Penicillin Imino Chlorides. II. A Novel Rearrangement Leading to Oxazoles

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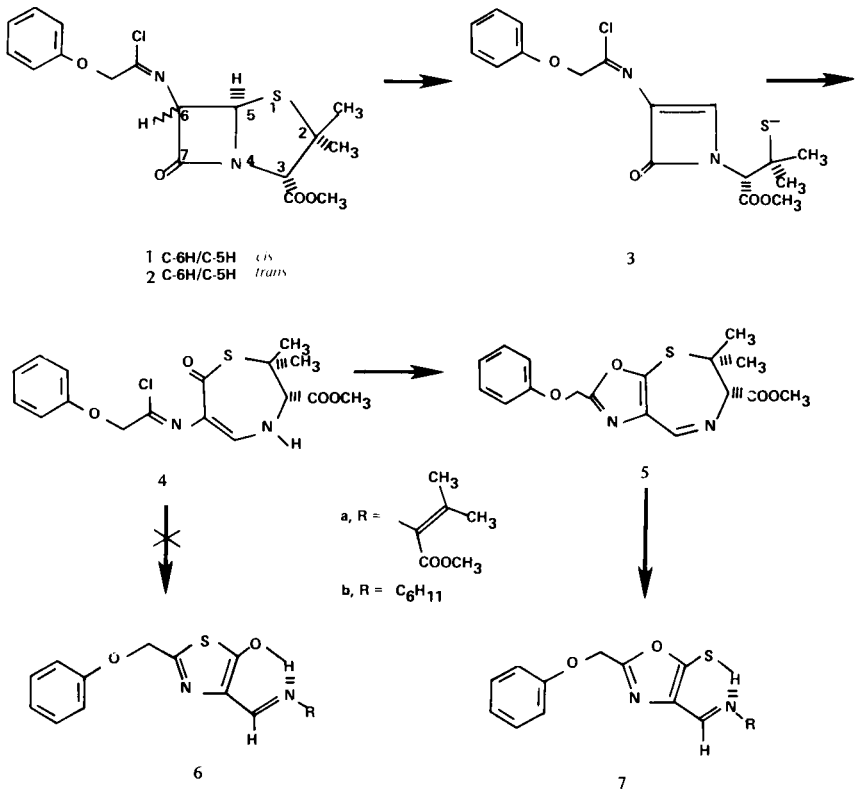
Sir:

In a previous communication (1) we described the conversion of a penicillin G ester to Ketenimine **13**, and noted the facile C-6 epimerization of the imino chloride intermediate leading to **13**. We report herein the analogous epimerization of the imino chloride **1** of penicillin V methyl ester and the finding of a novel rearrangement of the resulting 6-*epi* derivative **2** to oxazole **7a**.

Penicillin V methyl ester was converted by a known procedure (2) to imino chloride **1** [nmr (deuteriochloroform): 6.7-7.3 (m, 5, Ar*H*), 5.55 (d, 1, j = 4.0 Hz, C-6*H*), 5.27 (d, 1, j = 4.0 Hz, C-5*H*), 4.78 (d, 2, C_6H_5OCHH), 4.40 (s, 1, C-3*H*), 3.73 (s, 3, OCH_3), 1.50 ppm (d, 6, $C(CH_3)_2$)] in 94% weight yield and 78% purity (3). When **1** was treated with a catalytic amount of triethylamine (TEA) in methylene chloride for a few seconds, essentially complete epimerization to **2** resulted as indicated by shifts in the nmr spectrum for the β-lactam protons as well as a change in their coupling constant from 4.0 to 1.8 Hz (4) [nmr (deuteriochloroform): 6.7-7.4 (m, 5, Ar*H*), 5.28 (d, 1, j = 1.8 Hz, C-5*H*), 5.08 (d, 1, j = 1.8 Hz, C-6*H*), 4.80 (d, 2, C_6H_5OCHH), 4.50 (s, 1, C-3*H*), 3.73 (s, 3, OCH_3), 1.52 ppm (d, 6, $C(CH_3)_2$)]. During several hours at room temperature with one equivalent of TEA, or during about 10 minutes with a large excess of TEA, epimer **2** rearranged affording a 59% yield of an optically inactive yellow oil, [ir (dichloromethane): 5.81 (CO), 6.10 (C=N), 6.26 μ; uv max (methanol): 260 (10,000), 370 nm (5,700); mass spectrum *m/e* (rel intensity) 346 (54), 287 (9), 253 (100), 193 (48), 151 (60); nmr (deuteriochloroform): 12.12 (d, 1, j = 14.0 Hz, hydrogen bonded S*H*), 7.90 (d, 1, j = 14.0 Hz, C*H*=N), 6.7-7.3 (m, 5, Ar*H*), 5.00 (s, 2, $C_6H_5OCH_2$), 3.80 (s, 3, OCH_3),

Scheme I



2.10 ppm (d, 6, 7.0 Hz splitting, $C(CH_3)_2$); after shaking with deuterium oxide/sodium deuteroxide, the doublet at 12.12 disappeared and that at 7.90 collapsed to a singlet: *Anal.* Calcd. for $C_{17}H_{18}N_2O_4S$: C, 59.0; H, 5.2; N, 8.1; S, 9.2. Found: C, 59.4; H, 5.5; N, 8.0; S, 9.3]. Assignment of structure **7a** to the rearrangement product was based on these data and on the following mechanistic considerations.

