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(49) The intensity of the weak absorption band of *cis*-azobenzene is greater than that of the trans isomer in the visible spectrum (λ_{max} around 430 mμ) because of an electronic transition of the type N → A. This transition involves electrons localized in the azo group. The electronic transition which is associated with the polarized, excited state of azobenzene (and other azo dyes) is of the type N → V. The absorption band in the azobenzene isomers related to this N → V transition (which is generally responsible for the color of azo dyes) is of much greater intensity for *trans*-azobenzene. In simple azobenzene derivatives, however, this band is in the ultraviolet region; in more polar derivatives, the N → V transition is in the visible region and thus determines the color of the dye.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Ethyl *N*-Methyl-2-pyridone-4-carboxylate and Derivatives

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The alkaline potassium ferricyanide oxidation of *N*-alkylpyridinium salts has been used as a method for the preparation of 4-carboxy-*N*-methyl-2-pyridone which was converted into its ethyl ester and several other derivatives.

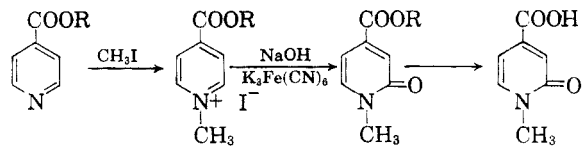
Although the 3-, 5-, and 6-, carboxy-*N*-methyl-2-pyridones have been reported in the literature,[2–5] we have found no report of *N*-methyl-4-carboxy-2-pyridone (I). The preparation of ethyl *N*-methyl-2-pyridone-4-carboxylate was undertaken in order to test the analgesic activity of this compound and several of its derivatives.

The alkaline potassium ferricyanide oxidation of *N*-methylpyridinium iodide to *N*-methyl-2-pyridone is a well established reaction.[6] Sugasawa and Suzuta[7] oxidized 1-(3,4-methylenedioxyphenethyl)-4-carbethoxypyridinium bromide with alkaline potassium ferricyanide to *N*-(3,4-methylenedioxyphenethyl)-4-carboxy-2-pyridone. M. L. Peterson[8] reported the alkaline ferricyanide oxidation of 2,5-dicarbomethoxy-*N*-methylpyridinium methosulfate and its betaine to *N*-methyl-5-carboxy-2-pyridone.

The alkaline ferricyanide oxidation of *N*-methyl-3-carboxamidopyridinium iodide has been widely studied. Most recently Pullman and Colowick[9] have demonstrated that both the 2- and 6-pyridones of *N*-methyl-3-pyridine carboxamide are formed upon oxidation.

Thyagarajan[10] has recently reviewed the alkaline potassium ferricyanide oxidation reaction.

The attempted alkaline potassium ferricyanide oxidation of both *N*-methyl-4-carboxypyridinium iodide and its betaine under the usual conditions[5,6] failed to yield any 2-pyridone, starting material being recovered. However the oxidation of the methiodides of isonicotinic acid esters were studied with greater success. The product isolated was the 4-carboxy-*N*-methyl-2-pyridone; the ester was never detected.



R = CH_3, CH_2CH_3, $CH(CH_3)_2$

It is generally accepted[10–12] that the oxidation takes place *via* the pseudo base. A more detailed postulation of the mechanism of the ferricyanide oxidation of *N*-alkylpyridinium hydroxides to form *N*-alkyl-2-pyridones is proposed by Bradlow and Vanderwerf.[13]

The yield of *N*-methyl-4-carboxy-2-pyridone depended on the rate of addition of the reagents to the reaction mixture. The sodium hydroxide solution was added to a concentrated aqueous solution

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of the pyridinium iodide at twice the rate of addition of the potassium ferricyanide solution. By decreasing the amount of pyridinium iodide used and keeping the rate of addition of reagents constant, the yield of 2-pyridone was increased from 46% to 96%.

When the addition time was kept constant, larger yields were obtained from the higher esters: 80% yield from the oxidation of *N*-methyl-4-carboisopropoxypyridinium iodide, 62% yield from *N* - methyl - 4 - carboethoxypyridinium iodide, and 46% from the oxidation of *N*-methyl-4-carbomethoxypryidinium iodide. The possibility of obtaining a quantitative yield from the oxidation of each of the pyridinium iodides would be greatly enhanced by adding the reagents over a period of several days.

Ethyl *N*-methyl-2-pyridone-4-carboxylate and *N*-methyl-2-pyridone-4-carboxamide were prepared from the acid *via* *N*-methyl-2-pyridone-4-carboxylic acid chloride and *N*-methyl-2-pyridone-4-carboxylic acid hydrazide was synthesized from the ester in the usual manner.

