

NOVEL PHOTOREACTIONS OF AN ISOTHIAZOLONE DERIVATIVE

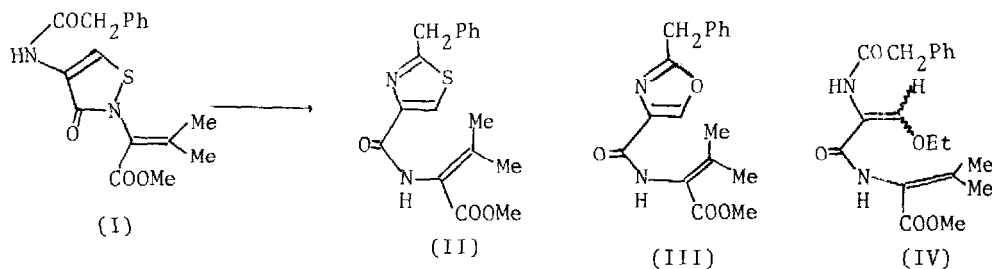
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In the course of our investigation on the photochemistry of penicillin and cephalosporin derivatives,¹ we found that irradiation of methyl α -isopropylidene 4-phenylacetamido-3-isothiazolone-2-acetate(I),² a degradation product of penicillin G sulfoxide methyl ester, causes the novel type of photoreactions leading to 2-benzylthiazole-4-carboxamide derivative(II), 2-benzylloxazole-4-carboxamide derivative(III) and an open-chain dipeptide(IV).

Formation of the desulfurization products, (III) and (IV), has interesting mechanistic implication, particularly in connection with photorearrangement of isoxazolones to oxazolones.³ Recyclization of (I) to the thiazole(II) can be explained in terms of intramolecular trapping of the intermediary thioaldehyde, which has been suggested as a possible biogenetic precursor of penicillins,^{4,5} with an amide side-chain.

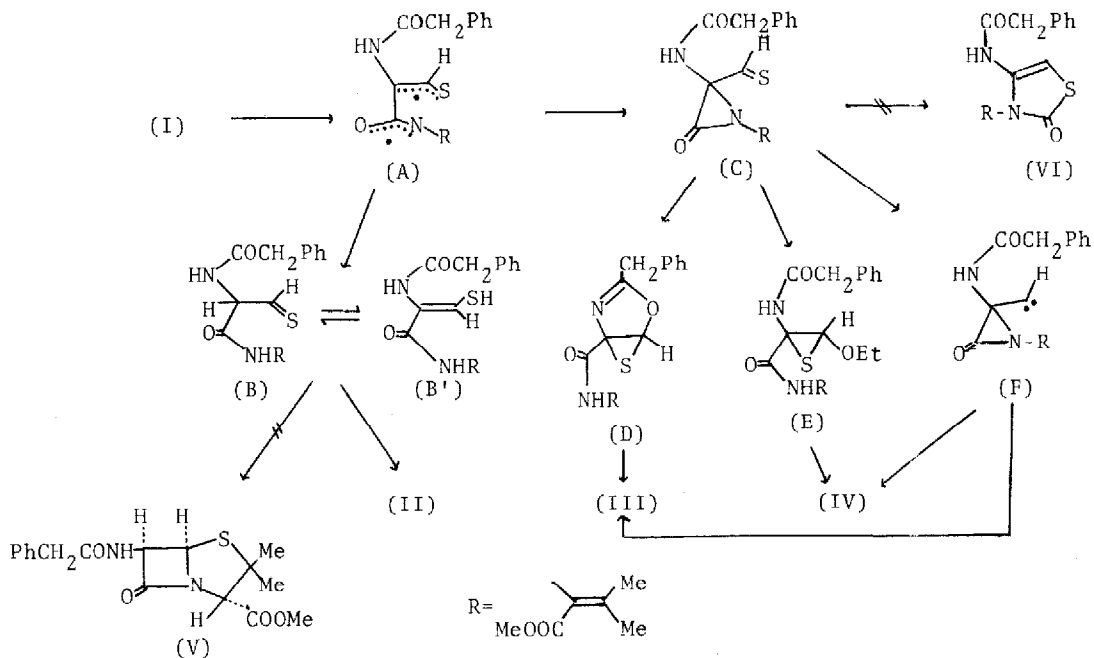


Irradiation of (I) in ethanol ($3 \times 10^{-3} M$) was carried out by using a 400W high-pressure mercury arc lamp through a Pyrex filter under nitrogen until disappearance of (I) (monitored by TLC, about 8 hr). Chromatographic separation allowed to isolate sulfur(2%), (II) (mp 113-5°, 29%), (III) (mp 108-9°, 28%) and

