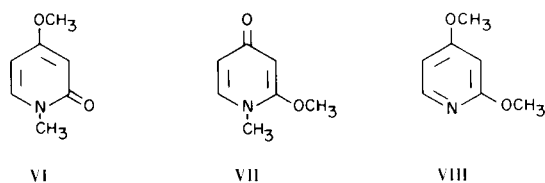




treating II and III with 28% aqueous ammonia, the oxygen atom which closes the chain is changed to the imide group -NH to give 2,6-dimethyl-4-pyridinol (IV) and 6-methyl-2,4-pyridinediol (V), respectively (2,4,5).

Collie reported V in the form of a diol, but no structural determination was carried out. Recent evidence obtained in this laboratory based upon structural determination of V by NMR, IR, and UV is consistent with form Va rather than Vb, Vc and Vd. The diol structure (Vb) can be ruled out immediately since compound V revealed a carbonyl absorption at  $1660\text{ cm}^{-1}$  in the infrared. The diketo structure (Vd) can be ruled out because of the lack of typical carbonyl absorption (expected  $\sim 1730\text{ cm}^{-1}$ ) and by  $pK_a$  measurements; V with a  $pK_a$  of 7.5 is much more acidic than can be rationalized by a diketo structure. A  $\text{COCH}_2\text{CO}$  NMR signal ( $\delta = 3.5\text{--}4.0$ ) is also not observed in V. The NMR spectrum in  $d_6\text{DMSO}$  supports the structural requirement of the Va molecule. There is a broad unresolved peak at  $\delta = 2.1$ , consistent with a methyl group at the 6 position; a doublet at  $\delta = 5.36$  with coupling constant  $J = 2.1$  cps is consistent with a ring hydrogen at the 3 position which is shifted up-field due to a neighboring keto group; a multiplet at  $\delta = 5.62$ , consistent with a ring hydrogen at the 5 position resulting from coupling with the neighboring  $-\text{CH}_3$  group; a broad peak at  $\delta = 10.75$ , consistent with  $-\text{NH}$  and  $-\text{OH}$  protons. Peak areas for the methyl hydrogens, two ring protons and  $-\text{NH}$ ,  $-\text{OH}$  protons were found to be in the ratio of 3:1:1:2.

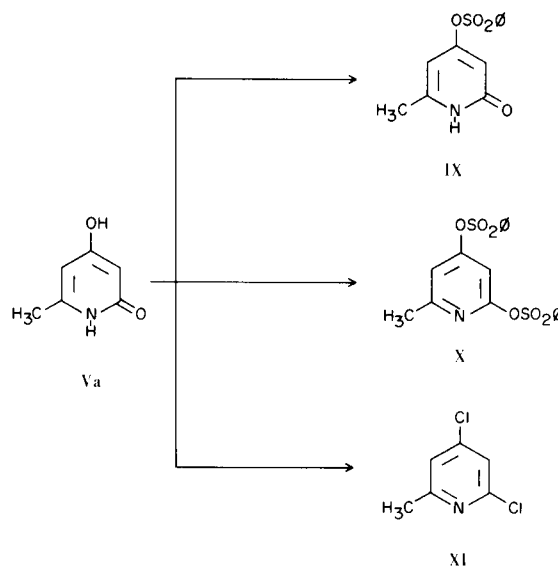
Conclusive evidence of the structure Va was obtained by comparison of the UV absorption maxima in ethanol with the model compounds. Hertog and Burrman prepared 1-methyl-4-methoxy-2-pyridone (VI), 1-methyl-2-methoxy-4-pyridone (VII), and 2,4-dimethoxypyridine (VIII) for UV comparison (6). Compounds VI, VII and VIII have no tautomeric properties. The absorption maxima for VI, VII and VIII were  $280\text{ m}\mu$ ,  $240\text{ m}\mu$  and  $260\text{ m}\mu$ , respectively.



