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Preliminary Communication

Synthesis of 2-Chloro-3-phthalimido-4-azetidinone and Related Derivatives from Penicillins[1]

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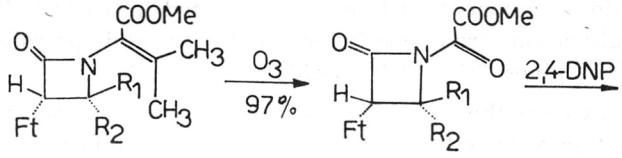
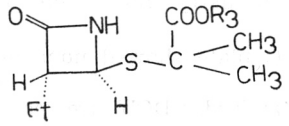
The current interest in new azetidinone antibiotics and their preparation has stimulated an intensive search for the synthesis of appropriately substituted monocyclic azetidinones.[2–6] Our initial efforts in this field resulted in the chlorinolysis of the carbon-sulfur bond in penicillins.[7] A parallel reaction with anhydropenicillin has been described by Wolfe and coworkers.[8] Consequently, compounds of type *1* can be prepared by a simple synthetic route with high yields. As an extension of our work the removal of the five-carbon olefinic moiety from the azetidinone nitrogen in *1* was undertaken. This effort resulted in the synthesis of azetidinones *3* which are versatile intermediates for the preparation of new azetidinone antibiotics. Closely related removals of the five-carbon unit by a pyrazoline route[6d] and by an oxidative method[3,9] have been recently published. We have developed two methods for the synthesis of *3a* which are, together with related chemistry, described in this communication.



1 2

3 4

a: $R_1 = Cl$, $R_2 = H$
b: $R_1 = H$, $R_2 = Cl$
c: $R_1 = OMe$, $R_2 = H$



Ft = phthalimido
5: $R_3 = CHPh_2$
6: $R_3 = H$

Ozonolysis of 2-chloro-3-phthalimido-1-(1'-methyloxycarbonyl-2'-methyl--prop-1'-enyl)-4-azetidinone *(1)* with ozone in methylene chloride at —20 °C gives 2-chloro-1-methoxyoxalyl-3-phthalimido-4-azetidinone *(2)* in 97% yield* The glyoxalate *2* is isolated as a colorless foam: IR ($CHCl_3$) 1850 (oxalyl C=O), 1799 and 1743 (phthalimido C=O) and 1778 cm^{-1} (azetidinone C=O); NMR** 240 (s, 3, OMe), 341 (d, 1, J = 2.5 Hz), 374.5 (d, 1, J = 2.5 Hz), and 474 (m, 4, Ar H).

An attempt to remove the glyoxalate substituent in *2* by methanolysis according to the method of Cooper and Jose[9] resulted in isolation of *3c:* m. p. 188—190 °C, IR (KBr) 1800 cm^{-1} (azetidinone C=O), NMR (DMSO-d_6) 200 (s, 3, OMe), 295 (d, 1, J = 1.5 Hz), 315.5 (d, 1, J = 1.5 Hz), 476 (m, 4, Ar H) and 560 (s, NH, exchangeable/D_2O); mass spectrum m/e 246, M^+. Apparently *3c* is formed from *2* by methanolysis of the oxamide group and concomitant solvolytic displacement of chloride by methoxy group.

Since we were interested in synthesizing *3a* and *3b* from *2,* other possibilities for the removal of the glyoxalate functionality from the azetidinone nitrogen were investigated. Thus, when *2* is relfuxed with an equivalent amount of 2,4-dinitrophenylhydrazine in tetrahydrofuran for 35 min, a mixture of *cis-* and *trans*-isomers *3a* and *3b* is obtained. This mixture is separated by chromatoqraphy over silica gel yielding 38% of 2*S*-chloro-3*R*-phthalimido-4--azetidinone (*3a*) as prisms, mp 154—155 °C; IR ($CHCl_3$) 1810 cm^{-1} (azetidinone C—O); NMR (acetone (d_6) 326 (d, 1, J = 1.8 Hz), 368 (d, 1, J = 1.8 Hz), and 473 (m, 4, Ar H); mass spectrum m/e 214 (M^+, HCl). The *cis*-isomer (*3b*) is obtained in 4% yield. The *cis* arrangement of the hydrogens on the four membered ring is established on the basis of the coupling constant (J = 4.5 Hz).[10]

