15–26°. Lead acetate was removed by filtration and the filtrate was washed thoroughly with water and sodium bicarbonate. After the removal of benzene on the rotary evaporator the remaining liquid was vacuum distilled. A fraction of b.p. 60–63° (1 mm.) was found by gas chromatographic analysis to be phenol-free.

A 0.162-g. sample of this phenoxyacetaldehyde was dissolved in 35 ml. of specially dried ether and reduced with a fourfold excess of lithium aluminum hydride in the Minilab reactor. The chromatogram of the benzene solution of the crude product showed 96.8% of 2-phenoxyethanol and 2.4% of phenol and less than 1% of unchanged aldehyde.

Reductive ozonolysis of crotyl phenyl ether. Crotyl phenyl ether was checked for homogeneity by gas chromatography using a two meter Perkin-Elmer "K" column. A single symmetrical peak indicated the absence of phenol or other impurities. A 1.1-mmole sample was dissolved in 25 ml. of dried hexane, cooled to −6°, and ozonized in the Minilab reactor assembly with a 10% excess of ozone. The peroxidic products in hexane were reduced with 400% of the required lithium aluminum hydride solution. Following hydrolysis, extraction, drying, and solvent removal, 0.134 g. (80%) of a pale yellow oil was obtained. Vapor fractometry of this material in benzene solution at a cabinet temperature of 216° on a Perkin-Elmer "K" column gave a fractogram from which weight per cents were determined. The results are recorded in Table I.

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LARAMIE, WYO.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Oxidation of 1-(3,4-Dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)pyridinium Bromide by Potassium Ferricyanide

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3-Ethylpyridine-4-carboxaldehyde diethylacetal was converted to a quaternary ammonium salt by treatment with 3,4-dimethoxyphenethyl bromide. Oxidation of the salt by potassium ferricyanide in alkaline solution gave approximately equal amounts of 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-5-ethyl-2-pyridone and 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-2-pyridone. The former pyridone was also prepared in an unequivocal manner by oxidation of 1-(3,4-dimethoxyphenethyl)-2-methyl-4-(carboxaldehyde diethylacetal)-5-ethylpyridinium bromide with iodine in pyridine solution and treatment of the resultant product with sodium hydroxide solution.

The subject of the preparation of pyridones by the oxidation of *N*-alkylpyridinium salts with potassium ferricyanide in alkaline solution has been reviewed recently.[1] With respect to the problem of orientation in the oxidation of 1-alkyl-3-substituted pyridinium salts, it has been reported that when the 3-substituent is alkoxycarbonyl,[2] 3-pyridyl,[3,4] *N*-methyl-3-pyrrolidyl,[3,4] 6,7-methylenedioxy-2-quinolyl,[5] 2-methyl-4-thiazolyl,[6] cyano,[7] carboxyl,[7] or phenyl,[8,9] pyridone formation takes place at the 6-position in the major if not the sole reaction path. However, when the 3-substituent is methyl, ethyl, or bromo, pyridone formation occurs at the 2-position exclusively.[7,10,11]

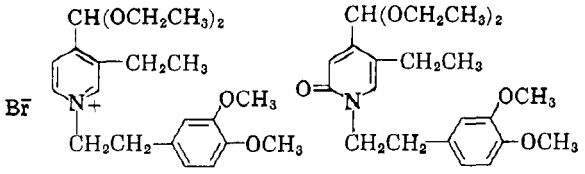
There has been a controversy as to which pyridone is formed on oxidation of nicotinamide methiodide. Some workers have reported that pyridone formation takes place at the 2-position,[7,12] while another has claimed that oxidation occurs at the 6-position.[13] The point has been clarified by Pullman and Colowick, who have shown that nearly equal amounts of the two isomeric pyridones are formed.[14] The claim of predominance of one pyridone over the other in earlier reports was attributed to the previous workers having effected preferential extraction of one or the other of the two possible isomers in the course of the isolation procedure.

