crude" product, usually single spot by tlc.

(2) H. von Pechmann, *Ber.*, **20**, 2539 (1887).

(3) In the equation shown, we have chosen to depict the bisulfite adduct of the oxo compound as an intermediate for the sake of simplicity. We have proven its intermediacy in the case of heptaldehyde, and would expect it in all cases where it would not be excluded on steric grounds (*e.g.*, aldehydes and cyclic and methyl ketones). Von Pechmann[2] isolated a product which he characterized as $C_6H_5CH(SO_3Na)NH(SO_3Na)\cdot 3H_2O$ by elemental analysis.

(4) We did not study the fate of the nitrogenous portion of the molecule. Little, if any, ammonia could be detected by warming a basified portion of the reaction. The work of H. H. Sisler and L. F. Andrieth [*J. Am. Chem. Soc.*, **61**, 3389 (1939)] suggests that it is converted to sulfamic acid.

The Reaction of α-Pyridone with Diazoalkanes[1]

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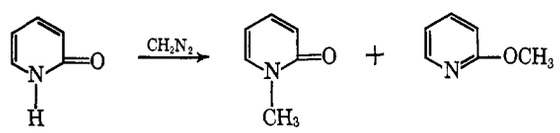
In 1895 it was reported that treatment of α-pyridone with diazomethane gives exclusively oxygen alkylation,[2] a view which has become widely accepted.[3-6] As part of a study of the alkylation of salts of α-pyridone, we have reexamined the reaction of α-pyridone with diazomethane. It transpires, contrary to the earlier report, that the reaction not only gives both nitrogen and oxygen methylation but actually gives more of the former, *i.e.*, about 55% N-methyl-α-pyridone and about 35% 2-methoxypyridine.



That this is a kinetically controlled result is shown by the following. (1) Both 2-methoxypyridine and N-methyl-α-pyridone are completely stable to diazomethane under the reaction conditions. (2) The product distribution does not change as a function of time. (3) The product distribution is the same whether 1 equiv of α-pyridone is treated with 2 of diazomethane or whether 2 equiv of α-pyridone are treated with 1 of diazomethane (Table I).

TABLE I

REACTIONS OF α-PYRIDONE WITH DIAZOMETHANE[a]

Solvent[b]	Reacn time	Yield of products, %[c] N-Methyl-α-pyridone	Yield of products, %[c] 2-Methoxypyridine
$(C_2H_5)_2O$ + CH_3OH (52:48)	45 min	53	39
$(C_2H_5)_2O$ + CH_3OH (52:48)	45 min	51	37
$(C_2H_5)_2O$ + CH_3OH (48:52)	24 hr	56	31
$(C_2H_5)_2O$ + CH_3OH (48:52)	48 hr	55	33
$(C_2H_5)_2O$ + CH_3OH (77:23)	24 hr	54	37
$(C_2H_5)_2O$ + CH_3OH (65:35)	24 hr	59[d]	38[d]
$(C_2H_5)_2O$ + CH_3OH (48:52)	24 hr	46[e]	30[e]
$(C_2H_5)_2O$ + CH_2Cl_2 (50:50)	96 hr	45	36

[a] At 0°. [b] Numbers in parentheses refer to mole % of solvent. [c] Material balances range from 90 to 95% (*cf.* the Experimental Section). [d] Two moles of diazomethane for each mole of α-pyridone was used. [e] One mole of diazomethane for 2 moles of α-pyridone was used.

The original methylation study[2] had been conducted in a methanol–ethyl ether solvent system and, hence, this was also employed in most of our experiments. On the chance that in an aprotic medium the reaction

(1) Paper VIII in the series "The Chemistry of Ambident Anions." Preceding paper: R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, **87**, 4520 (1965).

(2) H. von Pechmann, *Ber.*, **28**, 1624 (1895).

(3) H. Meyer, *Monatsh.*, **26**, 1311 (1905).

(4) H. S. Mosher, in "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, pp 435, 534.

(5) R. Gompper, *Advan. Heterocyclic Chem.*, **2**, 252, 254 (1963).

(6) H. Meislich, in "Pyridine and Its Derivatives," Part 3, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 641.

might proceed somewhat differently,[7] a run was made in methylene chloride–ethyl ether; as can be seen from Table I, the product distribution remains unchanged.