An alternate method for the preparation of *3a* and *3b* starting from *4* has also been found. When a methylene chloride solution of *4*[11] is treated with *2* equiv. of chlorine for 30 min, a mixture of *3a* and *3b* is obtained in the ratio of *ca.* 9 : 1. The major component *3a* is easily separated in a crystalline form by fractional crystallization from methylene chloride and petroleum ether.[12] Methanolysis of *3a* gives *3c* in 73% yield.

In order to explore the feasibility of the chloride displacement in compounds *3* the reaction of *3a* with sulfur containing nucleophiles was also investigated. When *3a* is reacted with diphenylmethyl 2-mercaptoisobutyrate in tetrahydrofuran in the presence of triethylamine at room temperature for 45 min, the compound *5* is obtained: NMR 96 (s, 6), 301 (d, 1, J = 2.5 Hz), 368 (s, 1, NH), 403 (s, 1, CH), 436 (s, 10), and 461 Hz (m, 4). Cleavage of ester *5* with a mixture of anisole, trifluoroacetic and formic acid at —5 °C for 15 min yields a viscous oil. After a work-up procedure and crystallization from ethyl acetate, colorless crystals of *6,* mp 219—222 °C are obtained: NMR (D_2O) 90 (s, 6) 311 (d, 1, J = 2 Hz), 317 (d, 1, J = 2 Hz), and 468 (4, m); IR (KBr) 1765 (azetidinone CO), 1741 and 1775 (phthalimido CO), and 1720 cm^{-1} (carboxy CO); mass spectrum m/e 334, M^+. The coupling constant (J = 2.5 Hz) for the azetidinone doublets indicates the *trans* stereochemistry of the corresponding protons in *6.* A closely related compound having the *cis* stereochemistry has been described by

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* The reaction was discontinued when a TLC plate showed none of the olefinic starting material (*ca.* 2 h).

** The NMR spectra (60 MHz, TMS internal standard, $CDCl_3$) are recorded in hertz.

Sheehan and Brandt.[11] Evidently the chloride in compound *3a* can be easily displaced by thio substituent. Further examples of a similar displacement will be described in a full paper.

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IZVOD

Sinteza 2-kloro-3-ftalimido-4-azetidinona i srodnih derivata penicilina

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Ozonoliza 2-kloro-3-ftalimido-1-(1′-metiloksikarbonil-2′-metil-prop-1′-enil)-4-azetidinona ozonom u CH_2Cl_2 kod — 20 °C daje 2-klor-1-metiloksioksalil-3-ftalimido-4--azetidinon *(2)* u 97%-tnom iskorištenju. Taj glioksalat metanolizom daje 2-metoksi--3-ftalimido-4-azetidinon, t. t. 188—190 °C. Kada se glioksalat *(2)* refluksira s ekvivalentnom količinom 2,4-dinitrofenilhidrazina u THF tijekom 30 min, dobiva se smjesa *cis-* i *trans*-izomera 2-kloro-3-ftalimido-4-azetidinona koja kromatografskom separacijom daje 38% *trans*-izomera *3a,* t. t. 154—155 °C, i 4% *cis*-izomera *(3b).* Kloro-izomeri *3a* i *3b* također su pripravljeni klorolizom 2-(1′-formil-1′-metiletiltio)--3-ftalimido-4-azetidinona. Djelovanjem difenil 2-merkaptoizobutirata na *3a* u THF uz prisustvo Et_3N tijekom 45 minuta, dobiva se odgovarajući ester *5.* Odstranjenje esterske grupe u *5* pomoću smjese anisola, trifluoroctene i mravlje kiseline kod — 5 °C tijekom 15 min daje slobodnu kiselinu *6,* t. t. 219—222 °C.

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