Indolizidine Synthesis by Transannular Cyclization

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Beckmann rearrangement of alkylcyclooctenone oximes VIa and VIb gave corresponding nine-membered lactams 1,3,4,5,8,9-hexahydro-3-methyl-2*H*-azonin-2-one (VIIIa) and 1,3,4,5,8,9-hexahydro-3-butyl-2*H*-azonin-2-one (VIIIb), respectively. A stereospecific transannular cyclization was induced by mercuric acetate leading to alkyl indolizinones Xa and Xb. Temperature and solvent dependent nmr spectra of the medium ring lactams indicates the stereochemical control is caused by steric interactions of the alkyl side chain. Lithium aluminum hydride reduced Xa/Xb to *cis*-octahydro-6-methylindolizidine (XIa) and *cis*-octahydro-3-*n*-butylindolizidine (XIb).

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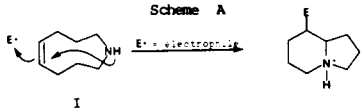
The indolizidine ring system frequently occurs in natural products with unique and varied structural features (2). A synthetic approach to these alkaloids based on *transannular cyclizations* is shown in Scheme A. Initial details of such amino- and amido-cyclizations have been

Scheme A



I

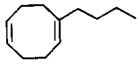
reported (3a-d). The key intermediate for this approach is a medium ring amine (I) suitable for transannular cyclization. These compounds can be prepared via Beckmann rearrangement of cyclooctenones.

The starting material for the synthesis was 5,6 epoxycyclooctene II. Ring opening of the epoxide II with dimethylcopper lithium produces a methyl-substituted

II

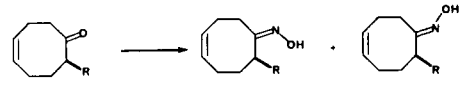
IIIa.R=CH_3
IIIb.R=nBu

alcohol IIIa in good yield (3d). Reaction of the epoxide II, however, with di-*n*-butylcopper lithium affords only a poor yield of *n*-butyl-substituted alcohol IIIb. The major product instead was a C_{12}-hydrocarbon which was assigned structure IV.



IV

Examples of rearrangement products in cuprate/epoxide reactions are known (4) and examples of the formation of olefins from the reaction of epoxides with organolithium reagents (5) have been reported. The *n*-butyl-substituted alcohol IIIb however, was formed in sufficient amount (28%) to continue the synthetic sequence. Jones oxidation of alcohols IIIa and b gave the substituted ketones Va and Vb, respectively. Ketones Va and Vb were



Va.R=CH_3
Va.R=nBu

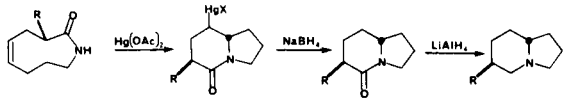
VIa.R=CH_3
VIb.R=nBu

VIIa.R=CH_3
VIIb.R=nBu

converted to their oximes with hydroxylamine hydrochloride affording both *syn* and *anti* oxime isomers VI/VII in a ratio of 1:2 respectively. The significant amount of *syn* oxime is in sharp contrast to the oxime formation from α-substituted cyclohexanones which yield only *anti*-oxime isomers (6). This was the first indication that the conformation of the medium ring would play an important part in future reactions.

Oxime isomers could be separated by column chromatography on silica gel and were identified with the aid of nmr shift reagents (7). The olefinic protons of the *syn* isomer were shifted more than those of the *anti* isomer (3d) in the presence of $Eu(FOD)_3$, due to steric hindrance to complexation with the *anti*-oxime isomer. Since the Eu^{+3} complexes with the *nitrogen* of oximes, complexation of the *anti*-isomer is hindered by the R-group. An example of the shifts used to distinguish the *syn/anti* *n*-butyl substituted oximes (VIb/VIIb) is shown in Table 1.

The major isomer oximes VIIa,b were discussed in our previous paper (3d). The oximes VIa and VIb were reacted with *p*-toluenesulfonyl chloride affording oxime tosylates which were separately treated with aqueous tetrahydrofuran leading to Beckmann rearrangement and lactams VIIIa and VIIIb, respectively.



