Aziridine Induced Isomerization of Isomaleimides to Maleimides[1]

P. JOSEPH-NATHAN, V. MENDOZA, AND E. GARCÍA G.[2]

Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P.O. Box 14-740, México 14, D.F., México

Received May 28, 1973

Treatment of *N*-phenylisomaleimide with aziridine gave 3-(*N'*-aziridinyl)-*N*-phenylsuccinimide identical with the adduct formed between *N*-phenylmaleimide and ethylenimine. The isomerization proceeded through the intermediate **2** whose decomposition in solution to a mixture of **3**, **4**, and **5** is also described.

Le traitement de la *N*-phénylmaleisoimide par l'aziridine fournit la (*N'*aziridinyl)-3 *N*-phényl succinimide identique avec le composé formé dans la réaction entre la *N*-phénylmaleimide et l'éthylenimine. L'isomérisation se produirait par l'intermédiaire de 2 dont la décomposition en solution pour donner **3**, **4** et **5** est aussi discuté. [Traduit par le journal]

Can. J. Chem., **52**, 129 (1974)

The cyclization of *N*-substituted maleamic acids either to the corresponding maleimides (**3**) or isomaleimides (**1**) under various reaction conditions, is well documented (1, 2). The isomerization (3, 4) of **1** into **3** may proceed (5) through nucleophilic attack of an acetate ion on the carbonyl carbon of **1**, followed by ring opening and a recyclization in which the nitrogen of the intermediate reexpels the acetate ion.

In a recent work we described (6) the reaction of substituted *N*-phenylmaleimides (**3**) with aziridine, which lead to adducts (**4**) showing unexpected p.m.r. spectra. Considering the analogy in structure between maleimides and isomaleimides and having also in mind the chemical properties of aziridine (7), it seemed interesting to react ethylenimine with isomaleimides, since either a direct adduct should be formed or an isomerization of the isomaleimide to maleimide could occur.

The latter process took place when room-temperature treatment of an ethereal solution of *N*-phenylisomaleimide (**1**) with aziridine gave in an almost quantitative yield exclusively 3-(*N'*-aziridinyl)-*N*-phenylsuccinimide (**4**), identified by direct comparison with a sample obtained (6) by treatment of aziridine with *N*-phenylmaleimide (**3**).

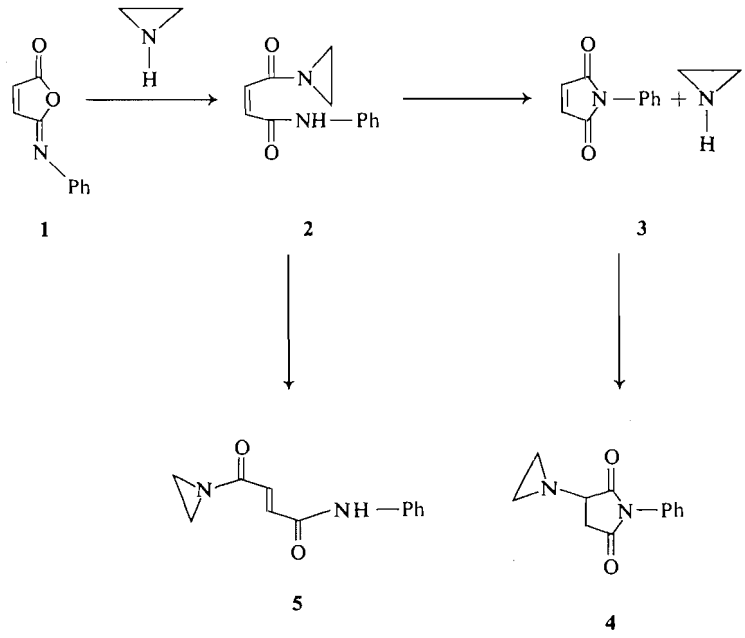
When aziridine is added dropwise to an ethereal solution of *N*-phenylisomaleimide (**1**) below 0 °C, a compound m.p. 80–81° (dec.) was isolated in almost quantitative yields. It showed i.r. absorption bands at 1715 and 1672 cm^{-1} due to carbonyl groups and u.v. maxima at 223 and 300 nm (ε 10 700 and 650). In the n.m.r. spectrum the presence of five aromatic protons located between 7.1 and 7.8 p.p.m., showing exactly the same pattern as the ring protons of acetanilide, were found. In addition, an AB system ($\delta_A = 6.35$, $\delta_B = 6.50$; $J_{AB} = 12$ Hz) attributable to a *cis* CH=CH moiety and a singlet (4H) at 2.45 p.p.m. corresponding to the aziridinyl ring protons, could be recognized. Therefore structure **2** was assigned to this intermediate, which is very unstable, since it easily undergoes transformation into **4** even when a solid sample is kept at −10 °C during two days.

