[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BUCKNELL UNIVERSITY]

The Isomerization of Some 1-Aroylaziridines. II

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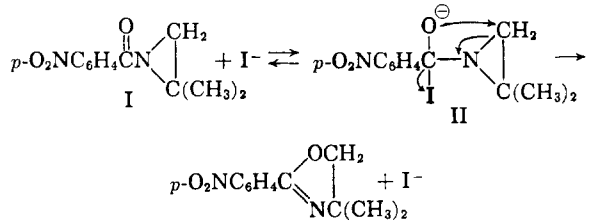
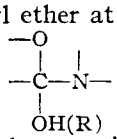
The selective isomerization of 1-*p*-nitrobenzoyl-2,2-dimethylaziridine into 2-*p*-nitrophenyl-4,4-dimethyl-2-oxazoline or 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline or to N-(β-methallyl)-*p*-nitrobenzamide is described. Three other new N-aroylaziridines have been prepared and isomerized. The methanolysis of 1-*p*-nitrobenzoylaziridine in the presence of nucleophilic reagents is also described.

Part I[1] of this series described the isomerization of 1-*p*-ethoxybenzoylaziridine to 2-*p*-ethoxyphenyl-2-oxazoline by means of aluminum halides or amine hydrobromides in refluxing heptane. We have now observed isomerization of 1-aroylaziridines in high yields in acetone–sodium iodide solutions and in concentrated sulfuric acid.

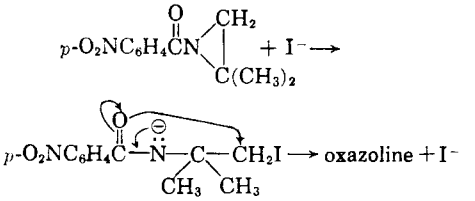
1-*p*-Nitrobenzoylaziridine is isomerized quickly at 0° in the presence of excess sodium iodide in acetone. Under similar circumstances, but with the exception that the reaction mixture required refluxing, 1-*p*-nitrobenzoyl-2,2-dimethylaziridine-(I) is converted in 93% yield to 2-*p*-nitrophenyl-4,4-dimethyl-2-oxazoline. Two mechanisms can be postulated for the isomerizations catalyzed by iodide ion. The first mechanism is a two-step process involving the formation of an amide addition complex II followed by, in the case of the unsymmetrical 1-aroylaziridine, a nucleophilic attack of the negatively charged oxygen on the most positive carbon of the aziridine ring



Amide addition complexes similar to II have been proposed recently to explain the alkaline hydrolysis of amides[2] and anilides.[3] Both the isotopic exchange and the spectrophotometric studies on the action of methoxide ion on trifluoroacetamide in di-*n*-butyl ether at room temperature indicate the structure  as a reaction intermediate.[4]

The higher reaction temperature required for the isomerization of I relative to 1-*p*-nitrobenzoylaziridine may be ascribed, in part, to the enhancement of the nitrogen basicity by C-alkyl substitution, which would tend to make the addition of iodide ion to the carbonyl carbon more difficult. It has been noted elsewhere that C-alkyl groups on aziridines have an effect of considerable size on the basicity of the ring nitrogen atom.[5]

The isomerization is also explicable on the basis of an attack of iodide ion on the aziridine ring to form a N-2-iodoethyl-*p*-nitrobenzamido ion which subsequently cyclizes to the oxazoline



One of us has previously demonstrated the cyclization of N-2-bromoethylbenzamido ions to oxazolines in methanol.[6] On the basis of this mechanism the methylene group of I which is attacked by the iodide ion is hindered by the two methyl groups on the adjacent carbon in a manner similar to the number one carbon of a neopentyl derivative. Thus a higher temperature for the reaction of I relative to 1-*p*-nitrobenzoylaziridine would be required.

The rearrangement of 1-aroylaziridines by the action of sodium iodide in acetone appears to be a general method for the preparation of 2-aryl-2-oxazolines. For example, besides the compounds already discussed 1-*p*-chlorobenzoyl-, 1-*p*-ethoxybenzoyl- and 1-(3,5-dinitrobenzoyl)-aziridine have also been isomerized. When the latter compound is added to the acetone–sodium iodide mixture a deep purple color develops immediately. After seveal days at room temperature the color changes to a beautiful shade of red.

