and the product was extracted with chloroform. Evaporation gave an oil which gave crystals from acetone–petroleum ether, 0.160 g., m.p. 85–95° (containing acetone of crystallization by infrared analysis). Two recrystallizations from ether–benzene gave the analytical sample, m.p. 128–130°, containing 1 mole of benzene of crystallization; λ_{max} 222 and 280 mμ (ε 7600 and 2280); $[\alpha]_D$ +27° (pyridine); ν_{max} 3420, 1620, and 678 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3 \cdot C_6H_6$ (382.54): C, 78.49; H, 8.96; OCH_3, 3.88. Found: C, 78.19; H, 8.72; OCH_3, 3.82.

15β-Cyanoestra-1,3,5(10)-trien-3,17β-diol (8b).—A solution of 15β-cyanoestra-1,3,5(10)-trien-3-ol-17-one (**7g**, 0.280 g.) and sodium borohydride (0.2 g.) in methanol–tetrahydrofuran (7:1, 40 ml.) was stirred at room temperature for 2 hr. Water was added and the product was collected by filtration to give 0.245 g., m.p. 280–282°. A sample for analysis was recrystallized twice from methanol, m.p. 284–286°; λ_{max} 222 and 280 mμ (ε 7500 and 2200); $[\alpha]_D$ ±0° (pyridine); ν_{max} 3460, 2250, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}O_2N$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.43; H, 7.96; N, 4.84.

4-Cyanoformyl-1-methylpyridinium Iodide Oxime and Derivatives

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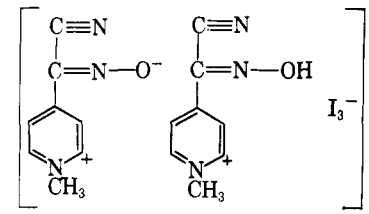
We wish to report on the synthesis of 4-cyanoformyl-1-methylpyridinium iodide oxime (I) and its derivatives, compounds which are more stable to light and oxygen than previously reported pyridinium oximes.

The synthesis of I was accomplished easily by the methylation of 4-pyridylglyoxylonitrile oxime. The glyoxylonitrile oxime was prepared either by isonitrosation of 4-pyridineacetonitrile or by reaction of potassium cyanide with isonicotinohydroxamic chloride.[3]

It was found that I with sodium ethoxide in ethanol or with concentrated ammonium hydroxide gave 4-cyanoformyl-1-methylpyridinium oximate (II). This conjugate base is soluble in water and slightly soluble generally in organic solvents.

4-Cyanoformyl-1-methylpyridinium cadmium triiodide oxime (III) was prepared from I and cadmium iodide in methanol. It was interesting to find that the residue obtained by evaporating the reaction mixture was *soluble* in ethyl ether. This important property may allow future investigations to be performed in other than a hydroxylic solvent.

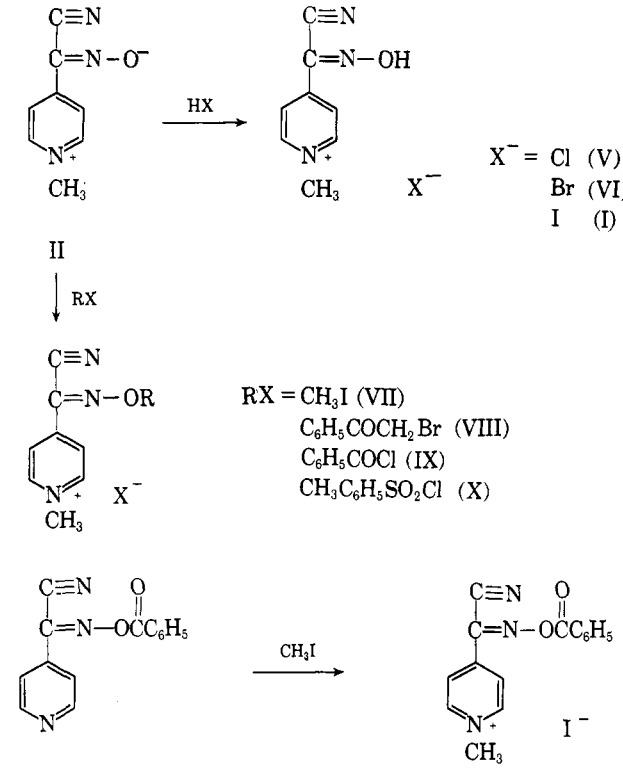
In previous experiences we found that quaternary heterocyclic aldoximes and ketoximes are not stable on exposure to intense ultraviolet light. Pyridinium aldoximates are especially sensitive to both oxygen and light.[4] Comparatively, aqueous solutions of I or II are stable to light and no precautions are needed in handling II in air. A 2% aqueous solution of I stored in quartz tubes for 7 months at 40° under intense ultraviolet light gave a solid which, on the basis of elemental analysis and a comparison of its infrared absorption spectrum to that of an authentic sample, was identified as the triiodide complex IV.