VIIIa.R=CH_3
VIIIb.R=nBu

IX

Xa.R=CH_3
Xb.R=nBu

XIa.R=CH_3
XIb.R=nBu

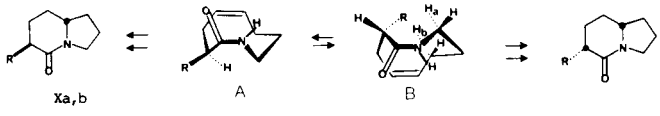
The Beckmann rearrangement is regiospecific. That is, there is no *syn/anti* isomerization of oxime isomers during the course of the reaction: VIa gave VIIIa, VIb gave VIIIb. Besides the expected lactam carbonyl and vinyl proton signals, a distinct solvent effect could be observed in the nmr spectrum of VIIIa. Two sets of doublets for the methyl group in lactam VIIIa appeared, whereas in DMSO the methyl group appeared as a single doublet centered at 0.89 ppm. These nmr effects in methyl substituted lactams such as VIIIa were attributed to (3d) slow ring inversion in the nine membered ring system. We now report the transannular cyclizations of lactams VIIIa,b.

While amides tend to react with electrophiles on oxygen (8), when steric or stereo-electronic constraints preclude this pathway, the weakly nucleophilic nitrogen can then serve as a reaction center.

Thus, when lactams XIIIa and XIIIb were treated with mercuric acetate, transannular amido-mercuration (8) of the double bond occurs, leading to IX. Mercury compound IX was not isolated but was reduced directly to Xa,b with sodium borohydride.

In both cases a single bicyclic product was produced. We have assigned these compounds the stereochemistry depicted based on the following argument. If one examines molecular models of the slow ring inversion of lactams VIIIa,b (as evidenced by their nmr spectra) a steric interaction between substituent R and the transannular hydrogens (labeled H_A and H_B in Scheme B) can be seen. This should lead to selective cyclization *via* the less

Scheme B



hindered (and consequently more highly populated conformer A). Reductions of lactams Xa,b with lithium aluminum hydride gave indolizidines XIa,b, respectively.

The results obtained in this and the previously reported (3d) study indicate that the transannular cyclization of nine membered ring amides is a viable pathway for the preparation of substituted indolizidines. The stereospecificity of ring closure is important for future synthetic applications of this method.

EXPERIMENTAL

Melting points were measured in capillary tubes on a Thomas-Hoover melting point aparatus and are uncorrected. The ^{1}H nmr spectra were recorded on Varian HR-220 and T-60A spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. The ir spectra were obtained in solution cells with chloroform or on neat samples using a Perkin-Elmer 137 Infracord. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, New York. Analytical gas chromatography was performed with a Varian Aerography Model 940 with FID detector on a 1.5% OV-101 on Chromasorb G column (5′ × 1/8″) with hedlium carrier gas. Preparative gas chromatography with a Varian Aerograph Model 920 on a 20% OV-101 on Chromasorb W column (5′ × ¼″). Column chromatography work was done with MCB silica gel, 100-200 mesh, grade 923. Distillations were performed with a Buchi/Brinkmann Standard Micro Distillaiton Oven Model KR and boiling points reported are approximate. Both ether and tetrahydrofuran were dried by distillation from lithium aluminum hydride. All experiments were routinely done under an inert atmosphere.

1,3,4,5,8,9-Hexahydro-3-methyl-2*H*-azonin-2-one (VIIIa).