By comparison of the UV absorption maxima, Hertog confirmed the structure of 4-hydroxy-2-pyridone ( $277\text{ m}\mu$ ), 4-methoxy-2-pyridone ( $276\text{ m}\mu$ ), 1-methyl-4-hydroxy-2-pyridone ( $280\text{ m}\mu$ ) and 2-methoxy-4-pyridone ( $248\text{ m}\mu$ ) (6). Compound Va with UV absorption maxima at  $282\text{ m}\mu$  is consistent with the 2-pyridone structure.

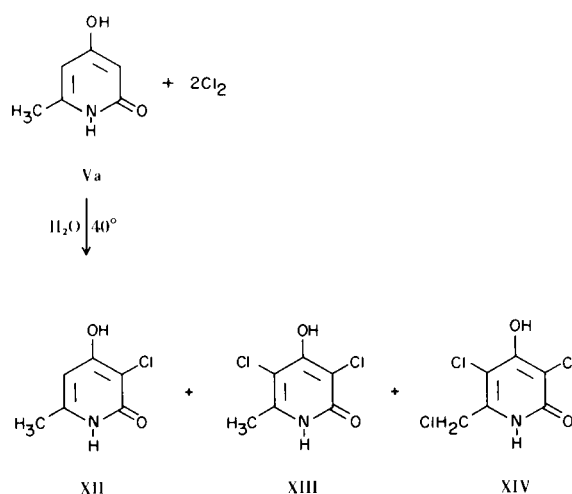
When Va is reacted with an equivalent amount of benzenesulfonyl chloride using triethylamine to absorb the hydrogen chloride evolved, 4-benzenesulfonyloxy-6-

methyl-2-pyridone (IX) is formed. With two equivalent amounts of benzenesulfonyl chloride, 2,4-dibenzenesulfonyloxy-6-picoline (X) is obtained. Refluxing Va with excess of phosphorous oxychloride gives 2,4-dichloro-6-picoline (XI) (7).



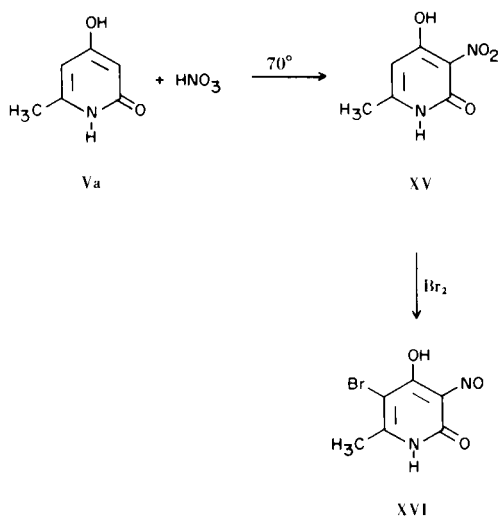
The IR spectrum of IX revealed  $\text{C}=\text{O}$  absorption but no OH absorption. The NMR spectrum in  $d_6\text{DMSO}$  showed a three proton broad peak at  $\delta = 2.15$ ; a one proton doublet at  $\delta = 5.7$ ; a one proton multiplet at  $\delta = 5.9$ ; a five proton multiplet at  $\delta = 7.9$  and a broad peak at  $\delta = 10.8$ . Absorption maxima of  $302\text{ m}\mu$  in ethanol was observed by UV, which is consistent with the structure of IX. IR spectrum of X has no  $\text{C}=\text{O}$  and OH absorption. Compound X gave UV absorption maxima at  $262\text{ m}\mu$  which is consistent with an aromatic pyridine structure.

Chlorination of Va using a 1:2 mole ratio of Va to



chlorine at 40° yielded a mixture of monochloro, dichloro and trichloro compounds in a ratio of 4:4:1 by mass spectral analysis. Separation of the chlorinated mixture was successfully carried out by fractional crystallization. The structures of XII, XIII and XIV were confirmed by mass spectral, NMR and elemental analyses.

