THE REDUCTION OF 4-ACYL-β-LACTAMS WITH SODIUM BOROHYDRIDE. A POSSIBLE DICHOTOMY OF STEREOCHEMICAL PATHWAYS

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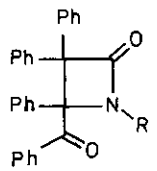
Abstract — Stereochemical result of the sodium borohydride reduction of 4-acyl-β-lactams to 4-(α-hydroxyalkyl)-β-lactams is reported. The stereoselectivity is accounted for by competition between two possible stereochemical pathways.

Although several cases of complex metal hydrides reductions of ketonic group in 3-acyl-β-lactams are known,[1] to the best of our knowledge only one case of this type of reaction in 4-acyl-β-lactams has been reported. Thus, Singh and Mehrotra[2] have studied the reduction of 4-benzoyl-β-lactams **1a** and **1b** with lithium aluminium hydride in ether to give carbinols **2a** and **2b** for which two or three pairs of diastereisomers are possible, respectively. However, no stereochemical conclusions may be deduced from Singh's paper. In our hands, the reaction of 4-benzoyl-β-lactam **1c**[3] with lithium aluminium hydride in the conditions reported by these authors gave a complex mixture of products from which we are unable to isolate the corresponding 4-(α-hydroxybenzyl)-β-lactam **2c**.[4] Nevertheless, treatment of compounds **1c-f** with sodium borohydride in ethanol[5] afforded 4-(α-hydroxybenzyl)-β-lactams **2c-f** in fairly good yields of isolated products without detection of other by-products. On the other hand, inspection of the crude reaction mixtures (by



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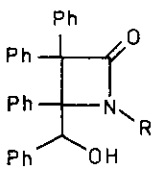
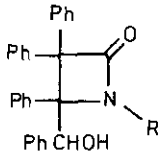


2

1, 2	R
a	$CH(CH_3)_2$
b	$CH(Ph)CH_3$
c	Ph
d	p-$CH_3C_6H_4$
e	p-$CH_3OC_6H_4$
f	p-BrC_6H_4

^{1}H-nmr) indicates that only one racemate has been formed in all cases (Table).

Table. 4-(α-Hydroxybenzyl)-β-lactams **2** prepared



Comp.	Yield [a] (%)	Mp (°C) (solvent)	Ir (cm^{-1}) [b] (OH)	(NC=O)	^{1}H-Nmr (δ, ppm) [c] OH	CH	J(CH-OH, Hz)
2c	64	179-181 (EtOH)	3400	1750	4.7	5.5	
2d	77	195-197 (MeOH)	3560	1735	2.0	6.2	4.5
2e	60	213-215 (MeOH)	3560	1730	2.0	6.2	4.5
2f	67	184-188 (EtOH)	3420	1760	4.8	5.3	

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a) Of pure, isolated products with correct elemental analyses.
b) In KBr pellet.
c) Spectra registered in $CDCl_3$ solutions at 80 MHz.

A suitable related compound **4** obtained by reduction of 4-acyl-β-lactam **3**[3] (only one racemate was obtained)[6] has been analyzed by X-ray difraction[7] (Figure 1). The configu-ration of compound **4** was determined as 4R,4'R-4S,4'S. In sharp contrast, the reduction of 4-benzoyl-β-lactam **5**, in the same experimental conditions to that used for β-lactams **1** and **3**, gave 4-(α-hydroxybenzyl)-β-lactam **6** as a mixture of diastereoisomers in the relative proportion 55:45.[8] Attemps of configurational assignment have been performed as follows: the coupling constant $J_{H4-H4'}$ is greater in the major isomer (10.0 Hz *vs.* 7.0 Hz). Conformational analysis of both stereoisomers with the aid of the appropriate stereomodels indicates that the more stable conformer with protons H4-H4' in antiperiplanar arrangement must

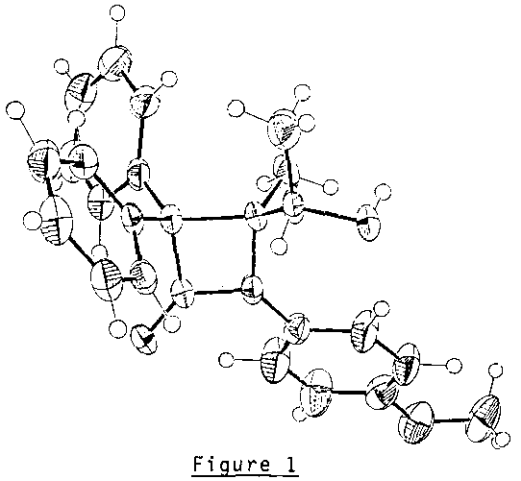
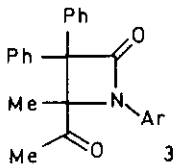


Figure 1

be more populated in 6β than in 6α (Figure). Thus the major coupling constant corresponds to the 4R,4'S-4S,4'R isomer, 6β.[9]



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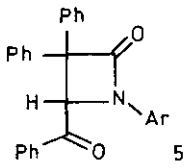

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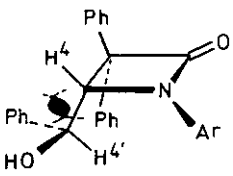
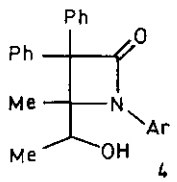