Various suggestions have been advanced in an attempt to explain for the whole series of known reactions the preferential formation of one or the

(1) B. S. Thyagarajan, *Chem. Revs.*, **58**, 439 (1958).
(2) S. Sugasawa, K. Sakurai, and T. Okayama, *Ber.*, **74**, 537 (1941).
(3) S. Sugasawa and T. Saito, *J. Pharm. Soc. Japan*, **65B**, 456 (1945).
(4) S. Sugasawa and T. Tatsuno, *J. Pharm. Soc. Japan*, **72**, 248 (1952).
(5) T. Tatsuno, *Pharm. Bull.*, **2**, 140 (1954).
(6) S. Sugasawa, T. Tatsuno, and T. Kamiya, *Pharm. Bull.*, **1**, 233 (1953).
(7) H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **16**. 73 (1951).
(8) S. Sugasawa and M. Kirisawa, *Pharm. Bull.*, **3**, 187 (1955).
(9) S. Sugasawa and M. Kirisawa, *Pharm. Bull.*, **3**, 190 (1955).
(10) S. Sugasawa and T. Tatsuno, *Pharm. Bull.*, **2**, 193 (1954).
(11) S. Sugasawa, T. Tatsuno, and T. Kamiya, *Pharm. Bull.*, **1**, 230 (1953).
(12) W. I. M. Holman and C. Wiegand, *Biochem. J.*, **43**, 423 (1948).
(13) J. W. Huff, *J. Biol. Chem.*, **171**, 639 (1947).
(14) M. E. Pullman and S. P. Colowick, *J. Biol. Chem*, **206**, 121 (1954).

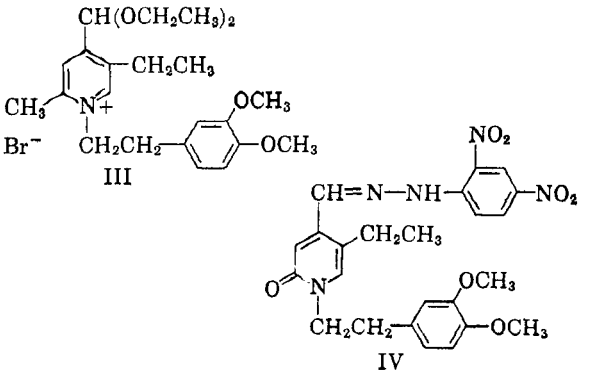
other of the two possible pyridones. Most of these suggestions, however, have proven to be at least partially unsatisfactory. A strictly electronic interpretation of the role of the 3-substituent is not completely adequate, and it appears that at least equal influence must be attributed to steric factors.[1]

The problem of orientation in the potassium ferricyanide oxidation of 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-pyridinium bromide (I) was of importance to us in that we had need of 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethylacetal)-5-ethyl-2-pyridone (II) for a synthesis project.[15] Although, on the basis of literature reports, the presence of an ethyl group in the 3-position of the pyridinium cation might have been expected to cause pyridone formation to take place at the 2-position, we felt that the buttressing effect of the acetal group in the 4-position could conceivably increase the steric requirements of the ethyl group to such a degree that oxidation at the 6-position would become an important competing reaction. Somewhat inconclusive evidence was presented in the previous paper[15] to indicate that at least some of the pyridone formed by attack of the oxidizing agent at the 6-position, specifically 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde diethyl acetal)-5-ethyl-2-pyridone (II), had indeed been obtained by the potassium ferricyanide oxidation of I.



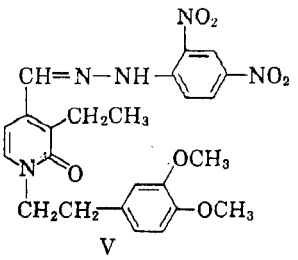
I II

As a starting point for the present research effort, an authentic sample of II was prepared in very low yield from 1-(3,4-dimethoxyphenethyl)-2-methyl-4-(carboxaldehyde diethylacetal)-5-ethylpyridinium bromide[15] (III) by the procedure of Berson and Cohen,[16] namely by oxidation of III with iodine in pyridine solution and treatment of the resultant product with sodium hydroxide solution. Actually, II was obtained in crude form only but was characterized as the derivative 1-(3,4-dimethoxyphenethyl)-4-(carboxaldehyde 2,4-dinitrophenylhydrazone)-5-ethyl-2-pyridone (IV). The infrared spectrum of crude II, taken in chloroform solution, showed a strong carbonyl group absorption peak at 1660 cm.$^{-1}$, whereas the spectrum of IV, taken in a potassium bromide pellet, showed the carbonyl group absorption peak at 1655 cm.$^{-1}$



