TABLE III

| $R_2$ | $R_3$ | $R_4$ | | Infrared,[a] $\mu$ | Ultraviolet, m$\mu$ ($\epsilon$) |
|---|---|---|---|---|---|
| H | H | $CH_3$ | | 6.09 (m), 6.18 (m), 6.36 (m) | 292 (2700) |
| H | $CH_3$ | $CH_3$ | | 6.0 (sh); 6.14 (s), 6.25 (sh) | 291 (5700) |
| $CH_3$ | $CH_3$ | $CH_3$ | *cis* | 6.05 (sh), 6.18 (m), 6.3 (sh) | 302 (6000) |
| | | | *trans* | 6.16 (s) | 299 (15000) |
| $PhCH_2$ | $CH_3$ | $CH_3$[b] | *cis* | 6.06 (s), 6.18 (sh), 6.32 (s) | 282 (4600) 300–315 (4400) |
| | | | *trans* | 6.17 (s) | 302 (14200) |

[a] s, strong; m, medium; w, weak; sh, shoulder. [b] Reported in ref. 1.

TABLE IV

| $R_2$ | $R_3$ | $R_4$ | | Infrared,[a] $\mu$ | Ultraviolet, m$\mu$ ($\epsilon$) |
|---|---|---|---|---|---|
| H | H | $CH_3$ | | 5.96 (m), 6.22 (s) | 288 (7100) |
| H | $CH_3$ | $CH_3$ | | 5.99 (m), 6.26 (s) | 288 (5200) |
| $CH_3$ | $CH_3$ | $CH_3$ | *cis* | 6.0 (m), 6.25 (s) | 292 (5500) |
| | | | *trans* | 6.0 (m), 6.24 (s) | 290 (6800) |
| $PhCH_2$ | H | $CH_3$ | | 6.0 (m), 6.24 (s) | 285 (5700) |
| $PhCH_2$ | $CH_3$ | $CH_3$[b] | *cis* | 6.01 (m), 6.29 (s) | 298 (4400) |
| | | | *trans* | 6.0 (m), 6.26 (s) | 282 (5800) |

[a] s, strong; m, medium. [b] Reported in ref. 1.

into a methylene chloride solution of the base II; the bands characteristic of the imonium salts IV were not observed. Its preparation is given below.

*trans*-**1,2,3,4-Tetramethyl-2,3-dihydropyridinium** (*trans* **V**) **Chloride.**—To 30 ml. of 0.01 *N* dry ethereal hydrogen chloride, contained in a three-neck flask equipped with two graduated separatory funnels and a stirrer, was added dropwise simultaneously through each funnel 3 ml. of a solution of the base in ether and 3 ml. of an ethereal solution of an equivalent amount of hydrogen chloride. The slightly oily crystalline material which formed was filtered and washed free of oil with acetone. In this manner 0.23 g. of 1,2,3,4-tetramethyl-1,2-dihydropyridine (II) gave 0.14 g. (48%) of the hydrochloride (*trans* V). The salt was hygroscopic. It was recrystallized by adding acetone to a solution in methylene chloride, m.p. 129–135°.

*Anal.* Calcd. for $C_9H_{16}ClN$: C, 62.23; H, 9.29; Cl, 20.41. Found: C, 61.47; H, 9.48; Cl, 20.25.

**6-Cyano-1,2,3,6-tetrahydropyridines** (**VI**).—These were made simply by adding enough aqueous sodium or potassium cyanide to cold solutions of salts V so that the final solution was alkaline. The nitriles were recovered with ether or petroleum ether and except for the following example were oils. **6-Cyano-1,4-dimethyl-1,2,3,6-tetrahydropyridine** was obtained crystalline in 60% yield. Recrystallized from petroleum ether (30–60°) it melted at 46–49°. The infrared spectra is given in Table V.

TABLE V

| $R_2$ | $R_3$ | $R_4$ | | Infrared, $\mu$, all strong bands |
|---|---|---|---|---|
| H | H | $CH_3$ | | 11.37 |
| H | $CH_3$ | $CH_3$ | | 11.25 |
| $CH_3$ | $CH_3$ | $CH_3$ | *cis* | 11.27 |
| | | | *trans* | 11.27 |
| $PhCH_2$ | H | $CH_3$ | | 11.32 |
| $PhCH_2$ | $CH_3$ | $CH_3$[a] | *cis* | 11.23 |
| | | | *trans* | 11.31 |

[a] Reported in ref. 1.

*Anal.* Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 71.06; H, 9.00; N, 19.83.

