Bridgehead Nitrogen Heterocycles. VI. The Reaction of 1-Amino- and 1,2-Diaminopyridinium Salts with β-Dicarbonyl Compounds (1)

K. T. Potts, R. Dugas (1d) and C. R. Surapaneni

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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1,2-Diaminopyridinium iodide underwent reaction with ethyl acetoacetate to form 1,4-dihydro-2-methyl-4-oxopyrido[1,2-*a*]pyrimidin-1-ium iodide, and with acetyl acetone it gave 2,4-dimethylpyrido[1,2-*a*]pyrimidin-5-ium iodide. Though 2-acetylcyclohexanone gave the corresponding 5-methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-11-ium iodide, no reaction was observed with 2,6-dimethyl-3,5-heptanedione, 1-benzoylacetone, 1,3-diphenyl-1,3-propanedione and its *p*-methoxyphenyl derivative. However, 1-aminopyridinium iodide and acetyl acetone in the presence of base gave 3-acetyl-2-methylpyrazolo[1,5-*a*]pyridine and 1-amino-2-methylpyridinium iodide yielded the corresponding 3-acetyl-2,7-dimethylpyrazolo[1,5-*a*]pyridine. With ethyl acetoacetate, the latter salt formed 3-ethoxycarbonyl-2,7-dimethylpyrazolo-[1,5-*a*]pyridine but with 2,6-dimethyl substituents in the pyridine ring no condensation occurred. Reaction of 1-amino-2-methylpyridinium iodide with benzaldehyde gave *N*-benzalimino-2-methylpyridinium iodide which, on treatment with base, resulted in the formation of 2-picoline and benzonitrile, providing a convenient method of deamination.

In earlier studies of bridgehead nitrogen heterocycles it was shown that reaction of 1,2-diaminopyridinium iodide with acid chlorides or carboxylic acids was a particularly efficient route for the synthesis of *s*-triazolo[1,5-*a*]-pyridines (2a). Similarly, the reaction of 1-amino-2-alkylpyridinium salts with acyl chlorides in pyridine afforded a new, convenient synthesis of various pyrazolo-[1,5-*a*]pyridine derivatives (2b). In an extension of these studies, we now describe the reactions of 1-amino- and 1,2-diaminopyridinium iodides with β-ketoesters and β-diketones.

The reaction of 1,2-diaminopyridinium iodide (**1**; R = NH_2) with ethyl acetoacetate in pyridine gave a well-defined, crystalline product containing iodide ion, m.p. 250-253°, and it could be readily converted into the corresponding chloride, picrate and perchlorate. Use of a methanol reaction medium containing 10% aqueous sodium hydroxide also gave the same product. Ammonia and formaldehyde (characterized as its 2,4-dinitrophenylhydrazone) were detected in the methanolic reaction medium. This characteristic, together with the analytical and spectral data, indicated the structure of the reaction product to be 1,4-dihydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium iodide (**2**; X = I).

This same compound was obtained in 90% yield from 2-aminopyridinium iodide and ethyl acetoacetate. In the condensation of 2-aminopyridine with β-dicarbonyl compounds ambiguity in the structure of the product formed results from the several reaction sites. The following transformations provide confirmatory evidence for structure (**2**) above.

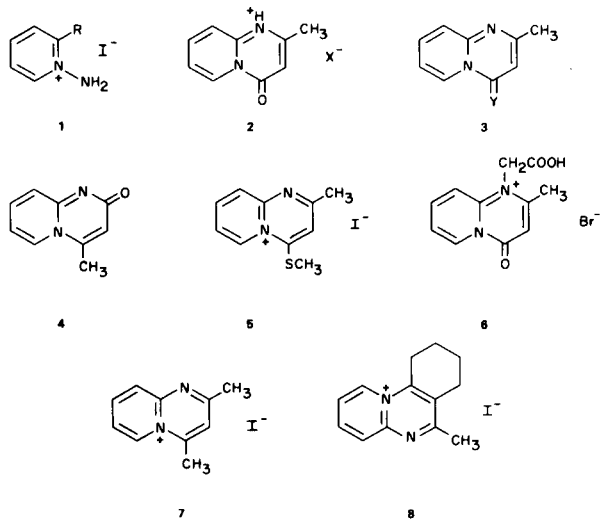
Oxidation of this iodide (**2**; X = I) with hot potassium permanganate solution gave 6-hydroxy-4-methylpyrimidine hydrochloride. This clearly shows the arrangement of the substituents in the precursor, in particular the location of the methyl group. The salt (**2**; X = I) was stable to hot, 10% hydrochloric acid over 2 hours. No hydrolysis product was detected, only exchange of the anion occurring. These reactions are consistent with those reported for other derivatives of this ring system (3a) which have been prepared recently (3b) from several 2-aminopyridine derivatives and methyl β-aminocrotonate.

