ASYMMETRICAL ALKYLATION OF 1-[(s)-α-PHENYLETHYL]-AZETHIDINONE-2

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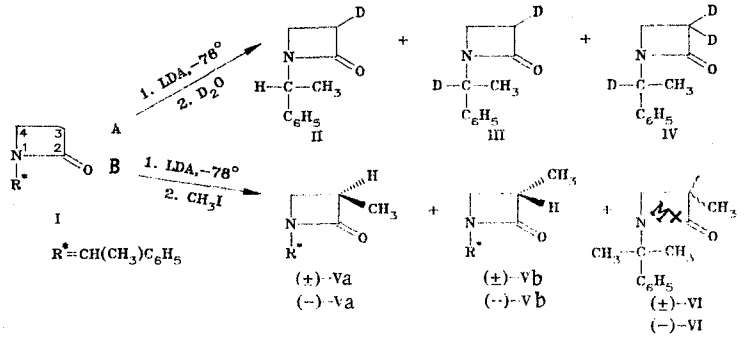
The methylation of the lithium derivative of azethidinone-2 which has a chiral substituent at the nitrogen atom is asymmetrical and leads, with an optical yield of 35%, to diastereomeric 3-methylated azethidinones-2. The reaction of these compounds with Na in liquid ammonia gives enantiomeric 3-methylazethidinones which confirms that an asymmetrical synthesis has taken place.

The antimicrobe action of natural β-lactam antibiotics such as the penicillins, cephalosporins, and monobactams is determined by the absolute configuration of the atoms $C_{(3)}$ and $C_{(4)}$ of the β-lactam ring [1, 2]. Recently, the main method for the preparation of the synthetic analogs of such biomolecules (the optically active β-lactams (azethidinones-2) with the required absolute configuration of the asymmetric centers) can become asymmetrical synthesis.

The 3-substituted azethidinones-2 are usually obtained by the reaction of metal derivatives of azethidinones-2 with different electrophiles [3, 4]. In [5] we have demonstrated that the asymmetrical methylation of 1-(α-phenylethyl)azethiadinone-2 (I) is possible in principle. In order to elucidate the stereochemical rules governing the asymmetrical synthesis, it was necessary to study the reactivity of the initial compound (±)-(I).

The reaction of (±)-azethidinone-2 I with the twofold excess of lithium diisopropylamide in an argon atmosphere in THF, followed by the treatment of the lithium derivative with the tenfold excess of heavy water, gives, according to mass-spectrometric data, a mixture of isotopomers II, III, and IV (route A) with the ratio 6:1:1. This indicates two directions of deprotonation: via the positions $C_{(3)}$ and $C_{(\alpha)}$ of the α-phenylethyl substituent at the nitrogen; the main direction of the reaction is the formation of 3-monodeuterated azethidinone II.



The methylation of the lithium derivative of (±)-I, obtained in the reaction with two equivalents of lithium amide, with a twofold excess of methyl iodide under the same conditions leads to the formation of the diastereomeric pair (±)-Va, b and the dimethylated azethidinone (±)-Vi (route B) with the ratio 1:1.5 (preparative column chromatography). According to PMR data, (±)-azethidinone V represents a mixture of diastereomeric racemates (±)-Va (with a large Rf value) and (±)-Vb (with a smaller Rf value). The azethidinones (±)-Va and (±)-Vb were separated by TLC on plates and isolated in the ratio 1:3.5. According to PMR data, the diastereomer purity of the isolated diastereomers Va and Vb was better than 98%. It must be pointed out that all physicochemical characteristics of the (±)-azethidinones Va and Vb coincide with

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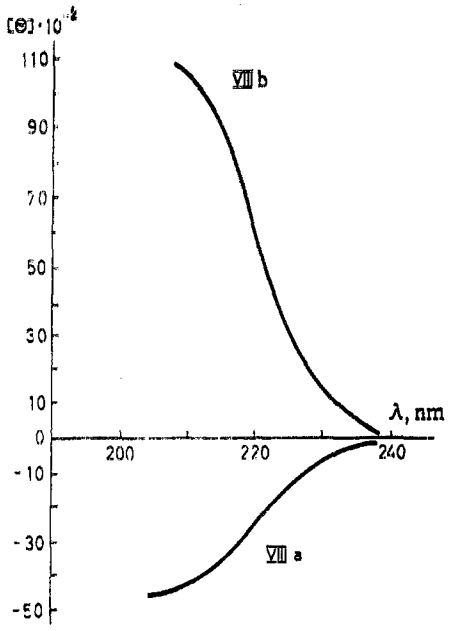
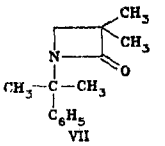


Fig. 1. CD Spectra of Compounds VIIIa, b in methanol.

the data given earlier in [6]; the predominant formation of one of the 3-methylated azethidinones-2 (55% Vb) allows us to use this reaction for asymmetrical methylation.