Further evidence of the preferential attack on the 3 position of Va by an electrophile was obtained by nitration of Va at 70°. The 3-nitro-4-hydroxy-6-methyl-2-pyridone (XV) was the sole product (8). The remaining ring proton in XV was completely replaced by bromine to give 3-nitro-5-bromo-4-hydroxy-6-methyl-2-pyridone (XVI) (8).



#### EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus (Arthur H. Thomas Co.) and were corrected. Elemental analyses were done by the staff of Dr. L. Swim, The Dow Chemical Company. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 237, the ultraviolet spectra on a Cary recording spectrophotometer, Model 15, and the nuclear magnetic resonance spectra on a Varian Associates Model A-60 spectrometer. Mass spectra were obtained by Dr. J. Tou, The Dow Chemical Company, on an Atlas CH4B mass spectrometer.

##### 6-Methyl-2H-pyran-2,4(3H)-dione (III).

6-Methyl-2H-pyran-2,4(3H)-dione was prepared by the method of Collie (2). Dehydroacetic acid (504 g., 3.0 moles) was dissolved in 1500 g. of 90% sulfuric acid with stirring. The mixture was then heated to 130°. The completion of the reaction was tested by adding a drop of the reaction mixture to water. As soon as no crystals formed in the water upon addition of a drop of the mixture, the contents of the flask were rapidly poured into 2000 g. of cracked ice. 6-Methyl-2H-pyran-2,4(3H)-dione crystallized out immediately. This operation should be carried out as quickly as possible, for prolonged boiling decomposed the lactone to a considerable extent. The solids were filtered, washed with 1000 ml. of cold water, then crystallized from hot water to give a white crystal, m.p. 186-188° (lit. (2) 188°), yield, 327 g. (86.7%).

##### 4-Hydroxy-6-methyl-2-pyridone (Va).

6-Methyl-2H-pyran-2,4(3H)-dione (200 g., 1.6 moles) was dissolved in 200 ml. of 28% ammonium hydroxide solution and the mixture was heated at 100° with vigorous stirring. It was exothermic and foaming started as soon as reaction took place. A crystalline substance very soon began to separate. The reaction mixture was evaporated to about 100 ml. and then heated at 100° for 6 hours. After addition of 200 ml. of water to the reaction mixture, it was allowed to cool to room temperature. The solid was separated by filtration and then recrystallized from an ethanol-water mixture to give 4-hydroxy-6-methyl-2-pyridone, m.p. 324-327° (lit. (2,9) 330°), yield, 167 g. (83.5%).

##### 2,4-Dibenzenesulfonyloxy-6-picoline (X).

4-Hydroxy-6-methyl-2-pyridone (10.7 g., 0.1 mole) was suspended in a mixture of 300 ml. of chloroform and 24.2 g. (0.21 mole) of triethylamine. The mixture was stirred at room temperature and 35.4 g. (0.2 mole) of benzenesulfonyl chloride was added. The resulting solution was then refluxed for five hours. A clear pink solution was formed. After cooling to room temperature, the solution was filtered and the solid on the filter was discarded. The filtrate was washed three times with 70 ml. portions of water. The chloroform solution was then dried on a rotary evaporator. Residue from this evaporation was crystallized two times from an ethanol-acetone mixture to give a white cubic crystal, m.p. 54-55°, 16.5 g. (40%). It was identified as 2,4-dibenzenesulfonyloxy-6-picoline by elemental, infrared, and UV analyses.

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>NO<sub>6</sub>S<sub>2</sub>: C, 53.33; H, 3.70; N, 3.46; S, 15.80. Found: C, 53.04; H, 3.64; N, 3.46; S, 15.6.

##### 4-Benzenesulfonyloxy-6-methyl-2-pyridone (IX).

The same procedure as that for the preparation of X was used. In this case, equivalent amounts of 4-hydroxy-6-methyl-2-pyridone, triethylamine and benzenesulfonyl chloride were applied. White needles, m.p. 193-195°, 41% yield, were obtained. Elemental, infrared, and nmr analysis confirmed the structure.

