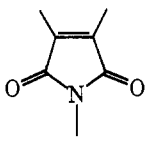
Communications to the Editor

Azetidinone Antibiotics. XIV.[1] Removal of a Phthaloyl Protective Group from Acid and Base Sensitive Compounds

Sir:

Phthaloyl protection of the amino group in penicillins, cephalosporins, and monocyclic azetidinones renders the azetidinone moiety of these compounds stable to a wide variety of reaction conditions. However, the obvious advantages of the phthaloyl protecting group[2] have been overshadowed by the lack of a selective method of removal of this protecting function in the presence of a highly sensitive azetidinone ring system. Ing-Manske's method[3] for the removal of the phthaloyl group by hydrazinolysis of N-substituted phthalimides has not been found applicable to phthalimido containing penicillins[4] and to Δ^3-cephalosporins.[5] Although various modifications of this method have been tried[6] the azetidinone carbonyl function is, in fact, more reactive toward hydrazine than the phthalimido carbonyl. To circumvent this problem we proposed to enhance the reactivity of the imido functionality with respect to that of the azetidinone ring by conversion of the imido function **1** to that of an isoimide **2**.[7]



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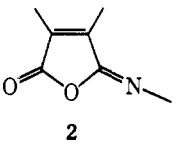

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We have studied dephthaloylation of monocyclic and bicyclic azetidinone compounds via the corresponding isoimides, and our results are reported here.

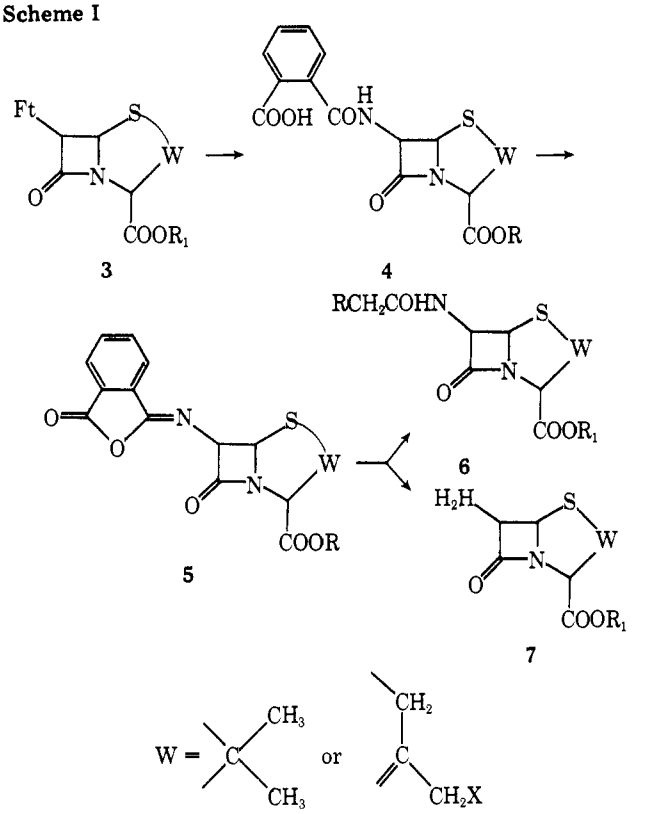
A survey of the literature revealed that isoimides could be prepared from amic acids by several methods.[8] Thus, the first step involved in the proposed dephthaloylation, or specifically in the phthalisoimide synthesis, was the hydrolysis of the phthalimido compounds[9] to their corresponding phthalamic acids. Hydrolysis of this type with sodium hydroxide has been described,[10] but we have found that in the case of phthalimido protected azetidinones, higher yields (68-90%) and products of higher purity are obtained when the hydrolysis is carried out with $Na_2S{\cdot}9H_2O$ in aqueous acetone or tetrahydrofuran (0-5°, 5-15 min).[11,12]

Cyclizations of phthalamic acids, **4**, to phthalisoimides, **5**, are performed by using three different dehydration methods:[8] (a) ethyl chloroformate-triethylamine (0-5°, THF, 20 min), (b) trifluoroacetic anhydride-triethylamine (22°, 10-30 min), and (c) *N,N'*-dicyclohexylcarbodiimide (0-5°, 20-30 min). All three methods were found equally applicable to the cephalosporin compounds, but method c was found to be the preferable one for the penicillin phthalamic acids.

The phthalisoimides **5** are obtained as stable crystalline compounds (67-97%).

