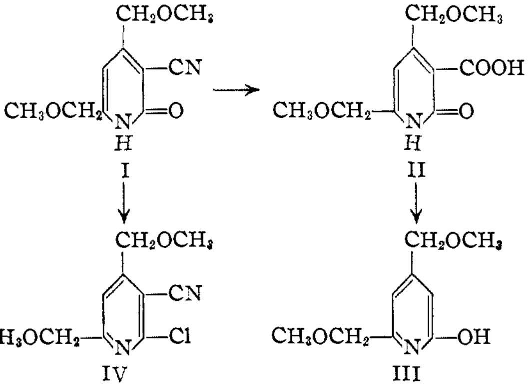
The Synthesis of Some Dimethoxymethylpyridines

BY RAYMOND P. MARIELLA AND ANTON J. HAVLIK[1]

1,5-Dimethoxy-2,4-pentandione,[2] formed in the condensation of methoxyacetone with methyl methoxyacetate, readily condensed with cyanoacetamide to form the pyridone (I). This pyridone was transformed into the compounds shown in Table I.

TABLE I



We were particularly interested in III because of its possible relationship to pyridoxin. When tested against *Neurospora sitophila*,[3] III did not exhibit any B_6 or anti-B_6 activity.

We wish to acknowledge a grant from the Graduate School of Northwestern University which has supported some of this work.

Experimental[4]

4,6-Dimethoxymethyl-3-cyano-2(1)-pyridone (I).—To 34 g. of 1,5-dimethoxy-2,4-pentandione[2] (b.p. 90° at 2.5 mm.), 18.7 g. of cyanoacetamide in 110 ml. of water were added 6 ml. of piperidine acetate. After refluxing for 2 hours, the contents were acidified and cooled. Filtration gave 26 g., m.p. 158–160°. Recrystallization from alcohol gave white needles, m.p. 160°. These gave a negative $FeCl_3$ test.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: N, 13.4. Found: N, 13.2.

4,6-Dimethoxymethyl-3-cyano-2-chloropyridine (IV).—To 2 g. of I dissolved in 6 ml. of phosphorus oxychloride were added 2.3 g. of phosphorus pentachloride, and the mixture refluxed for 2 hours. After taking the mixture to dryness under reduced pressure, the residue was treated with 20 ml. of methanol and then neutralized with sodium bicarbonate. Filtration gave 1.3 g. of solid (59% yield). Vacuum sublimation yielded long slender white needles, m.p. 77.5°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2$: N, 12.4. Found: N, 12.8.

4,6-Dimethoxymethyl-3-carboxy-2(1)-pyridone (II).—A mixture of 1.5 g. of I and 10 ml. of concentrated hydrochloric acid was refluxed for 14 hours. This was then taken to dryness under reduced pressure, and the residue crystallized from water, m.p. 230–240° (83%). Several recrystallizations from water yielded a white powder, m.p. 246° (dec.).

Anal. Calcd. for $C_{10}H_{13}NO_5$: N, 6.2. Found: N, 5.9. Compound II gave a negative $FeCl_3$ test.

4,6-Dimethoxymethyl-2-pyridol (III).—One gram of II was heated in a sublimation tube to 250° and kept there for 10 minutes till the carbon dioxide fumes were gone. The red residue was then vacuum sublimed and the pyridol was obtained as a white powder (2%), m.p. 202.5°. Compound III gave a positive (red) $FeCl_3$ test.

Anal. Calcd. for $C_9H_{13}NO_3$: N, 7.6. Found: N, 7.3.

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[1] Supported by the Abbott Research Fund of Northwestern University.

[2] W. Braker, E. J. Pribyl, J. T. Sheehan, E. R. Spitzmiller and W. A. Lott, THIS JOURNAL, **69**, 3072 (1947).

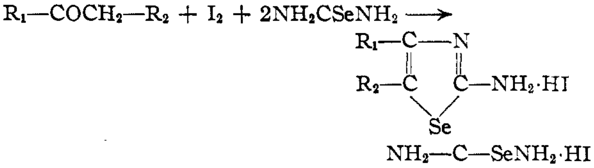
[3] Tests conducted by the Biological Group at the Eli Lilly Research Laboratories, Indianapolis, Indiana.

[4] Analyses by Misses Sorenson and Hobbs.

The Reaction of Ketones with Iodine and Selenourea[1]

BY L. CARROLL KING AND R. J. HLAVACEK

Recent papers from this Laboratory have described the synthesis of 2-aminothiazoles by allowing ketones to react with iodine and thiourea.[2] The *same reaction technique may be extended to* preparation of selenazoles. The selenazoles and acetaminoselenazoles prepared are listed in the Table I. The method of preparation differed from the corresponding thiazole synthesis in that a longer reaction time and a modified isolation procedure were necessary. In general an excess of the ketone was used in the reaction mixture and yields are reported in terms of iodine as the limiting reagent. The high yield of 2-amino-4-(*m*-nitrophenyl)-selenazole, over 100%, may be due to the presence of excess *m*-nitroacetophenone, where the nitro group acted as an oxidizing agent converting some of the hydrogen iodide of the selenourea hydroiodide to free iodine. This free iodine could then react with ketone and selenourea in the normal way to give the yield of selenazole reported.



Experimental

Test for Selenium.—The presence of selenium was qualitatively demonstrated by the following procedure: a sodium fusion was run on the compound. The basic solution was acidified with concentrated hydrochloric acid and sulfur dioxide was passed through the solution for several minutes. The separation of flocculent, red precipitate[3] as observed under a low power magnifying glass, indicated the presence of selenium.

Selenourea.—A slow, steady stream of hydrogen selenide[4] was passed through an aqueous or ethereal solution of cyanamide[5] to which had been added a few drops of concentrated hydrochloric acid or ammonia, until crystallization of the selenourea began. The reaction mixture was cooled and the product filtered in a good hood. The crude material was recrystallized from a minimum volume of hot water, using a small amount of Norite A to clarify the solution. Recrystallization produced colorless needles which slowly turned black on standing even when stored, almost dry, at

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[1] This investigation was partially supported by a grant from the Abbott Fund of Northwestern University.

[2] R. M. Dodson and L. C. King, THIS JOURNAL, **67**, 2242 (1945); *ibid.*, **68**, 871 (1946); L. C. King and I. Ryden, *ibid.*, **69**, 1813 (1947); L. C. King and R. J. Hlavacek, *ibid.*, **72**, 3722 (1950).

[3] Scott, "Standard Methods of Chemical Analysis," Vol. I, Fifth Ed., D. Van Nostrand Co., Inc., New York, N. Y., p. 775.

[4] Prepared by the addition of concentrated hydrochloric acid to a Kipp generator charged wuth lumpy ferrous selenide. It was sometimes necessary to heat the acid in order to start the reaction.

[5] Prepared by adding a slight excess (5%) of red mercuric oxide to the calculated amount of thiourea suspended in water or ether.