The compound I can be isomerized into 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline in 97% yield in concentrated sulfuric acid. This transformation is best explained by the addition of a proton to the amido nitrogen, scission of the ring to yield the tertiary carbonium ion [$ArCONHCH_2C^+(CH_3)_2$] and ring closure to form an oxazolinium ion. The direction of ring opening observed is in agreement with other reported work on the acid cleavage of unsymmetrical aziridines in which a tertiary carbonium ion is formed as an intermediate.[7,8]

The isomerization of I in refluxing heptane to N-(β-methallyl)-*p*-nitrobenzamide in 95% yield is quite analogous to the pyrolysis of 1-acetyl-2,2-dimethylaziridine reported recently.[9] The N-(β-methallyl)-*p*-nitrobenzamide was quantitatively converted in sulfuric acid to 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline.

(1) H. W. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958).

(2) (a) M. L. Bender and R. D. Ginger, THIS JOURNAL, **77**, 348 (1955); (b) M. L. Bender, R. D. Ginger and K. C. Kemp, *ibid.*, **76**, 3350 (1954).

(3) S. S. Biechler and R. W. Taft, *ibid.*, **79**, 4927 (1957).

(4) M. L. Bender, *ibid.*, **75**, 5986 (1953).

(5) C. E. O'Rourke, L. B. Clapp and J. O. Edwards, *ibid.*, **78**, 2159 (1956).

(6) H. W. Heine, *ibid.*, **78**, 3708 (1956).

(7) D. S. Tarbell and P. Noble, *ibid.*, **72**, 265 (1950).

(8) V. B. Schatz and L. B. Clapp, *ibid.*, **77**, 5113 (1955).

(9) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958).

Other solvents and nucleophilic reagents can cause isomerization. 1-*p*-Nitrobenzoylaziridine is rearranged by iodide ion in the solvent acetonitrile and by the thiocyanate ion in acetone. Interestingly, in methanol, iodide ion or methoxide ion converts 1-*p*-nitrobenzoylaziridine to methyl *p*-nitrobenzoate in 95% yield. Even traces of iodide ion or methoxide ion caused rapid methanolysis at room temperature. In contrast, solutions 0.18 *M* with respect to sodium iodide and 0.02 *M* with respect to *p*-nitroacetanilide, *p*-nitrobenzamide, N-*p*-nitrobenzoylpiperidine or N,N-dimethyl-*p*-nitrobenzamide may be refluxed for several hours without methanolysis taking place. Evidently the carbonyl carbon of the aroylaziridine is more positive than the above-mentioned amides. It has been noted already that the aziridine ring has electron withdrawing or aromatic characteristics.[10]

Experimental

1-*p*-Nitrobenzoyl-2,2-dimethylaziridine (I).—Into a Waring blender were placed 200 g. of ice, 200 g. of benzene, 6.5 g. of NaOH and 12 g. of 2,2-dimethylaziridine. To this mixture was added over a period of 10 minutes 30.4 g. of *p*-nitrobenzoyl chloride. The mixture was stirred for 1.5 hours with the continual addition of ice, the temperature never rising above 5°. The organic layer was separated and saved. The aqueous portion was extracted twice with ether. The ethereal extracts and the organic layer were pooled, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The crude material weighed 31.1 g. and melted at 65–67°. It was recrystallized in portions from petroleum ether, b. 60–110°. The recrystallized material melted at 69–71°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.72.

1-*p*-Nitrobenzoylethylenimine, m.p. 123.5–125.5°, was prepared analogously in 85% yield and was recrystallized from petroleum ether.

Anal. Calcd. for $C_9H_8N_2O_3$: N, 14.57. Found: N, 14.60.

1-*p*-Chlorobenzoylaziridine.—The 1-*p*-chlorobenzoylaziridine was prepared analogously. A crude yield of 24.2 g., m. 38–42° was obtained by reaction of 7.5 g. of ethylenimine with 28.7 g. of *p*-chlorobenzoyl chloride and 6.5 g. of NaOH. The product was also recrystallized in portions, from petroleum ether. The recrystallized 1-*p*-chlorobenzoylaziridine melted at 42–44°.

