Reaction of Alkylhydrazines. II. *vic*-Disubstituted Pyridines and Pyridopyridazines (1,2)

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Received January 22, 1974

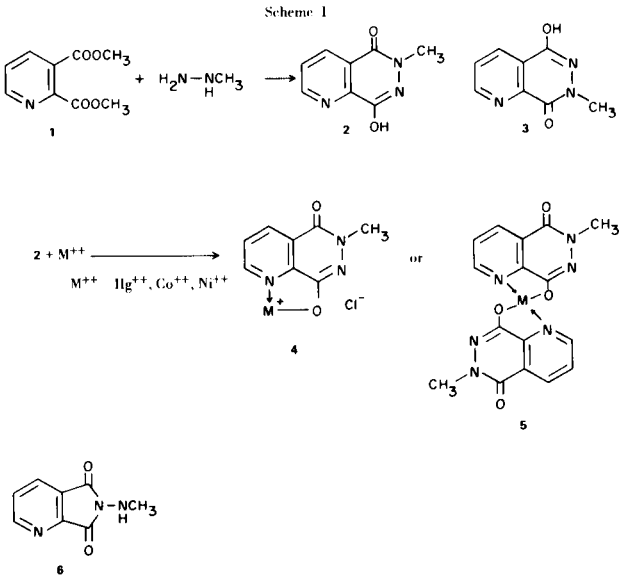
A series of 2,3-disubstituted pyridines and pyrido[2,3-*d*]pyridazines have been synthesized. The molecular structure of the compounds have been elucidated by using chromatography; ir, nmr, and mass spectrometry; and chemical methods, in particular metal complexation. The new compounds offer interesting chemistry and are envisaged to function as potential chemotherapeutic and pharmacodynamic agents.

In an earlier communication (3), we have reported the reaction of methylhydrazine and 1,1-dimethylhydrazine with alkyl benzoates and alkyl phthalates. The heterocyclic analogs of the resultant compounds were envisaged to be of interest, both chemically and biologically, because compounds of similar structures have been shown to be potential chemotherapeutic agents (4). Moreover, the methods devised for structural elucidation of reaction intermediates and products (*vide infra*) offer wide applicability in synthetic chemistry.

With these objectives in mind, dimethyl 2,3-pyridinedicarboxylate (**1**) was allowed to react with methylhydrazine, both at room temperature and under reflux (100° oil bath). The tlc and nmr analysis of the reaction product indicated the presence of two compounds, which were separated by differential solubility and identified by elemental analysis, ir, nmr, and mass spectrum as 4-hydroxy-2-methylpyrido[2,3-*d*]pyridazin-1-one (**2**) and 1-hydroxy-3-methylpyrido[2,3-*d*]pyridazin-4-one (**3**). Assignment of the correct molecular structure to each isomer was accomplished by allowing an aqueous solution of each compound to equilibrate at room temperature with an aqueous solution of Ni^{++}, Co^{++}, and Hg^{++}. Analogous to 8-hydroxyquinoline (5), compound **2** would be expected to chelate whereas such complexation should not occur with **3**. Only the low melting isomer gave a precipitate with the metal chlorides, presumably a chelate, whose structure was observed to be independent of the molar ratios of the reactants. The elemental analysis of the complex was indicative of a 1:1 ligand-metal structure **4** rather than **5**.

Corroborating evidence of a chelation reaction was obtained with far ir analysis. The far ir spectra of both the Ni and Co complex of **2** showed the appropriate O-Ni and N-Ni stretching frequencies ν at 304 cm^{-1} and 255 cm^{-1} and O-Co and N-Co ν at 300 cm^{-1} and 255 cm^{-1}, respectively. These data can only be attributed to chelate formation. The band positions assignment were based on the results of a series of investigations on the stretching frequencies of both Ni and Co complexes of a number of organic ligands and comparison of the bands positions with those for their isotopic analogs (5,6,7).

Scheme I



The possibility of **6** being one of the reaction products of **1** and methylhydrazine was excluded since the ir spectra of neither **2** nor **3** contains C=O stretching bands above 1700 cm^{-1}, a characteristic attributed to the five-membered rings and smaller imides.