The transformation of **1** to **4** can be rationalized as an attack of the aziridine electron pair on the carbonyl group of the isomaleimide, followed by cleavage of the carbonyl–oxygen single bond, leading to the anion of the enol of an amide, which, after electron redistribution and protonation, affords **2**; this in turn reacts to yield 3-(*N'*-aziridinyl)-*N*-phenylsuccinimide (**4**) by a stepwise process in which ring closure is accompanied by expulsion of the aziridine residue, followed by a Michael recombination of both species. Evidence for this process was obtained when a chloroform solution of pure **2** after standing at room temperature for several hours, gave a mixture of **3**, **4**, **5**, and some polymeric material which was not studied.

Compounds **3** and **4** were identified by direct comparison with authentic specimens (6), while

[1]Presented at the VIII Congreso Mexicano de Química Pura y Aplicada, Querétaro, Qro. México, March, 1973.

[2]Recipient of a CoNaCyT (México) Scholarship (1970–1973).



SCHEME 1

the structure of **5** was deduced spectroscopically. It analyzed correctly for $C_{12}H_{12}O_2N_2$, showing i.r. bands at 3425 and 3325 (NH group), 1665 (amide carbonyls), and 1600 cm^{-1} (aromatic double bonds) and u.v. absorption at 228 and 306 nm (ε 10 900 and 6200). The n.m.r. spectrum showed a singlet (2H) at 7.25 p.p.m. due to two vinyllic protons, superimposed on the signals of the five aromatic protons (7.1 to 7.8 p.p.m.), and a singlet (4H) at 2.36 p.p.m. corresponding to the aziridinyl methylene groups. Comparison of the i.r. (8), u.v. (9), and p.m.r. (10) properties of **2** and **5** is also congruent with a *cis–trans* pair of isomers.

Catalytic hydrogenation of **5** afforded *N*-(4-(*N'*-phenyl)succin)aziridine which showed in addition to the aromatic protons, the presence of a broad peak (4H) at 2.80 p.p.m. corresponding to the CH_2—CH_2 protons of the succinic chain and a sharp singlet (4H) at 2.30 p.p.m. attributable to the aziridinyl protons. It is interesting to mention that only a small amount of the three-membered ring was opened to an *N*-ethyl group during this hydrogenation performed in the presence of Adams catalyst, while compound **4** was transformed in high yields into 3-(*N'*-ethyl)-*N*-phenylsuccinimide using 10% Pd on charcoal catalyst (see Experimental). In addition, hydrogenation of **2** with Pd–C catalyst gave *N*-phenylsuccinimide identified with a sample obtained by hydrogenation of *N*-phenylmaleimide (**3**).

A sample of **2** was also treated under the acetate ion conditions in which the transformation of **1** into **3** was described (5). This resulted in the formation of **3** in good yields. Under the reaction conditions, the free aziridine that should be formed very probably reacts further with the acetic anhydride in a similar way as a compound of type **4** was derivatized previously (6), thereby precluding the Michael addition. These reactions are outlined in Scheme 1.

Experimental

3-(N'-Aziridinyl)-N-phenylsuccinimide (4)

A stirred solution of 5 g of *N*-phenylisomaleimide (**1**) in 200 ml of ether was treated dropwise with aziridine until the yellow color disappeared. The stirring was continued awhile and the precipitate filtered, yielding 5 g of **2** m.p. 119–120°. Recrystallization from acetone–hexane gave white needles: m.p. 122–123°; λ_{max} 221 nm; ε 7000; i.r. 1790 and 1722 (imide carbonyls), and 1600 cm^{-1} (aromatic double bonds). The n.m.r. showed the aromatic protons as a broad signal (5H) centered at 7.4 p.p.m. and the characteristic signals due to the succinimide and aziridine ring protons previously found (6) in similar compounds.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95; O, 14.80. Found: C, 66.46; H, 5.42; N, 12.94; O, 14.82.

The substance showed no depression on admixture

with a sample obtained by treatment of *N*-phenylmaleimide (**3**) (11) with aziridine (6) and their i.r. spectra were identical.

1-Aziridinyl-4-(N'-phenyl)maleidiamide (2)

A solution of 5 g of **1** in 200 ml of ether was treated as previously with aziridine, but the addition was performed very slowly (45 min) and the solution maintained in an ice bath with NaCl. The precipitate was filtered immediately after decoloration of the solution and washed with cold pentane. This yielded 5 g of solid: m.p. 82–83° (dec.); λ_{max} 223 and 300 nm; ε 10 700 and 650; i.r. 1715 and 1672 (amide carbonyls), 1620, and 1600 cm^{-1} (double bonds). No microanalytical results for the compounds were obtained, since when a sample is kept during 48 h at −10° it transforms quantitatively to 3-(*N'*-aziridinyl)-*N*-phenylsuccinimide (**4**), identified by standard procedures.

Decomposition of 2

A solution containing 1.5 g of freshly prepared **2** in 100 ml of chloroform was stored at room temperature for 6 h. Upon addition of 25 ml of hexane, a pink solid was precipitated and removed by filtration yielding around 100 mg of a polymeric material which was discarded. The filtrate was diluted with 50 ml of ethyl acetate and concentrated under vacuum at room temperature to a small volume (~20 ml). Addition of several drops of hexane caused precipitation of a white solid which was filtered yielding ~300 mg of **5**, m.p. 161–163° (dec.). Recrystallization from ethyl acetate – hexane gave white needles; m.p. 162–163° (dec.); λ_{max} 228 and 306 nm; ε 10 900 and 6180; i.r. 3425 and 3325 (N—H group), 1665 (amide carbonyls), and 1600 cm^{-1} (double bonds).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95; O, 14.80. Found: C, 66.60; H, 5.50; N, 12.98; O, 14.89.

