[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Rearrangements of N-Oxides. A Novel Synthesis of Pyridyl Carbinols and Aldehydes

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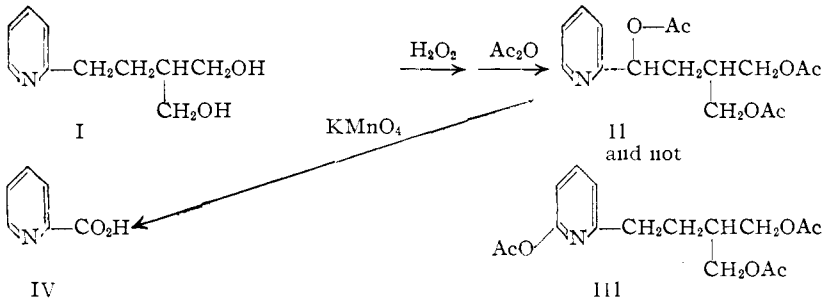
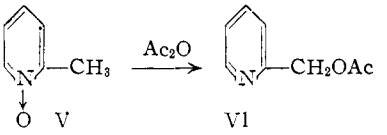
In 1947, Katada reported that the reaction of pyridine-N-oxide with acid anhydrides gives 2-pyridone. This rearrangement has now been investigated with alkyl substituted aromatic-N-oxides and it is shown that with the 2- and 4-alkyl derivatives the products of this reaction are not pyridones but, instead, are the corresponding pyridyl carbinol derivatives. For example, the reaction of 2-picoline-N-oxide with acetic anhydride gives 2-pyridinemethanol acetate in 78% yield and this, when subjected to a second rearrangement, gives 2-pyridinealdehyde diacetate in 46% yield. This procedure would appear to be the best method available at present for preparing either 2-pyridinealdehyde or simple 2- and 4-pyridinemethanol derivatives.

In 1947, Katada reported that the reaction of pyridine-N-oxide with either acetic or benzoic anhydride led, after hydrolysis, to 2-pyridone.[2] Later Ochiai and his collaborators, in their extensive studies on the reactions of aromatic-N-oxides,[3] showed that the N-oxides of quinine, dihydroquinine and benzo(h)quinoline underwent rearrangement in a similar fashion to give the corresponding α-pyridones.[4-7] Also, Montanari and Risaliti have recently applied this rearrangement to benzimidazole.[8] In the course of an investigation directed toward the synthesis of the alkaloid cytisine,[9] it occurred to us that this rearrangement might prove useful as a method for introducing the α-pyridone ring of cytisine. With this purpose in mind, we subjected 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol (I) to the action of hydrogen peroxide in acetic acid followed by heating with acetic anhydride. Unexpectedly, the resulting product did not have the properties expected for the desired pyridone acetate (III) but, instead, showed the behavior and composition to be expected for a triacetate such as II. That rearrangement of an acetoxy group into the side-chain had indeed occurred was shown by the fact that oxidation of the rearranged product with permanganate gave picolinic acid (IV) in high yield. The isolation of picolinic acid is in good agreement with the proposed triacetate structure II and cannot be accommodated by the α-pyridone structure (III).



In view of this surprising result and, also, in view of the recent revival of interest in aromatic-N-oxides, it seemed desirable to determine the generality and usefulness of the N-oxide rearrangement when alkyl substituents were present on the heterocyclic ring. The present communication summarizes the results of such a study. The compounds selected for investigation were the N-oxides of 2-, 3- and 4-picoline, 2-ethylpyridine, 2-*n*-butylpyridine, 2,6-lutidine and quinaldine. In all cases the reagent used for effecting the rearrangement was acetic anhydride. In the initial experiments the aromatic-N-oxides were isolated and purified, but later it was shown that the preparation of the N-oxides and their rearrangement with acetic anhydride could be carried out more conveniently and in higher yield when the two steps were combined as a single operation.



With the exception of 3-picoline-N-oxide (VII), all of the aromatic-N-oxides in the group mentioned above underwent rearrangement to give the corresponding derivative in which an acetoxy group had entered the alkyl side-chain at the α-position. This is illustrated above for the case of 2-picoline-N-oxide. For 2-picoline-N-oxide, 4-picoline-N-oxide and quinaldine-N-oxide, the proof of structure of the products was established by hydrolysis of the resulting acetates to the corresponding carbinols. The 2- and 4-pyridinemethanols were identified by direct comparison with authentic samples of these compounds prepared in an independent fashion, whereas the 2-quinolinemethanol was identified by the agreement of its properties and those of its phenylurethan and benzoate derivatives with the values recorded in the literature for 2-quinolinemethanol and its derivatives.

Proof that the rearrangement of 2,6-lutidine-N-oxide gave 6-methyl-2-pyridinemethanol acetate (X) was not provided directly but, as will be dis-

(1) Du Pont Postgraduate Fellow, 1952–1953.

(2) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947). See also A. Kliegl and A. Fehrle (*Ber.*, **47**, 1629 (1914)) for an earlier example of this rearrangement with acridine-N-oxide.

(3) For leading references to this work, see E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(4) E. Ochiai and T. Okamoto, *J. Pharm. Soc. Japan* **68**, 88 (1948).

(5) E. Ochiai, T. Okamoto and G. Kobayashi, *ibid.*, **68**, 109 (1948).

(6) I. Iwai, *ibid.*, **71**, 1288 (1951).

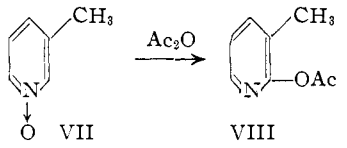
(7) T. Okamoto and H. Kondo, Japanese Patent 180,259, *C. A.*, **46**, 4030e (1952).