It was possible to relate the product (**2**; X = I) with one of established structure. Treatment of 1,4-dihydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium iodide (**2**; X = I) with sodium hydroxide solution readily gave the known 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3**; Y = O), formed by condensation of 2-aminopyridine and ethyl acetoacetate. In this last reaction, condensation in the alternative sense would give rise to 4-methyl-2*H*-pyrido-[1,2-*a*]pyrimidin-2-one (**4**). This was excluded by the synthesis of the 4-methyl compound from 2-aminopyridine and ethyl tetrolate, and the spectral characteristics of this compound, especially the ultraviolet absorption spectrum and the chemical shift of the 6-proton (see Experimental section) are consistent with this structure.

Reaction of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3**; Y = O) with phosphorus pentasulfide in pyridine gave the corresponding thione (**3**; Y = S). Analytical and spectral data (5,6) were again consistent with the assigned structure. The thione was further characterized by reaction with methyl iodide, with which it readily formed a quaternary salt whose properties were consistent (6) with the structure (**5**).

Several other reactions of 2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one are of interest and are described here. With bromoacetic acid in methanol, 1,4-dihydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium bromide (**2**; X = Br) was obtained. However, when anhydrous ether was used as the solvent, 1-carboxymethylene-1,4-dihydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium bromide (6) was formed.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was quite stable to lithium aluminum hydride in ether solution or sodium borohydride over long reaction periods. An unsuccessful attempt to reduce 4-quinolizone with lithium aluminum hydride has also been reported (5).



The reaction of 1,2-diaminopyridinium iodide with acetylacetone proceeded smoothly in pyridine or in methanol in the presence of base. Under the latter conditions, ammonia and formaldehyde were again generated in the reaction mixture. Analytical and spectral characteristics (6,7) established the structure of this product as 2,4-dimethylpyrido[1,2-*a*]pyrimidin-5-ium iodide (**7**). An alternative synthesis from 2-aminopyridinium iodide and acetylacetone in the presence of pyridine confirmed the above structure.

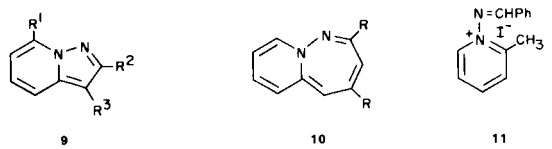
2,4-Dimethylpyrido[1,2-*a*]pyrimidin-5-ium iodide was not hydrolyzed by hot hydrochloric acid over 2 hours and the use of alkaline conditions resulted in deep-seated decomposition. Oxidation with potassium permanganate gave 2-acetamidopyridine hydrochloride, consistent with the assigned structure.

Similarly, the reaction of 1,2-diaminopyridinium iodide with 2-acetylcyclohexanone in pyridine gave 5-methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-11-ium iodide (**8**) as a well-defined crystalline product, m.p. 245° dec. Analytical and spectral data (6) were consistent with the assigned structure. The same product was obtained from 2-aminopyridinium iodide and 2-acetylcyclohexanone in pyridine. On oxidation with potassium permanganate the above iodide gave 2-acetamidopyridine hydrochloride, consistent with the structure (**8**).

Reaction of 1,2-diaminopyridinium iodide with 2,6-dimethyl-3,5-heptanedione in methanol and in the presence of 10% sodium hydroxide solution or in pyridine was unsuccessful. Similarly, no condensation of the salt occurred with 1,3-diphenyl-1,3-propanedione, 1-benzoylacetone and 1,3-bis(*p*-methoxyphenyl)-1,3-propanedione.

In the above reactions it appears that the 1,2-diaminopyridinium iodide is undergoing an initial decomposition to 2-aminopyridinium iodide and that it is the latter salt which is undergoing condensation with the β-dicarbonyl compounds. In support of this, it was found that when 1,2-diaminopyridinium iodide was heated under reflux under comparable reaction conditions, 2-aminopyridinium iodide was isolated from the reaction. This reaction pathway should be contrasted with that of 2,3-diaminopyridine with β-ketoesters from which the corresponding diazepine is obtained (8).

