Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.76. Found: C, 56.97; H, 4.58.

2-Chloro-3-methoxybenzothiophene 1-Dioxide Methanolate (IIg).—To a solution of 12.5 g. (0.053 m.) of 2,3-dichlorobenzothiophene 1-dioxide in 200 ml. of methanol there was added 3 g. (0.055 m.) of sodium methoxide. After refluxing 2.5 hours, sodium chloride was filtered off the hot solution and the filtrate was allowed to stand overnight at room temperature. The solid was filtered off and recrystallized from methanol to yield 10 g. (81.5%) of the product (IIg), m.p. 152–153°.

Anal. Calcd. for $C_9H_7O_3ClS \cdot CH_3OH$: C, 45.71; H, 4.18; Cl, 13.48. Found: C, 45.82; H, 4.03. Cl, 13.14.

3-Thiocyanomethylbenzothiophene (Ii).—3-Chloromethylbenzothiophene (Ih) was prepared from benzothiophene (Ia), formalin and hydrogen chloride according to Blicke and Sheets.[5] To a solution of 35 g. (0.192 m.) of (Ih) in 600 ml. of absolute ethanol there was added 19.4 g. (0.20 m.) of potassium thiocyanate. After a 30-minute period of refluxing, the solution was filtered hot and the filtrate concentrated *in vacuo*. Water was added, the oil separated and the aqueous phase was washed with chloroform. The oil and chloroform extract were combined and the solvent removed *in vacuo*. Distillation gave 8 g. of starting chloride (Ih), b.p. 121–137° at 2.5–3 mm., and 27 g. (69% conversion, 89% yield) of the thiocyanate (Ii), b.p. 172–176° at 2–2.5 mm., $n^{25}D$ 1.6790.

Anal. Calcd. for $C_{10}H_7NS_2$: C, 58.54; H, 3.42. Found: C, 58.99; H, 3.40.

3-Methoxymethylbenzothiophene (Ij).—To a refluxing suspension of 70 g. (1.08 m.) of potassium cyanide in 1.5 l. of methanol there was added 166 g. (0.91 m.) of 3-chloromethylbenzothiophene[5] (Ih). After 30 minutes the theoretical amount of potassium chloride was removed by filtration, water was added to the filtrate and the oil separated. A benzene extract of the aqueous phase was combined with the oil and the solution was dried over sodium sulfate. The benzene was removed *in vacuo* and the oil distilled. There was obtained 111 g. (68.5%) of the ether (Ij), b.p. 118–120° at 4 mm., $n^{25}D$ 1.6120.

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.47; H, 5.62. Found: C, 65.66, 65.59; H, 5.00, 5.16.

Since these analyses indicated the material to be impure, a derivative, the 1-dioxide, was prepared by hydrogen peroxide oxidation. This product gave analytical data in excellent agreement with the indicated structure (see Table I).

3-Cyanomethylbenzothiophene (Ik).—This material was prepared in 58.5% yield from the chloromethyl compound (Ih) and potassium cyanide in 50% acetone by the method of Blicke and Sheets.[5] However, it is essential that vigorous stirring be employed, no product being isolated when the reagents were merely refluxed.

Dibenzothiophene 5-Monoxide.[6]—To 20 g. (0.012 m.) of dibenzothiophene in 75 ml. of glacial acetic acid there was added 62 ml. (0.60 m.) of 30% hydrogen peroxide. The mixture was slowly warmed to 106° and heated at this temperature for ten minutes when it became homogeneous. The solution was cooled and poured into 200 ml. of water. The precipitate was collected by filtration and crystallized twice from absolute ethanol to give 13.2 g. (55.5%) of the 5-monoxide, m.p. 183.5–184.5°. No dioxide was detected even after refluxing for one hour.

Oxidation of Substituted Benzothiophenes to Dioxides.—The benzothiophene 1-dioxides listed in Table I were prepared by oxidation of the corresponding benzothiophene in a fashion similar to the procedure given for dibenzothiophene 5-monoxide.

In each case a sixfold excess of 30% hydrogen peroxide was used in glacial acetic acid. The reagents were always slowly and carefully heated to 106–108°, allowing for any exothermic reaction which might occur before that temperature was reached. The period of reflux at 106–108° was usually about 30 minutes.

In the case of 3-chloromethylbenzothiophene a violent oxidation occurred at about 65°. However, the product was always a sirup that could not be characterized.