(8) F. Montanari and A. Risaliti, *Gazz. chim. ital.*, **83**, 278 (1953).

(9) For a summary of the chemistry of cytisine, see F. Galinovsky, *Fortschr. Chem. Org. Naturstoffe*, **8**, 265 (1951).

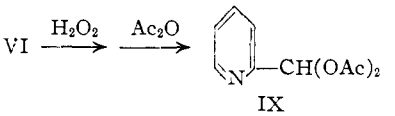
cussed later, was gained through subsequent studies when this product was carried through a second rearrangement. The assignment of structure for 2-(α-acetoxyethyl)-pyridine was based both on the fact that the material had the composition expected and that it gave a positive iodoform test. In the case of 2-(α-acetoxy-*n*-butyl)-pyridine, the assignment of structure was made entirely on the basis of its composition and by analogy to the preceding examples.

The rearrangement of 3-picoline-N-oxide with acetic anhydride gave a product which, after hydrolysis, was not identical with the known 3-pyridinemethanol. Since the melting point of this material was in good agreement with that reported for 3-methyl-2-pyridone[10] and its ultraviolet absorption spectrum corresponded very closely to that of 2-pyridone,[11] it can be safely concluded that, as illustrated below, the rearrangement of 3-picoline-N-oxide (VII) with acetic anhydride yields 2-acetoxy-3-methylpyridine (VIII). It would appear that rearrangement of the acetoxy group to an alkyl side-chain is limited to compounds in which the alkyl groups are located at the 2- or 4-positions with respect to the N-oxide function; in the absence of such groups normal rearrangement to the nucleus occurs.

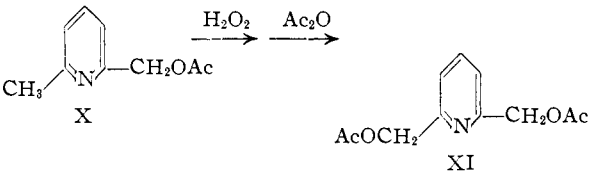


The yields obtained in the rearrangements of the 2- and 4-alkyl derivatives to the corresponding acetates ranged from 43 to 91%. Thus, in view of the convenience and simplicity of the method, this procedure would appear to have considerable promise as a preparative method for simple pyridylcarbinols.

In considering other possible applications of the rearrangement procedure as a tool for organic synthesis, we were struck by the possibility that repetition of the N-oxide rearrangement might lead to diacetates of heterocyclic aldehydes and ketones. At present, the preparation of pyridylaldehydes can only be accomplished with great difficulty and in poor yield.[12] Therefore, a representative number of the monoacetates obtained from the first experiments were converted to the corresponding N-oxides and treated with acetic anhydride in the hope of accomplishing a second rearrangement.

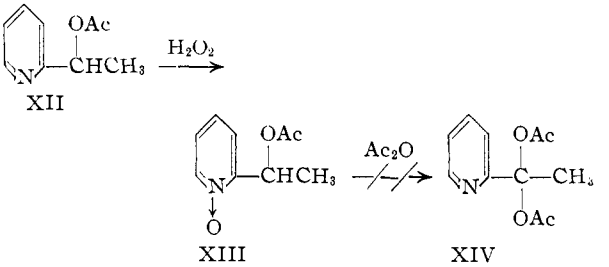


In the first case, 2-pyridinemethanol acetate (VI) was converted to 2-pyridinealdehyde diacetate in 46% yield. The identity of the product was established by its conversion to the corresponding oxime, *p*-nitrophenylhydrazone and 2,4-dinitrophenylhydrazone derivatives of 2-pyridinealdehyde. Undoubtedly this procedure offers the best method of preparing 2-pyridinealdehyde available at present. Unfortunately, this gratifying result was not duplicated in the other examples studied. When 4-pyridinemethanol acetate was carried through the same reaction sequence, 4-pyridinealdehyde diacetate was produced but in very poor yield.



6-Methyl-2-pyridinemethanol acetate (X) was next investigated to determine whether the position taken by the incoming acetoxy group would be influenced by the presence of a substituent group. As illustrated above, the product isolated in this case was 2,6-di-(acetoxymethyl)-pyridine (XI) and there was no evidence for the formation of the desired 6-methyl-2-pyridinealdehyde diacetate. The identity of the 2,6-di-(acetoxymethyl)-pyridine was established by its conversion on acid hydrolysis to 2,6-di-(hydroxymethyl)-pyridine. A comparison of our sample of 2,6-di-(hydroxymethyl)-pyridine with that prepared by Barnes and Fales[13] showed that the two samples had identical infrared spectra and mixtures of the two gave no depression of melting point. It should be noted that the isolation of 2,6-di-(hydroxymethyl)-pyridine also establishes the correctness of the structure assigned to the starting material, 6-methyl-2-pyridinemethanol acetate (X).

Finally, 2-(α-acetoxyethyl)-pyridine (XII) was subjected to the rearrangement procedure in the hope that the diacetate of 2-pyridyl methyl ketone (XIV) might result. Despite numerous attempts to accomplish this goal no evidence was obtained to indicate the formation of XIV. Under the usual conditions employed for these rearrangements, the attempted conversion led only to recovery of the intermediate N-oxide; whereas, under more strenuous conditions, a black tar resulted. It would seem that it is necessary to have at least two α-hydrogens available for replacement in order for the rearrangement to occur in good yield.



The question of the mechanism by which aromatic-N-oxides undergo rearrangement on heating

(10) H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **14**, 509 (1949).

