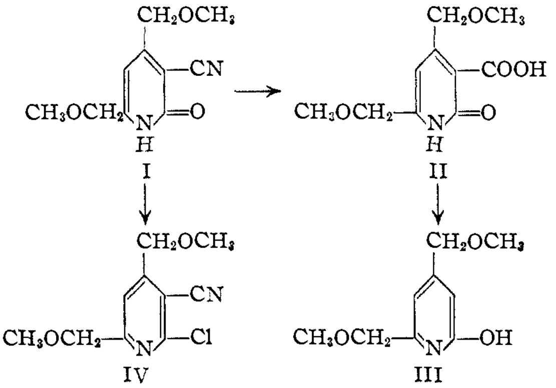
The Synthesis of Some Dimethoxymethylpyridines

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).

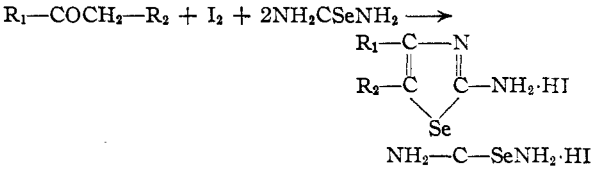
[3] Tests conducted by the Biological Group at the Eli Lilly Research Laboratories, Indianapolis, Indiana.

[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.

TABLE I

Ketone	Selenazole	Formula	M.p., °C. Found[a]	M.p., °C. Reported	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
Acetoacetic ester	2-Amino-4-methyl-5-carbethoxy	$C_7H_{10}N_2O_2Se$	180–181	181–182[h,i]	15[m]	12.02	12.25
	2-Acetamido-4-methyl-5-carbethoxy	$C_9H_{12}N_2O_3Se$	216–218	[l]		10.18	10.25
Acetophenone	2-Amino-4-phenyl	$C_9H_8N_2Se$	132–133	132–133[c,d,e,f,g,h]	65	12.56	12.45
	2-Acetamido-4-phenyl	$C_{11}H_{10}N_2OSe$	197–199	196.5–197.5[g]		10.57	10.62
Propiophenone	2-Amino-4-phenyl-5-methyl	$C_{10}H_{10}N_2Se$	141–142	[l]	84	11.81	11.81
	2-Acetamido-4-phenyl-5-methyl	$C_{12}H_{12}N_2OSe$	206–207	[l]		10.03	10.20
p-Chloroacetophenone	2-Amino-4-(*p*-chlorophenyl)-	$C_9H_7N_2ClSe$	160–162	160–160.5[g]	51	10.88	10.97
	2-Acetamido-4-(*p*-chlorophenyl)-	$C_{11}H_9N_2ClOSe$	269–270	263–264[g]		9.35	9.63
m-Nitroacetophenone	2-Amino-4-(*m*-nitrophenyl)-	$C_9H_7N_3O_2Se$	194–195	[l]	116[j]	15.67	15.18
	2-Acetamido-4-(*m*-nitrophenyl)-[b]	$C_{11}H_9N_3O_3Se$	306–307	[l]		13.55	12.85
Desoxybenzoin	2-Amino-4.5-diphenyl	$C_{15}H_{12}N_2Se$	189–190	[l]	15	9.36	9.42
	2-Acetamido-4.5-diphenyl	$C_{17}H_{14}N_2OSe$	204–205	[l]		8.21	8.46
Cyclohexanone	2-Amino-4.5.6,7-tetrahydrobenzo	$C_7H_{10}N_2Se$	126–127	125.5–126[g]	20[n]	13.93	13.20[k]
	2-Acetamido-4,5,6,7-tetrahydrobenzo	$C_9H_{12}N_2OSe$	142–143	140[g]		11.52	11.23
α-Tetralone	2-Amino-4.5-dihydronaphtho(1.2)-	$C_{11}H_{10}N_2Se$	149–150	[l]	44	11.24	11.06
	2-Acetamido-4,5-dihydronaphtho(1.2)-	$C_{13}H_{12}N_2OSe$	241–242	[l]		9.62	9.58

[a] All melting points observed on a Fisher–Johns melting point apparatus. [b] Low solubility of this compound required acetone–water as a solvent while alcohol–water was adequate for all other compounds reported. [c] G. Hofmann, *Ann.*, **250**, 304 (1888). [d] Backer and de Jonge, *Rec. trav. chim.*, **60**, 495–501 (1941). [e] Jensen and Schmith, *Dansk. Tids. Farm.*, 15, 197–199 (1941). [f] Guha and Roy, *Current Sci.*, **12**, 150 (1943). [g] Backer and Bos, *Rec. trav. chim.*, **62**, 580 (1943). [h] Roy and Guha, *J. Indian Chem. Soc.*, **22**, 82 (1945). [i] Mistakenly reported as 2-amino-4-methyl-5-carboxyselenazole by Roy and Guha (ref. *h*). [j] See discussion in text. [k] Calcd.: C, 41.71; H. 5.01. Found: C, 41.81; H, 4.93. [l] Not previously reported. [m] Average of three runs. [n] Average of two runs.