The reaction of **1** with excess 1,1-dimethylhydrazine afforded bis-trimethylhydrazonium 2,3-pyridinedicarboxylate (**7**) when reaction was carried out under reflux. At room temperature, as detected by using tlc, the product

consisted of a mixture of two compounds. Based on the ir and nmr spectral data, the compounds were assigned the structures of trimethylhydrazonium 2-carbomethoxy-3-pyridinecarboxylate (**8**) and trimethylhydrazonium 3-carbomethoxy-2-pyridinecarboxylate (**9**).

Attempts to separate **8** and **9** from the gummy product by differential solubility using various solvents were unsuccessful. The spectral data evidences were supported by conversion of the mixture of the two trimethylhydrazonium esters, by using silica gel column chromatography, to their corresponding mixture of acid esters, whose spectral data were identical to those of authentic samples (8). Likewise, the mixture of **8** and **9** was treated with methylhydrazine. The resulting mixture of two hydrazonium hydrazides, whose structures were proved by using ir and nmr spectrometry, upon heating in 1-butanol was converted to a mixture of the two bicyclic compounds, **2** and **3**, the preparations and spectral properties of which have been described above.

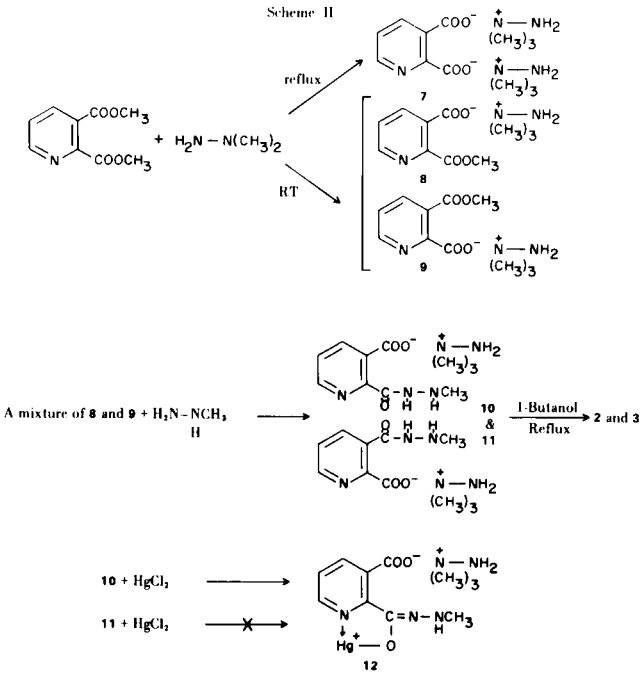
A partial separation of **8** and **9** was achieved by dry column chromatography. Structural assignment was made by the metal complexation method. The isomer with the nmr methoxy protons peak at δ 4.18 was assigned to **8** because its methylhydrazide derivative, **10**, gave a precipitate (chelate) with Hg^{++}.

Reaction of 2,3-pyridinecarboxylic acid anhydride (**13**) with methylhydrazine either by heating under reflux or at room temperature gave a mixture of **2** and **3**. Similarly, heating **13** under reflux with 1,1-dimethylhydrazine afforded a mixture of **2** and **3**. However, at room temperature the reaction product, as indicated by tlc, consisted of a mixture of two compounds which were separated by differential solubility and identified by elemental analysis, ir, and nmr (triplet δ 2.9 in TFA collapsed to a singlet in deuterium oxide) to be a mixture of dimethylammonium 2-(2,2-dimethylcarbohydrazide)-3-pyridinecarboxylate (**14**) and dimethylammonium 3-(2,2-dimethylcarbohydrazide)-2-pyridinecarboxylate, (**15**). The structural assignments were made by assuming that the enol form of **14** would be capable of forming a complex with Hg^{++} analogous to that of **2** or **10**; whereas, **15** would not. Since the half hydrazide with m.p. 165°, formed an insoluble chelate, structure **14** was assigned to this isomer and **15** to that with m.p. 172°. Upon heating in 1-butanol, either **14** or **15** was cyclized to **2** or **3** respectively. The two organic salts, therefore, were assumed to be possible intermediates in the formation of **2** or **3**.