EXPERIMENTAL[14]

Oxidation of N-methyl-4-carbomethoxypyridinium iodide. *N* - Methyl - 4 - carbomethoxypyridinium iodide,[15] 2.00 g. (0.0073*M*), dissolved in water (10 ml.), was placed in an Erlenmeyer flask. Solutions of sodium hydroxide, 4.0 ml. (1.68 g., 0.242*M* in 3 ml. of water), and potassium ferricyanide, 12 ml. (4.8 g., 0.019*M* in 8 ml. of hot water), were prepared. At one-hour intervals, 1.0-ml. portions of sodium hydroxide and 1.5-ml. portions of potassium ferricyanide were added to the pyridinium salt solution with agitation after each addition. The heat of the reaction kept the mixture slightly above room temperature. The potassium ferricyanide solution was added warm to prevent precipitation. After the addition of the final 1.5-ml. portion of potassium ferricyanide, the reaction mixture was kept warm (40–55°) on a steam bath for 1 hr., then cooled and acidified with 6*N* hydrochloric acid. Granular crystals precipitated and were removed by filtration. Recrystallization from hot methanol yielded *N*-methyl-4-carboxy-2-pyridone, 1.05 g. (96%), m.p. 254–254.5°.

Anal. Calcd.: C, 54.91; H, 4.61; N, 9.15. Found: C, 54.80; H, 4.81; N, 9.07.

When this reaction was carried out on 25 and 50 g. samples of *N*-methyl-4-carbomethoxypyridinium iodide, yields of only 50% could be attained.

The oxidation of both *N*-methyl-4-carboxypyridinium iodide and the betaine of *N*-methyl-4-carboxypyridine[16] with alkaline potassium ferricyanide failed to give *N*-methyl-4-carboxy-2-pyridone.

Isopropyl isonicotinate. Isonicotinic acid, 20.0 g. (0.162*M*), was refluxed with thionyl chloride (80 ml.) for 0.5 hr. The excess thionyl chloride was removed *in vacuo* and isopropyl alcohol, 100 g. (1.66*M*), added; the reaction mixture was refluxed for 3 hr. Crystallization began upon cooling. After standing at room temperature overnight, the isopropyl isonicotinate hydrochloride was collected on a filter, washed with 50% isopropyl alcohol–ether followed by ether and dried; 26.5 g. (0.13*M*, 82%), m.p. 186–187° dec.

Isopropyl isonicotinate hydrochloride was converted to the free base by neutralization in aqueous solution with calcium carbonate, extraction with ether and distillation; b.p. 94–104° (7 mm.), 13.0 g. (60%). A sample for analysis was redistilled, b.p. 94° (3 mm.).

Anal. Calcd.: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.08; H, 6.64; N, 8.40.

The attempted preparation of *t*-butyl isonicotinate using this same procedure was unsuccessful.

N-methyl-4-carboisopropoxypyridinium iodide. A 95% yield of *N*-methyl-4-carboisopropoxypyridinium iodide, m.p. 139–141° (recrystallized from absolute ethanol–ether), was obtained according to the method of Supniewski and Serafinowna.[15]

Anal. Calcd.: C, 39.10; H, 4.59; N, 4.55; I, 41.32. Found: C, 38.91; H, 4.72; N, 4.42; I, 41.35.

Oxidation of N-methyl-4-carboisopropoxypyridinium iodide. The alkaline potassium ferricyanide oxidation of this pyridinium salt was carried out as before to give an 80% yield of *N*-methyl-4-carboxy-2-pyridone.

Oxidation of N-methyl-4-carboethoxypyridinium iodide. N-Methyl-4-carboethoxypyridinium iodide, m.p. 110–113° (made in 89% yield as indicated for the isopropyl ester) was oxidized by the general procedure described for the methyl ester to give a 62% yield of *N*-methyl-4-carboxy-2-pyridone.

N-Methyl-2-pyridone-4-carboxylic acid chloride. *N*-Methyl-4-carboxy-2-pyridone, 1.0 g. (0.065*M*), and purified thionyl chloride,[17] 16.3 g. (10 ml., 0.137*M*), were warmed at 55–60° for 1.5 hr. and the excess thionyl chloride was then removed by vacuum distillation. The crude acyl chloride crystallized upon cooling and was used as such in the following reaction.

Ethyl N-Methyl-2-pyridone-4-carboxylate. This acid chloride and absolute ethanol, 15.8 g. (20 ml., 0.344*M*), were refluxed for 2 hr. The excess ethanol was removed by vacuum distillation and the residue, insoluble in ether, was taken up in 50 ml. of chloroform, washed twice with 20-ml. portions of 0.5*N* sodium carbonate, and the organic layer dried over anhydrous magnesium sulfate. The chloroform was removed *in vacuo*, care being taken not to overheat the oily residue. Upon cooling, the oil crystallized and was recrystallized from 30 ml. of anhydrous ether. Ethyl *N*-methyl-2-pyridone-4-carboxylate, 1.0 g. (83%), m.p. 89°, was obtained as luminous, white crystals which were insoluble in *n*-hexane and soluble in water, dioxane, and ethanol.

Anal. Calcd.: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.64; H, 5.90; N, 7.64.