Condensation of 1-amino-2-methylpyridinium iodide (2) (**1**; R = CH_3) with ethyl acetoacetate occurred readily in aqueous medium in the presence of potassium carbonate. Analytical data indicated a molecular formula of $C_{12}H_{14}N_2O_2$ for the product, consistent with its formulation as 3-ethoxycarbonyl-2,7-dimethylpyrazolo-[1,5-*a*]pyridine (**9c**). Spectroscopic data (2,9) were in accord with this structure which was established unambiguously by its synthesis from the pyridinium salt (**1**; R = CH_3) and ethyl tetrolate (10).



a: R^1 = H; R^2 = CH_3; R^3 = $COCH_3$
b: R^1 = R^2 = CH_3; R^3 = $COCH_3$
c: R^1 = R^2 = CH_3; R^3 = COOEt

Condensation of the pyridinium salts (**1**; R = H and CH_3) with acetyl acetone occurred in a similar fashion either in pyridine or in aqueous solution, with the formation of 3-acetyl-2-methylpyrazolo[1,5-*a*]pyridine

(**9a**) and 3-acetyl-2,7-dimethylpyrazolo[1,5-*a*]pyridine (**9b**). These products were also obtained by reaction of the appropriate pyridinium salts (**1**) with excess of acetyl chloride in pyridine (2b).

That the bicyclic system (**9**) is formed in these condensations rather than the alternative pyrido[1,2-*b*][1,2]-diazepine (**10**) is no doubt due to the greater acidity of the methylene hydrogens of the β-dicarbonyl systems compared to those of the α-methyl groups of the pyridinium nucleus. As the reaction is carried out under alkaline conditions, the resultant carbanion undergoes reaction at the electron deficient α-pyridine position.

Finally the reaction of 1-amino-2-methylpyridinium iodide with benzaldehyde provided a facile method for deamination of 1-aminopyridinium salts. The reaction gave 1-*N*-benzalimino-2-methylpyridinium iodide (**11**). Treatment of **11** with base gave 2-picoline and benzonitrile. This reaction is analogous to that described by Boekelheide (11), for the deoxygenation of the appropriate pyridine *N*-oxides.

EXPERIMENTAL (12)

1,4-Dihydro-2-methyl-4-oxopyrido[1,2-*a*]pyrimidin-1-ium Iodide (A).

1,2-Diaminopyridinium iodide (2a) (4.8 g., 0.02 mole) was dissolved in methanol (25 ml.) and sodium hydroxide (0.8 g., 0.02 mole, 10% solution) followed by ethyl acetoacetate (13.0 g., 0.1 mole) were added. The reaction mixture was refluxed for 63 hours in a nitrogen atmosphere, the effluent gas stream being passed into a freshly prepared solution of 2,4-dinitrophenylhydrazine. The 2,4-dinitrophenylhydrazone of formaldehyde was obtained as yellow precipitate, m.p. 168° which on recrystallization from ethanol gave yellow needles: m.p. 168° [lit. (13) m.p. 168°]. Ammonia was also found in this gas stream.

The reaction mixture was cooled, the solvent and excess ethyl acetoacetate were removed, and the residue, after several crystallizations from ethanol, afforded colorless needles: 1.1 g. (20%), m.p. 250-253°; ir (potassium bromide): 3100-2500 (=NH-), 1700 (>C=O), 1620 (>C=N-), 1500 (aromatic) cm^{-1}; uv λ max (methanol): 335 nm (log ε 4.00), 252 sh (3.91), 243 sh (4.00), 215 (4.39), 200 (4.58); nmr (deuterium oxide): δ 2.50 (s, 3, C-CH_3), 6.52 (s, 1, H-3), 7.83 (q, 2, H-7, H-8), 8.36 (t, 1, H-9), 9.06 (d, 1, H-6); mass spectrum m/e (rel. intensity) 160(100) (*M*-HI), 159(8), 145(5), 133(6), 132(80), 131(57), 105(5), 104(4), 79(22), 78(70), 76(5), 67(5), 64(5), 52(16), 51(40), 50(6).

Anal. Calcd. for $C_9H_9IN_2O$: C, 37.51; H, 3.13; N, 9.72; I, 44.10. Found: C, 37.47; H, 3.26; N, 9.83; I, 44.26.

When pyridine was used as solvent and the reaction mixture worked up as above, colorless needles of the above product were also obtained: 1.2 g. (20%), m.p. 250-253°.

B.

2-Aminopyridinium iodide (0.44 g., 0.002 mole) in pyridine (15 ml.) was treated with ethyl acetoacetate (0.52 g., 0.004 mole) and the mixture refluxed for 4 hours. Excess pyridine was removed, and the residue recrystallized from ethanol: 0.52 g. (90%), m.p. 250-253°.

The picrate crystallized from ethanol as yellow needles: m.p. 186°.

Anal. Calcd. for $C_{15}H_{11}N_5O_8$: C, 46.28; H, 2.83; N, 18.00. Found: C, 46.52; H, 2.75; N, 18.22.