In order to study the factors affecting the ratio of the diastereomers (±)-Va and (±)-Vb we have varied the reaction conditions: the temperature, the duration of the reaction with the metal and of the methylation, the polarity of the solvent, and the ratio of the reactants. Increasing the temperature of methylation (from −78 to −46°) and the duration of reaction with the metal (5-60 min) and of methylation (30-60 min) did not increase significantly the optical yield of the diastereomer (±)-Vb. Reducing the polarity of the solvent (THF–hexane mixture, 1:1) decreases the excess of the diastereomer (±)-Vb to 42%. When the reaction is performed in an even less polar medium (THF–hexane, 1:5), no monomethylated azethidinone V is formed; only dimethylated 1-(α-methyl-α-phenylethyl)-3-methylazethidinone-2 (VI) (yield 20%) and trimethylated 1-(α-methyl-α-phenylethyl)-3,3-dimethylazethidinone-2 (VII) (yield 15%) have been isolated, the structure of which was confirmed by IR, PMR, and mass spectrometry.



VII

Reducing the amount of lithium amide to an azethidinone–amide molar ratio of 1:1.15 increases the chemical yield of the monomethylated (±)-azethidinone V (39%) as well as the diastereomeric excess of (±)-Vb (60%).

The variation of the methylation conditions has shown that the maximum excess of the diastereomeric racemate (±)-Vb (60%) is formed in the reaction of 1-(α-phenylethyl)azethidinone-2 in THF with 1.15 equivalents of lithium diisopropylamide at −78° for 30 min, followed by methylation with two moles of methyl iodide at the same temperature for 45 min.

The methylation of the lithium derivative of the optically active 1-[(s)-α-phenylethyl]-azethidinone-2 under optimum conditions leads also to the predominant formation of the (−)-azethidinone Vb with an optical yield of 35%.* Improved values have been obtained for the specific rotation, somewhat different from those published in [6], for the isolated optically active diastereomers of Va and Vb.

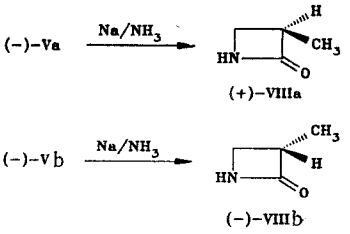
In order to establish the causes for the decrease in the optical yield in comparison with the diastereomeric racemates we have tested the stability of the individual diastereomer

*The configuration of the $C_{(3)}$ atoms in the compounds (−)-Va and (−)-Vb has not been established and has been assigned arbitrarily on the basis of chromatographic mobility.

(−)-Vb. It was found that a mixture of diastereomers (−)-Va and (−)-Vb 1:5 is formed when the lithium derivative of the individual isomer (−)-Vb, obtained under the usual conditions, is decomposed with water. This result indicates that the diastereomer (−)-Vb is converted to (−)-Va and requires a more detailed investigation.

Besides the optically active monomethylated diastereomers (−)-Va and (−)-Vb, a dimethylated optically active azethidinone (−)-VI was isolated with a yield of 14%; during the reaction methylation occured via the atoms $C_{(3)}$ and $C_{(\alpha)}$ of the chiral substituent at the nitrogen, i.e., destruction of the center of asymmetry in the initial molecule. It can be assumed that the retention of optical activity in the azethidinone (−)-VI indicates the sequence of deprotonation: Removal of a proton and methylation first takes place at the $C_{(3)}$ atom, then at the $C_{(\alpha)}$ atom.

In order to confirm the asymmetrical synthesis in the methylation of the lithium derivative of (−)-azethidinone-1, the chiral α-phenylethyl substituent was removed from the nitrogen in each of the diastereomers (−)-Va and (−)-Vb by the action of sodium in liquid ammonia, since it was found [7] that under these conditions no change takes place in the absolute configuration of the $C_{(3)}$ atom in the β-lactams:



Enantiomers of 3-methylazethidinone-2 (+)-VIIIa and (−)-VIIIb were obtained, having identical IR, PMR and mass spectra, but antipode CD curves.

