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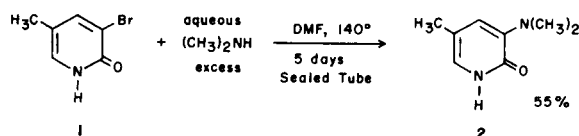
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Nucleophilic substitution of certain alkyl bromo-2(1H)-pyridones gave some unexpected products where the alkyl group is substituted and the ring bromine is replaced by hydrogen. The expected ring substituted product is also formed, but only as the minor product in most cases. Many reactions are cited with various nucleophiles, and a plausible mechanism is also presented.

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During an extensive synthetic study of substituted 2(1H)-pyridones, an unexpected side-chain substitution reaction was observed. A preliminary report of these interesting findings was presented earlier by B. W. Witzel [1] and a more complete report follows.

When 3-bromo-5-methyl-2(1H)-pyridone (**1**) is reacted with primary and secondary amines at elevated temperatures for extended periods of time, the expected 3-amino-5-methyl-2(1H)-pyridones are formed with good yields. For example,



A similar reaction is observed with other nucleophiles such as cuprous cyanide and cuprous methyl sulfide,

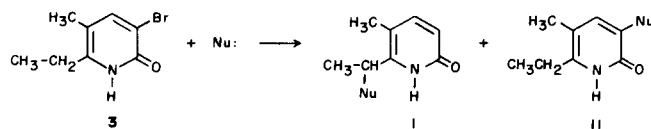
where only simple ring substitution products were obtained.

However, in the case of 3-bromo-6-ethyl-5-methyl-2(1H)-pyridone (**3**), the reaction takes an entirely different route and side-chain substitution becomes the major pathway as shown in Table A. Sometimes the ring substituted derivative is not detected.

The structure assignments are based on their characteristic nmr spectra. Instead of a triplet of a methyl group adjacent to the methylene of the starting 6-ethyl group of the pyridone, a doublet is present indicating a methine group. The spectra also shows the presence of an aromatic proton at the position where the bromine has been displaced. It is to be noted that a certain amount of decomposition occurs during the reaction and no product with substitution on the 5-alkyl is ever detected.

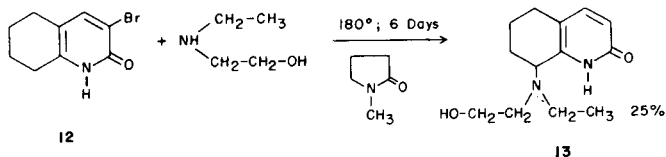
Similar side chain amination occurs at the corresponding group when 3-bromo-5,6,7,8-tetrahydro-2-quinolone (**12**) is treated with a substituted secondary amine.

Table A



Nucleophile	Ratio of Products, %			Mp, °C	C	Calcd., %			Found, %		
						H	N	C	H	N	
Methylamine	4	I	[a]	33	310	50.21	4.88	6.16	50.26	4.80	6.15
	5	II	[b]	3	185	65.03	8.49	16.85	64.77	8.10	16.60
Piperidine	6	I	[a]	17	259	59.33	6.64	7.69	59.31	6.76	7.50
	7	II	[a]	5	285	54.31	5.55	5.51	54.01	5.87	5.45
2-Ethylaminoethanol	8	I	[b]	18	172-173	64.26	8.99	12.49	64.08	8.79	12.36
		II		0							
Ammonium hydroxide	9	I	[a,c]	5	257	57.14	5.99	8.33	57.44	5.91	8.00
		II		0							
Aniline	10	I	[b]	13	221-225	73.66	7.06	12.27	73.98	7.16	11.91
		II		0							
Methoxide	11	I	[b]	35	136-138	64.65	7.84	8.38	64.48	7.87	8.26
		II		0							

[a] Product was analyzed as a salt of naphthalene-1,5-disulfonic acid. [b] Product was analyzed as the free base. [c] Crystallization in the presence of acetone formed the isopyridine derivative.

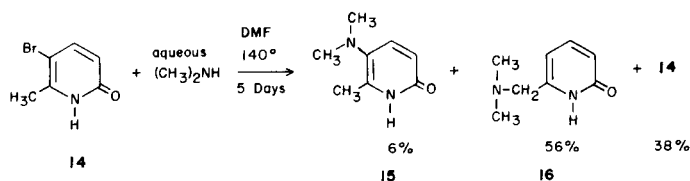


Some of these reactions are surprisingly clean, but most of them require column chromatography or preparative thin layer chromatography for separation. With nitrogen nucleophiles which give side chain products more basic than the ring substituted compounds, the use of naphthalene 1,5-disulfonic acid was sometimes effective in the separation of the product as a salt.

Encouraged by these findings, a study was then initiated to determine the generality and scope of the reaction. Included in the study were: (i) Reaction conditions; (ii) Effect of ring position of bromine atom on product ratio; (iii) Effect of ring position of alkyl group on product ratio; (iv) Effect of substitution on the pyridone nitrogen; (v) Variety of nucleophiles undergoing this reaction; (vi) Miscellaneous variables.

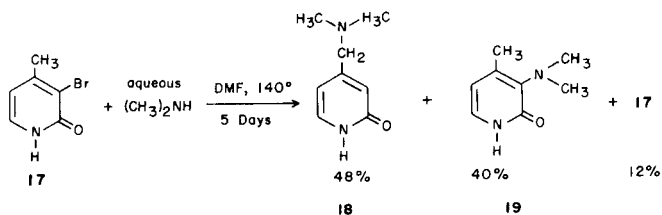
(i) Dimethylformamide, *N*-methylpyrrolidone, water, *t*-butyl alcohol and excess amine have all been used successfully as solvents. Temperatures ranging from 120° to 180° for two to six days in a bomb or sealed tube have been employed in the current investigation. Copper sulfate was sometimes used as a catalyst, but its merit is uncertain. One of the substitution reactions was performed with and without copper sulfate as the catalyst, and the one without catalyst gave a slightly better yield.

(ii) A bromine at either the 3- or 5-position readily takes part in this side-chain substitution reaction. An example of this is the reaction of 5-bromo-6-methyl-2(1*H*)-pyridone (14) with dimethylamine.