The final step in the dephthaloylation process (Scheme I) involves hydrazinolysis of phthalisoimides **5**. We have found that this reaction proceeds quickly and selectively. When **5** is treated with 1 equiv of anhydrous hydrazine (THF, −20°, 20-30 min), the phthaloyl group is removed and an amine salt of phthalylhydrazide is formed.[13] The desired

Scheme I



X = H or OAC; Ft = phthalimido; R = Ph or 2-thienyl; a = R_1 = H; b, R_1 = CH_3; c, R_1 = *t*-Bu; d, R_1 = *p*-methoxybenzyl; e, R_1 = *p*-nitrobenzyl

amine can be separated from phthalylhydrazide by mild digestion with *p*-toluenesulfonic acid or dilute hydrochloric acid. The highly insoluble phthalylhydrazide is filtered, and the hydrochloride or *p*-toluenesulfonate salt of the azetidinone nucleus is isolated from the filtrate (55-95%). Alternatively, the phthalylhydrazide complex[13] can be broken by an acyl chloride and the released amine simultaneously acylated (90°, 8-15 min). The amides **6** are soluble in organic solvents and separated from insoluble phthalylhydrazide (**6c**, R = thienyl, 75%; **6e**, R = phenyl, 60%). The free amino ester or acid can be obtained by thermolysis of the phthalhydrazide complex in refluxing chloroform. Filtration of the precipitated phthalhydrazide and evaporation of the filtrate gives the desired product.

A significant improvement in the yield and in the ease of isolation of the nucleus **7** is realized when methylhydrazine is employed instead of hydrazine. This is attributed to the fact that because of the decreased acidity of the by-product *N*-methylphthalhydrazide (with respect to phthalhydrazide) no complex is formed with the free amine. Therefore, no heating or acid treatment of the reaction mixture is required. *N*-Methylphthalhydrazide separates from a chloroform solution (25°) of the methylhydrazine-phthalisoimide adduct leaving the free amine in solution. The advantages of using methylhydrazine are thus particularly noticeable when applied to the dephthaloylation of more sensitive substrates (e.g., penicillins).

The isoimide carbonyl absorption (1821-1800 cm^{-1}) of **5**

indicates that this carbonyl group is the most reactive one in the molecule. Consequently, hydrazine attacks the isoimide carbonyl forming an addition intermediate. Opening of the imino lactone gives the corresponding hydrazide which in turn cyclizes to a six-membered cyclic intermediate. Finally, after the cleavage of the carbon–nitrogen bond, the desired nucleus, **7**, is formed.

The described dephthaloylation is relatively simple, fast, and high-yielding. No racemization has been observed during the dephthaloylation procedure. Therefore, we hope that the results of this study will expand the usefulness and applicability of the phthaloyl protective group in synthetic work.[14]

References and Notes

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(5) D. O. Spry, *J. Am. Chem. Soc.*, **92**, 5006 (1970); although D. O. Spry reports hydrazinolysis of Δ^2-cephalosporins in low yield (30%) according to experience in this laboratory, it is practically impossible to remove the phthaloyl group from penicillins and Δ^3-cephalosporins without disrupting the bicyclic azetidinone.
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(7) In our preliminary studies we have found that the carbonyl absorptions of **5e** are at 1821 (isoimide CO), 1785 (azetidinone CO), 1730 (ester CO), and 1710 (C=N) cm^{-1}. The absorption of **5e** at 1821 cm^{-1} indicates much higher reactivity of isoimide CO group in comparison with azetidinone CO at 1785 cm^{-1}.
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(9) Phthalimidoazetidinones **3a–e** are prepared by Nefkens method (*Recl. Trav. Chim. Pays-Bas*, **79**, 688 (1960)).
(10) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964); J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, **73**, 4367 (1951); G. V. Kaiser and C. W. Ashbrook, Eli Lilly and Company, unpublished work.
(11) All new compounds in this paper are characterized by elemental analysis and ir and NMR spectra.
(12) In the case of desacetoxycephalosporins **4a**, **4d**, and **4c** the corresponding 7-(2-carboxybenzamido)-3-methyl-2-cephem-4-carboxylic acid was also isolated in 7, 10, and 24% yield, respectively: mp 196–198° dec; ir (KBr) 1773, 1700, and 1658 cm^{-1}; NMR (DMSO-d_6), δ 1.88 (s, 3), 4.64 (s, 1), 5.15 (d, 1, J = 4.0 Hz), 5.5 (dd, 1, J = 4.0 and 8.0 Hz), 6.15 (s, 1) and 7.4–8 (m, 4 arom H).
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Azetidinone Antibiotics. XV. Synthesis of 2,3-Methylenecepham Derivatives via Intramolecular Cyclization of Diazosulfoxides