Treatment of α-pyridone with diazoethane gives significantly more oxygen alkylation and significantly less nitrogen alkylation than the reaction employing diazomethane (*cf.* Table II). In these reactions presumably a proton is transfered from α-pyridone to the diazoalkane and the resulting alkyl diazonium ion reacts with the α-pyridone anion. The increase in oxygen alkylation on going from diazomethane to diazoethane could conceivably derive from differences in the proportion of SN1 and SN2 character in the transition state.[8] However, the results of Table II can also be accounted for on steric grounds. The steric requirement of the alkylating agent increases on going from the methyldiazonium ion to the ethyldiazonium ion and, since the oxygen of the α-pyridone anion is presumably somewhat less hindered than the nitrogen, this operates to favor attack by oxygen.

TABLE II

THE REACTION OF α-PYRIDONE WITH DIAZOALKANES[a,b]

Run	Reagent	Yield of alkylate, %[c] N	O
1	Diazoethane	23 (21)[d]	68 (64)[e]
2	Diazoethane	25 (23)	64 (60)
3	Diazomethane	50 (45)	29

[a] At 0°; reaction time 45 min. [b] Solvent Et_2O–EtOH, 50:50 mole %. [c] Material balances range from 93 to 94%. [d] Numbers in parentheses refer to nitrogen alkylate isolated as the 3,5-dibromo derivative. [e] Numbers in parentheses refer to 2-ethoxypyridine isolated as its 1:1 adduct with mercuric chloride.

Support for the proposal that the graded SN1–SN2 factor[8] may be a significant factor in ambident anion chemistry is provided by comparing the reaction of the sodium salt of α-pyridone with triethyloxonium fluoroborate to the result obtained on treating α-pyridone with diazoethane; in both instances the anion of α-pyridone is being ethylated. From the point of view of steric hindrance oxygen alkylation should, if anything, be favored by the use of the triethyloxonium salt.[9] Now, however, the graded SN1–SN2 factor should produce an effect opposite to that of the steric factor. For it is reasonable to suppose that ethylation by the triethyloxonium ion proceeds *via* a transition state having more SN2 character than when the ethyldiazonium ion is involved (*i.e.*, the importance of the nucleophilic push is greater with the triethyloxonium ion) and this should operate to favor nitrogen alkylation.[8]

When a solution of the sodium salt of α-pyridone in absolute ethanol is treated with triethyloxonium fluoroborate a 77% yield of N-ethyl-α-pyridone and a 19% yield of 2-ethoxypyridine are obtained. This is to be contrasted with the 24% yield of N-alkylate and the 66% yield of O-alkylate obtained from the ethyldiazonium ion reaction (Table II). Previous examples[8] of the importance of the graded SN1–SN2 factor in controlling the course of ambident anion reactions have involved silver salts. From the present study it appears that the graded SN1–SN2 factor[8] may be of significance even when silver ions are absent.[10]

(7) N. Kornblum, P. J. Berrigan, and W. J. le Noble, *J. Am. Chem. Soc.*, **85**, 1141 (1963).

(8) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955).

(9) The significance, if any, of the sodium and fluoroborate ions is difficult to assess. Sodium fluoroborate precipitates soon after the reaction begins.

(10) It must be recognized that this conclusion is predicated on the assumption that the difference in solvent composition, absolute ethanol in the one instance, ethanol–ethyl ether (50–50 mole %) in the other, is not responsible for the change in proportion of N and O ethylation.

(11) Microanalyses were by Dr. C. S. Yeh, Purdue University, and Galbraith Microanalytical Laboratories, Inc., Knoxville, Tenn. Quantitative gas chromatographic analyses were carried out with either a Perkin-Elmer Model 154 vapor fractometer with printing integrator or an Aerograph Model A-90 dual-column gas chromatograph with disk integrator. A 5 ft × 0.25 in. 10% Dow 710 on Fluoropak column was used with each instrument. The column temperature was 160° with 30 psi of helium. The internal standard was 1-bromo-4-chlorobenzene. Relative response determinations were performed before each analysis using known mixtures of authentic oxygen and nitrogen alkylates.

(12) T. Grave, *J. Am. Chem. Soc.*, **46**, 1460 (1924).

(13) E. Prill and S. McElvain, *Org. Syn.*, **15**, 41 (1935).

(14) S. Babcock and R. C. Fuson, *J. Am. Chem. Soc.*, **55**, 2946 (1933).