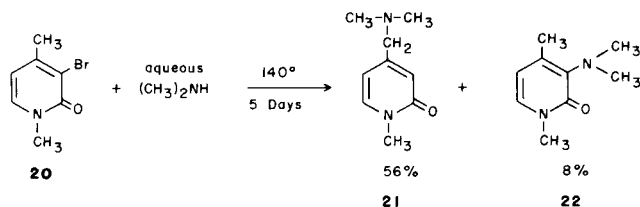
The product-ratio of the preceding reaction was estimated from the nmr spectrum of the total reaction mixture after concentration.

(iii) Both 4- and 6-alkylpyridones, but not 5-alkylpyridones, undergo this reaction:



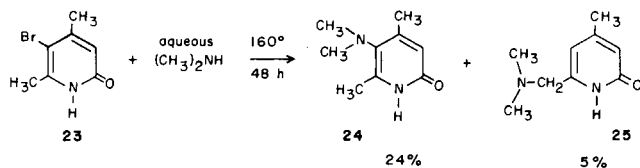
In other words, the nucleophile attacks the side chain α -carbon atom *para* or *ortho* to the bromine.

(iv) Based on a limited number of reactions, alkyl substituents on the nitrogen atom of the starting bromo pyridones appear to increase the yields of side-chain substitution products as compared with the corresponding *N*-unsubstituted pyridone.



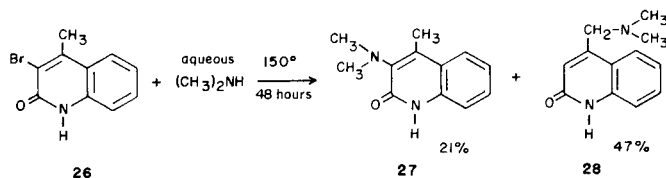
(v) A variety of aliphatic amines, *e.g.* methylamine, dimethylamine, ammonia, pyrrolidine, piperidine, methyl-ethylamine, diethylamine, and β -hydroxydiethylamine, yielded side-chain substitution compounds as the major product. Methoxide gave a similar substitution product and no 3-methoxy compound was observed. No reaction occurred with aniline alone, and this was thought to be due to its low basicity. This assumption was corroborated by the fact that aniline gave the side-chain substituted product when potassium *t*-butoxide in *t*-butyl alcohol was used as a catalyst.

(vi) A bromopyridone containing two competing alkyl groups at C_4 and C_6 gives two isolable products derived from both direct displacement and side-chain substitution at the C_6 methyl group.

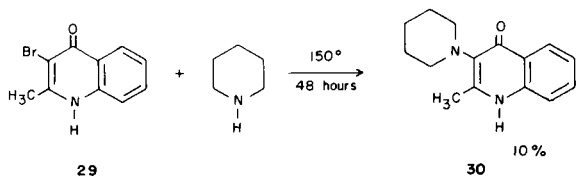


The assignment of 6-dimethylaminomethyl side-chain was based on ^{13}C -nmr determination (see Experimental).

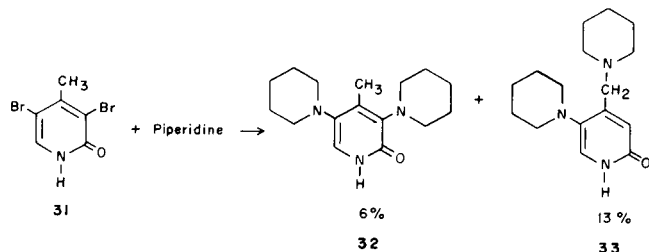
In the case of a 2(1*H*)-quinolone system 26, the side-chain substitution was likewise strongly favored over nucleophilic displacement of bromine.



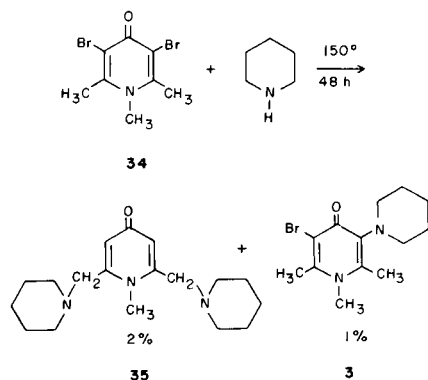
On the other hand, the reaction of a 4(1*H*)-quinolone yielded only the nucleophilic displacement product in low yield, and none of the alkyl substituted derivative was isolable.



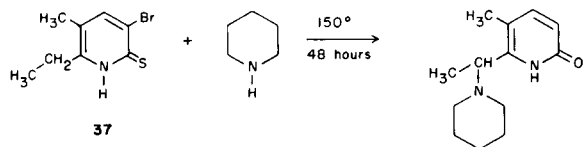
A reaction of 3,5-dibromo-4-methyl-2(1H)-pyridone **31** and piperidine was performed to determine which bromine would be preferably replaced. There were two compounds isolated from a multi-component reaction mixture. One was the direct replacement of both bromines **32** and the other was ring substitution of piperidine for one of the bromines and side-chain substitution of the 4-methyl group with loss of the second bromine **33**.



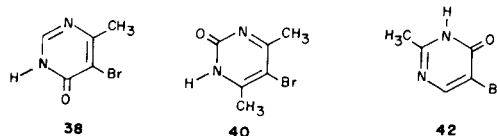
With 1,2,6-trimethyl-4(1H)-pyridone, bromination under several conditions in the literature [10] gave only the dibromo derivative. Attempts in our laboratories also failed to yield the desired monobromo derivative. As expected, treatment of the dibromopyridone **34** with piperidine gave a complex mixture of products, two of which were isolated in minute amounts and were positively identified as **35** and **36**.



The reaction of an alkyl bromo 2(1H)-thiopyridine **37** gave a multi-component reaction mixture, the only identifiable product being the side-chain substituted compound **6** in which the thione was converted to the pyridone.

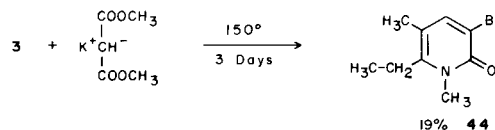


Three pyrimidinone [12,13,14] systems represented by **38**, **40** and **42** were reacted with piperidine under the usual conditions for obtaining side-chain substitution.



However, in all cases, nucleophilic substitution occurred only on the ring and no methyl group substitution was observed.

