The product on repeated crystallizations from methanol separated into colorless shining needles (90 mg.), m.p. 176–177°. It showed no depression in melting point on admixture with an authentic sample of 2,6-dimethyl-5,7-dimethoxyisoflavone (XIVc) obtained by the complete methylation of the probable 2,6-dimethyl-5-hydroxy-7-methoxyisoflavone (XIVb). The second product which separated from methanol as colorless needles (60 mg.) melted at 184–186° and was characterized as 2,8-dimethyl-5,7-dimethoxyisoflavone (XIIIc) (*cf.* lit.,[3a] 184-186°).

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found for the product, m.p. 176–177°: C, 73.26; H, 5.55; and for the product, m.p. 184–186°: C, 73.84; H, 5.62.

Acetic Anhydride–Sodium Acetate Method.—2,4,6-Trihydroxy-3-methyldeoxybenzoin[3a] (VIII) (0.75 g.), acetic anhydride (12 cc.), and fused sodium acetate (2.0 g.) were refluxed at 170–180° for 12 hr. The contents were cooled to room temperature and then poured into crushed ice and the mixture left overnight. The brown solid on fractional crystallization from ethanol gave various crops of crystals melting in the range of 176–207°. Ienger, *et al.*,[3a] reported the m.p. 188–190° and gave it the structure of 2,8-dimethyl-5,7-diacetoxyisoflavone (XIIId).

Deacetylation.—All the crops of crystals obtained above were dissolved in alcohol (100 cc.) and concentrated sulfuric acid (4 cc.) added. The mixture after refluxing for 2 hr. was diluted with an equal amount of water and the alcohol distilled. The solid obtained on cooling was filtered, washed with water, and dried (0.6 g.) On crystallization from ethanol it separated into fine colorless needles, m.p. 220–240°. Ienger, *et al.*,[3a] reported the melting point as 256–257° and assigned it the structure of 2,8-dimethyl-5,7-dihydroxyisoflavone (XIIIa).

Methylation.—The product, m.p. 220–240° (150 mg.), on monomethylation using exactly 1 mole of methyl sulfate yielded a product which on repeated crystallizations from methanol separated into a less soluble fraction in the form of colorless needles (30 mg.), m.p. 188–190° (*cf.*[3a,b] m.p. 188–190°). The mixed melting point with the probable 2,6-dimethyl-5-hydroxy-7-methoxyisoflavone (XIVb) obtained by acetyl chloride method was undepressed. Repeated crystallizations of the solid obtained from mother liquor gave very light yellow needles (70 mg.), m.p. 131–132°.

The product showed no depression in melting point on admixture with a sample obtained earlier by acetyl chloride pyridine method. Complete methylation of the product, m.p. 220–240° (100 mg.), using a large excess of methyl sulfate resulted in the separation of 2,6-dimethyl-5,7-dimethoxyisoflavone (XIVc) (20 mg.), m.p. 176–177°, and 2,8-dimethyl-5,7-dimethoxyisoflavone (XIIIc) (64 mg.), m.p. 184–186°[3a].

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found for the product, m.p. 176–177°; C, 73.31; H, 5.72 and found for the product, m.p. 184–186°: C, 73.29; H, 5.56.

Alkylation of Pyridine Carboxaldoximes

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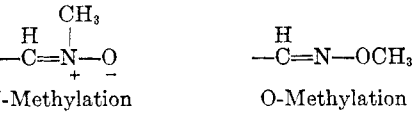
The reaction of methyl iodide with 6-methylpicolinaldehyde oxime was studied. It was found that the major reaction occurs at the nitrogen atom of the oxime function. A suitable synthesis of 1,6-dimethyl-2-formylpyridinium iodide oxime was accomplished by a route involving conversion of 6-methylpicolinaldehyde to its acetal, methylation, and hydrolysis to 1,6-dimethyl-2-formylpyridinium iodide followed by reaction with hydroxylamine.