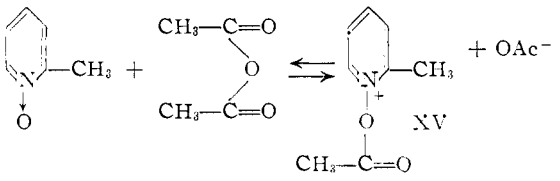
(11) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

(12) For example, see R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 587.

(13) R. A. Barnes and H. M. Fales, THIS JOURNAL, **75**, 3830 (1953). We are indebted to Dr. Barnes for his kindness in supplying us with a sample of 2,6-di-(hydroxymethyl)-pyridine.

with acid anhydrides is an intriguing one. There is a formal resemblance between this reaction and that of aromatic-N-oxides with acid chlorides and base. For example, the reaction of quinaldine-N-oxide with benzoyl chloride and alkali yields 2-quinolinemethanol benzoate,[14] just as in the present case quinaldine-N-oxide reacts with acetic anhydride to give 2-quinolinemethanol acetate.

In almost any mechanism that might be considered for the reaction, the logical first step would seem to be salt formation between the N-oxide and acetic anhydride, as illustrated below for 2-picoline-N-oxide. The subsequent steps, however, are not at all clear. It is possible that the reaction proceeds through a cyclic ionic mechanism of the type suggested by Pachter[14] for the reaction of quinaldine-N-oxide with benzoyl chloride and base, although such a mechanism would need to be modified to explain the rearrangement of 4-picoline-N-oxide. On the other hand, the possibility of a mechanism involving free radicals cannot be excluded at present. The fact that, for many of the examples investigated, there was an induction period followed by an exothermic reaction would suggest the likelihood of a chain reaction involving radicals. Also, it would be expected that the nitrogen–oxygen bond in compound XV would be thermally unstable and might readily undergo homolytic cleavage. A kinetic study of the reaction of picoline-N-oxide with acetic anhydride is in progress and it is hoped that this will lead to a clarification of the reaction mechanism.



Experimental[15]

2-Acetoxymethyl-1,4-diacetoxy-4-(2′-(pyridyl)-butane (II).—A mixture containing 15.0 g. of 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol,[16] 30 ml. of glacial acetic acid and 10 ml. of a 30% aqueous hydrogen peroxide solution was heated for 3 hours at 80–90°. Then another 5 ml. of aqueous 30% hydrogen peroxide was added and heating at 80–90° was continued for another 10 hours. After removal of the acetic acid and water under reduced pressure, the crude N-oxide was dissolved in 60 ml. of acetic anhydride and heated at 100° for 9 hours. Direct distillation of the reaction mixture gave 15.5 g. (58%) of a light yellow oil; b.p. 171–173° at 0.5 mm., $n^{20}D$ 1.4907. A test for the presence of the pyridone group was negative using ferric chloride as reagent and this is accepted as being significant since pyridone acetates generally give a positive result in this test.

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55. Found: C, 59.30; H, 6.69.

Oxidation of 2-Acetoxymethyl-1,4-diacetoxy-4-(2′-pyridyl)-butane with Permanganate.—A suspension of 3.2 g. of 2-acetoxymethyl-1,4-diacetoxy-4-(2′-pyridyl)-butane (II) and 1.9 g. of potassium permanganate in 50 ml. of water was stirred mechanically and heated on a steam-bath. When the purple color was discharged, another 1.9-g. portion of permanganate was added followed by 10 ml. of water. This addition of permanganate and water was repeated four more times. The manganese dioxide was then removed by filtration and washed thoroughly with hot water. The filtrate and washings were evaporated *in vacuo* to about 20 ml., acidified with concentrated hydrochloric acid using congo red as indicator and evaporated to dryness. The residual salts were extracted twice with 100-ml. portions of boiling ethanol and filtered. The filtrate was evaporated to 10 ml., cooled and saturated with dry hydrogen chloride. The crystals, which separated from the cold solution, were collected to give 0.82 g. (51%) of picolinic acid hydrochloride, m.p. 228–230° dec.[17]

2-Picoline-N-oxide (V).—The procedure employed for preparing 2-picoline-N-oxide was used essentially without modification for preparing all of the other N-oxides reported in this paper and will therefore be reported in detail, although it is similar to that reported by Ochiai for preparing pyridine-N-oxide.[3]

A mixture containing 46.6 g. (0.5 mole) of 2-picoline, 300 ml. of glacial acetic acid and 50 ml. of a 30% aqueous solution of hydrogen peroxide was heated at 70–80° for 3 hours. An additional 35 ml. of the aqueous 30% hydrogen peroxide solution was then added and the resulting mixture was heated at 70–80° for another 9 hours. The mixture was then concentrated to a volume of 100 ml., an equal volume of water was added, and the solution was again concentrated to a volume of 100 ml. (the steam distillation under reduced pressure was used to remove traces of acetic acid and hydrogen peroxide). The residue was taken up in 250 ml. of chloroform and shaken with an aqueous paste of potassium carbonate until no further carbon dioxide was evolved. The chloroform layer was then removed, dried and concentrated under reduced pressure. The residual oil (in those cases where the residue was crystalline, purification was effected by recrystallization rather than distillation) was distilled to give 45.0 g. (83%) of a colorless hygroscopic oil; b.p. 123–124° at 15 mm., $n^{20}D$ 1.5918. Anhydrous samples of 2-picoline-N-oxide crystallized on standing to a low-melting solid; however, on exposure to the atmosphere this solid immediately liquefied.

Anal. Calcd. for C_6H_7NO: C, 66.03; H, 6.47. Found: C, 65.73; H, 6.87.