IV

The same complex was isolated when toluene was used in conjunction with methanol (methanol alone is a good solvent for recrystallizing I) in a recrystallization of I. The facile oxidation of iodide undoubtedly reflects a strong association of iodide with the pyridinium ring. It was shown that pyridinium iodide charge-transfer transitions involve an electron transfer to the pyridinium ring.[5] Toluene which is less polar than methanol probably allows a greater contribution of charge-transfer character. Consequently, the iodide should be more prone to radical formation and this would explain the oxidation. Multifold reactivity of tri(*p*-nitrophenyl)methyl derivatives was discussed similarly *vs.* solvent polarity by Kosower.[6] Appropriate light wave length also should promote radical formation.

The reaction of II with hydrochloric, hydrobromic, and hydroiodic acids gave 4-cyanoformyl-1-methylpyridinium chloride (V), bromide (VI), and iodide (I) oximes, respectively. When purifying I we found it more convenient to add hydrogen iodide to II rather than recrystallize crude I a number of times. (This is because of the iodide oxidation.)



(1) U. S. Army Chemical Research and Development Laboratories.
(2) Battelle Memorial Institute.
(3) E. J. Poziomek and A. R. Melvin, *J. Org. Chem.*, **26**, 3769 (1961).
(4) L. Larsson and G. Wallenberg, *Acta Chem. Scand.*, **16**, 788 (1962).
(5) E. M. Kosower, D. Hofmann, and K. Wallenfels, *J. Am. Chem. Soc.*, **84**, 2755 (1962).
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O-Methyl-4-cyanoformyl-1-methylpyridinium iodide oxime (VII) and O-benzoylmethyl-4-cyanoformyl-1-methylpyridinium bromide oxime (VIII) were prepared from II, and methyl iodide and bromoacetophenone, respectively. Similarly, O-benzoyl-(and O-tosyl-)4-cyanoformyl-1-methylpyridinium chloride oximes, IX (and X) were prepared from II and the corresponding acyl (and sulfonyl) chloride. Also, O-benzoyl-4-cyanoformyl-1-methylpyridinium iodide oxime (XI) was prepared by the methylation of 4-pyridylglyoxylonitrile oxime benzoate.

Charge-transfer absorption bands are very sensitive to small changes in the electron affinity of the ring. In view of the strong electron-withdrawing power of the glyoxylonitrile grouping and the iodide oxidation, the charge-transfer transition response of I and its derivatives to solvent changes should be very interesting.

The conjugate base (II) is only slightly soluble in organic solvents but its solutions vary in color from yellow to blue depending on solvent polarity. Pyridinium cyclopentadienylide solutions are colored similarly and the visible absorption bands were attributed to intramolecular transitions.[7] Electrolytic or chemical reduction of I and its derivatives lead to colors as was also observed in the preparation of stable pyridinyl radicals.[8]

The versatility and stability of I and its derivatives make it attractive to investigate quantitatively the various effects found and we plan to discuss future studies in subsequent publications.

Experimental

4-Cyanoformyl-1-methylpyridinium Iodide Oxime (I). Method A.—To a suspension of 14.7 g. (0.1 mole) of 4-pyridylglyoxylonitrile oxime in methanol was added 42.3 g. (0.3 mole) of methyl iodide. The mixture was refluxed until complete solution occurred (2–3 days). Ether was added to precipitate a yellow-orange solid. Recrystallization from ethanol–ether and drying in a 60° oven for 2 hr. gave 20.6 g. (71.2%) of a bright orange solid, m.p. 183–184° dec.

Anal. Calcd. for $C_8H_8IN_3O$: C, 33.2; H, 2.8. Found: C, 33.4; H, 2.9.

Method B.—To 20.0 g. (0.124 mole) of II suspended in 200 ml. of ethanol was added slowly 20 ml. of 52% hydroiodic acid. The solution was allowed to stir magnetically for 2 hr. and then filtered. The filtrate was allowed to warm on a steam bath and ether was added to the point of cloudiness. On cooling a yellow solid crystallized. One recrystallization from ethanol gave an over-all yield of 18.5 g. (51.6%), m.p. 185–187° dec.