Thus, an assymetrical synthesis has been proposed (optical yield 35%) of optically active 3-substituted azethidinones-2, representing chiral syntons for different transformations of the β-lactam ring.

EXPERIMENTAL

The IR spectra were taken on an UR-20 spectrometer as a thin film, the PMR spectra on Varian T-60 and XL-100 spectrometer in CCl_4 with TMS as the internal standard; the mass spectra were obtained on an MX-1303 spectrometer at an energy of 50 eV, with direct introduction of the substance in the ion source. The specific rotation and CD spectra were measured on a Jasco J-20 instrument. The racemic 1-(α-phenylethyl)azethidinone-2 (I) and its optically active analog (−)-I with $[\alpha]_D^{20}$ −99.4° (c = 0.1, CCl_4) were prepared by the procedure given in [6]. The R_f values for the N-substituted azethidinones-2, which represented thin oils, were calculated for the system benzene—ethyl acetate 2:1, on Silufol UV-254 sheets.

Deuteration of 1-(α-Phenylethyl)azethidinone-2. A solution of 1 mmole lithium diisopropylamide, prepared from 1 ml 1.1 N solution of butyllithium in hexane and 0.14 ml (1 mmole) diisopropylamine in 0.5 ml THF, was treated dropwise with a solution of 87.5 mg (0.5 mmole) azethidinone (±)-I in 5 ml THF at −78° in a stream of argon and stirred for 5 min. 0.09 ml (5 mmoles) D_2O in 0.5 ml THF was added, followed by a saturated solution of ammonium chloride in D_2O. The mixture was extracted with absolute ether and dried with magnesium sulfate. After stripping of the ether the reaction mixture was investigated by mass spectrometry. It was found to consist of a mixture of isotopomers II, III, and IV with the molecular ions M^+ 176, 177, 178, corresponding to the presence of one (55%), two (9%), and three (9%) deuterium atoms in the molecule; the initial azethidinone I with M^+ 175 was also present (27%).

Methylation of 1-(α-Phenylethyl)azethidinone-2. A solution of 4 mmoles lithium diisopropylamide, prepared from 3.5 ml of a 1.14 N solution of n-butyllithium in hexane and 0.56 ml (4 mmoles) of a solution of diisopropylamine in 5 ml THF at −78°, was treated dropwise in a stream of argon with 350 mg (2 mmoles) azethidinone (±)-I in 5 ml THF. The reaction mixture acquired a yellow-brown color which disappeared after a few minutes. After 5 min 0.25 ml (4 mmoles) of methyl iodide in 5 ml THF was added. The reaction mixture was stirred at −78° for 30 min and decomposed with 20 ml of a saturated ammonium chloride solution. It was then extracted with ether and dried with $MgSO_4$. After removal of the ether the yellow oil was sepa-

rated on a column (SiO_2, L40/100; benzene–ethyl acetate, 2:1). Yield 51 mg of diastereomeric racemate of 1-(α-phenylethyl)-3-methylazethidinone-2 (±)-Vb, R_f 0.32; 41 mg of a mixture of diastereomers (±)-Va, b, R_f 0.33 (1:1 according to PMR); total yield of (±)-Va 20.5 mg (5%), of (±)-Vb 71.5 mg (19%); diastereomeric excess of (±)-Vb 55%. Isolated 67 mg (16%) 1-(α-methyl-α-phenylethyl)-3-methylazethidinone-2 (VI), R_f 0.47. IR spectrum: 1750 cm^{-1} (CO of β-lactam). PMR spectrum: 1.1 (3H, d, CH_3–$C_{(3)}$); 1.5 (6H, s, $2CH_3$–$C_{(\alpha)}$; 2.44 (1H, m, H–$C_{(3)}$); 2.86 (2H, m, CH_2); 7.13 ppm (5H, s, arom.) Found: C 76.5; H 8.5%; M+ 203. $C_{13}H_{17}NO$. Calculated: C 76.8; H 8.4%; M 203.