The **picrate of 2-picoline-N-oxide** was obtained after recrystallization from ethanol as yellow crystals, m.p. 125–126.5°.[18]

Anal. Calcd. for $C_{12}H_{10}N_4O_8$: C, 42.61; H, 2.98. Found: C, 42.39; H, 3.24.

2-Pyridinemethanol Acetate (VI).—To 37.0 g. of gently boiling acetic anhydride there was added dropwise 20.0 g. of 2-picoline-N-oxide. When the addition was complete, the solution was boiled under reflux for 15 minutes and then distilled directly under reduced pressure. After a forerun of acetic anhydride, there was collected 21.2 g. (78%) of a pale yellow oil; b.p. 115–118° at 22 mm., $n^{20}D$ 1.4969.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00. Found: C, 63.76; H, 6.06.

The **picrate of 2-pyridinemethanol acetate** was obtained after recrystallization from ethanol as yellow crystals, m.p. 168–168.5° dec.

Anal. Calcd. for $C_{14}H_{12}N_4O_9$: C, 44.22; H, 3.18. Found: C, 44.28; H, 3.36.

Hydrolysis of 2-Pyridinemethanol Acetate.—A solution of 1.0 g. of 2-pyridinemethanol acetate (VI) in 10 ml. of concd. hydrochloric acid was boiled under reflux for 10 hours. The solution was then evaporated to dryness in a stream of air, and the residue was taken up in chloroform and treated with an aqueous paste of potassium carbonate. After the chloroform solution had been dried, it was concentrated under reduced pressure to give an oily residue. This was converted directly to the corresponding picrate which, after recrystallization from ethanol, gave 1.1 g. of golden plates, m.p. 160.5–161°. Admixture of an authentic sample of 2-pyridinemethanol picrate[19] gave no depression of melting point.

(14) I. J. Pachter, THIS JOURNAL, **75**, 3026 (1953).

(15) Analyses by Miss Viola Williams and the Micro-Tech Laboratories. All melting points are corrected.

(16) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(17) E. A. Prill and S. M. McElvain, ("Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 419), give 228–230° dec. as the m.p. of picolinic acid hydrochloride.

(18) M. Ishikawa and S. Zai-Ren [*J. Pharm. Soc. Japan*, **63**, 78 (1943); *C. A.*, **44**, 7321f (1950)] give 125° as the m.p. for 2-picoline-N-oxide picrate.

(19) F. Šorm and L. Šedivy, *Collection Czech. Chem. Communs.*, **13**, 289 (1948).

In a second hydrolysis experiment the residual oil was converted to the corresponding *p*-nitrobenzoate derivative. This after recrystallization from ethanol was obtained as white crystals, m.p. 90.5–92.5°.[20]

2-Pyridinealdehyde Diacetate (IX).—A sample of 15.1 g. of 2-pyridinemethanol acetate (VI) was treated with hydrogen peroxide in glacial acetic acid in the manner as previously described for the preparation of 2-picoline-N-oxide. The resulting crude N-oxide was then treated directly with acetic anhydride in the same manner as before to effect rearrangement. Distillation of the final product gave 9.5 g. (46% from 2-pyridinemethanol acetate) of a colorless oil; b.p. 160–162.5° at 15 mm., n_D^{20} 1.4872.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.34; H, 5.63.

For identification purposes, 2-pyridinealdehyde diacetate was converted to the corresponding oxime, *p*-nitrophenylhydrazone and 2,4-dinitrophenylhydrazone derivatives. All formed in excellent yield. The oxime was obtained from water as white crystals, m.p. 113–116°[21]; the *p*-nitrophenylhydrazone was obtained from ethanol as yellow crystals, m.p. 242–245°[22]; and the 2,4-dinitrophenylhydrazone gave yellow crystals, m.p. 236.5–237°.[23]

4-Picoline-N-oxide.—From 46.6 g. of 4-picoline there was obtained 39.9 g. (73%) of white crystals which, after recrystallization from benzene, melted at 185–186°.[24]

Anal. Calcd. for C_6H_7NO: C, 66.03; H, 6.47. Found: C, 66.28; H, 6.87.

The **picrate of 4-picoline-N-oxide** was obtained after recrystallization from ethanol as yellow crystals, m.p. 158.7–159.7°.

Anal. Calcd. for $C_{12}H_{10}N_4O_8$: C, 42.61; H, 2.98. Found: C, 42.93; H, 3.20.

4-Pyridinemethanol Acetate.—The procedure for the rearrangement was modified in this case because initial experiments indicated that the reaction was exothermic and would become violent unless a diluent was used. A solution of 10.0 g. (0.09 mole) of 4-picoline-N-oxide, 100 ml. of dioxane and 19.0 g. of acetic anhydride was boiled under reflux for five hours. After removal of the dioxane, the residue was cooled and poured into 100 ml. of ice water containing 5 ml. of pyridine. This solution was cooled in an ice-bath and made basic by the addition of solid potassium carbonate. After the mixture was extracted five times with ether the combined ethereal extracts were dried with anhydrous sodium sulfate, the ether was removed and the residue was distilled. There was collected 5.8 g. (42.5%) of a nearly colorless oil; b.p. 53–55° at 0.3 mm., $n^{20}D$ 1.5023.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.21. Found: C, 62.78; H, 6.03; N, 9.30.