The perchlorate crystallized from ethanol:ether as colorless needles: m.p. 200°; ir (potassium bromide): 3270 (-NH-), 3250-2500 (-NH-), 1750 (>C=O), 1650 (>C=N-), 1510 (aromatic) cm^{-1}; uv λ max (methanol): 335 nm (log ε 3.95), 252 sh (3.88), 244 sh (3.92), 210 sh (4.11), 200 (4.50); nmr (DMSO-d_6) δ 2.50 (s, 3, C-CH_3), 5.83 (broad, 1, NH), 6.47 (s, 1, H-3), 7.75 (q, 2, H-7, H-8), 8.33 (t, 1, H-9), 9.06 (d, 1, H-6).

Anal. Calcd. for $C_9H_9ClN_2O_5$: C, 41.46; H, 3.45; N, 10.75. Found: C, 41.36; H, 3.48; N, 10.69.

The chloride, prepared from the iodide and hydrochloric acid, was purified by sublimation *in vacuo* (160°/0.1 mm), forming cream irregular prisms: 0.6 g. (88%), m.p. 310°; ir (potassium bromide): 3050 (aromatic), 2800-2300 (=$\overset{+}{N}$H-), 1730 (>C=O), 1650 (>C=N-), 1500 (aromatic) cm^{-1}; uv λ max (methanol): 335 nm (log ε 3.87), 252 sh (3.85), 245 sh (3.88), 215 sh (4.24), 205 sh (4.44), 202 (4.48); nmr (deuterium oxide): δ 2.67 (s, 3, C-CH_3), 6.60 (s, 1, H-3), 7.90 (q, 2, H-7, H-8), 8.55 (t, 1, H-9), 9.25 (d, 1, H-6).

Anal. Calcd. for $C_9H_9ClN_2O$: C, 54.95; H, 4.58; N, 14.25. Found: C, 55.09; H, 4.71; N, 13.94.

These salts were identical in all respects with those obtained from 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and the appropriate acid.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

1,4-Dihydro-2-methyl-4-oxopyrido[1,2-*a*]pyrimidin-1-ium iodide (1.0 g.) was treated with warm sodium hydroxide solution (20 ml., 10%). The aqueous solution was extracted with ether, the ether layer dried (sodium sulfate), and then evaporated to dryness. The residue, after recrystallization from benzene:petroleum ether, afforded colorless needles: 0.44 g. (80%), m.p. 122° [lit. (4), m.p. 122°]; ir (potassium bromide), 3100 (aromatic), 3040 (aromatic), 1700 (>C=O), 1630 (>C=N-), 1525 (aromatic) cm^{-1}; uv λ max (methanol): 335 nm (log ε 3.97), 250 (3.95), 244 (4.01), 235 (3.98), 210 sh (4.22), 200 (4.40); nmr (deuteriochloroform): δ 2.50 (s, 3, C-CH_3), 6.36 (s, 1, H-3), 7.16 (d, 1, H-9), 7.66 (d, 2, H-7, H-8), 9.05 (d, 1, H-6); mass spectrum m/e (rel. intensity) 160(100) (M^+), 159(8), 145(5), 133(6), 132(80), 131(57), 105(6), 104(5), 79(22), 78(70), 76(5), 67(5), 66(5), 64(5), 52(16), 51(40), 50(6).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03. Found: C, 67.05; H, 5.13.

Potassium Permanganate Oxidation of 1,4-Dihydro-2-methyl-4-oxopyrido[1,2-*a*]pyrimidin-1-ium Iodide.

The iodide (2.9 g., 0.01 mole) was dissolved in water (250 ml.) and potassium permanganate (15.0 g.) in water (500 ml.) was added, the reaction mixture being heated at 50-60° for 2 hours. On cooling to room temperature, methanol was added to remove excess potassium permanganate and the manganese dioxide filtered. The filtrate was evaporated to dryness and the residue was extracted with absolute alcohol. The alcohol extract was acidified with dilute hydrochloric acid, inorganic material filtered and the filtrate was then evaporated and the residue was recrystallized from ethanol giving colorless needles of 6-hydroxy-4-methylpyrimidine hydrochloride, purified further by sublimation *in vacuo* (140°/0.1 mm), forming colorless needles: 1.0 g. (65%), m.p. 213°; ir (potassium bromide): 3150 (aromatic), 3050 (aromatic), 2900-2400 (=NH-), 1710 (>C=O), 1660 (>C=N-), 1560 (aromatic) cm^{-1}; mass spectrum m/e (rel. intensity)

110(52) (*M*-HCl), 82(5), 81(8), 68(9), 55(7), 42(57).