Anal. Calcd. for $C_8H_8IN_3O$: C, 33.2; H, 2.8. Found: C, 33.4; H, 2.8.

The pK_a of I was determined by potentiometric titration to be 4.6. Using the method reported by Rosenblatt[9] and recording absorbance changes of the long wave-length band of maximum absorption with pH (342 mμ; pH, absorbance: 3.86, 0.061; 4.67, 0.231; 5.90, 0.410) we found a pK_a value of 4.59.

4-Cyanoformyl-1-methylpyridinium Oximate (II).—To 19.5 g. (0.07 mole) of I dissolved in the minimum amount of ethanol was added at 5–10° an equimolar solution of freshly prepared sodium ethoxide. In 30 sec. a reprecipitate formed. The mixture was filtered to give 10.1 g. (83%) of a crystalline dusty rose precipitate, m.p. 247–250° dec.

Anal. Calcd. for $C_8H_7N_3O \cdot {}^3/_4H_2O$: C, 55.0; H, 5.0; N, 24.1; neut. equiv., 175. Found: C, 55.0; H, 4.1; N, 24.1; neut. equiv., 180; pK_a 4.6.

The above synthesis was repeated to give a water-free product, m.p. 263–265° dec.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1; neut. equiv., 161. Found: C, 59.9; H, 4.5; N, 25.7; neut. equiv., 162.

Similarly, addition of I (50 g., 0.17 mole) to 200 ml. of concentrated ammonium hydroxide gave a precipitate of II, 24.4 g. (85.3%).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.6; H, 4.4. Found: C, 59.5; H, 4.3.

4-Cyanoformyl-1-methylpyridinium Cadmium Triiodide Oxime (III).—A 150-ml. methanolic solution of 2.9 g. of I and 3.7 g. (0.01 mole) of cadmium iodide was refluxed for 1 hr. on a steam bath. The solution was evaporated to dryness; the residue (completely ether soluble) was recrystallized from methanol to give 1.3 g. (20%) of a yellow solid, m.p. 110°.

Anal. Calcd. for $C_8H_5N_3OCdI_3$: C, 14.7; H, 1.2; N, 6.4; I, 58.1. Found: C, 14.7; H, 1.5; N, 6.3; I, 57.1.

4-Cyanoformyl-1-methylpyridinium Oximate, 4-Cyanoformyl-1-methylpyridinium Triiodide Oxime Complex (IV).—To 1.27 g. (0.005 mole) of iodine in 125 ml. of methanol was added 0.8 g. (0.005 mole) of II and 1.4 g. (0.005 mole) of I. The mixture was heated to boiling on a steam bath and cooled to room temperature. Filtration gave 2.8 g. (76%) of maroon-brown crystals, m.p. 193–195° dec.

Anal. Calcd. for $C_{16}H_{15}I_3N_6O_2 \cdot CH_3OH$: C, 27.7; H, 2.6; I, 51.7. Found: C, 28.2; H, 2.4; I, 51.7.

4-Cyanoformyl-1-methylpyridinium Chloride Oxime (V).—To a mixture of 3.0 g. (0.019 mole) of II in 50 ml. of methanol was added an equimolar amount of aqueous hydrogen chloride. Solution was effected immediately; ether was added to give a yellow oil. The oil was dissolved in methanol; addition of ether precipitated a pale yellow solid, m.p. 225–229° dec. The solid was dissolved in the minimum amount of methanol. The solution was refluxed with activated charcoal. Filtration followed by precipitation with ether gave 1.3 g. (33.6%) of a colorless solid, m.p. 229–233° dec.

Anal. Calcd. for $C_8H_8N_3OCl \cdot {}^1/_3H_2O$: C, 47.5; H, 4.2; N, 20.7. Found: C, 47.8; H, 4.0; N, 20.6.

4-Cyanoformyl-1-methylpyridinium Bromide Oxime (VI).—To a mixture of 1.9 g. (0.012 mole) of II in 50 ml. of methanol was added fuming hydrogen bromide dropwise until complete solution was evident. The colorless product, m.p. 247–252° dec., 1.35 g. (46.6%), was isolated and purified as described for V.

Anal. Calcd. for $C_8H_8BrN_3O$: C, 39.6; H, 3.3; Br, 33.3. Found: C, 40.1; H, 3.4; Br, 32.9.

