The Reaction of Two Oxazolo(4′,5′-3,4)-coumarins with Alkali

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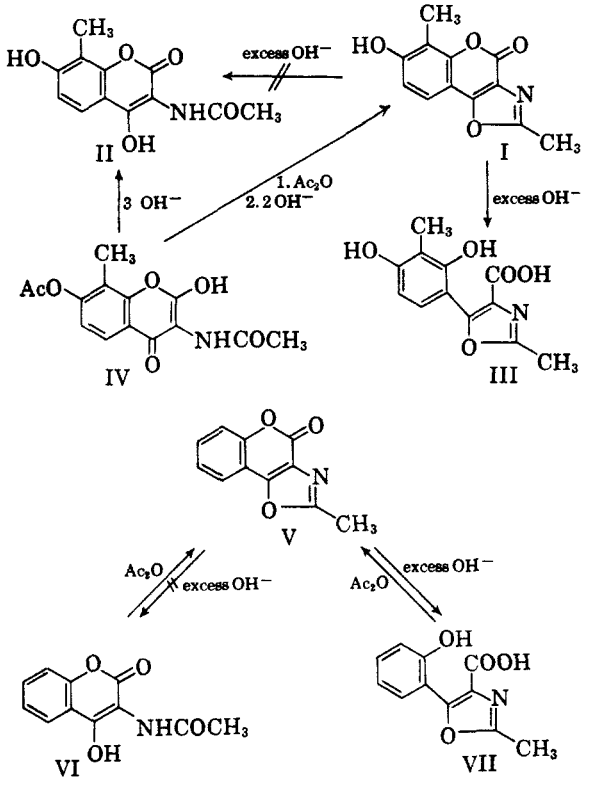
In connection with structure studies on the antibiotic novobiocin,[1,2] we examined the reaction of the substituted oxazole I with alkali. Because of



Arndt's[3] report that the unsubstituted oxazole V was converted to the coumarin VI by alkali, we expected I to be converted into the known coumarin[4] II. However, II was not the product obtained. Present evidence discussed in this paper indicates that the acid III was the product.

We prepared the oxazole I by the conversion of IV[2] into *O*-acetyl I[1] with boiling acetic anhydride. Deacetylation of this material with two equivalents of alkali gave the phenol I in 62% yield over-all. When I was treated with excess alcoholic sodium hydroxide at room temperature, the product was more acidic (pK'_a 4.2) than II (pK'_a 5.3) and its ultraviolet and infrared spectra were different from those of II. In view of the considerable stability of the oxazole ring to alcoholic alkali,[5] it seemed likely that the *lactone* ring of I had been opened giving the carboxylic acid III. The physical properties of III were consistent with this formulation. Sublimation of V at 200° did not reform the lactone ring, but treatment with boiling acetic anhydride did cause lactonization to *O*-acetyl I.

In view of these results, we examined the reaction of the unsubstituted oxazole V with alkali. The coumarin VI was prepared by the procedure of Huebner and Link[6] and was converted into the oxazole V with boiling acetic anhydride. When V was allowed to react with excess alcoholic sodium hydroxide at room temperature, the product was *not* VI but an isomeric compound more acidic (pK'_a 4.4) than VI (pK'_a 5.0). The ultraviolet and infrared spectra of the new acid, formulated as VII, were different from those of VI and were consistent with structure VII. As in the case of the acid III, VII could be sublimed at 150° unchanged. However, lactonization occurred readily in boiling acetic anhydride to give VII.

The results outlined above show that the oxazole rings of III and VII were not opened by alkali forming an acetamido 4-hydroxycoumarin. The available data indicate that the lactone rings were cleaved giving oxazole carboxylic acids such as III and VII.

EXPERIMENTAL

7-Acetoxy-8-methyl-2-methyloxazolo (4′,5′-3,4)coumarin (O-acetyl I). A mixture of 1.0 g. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (IV) and 20 ml. of acetic anhydride was refluxed for 2 hr. during which time the solid dissolved. The solution was allowed to stand at room temperature overnight. The crystalline precipitate, 0.64 g. (66%), m.p. 211–212°,[7] was collected on a filter and dried. This product, 7-acetoxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin, was the same as that obtained by refluxing a solution of novobiocic acid in acetic anhydride.[1] Obtained by the latter method and recrystallized from ethyl acetate, the compound melted at 208–209° and showed $\lambda_{max}^{CH_3OH}$ 321 mμ (ε 9330), shoulder 314 (ε 10,700), 307 (ε 12,200), 284 (ε 12,800), shoulder 275 (ε 10,800), 212 (ε 24,000).

Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.64; H, 4.06; N, 5.13. Found: C, 61.34; H, 3.84; N, 5.37.

7-Hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I). A slurry of 546 mg. (2 mmoles) of 7-acetoxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin in 5 ml. of ethanol was cooled in an ice bath and four 1-ml. portions of 1*N* sodium hydroxide were added at 5-min. intervals. The solid did not dissolve until the solution was diluted to 20 ml. with water. The final *p*H of the solution was 10.5–11.0. The solution was filtered and the filtrate was acidified to *p*H 4 with 2.5*N* hydrochloric acid. The white precipitate, 437 mg. (95%), m.p. 310–317° (dec.), was collected on a filter and dried.

(1) J. W. Hinman, E. L. Caron, and H. Hoeksema, *J. Am. Chem. Soc.*, **79**, 3789 (1957).

(2) C. H. Stammer, E. Walton, A. N. Wilson, R. W. Walker, N. R. Trenner, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 137 (1958).

(3) F. Arndt, L. Louve, R. Un, and E. Ayca, *Ber.*, 319 (1951).

(4) Compound IV is written in the chromone rather than the coumarin form for reasons discussed in ref. 2.

(5) R. H. Wiley [*Chem. Revs.*, **37**, 401 (1945)] states that 2-methyl-5-phenyloxazole, analogous to I, is stable to alcoholic potassium hydroxide at 200°.

(6) C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.*, **67**, 99 (1945).

(7) All melting points were taken on a Kofler Micro Hot Stage.

The product was recrystallized from 1:5 water–dimethylformamide giving 341 mg., m.p. 295–303° (dec.), of 7-hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I). An analytical sample was prepared by recrystallization of a small sample from 1:3 water–dimethylformamide and 1:1 water–dimethylformamide successively.

Anal. Calcd. for $C_{21}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.22; H, 3.89; N, 6.51.

Other physical properties of I were: $\lambda_{max}^{CH_3OH}$ 316 mμ (ε, 18,500), shoulder 295 (ε, 9450), shoulder 249 (ε, 10,150), 2440 (ε, 10,500); pK_a'[8] 9.6; λ_{max}^{Nujol} 5.72 (C=O), 6.03.

(8) All pK_a' values are $pH\ ^1/_2$ values obtained by potentiometric titration of the compounds in 70% acetone-water mixtures.

4-Carboxy-5-(2,4-dihydroxy-3-methylphenyl)-2-methyloxazole (III). To a slurry of 231 mg. (1 mmole) of 7-hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I) in 5 ml. of ethanol was added 10 ml. of 0.6*N* sodium hydroxide. The yellow-green solution was allowed to stand overnight at room temperature and then evaporated *in vacuo* to about 3 ml. The solution was diluted to about 8 ml. with water and acidified with 2.5*N* hydrochloric acid. The precipitate weighed 273 mg. When this material was heated on the Micro Hot Stage, it changed crystal form at 115–125°, sublimed at 180°, and decomposed at 290–300°. Two crystallizations of this product from water gave 88 mg. of 4-carboxy-5-(2,4-dihydroxy-3-methylphenyl)-2-methyloxazole, transition 228–233°, 290–300° (dec.).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.59; H, 4.40; N, 6.17.

Other physical properties were $\lambda_{max}^{CH_3OH}$ 300 mμ (ε, 13,200), 222 (ε, 20,400); pK_a' 4.2; λ_{max}^{Nujol} 5.89 (C=O), 6.17.

For comparison with II, we here record our physical data on 3-acetamido-4,7-dihydroxy-8-methylcoumarin (II): m.p. 280–281°; λ_{max}^{MeOH} 316 mμ (ε, 5270), 292 (ε, 2660), shoulder 249 (ε, 3160), 245 (ε, 3210); pK_a' 5.3; λ_{max}^{Nujol} 6.09, 6.18.

When III was sublimed at 200–220° and *ca.* 0.1 mm., the crystalline sublimate melted at 315–325° (dec.) with a transition 220–230°. Apparently no lactonization to I had occurred. Refluxing acetic anhydride, however, converted III into *O*-acetyl I in 40 min. The crude product obtained melted at 200–204° and its mixture with authentic *O*-acetyl I melted at 204–209°.