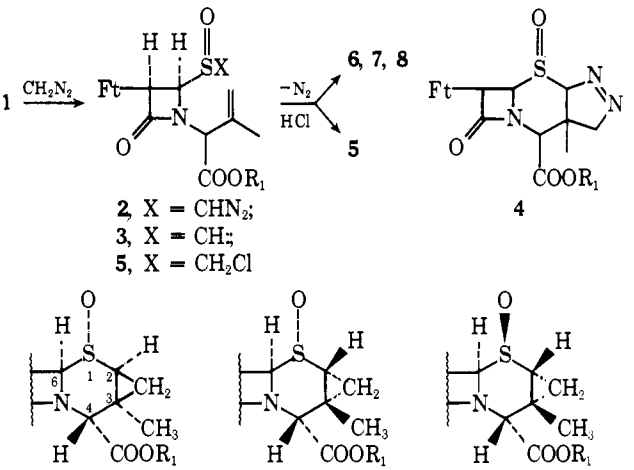
Sir:

The outstanding antibacterial activity of penicillins and cephalosporins has stimulated numerous investigations of chemical modifications of azetidinone antibiotics. Recently, there has been an active interest in the variations of the heterocyclic system attached to the azetidinone ring.[1] The present investigation was initiated to prepare azetidinone containing compounds that contain ring systems other than the thiazolidine or dihydrothiazine found in penicillins and cephalosporins. The proximity of the sulfinyl group in *p*-nitrobenzyl 3-methyl-2-(2-chlorosulfinyl-4-oxo-3-phthalimido-1-azetidinyl)-3-butenoate (**1**)[2] and the olefinic double bond has prompted us to study cyclization of **1** to tricyclic azetidinone derivatives. We postulated that the diazosulfoxide **2** (derived from sulfinyl chloride **1** by reaction with diazomethane) would undergo a cyclization analogous to that observed in olefinic diazoketones.[3,4]

When a solution of **1** was added dropwise to 2.2 equiv of diazomethane (CH_2Cl_2, 0–5°), vigorous nitrogen evolution was noted (2 hr, 5°, and then 2 hr, 25°). The crude mixture was chromatographed to provide four compounds: **5**, mp 177.5–178.5° (27%);[5] **6**, mp 272–273° dec (12%); **7**, mp 236.5–238° dec (20%); and **8**, mp 237–238° dec (2%). The tricyclic ring structure of the title compounds is supported by their NMR spectra (Table I). Quite conspicuous was the disappearance of the olefinic protons and methyl group of the starting sulfinyl chloride **1**, as well as the appearance of a saturated methyl group, the upfield multiplet attributed to the methylene protons of a cyclopropyl group, and a new quartet due to the methine proton at the C-2 position.

The stereochemical assignments of the tricyclic cephams made in regard to the 2,3-methylene substituent are based primarily on NOE measurements. The 2α,3α-methylene and 3β-methyl groups in **7** and **8** exhibit an NOE of 8 and 11%, respectively, indicating a substantial interaction between the vicinal 3-methyl protons and H-4, thus indicating the cis relationship of these substituents. On the other hand, an NOE determination based on the 3-methyl protons and H-4 of compound **6** showed only trace interaction; this is indicative of the 2β,3β-methylene-3α-methyl stereochemistry. Furthermore, irradiation of the 2,3-methylene protons in **6** resulted in enhancement of the H-4 signal, a phenomenon which could be expected considering the spatial proximity of the H-4 and methylene protons in **6**.

The stereochemical assignments of the sulfoxide functionality were made in accordance with the procedure of Cooper et al.[6]



Ft = phthalimido, R_1 = *p*-nitrobenzyl (pNB)

The reaction of **1** with diazomethane to give the proposed intermediate diazosulfoxide **2** probably proceeds in much the same way as a carboxylic acid chloride with diazomethane produces a diazoketone. However, in general, a diazosulfoxide seems to be considerably more reactive than a diazoketone. The diazosulfoxide **2** reacts at low temperature without the use of a catalyst in sharp contrast to the standard thermal copper-catalyzed decomposition of diazoketones.[7]

The formation of products **5**, **6**, **7**, and **8** suggest two, or