**1,2,3,4-Tetramethyl-1,2,5,6-tetrahydropyridine**, obtained by the action of sodium borohydride on the nitrile as previously described,[1] gave a picrate in 55% over-all yield. Recrystallized from alcohol it melted at 155–158°. The integrated n.m.r. diagram of the base showed two unsplit methyl groups at $\tau$ 8.4, and one split methyl group centered at 8.9.

*Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.23; H, 5.27.

*cis*-**1,2,3,4-Tetramethyl-1,2,3,6-tetrahydropyridine picrate**, obtained as above in 60% yield, melted at 167–169°, slight previous sinter. It did not depress the melting point of the $\Delta^3$-compound. The n.m.r. diagram showed one vinylic hydrogen at $\tau$ 4.7.

*Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 48.85; H, 5.27.

*trans*-**1,2,3,4-Tetramethyl-1,2,3,6-tetrahydropyridine.**—The crude material, obtained as above from the nitrile, was distilled at about 60° (10 mm.). It was converted to the picrate in 41% over-all yield (five steps) starting from the isomeric nitrile III. The base n.m.r. diagram showed one vinylic hydrogen at $\tau$ 4.6. The picrate melted at 162–165° and the melting point was not depressed on admixture with the *cis* isomer.

*Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.10; H, 5.56.

**1,2,3-Trimethyl-1,2,5,6-tetrahydropyridine** was obtained in like manner from the crystalline perchlorate of the cyano derivative (III). After distillation at <100° (9 mm.), it was converted to the picrate in an over-all yield of 45%. Recrystallized from alcohol, it melted 194–195°. Its n.m.r. spectrum showed one vinylic hydrogen at $\tau$ 4.55. This picrate was obtained also from the noncrystalline portion of the preparation of the nitrile III perchlorate in an amount that signified a yield increase of 50% over that represented by crystalline material. Diastereoisomerism of the nitriles is thereby indicated.

*Anal.* Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.10. Found: C, 47.46; H, 5.11.

## Rearrangements of Alkoxypyridine 1-Oxides

FRANK J. DINAN[1] AND HOWARD TIECKELMANN

*Department of Chemistry, State University of New York at Buffalo, Buffalo 14, New York*

*Received November 4, 1963*

Although a number of 2-alkoxypyridine 1-oxides are known,[2,3] thermal rearrangements of these compounds are, to our knowledge, unreported.[4] It was of interest to determine whether rearrangement of 2-alloxypyridine 1-oxide (I) would give a mixture of products such as had been obtained from 2-alloxypyridines[5] and 4-alloxypyrimidines,[6] or whether exclusive rearrangement to either the 3-carbon or 1-oxygen atom would occur.

For this purpose, I was prepared by treatment of 2-chloropyridine 1-oxide[7] (II) with the sodium salt of allyl alcohol under mild conditions, a procedure similar to that previously used by Gardner and Katritzky for the preparation of other 2-alkoxypyridine 1-oxides.[3] Rearrangement of I took place under very mild conditions to give 1-alloxy-2-pyridone (III) in nearly quantitative yield.

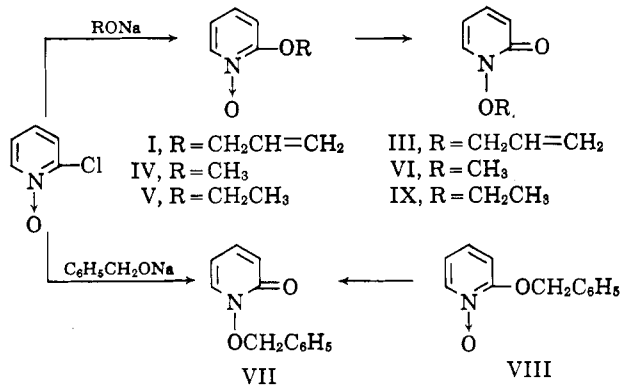
The identification of I is based on infrared and ultraviolet spectral data as well as on the method of synthesis. The infrared spectrum of I has sharp absorption bands in the 1200–1300-cm.$^{-1}$ region characteristic of

(1) Allied Chemical Corp. Fellow, 1963.
(2) E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).
(3) J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.*, 4375 (1957).
(4) It should be noted that Shaw[2] observed the formation of 1-benzyloxy-2-pyridone as a minor product resulting from an acid-catalyzed debenzylation of 2-benzyloxypyridine 1-oxide.
(5) F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, **29**, 892 (1964).
(6) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *ibid.*, **28**, 1015 (1963).
(7) A. R. Katritzky, *J. Chem. Soc.*, 191 (1957).

pyridine 1-oxides.[8] The ultraviolet spectrum is in agreement with the data reported for 2-methoxypyridine 1-oxide (IV) and 2-ethoxypyridine 1-oxide (V).[3] The ultraviolet spectrum of the 1-alloxy isomer III is nearly identical with the spectrum reported for 1-methoxy-2-pyridone (VI).[3] In addition, a strong band at 6.01 $\mu$ in the infrared spectrum of III is consistent with the presence of a carbonyl group.