Alkylation of the oximino group has been studied extensively.[2] Common reagents for this purpose are dimethyl sulfate and alkyl iodides either alone or in the presence of base. Methylation of an oxime usually gives a mixture of N- and O-alkylation products.[2]



N-Methylation

O-Methylation

These have been distinguished by hydrolysis to either N-methylhydroxylamine or hydroxylamine and methanol.

In the reaction of pyridine carboxaldoximes with alkylating agents one normally obtains the corresponding pyridinium carboxaldoximes in high yield.[3] When the ring nitrogen is hindered sterically, as in 6-methylpicolinaldehyde oxime (I), alkylation occurs instead on the oximino group. Thus Ginsburg and Wilson[3] report that "Methylation of 6-methylpyridine-2-aldoxime with methyl iodide yielded the hydroiodide of the methyl ether"; however, no experimental details for this reaction or further characterization of the product was made.

It was the dual purpose of this work to restudy the oxime alkylation reaction of I and to develop a suitable synthesis for hindered pyridinium carboxaldoximes.

Reaction of methyl iodide with I in alcohol or dimethylformamide afforded a single product in 72% yield. In order to establish the identity of the alkylation product, N-methyl-6-methylpicolinealdehyde oxime hydroiodide (II) and O-methyl-6-methylpicolinealdehyde oxime hydroiodide (III) were prepared *via* the reaction of 6-methylpicolin-

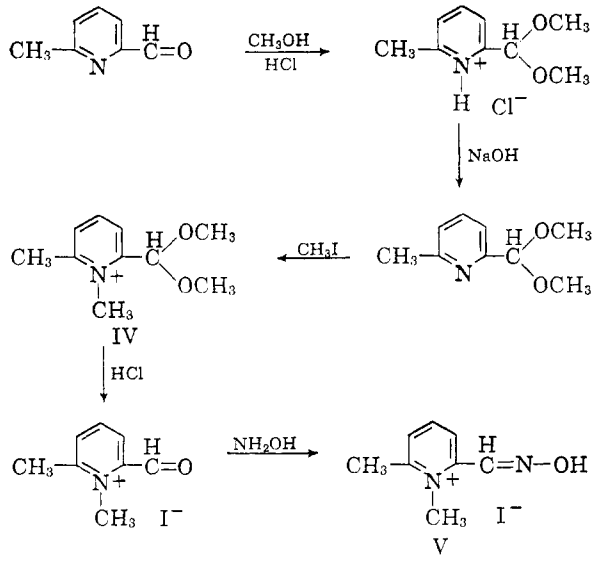
(1) (a) To whom inquiries regarding this paper should be submitted; (b) this paper was prepared in part from a dissertation by E. J. P. submitted to the faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1961.

(2) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, London, 1942, p. 173.

(3) (a) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958); (b) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

aldehyde with N-methyl- and O-methylhydroxylamine, respectively. Comparison of the infrared and ultraviolet spectra showed the reaction product to be N-methyl-6-methylpicolinaldehyde oxime hydroiodide (II).

The methylation of I was repeated a number of times under various conditions. It was found that short reaction times, high reaction temperatures, and nonhydroxylic solvents yielded predominantly II but did afford a small amount (5%) of 1,6-dimethyl-2-formylpyridinium iodide oxime (V).



The preparation of V was accomplished in 19% over-all yield *via* a route involving conversion of 6-methylpicolinaldehyde to its dimethyl acetal, methylation, and hydrolysis to 1,6-dimethyl-2-formylpyridinium iodide followed by reaction with hydroxylamine.

Experimental

Physical Data.—The pK_a values were determined at room temperature (25–27°), from potentiometric titration data, assuming pK_a to be the pH of half neutralization. In each case approximately 100 mg. of sample dissolved in 10 ml. of water was titrated with 0.1 *N* sodium hydroxide. Melting points are uncorrected. The infrared absorption spectra were determined in potassium bromide disks with a Perkin–Elmer Infracord (Model 137). Ultraviolet absorption spectra were determined using a Beckman Model DU spectrophotometer.