III IV

Oxidation of I by potassium ferricyanide in alkaline solution gave a mixture of products. The infrared spectrum of the mixture, taken in chloroform solution, showed carbonyl group absorption peaks of very nearly equal intensity at 1645 cm.$^{-1}$ and 1660 cm.$^{-1}$ Treatment of the mixture with 2,4-dinitrophenylhydrazine in an acid medium gave a mixture of 2,4-dinitrophenylhydrazones which could be separated by preferential solvent action of ethanol and ethyl acetate. The less soluble derivative proved to be identical with the sample of IV obtained by the Berson and Cohen procedure. The more soluble derivative was shown by analysis to be an isomer of IV and, accordingly, was assigned the structure of 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde-2,4-dinitrophenylhydrazone)-2-pyridone (V). The infrared spectrum of V, taken in a potassium bromide pellet, showed a carbonyl group absorption peak at 1640 cm.$^{-1}$



V

Although separation of IV and V by the preferential solvent action of ethanol and ethyl acetate was not quantitative, nearly equal amounts of the two compounds were obtained. For this reason and also because the intensities of the two characteristic carbonyl group absorption peaks in the original reaction mixture were very nearly the same, it is estimated that the potassium ferricyanide oxidation of I gave approximately equal amounts of the two isomeric pyridones. This fact, together with the information in the literature that salts of 3-ethylpyridine give exclusively the corresponding 2-pyridones[10,11] and that the orientation is not affected by changes in the nature of the 1-alkyl group provided the 3-substituent remains the same,[4,6] suggest that the buttressing effect of a substituent in the 4-position of a 3,4-

(15) F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1181 (1958).

(16) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).

disubstituted pyridinium salt does exert an important influence on the orienting effect of a group at the 3-position in the potassium ferricyanide oxidation reaction. Furthermore, it seems probable that the relatively small hydroxide ion can add in a fast, reversible manner to either the 2- or 6-position of an unsymmetrically substituted pyridinium salt to give small concentrations of the respective pseudo bases and that the rate-determining step is the one in which the secondary hydroxyl group of each pseudo base (or the alkoxide group of the conjugate base) is oxidized to a carbonyl group by the relatively bulky ferricyanide ion. Thus, on the basis of this interpretation, it is the latter step which is most sensitive to the steric requirements and electronic effects of the 3-substituent. Specifically, it is felt that the relative rates of oxidation of the isomeric pseudo bases determine the product ratio of the pyridones produced in the reaction, and both the steric requirements and the electronic effects of the 3-substituent have a marked influence on these relative rates.

EXPERIMENTAL[17]

1-(3,4-Dimethoxyphenethyl)-4-(carboxaldehyde 2,4-dinitrophenylhydrazone)-5-ethyl-2-pyridone (IV). A mixture of 2.00 g. (0.00428 mole) of the quaternary bromide III,[15] 2.0 g. of iodine, and 25 cc. of pyridine was heated on a steam bath for 4 hr. The excess pyridine was evaporated in an air stream and the dark residue leached with six 20-cc. portions of cold water. The aqueous extract was washed with ether, cooled in an ice bath and treated with 15 cc. of 2*N* sodium hydroxide solution. A transient red color appeared upon the addition of base. After having been saturated with sodium carbonate, the solution was extracted with chloroform. Evaporation of the chloroform yielded a black viscous material. Attempts to purify this material by washing it with various solvents and solvent combinations failed. An infrared spectrum of the oil, taken in chloroform solution, showed a strong band due to carbonyl group absorption at 1660 cm.$^{-1}$

Treatment of an ethanol solution of the black viscous material with an ethanol solution of 2,4-dinitrophenylhydrazine, followed by a few drops of concentrated sulfuric acid,[18] gave the 2,4-dinitrophenylhydrazone IV which melted with decomposition at 268–269° after it had been washed with hot ethanol and hot acetone.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.09; N, 14.14. Found: C, 58.34; H, 5.06; N, 14.19.