Oxidation of 3-thiocyanomethylbenzothiophene in the usual fashion with 30% hydrogen peroxide produced in good yield, a solid, m.p. 124.0–125.0° (dec. with evolution of gas). Analyses gave no clue as to its structure.

Procedure for Herbicidal Assay.—The method is substantially that described by Thompson, *et al.*,[10] with the modifications noted below. For each compound tested, twenty-five cucumber seeds (variety, Early Fortune) were placed on a filter paper in each of three covered petri dishes. Twenty ml. of the solution at the dilution desired was then placed on the paper. The seeds were allowed to germinate for four days at 76°F. The average length of the primary root of the seventy-five seeds was then determined and compared to the average length of the controls germinated in water alone (arbitrarily designated 100).

The data obtained are listed in Table II.

Acknowledgment.—The authors wish to express their gratitude to Dr. R. M. Hedrick and Messrs. Richard Martin and Norman Phillips for the herbicidal evaluation data and to Miss Mary Neal and Messrs. Paul Adams and Donald Stoltz for the microanalyses.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Alpha-oxygenated Pyridines. I. The Synthesis of an Isomer of 4-Desoxypyridoxin

BY RAYMOND P. MARIELLA AND ELIZABETH P. BELCHER[1,2]

An α-oxygenated isomer of 4-desoxypyridoxin, 3-hydroxymethyl-4,6-dimethyl-2-pyridol, and several related compounds were prepared. None of these compounds possesses any B_6 or anti-B_6 activity.

As a continuation of our studies of compounds related to pyridoxin,[3] we are investigating the effect of the presence of oxygen attached to the α position of the pyridine ring on vitamin B_6 and anti-B_6 activity. All the known compounds possessing B_6 or anti-B_6 activity have one α-position open. In this work, several new substances, all of which possess one oxygen atom in some form in the α-position, have been prepared. These compounds are related to the natural vitamin in that the oxygen atom, normally present in the β-position, is now in the α-position on the other side of the ring. In this regard, IX is an isomer of 4-desoxypyridoxin, a compound of known anti-B_6 activity.

Compounds IV, V and IX, and two previously reported compounds, 4,6-dimethyl-2-pyridol (VI) and 4,6-dimethyl-3-carbethoxy-2-pyridol (VIIIb), exhibited no B_6 or anti-B_6 activity when tested against *Neurospora Sitophila*.[4]

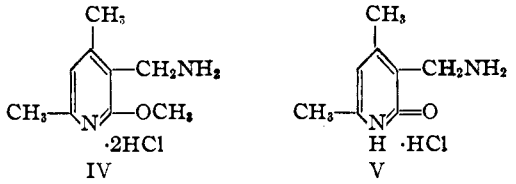
Attempts to reduce 4,6-dimethyl-3-cyano-2-methoxypyridine (III) in the presence of a strong

(1) Eli Lilly and Co. Fellow, 1949–1951.

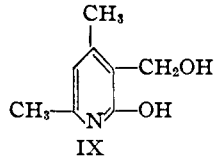
(2) Taken in part from the Ph.D. Thesis of E. P. Belcher.

(3) For the previous paper in this series see R. P. Mariella and J. L. Leech, THIS JOURNAL, 71, 331 (1949).

(4) Tests conducted by the biochemical group at the Eli Lilly Research Laboratories, Indianapolis, Indiana.



IV V



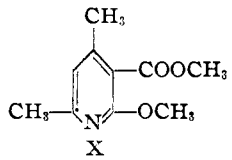
IX

acid (HCl) resulted in the formation of 4,6-dimethyl-3-cyano-2-pyridone (I). Apparently, the α-ether cleaved rapidly to form I, which was resistent to hydrogenation under the experimental conditions. This was confirmed by duplicating the reaction in the absence of hydrogen, and I was formed quantitatively. Acetic acid is too weak an acid to cleave the ether (III) and reduction proceeded satisfactorily in this solvent to give IV. The presence of the β-cyano neighboring group in III makes the ether linkage very sensitive to acid cleavage, but when the strongly electronegative cyano group is converted to the aminomethyl group, this sensitivity is greatly decreased. This is evident in that III is readily cleaved by hydrochloric acid, whereas IV, also an α-ether, can actually be isolated as the dihydrochloride.

