REARRANGEMENT OF N-HYDROXY-2-AZETIDINONES TO 5-ISOXAZOLIDINONES

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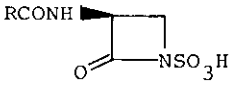
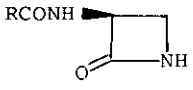
Abstract——N-Hydroxy-2-azetidinodes (IV) underwent a new rearrangement to 5-isoxazolidinones (V). By use of this rearrangement, one (Ve) of isomers of cycloserine was synthesized.

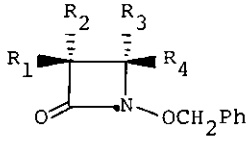
Monocyclic beta-lactam antibiotics, "monobactams" (I)[1], have aroused much interest chemically and biologically. The compound (I) has a sulfonic acid moiety attached to nitrogen atom of the azetidine ring and is synthesized by the direct sulfonation[2] of 2-azetidinone (II), which can be easily synthesized from N-hydroxy-2-azetidinone (IV) by the method of Miller[3]. Although the compound (IV) is an important intermediate for the synthesis of I, data on its chemical properties are insufficient. In our studies on chemical properties of IV, the stability of IV to heat was investigated and it was found that IV underwent a new rearrangement to 5-isoxazolidinones (V).



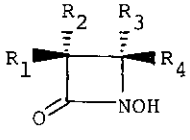
(I)



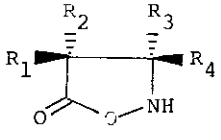
(II)



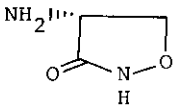
(IIIa-d)



(IVa-d)



(Va-g)



Cycloserine

According to the method of Miller[3], III (a; R_1R_2=H and BocNH, R_3=R_4=H b; R_1=BocNH, R_2=R_4=H, R_3=CH_3 c; R_1=R_3=H, R_2=BocNH, R_4=CH_3 d; R_1=R_3=H, R_2=PhCONH, R_4=CH_3) was obtained from DL-serine, D or L-threonine. III was hydrogenated over palladium-charcoal to give IV (a; R_1R_2=H and BocNH, R_3=R_4=H b; R_1=BocNH, R_2=R_4=H, R_3=CH_3 c; R_1=R_3=H, R_2=BocNH, R_4=CH_3 d; R_1=R_3=H, R_2=PhCONH, R_4=CH_3). IV was refluxed in ethyl acetate for 2-16 h and the resulting product (V)[4] exhibited no color change to ferric chloride solution, whereas IV was positive to this test[5]. Elementary analysis and ci-ms spectra of V established that V had the same composition as IV. The ir spectra of V showed a peak at about 1790 cm^{-1} attributed to carbonyl function and on pmr spectra of V in DMSO-d_6, the coupling between the proton attached to nitrogen atom at position 2 and the proton at position 3 was observed. The above data suggested that V was 5-isoxazolidinone derivative. Moreover, spectral data and results of tlc of Vd (D isomer) were identical with those of the authentic Vd (racemic mixture)[6], which was obtained from 2-phenyl-4-ethylidene-5-oxazolone. Thus the structure of V was confirmed to be 5-isoxazolidinone derivative. The physical data for V are shown in Table 1.

In general, O-acylhydroxylamine undergoes easily a rearrangement to hydroxamic acid[7], but it has not been previously reported that hydroxamic acid rearranged to O-acylhydroxylamine as shown in this case. Few papers on the ring enlargement of azetidines to isoxazolidines have been published. Reinhoudt[8] has recently reported that 2,3-dihydroazete-1-oxides reacted with base to give 5-hydroxyisoxazolidines and Suzuki[9] described a thermal ring enlargement of azetidine N-oxides to isoxazolidines. The new rearrangement described in this paper is an another example of the ring enlargement of azetidine to isoxazolidine.

Deacylated compound (Ve) is an isomer of antibiotics "cycloserine", in which nitrogen atom and oxygen atom in the ring are exchanged each other. Kochetkov[6] had synthesized 3-alkyl-4-acylamino-5-isoxazolidinones, but had not synthesized 4-amino-5-isoxazolidinone (Ve) itself. To examine the antibacterial activity, the deacylated compounds (Ve-g) were prepared as p-toluenesulfonate by the treatment of Va-c with p-toluenesulfonic acid in dioxane at room temperature. These compounds (Ve-g) exhibited no antibacterial activity.