*Anal.* Calcd. for C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>S: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.1; H, 4.14; N, 5.41.

##### 4-(p-Chlorobenzenesulfonyloxy)-6-methyl-2-pyridone.

This compound was prepared by the reaction of Va with an equivalent amount of p-chlorobenzenesulfonyl chloride and crystallized from ethanol to yield a white crystalline solid, m.p. 173-175°, 39% yield.

*Anal.* Calcd. for C<sub>12</sub>H<sub>10</sub>ClNO<sub>4</sub>S: C, 48.08; H, 3.34; N, 4.67. Found: C, 47.9; H, 3.29; N, 4.5.

##### 2,4-Dichloro-6-picoline (XI).

This compound was prepared by the method of Sedgwick (7). 4-Hydroxy-6-methyl-2-pyridone (25 g., 0.2 mole) was treated with 70 g. of phosphorus oxychloride with stirring. The temperature was kept at 115-120° until feathery crystals began to sublime on the neck of the flask. It took about three to four hours for the reaction to be complete. Then the reaction mixture was carefully distilled. 2,4-Dichloro-6-picoline, a colorless oil, boiling at 200-205°/760 mm or 110-112°/50 mm (lit. (7) 200°/760 mm) was collected (21 g., 65%).

##### Chlorination of 4-Hydroxy-6-methyl-2-pyridone.

4-Hydroxy-6-methyl-2-pyridone (25 g., 0.2 mole) was suspended with stirring in 287 ml. of water. Chlorine gas was bubbled through this solution at 40°. After one hour, all the starting material was dissolved and a clear solution was obtained. The

reaction was slightly exothermic so that no external heating was required to keep the mixture at 40°. The completion of the reaction was checked by the chlorine consumption and the gain in weight of the flask. After 28.2 g. (0.4 mole) of chlorine was consumed, the flask was cooled overnight. The yellow solid was filtered and dried. It weighed 14.5 g. Mass spectral analysis indicated that it was a mixture of monochloro, dichloro and trichloro compounds in a ratio of 4:4:1. The filtrate was concentrated on a rotary evaporator to 30 ml. and then allowed to stand in a refrigerator for several days. A yellow solid deposited from the solution was filtered and then recrystallized three times from ethanol with a Norite treatment to give pink crystals, m.p. 166-170°. It was identified as 3,5-dichloro-4-hydroxy-6-chloromethyl-2-pyridone (XIV) by infrared, nmr and mass analyses. Compound XIV,  $m/e = 227$ , a  $-CH_3$  group, was not evident in the ir spectrum. A band at  $1267\text{ cm}^{-1}$  supported a  $-CH_2Cl$  wagging vibration on an olefinic carbon. No aromatic hydrogens were evident in the nmr spectrum. Some deuterium exchangeable hydrogen was present which most likely is  $-NH$  or  $-OH$ . The peak at  $\delta = 4.48$  supported a  $-CH_2Cl$  proton rather than a  $-CH_3$  proton.

The solid obtained from the chlorination of Va was recrystallized four times from an ethanol-acetone mixture with a Norite treatment to give white needles, m.p.  $> 300^\circ$ . It was confirmed as 3-chloro-4-hydroxy-6-methyl-2-pyridone (XII) by elemental, mass and nmr analyses. Compound XII was consistent with  $m/e = 159$  and the nmr spectrum showed a three proton peak at  $\delta = 2.14$ . A ring proton at  $\delta = 5.85$  and a broad two proton peak at  $\delta = 11.24$ .

*Anal.* Calcd. for  $C_6H_6ClNO_2$ : C, 45.14; H, 3.76; N, 8.77; Cl, 22.26. Found: C, 45.3; H, 3.61; N, 8.7; Cl, 22.2.