O-Methyl-4-cyanoformyl-1-methylpyridinium Iodide Oxime (VII).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 13.5 g. (0.096 mole) of methyl iodide. The mixture was allowed to stand (stirred occasionally) until complete solution occurred (2 weeks). Ether was added and an hygroscopic orange solid was filtered The compound was spread on a porous plate and dried in a vacuum oven at 60°. The color changed to brick red, 5.3 g. (87.4%), m.p. 134–136° dec.

Anal. Calcd. for $C_9H_{10}IN_3O$: C, 35.6; H, 3.3; O, 5.2. Found: C, 35.2; H, 3.4; O, 5.2.

O-Benzoylmethyl-4-cyanoformyl-1-methylpyridinium Bromide Oxime (VIII).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 4.7 g. (0.024 mole) of bromoacetophenone. The mixture was allowed to stir and the product precipitated. More methanol was added and the mixture was warmed on a steam bath until solution took place. Ether was then added to the cooled solution to give 5.5 g. (76.4%) of a tan solid, m.p. 192–193° dec.

Anal. Calcd. for $C_{16}H_{14}BrN_3O_2$: C, 53.4; H, 4.0; Br, 22.2. Found: C, 53.1; H, 4.1; Br, 21.6.

O-Benzoyl-4-cyanoformyl-1-methylpyridinium Chloride Oxime (IX).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 2.8 g. (0.02 mole) of benzoyl chloride. The mixture was stirred until solution occurred, then 30 min. more. Ether was added to precipitate 6.4 g. of a colorless solid, m.p. 148–188° dec. Recrystallization from methanol–ether gave 5.0 g. (69.6%) of a colorless solid, m.p. 187–190° dec.; elemental analysis corresponded to an alcoholate of the desired benzoate ester.

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2 \cdot 1.8CH_3OH$: C, 56.1; H, 5.4. Found: C, 56.1; H, 4.9.

O-Tosyl-4-cyanoformyl-1-methylpyridinium Chloride Oxime (X).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 4.5 g. (0.024 mole) of *p*-toluenesulfonyl chloride. The mixture was stirred until solution occurred, then 30 min. more. Ether was added to precipitate a colorless solid which on recrystallization from methanol–ether gave 3.5 g. (42.5%) of

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colorless crystals, m.p. 169–171° dec. Elemental analyses corresponded to that of an alcoholate of the desired tosylate ester. An infrared absorption spectrum obtained in potassum bromide did not show a peak at 9.1 μ, the major absorption band of 4-cyanoformyl-1-methylpyridinium chloride oxime (V). This would eliminate the possibility that appreciable alcoholysis of *p*-toluenesulfonyl chloride occurred to give V as an impurity.

Anal. Calcd. for $C_{15}H_{14}ClN_3S\cdot 1.9CH_3OH$; C, 49.2; H, 5.2. Found: C, 49.2; H, 5.2.

O-Benzoyl-4-cyanoformyl-1-methylpyridinium Iodide Oxime XI.—To 1.0 g. (0.004 mole) of 4-pyridylglyoxylonitrile oxime benzoate[10] in 15 ml. of acetone was added 5 ml. of methyl iodide. The solution was allowed to stand for 2 days, then filtered to give 1.0 g. (63.6%) of orange-red needles, m.p. 137° dec.[1] An infrared absorption spectrum obtained in potassium bromide corresponded closely to that of IX.

Anal. Calcd. for $C_{15}H_{12}IN_3O_2$: C, 45.8; H, 3.1; I, 32.3. Found: C, 45.7; H, 3.2; I, 32.3.

Attempted Recrystallization of 4-Cyanoformyl-1-methylpyridinium Iodide Oxime from Benzene–Methanol and Toluene–Methanol.—To 1.0 g. of I dissolved in the minimum amount of hot methanol was added benzene dropwise until cloudiness was observed. The solution was kept hot during the addition. On allowing the solution to cool to room temperature an orange-brown solid precipitated, m.p. 184–189° dec.

Anal. Calcd. for $C_8H_8IN_3O\cdot C_6H_6$: I, 34.4; N, 11.4. Found: I, 34.4; N, 11.1.

The previous procedure was repeated using toluene to give XI, m.p. 193–196° dec. (an infrared absorption spectrum obtained in potassium bromide corresponded to this of an authentic sample of XI).

Anal. Calcd. for $C_{16}H_{15}I_3N_6O_2$: C, 27.3; H, 2.2; I, 54.1; N, 11.9. Found: C, 27.4; H, 2.4; I, 52.9; N, 11.9.

Synthesis of the benzene solvate was not reproducible and evidence for iodide oxidation also was obtained.

Acknowledgment.—Elemental analyses were performed by the Analytical Research Branch, U. S. Army Chemical Research and Development Laboratory.