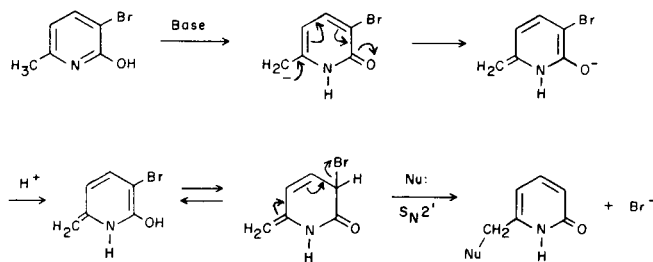
In an attempt to react a carbon nucleophile with **3**, the dimethyl malonate anion was used and the major product was the *N*-methyl derivative **44**.



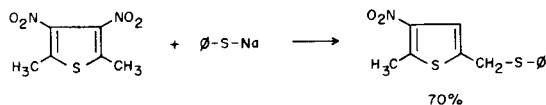
This is rather unexpected since deliberate attempts to methylate the nitrogen of **3** with methyl iodide gave a low yield of the *O*-methyl compound only. A model of **3** shows severe steric hindrance around the pyridone nitrogen.

A number of nucleophiles which did not demonstrate this alkyl substitution were sodium methyl mercaptide, sodium benzyl mercaptide, sodium phenylsulfinate, sodium and potassium cyanides, potassium hydroxide and potassium formate. The carbonyl of the pyridone nucleus is needed for this reaction to occur in as much as the pyridine analog, 3-bromo-4-picoline, under reaction conditions successful for substitution of 3-bromo-4-methyl-2(1H)-pyridone, was recovered unchanged.

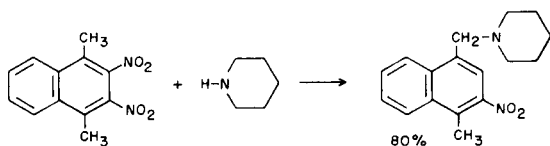
With the facts that a weak nucleophile like aniline requires a strong base to catalyze the alkyl substitution reaction, the alkyl group must be at position four or six of the 2-pyridone nucleus, and the bromo must be *ortho* or *para* to the alkyl substituent, then the following scheme seems a plausible mechanism.



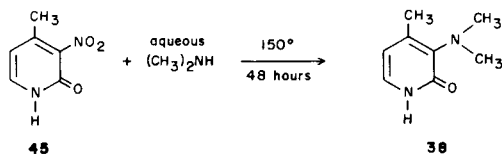
After this work was completed, a recent publication, Novi *et al.* [2] reported an unusual nucleophilic substitution on 2,5-dimethyl-3,4-dinitrothiophene with sodium anthiolates.



In another report Guanti *et al.* [3] investigated the reaction of 1,4-dimethyl-2,3-dinitrothalene with secondary aliphatic amines like piperidine. The term of *tele*-substitution was used to describe another example of nucleophilic substitution occurring on an aromatic carbocyclic substrate, where the nucleophile attacks on a side-chain α -carbon atom and the leaving group departs from the ring.



In view of these reactions, it was of interest to see whether a nitropyridone would undergo a similar reaction to bromopyridone. Under our usual conditions for nucleophilic substitution, treatment of 4-methyl-3-nitro-2(1H)-pyridone [15] with aqueous dimethylamine gave a complex mixture.



About 10% of starting material was recovered and a very low yield of the 3-dimethylamino displacement compound was observed by nmr studies and comparison with an authentic sample. None of the methyl substituted product was observed. The results of this reaction suggests that our nucleophilic substitution reaction proceeds by another mechanism than that of Guanti *et al.*

The scope of this nucleophilic substitution reaction remains to be investigated. Other halogens were not tried as leaving groups mainly due to the more accessible preparation of the bromo derivatives. It will be of interest to compare the effect of the other halogens on the ratio of the side-chain product *versus* that of ring substitution, and also their effects on yields. Optimum reaction conditions and other heterocyclic systems also need to be investigated.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and were corrected. The ^1H -nmr spectra were obtained on the Varian T-60, T-60A and HA 100D spectrometers. The ^{13}C -nmr was carried out on the Varian SC 300. These spectra were measured in deuteriochloroform, DMSO- d_6 , etc. as indicated. The chemical shifts were measured in ppm (δ) with respect to tetramethylsilane. The "LKB" model 9000 was used for mass spectral studies.

3-Bromo-5-methyl-2(1H)-pyridone (1).

To a stirred solution of 6.5 g (0.06 mole) of 5-methyl-2(1H)-pyridone [4] in 200 ml of chloroform cooled to 2° was added a solution of 9.6 g (0.06 mole) of bromine in 20 ml of chloroform over 75 minutes. After stirring at room temperature overnight, 40 ml of water was added, followed by a slight excess of solid potassium carbonate. The chloroform layer was separated, dried and evaporated giving 10.7 g of the crude bromo compound. Crystallization from benzene-petroleum ether gave 6.6 g (59%) of pure product which melted at 154-158°.

Anal. Calcd. for $\text{C}_6\text{H}_7\text{BrNO}$: C, 38.33; H, 3.22; N, 7.45; Br, 42.51. Found: C, 38.30; H, 3.09; N, 7.20; Br, 42.42.

3-Dimethylamino-5-methyl-2(1H)-pyridone (2).

A mixture of 7.5 g of 3-bromo-5-methyl-2(1H)-pyridone (1), 20 ml of 40% aqueous dimethylamine and 100 ml of dimethylformamide in a sealed tube was heated at 125° for eight days. The dark reaction mixture was evaporated *in vacuo* and the residue was chromatographed on a silica gel column with 0.5% methanol to 10% methanol in methylene chloride. The yield of product was 3.3 g (55%) and melted at 118.5-120°; ^1H -nmr (deuteriochloroform): δ 6.82 [m (unresolved), 1H, proton six of the pyridone], 6.57 [m, (unresolved) 1H, proton four of the pyridone], 2.84 [s, 6H, $\text{PyN}(\text{CH}_3)_2$], 2.08 [s, 3H, PyCH_3].

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{N}_2\text{O}$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.73; H, 8.10; N, 18.54.

3-Bromo-6-ethyl-5-methyl-2(1H)-pyridone (3).

Five g of 6-ethyl-5-methyl-2(1H)-pyridone [5] in 50 ml of acetic acid was brominated with 5 g of bromine in 10 ml of acetic acid. The solution was allowed to evaporate and the solid residue was crystallized from benzene-petroleum ether. The product weighed 4.0 g (56%) and melted at 170-172°; ^1H -nmr (deuteriochloroform): δ 7.63 (s, 1H, proton four of the pyridone), 2.63 (q, 2H, CH_3CH_2), 2.06 (s, 3H, PyCH_3), 1.24 (t, 3H, CH_3CH_2).