Although IV forms a dihydrochloride and a diacetate salt, only a monopicrate of IV could be isolated. Although the ether IV is more stable than the ether III, IV itself is readily cleaved, by refluxing with strong acid, to form V. It was also possible to produce V directly in a one-step reduction from I by means of a mixed platinum–palladium catalyst. V forms only a monohydrochloride, a monopicrate, and gave a negative ferric chloride test. It probably exists in the pyridone form.

The condensation of ethyl cyanoacetate and acetylacetone gave VIIIb,[5] which is readily saponified to give the acid, 4,6-dimethyl-3-carboxy-2-pyridol (VII). This acid is identical with the product formed by the hydrolysis of I. Strong hydrolysis of I yielded VI, which was also formed by the pyrolysis of VII. When I is converted into VI directly, VII very probably is the intermediate.

Treatment of VII with methanolic hydrogen chloride gave 4,6-dimethyl-3-carbmethoxy-2-pyridol (VIIIa), but treatment of VII with diazomethane gave X. The reduction of VIIIb with



X

lithium aluminum hydride proceeded smoothly to give IX.[6]

Diazotization experiments with IV and V were uniformly unsuccessful. The diazotizations were conducted in boiling concentrated hydrochloric acid, at room temperature in buffered acetic acid, and in acetic acid in the presence of hydroquinone. The products were colored amorphous substances from which no pure compounds could be isolated.

We are indebted to the Graduate School of Northwestern University for a grant in support of this work and to the Abbott Research Fund of Northwestern University.

Experimental[7]

2-Methoxy-3-cyano-4,6-dimethylpyridine (III).—III was prepared from 3-cyano-4,6-dimethyl-2-chloropyridine (II).[3] Attempts to reduce III in 15% alcoholic hydrogen chloride with palladium chloride in concentrated hydrochloric acid using twenty pounds of hydrogen pressure resulted in the formation of I. To show that a simple ether cleavage was occurring, 0.05 g. of III was shaken with 20 ml. of 15% alcoholic hydrogen chloride containing 1 ml. of concentrated hydrochloric acid; I was formed quantitatively, m.p. 282–284°, and did not depress the m.p. of the original pyridone.

2-Methoxy-3-aminomethyl-4,6-dimethylpyridine Dihydrochloride (IV).—To a solution of 5.0 g. of III in 125 ml. of glacial acetic acid were added 0.15 g. of platinum oxide, 3.0 g. of anhydrous sodium acetate and 2.5 g. of 5% palladium-on-charcoal.[8] The suspension was shaken under forty pounds of hydrogen pressure for seven hours, during which time the theoretical absorption had occurred. The mixture was then filtered and the solvent removed by evaporation in a stream of air. The oily residue was dissolved in 20 ml. of concentrated hydrochloric acid, filtered from sodium chloride, and again evaporated to an oil. To a solution of this yellow oil in 1–2 ml. of concentrated hydrochloric acid was added 20 ml. of absolute alcohol. Cooling and scratching caused the formation of a voluminous white precipitate (53%). Recrystallization from hydrochloric acid and absolute alcohol gave colorless crystals, m.p. 272–275° (dec.).

Anal. Calcd. for $C_9H_{16}Cl_2N_2O$: N, 11.7. Found: N, 11.6.

The diacetate salt was isolated during an attempted diazotization in glacial acetic acid, m.p. 208–209° (dec.).

Anal. Calcd. for $C_{13}H_{22}N_2O_5$: N, 9.8. Found: N, 9.8.

When the free base was added to an alcoholic solution containing an excess of picric acid, the monopicrate separates very slowly, m.p. 226–228°.

Anal. Calcd. for $C_{15}H_{17}N_5O_8$: C, 45.58; H, 4.33; N, 17.7. Found: C, 46.20; H, 4.32; N, 18.2.

3-Aminomethyl-4,6-dimethyl-2-(*l*)-pyridone Hydrochloride (V). A. By Ether Cleavage.—A solution of 2 g. of IV in 40 ml. of 48% hydrobromic acid was refluxed for ten minutes. The solution was then taken to dryness, leaving a brown residue, which, after several recrystallizations from 10% hydrobromic acid, gave white needles, m.p. 305° (dec.) (70% yield). These crystals, evidently the hydrobromide salt, decomposed on standing. To avoid this decomposition, the salt was converted into the hydrochloride. A solution of 1 g. of the hydrobromide was refluxed in 100 ml. of water for one-half hour. Freshly prepared silver chloride was then added, the suspension filtered, and the filtrate taken to dryness. Recrystallization of the residue from 90% ethanol gave white crystals of the monohydrochloride, m.p. 310–312° (dec.), 75% yield. These gave a negative ferric chloride test.