Hydrolysis of 4-Pyridinemethanol Acetate.—A solution of 1.0 g. of 4-pyridinemethanol acetate in 10 ml. of concentrated hydrochloric acid was boiled under reflux for three hours. The solution was evaporated to dryness on a steam-bath in a current of air and the residual solid was taken up in hot *n*-butanol. As the solution cooled, crystals formed and these were collected in an atmosphere of *dry* nitrogen, since they were quite hygroscopic. After another recrystallization from 1-butanol using charcoal for clarification, 0.70 g. (72%) of white needles, m.p. 176–178°, was obtained.[25]

A sample of 4-pyridinemethanol was prepared independently for comparison. From the lithium aluminum hydride reduction of ethyl isonicotinate[26] following the procedure of Protiva,[27] 4-pyridinemethanol was obtained as white hygroscopic crystals, m.p. 57–60° (Protiva[27] gives 57° as the m.p.). This, on conversion to the corresponding hydrochloride, gave white needles, m.p. 177–179°, alone or mixed with the sample of hydrochloride from the N-oxide rearrangement. As further proof of their identity, the two samples of the hydrochloride of 4-pyridinemethanol were shown to have identical infrared spectra.

4-Pyridinealdehyde Diacetate.—When a 9.2-g. sample of 4-pyridinemethanol acetate was subjected to the same reaction sequence described previously for the preparation of 2-pyridinealdehyde diacetate (IX), there was obtained 1.1 g. of a pale yellow oil, b.p. 105–110° at 0.3 mm.; a considerable residue of tarry material remained in the still pot. For identification, the 4-pyridinealdehyde diacetate was converted directly to the corresponding phenylhydrazone and *p*-nitrophenylhydrazone derivatives. The phenylhydrazone derivative was obtained in 52% yield as yellow needles, m.p. 178.5–179.5°.[28] The *p*-nitrophenylhydrazone was obtained from aqueous ethanol as yellow crystals, m.p. 268.5–269.5° dec.

2,6-Lutidine-N-oxide.—This compound has previously been reported by Ishikawa and Zai-Ren[18] but the data regarding its physical properties are not readily available. From 53.6 g. of 2,6-lutidine we obtained 46.1 g. (75%) of 2,6-lutidine-N-oxide as a colorless oil; b.p. 115–119° at 18 mm. As was the case with 2-picoline-N-oxide, an anhydrous sample of the oil crystallized on standing to a low melting solid but, on exposure to the atmosphere, the crystals quickly liquefied.

The **picrate of 2,6-lutidine-N-oxide** was obtained after recrystallization from ethanol as yellow crystals, m.p. 127.5–129°.

Anal. Calcd. for $C_{13}H_{12}N_4O_8$: C, 44.32; H, 3.43. Found: C, 44.65; H, 3.59.

6-Methyl-2-pyridinemethanol Acetate (X).—A solution of 20.0 g. of 2,6-lutidine-N-oxide in 17.0 g. of acetic anhydride was allowed to stand at room temperature until the initial exothermic reaction was over. The reaction mixture was then heated at 100° for 10 hours and worked up as in the other examples. There was obtained 18.7 g. (71%) of a colorless oil; b.p. 110–114° at 15 mm., $n^{20}D$ 1.5043. When the formation of 2,6-lutidine-N-oxide and its rearrangement were carried out as a single operation, 6-methyl-2-pyridinemethanol acetate was obtained in essentially the same yield.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71. Found: C, 65.81; H, 7.04.

The **picrate of 6-methyl-2-pyridinemethanol acetate** was obtained after recrystallization from ethanol as yellow crystals, m.p. 114–115°.

Anal. Calcd. for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58. Found: C, 45.81; H, 3.50.

2,6-Di-(acetoxymethyl)-pyridine (XI).—A 12.0-g. sample of 6-methyl-2-pyridinemethanol acetate was carried through the two-step sequence of oxidation with hydrogen peroxide and rearrangement with acetic anhydride, as previously described. There was obtained 5.0 g. of a pale yellow oil, b.p. 135–139° at 0.3 mm.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87. Found: C, 58.47; H, 5.92.

The **picrolonate of 2,6-di-(acetoxymethyl)-pyridine** was obtained from ethanol as yellow crystals, m.p. 110.5–111°.

Anal. Calcd. for $C_{21}H_{21}N_5O_9$: C, 51.74; H, 4.34. Found: C, 52.37; H, 4.50.

In one instance, where the preparation of 2,6-di-(acetoxymethyl)-pyridine was carried out on the same scale, there was obtained 8.1 g. of a pale yellow oil; b.p. 130–133° at 0.3 mm. This, on standing, partially solidified and, when the mixture was taken up in hot ether and cooled, it was possible to separate 2.0 g. of white crystals, m.p. 94–94.5°. As indicated below, the composition of this material suggested that it was either 6-methyl-2-(acetoxymethyl)-pyridine-N-oxide or 2-hydroxymethyl-6-(acetoxymethyl)-pyridine. Since its infrared spectrum shows the complete absence of a hydroxyl band, we have assumed that the 6-methyl-2-(acetoxymethyl)-pyridine N-oxide structure is correct. It is probable that the poor analyses obtained for

(20) R. Graf (*J. prakt. Chem.*, **88**, 146 (1936)) gives 92° as the m.p. of 2-pyridinemethanol *p*-nitrobenzoate.

(21) G. Lénárt (*Ber.*, **47**, 808 (1914)) gives 113.5° as the m.p. of 2-pyridinealdoxime.

(22) P. Dyson and D. Hammick (*J. Chem. Soc.*, 781 (1939)) give 245° as the m.p. of the *p*-nitrophenylhydrazone of 2-pyridinealdehyde.

(23) T. Klein (*Ber.*, **86**, 584 (1953)) gives 239–240° as the m.p. of the 2,4-dinitrophenylhydrazone of 2-pyridinealdehyde.