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{BrNO}$: C, 44.46; H, 4.67; N, 6.48; Br, 36.98. Found: C, 44.21; H, 4.72; N, 6.52; Br, 37.04.

Reaction of 3 with Methylamine.

A mixture of 8.6 g of 3, 100 ml of 40% aqueous methylamine, and 50 mg of copper sulfate was heated in a bomb at 150° for 48 hours. The reaction mixture was evaporated and the residue was extracted with chloroform. The insoluble material was extracted with water leaving 200 mg of 6-ethyl-5-methyl-3-methylamino-2(1H)-pyridone (5); ^1H -nmr (deuteriochloroform): δ 6.08 (s, 1H, proton four of the pyridone), 2.80 (m, 3H, CH_3NH), 2.51 (q, 2H, CH_3CH_2), 2.03 (s, 3H, PyCH_3), 1.16 (t, 3H, CH_3CH_2). See Table A for the elemental analysis.

The chloroform extract was evaporated and the residue was treated with naphthalene-1,5-disulfonic acid in methanol to form the salt. The yield of salt was 4.3 g and recrystallization from water-acetone did not raise the melting point. The nmr study of the free base showed this to be 6-(1-methylaminoethyl)-5-methyl-2(1H)-pyridone (4); ^1H -nmr (deuteriochloroform): δ 7.23 (d, J = 9.5 Hz, 1H, proton four of the pyridone), 6.38 (d, J = 9.5 Hz, 1H, proton three of the pyridone), 3.78 (q, 1H, CH_3CH), 2.30 (s, 3H, CH_3NH), 2.05 (s, 3H, PyCH_3), 1.28 (d, 3H, CH_3CH). See Table A for the elemental analysis.

Reaction of 3 with Piperidine.

A mixture of 6.5 g of 3, 50 mg of copper sulfate, and 25 ml of piperidine was heated in a bomb at 150° for 48 hours. The reaction mixture was evaporated to dryness and extracted with ethyl acetate. The extract was evaporated and the residue was taken up in ethanol to which was added a solution of 6 g of naphthalene-1,5-disulfonic acid in methanol. There was obtained 3.6 g of the salt of 5-methyl-6-[1-(1-piperidyl)ethyl]-2(1H)-pyridone (6); ^1H -nmr of the free base (deuteriochloroform): δ 7.22 (d, 1H, J = 9.5 Hz, proton four of the pyridone), 6.37 (d, 1H, J = 9.5 Hz, proton three of the pyridone), 3.35 (q, 1H, CH_3CHPy), 2.44 (m, 4H, CH_2NCH_2), 2.04 (s, 3H, PyCH_3), 1.54 [m, 6H, (CH_2) $_3$], 1.22 (d, 3H, CH_3CH). The elemental analysis appears in Table A.

Fractional crystallization of the mother liquors gave 700 mg of the isomeric 6-ethyl-5-methyl-3-(1-piperidyl)-2(1*H*)-pyridone salt (**7**); ¹H-nmr of the salt (deuterium oxide): δ 7.80 (s, 1H, proton four of the pyridone), 3.64 (q, 2H, CH₃CH₂Py), 2.96 (m, 4H, CH₂NCH₂), 1.98 (s, 3H, PyCH₃), 1.40 [m, 6H, (CH₂)₂], 1.15 (t, 3H, CH₃CH₂Py). See Table A for the elemental analysis.

Reaction of **3** with 2-Ethylaminoethanol.

A mixture of 6.6 g of **3** and 33 ml of 2-ethylaminoethanol in 150 ml of *N*-methylpyrrolidinone was heated in a bomb at 180° for five days. The reaction was evaporated at the vacuum pump and the residue was extracted with warm ethyl acetate. The insolubles were removed by filtration and the filtrate was concentrated to a small volume. Ether was carefully added to crystallize 1.2 g of 5-methyl-6-(β-hydroxydiethylaminoethyl)-2(1*H*)-pyridone (**8**); ¹H-nmr (deuteriochloroform): δ 7.18 (d, J = 9.5 Hz, 1H, proton four of the pyridone), 6.42 (d, J = 9.5 Hz, 1H, proton three of the pyridone), 3.84 (q, 1H, CH₃CH), 3.63 (t, 2H, CH₂CH₂OH), 2.06 (s, 3H, PyCH₃), 1.30 (d, 3H, CH₃CH), 0.92 (t, 3H, CH₃CH₂), remaining hydrogens were unresolved. Table A contains the elemental analysis.

Reaction of **3** with Ammonium Hydroxide.

A mixture of 3.3 g of **3** and 100 ml of concentrated ammonium hydroxide was heated in a bomb at 180° for 5 days. The reaction was evaporated to dryness and extracted with methylene chloride. The inorganics were removed and the filtrate was evaporated to dryness. The residue was converted into a salt with 1,5-naphthalene disulfonic acid in methanol. Purification of the salt was accomplished with the aid of acetone. The product weighed 300 mg and proved to be 6-(α-isopropylideneamino)ethyl-5-methyl-2(1*H*)-pyridone (**9**); ¹H-nmr (deuterium oxide): δ 7.51 (d, 1H, J = 9.0 Hz, proton four of pyridone), 6.55 (d, 1H, J = 9.0 Hz, proton three of pyridone), 5.25 (m, 1H, CH₃CHN), 2.20 [s, 6H, N=C(CH₃)₂], 2.12 (s, 3H, PyCH₃), 1.55 (d, 3H, CH₃CH). See Table A for the elemental analysis.

Reaction of **3** with Aniline.

A sealed tube containing 4.3 g of **3**, 6 ml of aniline, 6 g of potassium *t*-butoxide, and 80 ml of dry *t*-butyl alcohol was heated at 150° for 48 hours. The reaction mixture was filtered and the filtrate evaporated under high vacuum. This residue was extracted with 2.5 *N* hydrochloric acid and refiltered. The acid extract was treated with an excess of solid sodium bicarbonate and the crude product which separated was collected. Purification from benzene gave 600 mg of 6-(α-anilinoethyl)-5-methyl-2(1*H*)-pyridone (**10**); ¹H-nmr (deuteriochloroform): δ 7.25 (d, 1H, J = 9.0 Hz, proton four of pyridone), 6.38 (d, 1H, J = 9.0 Hz, proton three of pyridone), 4.58 (m, 1H, CH₃CH), 2.19 (s, 3H, PyCH₃), 1.45 (d, 3H, CH₃CH). Table A contains the elemental analysis.