The Alkylation of 6-Methylpicolinaldehyde Oxime. Method A.—To 5.0 g. (0.038 mole) of 6-methylpicolinaldehyde oxime (a product of Aldrich Chemical Co.) in 40 ml. of ethanol was added 25 g. (0.18 mole) of methyl iodide. The solution was heated in a capped bottle of the carbonated beverage variety for 4 hr. at 100°. The yellow-orange solution was cooled to room temperature; ether was added to give 7.6 g. (72%) of a yellow orange solid (II), microscopic needles, m.p. 179° dec., pK_a 4.4. The pK_a value of 4.4 (pK_a expected[2] for oxime of this class, approx. 8) indicated that an hydroiodide of an O- and/or N-methyl oxime was obtained. Ultraviolet spectrum: pH 1, λ_{max} 330 mμ, log ε 4.17; pH 7, λ_{max} 298, log ε 4.10; pH 14, λ_{max} 298, log ε 4.00.

Anal. Calcd. for $C_8H_{11}IN_2O$: C, 34.6; H, 4.0; I, 45.7; neut. equiv., 278. Found: C, 34.5; H, 3.9; I, 45.3; neut. equiv., 278.

Method B.—To 15.0 g. (0.114 mole) of 6-methylpicolinaldehyde oxime in the minimum amount of boiling nitrobenzene was added dropwise 50 g. (0.36 mole) of methyl iodide. In 15 min. the mixture was filtered to give 13.0 g. of a yellow-orange solid. Titration with base gave an indication of two acid functions with pK_a values of 4.5 and 8. The product in acetone containing sufficient triethylamine to neutralize the stronger acid function was stirred magnetically for 30 min. The mixture was filtered and recrystallization of the product from methanol–ether gave 0.55 g. (5%) of V, m.p. 210°, neut. equiv., 279, pK_a 8.0. The material with pK_a 4.5 was identical with II.

N-Methyl-6-methylpicolinaldehyde Oxime Hydrochloride.—To 4.2 g. (0.050 mole) of N-methylhydroxylamine hydrochloride,[4] in the minimum amount of methyl alcohol required for complete solution at room temperature, was added 6.2 g. (0.051 mole) of 6-methylpicolinaldehyde. The reaction solution was allowed to stand overnight; approximately one half of the methanol was evaporated on a rotating type evaporator. Ether was added to the point of cloudiness and the mixture was allowed to stand overnight in a Dry Ice chest to give 4.1 g. (40%) of a crystalline colorless solid, m.p. 178–179° dec.

Anal. Calcd. for $C_8H_{11}ClN_2O$: C, 51.4; H, 6.0; neut. equiv., 187. Found: C, 51.4; H, 6.0; neut. equiv., 185; pK_a 4.4.

N-Methyl-6-methylpicolinaldehyde Oxime Hydroiodide (II).—N-Methyl-6-methylpicolinaldehyde oxime hydrochloride was dissolved in methanol together with a slight excess of methyl iodide. The solution turned yellow within a few seconds and was allowed to stand overnight.[5] Addition of ether precipitated in nearly quantitative yield the iodide salt, m.p. 181–183° dec. Ultraviolet spectrum: pH 1, λ_{max} 332 mμ, log ε 413; pH 7.0, λ_{max} 300, log ε 4.10; pH 14, λ_{max} 299, log ε 3.99.

Anal. Calcd. for $C_8H_{11}IN_2O$: C, 34.6; H, 4.0; I, 45.7; neut. equiv., 278. Found: C, 34.7; H, 4.1; I, 46.1; neut. equiv., 278, pK_a 4.3.