We suggest that oxazole **7a** arises from enethiolate **3** which in turn rearranges to thiazepine **4**. Thiazepines are well documented in other penicillin rearrangements (5). However, in the present case, the imino chloride function present in **4** allows facile oxazole ring closure to give imine **5**. Base catalyzed ring opening of **5** then affords **7a**. Exclusion of the alternative thiazole structure **6a** (which might have formed by direct base catalyzed ring opening of **4** and which would be expected to exhibit spectral data quite similar to those for **7a**) was achieved as follows. Treatment of the rearrangement product **7a** with cyclohexylamine afforded a new material isolated in 90% yield as a yellow oil. [Ir (dichloromethane): 6.08 (C=N), 6.27 μ; uv max (methanol): 239 (13,700), 270 (5,000), 276 (5,000), 391 nm (11,000); nmr (deuteriochloroform): 11.27 (broad d, 1, S*H*), 7.92 (d, 1, j = 14.0 Hz, C*H*=N), 6.8-7.4 (m, 5, Ar*H*), 5.01 (s, 2, $C_6H_5OCH_2$), 3.46 (m, 1, C*H*N), 1.0-2.0 ppm (m, 10, 5 x CH_2)]. These data were fully consitent with **7b** (or **6b**). Thus an unambiguous synthesis of either **7b** or **6b** would confirm the structure of the rearrangement product.

Thiazole **6b** was prepared straightforwardly by the route **8** → **9** → **10** → **11** + **12** → **6b** (6) in 67% yield (based on **11**) following chromatography and recrystallization [m.p. 118-119° (ether); ir (dichloromethane): 6.08 (C=N), 6.29 μ; uv max (methanol): 269 (20,000), 277 (21,000), 283 (19,500), 344 nm (19,500); nmr (deuteriochloroform): 9.05 (broad d, 1, O*H*), 7.65 (d, 1, j = 14.0 Hz, C*H*=N), 6.8-7.4 (m, 5, Ar*H*), 5.01 (s, 2, $C_6H_5OCH_2$), 3.20 (m, 1, C*H*N), 1.2-2.2 ppm (m, 10, 5 x CH_2); *Anal.* Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.5; H, 6.3; N, 8.9; S, 10.1. Found: C, 64.7; H, 6.5; N, 9.3; S, 10.0]. These data were distinctly different from those exhibited by **7b** obtained above from the reaction of cyclohexylamine with **7a**, and thus confirmed **7a** as the rearrangement product.

Finally, after discovery of the rearrangement described above we were prompted to reinvestigate the behavior of ketenimine **13** (1) under these conditions since it seemed reasonable that oxazole formation should result. Both in previous (1) and, as yet, unreported studies we used **13** in crude form immediately after preparation and never undertook the isolation or identification of minor side products. In our hands **13** afforded a complex degraded mixture after prolonged standing in TEA. However, chromatographic fractions were isolated whose nmr spectra were consistent with impure oxazole **14**. The 4-nitro derivative **15** rearranged more cleanly, however, with a large excess of TEA and oxazole **16** was isolated in about 25% yield. A detailed account of this and related work will be forthcoming.

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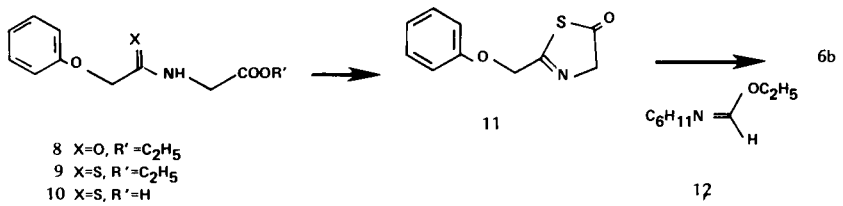
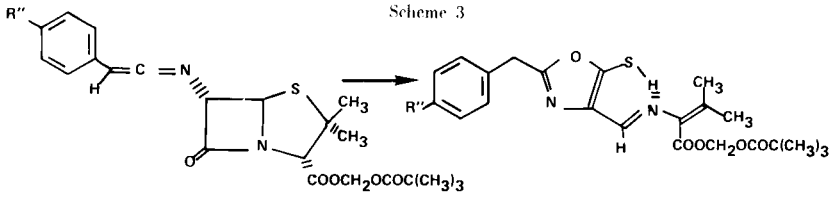
Scheme 2



8 X=O, R'=C_2H_5
9 X=S, R'=C_2H_5
10 X=S, R'=H

Scheme 3



13 R''=H
15 R''=NO_2

14 R''=H
16 R''=NO_2

REFERENCES

(1) For paper I of this series, see R. D Carrol, E. S. Hamanaka, D. K. Pirie and W. M. Welch, *Tetrahedron Letters*, 1515 (1974).

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(3) The single contaminant was penicillin V methyl ester which arose from partial hydrolysis of **1** during work-up.

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(6) The references which teach how to prepare **6b** by this route are the following: (a) D. Thorne, West German Patent 1,927,692 (1969); (b) E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951); (c) R. Glushkov and O. Magidson, *Zh. Obshch. Khim.*, **30**, 1855 (1960); *J. Gen. Chem. USSR*, **30**, 1839 (1960). All compounds afforded corroborating spectral data.