Reaction of **3** with Sodium Methoxide.

In a sealed tube at 180° for five days was reacted 8.6 g of **3** and 6.5 g of sodium methoxide in 150 ml of methanol. The reaction mixture was evaporated and the residue was extracted with benzene. After filtration the filtrate was concentrated and chromatographed on basic alumina with 5% methanol in methylene chloride. This gave 3.9 g of 6-(1-methoxyethyl)-5-methyl-2(1*H*)-pyridone (**11**); ¹H-nmr (deuterium oxide): δ 7.44 (d, J = 9.0 Hz, 1H, proton four of the pyridone), 6.40 (d, J = 9.0 Hz, 1H, proton three of the pyridone), 4.56 (q, 1H, CH₃CH), 3.23 (s, CH₃O), 2.08 (s, 3H, PyCH₃), 1.36 (d, 3H, CH₃CH). Table A contains the elemental analysis.

Reaction of 3-Bromo-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**12**) and 2-Ethylaminoethanol.

A sealed tube containing 1.1 g of bromo compound, 5 ml of 2-ethylaminoethanol, and 30 ml of *N*-methylpyrrolidinone was heated at 180° for 6 days. The reaction mixture was evaporated *in vacuo*. The residue was triturated with ether and decanted then triturated with acetone. The insoluble residue was crystalline 8-(2-hydroxydiethylamino)-5,6,7,8-tetrahydro-2(1*H*)-quinolone hydrobromide (**13**). It weighed 400 mg (25%) and melted at 184-185°. Recrystallization from methanol did not change the melting point; ¹H-nmr (deuteriochloroform): δ 7.16 (d, J = 10 Hz, 1H, proton four

of quinolone), 6.45 (d, J = 10 Hz, 1H, proton three of quinolone), 3.90 (m, 1H, tertiary proton at position eight), 3.67 (q, 2H, HOCH₂CH₂), 1.00 (d, 3H, CH₃CH). The remaining protons were unresolved.

Anal. Calcd. for C₁₃H₂₀N₂O₂·HBr: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.10; H, 8.61; N, 11.70.

Reaction of 5-Bromo-6-methyl-2(1*H*)-pyridone [**7**] and Dimethylamine.

A sealed tube containing 1.9 g of bromo compound **14**, 9 ml of 40% aqueous dimethylamine, and 30 ml of dimethylformamide was heated at 140° for 5 days. The orange solution was evaporated to dryness and the residue was triturated with warm ether. The ether insoluble material was further extracted with acetone and the nmr of the soluble fraction proved to be mainly 5-dimethylamino-6-methyl-2(1*H*)-pyridone (**15**) when compared with an authentic sample; ¹H-nmr (DMSO-*d*₆): δ 7.49 (d, J = 10 Hz, proton four of the pyridone), 6.16 (d, J = 10 Hz, 1H, proton three of pyridone), 2.47 [s, 6H, N(CH₃)₂], 2.18 (s, 3H, PyCH₃). The acetone insoluble material from above was crystallized from ethanol giving 400 mg (17%) of 6-dimethylaminomethyl-2(1*H*)-pyridone hydrobromide (**16**) which melted at 240°; ¹H-nmr (DMSO-*d*₆): δ 7.60 (m, J = 7 Hz and 9 Hz, proton four of pyridone), 6.70 (d, J = 7 Hz, 1H, proton three of pyridone), 6.55 (d, J = 9 Hz, 1H, proton five of pyridone), 4.32 [s, 2H, PyCH₂N(CH₃)₂], 2.83 [s, 6H, N(CH₃)₂].

Anal. Calcd. for C₈H₁₂N₂O·HBr: C, 41.21; H, 5.62; N, 12.01. Found: C, 40.99; H, 5.68; N, 11.89.

Reaction of 3-Bromo-4-methyl-2(1*H*)-pyridone [**6**] with Dimethylamine.

A sealed tube containing 1.9 g of bromo compound **17**, 9 ml of 40% aqueous dimethylamine, and 30 ml of dimethylformamide was heated at 140° for five days. After drying the contents in a high vacuum, the residue was extracted with ether, and the insoluble material crystallized from methanol. The 4-dimethylaminomethyl-2(1*H*)-pyridone hydrobromide (**18**) weighed 900 mg (39%) and melted at 280° dec; ¹H-nmr (DMSO-*d*₆): δ 7.50 (d, J = 7 Hz, 1H, proton six of the pyridone), 6.50 [m (unresolved), 1H, proton three of the pyridone], 6.38 (q, J = 2 Hz and 7 Hz, 1H, proton five of the pyridone), 4.17 (s, 2H, PyCH₂N), 2.77 [s, 6H, N(CH₃)₂].

Anal. Calcd. for C₈H₁₂N₂O·HBr: C, 41.21; H, 5.62; N, 12.01; Br, 34.28. Found: C, 40.97; H, 5.68; N, 11.96; Br, 34.53.

The ether soluble fraction was evaporated to give the ring substituted 3-dimethylamino-4-methyl-2(1*H*)-pyridone (**19**). The crude material was crystallized from toluene and the pure product weighed 350 mg (30%) melting at 119-121°; ¹H-nmr (deuteriochloroform): δ 6.80 (d, 1H, J = 7 Hz, proton six of pyridone), 6.15 (d, 1H, J = 7 Hz, proton five of pyridone), 2.96 [s, 6H, N(CH₃)₂], 2.1 (s, 3H, PyCH₃).

Anal. Calcd. for C₈H₁₂N₂O: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.64; H, 8.29; N, 17.98.

3-Bromo-1,4-dimethyl-2(1*H*)-pyridone (**20**).