This product was identical in all respects with a sample of 6-hydroxy-4-methylpyrimidine hydrochloride prepared from 6-hydroxy-4-methylpyrimidine and hydrogen chloride.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (1.6 g., 0.01 mole), pyridine (50 ml.) and phosphorus pentasulfide (2.2 g.) were refluxed for 14 hours. The reaction mixture was cooled, poured into ice water and extracted with ether. The ether layer was collected, dried (magnesium sulfate) and evaporated to dryness under reduced pressure. The product was purified by chromatography on silica gel, using benzene as eluent. Recrystallization from benzene:petroleum ether afforded yellow needles of the thione: 1.4 g. (80%), m.p. 158°; uv λ max (methanol): 380 nm (log ε 4.42), 280 sh (4.43), 271 (4.36), 220 (4.73), 206 (4.58); nmr (deuteriochloroform): δ 2.50 (s, 3, C-CH_3), 8.0 (m, 5, H-3, H-6, H-7, H-8, H-9); mass spectrum m/e (rel. intensity) 176(100) (M^+), 133(13), 132(90), 131(20), 119(10), 79(18), 78(40), 52(17), 51(12), 50(10).

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.26; H, 4.57; N, 15.79.

2-Methyl-4-methylthiopyrido[1,2-*a*]pyrimidin-5-ium Iodide.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (1.76 g., 0.01 mole) was dissolved in benzene and methyl iodide (5 ml.) was added. After standing at room temperature overnight, the product separated and was collected and recrystallized from ethanol, forming yellow irregular prisms: 2.7 g. (85%), m.p. 213-220° dec.; ir (potassium bromide): 3000 (aromatic), 1640 (>C=N-), 1600 (aromatic), 1560 (aromatic) cm^{-1}; uv λ max (methanol): 325 nm (log ε 4.30), 312 (4.18), 280 (3.78), 223 (4.77), 206 (4.68); nmr (D_2O) δ 2.81 (s, 3, C-CH_3), 2.94 (s, 3, S-CH_3), 8.33 (m, 5, H-3, H-6, H-7, H-8, H-9).

Anal. Calcd. for $C_{10}H_{11}IN_2S$: C, 37.74; H, 3.46; N, 8.81. Found: C, 37.69; H, 3.39; N, 8.70.

Reaction of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with Bromoacetic Acid.

The pyrimidin-4-one (1.6 g., 0.01 mole) in anhydrous ether (30 ml.) and bromoacetic acid (1.4 g., 0.01 mole) were refluxed for 4 hours. The ether was removed and the residue recrystallized from benzene:petroleum ether, affording colorless needles of 1-carboxymethylene-1,4-dihydro-2-methyl-4-oxopyrido[1,2-*a*]-pyrimidin-1-ium bromide: 1.9 g. (63%), m.p. 85-87°; ir (potassium bromide): 3100 (aromatic), 2600-2100 (=$\overset{+}{N}$<), 1730 (>C=O), 1650 (>C=N-), 1600 (aromatic), 1550 (aromatic) cm^{-1}; uv λ max (methanol): 335 nm (log ε 4.32), 252(5.25), 245(4.30), 230 sh (4.34), 212 sh (4.61), 201 (4.85); nmr (deuterium oxide): δ 2.50 (s, 3, C-CH_3), 3.85 (s, 2, -CH_2-), 6.38 (s, 1, H-3), 7.66 (t, 2, H-7, H-8), 8.16 (t, 1, H-9), 9.00 (d, 1, H-6).

Anal. Calcd. for $C_{11}H_{11}BrN_2O_3$: C, 44.15; H, 3.68; N, 9.36. Found: C, 44.33; H, 3.75; N, 9.51.

4-Methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one.

A mixture of 2-aminopyridine (4.7 g., 0.05 mole) in ether (150 ml.) and ethyl tetrolate (5.6 g., 0.05 mole), after standing overnight, gave a product that crystallized from chloroform: petroleum ether as colorless needles: 2.4 g. (30%), m.p. 217°; ir (potassium bromide): 3100 (aromatic), 1670 (>C=O), 1600 (aromatic), 1550 (aromatic) cm^{-1}; uv λ max (methanol): 326 nm (log ε 3.52), 280 sh (3.93), 270 (3.99), 245 (4.30), 225 (4.54); nmr (deuterium oxide): δ 2.55 (s, 3, C-CH_3), 6.50 (s, 1, H-3), 7.23 (d, 2, H-7, H-8), 7.75 (d, 1, H-9), 8.25 (d, 1, H-6); mass spectrum m/e (rel. intensity) 160(100) (M^+), 133(7), 132(73), 131(64), 120(20), 92(90), 79(18), 78(60), 68(11), 67(16), 66(22), 65(10), 52(12), 51(9).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.30; H, 4.98; N, 17.40.

2,4-Dimethylpyrido[1,2-*a*]pyrimidin-5-ium Iodide. A.