Table 1. Physical and Spectral Data for V.

	R_1	R_2	R_3	R_4	Yield %	$[\alpha]_D^{26°}$ MeOH C=1	mp °C	ν_{KBr}^{max} cm^{-1}	ci-ms[10] M^++1	pmr, in DMSO-d_6 J in Hz
Va	H and	BocNH	H	H	20	-	99-101	1785 1685	203	8.2 (b, 1H, N_2-H) 1.18 (S, 9H, t-Bu)
Vb	BocNH	H	CH_3	H	64	-77.2°	178-179	1795 1685	217	8.03 (d, 1H, J=12, N_2-H) 1.13 (d, 3H, J= 6, CH_3)
Vc	H	BocNH	H	CH_3	93	+75.9°	179-180	1795 1685	217	8.03 (d, 1H, J=12, N_2-H) 1.13 (d, 3H, J= 6, CH_3)
Vd	H	PhCONH	H	CH_3	57	+63.0°	190-192	1795 1645	221	8.11 (d, 1H, J=12, N_2-H) 1.18 (d, 3H, J= 6, CH_3)
Ve[11]	H and	NH_2	H	H	86	-	155-166	1740	-	4.3 (m, 1H, C_4-H) 3.6 (m, 2H, C_3-H)
Vf[11]	NH_2	H	CH_3	H	94	+ 1.4°	167-176	1750	-	4.31 (m, 1H, C_4-H) 3.88 (m, 1H, C_3-H)
Vg[11]	H	NH_2	H	CH_3	96	- 2.0°	183-187	1750	-	4.31 (m, 1H, C_4-H) 3.88 (m, 1H, C_3-H)

ACKNOWLEDGMENT The authors wish to thank Drs. M.Shimizu, H.Nishimura and J.Matsumoto for their encouragement throughout this work. Thanks are also due to the analytical section of these laboratories for spectral measurements and elemental analyses.

REFERENCES and NOTES

1 a) A.Imada, K.Kitano, K.Kintaka and M.Asai, Nature, 1981, 289, 590.

b) M.Asai, K.Haibara, M.Muroi, K.Kintaka and T.Kishi, J. Antibiotics, 1981, 34, 621.

c) R.B.Sykes, C.M.Cimarusti, D.P.Bonner, K.Bush, D.M.Floyd, N.H.Georgopapadakou, W.H.Koster, W.C.Liu, W.L.Parker, P.A.Principe, M.L.Rathnum, W.A.Slusarchyk, W.H.Trejo and J.S.Wells, Nature, 1981, 291, 489.

2 T.Matsuo, T.Sugawara, H.Masuya and Y.Kawano, Jpn. Kokai Tokkyo Koho, 80-164672.

3 a) M.J.Miller, P.G.Mattingly, M.A.Merison and J.F.Kerwin, Jr., J. Am. Chem. Soc., 1980, 102, 7026.

b) P.G.Mattingly and M.J.Miller, J. Org. Chem., 1980, 45, 410.

4 All new compounds reported in this paper gave satisfactory spectral and analytical data.

5 This test is a color test of hydroxamic acid moiety; F.Feigl, V.Anger and O.Frehden, Mikrochemie, 1934, 15, 9.

6 N.K.Kochetkov, R.M.Khomutov, E.I.Budovskii, M.Ya.Karpeiskii and E.S.Severin, Zhur. Obshchei Khim., 1959, 29, 4069 [C.A., 1960, 54, 21046].

7 Y.Tamura, J.Minamikawa and M.Ikeda, Synthesis, 1977, 1.

8 M.L.Pennings and D.N.Reinhoudt, Tetrahedron Letters, 1981, 22, 1153.

9 Y.Suzuki, T.Watanabe, K.Tsukamoto and Y.Hasegawa, German Offen., 1973,2317980 [C.A., 1973, 80, 37092].

10 Chemical ionization mass spectra were recorded on JMS-D 300 mass spectrometer using isobutane as a reactant gas.

11 These compounds were obtained as di-p-toluenesulfonate.

Received, 1st February, 1982