Anal. Calcd. for $C_8H_{13}ClN_2O$: N, 14.8. Found: N, 14.5.

The picrate melted at 223–224°.

Anal. Calcd. for $C_{14}H_{15}N_5O_8$: N, 18.4. Found: N, 18.4.

B. By Reduction of I.—To a solution of 2 g. of pyridone (I) in 175 ml. of glacial acetic acid was added 2 g. of anhydrous sodium acetate, 2 g. of palladium-on-charcoal (5%) and a few crystals of platinum oxide. The suspension was shaken under forty pounds of hydrogen pressure until the

(5) J. L. Simonsen and M. Nayak, *J. Chem. Soc.*, 792 (1915).

(6) We are indebted to Dr. Reuben Jones of the Lilly Research Laboratories for details concerning this reaction.

(7) Analyses by Misses Sorensen, Hobbs and Brauer.

(8) A. Ichiba and S. Emoto, *Sci. Papers, Inst. Phys. Chem. Research (Tokyo)*, **39**, 131 (1941); *C. A.*, **41**, 6246 (1947).

uptake of hydrogen ceased. The product (64%), isolated according to the method outlined above, was obtained as a heavy white precipitate, m.p. 312–315° (dec.), which did not depress the m.p. of the sample prepared by method A. Reduction of the pyridone (I) in absolute alcohol or in glacial acetic acid, using Raney nickel as a catalyst, was not successful at either low or high pressures.

3-Carboxy-4,6-dimethyl-2-pyridol (VII). A. From I.—VII was prepared from I by acid hydrolysis by the method of Wenner and Plati,[9] in a 30% yield, m.p. 257–258°. Hydrolyses of I in more dilute acid gave VI,[10] which was identical to the product obtained by decarboxylation of VII.

B. **From VIIIb.**—VII was prepared from VIIIb by saponification. The product did not depress the m.p. of the sample obtained by method A.

3-Carbomethoxy-4,6-dimethyl-2-pyridol (VIIIa).—A solution of 1 g. of VII in 100 ml. of methanol containing 10 ml. of concentrated sulfuric acid was refluxed three hours. After neutralization of the acid with sodium bicarbonate, and removal of the excess methanol, the aqueous solution was extracted with ether. Removal of the organic solvent and recrystallization from ethyl acetate gave white crystals, m.p. 182–183° (50% yield). The material gave a positive ferric chloride test.

Anal. Calcd. for $C_9H_{11}NO_3$: N, 7.7. Found: N, 8.0.

2-Methoxy-3-carbomethoxy-4,6-dimethylpyridine (X).—To a cooled suspension of 1 g. of the acid (VIII) in methanol was added, with swirling, an ethereal solution of diazomethane (approximately 4.2 g.). Bubbles appeared immediately accompanied by the disappearance of the yellow color and fairly rapid solution of the acid. After standing for 24 hours, the solution was distilled to dryness leaving a yellow oil. An ethereal solution of this was washed with sodium bicarbonate solution and then with water. The ethereal solution was then dried over potassium carbonate and distilled. The residue was vacuum sublimed to give a colorless solid, m.p. 57–58° (56% yield).

Anal. Calcd. for $C_{10}H_{13}NO_3$: N, 7.2. Found: N, 7.4.

The solubility of X in ether rules out any possible zwitterion structure. The low melting point and the marked ability of the compound to sublime are consistent with the α-methoxy structure.

3-Hydroxymethyl-4,6-dimethyl-2-pyridol (IX).—Two grams of ethyl ester (VIIIb) were placed in a Soxhlet extractor above a refluxing solution of 4 g. of lithium aluminum hydride in 150 ml. of anhydrous ether. Refluxing was continued until all the ester had been carried down into the ether solution (24 hours). The solution was then allowed to stand overnight and then 15 ml. of methanol followed by 15 ml. of water were added dropwise through the condenser. The suspension was filtered and the precipitate thoroughly extracted with several portions of methanol. The methanol solution was then saturated with carbon dioxide and the solvent removed under reduced pressure. The residue was then taken up in hot 95% ethanol. Removal of the ethanol at reduced pressure left a white residue which was recrystallized from ethyl acetate containing a little ethanol. The product, m.p. 211–212° (60% yield), gave a positive ferric chloride test.