O-Methyl-6-methylpicolinaldehyde Oxime Hydrochloride.—To a methanol–water (1:4) solution of 6.1 g. (0.050 mole) of 6-methylpicolinaldehyde was added a previously neutralized solution (pH 7) of 8.4 g. (0.10 mole) O-methylhydroxylamine hydrochloride (Eastman Kodak White Label). Two layers immediately formed; the mixture was heated on a steam bath for 20 min. then cooled while stirring. The mixture was extracted with three 100-ml. portions of ethyl ether; the etherates were evaporated and the liquid residue washed with 100 ml. of distilled water. The water was decanted; the residue was dissolved in 200 ml. of ether. The etherate was dried over sodium sulfate, filtered, and hydrogen chloride passed in to give 8.2 g. (88%) of a colorless hygroscopic powder. This product melted at 62.64°, resolidified in the range 90–95° and remelted at 123–125°.[6]

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(4) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green & Co., New York, N. Y., 1957, p. 450.

(5) This reaction for anion conversion, appears to be very rapid with compounds that form charge–transfer complexes with iodide ion and offers a convenient method for the conversion of chloride and bromide salts to the corresponding iodides.

(6) It was observed that irrespective of reaction conditions a product was obtained which melted in the area of either 60 or 120°. Elemental analyses in each case corresponded to a monohydrate of the desired compound. A carbinolamine type structure was eliminated on the basis of a comparison of ultraviolet absorption with previously reported[7] data for pyridinium carbinolamines. The differences in melting point may be due to a variation in type of molecular association with water. It is difficult to specify the role of water in any exact fashion without infrared absorption data in solution or a knowledge of the geometrical disposition of the oxime function.

(7) E. J. Poziomek, D. N. Kramer, B. W. Fromm, and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961).

Anal. Calcd. for $C_8H_{11}ClN_2O \cdot H_2O$: C, 47.1; H, 6.4; Cl, 17.4; neut. equiv., 204. Found: C, 47.1; H, 6.4; Cl, 17.4; neut. equiv., 200; pK_a 4.0.

O-Methyl-6-methylpicolinaldehyde Oxime Hydroiodide (III).—The same procedure of anion conversion described for II was followed to give yellow needles, m.p. 150°. Ultraviolet spectrum: pH 1, λ_{max} 306 mμ, log ε 4.18; pH 7.0, λ_{max} 285, log ε 4.05; pH 14, λ_{max} 285, log ε 4.05.

Anal. Calcd. for $C_8H_{11}IN_2O \cdot 1/2H_2O$: C, 33.4; H, 4.2; I, 44.3; neut. equiv., 287. Found: C, 33.2; H, 4.6; I, 44.3; neut. equiv., 282.

1,6-Dimethyl-2-formylpyridinium Iodide Dimethyl Acetal (IV).—Freshly distilled (b.p. 76° at 10 mm.) 6-methylpicolinaldehyde (43 g., 0.36 mole) was dissolved in 100 ml. of methyl alcohol. Hydrogen chloride gas was passed for 20 min. through the refluxing solution. The cooled (ice water) pale yellow solution was added slowly to a saturated solution of potassium carbonate. Distillation of the red oil which separated gave 40.0 g. (67.5%) of the colorless acetal, b.p. 94–96° at 10 mm. This material was heated in a capped bottle for 15 hr. at 60° with 41 g. (0.28 mole) of methyl iodide. The reaction mixture was cooled and the supernatant liquid was decanted. The remaining yellow solid and red gum were dissolved in methyl alcohol. Ether was added to the point of cloudiness; cooling in a Dry Ice chest gave 19 g. (49%) of a yellow crystalline solid, m.p. 146–149°.

Anal. Calcd. for $C_{10}H_{16}INO_2$: C, 38.8; H, 5.2; N, 4.6. Found: C, 38.8; H, 5.1; N, 4.7.