Examination of the infrared spectrum of this compound, taken in a potassium bromide pellet, revealed the presence of a strong carbonyl group absorption peak at 1655 cm.$^{-1}$

Reaction of 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)pyridinium bromide (I) *with alkaline potassium ferricyanide.* A. A solution of 14.6 g. (0.044 mole) of potassium ferricyanide in 40 cc. of water was added to a stirred solution of 4.54 g. (0.01 mole) of the pyridinium bromide I[15] in 40 cc. of water. To the resulting solution was added 65 cc. of benzene and a solution of 6.64 g. (0.166 mole) of sodium hydroxide in 65 cc. of water. After the mixture had been stirred for 10 min., the benzene layer was separated and the aqueous phase washed once with benzene. The organic phases were combined (Fraction I) and dried over Drierite.

Additional benzene was added to the aqueous layer and the reaction allowed to continue for an hour. The benzene layer was separated from the aqueous phase and the latter washed once with benzene. The combined organic phases (Fraction II) were dried over Drierite.

The aqueous phase was treated in approximately the same manner again, but this time stirring was continued overnight after addition of benzene. Separation of the layers, extraction of the aqueous layer with benzene, combination of the organic phases (Fraction III) and drying were carried out as before.

Evaporation of the benzene extracts and examination of the residues gave the following results:

	Weight	Relative Intensities of Infrared Peaks (chloroform solution)
Fraction I	2.52 g.	1645 cm.$^{-1}$ and 1660 cm.$^{-1}$ equal
Fraction II	0.16 g.	1660 cm.$^{-1}$ greater than 1645 cm.$^{-1}$
Fraction III	Trace	1660 cm.$^{-1}$ greater than 1645 cm.$^{-1}$
Total yield of mixed pyridones	2.68 g. (69% yield)	

The mixture of 2,4-dinitrophenylhydrazones, first crop, of Fraction I formed very slowly (overnight) while that of Fraction II formed within 30 min. After collection of the first crops by filtration, addition of more 2,4-dinitrophenylhydrazine reagent resulted in immediate formation of more of the derivatives from Fractions I and II. The same procedure was used to obtain a third crop from each of Fractions I and II. The total yield of the 2,4-dinitrophenylhydrazone derivatives from each of Fractions I and II amounted to 85% of the calculated value. The detailed results were as follows:

	Fraction I	Fraction II
Wt. used	0.37 g.	0.16 g.
First crop		
M.p.	215.0–216.5°	214–216
Wt.	0.015 g.	0.050 g.
Second crop		
M.p.	205–207°	245–248°
Wt.	0.19 g.	0.12 g.
Third crop		
M.p.	206–211°	254–256°
Wt.	0.20 g.	0.005 g.

Since the phenylhydrazone, m.p. 245–248°, obtained as the second crop from Fraction II was insoluble in ethanol, it was recrystallized from a mixture of chloroform and ethanol. After it had been allowed to stand for an extended period, the solid was separated and dried; it melted with decomposition at 268–269°, also in admixture with the sample obtained from III by way of the Berson and Cohen[16] procedure. The infrared spectra of the two samples, taken in potassium bromide pellets, were found to be identical, both having carbonyl absorption peaks at 1655 cm.$^{-1}$

In attempts to recrystallize the second crop of the mixed 2,4-dinitrophenylhydrazones, m.p. 205–207°, derived from Fraction I from an ethanol–ethyl acetate mixture in the usual manner, it was found that the solid was not completely soluble. After the insoluble portion had been collected by filtration and dried, it melted at 260–265° with decomposition. From the filtrate there was obtained a solid of

(17) All melting points are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(18) Reversal of the order of addition of the 2,4-dinitrophenylhydrazine solution and sulfuric acid resulted in very slow, if any, formation of a derivative.

melting point 216–217° (uncorrected). Several recrystallizations from ethanol yielded material of m.p. 217.0–217.5°.

Anal. Calcd. for $C_{24}H_{25}N_3O_7$: C, 58.17; H, 5.09; N, 14.14. Found: C, 57.88; H, 5.15; N, 14.14.