1,2-Diaminopyridinium iodide (4.8 g., 0.02 mole) was dissolved in methanol (25 ml.), sodium hydroxide (0.8 g., 0.02 mole, 10% solution) was added while stirring, followed by acetylacetone (10.0 g., 0.1 mole). After using the reaction procedure essentially as described above, the iodide, on recrystallization from methanol, gave yellow needles: 1.0 g. (16%), m.p. 280° dec.; ir (potassium bromide): 3080 (aromatic), 3010 (aromatic), 1650 (>C=N-), 1565 (aromatic), 1500 (aromatic) cm^{-1}; uv λ max (methanol): 317 nm (log ε 4.01), 312 (3.89), 305 (3.94), 227 (4.81), 212 (4.68); nmr (deuterium oxide): δ 3.00 (s, 3, 2-C-CH_3), 3.17 (s, 3, 4-C-CH_3), 8.34 (m, 4, H-3, H-7, H-8, H-9), 9.20 (d, 1, H-6); mass spectrum m/e (rel. intensity) 158(100) (*M*-HI), 157(27), 143(5), 129(5), 128(5), 119(16), 99(9), 98(5), 79(10), 78(31), 73(6), 70(6), 69(7), 67(7), 60(10), 57(8), 56(8), 55(15), 51(7).

Use of pyridine as solvent, resulted in isolation of the product (1.36 g.) in 23% yield.

B. 2-Aminopyridinium iodide (0.44 g., 0.002 mole) in pyridine (15 ml.) was treated with acetylacetone (0.4 g., 0.004 mole) and the mixture allowed to stand at room temperature. After 12 hours the product which had separated was collected, washed with ether and dried, 0.56 g. (98%), m.p. 280°.

Anal. Calcd. for $C_{10}H_{11}IN_2$: C, 41.96; H, 3.85; N, 9.79. Found: C, 42.18; H, 3.76; N, 9.75.

The picrate crystallized from ethanol as yellow needles: m.p. 135°.

Anal. Calcd. for $C_{16}H_{13}N_5O_7$: C, 49.62; H, 3.38; N, 18.08. Found: C, 49.57; H, 3.39; N, 18.17.

The perchlorate crystallized from methanol:ether as colorless needles: m.p. 226.5°; ir (potassium bromide): 3140 (aromatic), 3070 (aromatic), 1650 (>C=N), 1570 (aromatic), 1500 (aromatic) cm^{-1}; uv λ max (methanol): 317 nm (log ε 3.84), 312 (3.72), 305 (3.79), 229 (4.51), 207(4.37); nmr (DMSO-d_6) δ 3.00 (s, 3, C-CH_3), 3.17 (s, 3, C-CH_3), 8.34 (m, 4, H-3, H-7, H-8, H-9), 9.20 (d, 1, H-6).

Anal. Calcd. for $C_{10}H_{11}ClN_2O_4$: C, 46.41; H, 4.25; N, 10.83. Found: C, 46.39; H, 4.22; N, 10.90.

Potassium Permanganate Oxidation of 2,4-Dimethylpyrido[1,2-*a*]-pyrimidin-5-ium Iodide.

The iodide (2.86 g., 0.01 mole) in water (250 ml.) and potassium permanganate (15.0 g.) in water (500 ml.) were kept at 50-60° for 2 hours. After reaction work-up as in the oxidation described above, the 2-acetamidopyridine hydrochloride obtained was further purified by sublimation *in vacuo* (150°/0.1 mm), giving colorless needles: 1.0 g. (65%), m.p. 226°; ir (potassium bromide): 3050 (aromatic), 2900-2700 (=$\overset{+}{N}$H-), 1700 (>C=O), 1650 (>C=N-), 1570 (aromatic) cm^{-1}; uv λ max (methanol): 275 nm (log ε 3.72), 236 (4.02); nmr (deuterium oxide): δ 2.25 (s, 3, -$COCH_3$), 7.75 (m, 4, H-3, H-4, H-5, H-6).

This product was identical in all respects with a sample of 2-acetamidopyridine hydrochloride prepared from 2-acetamidopyridine and hydrogen chloride.

Anal. Calcd. for $C_7H_9ClN_2O$: C, 48.71; H, 5.22; N, 16.24. Found: C, 48.76; H, 5.25; N, 15.98.

5-Methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-11-ium Iodide. A.

1,2-Diaminopyridinium iodide (2.4 g., 0.01 mole) in pyridine (25 ml.) and 2-acetylcyclohexanone (1.4 g., 0.01 mole) were refluxed for 72 hours. Pyridine was removed at 45-50°, and the residue crystallized from ethanol:ether as yellow needles: 0.33 g. (10%), m.p. 245° dec.; ir (potassium bromide): 3100 (aromatic), 2950 (-CH_2-), 1650 (>C=N-), 1610 (aromatic), 1570 (>C=C<), 1500 (aromatic) cm^{-1}; uv λ max (methanol): 322 nm (log ε 3.90), 308 (3.74), 242 sh (4.65), 236 (4.70), 217 (4.58); nmr (deuterium oxide) δ 2.91 (s, 3, C-CH_3), 2.00 (m, 4, H-2, H-3); 3.12 (q, 4, H-1, H-4), 8.50 (m, 4, H-7, H-8, H-9, H-10).