Anal. Calcd. for C_9H_8ClNO: N, 7.7. Found: N, 7.67.

1-(3,5-Dinitrobenzoyl)-aziridine was prepared in a similar fashion as I. Unfortunately a yield was not noted. The material was recrystallized from petroleum ether and melted at 125–127°.

Anal. Calcd. for $C_9H_7N_3O_6$: N, 17.71. Found: N, 17.50.

Isomerization of I to 2-*p*-Nitrophenyl-4,4-dimethyl-2-oxazoline.—A mixture of 438 mg. of I, 2.13 g. of NaI and 50 ml. of acetone was refluxed for 19 hours. The solvent was evaporated and the yellow residue washed with 10 ml. of ice-water and filtered. The solid was washed with an additional 20 ml. of ice-water. The crude product which weighed 409 mg. (93%) and melted 90–97° was recrystallized from aqueous methanol. The recrystallized oxazoline melted 97.5–99°. An infrared absorption spectrum of the crude product was identical with the spectrum made from an authentic sample of 2-*p*-nitrophenyl-4,4-dimethyl-2-oxazoline (m.p. 96.5–98.0°) by the method of Boyd and Hansen[11] and showed no trace of the prominent peaks at 7.83 and 12.4 μ characteristic of the isomeric 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline. A mixed melting point with the authentic material melted at 97–99°.

Isomerization of I to 2-*p*-Nitrophenyl-5,5-methyl-2-oxazoline.—To 10 ml. of concentrated sulfuric acid was added 102.5 mg. of I. The mixture was allowed to stand for 2.5 hours at room temperature, then chilled and finally added to 40 g. of ice-water. The reaction mixture was placed in an ice-bath and made basic by the gradual addition of concentrated sodium hydroxide. The precipitate was filtered and dried. The crude oxazoline weighed 100 mg. (97%) and melted at 141–145°. A sample, recrystallized from 70% aqueous methanol, melted at 146–147.5°. An authentic sample of 2-nitrophenyl-5,5-methyl-2-oxazoline, prepared by the method of Leffler and Adams,[12] also melted at 146–147.5°. A mixed melting point of the isomerized product with the authentic sample was not depressed. The infrared absorption spectra of the two samples were identical.

Isomerization of I to N-(β-Methallyl)-*p*-nitrobenzamide (III).—To 80 ml. of heptane was added 883 mg. of I. The reaction mixture was refluxed for 48 hours (after 5.5 hours pale yellow crystals appeared on the walls of the flask). The heptane was evaporated to give 842 mg. (95%) of III, which melted at 125–127.5°; III was recrystallized from benzene and melted at 126–127.5°. An infrared absorption spectrum was in agreement with III, *i.e.*, a strong NH band at 3.0 μ and a $=CH_2$ band at 3.2 μ. As described below it was converted quantitatively in sulfuric acid to 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.82.

Isomerization of III to 2-*p*-Nitrophenyl-5,5-dimethyl-2-oxazoline.—To 10 ml. of concentrated sulfuric acid was added 101 mg. of III and the mixture was allowed to stand at room temperature for four hours. The solution was cooled and then added to 40 g. of ice-water. The mixture was placed in an ice-bath and neutralized with cold concentrated NaOH. The precipitate was filtered and the crude yield was quantitative. The crude product melted at 137–142°. The oxazoline was recrystallized from 70% aqueous methanol and melted at 144–147°. A mixed melting point with an authentic sample of 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline melted at 144–147°.

Isomerization of 1-*p*-Nitrobenzoylaziridine in Acetonitrile.—To 100 ml. of acetonitrile was added 2.1 g. of NaI and 384 mg. of 1-*p*-nitrobenzoylaziridine. The mixture was allowed to stand at room temperature for 23 hours. The solvent was evaporated, the residue washed with water and the precipitate filtered. The yield of oxazoline, m.p. 180–181°,[6] was 369 mg. (96%).