(24) E. Ochiai, M. Ishikawa and S. Zai-Ren (*J. Pharm. Soc. Japan*, **64**, 72 (1944)) give 181° as the m.p. of 4-picoline-N-oxide.

(25) P. Šorm and L. Šedivy (ref. 19) give 176° as the m.p. of 4-pyridinemethanol hydrochloride.

(26) N. V. Rubtsov, *J. Gen. Chem.* (*U.S.S.R.*), **18**, 702 (1943); *C. A.*, **39**, 706 (1945).

(27) M. Protiva, *Chem. Listy*, **45**, 20 (1951); *C. A.*, **45**, 8997e (1951).

(28) J. P. Wibaut, E. C. Kooyman and H. Boer (*Rec. trav. chim.*, **64**, 30 (1945)) give 178–179° as the m.p. of the phenylhydrazone and 270° dec. as the m.p. of the *p*-nitrophenylhydrazone derivatives of 4-pyridinealdehyde.

2,6-di-(acetoxymethyl)-pyridine are due to contamination by this N-oxide.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12. Found: C, 59.75; H, 6.20.

2,6-Di-(hydroxymethyl)-pyridine.—A solution of 0.5 g. of 2,6-di-(acetoxymethyl)-pyridine (XI) in 10 ml. of concd. hydrochloric acid was boiled under reflux for 8 hr. After the solution had been allowed to evaporate to dryness, the residue was taken up in methanol and passed over an ion-exchange column (Amberlite IRA-400, previously washed with aqueous sodium hydroxide). Concentration of the methanol eluate followed by crystallization of the residue from benzene gave 0.27 g. (87%) of white needles, m.p. 114–115°.[29] A mixed melting point determination of our sample with that of an authentic sample of 2,6-di-(hydroxymethyl)-pyridine[13] showed no depression of melting point. Likewise, the infrared spectra of the two samples of 2,6-di-(hydroxymethyl)-pyridine were identical.

2-[α-(Acetoxy)-*n*-butyl]-pyridine.—The conversion of 2-*n*-butylpyridine to the corresponding N-oxide and rearrangement of this to 2-[α-(acetoxy)-*n*-butyl]-pyridine was carried out as a single operation in the same manner previously described. From 4.1 g. of 2-*n*-butylpyridine there was obtained 5.0 g. (91%) of a light yellow oil; b.p. 135–137° at 15 mm., $n^{20}D$ 1.4895.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.29; H, 7.60.

2-(α-Acetoxyethyl)-pyridine (XII).—The conversion of 2-ethylpyridine[30] to 2-(α-acetoxyethyl)-pyridine was likewise carried out as a single operation. From 20.0 g. of 2-ethylpyridine there was obtained 17.7 g. (56%) of a colorless oil; b.p. 109–111° at 16 mm., $n^{20}D$ 1.4937. A sample of this material, when treated with sodium hypoiodite, gave a good yield of iodoform.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71. Found: C, 65.72; H, 7.01.

The **picrate** of 2-(α-**acetoxyethyl**)-**pyridine** was prepared in methanol and, after recrystallization from a hexane–ethyl acetate mixture, was obtained as yellow crystals, m.p. 112–113.5°.

Anal. Calcd. for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58. Found: C, 45.86; H, 3.84.

Attempted Conversion of 2-(α-Acetoxyethyl)-pyridine to XIV.—The conversion of XII to the corresponding N-oxide XIII and rearrangement of this with acetic anhydride to give XIV was attempted as a single operation in the same manner previously described. From 12.0 g. of 2-(α-acetoxyethyl)-pyridine there was obtained 10.7 g. of a light yellow oil, b.p. 125–126° at 0.7 mm. This oil was hygroscopic, it did not give a positive test with carbonyl reagents and it appeared to be impure. For identification purposes, a 1.0-g. sample of this oil was hydrolyzed with aqueous sodium hydroxide. After acidification and concentration, the residue was extracted with chloroform, the chloroform extract was shaken with an aqueous paste of potassium carbonate and then dried. Concentration of the chloroform extract gave 0.60 g. (79%) of white crystals which, after recrystallization from benzene, melted at 99–99.5°. This material was shown by independent synthesis (see below) to be 2-[α-hydroxyethyl]-pyridine-N-oxide.

Since this result indicated that the conditions of rearrangement (heating with acetic anhydride at 100° for seven hours) were not sufficiently strenuous to effect reaction, another experiment was run in which the crude N-oxide (XIII) was boiled under reflux in excess acetic anhydride for seven hours. In this case the reaction mixture turned black and nothing useful could be recovered from the tarry mass.

2-(α-Hydroxyethyl)-pyridine-N-oxide.—A solution containing 6.7 g. of 2-(α-acetoxyethyl)-pyridine (XII), 30 ml. of glacial acetic acid and 8 ml. of an aqueous 30% solution of hydrogen peroxide was heated at 72° for 12 hr. After concentration of the solution *in vacuo*, the residual oil was dissolved in 50 ml. of concd. hydrochloric acid and boiled under reflux for 4 hr. The solution was then evaporated to dryness *in vacuo*, the residue was taken up in methanol and passed over an ion exchange column (Amberlite IRA-400, which had previously been treated with aqueous sodium hydroxide). Concentration of the methanol eluate followed by recrystallization of the residue from benzene gave 2.9 g. (52%) of white crystals, m.p. 97–99°. A sample of these crystals, when mixed with a sample of the crystals from the preceding experiment, showed no depression of melting point.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.92; H, 6.81.