Anal. Calcd. for $C_8H_{11}NO_2$: N, 9.1. Found: N, 9.2.

The picrate melted at 124.5–125.5°.

Anal. Calcd. for $C_{14}H_{14}N_4O_9$: N, 14.6. Found: N, 14.6.

The hydrochloride of IX was a very hygroscopic substance.

Diazotization Experiments.—The following attempts to convert the β-aminomethyl group into a β-hydroxymethyl group were carried out without success. (A) IV was treated with sodium nitrite in (a) hot *M* sulfuric acid, (b) in hot 4 *M* hydrochloric acid, (c) in cold 0.8 *M* acetic acid and (d) in cold acetic acid solution buffered to *p*H of 5 with sodium acetate. (B) V was treated with sodium nitrite in (a) 3.3 *M* cold acetic acid, and (b) in cold acetic acid solution buffered to *p*H of 5 with sodium acetate and in the presence of hydroquinone.

EVANSTON, ILL. RECEIVED NOVEMBER 24, 1950

(9) W. Wenner and J. T. Plati, *J. Org. Chem.*, **11**, 751 (1946).

(10) J. C. Bardhan, *J. Chem. Soc.*, 2223 (1929).

[CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Azo-bis-nitriles. III.[1] The Preparation and Decomposition of Azo-nitriles. Steric Factors

BY C. G. OVERBERGER AND M. B. BERENBAUM

This work was undertaken to prepare both the *meso*- and DL-forms of several aliphatic azo compounds in order to measure their rates of decomposition to test previous predictions. (1) The preparation of 1,2-disubstituted hydrazines of the type $CH_3R(CN)C-NH-NH-C(CN)RCH_3$ from sterically hindered ketones by the addition of hydrogen cyanide to the corresponding azine is described. (2) The preparation and characterization of the *meso*- and DL-forms of the azo compounds of the type $CH_3R(CN)C-N=N-C(CN)RCH_3$ where $R=(CH_3)_2CH-CH_2-$, cyclo-C_3H_5- and $(CH_3)_3C-$ is described. (3) The rate of decomposition for the isomeric azo compounds have been determined. In no case, is there an appreciable difference in the rate of decomposition of the isomers in toluene at the same temperature. (4) Accurate activation energies for these decompositions have been determined. (5) Differences in decomposition rate of the various azo compounds are attributed to steric and resonance factors.

In a previous paper,[2a] the preparation and decomposition of some aliphatic azo nitriles were reported. Differences in decomposition rates were attributed to steric factors. We have now extended several phases of this work. This paper will describe the preparation, separation and decomposition of two stereoisomeric forms (probably the *meso*- and *dl*-forms of the *trans*-azo configuration) of the azo compounds derived from methyl cyclopropyl ketone, methyl isobutyl ketone and pinacolone, and the extension of a new procedure of Alderson and Robertson[3] for the preparation of azo-bis-nitriles from hindered ketones.

(A) Preparation of Azo Compounds

I. **Discussion.**—The isomeric azo compounds from methyl cyclopropyl ketone were prepared as described previously.[2a] This azo compound has also been reported recently by Pinkney,[4] prepared in a similar way. His product appears to be a mixture of isomers and the analysis reported is subject to some question.

The 1,2-disubstituted hydrazine from methyl isobutyl ketone (prepared previously by another method[2a]), and that from pinacolone, were prepared

(1) This work was supported by a grant from the Research Corporation. For the second paper in this series, see C. G. Overberger, P. Fram and T. Alfrey, Jr., *J. Polymer Sci.*, in press.

(2) (a) C. G. Overberger, M. T. O'Shaughnessy and H. Shalit, THIS JOURNAL, **71**, 2661 (1949); (b) F. M. Lewis and M. S. Matheson, *ibid.*, **71**, 747 (1949).

(3) W. L. Alderson and J. A. Robertson, U. S. Patent 2,469,358, May 10, 1949.

(4) P. S. Pinkney, U. S. Patent 2,492,763, December 27, 1949.