A solution of 9.4 g (0.05 mole) of 3-bromo-4-methyl-2(1*H*)-pyridone (**17**) and 3.7 g (0.057 mole) of 85% potassium hydroxide in 150 ml of ethanol was stirred and heated to reflux in a nitrogen atmosphere. Over a 2 hour period was added a solution of 9.5 g (0.07 mole) of methyl iodide to the refluxing mixture. After refluxing an additional hour the reaction was cooled, filtered and the filtrate was evaporated to dryness. The residue was extracted with methylene chloride and filtered from some insoluble materials. The methylene chloride extract was evaporated and the pale yellow oil crystallized on standing. The crude product weighed 8.8 g (88%) and melted at 61-63°. A small amount was recrystallized from water which did not raise the melting point; ¹H-nmr (deuteriochloroform): δ 7.28 (d, J = 7 Hz, 1H, proton six of pyridone), 6.09 (d, J = 7 Hz, 1H, proton five of pyridone), 3.57 (s, 3H, NCH₃ of pyridone), 2.29 (s, 3H, PyCH₃).

Anal. Calcd. for C₇H₈BrNO·H₂O: C, 38.20; H, 4.58; N, 6.37. Found: C, 38.17; H, 4.48; N, 6.55.

Reaction of **20** with Dimethylamine.

In a sealed tube a mixture of 1.3 g of bromo compound and 5.8 ml of 40% aqueous dimethylamine was heated at 140° for 5 days. The contents

of the tube were evaporated to dryness and the residue was extracted with ether. The ether insoluble material was crystallized from methanol yielding 900 mg (56%) of the hydrobromide salt of 4-dimethylamino-methyl-1-methyl-2(1*H*)-pyridone (**21**) which melted at 242-246°. The spectral study was done with the free base; ¹H-nmr (deuteriochloroform): δ 7.25 (d, J = 5 Hz, proton six of the pyridone), 6.46 [m (unresolved), 1H, proton five of the pyridone], 6.28 (dd, J = 5 Hz and 2 Hz, 1H, proton three of the pyridone), 3.54 (s, 3H, NCH₃ of the pyridone), 3.23 (s, 2H, PyCH₂), 2.26 (s, 6H, N(CH₃)₂).

Anal. Calcd. for C₉H₁₄N₂O·HBr: C, 43.74; H, 6.12; N, 11.33; Br, 32.33. Found: C, 43.20; H, 5.89; N, 11.21; Br, 32.61.

The ether extract above was separated by prep tlc with 5% methanol in methylene chloride. The main fraction was dissolved in ethanol and treated with an excess of 1,5-naphthalene disulfonic acid and diluted with acetone to crystallize the salt. The yield was 300 mg (8%) and it melted at 253° dec. Spectral study indicated this compound to be the isomeric 1,4-dimethyl-3-dimethylamino-2(1*H*)-pyridone (**22**); ¹H-nmr (deuteriochloroform): δ 7.02 (d, J = 5 Hz, 1H, pyridone), 5.97 (d, J = 5 Hz, 1H, proton five of pyridone), 3.45 (s, 3H, NCH₃ of pyridone), 2.76 [s, 6H, N(CH₃)₂], 2.20 (s, 3H, PyCH₃).

Anal. Calcd. for C₉H₁₄N₂O·C₁₀H₈O₆S₂·½H₂O: C, 49.23; H, 5.00; N, 6.05. Found: C, 49.29; H, 5.34; N, 6.1.

5-Bromo-4,6-dimethyl-2(1*H*)-pyridone (**23**).

A mixture of 8.7 g of ethyl-5-bromo-4,6-dimethyl-2(1*H*)-pyridone-3-carboxylate [8] and 100 ml concentrated hydrochloric acid was heated on the steam bath for 15 hours. The hydrochloride salt of 5-bromo-4,6-dimethyl-2(1*H*)-pyridone crystallized. The salt was collected and converted to the free base which melted at 257-259°; ¹H-nmr (DMSO-d₆): δ 6.49 (s, 1H, proton three of pyridone), 2.40 (s, 3H, 6-CH₃ of pyridone), 2.28 (s, 3H, 4-CH₃ of pyridone).

Anal. Calcd. for C₇H₈BrNO: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.73; H, 4.11; N, 6.79.

Reaction of **23** with Dimethylamine.

A mixture of 3 g of the bromo compound and 45 ml of 40% aqueous dimethylamine was heated in a bomb at 160° for 48 hours. The reaction mixture was evaporated to dryness, extracted with methylene chloride and filtered from the dimethylamine salt. The residue was eluted with 2.5% methanol in methylene chloride on a medium pressure liquid chromatography column. The first compound to be isolated was 4,6-dimethyl-5-dimethylamino-2(1*H*)-pyridone (**24**), which weighed 500 mg (24%) and melted at 168-170°; ¹H-nmr (deuteriochloroform): δ 6.20 (s, 1H, proton three of pyridone), 2.71 [s, 6H, N(CH₃)₂], 2.32 (s, 3H, 6-methyl of the pyridone), 2.17 (s, 3H, 4-methyl of the pyridone).

Anal. Calcd. for C₉H₁₄N₂O: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.93; H, 8.67; N, 16.88.

The second compound to be isolated from the column weighed 100 mg (5%) and melted at 95-96°; ¹H-nmr (deuteriochloroform): δ 6.28 (unresolved d, 1H, proton three of pyridone), 5.98 (unresolved d, 1H, proton five of the pyridone), 3.31 (s, 2H, NCH₂Py), 2.27 [s, 6H, N(CH₃)₂], 2.20 (s, 3H, PyCH₃). The ¹H-nmr was not enough to determine which methyl had been substituted. This was determined by ¹³C-nmr (deuteriochloroform). The chemical shift of the model 2-pyridones are 21.70 (4-methyl) and 18.96 (6-methyl). This compound shows a methyl chemical shift of 21.68, which means that the 6-methyl has been substituted, and is unequivocally the isomeric 6-dimethylaminomethyl-4-methyl-2(1*H*)-pyridone (**25**).

Anal. Calcd. for C₉H₁₄N₂O·½CH₃OH: C, 62.62; H, 8.85; N, 15.38. Found: C, 63.00; H, 8.44; N, 15.68.

Reaction of 3-Bromo-4-methyl-2(1*H*)-quinolone [9] with Dimethylamine.

A mixture of 4 g of bromo compound **26** and 50 ml of 40% aqueous dimethylamine was heated in a bomb at 150° for 48 hours. The insoluble material was removed by filtration and placed on a silica gel column and eluted with ethyl acetate, which cleanly separated 700 mg (21%) 3-dimethylamino-4-methyl-2(1*H*)-quinolone (**27**) melting at 194-195°; ¹H-nmr (deuteriochloroform): δ 2.92 [s, 6H, ArN(CH₃)₂], 2.56 (s, 3H, ArCH₃).