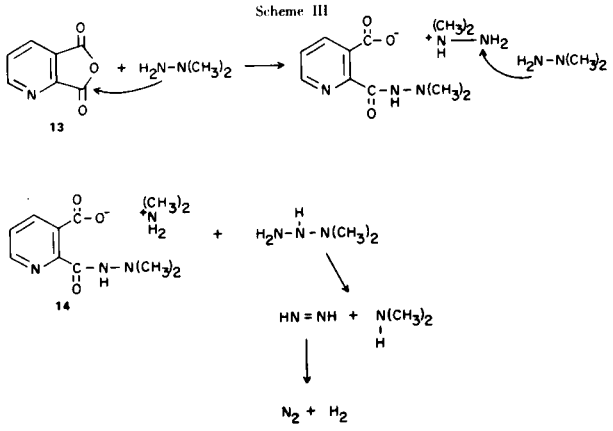
In conclusion, the reactions presented as a result of the current investigation offer wide synthetic applicability. The chemotherapeutic activity of the reported compounds are under investigation. Additionally, since assignment of molecular structure to isomers is often difficult by spectrometry alone, the development of the metal complexation method coupled with far infrared analysis offers an unambiguous means of structural elucidation in analogous systems.

Certain mechanistic pathways have been implicated as a result of the identification of intermediates leading to the final bicyclic products in the pyridine system. This is illustrated in Scheme III.

Scheme II



Scheme III



EXPERIMENTAL

The melting points (m.p.) (uncorrected) were determined on a Thomas-Hoover apparatus using open capillaries. The infrared (ir) spectra were taken on a Beckman IR-8; using potassium bromide disks for the solid compounds and sodium chloride windows for sandwiching the semisolid and liquid compounds. Only the bands for C=O stretching frequencies in wave number ν max (cm^{-1}) were reported. The far ir spectra were taken on a Beckman IR-11;

a Nujol mull of the sample was prepared and pressed between two strips of polyethylene. The nuclear magnetic resonance (nmr) spectra were determined on a Jeol C-60 HL using trifluoroacetic acid (TFA) as a solvent and sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionate (TTP) as a reference. The mass spectra (ms) were measured on a DuPont 21-491 instrument. The thin layer chromatography (tlc) was done on microscope slides coated with silica gel HF 254 + 366 (Brinkmann Instruments, Inc.). All evaporations were carried out *in vacuo* in a rotatory evaporator. The elemental analyses were done by Schwarzkopf Microanalytical Laboratories, Woodside, New York.

4-Hydroxy-2-methylpyrido[2,3-*d*]pyridazin-1-one (**2**) and 1-Hydroxy-3-methylpyrido[2,3-*d*]pyridazin-4-one (**3**).

To 5.0 g. (0.026 mole) of dimethyl 2,3-pyridinedicarboxylate was added 12.0 g. (0.26 mole) of methylhydrazine. The mixture was heated under reflux for 24 hours during which time a yellow solid was formed. The excess methylhydrazine was evaporated and the residue was washed several times with ether to give 3.30 g. (72%) of a mixture of **2** and **3**, as determined by using tlc, (2 spots, methanol:chloroform, 25:1) and nmr (2 peaks for N-CH_3 at δ 3.88 and 3.90 with an integral ratio of 6 to 4 respectively).

The two structural isomers were separated by heating the reaction product in ethyl acetate, in which **2** was found to be more soluble. The yield of **2** was 1.9 g. (40%). The sample for analysis was crystallized from a mixture of benzene and methanol, m.p. 204-205°; ir: 1630, 1575 cm^{-1} (C=O); nmr: δ 3.88 (N-CH_3, s), 8.53-9.80 (pyridine, m); ms: M^+ (m/e) 177.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.01; H, 4.09; N, 23.97.

The yield of **3** was 1.4 g. (30%). The sample for analysis was crystallized from a mixture of ethyl acetate and methanol, m.p. 288-290°; ir: 1650, 1590 cm^{-1} (C=O); nmr: 3.90 (N-CH_3, s) 8.58-9.58 (pyridine, m); ms: M^+ (m/e) 177.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 53.94; H, 4.03; N, 23.97.

Mercury Chelate of 4-Hydroxy-2-methylpyrido[2,3-*d*]pyridazin-1-one (**4**).

To 2.0 g. (0.0113 mole) of **2** in 75 ml. of distilled water was added an excess of saturated solution of mercuric chloride. After leaving at room temperature for 2 hours, the resulting yellow precipitate was filtered and washed twice with water and crystallized from 10% methanol to give 3.80 g. (84%) of **4**, m.p. >360°; ir: 1630 and 1570 cm^{-1} (C=O). Far ir: 299, 271, and 255 cm^{-1}.