B.

2-Aminopyridinium iodide (0.44 g., 0.002 mole) in pyridine (15 ml.) was treated with 2-acetylcyclohexanone (0.56 g., 0.004 mole) and the mixture was warmed at 50-60° for 24 hours. Excess pyridine was removed *in vacuo*, and the residue recrystallized from ethanol:ether, 0.26 g. (40%), m.p. 245° dec.

Anal. Calcd. for $C_{13}H_{15}IN_2$: C, 47.85; H, 4.60; N, 8.59. Found: C, 48.12; H, 4.68; N, 8.62.

Potassium Permanganate Oxidation of 5-Methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-11-ium Iodide.

The iodide (3.3 g., 0.01 mole) and potassium permanganate (15.0 g.) in water (750 ml.) were heated at 50-60° for 2 hours. After reaction work-up as described above, colorless needles of 2-acetamidopyridine hydrochloride were obtained: 1.0 g. (65%), m.p. 226°.

3-Ethoxycarbonyl-2,7-dimethylpyrazolo[1,5-*a*]pyridine (**9c**).

1-Amino-2-methylpyridinium iodide (9.60 g., 0.041 mole) dissolved in water (50 ml.), potassium carbonate (20.0 g.), and ethyl acetoacetate (10.7 g., 0.082 mole) were heated at 70-80° for 2 hours. On cooling, the reaction mixture was extracted with ether (4 x 100 ml.), the ether extract was dried (magnesium sulfate) and evaporated to yield an orange oil which distilled *in vacuo* as a yellow oil: b.p. 149-151°/2 mm; the oil solidified on standing. It crystallized from aqueous methanol as colorless plates: 4.1 g. (47%), m.p. 55-56°; ir (film) 1700 cm^{-1} (C=O); λ max (methanol): 308 nm (log ε 4.18), 243 (4.08), 222 (4.65), 200 (4.18); nmr (deuteriochloroform): δ 1.4 (t, 3, J = 7.0 Hz, -CH_2-CH_3), 2.7 (s, 3, CH_3), 2.8 (s, 3, CH_3), 4.4 (q, 2, J = 7.0 Hz, -CH_2CH_3), 7.3 (m, 3, aromatics); mass spectrum (70 eV) M^+, m/e (rel. intensity) 218(61).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.60; N, 12.78.

When the iodide (**1**; R = CH_3) (9.60 g., 0.041 mole) in DMF (50 ml.) was stirred with solid potassium carbonate (20 g.) at room temperature for 30 minutes and ethyl tetrolate (9.18 g., 0.082 mole) was added to the deep blue solution, a vigorous exothermic reaction occurred. After dilution with water, extraction with ether, and purification as described above, 3-ethoxycarbonyl-2,7-dimethylpyrazolo[1,5-*a*]pyridine was obtained: m.p. 55-56° (40%).

3-Acetyl-2,7-dimethylpyrazolo[1,5-*a*]pyridine (**9b**).

1-Amino-2-methylpyridinium iodide (4.0 g., 0.017 mole) in water (50 ml.) was treated with potassium carbonate (8.0 g.) and acetylacetone (3.4 g., 0.034 mole). After heating at 80° for 2 hours and standing at room temperature for 12 hours, the product which separated was recrystallized from water, separating as colorless irregular prisms: 2.4 g. (65%), m.p. 109-110° (lit. (2) m.p. 110°); ir (potassium bromide): 1640 cm^{-1} (C=O); λ max (methanol): 329 sh nm (log ε 4.13), 320 (4.21), 257 (3.62), 250 sh (3.47), 223 (4.43); nmr (deuteriochloroform): δ 2.5 (s, 3, COCH_3), 2.7 (s, 6, 2- and 7-CH_3), 6.7 (d, 1, J = 7.0 Hz, 6-H), 7.3 (m, 1, 5-H), 8.1 (d, 1, J = 9.0 Hz, 4-H); mass spectrum M^+, m/e (rel. intensity) 188(96). Similarly, 3-acetyl-2-methylpyrazolo[1,5-*a*]pyridine (**9a**) was obtained from 1-aminopyridinium iodide (**1**; R = H) as colorless needles from benzene: petroleum ether (b.p. 60-80°): 58%, m.p. 90° (lit. (2) m.p. 90°); ir (potassium bromide): 1640 cm^{-1} (CO); λ max (methanol): 308 nm (log ε 3.96), 259 (3.67), 253 sh (3.58), 225 (4.40); nmr (deuteriochloroform): δ 2.5 (s, 3, COCH_3), 2.6 (s, 3, 2-CH_3), 6.9 (m, 1, $J_{6,7}$ = 6.8 Hz, $J_{5,6}$ = 7.1 Hz, 6-H), 7.4 (m, 1, $J_{4,5}$ = 9.1 Hz, 5-H), 8.2 (d, 1, 4-H), 8.4 (d, 1, 7-H); mass spectrum, M^+, m/e (rel. intensity) 174(80).