2-Pyridinemethanol-N-oxide.—In the conversion of 2-pyridinemethanol acetate (VI) to 2-pyridinealdehyde diacetate (IX), it was of interest to show that the only action of hydrogen peroxide on VI was that of effecting N-oxide formation and that formation of the aldehyde diacetate IX was entirely due to the rearrangement of the N-oxide with acetic anhydride. For this purpose then, a 10.0-g. sample of 2-pyridinemethanol acetate was treated with hydrogen peroxide and glacial acetic acid in the usual fashion for N-oxide formation and then hydrolyzed with hydrochloric acid as described in the preceding experiment. As expected, there was no evidence for the formation of 2-pyridinealdehyde and the only product isolated was 2-pyridinemethanol-N-oxide. This was obtained, after recrystallization from ethyl acetate, as white crystals, m.p. 143–143.5°, in 60% yield.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64. Found: C, 57.72; H, 5.74.

2-Quinolinemethanol Acetate.—A solution of 25 g. (0.17 mole) of freshly distilled quinaldine, 110 ml. of glacial acetic acid and 18 ml. of 30% hydrogen peroxide was heated for three hours at 70–80°. An additional 12 ml. of peroxide was added and the heating was continued for 16 hours. The solution was concentrated under reduced pressure and the residue was then dissolved in 35 g. of acetic anhydride. After the reaction mixture had stood for a short time at room temperature an exothermic reaction took place. When this was complete, the reaction mixture was heated at 100° for ten hours and then distilled. There was collected 19.3 g. (56.5%) of a yellow oil; b.p. 118–122.5° at 0.4 mm., $n^{20}D$ 1.5837.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51. Found: C, 72.19; H, 5.39.

The **picrate** of **2-quinolinemethanol acetate** formed readily in ethanol and, after recrystallization from ethanol, was obtained as yellow crystals, m.p. 156.5–157.5°.

Anal. Calcd. for $C_{18}H_{14}N_4O_9$: C, 50.24; H, 3.28. Found: C, 50.04; H, 3.39.

Acid Hydrolysis of 2-Quinolinemethanol Acetate.—A solution of 1.0 g. of 2-quinolinemethanol acetate in 10 ml. of concentrated hydrochloric acid was boiled under reflux for three hours. The solution was then cooled in an ice-bath and made basic by the addition of a 10% aqueous sodium hydroxide solution. The solution was then extracted three times with ether. The ethereal solution was washed with water and dried with Drierite. Evaporation of the ether and trituration of the residue with petroleum ether gave 0.70 g. (88.5%) of white crystals, m.p. 66–68°, after recrystallization from a benzene–petroleum ether mixture.[31]

The **phenylurethan** of **2-quinolinemethanol** was obtained as white crystals, m.p. 129–130° (ref. 31 gives 125–126°).

The **benzoate** of **2-quinolinemethanol** was obtained after recrystallization from aqueous methanol as white crystals, m.p. 50–51°.[32]

3-Picoline-N-oxide (VII).—This was prepared in the same manner described previously for the preparation of 2-picoline-N-oxide. From 46.6 g. of 3-picoline there was obtained 42.2 g. (77%) of a colorless, hygroscopic oil, b.p. 146–149° at 15 mm. When completely anhydrous, the material became crystalline, but on exposure to the atmosphere it quickly reverted to an oil. It was not isolated in the pure state but, instead, was characterized through its picrate derivative. This was obtained, after recrystallization from ethanol, as yellow crystals, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_{10}N_4O_8$: C, 42.61; H, 2.98. Found: C, 42.38; H, 2.94.

2-Acetoxy-3-methylpyridine (VIII).—The rearrangement of 3-picoline-N-oxide with acetic anhydride was carried out by boiling a solution of 10.0 g. of VII in 50 ml. of acetic

(29) W. Mathes, W. Sauermilch and T. Klein (*Ber.*, **86**, 584 (1953)) give 114.5–115° as the m.p. of 2,6-di-(hydroxymethyl)-pyridine.

(30) R. L. Frank and R. P. Phillips, THIS JOURNAL, **71**, 2804 (1949).

(31) C. E. Kaslow and W. R. Clark (*J. Org. Chem.*, **18**, 55 (1953)) give 66–67° as the m.p. of 2-quinolinemethanol.

(32) Pachter (ref. 14) gives 52–53° as the m.p. for the benzoate of 2-quinolinemethanol.

anhydride under reflux for 5 hr. Distillation of the reaction mixture gave 4.1 g. of a colorless oil; b.p. 61–62° at 0.5 mm., $n^{20}D$ 1.4997

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00. Found: C, 63.47; H, 6.22.

Acid Hydrolysis of 2-Acetoxy-3-methylpyridine (VIII).—A 1.0-g. sample of 2-acetoxy-3-methylpyridine (VII) was hydrolyzed following the same procedure described previously for the preparation of 2,6-di-(hydroxymethyl)-pyridine. The product was obtained, after recrystallization from a benzene–hexane mixture, as light tan crystals, m.p. 138–140°.[33] The ultraviolet absorption spectrum of this material is very similar to that of 2-pyridone in that it has absorption maxima at 230 (log ε 3.83) and 289 mμ (log ε 3.83), whereas 2-pyridone has its maxima at 227 (log ε 4.00) and 297 mμ (log ε 3.80).[11]

(33) H. L. Bradlow and C. A. VanderWerf (*J. Org. Chem.*, **14**, 509 (1949)) give 138–139.5° as the m.p. of 3-methyl-2-pyridone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

Condensation of 2-Naphthol with Acetaldehyde Ammonia

BY WILLIAM J. BURKE AND RICHARD J. REYNOLDS[1]

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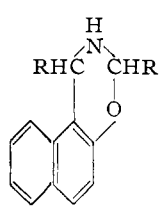
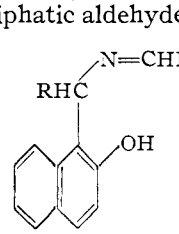
Condensation of 2-naphthol with acetaldehyde ammonia resulted in a high yield of 1,2-dihydro-1,3-dimethyl-3H-naphth-[1.2-e]-*m*-oxazine (Ib). Evidence is presented for the structure assigned. Hydrolysis of Ib yielded 1-α-aminoethyl-2-naphthol (IIIb). Reactions of Ib and IIIb were studied.