6α



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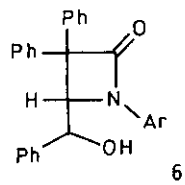

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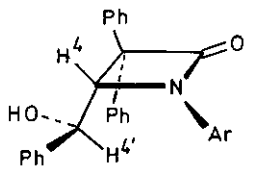
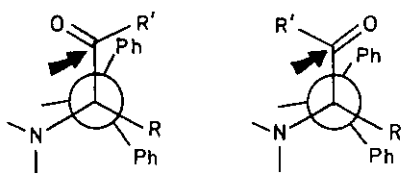


6β

(Ar = p-$CH_3OC_6H_4$)

We speculate with two stereochemical pathways to explain the observed results (Figure 2). Reactive conformation 7, like rigid Cram model,[10] could account for the formation of 4R,4'S-4S4'R diastereoisomers by attack to the less hindered side of the carbonyl group. On the other hand, reactive conformation 8, like antiperiplanar Conforth model,[11] could account for the formation of 4R,4'R-4S,4'S isomers. When R is phenyl or methyl group (β-lactams 1 and 3) steric interaction between R and the R' moiety of the acyl group on the C-4 position destabilizes reactive conformation 7. When R = H both models are possible.



7 8

(R'= Me or Ph)

Figure 2

ACKNOWLEDGEMENTS

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1. See, for example: (a) T. Kametani, T. Nagahara, and M. Ihara, Heterocycles, 1981, 16, 539; (b) F. A. Bouffard and B. G. Christensen, J. Org. Chem., 1981, 46, 2208; (c) F. Pecquet and J. D'Angelo, Tetrahedron Lett., 1982, 23, 2777; (d) H. H. Otto, R. Mayrhofer, and H. J. Bergmann, Liebigs Ann. Chem., 1983, 1152.

2. S. B. Singh and K. N. Mehrotra, Can. J. Chem., 1982, 60, 1901.

3. For the synthesis of 4-acyl-β-lactams used in this report, see: B. Alcaide, G. Domínguez, A. Martín-Domenech, J. Plumet, A. Monge, and V. Pérez-García, Heterocycles, 1987, 26, 1461, and references therein.

4. It has been reported that LAH reduction of N-substituted β-lactams gives aminoalcohols. See, for instance: (a) E. Testa, L. Fontenella, and G. F. Cristiani, Liebigs Ann. Chem., 1959, 626, 114; (b) J. W. Wells and O. R. Tarwater, J. Pharm. Sci., 1971, 60, 156; (c) A. K. Mukerjee and A. K. Singh, Synthesis, 1975, 547.

5. To a suspension of the 4-benzoyl-β-lactam (1 mmol) in hot ethanol (60 ml), sodium borohydride (2 mmol) was added portionwise and the reaction mixture was heated at reflux for 20 min. After hydrolysis and filtration, the solid reaction crude was extracted (chloroform), dried (Na_2SO_4) and the solvent evaporated in vacuo. Finally the solid product obtained was recrystallized from methanol or ethanol.

6. Yield, 52%. mp 132-134°C (methanol). Ir (KBr): 3450 (OH), 1720 (C=O) cm^{-1}. ^{1}H-Nmr ($DCCl_3$): δ 0.9 (d, 3H, J = 7 Hz, CH_3), (1.3 s, 3H, CH_3), 1.6 (s, 1H, OH), 3.8 (s, 3H, OCH_3), 4.2 (m, 1H, CH), 7.6-7.7 (m, 14H, arom.).

7. X-Ray analysis has been performed by Dr. A. Monge and Miss V. Pérez-García (Instituto de Química Inorgánica "Elhuyar"). Full data will be published by the authors in due course. We thank this private communication.

8. Overall yield, 58%. Isomer separation was performed by fractional crystallization from ethanol. Major isomer, 6β: mp 164-166°C; ir (KBr) 3440 (OH) and 1725 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.0 (d, 1H, J = 4 Hz, OH), 3.6 (s, 3H, OCH_3), 4.2-4.2 (dd, 1H, J_1 =10 Hz, J_2 = 4 Hz, CHOH), 4.9 (d, 1H, J = 10 Hz, H-4), 6.4-7.8 (m, 19H, arom.). Minor isomer, 6α: mp 188-190°C; ir (KBr) 3440 (OH) and 1720 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.9 (d, 1H, J = 3 Hz, OH); 3.8 (s, 3H, OCH_3); 4.6-4.9 (dd, 1H, J_1 = 7 Hz, J_2 = 3 Hz, CHOH), 5.2 (d, 1H, J = 7 Hz, H-4), 6.6-7.7 (m, 19H, arom.).

9. For related examples of assignment of configurations on the basis of ^{1}H-nmr spectra and conformational analysis, see: (a) B. Alcaide, R. Fernández de la Pradilla, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, J. Org. Chem., 1981, 46, 3234; (b) B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, J. Chem. Soc., Perkin Trans.2, 1983, 1649; (c) B. Alcaide, G. Escobar, R. Pérez-Ossorio, and J. Plumet, J. Heterocyclic Chem., 1984, 21, 919; (d) For a general treatment, see: H. B. Kagan, " Determination of Configurations by Spectrometric Methods", vol. 1, Verlag Thieme, 1977.

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