The literature pertaining to 2-alkoxypyridine 1-oxides and 1-alkoxy-2-pyridones was found to contain some anomalous and conflicting reports. It appeared that some of these data could be explained if the ease of conversion of I to III was general for 2-alkoxypyridine 1-oxide rearrangements.

Gardner and Katritzky[3] obtained 2-ethoxypyridine 1-oxide (V) and the 2-methoxy compound IV by treatment of the chloropyridine II with the sodium salts of the corresponding alcohols. However, treatment of II with the sodium salt of benzyl alcohol gave 1-benzyloxy-2-pyridone (VII) rather than the expected 2-benzyloxypyridine 1-oxide (VIII).




In our hands, treatment of II with the sodium salt of benzyl alcohol also gave VII. This reaction required more severe conditions than those used for the synthesis of the 2-alloxy compound I and, in view of the facile rearrangement of I to the isomeric pyridone III, it seems likely that the VII obtained in the former reaction results from isomerization of initially formed VIII.

The synthesis of VIII by room temperature oxidation of 2-benzyloxypyridine with perbenzoic acid was reported by Shaw.[2] Gardner and Katritzky,[3] however, reported that this procedure gave the 1-benzyloxy isomer VII rather than VIII. In our hands, VIII was formed. The ultraviolet spectrum of VIII from this reaction is in agreement with the data reported by Shaw. In addition, the infrared spectrum of VIII shows bands characteristic of the amine oxide function.[8]

The 1-benzyloxy compound VII was obtained when VIII was heated for a short time at 100°. Identification of VII is based on ultraviolet[3] and infrared spectral data. In addition, the melting point of VII prepared by rearrangement of VIII was not depressed when mixed with VII prepared by the method of Gardner and Katritzky.[3]

The conditions used to effect the rearrangement of VIII to VII are milder than those required for the attempted preparation of VII from the chloro compound II. Thus, any VIII formed in the latter reaction would be rearranged to VII under the reaction conditions. The facile rearrangement of VIII to VII may account for the different products obtained by Shaw,[2] and Gardner and Katritzky[3] from the perbenzoic acid oxidation of 2-benzyloxypyridine.

For comparison with the allyl and benzyl rearrangements, the 2-methoxy and 2-ethoxy compounds IV and V were prepared.[3] Rearrangement of IV and V gave 1-methoxy-2-pyridone (VI) and 1-ethoxy-2-pyridone (IX), respectively.

The identification of VI is based on ultraviolet spectral data,[3] and on the presence of a strong absorption band at 6.02 $\mu$ in the infrared spectrum, consistent with the presence of a carbonyl group. The ultraviolet spectrum of the 1-ethoxy compound IX is in agreement with the spectra of the 1-methoxy and 1-alloxy compounds, VI and III. Additionally, the presence of a carbonyl group is indicated by the infrared spectrum of IX.

Rearrangements of the 2-alloxy and 2-benzyloxy compounds I and VIII to the corresponding 1-alkoxy-2-pyridones were investigated at 100°. The benzyloxy rearrangement was judged complete after 2.5 hr. at this temperature, and the alloxy rearrangement after 3.5 hr. The rearrangements of the 2-methoxy isomer IV and the 2-ethoxy compound V to the 1-alkoxy compounds VI and IX were conducted at 140°. The methoxy rearrangement was complete after 1.5 hr., and the ethoxy rearrangement after 3 hr.

The mild conditions required for these rearrangements indicate that homolytic cleavage of the ether bond does not take place. The rearrangement of 2-methoxypyridine to 1-methyl-2-pyridone, a demonstrated free-radical process, requires 14 hr. at 200°.[9] Additional evidence against a radical intermediate was provided by an experiment in which the addition of 3% of a free-radical scavenger, *p*-benzoquinone, did not retard the rate of rearrangement of the 2-alkoxypyridine 1-oxides, I, VIII, or VI.