0°. The yield of pure selenourea, m.p. 200–205°, varied from 20–30%.

Preparation of Selenazoles.—To a mixture of 0.02 mole of selenourea and 0.02 mole of ketone (100% excess) was added 0.01 mole of iodine. After thorough mixing, the reaction mixture was heated on a steam-bath for about 36 hours. The mixture was then extracted three times with ether to remove excess ketone or unreacted iodine.

The ether-moist salt was treated with concentrated ammonia to decompose the salt. The ammoniacal suspension was cooled in an ice-bath and the precipitate, red to purplish-black in color, separated and thoroughly extracted with boiling alcohol. The alcoholic extracts were combined, diluted with water and the precipitated selenazole filtered and dried. The selenazole was recrystallized to constant melting point from alcohol–water.

The acetyl derivatives were prepared by heating the selenazole with acetic anhydride. The derivatives were recrystallized from alcohol–water.

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Exchange between Radioactive Iodine and Derivatives of Monopyridine Iodine(I) in Pyridine[1,2]

BY JACOB KLEINBERG[3] AND JAMES SATTIZAHN

It is generally accepted that in violet solutions iodine exists primarily as I_2 molecules, whereas in brown solutions the iodine is bound chemically in some manner to the solvent.[4] The exact nature of the binding between iodine and the solvent molecules in brown solutions has not, in general, been determined.

Solutions of iodine in pyridine are brown. Conductivity studies on iodine–pyridine solutions[5] have been interpreted in large measure on the basis of the assumption of the dissociation of dissolved iodine into positive IPy^+ and negative I_3^- ions. A recent investigation[6] of the absorption spectra of pyridine solutions of iodine and positive iodine salts of the type IPyX (where X = NO_3 or OOCR) has given considerable support to this assumption. These spectrophotometric studies also give added significance to the data now to be presented, based on earlier work on the exchange in pyridine solution between radioactive iodine and pyridine-coördinated unipositive iodine complexes of the general formula IPyOOCR. In all the cases studied, complete exchange was found to have taken place immediately after the iodine and the positive iodine compound were brought into contact. The rapidity of the exchange is in complete harmony with the ionization mechanism postulated for iodine in pyridine solution.

Experimental

Materials.—The radioactive iodine, I^{128}, was prepared in a nuclear pile by neutron irradiation of and capture by iodine of Mallinckrodt reagent grade. The time of irradiation depended on the ultimate concentration of iodine desired; for the more dilute solutions the sample was irradiated to saturation. Monopyridine iodine(I) β-naphthoate,[7] *p*-chlorobenzoate and *m*-nitrobenzoate[8] were prepared by the reaction of inactive iodine with the silver salts of the appropriate acids in the presence of pyridine. Pyridine (Eastman Kodak Co. white label quality) was dried for at least two weeks over sodium hydroxide pellets and then distilled directly before use, an intermediate fraction of b.p. 104–106° at approximately 590 mm. pressure being collected. The petroleum ether, Mallinckrodt analytical reagent grade, b.p. 30–60°, was used without further purification.

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(1) Work done under the auspices of the Atomic Energy Commission.

(2) The unipositive iodine–pyridine complex ion of the formula IPy^+ will be designated as monopyridine iodine(I).

(3) Department of Chemistry, University of Kansas, Lawrence, Kansas. The work herein described was performed during the summer of 1948, when the senior author was an employee of the Los Alamos Scientific Laboratory.

(4) For discussions of the nature of iodine solutions, see J. Kleinberg and A. W. Davidson, *Chem. Revs.*, **42**, 601 (1948); H. A. Benesi and J. H. Hildebrand, THIS JOURNAL, **71**, 2703 (1949); **72**, 2273 (1950).

(5) L. F. Audrieth and E. J. Birr, THIS JOURNAL, **55**, 668 (1933).

(6) R. A. Zingaro, C. A. VanderWerf and J. Kleinberg, *ibid.*, **73**, 88 (1951).

(7) H. Carlsohn, "Über eine neue Klasse von Verbindungen des positiv einwertigen Iods," Verlag von S. Hirzel, Leipzig, 1932.

(8) R. A. Zingaro, Master's Thesis, University of Kansas, 1948. We are indebted to Mr. Zingaro for our supply of these positive iodine complexes.