Betti[2] reported that 2-naphthol reacted with aldehydes and ammonia in a molar ratio of 1:2:1 to yield crystalline products, which were assigned either a *m*-naphthoxazine (I) or isomeric Schiff base structure II on the basis of a ferric chloride test. Related compounds were obtained when the product III of the condensation of equimolar quantities of the reactants was condensed with a second molecule of an aldehyde. Aromatic aldehydes were reported to yield the corresponding Schiff base II upon reaction with IIIa, while naphthoxazines were obtained when aliphatic aldehydes were employed.[3]



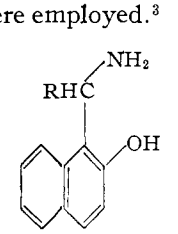
I

Ia, R = C_6H_5
Ib, R = CH_3



II

IIa, R = C_6H_5
IIb, R = CH_3



III

IIIa, R = C_6H_5
IIIb, R = CH_3

Ahmed, Hemphill and Ray[4] uncovered evidence to show that the product from the condensation of 2-naphthol, benzaldehyde and ammonia in a molar ratio of 1:2:1 was the *m*-naphthoxazine (Ia). Betti initially[2b] proposed this structure but later[5] assigned the Schiff base formula IIa to the product.

Considering the attention given to the condensation of hydroxyaromatic compounds with aldehydes and amines or ammonia, it is rather surprising that products from such reactions involving the use of acetaldehyde ammonia have not been described in the literature. This general type of reaction has provided a convenient route to a variety of complex substances difficultly accessible by other methods. It has been found that the course of the condensation and the type of products obtained depend upon several factors including the nature of the hydroxyaromatic compounds,[2a,6] amine[2d,7] and aldehyde components,[3,8,9] their ratio in the reaction system[2,6] and the particular conditions employed.[7,10,11] The lack of sufficient experimental evidence has frequently prohibited the definite assignment of structure to the resulting condensates. In view of these factors, the present study of the condensation of 2-naphthol with acetaldehyde ammonia was undertaken.

2-Naphthol and acetaldehyde ammonia in a molar ratio 1:2.4 reacted readily in refluxing benzene to give a 74% yield of 1,2-dihydro-1,3-dimethyl-3H-naphth[1.2-e]-*m*-oxazine (Ib) with the liberation of ammonia. A reaction time in excess of 45 minutes did not result in a higher yield, but the use of benzene rather than ethanol as a solvent was advantageous. The conversion to Ib was over 95% based on the 2-naphthol consumed. Ib was appreciably less sensitive to acids than the corresponding 1,3-benzoxazines,[12] derived from phenols, formaldehyde and primary amines, and formed a stable hydrochloride. In a refluxing solution of propanol-2 in the presence of hydrochloric acid, Ib was converted smoothly to 1-α-aminoethyl-2-naphthol (IIIb) hydrochloride, which upon treatment with 2-aminoethanol yielded the crystalline free base. The latter, however, was unstable and slowly liberated ammonia. Reaction of IIIb in ether solution with acetaldehyde at room temperature re-

(1) Atomic Energy Commission Fellow at the University of Utah, 1950–1951. Jackson Laboratory, E. I. du Pont de Nemours and Co., Deepwater Point, N. J.

(2) (a) M. Betti, *Gazz. chim. ital.*, [II] **30**, 310 (1900); *J. Chem. Soc.*, **80**, 81 (1901); (b) M. Betti, *Gazz. chim. ital.*, [II] **31**, 377 (1901); *J. Chem. Soc.*, **80**, 611 (1901); (c) M. Betti and A. Torricelli, *Gazz. chim. ital.*, [I] **33**, 1 (1903); *J. Chem. Soc.*, **84**, 480 (1903); (d) M. Betti, *Gazz. chim. ital.*, [I] **33**, 17 (1903); *J. Chem. Soc.*, **84**, 510 (1903).

(3) M. Betti and V. Foa, *Gazz. chim. ital.*, [I] **33**, 27 (1903); *J. Chem. Soc.*, **84**, 511 (1903).

(4) N. Ahmed, M. G. Hemphill and F. E. Ray, THIS JOURNAL, **56**, 2403 (1934).

(5) M. Betti, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 381.

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(7) W. J. Burke, M. J. Kolbezen and C. W. Stephens, *ibid.*, **74**, 3601 (1952).

(8) M. Betti, *Gazz. chim. ital.*, [I] **34**, 212 (1904); *J. Chem. Soc.*, **86**, 581 (1904).

(9) F. W. Holly and A. C. Cope, THIS JOURNAL, **66**, 1875 (1944).

(10) J. C. Duff and E. J. Bills, *J. Chem. Soc.*, 1307 (1934).

(11) J. C. Duff and U. I. Furness, *ibid.*, 1512 (1951).

(12) (a) W. J. Burke, THIS JOURNAL, **71**, 609 (1949); (b) W. J. Burke and C. W. Stephens, *ibid.*, **74**, 1518 (1952).