N-Methyl-2-pyridone-4-carboxylic acid hydrazide. A solution of ethyl *N*-methyl-2-pyridone-4-carboxylate, 1.0 g. (0.005*M*), in ethanol (2 ml.) and 95 hydrazine hydrate, 0.5 g. (0.01*M*), was warmed on a steam bath for 15 min. The hydrazide which crystallized upon cooling, was recrystallized twice from hot water; 0.74 g. (67%), m.p. 258–260°.

Anal. Calcd.: C, 50.29; H, 5.42; N, 25.14. Found: C, 50.33; H, 5.37; N, 25.32.

N-Methyl-2-pyridone-4-carboxamide. *N*-Methyl-4-carboxy-2-pyridone, 15.0 g. (0.98*M*), was converted to the acid chloride with thionyl chloride and was added slowly as the warm molten liquid to a vigorously stirred solution of concentrated ammonium hydroxide, 250 ml., over a period of 2.5 hr. The reaction mixture was then stirred on a steam bath for 1 hr. and evaporated to dryness under vacuum. The residue was extracted three times with 50-ml. portions

(14) All melting points are uncorrected. Microanalyses by Microchemical Specialties Co., Berkeley, Calif. The infrared spectra of each compound was taken and found to be compatible with the structures reported.

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of boiling methanol and the combined methanol extracts were cooled and filtered to recover the crude amide, which was recrystallized twice from methanol; 4.2 g. (28%) m.p. 234–36°.

Anal. Calcd.: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.45; H, 5.07; N, 18.05.

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STANFORD, CALIF.

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

2-Trifluoromethylpyrimidines[1]

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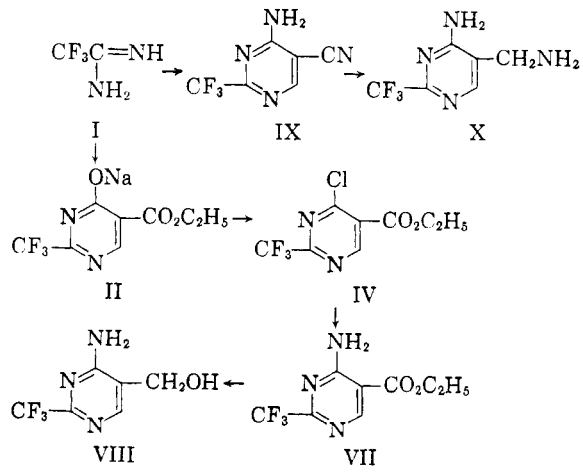
A series of 2-trifluoromethylpyrimidines has been synthesized from trifluoroacetamidine. Included was 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine which showed biological activity.

The discovery of 5-hydroxymethylcytosine in the deoxyribonucleic acid of the T-even bacteriophages of *Escherichia coli*[3a,b] is largely responsible for recent interest in related pyrimidines. The subsequent synthesis of this[4a,b] and other 5-hydroxymethylpyrimidines has led to compounds with interesting biological activity. Ulbricht and Price,[5] for example, have synthesized 4-amino-5-hydroxymethyl-2-methylthiopyrimidine (Methioprim) which has received some attention.[6]

It has been noted[7] that amethopterin-resistant mutants of *Bacillus subtilis* are collaterally sensitive to certain 2-substituted-4-amino-5-(substituted methyl)pyrimidines. The reversal of this inhibition by 4-amino-5-hydroxymethyl-2-methylpyrimidine suggested that these compounds are thiamine pyrimidine antagonists in this organism. Furthermore, since amethopterin is used clinically in cancer chemotherapy it was of interest to investigate further those pyrimidines related to the thiamin pyrimidine.

It is well known that there is a large difference in the electronic effect of the trifluoromethyl group and the methyl group but not a large difference in size. Since this type of substitution can lead to different biological activity, some 2-trifluoromethyl analogs of the thiamin pyrimidine were synthesized. Among the compounds prepared were 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (VIII) and 4-amino-5-aminomethyl-2-trifluoromethylpyrimidine (X). Because the reaction of acetamidine with (1) diethyl ethoxymethylenemalonate,[8] (2) ethoxymethylenemalononitrile,[9] and (3) ethyl ethoxymethylenecyanoacetate[8,10] had led to pyrimidines, these three routes were investigated with trifluoroacetamidine (I)[11,12] as starting material.

Diethyl ethoxymethylenemalonate was condensed with I in the presence of sodium ethoxide to form 5-carbethoxy-2-trifluoromethyl-4-hydroxypyrimidine (III). This was converted to 5-carbethoxy-4-chloro-2-trifluoromethylpyrimidine (IV). Low yields of IV were obtained from III but its sodium salt (II), obtained directly from the condensation, gave IV in 56% yield when treated with phosphorus oxychloride. This procedure is similar



(1) Supported by a research grant, G5619, from the National Science Foundation and in part by a grant, CY-2857(C1), from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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