Anal. Calcd. for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.80; H, 7.00; N, 13.59.

By gradually increasing the methanol from 1 to 10% in ethyl acetate a total of 1.5 g (47%) of the isomeric 4-dimethylaminomethyl-2(1*H*)-quinolone (**28**) melting at 200-201° was obtained; ¹H-nmr (deuteriochloroform): δ 6.77 (s, 1H, proton three of quinolone), 2.65 (s, 2H, ArCH₂N), 2.33 [s, 6H, CH₂N(CH₃)₂].

Anal. Calcd. for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.36; H, 7.06; N, 13.67.

3-Bromo-2-methyl-4(1*H*)-quinolone (**29**).

To a solution of 9.55 g (0.06 mole) of 2-methyl-4(1*H*)-quinolone in 250 ml of acetic acid containing a crystal of iodine was added a solution of 9.6 g (0.06 mole) of bromine in 75 ml of acetic acid over 2 hours with good stirring. A crystalline solid was collected, and this solid was stirred with 150 ml of concentrated ammonium hydroxide. The crude bromo compound was collected and crystallized from dimethylformamide giving 10.5 g (52%) of product which melted at 285°. The ¹H-nmr (trifluoroacetic acid): δ shows that proton three has been substituted.

Anal. Calcd. for C₁₀H₈BrNO: C, 50.44; H, 3.38; N, 5.88; Br, 33.50. Found: C, 50.37; H, 3.29; N, 5.83; Br, 33.99.

Reaction of **29** with Piperidine.

A mixture of 3 g of the bromo compound, 25 mg of copper sulfate and 45 ml of piperidine was heated in a bomb at 150° for 48 hours. The reaction mixture was evaporated and the residue was extracted with a little cold water. The insoluble material was separated by chromatography on silica gel using 10% methanol in methylene chloride as the eluent. The main product was 2-methyl-3-(1-piperidyl)-4(1*H*)-quinolone (**30**) which weighed 300 mg (10%) and melted at 278-280°; ¹H-nmr (deuteriochloroform): δ 3.06 (m, 4H, CH₂NCH₂), 2.43 (s, 3H, PyCH₃), 1.54 [m, 6H, (CH₂)₂].

Anal. Calcd. for C₁₂H₁₆N₂O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.23; H, 7.48; N, 11.41.

The only other identifiable product was the known 2-methyl-4(1*H*)-quinolone. None of the nucleophilic substitution product on the methyl was found.

Reaction of 3,5-Dibromo-4-methyl-2(1*H*)-pyridone [10] and Piperidine.

In a bomb at 150° was reacted 3 g of the dibromo compound **31** and 45 ml of piperidine for 48 hours. The reaction was evaporated to dryness and the residue was extracted with methylene chloride. The piperidine hydrobromide was removed by filtration and the filtrate was evaporated leaving 1.5 g of oil. Two products were isolated using prep tlc silica gel plates. They were eluted with 8% methanol in methylene chloride. The less polar compound was isolated first and it weighed 180 mg (6%), and proved to be 4-methyl-3,5-bis-(1-piperidyl)-2(1*H*)-pyridone (**32**), which melted at 234-236°; ¹H-nmr (deuteriochloroform): δ 6.90 (s, 1H, proton six of pyridone), 2.71 (m, 4H, α-protons of the piperidyl at 3-position of the pyridone), 2.30 (s, 3H, PyCH₃), 1.60 (m, 12H, remaining protons of both piperidyls).

Anal. Calcd. for C₁₆H₂₂N₃O: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.99; H, 8.97; N, 15.08.

The major product was the isomeric 5-(1-piperidyl)-4-(1-piperidylmethyl)-2(1*H*)-pyridone (**33**). It weighed 400 mg (13%) and melted at 153-154°; ¹H-nmr (deuteriochloroform): δ 7.09 (s, 1H, proton six of pyridone), 6.80 [m (unresolved singlet), 1H, proton three of pyridone], 3.42 [m (unresolved singlet), 2H, CH₂N], 2.72 (m, 4H, α-protons of piperidyl at 5-position of pyridone), 2.45 (m, 4H, α-protons of piperidyl on methyl group), 1.57 (m, 12H, remaining protons of both piperidyls).

Anal. Calcd. for C₁₆H₂₂N₃O: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.79; H, 8.75; N, 15.12.

Reaction of 3,5-Dibromo-1,2,6-trimethyl-4(1*H*)-pyridone [11] with Piperidine.

Five g of the dibromo compound **34**, 24 mg of copper sulfate, and 45 ml of piperidine were heated in a bomb at 150° for 48 hours. The reaction was evaporated *in vacuo* and the residue was rubbed with a little

water causing the oil to solidify. The aqueous extract yielded 200 mg (2%) of 1-methyl-bis-2,6-(1-piperidylmethyl)-4(1*H*)-pyridone (**35**) which melted at 162-164°. The ¹H-nmr (deuteriochloroform): δ 6.32 (s, 2H, protons two and six of pyridone), 3.81 (s, 3H, NCH₃), 3.34 (s, 4H, piperidyl-CH₂), 2.40 (m, 8H, the α-protons of both piperidyls), 1.54 (m, 12H, the remaining protons of both piperidyls).

Anal. Calcd. for C₁₈H₂₉N₃O: C, 71.25; H, 9.63; N, 13.85. Found: C, 71.28; H, 9.62; N, 13.41.

Chromatography of the crude water insoluble material on silica gel with 3% methanol in methylene chloride as the eluent gave 45 mg (1%) of 3-bromo-5-(1-piperidyl)-1,2,6-trimethyl-4(1*H*)-pyridone (**36**) melting at 221-223°; ¹H-nmr (deuteriochloroform): δ no aromatic protons, 3.60 (s, 3H, NCH₃), 2.60 (s, 3H, 2-CH₃ of pyridone), 2.57 (m, 4H, α-protons of piperidyl), 2.52 (s, 3H, 6-CH₃ of pyridone), 1.58 (m, 6H, remaining protons of piperidyl).

Anal. Calcd. for C₁₃H₁₉BrN₂O: C, 52.18; H, 6.40; N, 9.36. Found: C, 52.45; H, 6.87; N, 9.14.

3-Bromo-6-ethyl-5-methyl-2(1*H*)-pyridinethione (**37**).