Examination of the infrared spectrum, taken in a potassium bromide pellet, of the above analyzed compound, m.p. 217.0–217.5°, revealed the presence of a carbonyl group absorption peak at 1640 cm.$^{-1}$ No peak was present in the 1660 cm.$^{-1}$ region.

Several attempts were made to separate the original mixture of pyridones by chromatographic means. Use of alumina of various activities in combination with different eluents gave only a limited separation of products. It was observed that, in general, 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-2-pyridone was more readily displaced from an alumina column than its isomer.

B. In a second run similar to that described above the yield of mixed pyridones was 3.26 g. (84%). An exception to the procedure employed in the first run was that the potassium ferricyanide oxidation was allowed to proceed without interruption for a period of 12 hr. An infrared spectrum of the resultant oil, taken in chloroform solution, showed absorption peaks at 1645 cm.$^{-1}$ and 1660 cm.$^{-1}$ of approximately equal intensity.

Acknowledgment. This investigation was supported by a research grant, E-1961, from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL CO.]

Autoxidative Formation and Chemical Properties of α-Alkoxybenzyl and α-Alkoxyallyl Hydroperoxides[1]

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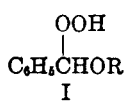
Alkyl benzyl ethers and alkyl allyl ethers autoxidize readily at 100° in liquid phase to α-alkoxybenzyl and α-alkoxyallyl hydroperoxides, respectively. Conversion of the former to the corresponding aromatic aldehyde is effected by reduction; ferrous ion catalyzes *gem*-dehydration to the carboxylate ester. *gem*-Dehydration of α-alkoxyallyl hydroperoxide gives low yields of acrylate ester; a concomitant polymerization of the monomer in the presence of peroxide limits the yields of this potential acrylate synthesis.

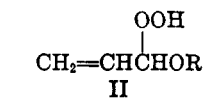
Clover[2] reported the autoxidation of benzyl ethers and an allyl ether in the presence of light. He exposed ether samples at ordinary temperature to oxygen for prolonged periods, and reported development of active oxygen, hydrolysis of the peroxidic intermediate to hydrogen peroxide, and isolation of secondary products which were derived by oxidation of the activated methylene group. Clover suggested that the primary product of oxidation of a benzyl ether amounted to addition of an oxygen molecule, and formulated it as an α-alkoxybenzyl hydroperoxide (I). Milas[3] proposed a different intermediate.



I

As a part of a liquid phase oxidation program at this laboratory, the preparation of I by more efficient means and its decomposition to benzaldehyde appeared worthy of investigation as a possible route to aromatic aldehydes. *gem*.-Dehydration of I would also constitute an interesting route to arylcarboxylate esters.

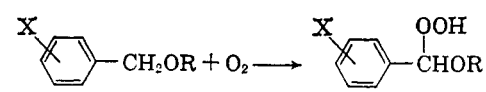
Similar considerations were applied to oxidation of an allyl ether, which presumably would give α-alkoxyallyl hydroperoxide (II).



II

Compound II is of interest as a possible precursor for an acrylic ester *via gem*-dehydration.

Liquid-phase autoxidation at 100° of a series of alkyl benzyl ethers gives, in the more successful cases, the corresponding α-alkoxybenzyl hydroperoxides in 33–56% yields (Table III). Time pe-



riods of three to six hours were required to reach the maximum hydroperoxide value. In these oxidations, as well as in oxidations of the alkyl allyl ethers (Table III), exothermic decompositions occasionally resulted in loss of hydroperoxide. In this work none of these decompositions was explosive in nature; however, adequate shielding was used for all oxidations.

Benzyl, 4-isopropylbenzyl, and 3,4-dichlorobenzyl ethers gave the highest conversions (20–23%) and yields (42–56%) of the corresponding α-alkoxy-

(1) Presented before the Organic Division, American Chemical Society, New York Meeting, September 8–13, 1957.

(2) A. M. Clover, *J. Am. Chem. Soc.*, **46**, 419 (1924).

(3) N. A. Milas, *J. Am. Chem. Soc.*, **53**, 221 (1931).