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Pyridineamidoximes

EDWARD BERNASEK

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In a recent publication,[1] Buu-Hoï, *et al.* reported that the 5-chloro-, 3,5-dichloro-, 5-bromo- and 5-iodo-salicylamidoximes inhibited the *in vitro* growth of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of the order of one microgram per milliliter. In view of the above findings, an investigation of the amidoximes derived from the pyridine monocarboxylic acids was undertaken.

The pyridineamidoximes were prepared according to the procedure of Tiemann and Krüger,[2] which involves the heating of the appropriate cyanopyridine at 80–85° with an aqueous solution of hydroxylamine. In the case of 3-pyridineamidoxime, the reaction was carried out in a sealed tube at 70°.[3] If the cyanopyridine was not soluble in water, as was the case with 2-cyanopyridine, sufficient ethyl alcohol was added to effect solution.

The pyridineamidoximes reported here were tested for *in vitro* tuberculostatic activity but were found to be inactive.

EXPERIMENTAL[4,5]

2-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 2-cyanopyridine was added in one portion, followed by sufficient ethyl alcohol (approximately 7 ml.) to dissolve the 2-cyanopyridine. The temperature of the mixture was raised to 85° and maintained for 2 hr. The alcohol was removed under reduced pressure and a tan oil separated from solution. On cooling to 0°, the oil solidified. The crystalline solid was filtered, washed twice with 10 ml. of ice-cold water, and dried in a vacuum desiccator over calcium chloride. The crude product (3.9 g.; 98%) melted at 114–116°. A sample recrystallized from water and dried *in vacuo* at 110° melted at 115.5–116°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.0; N, 30.4.

3-Pyridineamidoxime. Prepared according to the procedure of Michaelis[3] in 70% yield, m.p. 127.5–128°.

4-Pyridineamidoxime. A solution of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride and 1.9 g. (0.015 mole) of sodium carbonate monohydrate in 10 ml. of water was heated to 60°. Three grams (0.029 mole) of 4-cyanopyridine was added in one portion. An exothermic reaction took place causing the temperature to rise to 75°. Almost immediately a mass of colorless crystals separated from solution. Heating was continued at 80° for 0.5 hr. to complete the reaction. The suspension was cooled to 0°, filtered and dried in a vacuum desiccator over calcium chloride. The crude product (3.6. g.; 90%) melted at 175–177°. Recrystallization from ethyl alcohol gave colorless needles, m.p. 178–179°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.5; H, 5.1; N, 30.6. Found: C, 52.9; H, 5.1; N, 30.4.

Acknowledgment. The author wishes to thank Irene Melvin for performing the *in vitro* testing of compounds reported in this paper.

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[1] N. P. Buu-Hoï, M. Welsch, N. D. Xuong, and K. V. Thang, *Experientia*, **10**, 169 (1954).

[2] F. Tiemann and P. Krüger, *Ber.*, **17**, 1685 (1884).

[3] L. Michaelis, *Ber.*, **24**, 3439 (1891).

[4] All melting points are uncorrected.

[5] Carbon and hydrogen analyses by Schwarzkopf Microanalytical Laboratory.

Kinetics of the Thermal Isomerization of 2-*tert*-Butyl-3-Phenyloxazirane

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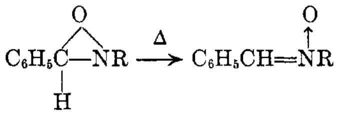
The observation[1] that 2-*tert.*-alkyl-3-phenyloxaziranes (I) isomerize on heating to the corresponding nitrones (II) and the novelty of the oxazirane ring system prompted the immediate investigation



I II

R = *tert*-alkyl

of the kinetices of this reaction. This kinetic study was primarily designed to determine the enthalpy and entropy of activation for the rearrangement of 2-*tert.*-butyl-3-phenyloxazirane, III, in diethyleneglycol diethyl ether (diethyl carbitol) solvent over a 40° temperature range.

Preliminary experiments showed that the rearrangement of III to *N-tert.*-butyl benzaldoxime, IV, proceeded quantitatively in the 60–100° temperature range and that the ultraviolet absorption spectra of these two materials were sufficiently different in acetonitrile to afford an analytical method for IV in the presence of III. The nitrone (IV) has an extinction coefficient of 1.68×10^4 at λ_{max} 298 mμ while III has an extinction coefficient of only 92 at this same wave length.

The isomerization of III to IV was carried out in diethyl carbitol solvent at 60, 85, and 100° and the

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[1] W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956).

initial concentration of III was varied from 0.1 to 0.44*M*. In each case the kinetic experiments were followed to at least 75% completion and then allowed to proceed for infinite time. Final values of conversion always corresponded to from 95 to 100% isomerization to IV. Graphical treatment of the rate data afforded very clean first-order plots. Table I records the first-order rate constants which were obtained.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE THERMAL ISOMERIZATION OF 2-*tert.*-BUTYL-3-PHENYLOXAZIRANE TO *N*-*tert.*-BUTYL BENZALDOXIME

Temp., °C. ± 0.05°	Initial Oxazirane Concentration, (mole/l.)	k_1,[a] (sec.$^{-1}$) × 10^7
100.0	0.437	545
	0.252	537
85.0	0.116	530
	0.241	119
	0.229	113
	0.120	113
	0.115	117
	0.233	5.40
60.0	0.127	5.40

[a] Average k_1 values are 5.37 × 10^{-5} at 100.0°, 1.16 × 10^{-5} at 85.0° and 5.40 × 10^{-7} (sec.$^{-1}$) at 60.0°.