A mixture of 2.5 g of **3** and 10 g of phosphorus pentasulfide in 120 ml of dry toluene was stirred and refluxed for 3 hours. This was evaporated to dryness and the residue was stirred with 75 ml of 2.5 *N* sodium hydroxide. The alkaline solution was treated with an excess of acetic acid, and the precipitated thione was purified from methylene chloride-ether. The pure product weighed 1.1 g (42%) and melted at 212-214°; ¹H-nmr (deuteriochloroform): δ 7.66 (s, 1H, proton four of the thiopyridone), 2.75 (q, 2H, CH₃CH₂), 2.14 (s, 3H, PyCH₃), 1.23 (t, 3H, CH₃CH₂).

Anal. Calcd. for C₉H₁₀BrNS: C, 41.39; H, 4.34; N, 6.03. Found: C, 41.60; H, 4.37; N, 6.30.

Reaction of **37** with Piperidine.

In a bomb at 150° was heated 1 g of the thione and 40 ml of piperidine for 48 hours. The reaction was evaporated and the residue was extracted with methylene chloride. The crude residue, after evaporation of the methylene chloride, was placed on prep tlc silica gel plates and eluted with 2% methanol in methylene chloride. The only compound that was positively identified was 5-methyl-6-[1-(1-piperidyl)ethyl]-2(1*H*)-pyridone (**6**). This compound is identical to that from the reaction of **3** with piperidine.

Reaction of 5-Bromo-6-methyl-4(3*H*)-pyrimidinone [12] with Piperidine.

A mixture of 3.5 g of bromo compound **38**, 25 mg of copper sulfate and 40 ml of piperidine was heated in a bomb at 150° for 48 hours. The reaction was evaporated *in vacuo* and the residue was extracted with methylene chloride. The insoluble piperidine hydrobromide was removed and the filtrate was evaporated. The dark residue was treated with an ethanolic solution of 1,5-naphthalene disulfonic acid to form the salt which weighed 400 mg. This salt was treated with ammonium hydroxide to generate the free base which weighed 250 mg (7%) and melted at 145-147°. The nmr study showed this product to be 5-(1-piperidyl)-6-methyl-4(3*H*)-pyrimidinone (**39**); ¹H-nmr (deuteriochloroform): δ 8.00 (s, 1H, proton two of pyrimidinone), 3.10 (m, 4H, CH₂NCH₂), 2.40 (s, 3H, PyCH₃), 1.64 [m, 6H, (CH₂)₃].

Anal. Calcd. for C₁₀H₁₅N₃O: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.37; H, 7.63; N, 21.53.

Reaction of 5-Bromo-4,6-dimethyl-2(1*H*)-pyrimidinone [13] with Piperidine.

A mixture of bromo compound **40**, 25 mg of copper sulfate and 45 ml of piperidine was heated at 150° for 48 hours. The dark reaction mixture was evaporated *in vacuo* and the residue was extracted with methylene chloride. The piperidine hydrobromide was removed and the filtrate was evaporated. The black tarry residue was chromatographed on silica gel with 1% methanol in methylene chloride and with gradually increasing amounts of methanol up to 10%. One g (20%) of 4,6-dimethyl-5-(1-piperidyl)-2(1*H*)-pyrimidinone (**41**) was isolated, which melted at 210°; ¹H-nmr

(deuteriochloroform): δ no aromatic H, 2.90 (m, 4H, CH₂NCH₂), 2.42 [s, 6H, Py(CH₃)₂], 1.60 [m, 6H, (CH₂)₃].

Anal. Calcd. for C₁₁H₁₇N₃O: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.86; H, 8.33; N, 20.42.

Reaction of 5-Bromo-2-methyl-4(3*H*)-pyrimidinone [14] with Piperidine.

A mixture of 700 mg of bromo compound **42**, 10 mg of copper sulfate and 40 ml of piperidine was heated in a bomb at 150° for 48 hours. The reaction mixture was evaporated *in vacuo* and the residue was extracted with methylene chloride. Piperidine hydrobromide was removed by filtration and the filtrate evaporated to dryness. The residue was crystallized from ethanol-water to give 150 mg (22%) of 2-methyl-5-(1-piperidyl)-4(3*H*)-pyrimidinone **43** which melted at 235°; ¹H-nmr (deuteriochloroform): δ 5.34 (s, 1H, PyH), 3.56 (m, 4H, CH₂NCH₂), 2.37 (s, 3H, PyCH₃), 1.62 [m, 6H, (CH₂)₃].

Anal. Calcd. for C₁₀H₁₅N₃O: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.48; H, 7.83; N, 21.51.

The nmr study of other fractions did not indicate any side chain substitution.

Reaction of **3** with the Anion of Dimethylmalonic Ester.

In a sealed tube was mixed 1.51 g (0.007 mole) of **3**, 3.3 g (0.025 mole) of dimethylmalonate, 2.7 g (0.025 mole) of potassium *t*-butoxide, and 20 ml of dry *t*-butyl alcohol. This was heated at 150° for three days. The reaction mixture was evaporated and the residue was extracted with 25 ml of 1*N* sodium hydroxide. The insoluble material was crystallized from benzene-petroleum ether giving 300 mg (19%) of 1-methyl-3-bromo-6-ethyl-5-methyl-2(1*H*)-pyridone (**44**) melting at 110-111°; ¹H-nmr (deuteriochloroform): δ 7.58 (s, 1H, proton four of pyridone), 3.66 (s, 3H, NCH₃), 2.72 (m, 2H, CH₃CH₂), 2.12 (s, 3H, PyCH₃), 2.20 (t, 3H, CH₃CH₂).

Anal. Calcd. for C₉H₁₂BrNO: C, 46.96; H, 5.26; N, 6.09; Br, 34.72. Found: C, 46.87; H, 5.24; N, 6.45; Br, 34.71.

Reaction of 4-Methyl-3-nitro-2(1*H*)-pyridone [15] with Dimethylamine.

In a bomb was mixed 5 g of the nitro compound **45** and 50 ml of 40% aqueous dimethylamine, and this was heated at 150° for 48 hours. The very dark reaction mixture was filtered from a small amount of dark amorphous solid. The filtrate was evaporated *in vacuo* and the residue was taken up in 75 ml of warm ethanol. Dilution with ether caused starting material to crystallize and 1 g was recovered. Chromatography on silica gel with 5% methanol and methylene chloride gave more starting material, and one more impure fraction which was identified as mostly 3-dimethylamino-4-methyl-2(1*H*)-pyridone (**19**) in low yield.

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