(IV) (mp 164-5°, 18%). The structure of (II) was confirmed by its independent synthesis.⁶ The spectral data and microanalytical results fully accommodate to the structures of (III) and (IV) [(III): ir(KBr)cm⁻¹3350(NH), 1720(COOCH₃), 1670(NHCO); nmr(CDCl₃)δ 1.92(3H, s, CH₃-C=C-), 2.24(3H, s, CH₃-C=C-), 3.77(3H, s, CH₃OOC-), 4.15(2H, s, C₆H₅CH₂-), 7.40(5H, broad s, phenyl protons), 8.15(1H, broad, NH, deuterium exchangeable), 8.21(1H, s, an oxazole ring proton); uvλ^{MeOH}_{max} nm(ε) 215(2×10⁴); mass m/e M⁺= 314. (IV); ir(KBr)cm⁻¹3400,3300(NH),1700(COOCH₃), 1670, 1620(NHCO); nmr(CDCl₃)δ 1.25(3H, t, CH₃CH₂O-), 1.83(3H, s, CH₃-C=C-), 2.12(3H, s, CH₃-C=C-), 3.75(5H, s, CH₃OOC- and C₆H₅CH₂-), 4.02(2H, q, CH₃CH₂O-), 6.57(1H, broad, NH, deuterium exchangeable), 7.40(6H, broad s, a vinyl proton and phenyl protons), 7.85(1H, broad, NH, deuterium exchangeable); uvλ^{MeOH}_{m=x} nm(ε) 242(2×10⁴); mass m/e M⁺=360].

When (I) was irradiated in acetonitrile under analogous conditions, sulfur, (II) and (III) were obtained in 1%, 2% and 42% yields, respectively.

In above experiments, expected β-lactam derivative such as penicillin G methyl ester(V) and thiazolone derivative(VI) were not detected. (see Scheme 2)



Scheme 2

Although some mechanisms can be written for the present photoreactions, we propose the conceivable reaction sequences as depicted in Scheme 2.

Homolytic cleavage of the S-N bond of an excited (I) could give a biradical intermediate(A). Hydrogen abstraction of (A) from ethanol may generate a labile thioaldehyde(B) which isomerizes to a thioenol(B'). The thioenol(B') thus formed could be trapped intramolecularly with an amide function to give the thiazole derivative(II).⁷ A significant decrease of the yield of (II) by employment of acetonitrile as a solvent may be ascribed to that ethanol is a better hydrogen donor than acetonitrile for the reduction of (A) to (B or B').

An intermediacy of α -lactam aldehyde has been assumed in the photorearrangement of isoxazolones to oxazolones.^{3,8} An analogous key intermediate, α -lactam thioaldehyde(C), could rationalize the formation of (III) and (IV).

Photochemical elimination of sulfur from episulfide has been demonstrated.⁹ In this view, episulfides, (D) and (E), are conceivable as intermediates leading to (III) and (IV). Generation of (D) from (C) appears to involve attacks of an amide oxygen at the thioaldehyde carbon and of thioaldehyde sulfur at the electron deficient carbon which could be concurrently produced by ring cleavage of the α -lactam moiety. The reaction of (C) with ethanol also could give ethoxy-substituted episulfide(E).

An alternative intermediate for the formation of (III) and (IV) is a carbene species(F)¹⁰ which may be formed photochemically from (C) by desulfurization and trapped with an amide oxygen or ethanol. No formation of (VI) via (C), which is contrary to our expectation, may be explained in terms of this attractive intermediate(F).

When analogous irradiation of (I) was carried out in ethanol-d₁, incorporation of deuterium¹¹ on the five membered ring of isolated (II) and (III) were not observed. The above reaction sequences are parallel to this observation.

We, however, are unable to obtain evidence favoring any one over the others. Work is underway in an effort to clarify the course of the present photoreactions.

References and Footnotes

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- 7 The thioaldehyde(B), a possible biogenetic precursor of penicillins, has been generated via some routes and its thioenol tautomer(B') has been trapped intermolecularly with 2,4-dinitrochlorobenzene. (see references 4 and 5)
- 8 A key intermediate in the isoxazole-oxazole photorearrangement has been proved to be an azirine derivative(cf. J. P. Ferris and F. R. Antonucci, J. Amer. Chem. Soc., 96, 2010, 2014(1974) and references cited therein).
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