A solution containing 170 mg (1.11 moles) of *syn* oxime VIa (3d) and 50 ml of methylene chloride was cooled to -10° and 0.2 ml of pyridine was added. To this mixture was added dropwise over 15 minutes a solution of *p*-toluenesulfonyl chloride (350 mg, 1.84 mmoles) in 10 ml of methylene chloride. The mixture was allowed to stand overnight and the yellow solution poured into 10% hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate solution and dried over sodium sulfate. Evaporation of the solvent afforded the crude tosylate as a yellow oil which was dissolved in 10 ml of tetrahydrofuran and added dropwise to 10 ml of water and 100 mg of potassium carbonate. The reaction was stirred overnight and extracted several times with chloroform. The yellow organic extracts were dried over sodium sulfate and evaporated off the solvent left the crude lactam VIIIa. Purification by column chromatography using 10:90-20:80 ethyl acetate-ether yielded 82 mg (48%) of white crystals, mp 143-144°; ir (chloroform): 3300, 1650 cm^{-1}; nmr (DMSO-d$_6$): δ 7.30 (broad m, 1H, -N-*H*), *5.23 (m, 2H), 3.34 (m, 2H), 2.66 (m, 1H), 1.8-2.3 (m, 6H), 0.89 (d, 3H, J = 7 Hz); ms: m/e (relative intensity), 153 (8, M*$^+$), 125 (23), 124 (11), 96 (38), 82 (29), 81 (41), 54 (100).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.51; H, 9.91; N, 9.00.

1,3,4,5,8,9-Hexahydro-3-butyl-2*H*-azonin-2-one (VIIIb).

Into a 50 ml flask was added 50 mg (0.26 mmole) of the *syn* oxime VIb and 20 ml of methylene chloride. The reaction mixture was cooled to -10° and 0.1 ml of puridine added. A solution containing 100 mg (0.52 mmoles) of *p*-toluenesulfonyl chloride in 5 ml of methylene chloride was added over 20 minutes and the workup procedure was identical as that for VIIIa. The crude lactam was purified by column chromatography using 10:90-20:80 ethyl acetate-ether as the eluant to yield white crystals of VIIIb, 32 mg (64%), mp 112-115°; ir (chloroform): 3500, 1670 cm^{-1}; nmr (deuteriochloroform): δ 6.64 (broad s, 1H, -N -*H*), 5.3-5.7 (m, 2H), 3.23 (m, 1H), 1.6-2.3 (m, 6H), 1.1-1.6 (m, 8H), 0.89 (m, 3H); ms: m/e (relative intensity), 195 (2, M$^+$), 167 (4), 139 (22), 125 (17), 110 (100), 96 (14), 82 (25), 81 (22), 67 (30).

Anal. Clacd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.84; H, 10.72; N, 7.19.

cis-Hexahydro-6-methyl-5(1*H*)-indolizinone (Xa).

Into a 20 ml centrifuge tube was placed 100 mg (0.31 mmole) of mercuric acetate, 5 ml of water and 5 ml of tetrahydrofuran. To this mixture was added 40 mg (0.26 mmole) lactam VIIIa in 2 ml of tetrahydrofuran over 5 minutes. The reaction mixture was stirred 2 hours at room temperature. The alkyl mercurial formed was reduced with excess sodium borohydride solution and stirred 30 minutes. The clear solution was decanted from the metallic mercury and extracted several times with methylene chloride. The organic extracts were dried over sodium sulfate and the solvent evaporated. Chromatography (silica gel, 10:90 methanol-ether) left lactam Xa as a clear liquid, 36 mg, 90% yied, bp 120-130° (0.7 mm); ir (neat): 1640 cm^{-1}; nmr (deuteriochloroform): δ 3.3-3.6 (m, 3H), 2.45 (m, 1H), 1.3-2.1 (m, 8H), 1.23 (d, 3H, J = 7 Hz); ms: m/e (relative intensity), 153 (65, M$^+$), 152 (25), 138 (39), 125 (29), 97 (67), 70 (100), 55 (46).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.38;

H, 9.87; N, 9.00.

cis-Octahydro-6-methylindolizine (XIa).

A solution containing 10 mg (0.065 mmole) of lactam Xa in 3 ml of ether was added dropwise to a mixture containing 20 mg (0.52 mmole) of lithium aluminum hydride in 20 ml of ether. The solution was heated to reflux for 5 hours and stirred overnight. After quenching with water, the solvent was evaporated leaving the amine XIa which was isolated as the picrate salt, 13 mg (54%), mp 156-159° (recrystallized from ethanol); ir (neat): 2800 cm^{-1} (weak); nmr (DMSO-d_6): δ 9.09 (s, 2H), 1.1-3.6 (m, 15H), 0.93 (d, 3H, J = 7 Hz); ms: m/e (relative intensity), 139 (39, M^+), 138 (73), 124 (18), 111 (41), 110 (31), 83 (46), 82 (19), 55 (23).