(15) H. Decker and A. Kaufmann, *J. Prakt. Chem.*, [2] **84**, 425 (1911).

(16) L. Walter and S. McElvain, *J. Am. Chem. Soc.*, **57**, 1891 (1935).

Experimental Section[11]

α-Pyridone (Aldrich Chemical Co.) was sublimed at 1 mm and then recrystallized from benzene–hexane, mp 107.5–108.5°.

2-Methoxypyridine was prepared according to Grave;[12] the colorless liquid boiled at 141–142°; $n^{21}D$ 1.5033. *Anal.* Calcd for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.96; H, 6.46; N, 12.60.

N-Methyl-α-pyridone was prepared according to Prill and McElvain;[13] the colorless liquid had bp 108° (5 mm); $n^{20}D$ 1.5685. *Anal.* Calcd for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.20; H, 6.40; N, 13.13.

2-Ethoxypyridine was made from 2-bromopyridine and ethanolic sodium ethoxide using the procedure for 2-methoxypyridine. A 64% yield of a colorless liquid, $n^{20}D$ 1.4966, bp 63–64° (25 mm), was obtained. *Anal.* Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.27; H, 7.34; N, 11.57.

N-Ethyl-α-pyridone was obtained in 58% yield by a procedure similar to that used for N-methyl-α-pyridone.[13] The colorless liquid boiled at 118–119° (7 mm), $n^{21}D$ 1.5502. *Anal.* Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.29; H, 7.65; N, 11.51.

3,5-Dibromo-N-methyl-α-pyridone was prepared by treating a methanolic solution of N-methyl-α-pyridone with excess bromine in carbon tetrachloride at room temperature. The product was purified by chromatography on Merck alumina using methylene chloride and chloroform as eluents, mp 182–183°, yield 86%. Recrystallization from hexane afforded the analytical sample, mp 182.5–183° (lit.[14,15] mp 176°). *Anal.* Calcd for $C_6H_5Br_2NO$: C, 27.00; H, 1.89; Br, 59.87; N, 5.25. Found: C, 27.19; H 1.85; Br, 59.82; N, 5.11.

The nmr spectrum in $CDCl_3$ exhibits a singlet at δ 3.58 (3 H), a doublet centered at 7.42 (1 H), and another doublet centered at 7.73 (1 H).

3,5-Dibromo-N-ethyl-α-pyridone was obtained in 93% yield by analogous treatment of ethanolic N-ethyl-α-pyridone with excess bromine in carbon tetrachloride, mp 109.5–110° (lit.[14] mp 109°). *Anal.* Calcd for $C_7H_7Br_2NO$: C, 29.92; H, 2.51; Br, 56.89; N, 4.99. Found: C, 29.99; H, 2.72; Br, 57.01; N, 5.12.

Adduct of 2-Ethoxypyridine and Mercuric Chloride.—To a mixture of 1.0 g of 2-ethoxypyridine and 50 ml of water was added 15 ml of a solution containing 33 g of mercuric chloride dissolved in 100 ml of absolute ethanol. The white precipitate which formed at once was isolated, washed with water, and then recrystallized twice from water as white crystals, mp 152–153° (lit.[16] mp 152–153°). *Anal.* Calcd for $C_7H_9Cl_2HgNO$: C, 21.30; H, 2.30; Cl, 17.97; Hg, 50.83; N, 3.55. Found: C, 21.37; H, 2.31; Cl, 17.86; Hg, 50.90; N, 3.53.

Thus, the stoichiometry of the adduct is 1:1. Conversion of 2-ethoxypyridine to the adduct generally occurs in over 95% yield.

Reaction of α-Pyridone with Diazomethane in Methanol–Ethyl Ether.—The following is typical of the various runs summarized in Table I. A solution of 1.90 g (20 mmoles) of α-pyri-

done in 25 ml of ice-cold dry methanol was poured into 69 ml of 0.29 *N* ethereal diazomethane[17] (20.0 mmoles) (precooled to 0°). The system was protected from light and maintained at 0° for 45 min. Unreacted diazomethane was then destroyed with a few drops of glacial acetic acid. The product was extracted with 15% aqueous sodium hydroxide and then with water. The aqueous layers were combined, saturated with sodium chloride, and extracted exhaustively with methylene chloride. The organic extracts were combined, dried over annydrous magnesium sulfate, and concentrated to a final volume of *ca.* 25 ml by distillation at atmospheric pressure through a 2-ft tantalum-packed column. (Vacuum evaporation of solvents results in some loss of 2-methoxypyridine.) Vpc analysis[11] showed 0.53 g (4.86 mmoles) of 2-methoxypyridine and 0.73 g (6.70 mmoles) of N-methyl-α-pyridone.