The high electron density[10] and resultant nucleophilicity of the 1-oxygen atom of pyridine 1-oxides provides an effective nucleophile. The enhanced reactivity of the 2-methoxy compound IV relative to the ethoxy isomer V is consistent with a nucleophilic substitution process and indicates that these rearrangements may take place by either intra- or intermolecular nucleophilic attack of the 1-oxygen atom on the alkyl group.

The transition state required for an intramolecular substitution reaction would, except for the 2-alloxy isomer I, involve a rather unlikely front-side displacement on the alkyl group. Both intermolecular nucleophilic substitution and rearrangement *via* ion pair formation with internal return to give product are more probable mechanisms for this transformation. The amount of ionic character may vary with the nature of the migrating group, being more important in the allylic and benzylic rearrangements and relatively unimportant in the alkyl rearrangement.

## Experimental

**2-Alloxypyridine 1-Oxide (I).**—2-Chloropyridine 1-oxide[7] (5.2 g., 0.04 mole) was added to a solution of 0.92 g. (0.04 g.-

(8) L. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 307–308.

(9) K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Am. Chem. Soc.*, **79**, 3160 (1957).

(10) R. A. Barnes, *ibid.*, **81**, 1935 (1959).

atom) of sodium in 40 ml. of allyl alcohol, and the mixture was heated for 1 hr. at 50°. Excess allyl alcohol was removed at reduced pressure (50° at 0.5 mm.) and the residue was extracted with chloroform. Removal of the solvent under reduced pressure gave a crude yield of 2.8 g. (46%) of I as a light tan oil.

The product contained approximately 5% 1-alloxy-2-pyridone (III) as determined by infrared analysis. Further purification by alumina chromatography using chloroform as the eluent gave 2.3 g. (38%) of pure I.

*Anal.* Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.57; H, 6.10; N, 9.40.

**1-Alloxy-2-pyridone (III).**—2-Alloxypyridine 1-oxide, 1.00 g. was heated at 100° for 3.5 hr. After cooling, the resulting dark brown oil was purified by chromatography on alumina. Gradient elution with benzene, chloroform, and ethyl acetate gave 0.83 g. (83%) of III as a light tan oil. This material was further purified by preparative scale gas chromatography to obtain an analytical sample. A 2-ft. 20% General Electric XF-1150 polymer on Chromosorb-W was used. The column temperature was maintained at 190° with a helium flow of 60 ml./min. The ultraviolet spectrum showed $\lambda_{max}^{water}$ 296 mμ (ε 5400) and 226 mμ (ε 5500); and the infrared spectrum showed carbonyl absorption at 6.01 μ.

*Anal.* Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 61.98; H, 6.25; N, 9.47.

**1-Benzyloxy-2-pyridone (VII).**—2-Benzyloxypyridine 1-oxide (VIII),[2] 1.00 g., was heated for 2.5 hr. at 100°. Upon cooling, the reaction mixture solidified. Recrystallization from ethyl acetate–ligroin gave 0.92 g. (92%) of VIII, m.p. 78–79°, lit.[3] m.p. 76–78°. A mixture melting point of VIII prepared by the literature procedure and as above was not depressed. The infrared spectra of the two products are identical.

**1-Methoxy-2-pyridone (VI).**—2-Methoxypyridine 1-oxide (IV), 1.00 g., was heated for 1.5 hr. at 140°. The resulting dark brown oil was purified by chromatography on alumina. Gradient elution with benzene, chloroform, and ethyl acetate gave 0.89 g. (89%) of VI as a tan oil which could not be crystallized.[11] An aqueous solution of the product gave the same ultraviolet spectrum reported for authentic VI.[3] The infrared spectrum showed carbonyl absorption at 6.02 μ.

This procedure is also typical for the preparation of the following compound.

**1-Ethoxy-2-pyridone (IX).**—2-Ethoxypyridine 1-oxide (V) was heated for 3 hr. at 140° to give crude IX. Gradient elution chromatography as above gave 85% of IX as a light tan oil. The ultraviolet spectrum showed $\lambda_{max}^{water}$ 295 mμ (ε 5900) and 225 mμ (ε 6100); the infrared spectrum showed carbonyl absorption at 6.02 μ.

*Anal.* Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.62; H, 6.90; N, 9.89.