Isomerization of 1-*p*-Nitrobenzoylaziridine by Potassium Thiocyanate.—To 100 ml. of acetone was added 1.56 g. of KCNS and 384 mg. of the aroylaziridine. The reaction mixture was refluxed for 1.5 hours. The solvent was evaporated, the residue washed with water and the precipitate filtered. A yield of 353 mg. (92%) of oxazoline was obtained.

Isomerization of 1-*p*-Chlorobenzoylaziridine.—To 100 ml. of acetone was added 1.54 g. of NaI and 379 mg. of 1-*p*-chlorobenzoylaziridine. The mixture was refluxed for 20.5 hours, the solvent evaporated, and the residue washed with ice-water and filtered. The crude 2-*p*-chlorophenyl-2-oxazoline weighed 344 mg. (90%) and melted 81.5–84°. Recrystallization from aqueous methanol gave material melting 88.5–89.5°. A melting point of 85–87° had been reported previously for this oxazoline.[6]

Isomerization of 1-(3,5-Dinitrobenzoyl)-aziridine.—A few experiments were run successfully using smaller quantities of NaI and a shorter reaction time. Thus when 100 ml. of acetone, 10 mg. of NaI and 2 mmoles of 1-(3,5-dinitrobenzoyl)-aziridine were refluxed for 1 hour and the solvent evaporated, a 94% yield of crude 2-(3,5-dinitrophenyl)-2-oxazoline was obtained. The recrystallized product melted at 131–132.5°. A mixed melting point with the starting material melted at 100°. A mixed melting point with an authentic sample prepared by the methanolysis of N-2-bromoethyl-3,5-dinitrobenzamide was 131–132°. An exactly analogous experiment as above but using 2 mmoles of 1-*p*-nitrobenzoylaziridine gave a 95% yield of oxazoline.

Methanolysis of 1-*p*-Nitrobenzoylaziridine.—To 100 ml. of methanol was added 1.4 g. of NaI and 192 mg. of 1-*p*-nitrobenzoylaziridine. After 1 hour at room temperature the solvent was evaporated and the residue washed with

(10) S. Searles, M. Tamres, F. Block and L. A. Quarterman, THIS JOURNAL, **78**, 4917 (1956).

(11) R. N. Boyd and R. H. Hansen, *ibid.*, **75**, 5896 (1953).

(12) M. T. Leffler and R. Adams, *ibid.*, **59**, 2252 (1937).

cold water. The yield of *p*-nitrobenzoate was 95% and the crude product did not require recrystallization. It was identified by a mixed melting point with an authentic sample and by a comparison of infrared spectra of the reaction product and the authentic sample.

Smaller quantities of sodium methoxide or sodium iodide, *i.e.*, 10 mg., are sufficient to cause methanolysis at room temperature.

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The Interaction of α-Chymotrypsin with a Series of α-N-Acylated-L-tyrosinmethylamides[1]

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α-N-Formyl-, α-N-acetyl-, α-N-nicotinyl- and α-N-benzoyl-L-tyrosinmethylamide have been evaluated as apparent competitive inhibitors in a representative α-chymotrypsin catalyzed hydrolysis. Operationally valid K_I' values have been obtained for the first three compounds. A comparison of these K_I' values with the K_S values previously obtained for systems involving α-chymotrypsin and the corresponding amides and hydrazides has provided further evidence regarding the interpretation of the above K_S and K_I' values as apparent dissociation constants.

In 1951 Huang and Niemann[4] evaluated α-N-acetyl-D- and L-tryptophanmethylamide as competitive inhibitors of the α-chymotrypsin catalyzed hydrolysis of α-N-nicotinyl-L-tryptophanamide and more recently Manning and Niemann[5] performed a similar evaluation of α-N-carbethoxy-D- and L-tyrosinmethylamide using acetyl-L-tyrosinhydroxamide as the specific substrate. In both of these studies it was assumed that the methylamides possessing the L-configuration would be hydrolyzed so slowly, relative to the analogous or corresponding amide or hydroxamide, as to permit their evaluation as competitive inhibitors rather than as components of a binary mixture of specific substrates. Since it has been shown[6] that a dissociation constant cannot be evaluated for the less reactive of two competitive specific substrates solely on the basis of the dependence of the rate of reaction upon the concentration of the specific substrates, despite an earlier claim to the contrary,[7] our immediate concern is the development of an argument, based upon operational rather than theoretical considerations, that can be used as a guide to determine when a given compound can be considered as a competitive inhibitor rather than as a competitive specific substrate.