The aqueous extract was acidified with sulfuric acid and exhaustively extracted with chloroform. The dried extract was concentrated by rotary evaporation under reduced pressure; this gave 0.70 g (7.37 mmoles) of pale yellow crystals of α-pyridone, mp 104–106°. The infrared spectrum in chloroform is identical with that of authentic α-pyridone. (In a number of instances comparison was also made with the mercuric chloride adduct of α-pyridone, mp 196.5–197.5° when recrystallized from toluene.)

The amount of unreacted α-pyridone corresponds to a 37% recovery. Thus, the maximum number of millimoles of alkylated products is 0.63(20.0) or 12.6. The per cent yield of 2-methoxypyridine is 4.86/12.6 or 39%. The per cent yield of N-methyl-α-pyridone is 6.70/12.6 or 53%. The material balance is (4.86 + 6.70 + 7.37)/20.0 or 95%.

Stability of 2-Methoxypyridine and N-Methyl-α-pyridone to Diazomethane in Methanol–Diethyl Ether.—A methanolic solution of 2-methoxypyridine and an equivalent amount of ethereal diazomethane were allowed to stand together at 0° for 48 hr. Analysis by vpc showed 95% recovery of 2-methoxypyridine after appropriate work-up. No dialkylation was detected with sodium tetraphenylboron[18] and no N-methyl-α-pyridone was found. N-methyl-α-pyridone could have been detected to the extent of 2% by the vpc analysis. In the same way, equivalent amounts of methanolic N-methyl-α-pyridone and ethereal diazomethane were allowed to stand together for 48 hr at 0°. Vpc analysis, after work-up, showed 98% recovery of N-methyl-α-pyridone. No dialkylation[18] could be detected, and vpc could detect no 2-methoxypyridine; if present, it could have been detected to the extent of 0.4%.

Reaction of α-Pyridone with Diazomethane in Ethanol–Ethyl Ether.—A 100-ml aliquot of 0.20 *N* ethereal diazomethane (20.0 mmoles) was diluted with ether to a final volume of 167 ml. A solution containing 1.90 g (20.0 mmoles) of α-pyridone dissolved in 94 ml of absolute ethanol was cooled to 0° and poured into the cold (0°) ethereal diazomethane. After 45 min in the cold, with protection from light, the product was treated with a few drops of glacial acetic acid and divided into two parts. Part A (130 ml) was worked up in the usual way and analyzed by vpc (*vide supra*). In this way 0.11 g (29% yield) of 2-methoxypyridine, 0.19 g (50% given) of N-methyl-α-pyridone, and 0.64 g of α-pyridone were obtained. Part B (125 ml) was brominated (*vide supra*) to yield 0.52 g of light yellow crystals which, when chromatographed on alumina, gave 0.40 g (45% yield, of 3,5-dibromo-N-methyl-α-pyridone) of white crystals, mp 181.5–182.5°. A mixture melting point with authentic 3,5-dibromo-N-methyl-α-pyridone of mp 182.5–183° was 181.5–182.5°. The infrared spectrum was identical with that of an authentic sample of the dibromo derivative.

The reaction was repeated in order to isolate N-methyl-α-pyridone; it was conducted and worked up as usual. The internal standard was not added. Instead, the solvent was removed by rotary evaporation to yield an oil which was pumped at 1 mm for 1 hr at 60° to remove 2-methoxypyridine. The residual 0.44 g of oil had the infrared spectrum of N-methyl-α-pyridone.