A plot of reciprocal temperature *versus* log k_1 produced a good straight line from which $\Delta H\ddagger$ was found to be 28 kcal. per mole between 60 and 100°. The entropy of activation, $\Delta S\ddagger$ was found to be -3 ± 1 entropy units, a value which indicates that the structures of oxazirane reactant and nitrone product are equally rigid. The slight negative value may indicate increased solvation of the transition state due to the development of a strong $N \rightarrow O$ dipole.

EXPERIMENTAL

Materials. Acetonitrile was Eastman Spectrograde. Diethyl carbitol was technical grade which had been rigorously purified according to the procedure given by Brown, Meade, and Subba Rao[2] for the purification of diglyme. The material so obtained boiled at 94–96° at 33 mm., n^{20}_D 1.4115. 2-*tert.*-Butyl-3-phenyloxazirane (III) was generously supplied by W. D. Emmons (ref. 1) and was further purified by chromatography on silica gel using methylene chloride solvent followed by vacuum distillation. The pure material boiled at 63° at 0.8 mm., n^{24}_D 1.5081. The ultraviolet spectrum of the compound in acetonitrile solvent showed only end absorption.

Pure N-*tert.*-butylbenzaldoxime (IV) was obtained from the same source, m.p. 75–77°. The ultraviolet spectrum of this compound in acetonitrile solvent gave λ_{max} 289 mμ with an extinction coefficient of 1.68 × 10^4.

Kinetic procedure. Solutions of 2-*tert.*-butyl-3-phenyloxazirane (0.1 to 0.44*M*) in pure diethyl carbitol were prepared in 10-ml. volumetric flasks. The flasks were placed in the appropriate thermostat at zero time. At intervals small aliquots were removed and delivered to a volume of acetonitrile which was subsequently made up to 10 ml. with the same solvent. Optical density readings were made at 298 mμ with a Model DK-1 Beckman spectrophotometer and the concentration of nitrone (IV) was computed. Points were taken until the reaction had progressed to 75% completion. After several days (or weeks at lower temperatures) the rearrangement of III to IV was found to be essentially complete as determined by the ultraviolet absorption spectrum of the reaction mixture.

First-order plots were prepared by plotting log (oxazirane) *vs.* time. The first-order constants obtained are shown in Table I.

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[2] H. C. Brown, E. J. Meade, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

Cyanoethylation of Phenol; Isolation of an *ortho*- Addition Product[1]

H. W. JOHNSTON[2] AND F. J. GROSS[3]

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The carbon-carbon cyanoethylation of the more active phenols, such as resorcinol, to give *beta*-substituted propionitriles in the presence of anhydrous zinc chloride and anhydrous hydrogen chloride is well known.[4] Phenol itself does not react under these conditions, but if a more active catalyst, anhydrous aluminum chloride, is used, a good yield of β-(*p*-hydroxyphenyl)propionitrile is obtained.[5] Recently Westfahl and Gresham reported the addition of vinylidene cyanide to phenol in the presence of anhydrous aluminum chloride at 30–35° to give β-(*p*-hydroxyphenyl)α-cyanopropionitrile in 45% yield.[6] A trace of the δ-lactone of β-(*o*-hydroxyphenyl)propionic acid (melilotol), I, was tentatively identified by means of its infrared spectrum. This compound was formed, presumably, by hydrolysis and decarboxylation of the parent cyano compound during isolation of the products of the Friedel-Crafts reaction.

The authors have noted a result similar to that of Westfahl and Gresham. Phenol was cyanoethylated in the presence of anhydrous aluminum chloride and dry hydrogen chloride. (It was noted that the use of hydrogen chloride considerably lowered the viscosity of the reaction mixture, presumably by minimizing the formation of the insoluble salt, $C_6H_5OAlCl_2$.) The expected β-(*p*-

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[1] In part, an undergraduate senior research project by F. J. Gross.

[2] Present address: Whitworth College, Spokane 53, Wash.

[3] Present address: Swift and Co., Newark, N. J.

[4] W. D. Langley and R. Adams, *J. Am. Chem. Soc.*, **44**, 2326 (1922); L. C. Behr, J. E. Kirby, R. N. MacDonald, and C. W. Todd, *J. Am. Chem. Soc.*, **68**, 1296 (1946).

[5] R. Schnabel, German Patent **870,273**, March 12, 1953.

[6] J. C. Westfahl and T. L. Gresham, *J. Am. Chem. Soc.*, **76**, 1076 (1954).