The first ethanol-acetone filtrate from the above recrystallizations were concentrated to 10 ml. on a hot plate. Upon cooling, it deposited out yellow crystals which were recrystallized three times from an ethanol-acetone mixture to give white needles, m.p. 250-252°. It was identified as 3,5-dichloro-4-hydroxy-6-methyl-2-pyridone (XIII) by elemental, nmr and mass analyses. Compound XIII was consistent with  $m/e = 193$  and its nmr spectrum revealed a three proton peak at  $\delta = 2.25$  and a broad two proton peak at  $\delta = 11.0$ .

*Anal.* Calcd. for  $C_6H_5Cl_2NO_2$ : C, 37.11; H, 2.58; Cl, 36.60. Found: C, 37.1; H, 2.81; Cl, 36.5.

#### 3,5-Dichloro-2,4-dibenzenesulfonyloxy-6-picoline.

This compound was obtained by the reaction of XIII with two equivalent amounts of benzenesulfonyl chloride and then crystallized from ethanol to yield white crystalline solids, m.p. 97-98°, in 66% yield.

*Anal.* Calcd. for  $C_{18}H_{13}Cl_2NO_6S_2$ : C, 45.57; H, 2.74; N, 2.95. Found: C, 45.58; H, 2.76; N, 2.89.

#### 3,5-Dichloro-2,4-di-*o*-nitrobenzenesulfonyloxy-6-picoline.

This compound was also prepared in the same manner by the reaction of XIII with two equivalent amounts of *o*-nitrobenzenesulfonyl chloride and crystallized from ethanol to yield a white crystalline solid, m.p. 197-199°, in 58% yield.

*Anal.* Calcd. for  $C_{18}H_{11}Cl_2N_3O_{10}S_2$ : C, 38.30; H, 1.95; N, 7.45. Found: C, 38.33; H, 2.11; N, 7.35.

#### 3-Nitro-4-hydroxy-6-methyl-2-pyridone (XV).

Compound XV was prepared by the method of Lapworth (8).

4-Hydroxy-6-methyl-2-pyridone (20 g., 0.16 mole) was dissolved in 600 ml. of 70% nitric acid solution (sp. gr. 1.42) and 120 ml. of water. The flask was heated to 70°, a further quantity of 200 ml. of 70% nitric acid was added, and the temperature of the reaction mixture was allowed to rise to 80°. As soon as red fumes began to appear, the flask was cooled and the contents poured into one liter of ice water. The nitro compound which separated as a yellowish-white solid was collected and washed with cold water. It was recrystallized from water to yield glistening yellow needles, m.p. 285-286° (lit. (8) 285°), yield 22 g. (82%). Its structure was confirmed by nmr analysis. The nmr spectrum of XV in  $d_6$ DMSO showed a three proton broad peak at  $\delta = 2.24$ , a one proton multiplet at  $\delta = 5.91$  and a two proton broad peak at  $\delta = 11.05$ , which was consistent with the structure XV.

#### 3-Nitro-4-hydroxy-5-bromo-6-methyl-2-pyridone (XVI).

3-Nitro-4-hydroxy-6-methyl-2-pyridone (8 g., 0.047 mole) was suspended in 250 ml. of glacial acetic acid by mechanical stirring. To this mixture, 10.8 g. (0.06 mole) of bromine was added dropwise. After the addition of bromine was complete, the reaction mixture was heated at 40-50° for three hours. The contents of the flask were then allowed to stand at room temperature overnight. The yellow solid which separated out from the solution was filtered and then recrystallized from 1000 ml. of hot water. One more recrystallization from acetone gave yellow needles, m.p. 263-265°. It weighed 8.8 g. (74%). It was identified as 3-nitro-4-hydroxy-5-bromo-6-methyl-2-pyridone by elemental and nmr analyses.

*Anal.* Calcd. for  $C_6H_5BrN_2O_4$ : C, 28.9; H, 2.02; Br, 32.1. Found: C, 29.2; H, 2.3; Br, 32.0.

#### Acknowledgment.

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