1-*N*-Benzalimino-2-methylpyridinium Iodide (**11**).

1-Amino-2-methylpyridinium iodide (5.0 g., 0.021 mole) in methanol (50 ml.) was treated with benzaldehyde (2.2 g., 0.021 mole) and concentrated sulfuric acid (0.5 ml.). After 2 hours reflux and cooling to room temperature, the reaction mixture was diluted with ether until precipitation occurred. The product was collected, dried and recrystallized from chloroform:ether forming light-yellow irregular prisms: 6.2 g. (90%), m.p. 182-184°; ir (potassium bromide): 1640, 1620 (C=N) cm^{-1}; uv λ max (methanol): 276 nm (log ε 4.30), 220 (4.39), 199 (4.69); nmr (deuteriochloroform): δ 2.9 (s, 3, 2-CH_3), 8.2 (m, 8, aromatic), 9.5 (d, 1, J = 6.0 Hz, H-6), 10.0 (s, 1, CH=N).

Anal. Calcd. for $C_{13}H_{13}IN_2$: C, 48.16; H, 4.04; N, 8.64. Found: C, 48.21; H, 4.29; N, 8.42.

On treatment of the above iodide (1.0 g.) in aqueous methanol (20 ml. of 10%) with sodium carbonate (2.0 g.) a deep-purple solution was obtained. Extraction with ether gave benzonitrile.

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Note Added in Proof:

A recent publication [J. R. H. Sawyer and D. G. Wibberley, *J. C. S. Perkin I*, 1138 (1973)] also describes the preparation of a series of pyrido[1,2-*a*]pyridinium perchlorates from 2-aminopyridines and 1,3-dicarbonyl compounds or their acetals.

REFERENCES

(1a) Financial support of this work by U.S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) Abstracted in part from the Ph.D theses (CRS, 1969; and RD, 1970), Rensselaer Polytechnic Institute; (c) Part V: K. T. Potts and R. Armbruster, *J. Org. Chem.*, 36, 1846 (1971); (d) NSF Trainee.

(2a) K. T. Potts, H. R. Burton and J. Bhattacharyya, *ibid.*, 31, 260 (1966); (b) K. T. Potts, U. P. Singh and J. Bhattacharyya, *ibid.*, 33, 3766 (1968).

(3a) J. K. Landquist, *J. Chem. Soc.* (C), 2735 (1971); (b) H. L. Yale and J. T. Sheehan, *J. Heterocyclic Chem.*, 10, 143 (1973).

(4) R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, 74, 5491 (1952); M. Shur and S. S. Israelstam, *J. Org. Chem.*, 33, 3015 (1968).

(5) V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.*, 73, 3681 (1951).

(6) A. N. Nesmeyanov, M. I. Rybinskaya and N. K. Belskii, *Dokl. Akad. Nauk SSSR*, 113, 343 (1957); *Chem. Abstr.*, 51,

14712f (1957).

(7) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **118**, 297 (1958); *Chem. Abstr.*, **52**, 10080f (1958).

(8) M. Israel and L. C. Jones, *J. Heterocyclic Chem.*, **10**, 201 (1973).

(9) K. T. Potts and U. P. Singh, *Org. Mass Spectrom.*, **3**, 433 (1970).

(10) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).

(11) W. E. Feely, W. L. Lehn and V. Boekelheide, *ibid.*, **22**, 1135 (1957).

(12) Ir spectra were determined using either a Perkin-Elmer Model 421 or Perkin-Elmer Model 337 recording spectrophotometer. Uv spectra were measured on a Cary-14 spectrophotometer. Nmr spectra were determined using a Varian A-60 spectrometer and chemical shifts are reported in δ units using tetramethylsilane as an internal standard and standard calibration procedures. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV unless stated otherwise, all samples being introduced *via* a direct inlet (*ca.* 200°) system. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

The identity of products was established by means of superimposable infrared spectra and less than 2° depression in a mixture melting point determination. All evaporations were done under reduced pressure using a rotatory evaporator. All melting points were determined in capillaries.

(13) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N.Y., Fifth Edition, 1964, p. 320.