**Effect of *p*-Benzoquinone on Rate of Rearrangement.**—*p*-Benzoquinone, 3% by weight, was added to the 2-alkoxypyridine 1-oxide to be investigated. Portions of this sample together with pure samples of the same 2-alkoxypyridine 1-oxide were heated together in sealed tubes in a stirred oil bath set at the desired temperature so that variations in the bath temperature could not change the rate of one rearrangement with respect to the other. Tubes containing the experimental and control samples were simultaneously withdrawn from the bath at 15-min. intervals and the infrared spectra were determined. The rate of rearrangement of the 2-alkoxypyridine 1-oxide was determined by the disappearance of the 1-oxide bands in the 7.8–8.4-μ region. Formation of product was indicated by the appearance of a carbonyl absorption band at approximately 6.0 μ.

In this manner, the rearrangements of 2-alloxypyridine 1-oxide, 2-benzyloxypyridine 1-oxide, and 2-methoxypyridine 1-oxide to the corresponding 1-alkoxy-2-pyridones were shown to proceed at the same rate in the presence and absence of added *p*-benzoquinone.

**Rates of Rearrangement of 2-Alkoxypyridine 1-Oxides.**—The 2-alkoxypyridine 1-oxides were heated in a stirred oil bath set at the desired temperature. Samples were withdrawn at 15-min. intervals and their ultraviolet spectra were determined on a Beckman DK-2 spectrophotometer.

(11) Gardner and Katritzky reported that this material partially solidified on standing. This has not been observed in the present case.

Rearrangements were judged complete when the maximum at approximately 250 mμ, which characterizes the spectra of 2-alkoxypyridine 1-oxides and is missing in 1-alkoxy-2-pyridones, had disappeared. At this time, the spectra corresponded to those of the corresponding 1-alkoxy-2-pyridones.

The rearrangements of 2-alloxypyridine 1-oxide (I) and 2-benzyloxypyridine 1-oxide (VIII) were found to be complete after 3.5 and 2.5 hr. at 100°, respectively. 2-Methoxypyridine 1-oxide (IV) and 2-ethoxypyridine 1-oxide (V) were rearranged at 140° and found to be complete after 1.5 and 3 hr., respectively.

## Model Reactions for the Biosynthesis of Thyroxine. V. Reaction of 4-Hydroxy-3-iodophenylpyruvic Acid and of 4-Hydroxy-3,5-diiodophenylpyruvic Acid with L-Tyrosine or Its Iodinated Congeners. A Novel Synthesis of 3,3′,5′-Triiodo-L-thyronine[1,2]

TETSUO SHIBA[3] AND H. J. CAHNMANN

*The National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014*

*Received April 22, 1963*

DIHPPA[4] reacts with DIT[4] in the presence of oxygen to form thyroxine in over 20% yield.[5] The reaction takes place rapidly at room temperature and at or near neutrality. No racemization takes place when L-DIT is used.[6] It has been shown through experiments with labeled starting materials that the keto acid furnishes the phenolic ring of thyroxine, and the amino acid—the nonphenolic ring and the aliphatic side chain.[6] The side chain of the keto acid is eliminated in the course of the reaction.

The present investigation was undertaken in order to determine whether in this coupling reaction DIHPPA can be replaced with MIHPPA,[4] and DIT with MIT[4] or with tyrosine and to what extent the corresponding iodinated thyronines are formed in each case.

The coupling reaction was carried out essentially as described previously for the synthesis of thyroxine.[5,6] The amount of iodinated thyronine formed in each reaction was determined by isolation and weighing. A modification of the procedure of Nakano and Danowski[7] was used for the preparation of MIHPPA.

When in the coupling reaction described by Meltzer and Stanaback[5] L-DIT was replaced with L-MIT, the yield of the coupling product dropped from over 20% to 17%. When L-DIT was replaced with L-tyrosine, the yield of 3′,5′-diiodo-L-thyronine was about 0.2%. Reaction of MIHPPA with L-DIT gave 3,5,3′-triiodo-L-thyronine in about 2% yield. In view of this low

(1) For a preliminary report of this work see Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 9C.

(2) Paper IV: T. Matsuura and A. Nishinaga, *J. Org. Chem.*, **27**, 3072 (1962).

(3) Visiting Scientist from the Department of Chemistry, Faculty of Science, Osaka University, Osaka, Japan.

(4) Abbreviations: HPPA, *p*-hydroxyphenylpyruvic acid; MIHPPA, 4-hydroxy-3-iodophenylpyruvic acid; DIHPPA, 4-hydroxy-3,5-diiodophenylpyruvic acid; MIT, 3-iodotyrosine; DIT, 3,5-diiodotyrosine.

(5) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(6) T. Shiba and H. J. Cahnmann, *ibid.*, **27**, 1773 (1962).

(7) N. Nakano and T. S. Danowski, *Endocrinology*, **65**, 889 (1959).