Anal. Calcd. for $C_8H_6ClN_3O_2Hg$: C, 23.33; H, 1.46; N, 10.21. Found: C, 23.56; H, 1.78; N, 10.65.

Bistrimethylhydrazonium 2,3-Pyridinedicarboxylate (**7**).

To 5.0 g. (0.026 mole) of dimethyl 2,3-pyridinedicarboxylate was added 12.0 g. (0.20 mole) of 1,1-dimethylhydrazine. The mixture was heated under reflux for 24 hours. The workup was analogous to that of **2** or **3** to yield 6.5 g. (79%) of **7**. The sample for analysis was crystallized from a mixture of ethyl acetate and methanol, m.p. 208° (dec.); ir: 1595, 1573 cm^{-1} (C=O); nmr: δ 3.44 ($N^+(CH_3)_3$, s), 8.34-9.40 (pyridine, m).

Anal. Calcd. for $C_{13}H_{25}N_5O_4$: C, 49.52; H, 7.94; N, 22.22. Found: C, 49.26; H, 8.07; N, 22.06.

Trimethylhydrazonium 2-Carbomethoxy-3-pyridinecarboxylate (**8**) and Trimethylhydrazonium 3-Carbomethoxy-2-pyridinecarboxylate (**9**).

To 5.0 g. (0.026 mole) of dimethyl 2,3-pyridinedicarboxylate was added 12.0 g. (0.20 mole) of 1,1-dimethylhydrazine. The mixture was left at room temperature for 24 hours at which time a gummy substance was formed. Washing this successively with ether eliminated the unreacted diester and 1,1-dimethylhydrazine. The residue was stripped of the solvent to give 1.5 g. (23%) of a mixture of **8** and **9** which was found to be extremely hygroscopic; ir (neat): 1740 and 1605 cm^{-1} (C=O); nmr: δ 3.47 ($N^+(CH_3)_3$, s), 4.18 and 4.20 (OCH_3, s), 8.40-9.27 (pyridine, m); ms: (m/e) 164 (A mass ion peak for the OH-cleaved acid esters formed from **8** and **9**).

Dimethylammonium 2-(2,2-Dimethylhydrazide)-3-pyridinecarboxylate (**14**) and Dimethylammonium 3-(2,2-Dimethylhydrazide)-2-pyridinecarboxylate (**15**).

To 5.0 g. (0.034 mole) of 2,3-pyridinedicarboxylic anhydride was added 12.0 g. (0.20 mole) of 1,1-dimethylhydrazine and left at room temperature for 24 hours. The reaction product, whose formation was observed by tlc, was collected as a solid after evaporation of the excess 1,1-dimethylhydrazine and washings with ether. The yield, consisting of a mixture 35:65 of **14** and **15** respectively (*vide infra*) was 7.1 g. (82%). The two isomers were separated by differential solubility in a mixture of ethyl acetate and methanol, in which the more soluble isomer was **14** (with a yield of 2.6 g. (30%)). The sample for analysis was crystallized from ethyl acetate, m.p. 164-165°; ir: 1650 and 1590 cm^{-1} (C=O); nmr: δ 2.95 ($N^+(CH_3)_2$, t), 3.60 ($N(CH_3)_2$, s) 8.40-9.43 (pyridine, m); ms: (m/e) 191 (A mass ion probably for *N,N*-dimethylaminoquinolineimide formed from **14**).

Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.97; H, 7.08; N, 22.04. Found: C, 51.88; H, 7.18; N, 21.86.

The yield of **15** was 4.4 g. (50%). The sample for analysis was crystallized from ethyl acetate, m.p. 171-172°; ir: 1660 and 1600 cm^{-1} (C=O); nmr: δ 2.95 ($N^+(CH_3)_2$, t), 3.60 ($N(CH_3)_2$, s) 8.33-9.46 (pyridine, m); ms: (m/e) 191 (same as **14**).

Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.97; H, 7.08; N, 22.04. Found: C, 52.25; H, 7.19; N, 21.92.

The structural assignments were done analogous to those of **10** and **11**.

Acknowledgements.

The authors wish to thank Dr. Phillip Stotter of the University of Texas Chemistry Department for discussions and suggestions.

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(1) This investigation was supported in part by a grant from the University of Texas Research Institute.

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