4-Carboxy-5-(2-hydroxyphenyl)-2-methyloxazole (VII). A slurry of 380 mg. (2 mmoles) of the 2-methyloxazolo(4′,5′-3,4)coumarin[6] V (m.p. 195–196°) in 10 ml. of ethanol was treated with 20 ml. of 0.6*N* sodium hydroxide. A yellow-green color formed in the solution and the oxazole slowly dissolved. After 16 hr. at room temperature, the solution was evaporated *in vacuo* to a volume of about 2 ml. and acidified with concentrated hydrochloric acid. The crude product, 380 mg. (92%), melted at 165–170°. After one recrystallization from ethyl acetate, the 4-carboxy-5-(2-hydroxyphenyl)-2-methyloxazole (VII), 175 mg., melted at 170–173°. After one further recrystallization from ethyl acetate, the product had m.p. 171–174°; $\lambda_{max}^{CH_3OH}$ 295 mμ (ε, 5400), 262 (ε, 8240), pK_a' 4.4; λ_{max}^{Nujol} 6.01, 6.18.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.44; H, 4.38; N, 6.47.

We obtained the following physical data on 3-acetamido-4-hydroxycoumarin (VI) in order to compare it with the acid VII obtained above: m.p. 229–230°, $\lambda_{max}^{CH_3OH}$ 316 mμ (ε, 11,700), shoulder 295 (ε, 9450), 282 (ε, 8320); pK_a' 5.0; λ_{max}^{Nujol} 5.93 (C=O), 6.13.

When the acid VII was sublimed at 150–160° and *ca.* 0.05 mm., the sublimate melted at 175–178°. Apparently no lactonization to V, m.p. 195–196°, had occurred. However, when VII was treated with refluxing acetic anhydride for 30 min., a 64% yield of oxazole V crystallized from the solution.

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The Isomerization of Some Aziridine Derivatives. III. A New Synthesis of 2-Imidazolines

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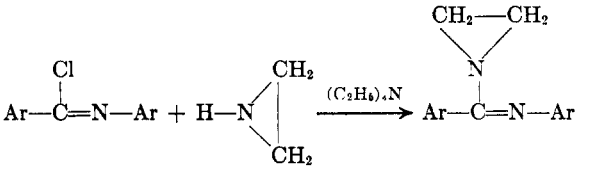
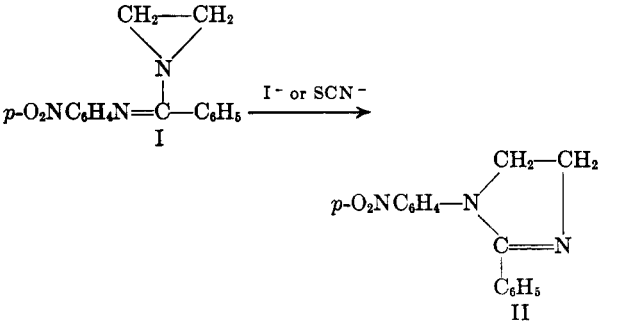
Previous work in this laboratory has been concerned with the isomerization of 1-aroylaziridines.[1,2] For example, 1-*p*-nitrobenzoyl-2,2-dimethylaziridine has been selectively isomerized to 2-*p*-nitrophenyl-4,4-dimethyl-2-oxazoline, 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline, or *N*-(β-methallyl)-*p*-nitrobenzamide by sodium iodide in acetone, concentrated sulfuric acid, or refluxing heptane respectively. We now wish to report the synthesis and isomerization of a new class of aziridine derivatives, the 1-(*N*-arylbenzimidoyl)aziridines.

The 1-(*N*-*p*-nitrophenylbenzimidoyl)aziridine (I) and the 1-(*N*-phenyl-*p*-nitrobenzimidoyl)aziridine used in the present study were prepared by reaction of the corresponding *N*-arylbenzimidoyl chloride with aziridine in benzene containing triethylamine:



The *N*-*p*-nitrophenylbenzimidoyl chloride reacted much faster with aziridine than did *N*-phenyl-*p*-nitrobenzimidoyl chloride. Evidently *N*-arylbenzimidoyl chlorides are much less susceptible to nucleophilic attack when a strong electron-withdrawing group is attached to the benzimidoyl moiety than when it is attached to the *N*-aryl moiety.

The 1-(*N*-arylbenzimidoyl)aziridines in acetone solutions containing iodide ion or thiocyanate ion smoothly undergo isomerization to 2-imidazolines. Thus I was converted in over 90% yield to 1-*p*-nitrophenyl-2-phenyl-2-imidazoline (II):



The structure of II was confirmed by comparison of infrared spectra and by mixed melting point

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

(2) H. W. Heine, M. E. Fetter and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).