1,6-Dimethyl-2-formylpyridinium Iodide Oxime (V).[8]—To 15 g. (0.049 mole) of V was added 90 ml. of 10% hydrochloric acid. The solution was refluxed for 90 min. and allowed to stand overnight. The pH was adjusted to 7.0 with sodium carbonate and a solution of hydroxylamine hydrochloride (7.0 g., 0.10 mole) and sodium hydroxide (4.0 g., 0.10 mole) in 25 ml. of water was added and the resulting mixture heated on a steam bath for 30 min. Upon cooling in a freezer, 4.5 g. of a pale yellow crystalline solid (m.p. 191–192° dec.) was obtained. Cooling overnight gave an additional 2.2 g. (total yield 49.5%). The compound was recrystallized from ethanol–ether to give yellow needles m.p. 212°. Ultraviolet spectrum: pH 1, λ_{max} 297 mμ, log ε 4.10; pH 7.0, λ_{max} 2.97, log ε 4.10; pH 14, λ_{max} 336, log ε 4.24.

Anal. Calcd. for $C_8H_{11}IN_2O$: C, 34.6; H, 4.0; I, 45.7; neut. equiv., 278. Found: C, 34.5; H, 4.1; I, 45.7; neut. equiv., 272; pK_a 8.1.

Acknowledgment.—We wish to express our gratitude to the Analytical Research Branch of the U.S. Army Chemical Research and Development Laboratories for the analyses here reported.

(8) The same procedure described for the preparation of VI was used to prepare O-methyl-1,6-dimethyl-2-formylpyridinium iodide oxime with the exception that O-methylhydroxylamine was used in place of the hydroxylamine. Yellow solid, 38%, m.p. 155°, calcd. for $C_9H_{13}IN_2O$: C, 37.0; H, 4.5; I, 43.3. Found: C, 36.8; H, 4.5; I, 43.7.

Thiolethylation of Amines with Ethylene Sulfide[1]

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The use of ethylene sulfide as a direct thiolethylation reagent has been extended to a variety of aliphatic amino compounds. Amines of varying polarity, diamines, and alkanolamines, have been thiolethylated without extensive polymer formation. The aminothiols were converted to the hydrochloride salts for characterization.

In the search for agents that offer chemical protection against radiation effects in animal tissue much interest has centered around 2-aminoethanethiol, its derivatives, and other aminothiols.[2,3] This paper reports the synthesis of a number of 2-mercaptoethylated amines and amino alcohols *via* thiolethylation with ethylene sulfide.

Several routes are available for the synthesis of 2-aminoethanethiols starting with S-blocked compounds using established procedures. Examples are the alkylation of amines with benzyl 2-chloroethyl sulfide,[4] followed by debenzylation[5]; and the amination of epoxides[6] and ethylenimines[7] with 2-(benzylthio)ethylamine, followed by debenzylation.[5]

$$RNH_2 \xrightarrow{ClCH_2CH_2SCH_2C_6H_5} RNHCH_2CH_2SCH_2C_6H_5 \xrightarrow[2.\ HCl]{1.\ Na/NH_3} RNHCH_2CH_2SH\cdot HCl$$

$$\underset{\diagdown O \diagup}{CH_2—CH_2} \xrightarrow{H_2NCH_2CH_2SCH_2C_6H_5} HOCH_2CH_2NHCH_2CH_2SCH_2C_6H_5 \xrightarrow[2.\ HCl]{1.\ Na/NH_3} HOCH_2CH_2NHCH_2CH_2SH\cdot HCl$$

$$\underset{\diagdown N \diagup \\ H}{CH_2—CH_2} \xrightarrow{H_2NCH_2CH_2SCH_2C_6H_5} H_2NCH_2CH_2NHCH_2CH_2SCH_2C_6H_5 \xrightarrow[2.\ HCl]{1.\ Na/NH_3} H_2NCH_2CH_2NHCH_2CH_2SH\cdot 2HCl$$

Direct thiolethylation of amines and amino

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2109.

(2) D. R. Kalkwarf, *Nucleonics*, **18**, 76 (1960), and references therein cited.

(3) A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958), and references therein cited.

(4) G. Cavallini and F. Ravenna, *Farmaco (Pavia) Ed. sci.*, **12**, 151 (1957).

(5) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 800 (1952).

(6) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, N. Y., 1950, p. 1, and references therein cited.

(7) L. B. Clapp, *J. Am. Chem. Soc.*, **70**, 184 (1948).