Reaction of α-Pyridone with Diazoethane in Ethanol–Diethyl Ether.—A 1.90-g sample (20.0 mmoles) of α-pyridone was dissolved in 94 ml of abolute ethanol, cooled to 0°, and poured into 167 ml of precooled 0.12 *N* ethereal diazoethane[19] (20 mmoles). After 45 min in the cold, the product was treated with a few drops of glacial acetic acid and was divided. Part A (130 ml) was treated as usual (*vide supra*) to yield 0.17 g (23% yield) of N-ethyl-α-pyridone, 0.51 g (68% yield) of 2-ethoxypyridine, and 0.41 g of α-pyridone, mp 105–106°. Part B (65 ml) was brominated (*vide supra*) to yield 0.42 g of light yellow solid (I). On chromatographing a benzene solution of I on Merck basic alumina, 0.18 g (21% yield of 3,5-dibromo-N-ethyl-α-pyridone) of white crystals, mp 109–110°, was obtained. The infrared spectrum was identical with that of an authentic sample of dibromo compound. Part C (54 ml) was poured into 300 ml of water and the ethereal layer was separated. The aqueous phase was saturated with sodium chloride and extracted with seven 50-ml portions of benzene. The organic phases were combined, washed with two 10-ml portions of water, and dried over anhydrous magnesium sulfate. The extract was filtered and 6 ml of mercuric chloride in absolute ethanol (*vide supra*) was added. Rotary evaporation of the solvent under vacuum yielded white crystals which were transferred to a sintered-glass funnel and washed with 200 ml of water.[20] The crystals were dried under slight vacuum. By this procedure, 0.64 g (64% yield) of the 1:1 adduct of 2-ethoxypyridine and mercuric chloride, mp 151–152°, was obtained. The infrared spectrum in a Nujol mull was identical with that of an authentic sample of the adduct.

Reaction of the Sodium Salt of α-Pyridone with Triethyloxonium Fluoroborate in Ethanol.—To a dry flask equipped with a nitrogen inlet tube was added 3.16 g (27.0 mmoles) of the sodium salt of α-pyridone dissolved in 90 ml of absolute ethanol. The solution was cooled to *ca.* 12° and 2.01 g (10.6 mmoles) of triethyloxonium fluoroborate[21] was added; only part of the oxonium salt dissolved. Sodium fluoroborate precipitated shortly after the oxonium salt was added. The ice bath was removed and the mixture was stirred for 30 min during which the temperature rose to *ca.* 20°. Using two 1-ml aliquots, no dialkylation[18] could be detected. The mixture was then filtered and diluted to 100 ml with absolute ethanol. A 50-ml aliquot was poured into 75 ml of water, saturated with sodium chloride, and exhaustively extracted with methylene chloride. The combined extract was dried over anhydrous magnesium sulfate and concentrated (*vide supra*). Vpc analysis showed 0.12 g (19% yield) of 2-ethoxypyridine and 0.49 g (77% yield) of N-ethyl-α-pyridone.

A 25-ml aliquot was brominated as described above. Work-up yielded 0.57 g of yellow crystals which were chromatographed to yield 0.48 g (66% yield of 3,5-dibromo-N-ethyl-α-pyridone) of white crystals, mp 108.5–109.5°. A mixture melting point with authentic 3,5-dibromo-N-ethyl-α-pyridone, mp 109.5–110°, was 108.5–109.5°. The infrared spectrum was identical with that of the authentic dibromo derivative.

Acknowledgment.—It is a pleasure to thank the Explosives Department of the du Pont Company and the Purdue Research Foundation for financial support.

(17) Th. J. de Boer and H. Backer, *Org. Syn.*, **36**, 16 (1956).

(18) N. Kornblum and G. P. Coffey, *J. Org. Chem.*, **31**, 3449 (1966).

(19) The procedure employed by A. McKay, W. Ott, G. Taylor, M. Buchanan, and J. Crooker [*Can. J. Res.*, **28B**, 683 (1950)] for diazomethane was used.

(20) Both 2-ethoxypyridine and N-ethyl-α-pyridone form adducts with mercuric chloride. However, the adduct of the latter is extremely water soluble; it can be preferentially dissolved by washing the combined adducts. Care must be exercised since too much water will cause partial solubilization of the adduct of 2-ethoxypyridine.

(21) N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.*, **86**, 2681 (1964).

The Reaction of Triethyloxonium Fluoroborate with the Sodium Salt of α-Pyridone[1]

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As part of a study of the alkylation of the salts of α-pyridone, we have examined the reaction of the sodium salt of α-pyridone with triethyloxonium fluoroborate.

(1) Paper IX in the series "The Chemistry of Ambident Anions." Paper VIII: N. Kornblum and G. P. Coffey, *J. Org. Chem.*, **31**, 3447 (1966).

(2) Purdue Research Foundation Fellow 1963–1965.