(10) E. J. Poziomek, unpublished results.

Pyrano[2,3-*d*]- and Pyrido[2,3-*d*]pyrimidines

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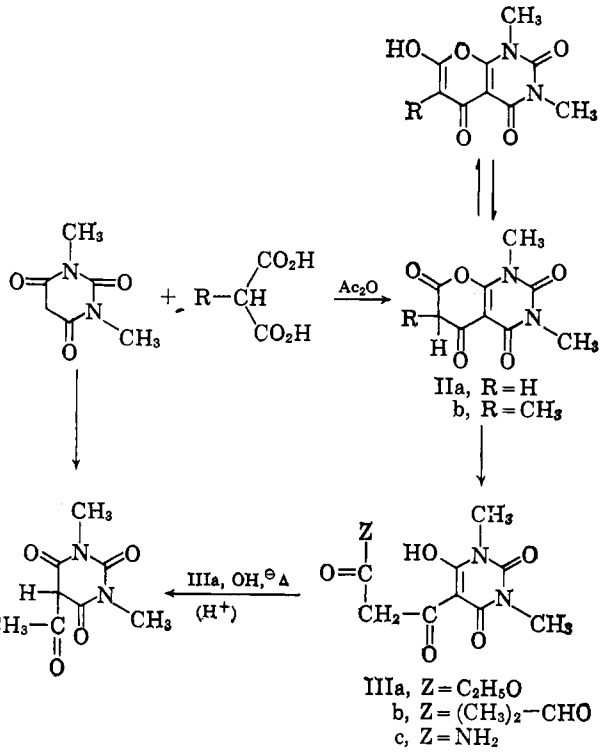
Pyrano[2,3-*d*]- and pyrido[2,3-*d*]pyrimidines in which the pyrano or pyrido ring incorporates an enolizable 1,3-dicarbonyl system have been investigated. These compounds were desired because of their acidic hydrogen which might be functionally analogous to that of the imidazole ring of xanthines.

The pyranopyrimidines were prepared by the condensation of malonic acid or methylmalonic acid with 1,3-dimethylbarbituric acid in the presence of acetic anhydride. A related 1,3-diphenyl-2-thiopyrano[2,3-*d*]pyrimidine has been prepared by the condensation of malonyl dichloride with 1,3-diphenyl-2-thiobarbituric acid.[1]

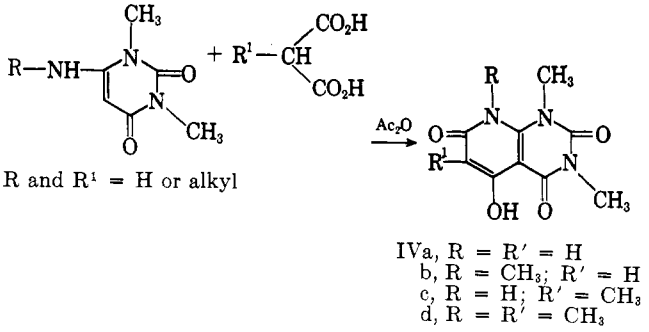
Earlier workers postulated the existence of compound IIa in rationalizing the isolation of IIIa accompanying the synthesis of 1,3-dimethylbarbituric acid.[1] We found that the lactone function of compound IIa was indeed chemically reactive although both IIa and IIb were hydrolytically stable during isolation.



Compound IIa reacted readily with ethanol to form IIIa and with isopropyl alcohol to form IIIb. The isopropyl ester IIIb also was obtained upon attempted recrystallization of IIa from isopropyl acetate. The reaction of IIa with aqueous ammonium hydroxide furnished the amide (IIIc). Compound IIa was precipitated unchanged after standing in 0.1 *N* aqueous sodium hydroxide at 25° for 0.5 hr. The compounds were insoluble in 10% aqueous sodium carbonate solution.

When the ester (IIIa) was heated with aqueous sodium hydroxide and the solution acidified, 5-acetyl-1,3-dimethylbarbituric acid was obtained in 90% yield. The latter was identical with the product obtained from the reaction of 1,3-dimethylbarbituric acid with acetic anhydride.

The pyridopyrimidines were obtained when 4-amino-1,3-dimethyluracils were acylated with malonic acid or alkyl malonic acids in the presence of acetic anhydride. These pyrido[2,3-*d*]pyrimidines (IV) are listed in Table I. Since this work was completed, compound IVa has been reported in 17% yield from a malonic acid preparation using phosphorus oxychloride as condensing agent.[3] No structural proof for IVa was presented.[3]



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