The filtrate was concentrated at room temperature yielding ~200 mg of white needles, m.p. 122–123° which were identified as 3-(*N'*-aziridinyl)-*N*-phenylsuccinimide (**2**) by standard procedures.

Further concentration of the filtrate followed by addition of hexane yielded around 100 mg of yellow needles, m.p. 88–89° identified by direct comparison with an authentic sample (11) of *N*-phenylmaleimide.

Hydrogenation of 5

A solution of 180 mg of **5** was hydrogenated as previously. The residue was treated with hexane yielding 100 mg of *N*-(4-(*N'*-phenyl)succin)aziridine, m.p. 102–104°. The analytical sample from ether–hexane showed m.p. 105–107°; λ_{max} 207 and 243 nm; ε 16 000; i.r. 3430 (N—H group), 1670 (carbonyls), and 1590 cm^{-1} (double bonds).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C; 66.04, H; 6.47; N, 12.89; O, 14.66. Found: C, 65.97; H, 6.40; N, 12.66; O, 14.79.

From the mother liquors, a small amount (20 mg) of *N*-(4-(*N'*-ethyl)succin)aniline, m.p. 165–166° was isolated. The analytical sample obtained from chloroform–hexane showed m.p. 166–167°; λ_{max} 206 and 244 nm; ε 14 200 and 12 000; i.r. 3430 (NH group), 1670 (carbonyls), and 1605 cm^{-1} (double bonds). The p.m.r. spectrum showed the aromatic protons between 7.0 and 7.6 p.p.m., a broad singlet (4H) at 2.65 p.p.m. due to the CH_2—CH_2 moiety and an ethyl group as quartet and triplet (J_t = 7 Hz) at 3.23 and 1.12 p.p.m. respectively.

3-(N'-Ethyl)-N-phenylsuccinimide

An ethyl acetate solution containing 500 mg of **4** was hydrogenated in the presence of 50 mg of 10% Pd on charcoal and worked-up as usual. The residue crystallized from carbon tetrachloride yielding 450 mg of the title compound, m.p. 103–104°. The analytical sample obtained from the same solvent showed m.p. 105–106°; λ_{max} 220 nm; ε 7000; i.r. 1785 and 1718 (imide carbonyls), and 1595 cm^{-1} (double bonds). The n.m.r. spectrum showed the aromatic protons between 7.2 and 7.6 p.p.m., a quartet (J = 7 Hz) at 2.83 (2 H) and a triplet (J = 7 Hz) at 1.20 p.p.m. (3 H) corresponding to the *N*-ethyl group and an ABX system $\delta_A = 2.75$, $\delta_B = 3.12$, $\delta_X = 3.97$ p.p.m.; $J_{AB} = 18$, $J_{AX} = 6$, and $J_{BX} = 8$ Hz corresponding to the succinimide ring protons.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; O, 14.66. Found: C, 65.89; H, 6.29; N, 12.97; O, 14.77.

Transformation of 2 into 3

A solution containing 1 g of freshly prepared **2** and 2 g of AcONa in 4 ml of Ac_2O was kept at room temperature during 48 h. Addition of ice water and extraction with ether followed by work-up as usual, gave a residue from which 523 mg of **3** could be isolated and identified with an authentic sample by standard methods.

1. T. M. Pyriadi and H. J. Harwood. J. Org. Chem. **36**, 821 (1971).
2. T. M. Pyriadi. J. Org. Chem. **37**, 4184 (1972).
3. D. Y. Curtin and L. L. Miller. Tetrahedron Lett. 1869 (1965).
4. M. L. Ernst and G. L. Schmir. J. Am. Chem. Soc. **88**, 5001 (1966).
5. R. J. Cotter, C. K. Sawer, and J. M. Whelan. J. Org. Chem. **26**, 10 (1961).
6. P. Joseph-Nathan, V. Mendoza, and E. García G. J. Org. Chem. **37**, 3950 (1972).
7. O. C. Dermer and G. E. Man. Ethylenimine and other aziridines. Academic Press, New York. 1969. Chapt. 3.
8. N. B. Colthup, L. H. Daly, and S. E. Wiberley. Introduction to infrared and Raman spectroscopy. Academic Press, New York. 1964. p. 378.
9. A. E. Gillman and E. S. Stern. An introduction to electronic absorption spectroscopy in organic chemistry. E. Arnold Ltd., London. 1962. pp. 267–274.
10. P. Joseph-Nathan and E. Díaz. Introducción a la resonancia magnética nuclear. Limusa-Wiley, Mexico City. 1970. pp. 128–131.
11. V. Mendoza, P. Joseph-Nathan, and C. Pérez. Rev. Soc. Quím. Méx. **15**, 103 (1971).