Anal. Calcd. for $C_9H_{17}N$: C, 48.91; H, 5.47; N, 15.21. Found: C, 49.24; H, 5.85; N, 15.37.

cis-Hexahydro-6-*n*-butyl-5(1*H*)-indolizinone (Xb).

A solution containing 17 mg (0.087 mmole) of the lactam VIIIb prepared above in 1 ml of tetrahydrofuran was added dropwise to a mixture containing 33 mg (0.10 mmole) of mercuric acetate in 1 ml of water and 1 ml of tetrahydrofuran. The cloudy yellow solution was stirred at room temperature for 2 hours. The workup was identical to that for Xa. The product Xb was collected by preparative gas chromatography (160°) to afford a clear liquid, 9 mg, 58% yield; ir (neat): 1640 cm^{-1}; nmr (deuteriochloroform): δ 3.41 (m, 3H), 2.20 (m, 1H), 1.6-2.1 (m, 6H), 1.1-1.4 (m, 8H), 0.86 (m, 3H).

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.54; H, 10.56; N, 7.00.

cis-Octahydro-6-*n*-butylindolizine (XIb).

To a mixture containing 50 mg (1.3 mmoles) of lithium aluminum hydride and 30 ml of ether was added 20 mg (0.1 mmole) of lactam Xb in 5 ml of ether. Workup was identical to that for XIa. Evaporation of the solvent afforded a clear liquid, 10 mg, 54% yield; ir (neat): 2780 cm^{-1} (weak shoulder); nmr (deuteriochloroform): 2.86 (m, 2H), 1.1-2.1 (m, 18H), 0.89 (t, 3H, J = 10 Hz); ms: m/e (relative intensity), 181 (1, M^+), 124 (14), 106 (3), 105 (3).

The picrate was recrystallized from ethanol, mp 108-110°.

Picrate.

Anal. Calcd. for $C_{18}H_{25}N_4O_7$: C, 52.81; H, 6.11; N, 13.69. Found: C, 52.60; H, 6.36; N, 13.50.

Acknowledgement.

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Table 1

$Eu(FOD)_3$ Study of VIb/VIIb

$Eu(FOD)_3$ (equivalents)	Olefinic Protons δ	
	VIb	VIIb
0.0	5.57	5.61
0.1	5.93	5.66
0.2	6.04	5.70
0.3	6.27	5.79
0.4	6.43	5.84

REFERENCES AND NOTES

(1) Current address: Department of Chemistry, New York University, Washington Square, New York, New York 10003. This work was taken in part from the Ph. D. Thesis of R. A. Sawicki submitted to the Department of Chemistry, Indiana University, August, 1978.

(2) "Natural Products Chemistry," Vol. 2, K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Nozoe, eds., Kodansha Ltd., Tokyo and Academic Press, Inc., New York, NY, 1975.

(3a) S. R. Wilson and R. A. Sawicki, *J. Chem. Soc., Chem. Commun.*, 431 (1977); (b) S. R. Wilson and R. A. Sawicki, *Tetrahedron Letters*, 2969 (1978; (c) S. R. Wilson and R. A. Sawicki, *J. Org. Chem.*, **44**, 287 (1979); (d) S. R. Wilson and R. A. Sawicki, *ibid.*, **44**, 330 (1979).

(4) B. C. Hartman, T. Livinghouse and B. Rickborn, *ibid.*, **38**, 4346 (1973).

(5) J. K. Crandall and L-H. C. Lin, *J. Am. Chem. Soc.*, **89**, 4527 (1967).

(6) M. E. Jung, P. A. Blair and J. A. Lowe, *Tetrahedron Letters*, 1439 (1976).

(7) Z. W. Wolkowski, *ibid.*, 825 (1971).

(8) Cyclization reactions of this type have been reviewed: V. I. Staninets and E. A. Shilov, *Russ. Chem. Rev.*, **40**, 272 (1971).

(9) F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. J. Verwiel and F. Stein, *Experientia*, **29**, 530 (1973).