The case of two competitive specific substrates has been considered by Foster and Niemann[8] who showed that the combined rate of disappearance of the two specific substrates is given by

$$1/v_T = \{([S_1]/K_{S_1}) + ([S_2]/K_{S_2})\}/\{(V_1[S_1]/K_{S_1}) + (V_2[S_2]/K_{S_2})\} + 1/[S_T]\{\{([S_1] + [S_2])\}/\{(V_1[S_1]/K_{S_1}) + (V_2[S_2]/K_{S_2})\}\} \quad (1)$$

eq. 1, where $[S_T] = ([S_1] + [S_2])$, $-d[S_T]/dt = v_T$, $V_1 = k_{3.1}[E]$, $V_2 = k_{3.2}[E]$, $K_{S_1} = (k_{2.1} + k_{3.1})/k_{1.1}$ and $K_{S_2} = (k_{2.2} + k_{3.2})/k_{1.2}$. Rearrangement of eq. 1 and substitution of the quantities $p = K_{S_1}/K_{S_2}$, $q = V_2/V_1$ and $r = [S_2]/[S_1]$ leads to equation 2

$$1/v_T = \{K_{S_1}(1 + ([S_2]/K_{S_2}))\}/\{V_1[S_1](1 + p\cdot q\cdot r)\} + 1/V_1(1 + p\cdot q\cdot r)\} \quad (2)$$

If we limit consideration to the operational situation where the magnitude of $p.q.r$ is less than that associated with experimental error it follows that $V_1 \doteq V_1(1 + p.q.r)$ and eq. 2 may be reduced to eq. 3

$$1/v_T \doteq \{K_{S_1}(1 + [S_2]/K_{S_2})\}/\{V_1[S_1]\} + 1/V_1 \quad (3)$$

It will be recognized that eq. 3 is, in an operational sense, the equivalent of eq. 4, which may be employed for the evaluation of K_I of a competitive

$$1/v = \{K_S(1 + [I]/K_I)\}/\{V[S]\} + 1/V \quad (4)$$

inhibitor. As long as it is realized that the act of replacing $[S_1]$ by $[S]$, $[S_2]$ by $[I]$, V_1 by V, K_{S_1} by K_S and K_{S_2} by K_I' is an approximation that is dependent upon the validity of the assumption that operationally $V_1 \doteq V_1(1 + p.q.r)$ it is not unreasonable to use eq. 4, or its equivalent, for the approximate evaluation of the more slowly reacting component as an apparent competitive inhibitor provided every effort is made to minimize experimental error and to be certain that the magnitude of $(1 + p.q.r)$ approximates unity within the limits of experimental error.[9]

If the quantities p, q and r are considered individually, it is clear that $p = K_{S_1}/K_{S_2} \doteq K_S/K_I'$ can be minimized only to a limited degree by the use of specific substrates with low K_S values relative to the K_I' values of the apparent competitive inhibitors. The quantity $q = V_2/V_1$ is more amenable to minimization since many pairs of potential reactants can be selected as to yield differences in reactivity, with respect to the production of reaction products, of the order of 10^2 to 10^3, or even greater, between the members of a given pair. However, the advantage so gained can be lost if the

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(2) National Science Foundation Postdoctoral Fellow.

(3) To whom inquiries regarding this article should be sent.

(4) H. T. Huang and C. Niemann, THIS JOURNAL, **73**, 3223 (1951).

(5) D. T. Manning and C. Niemann, *ibid.*, **81**, 747 (1959).

(6) L. L. Ingraham, *ibid.*, **79**, 666 (1957).

(7) S. A. Bernhard, *ibid.*, **77**, 1973 (1955).

(8) R. J. Foster and C. Niemann, *ibid.*, **73**, 1552 (1951).

(9) This condition implies that S_2 will not be hydrolyzed at a sufficient rate nor be present in a high enough concentration to contribute significantly to the total rate of formation of reaction products. Its function will then be restricted to combination with the active site of the enzyme thus limiting the hydrolysis of S_1.