B. A solution of 1.15 mmoles lithium diisopropylamide, obtained from 1.15 mmoles diisopropylamine in 5 ml THF and 1.2 ml (1.15 mmoles) 0.99 N hexane solution of butyllithium, was treated in an atmosphere of argon at −78° with 175 mg (1 mmole) of azethidinone (±)-I in 5 ml THF. The reaction mixture was stirred at −46° for 30 min. The usual decomposition of the reaction mixture and chromatographic separation gave 20 mg (11%) (±)-Va, 54.2 mg (29%) (±)-Vb (diastereomeric excess of (±)-Vb 46%), and 12.2 mg (6%) (±)-VI.

C. A solution of 4 mmoles lithium diisopropylamide, prepared from 3.5 ml of a 1.14 N solution of butyllithium in hexane and 0.56 ml (4 mmoles) of a solution of diisopropylamine in 3.5 ml THF, was treated dropwise in a stream of argon with 350 mg (2 mmoles) azethidinone (±)-I in 8.5 ml of a solvent mixture (hexane–THF 1:1) and stirred for 1 h at −78°. A solution of 0.5 ml (8 mmoles) CH_3I in 5 ml of the same solvent mixture was added and the reaction mixture stirred for 1 h at the same temperature. The usual treatment of the reaction mixture and chromatographic separation on a column gave 31 mg (8.2%) (±)-Va, 60.4 mg (18.3%) (±)-Vb (diastereomeric excess of (±)-Vb 42%), 238 mg (6.7%) (±)-VI, and 44.8 mg (12.8%) of the initial azethidinone (±)-I with R_f 0.35.

D. A solution of 4 mmoles lithium diisopropylamide, prepared from 3.5 ml 1.14 N solution of butyllithium in hexane and 0.56 ml (4 mmoles) of a solution of diisopropylamine in a solvent mixture of 1 ml THF and 1.5 ml hexane, was treated dropwise in a stream of argon at −78° with 350 mg (2 mmoles) azethidinone (±)-I in a mixture of 1 ml THF and 5 ml hexane and stirred at −78° for 1 h. A solution of 0.5 ml (8 mmoles) methyl iodide in 6 ml of a solvent mixture (THF–hexane 1:5) was added, and the reaction mixture decomposed in the usual way after stirring it at −78° for 1 h. Separation on the chromatographic column gave 69 mg (20%) of azethidinone (±)-VI and 54 mg (15%) of (±)-VII with R_f 0.54. IR spectrum: 1760 cm^{-1} (CO of β-lactam). PMR spectrum: 1.20 (6H, s, $2CH_3C_{(3)}$); 1.63 (6H, s, $2CH_3$–$C_{(\alpha)}$; 2.45 (2H, s, CH_2); 7.25 ppm (5H, s, arom.). Isolated 58.5 mg (17%) of initial azethidinone (±)-I.

E. 2.3 mmoles of lithium diisopropylamide, prepared from 2.3 mmoles diisopropylamine in 10 ml THF and 2.4 ml (2.3 mmoles) 0.99 N hexane solution of butyllithium, was treated in an argon atmosphere at −78° dropwise with stirring on a magnetic stirrer with 350 mg (2 mmoles) azethidinone (±)-I in 10 ml THF. After 30 min, 4 mmoles CH_3I in 10 ml THF was added dropwise, and the solution was stirred for 45 min at −78°. The usual treatment of the reaction mixture and chromatographic separation on a column gave 14.7 mg (8%) (±)-Va, 59 mg (31%) (±)-Vb (diastereomeric excess 60%), and 15 mg (7%) (±)-VI.

F. Methylation of the optically active 1-[(s)-α-phenylethyl]azethidinone-2 under the conditions of the previous experiment gave 40.7 mg (33%) of the diastereomer (−)-Va ($[\alpha]_D^{20}$ 68.7° (c = 2.5, CCL_4)), 83.7 mg (68%) diastereomer (−)Vb ($[\alpha]_D^{20}$ 120° (c = 2.5, CCl_4, optical yield of (−)-Vb (35%)), and 57 mg (14%) of azethidinone (−)-VI ($[\alpha]_{300}^{20}$ 71.1° (c = 0.19, CCl_4)). IR spectrum: 1750 cm^{-1} (CO of β-lactam). PMR spectrum: 1.2 (3H, d, CH_3–$C_{(3)}$), 1.6 (6H, s, $2CH_3$–$C_{(\alpha)}$), 2.44 (1H, m, 3-H); 2.90 (2H, m, CH_2), 7.20 ppm (5H, s, arom.).

Isomerization of 1-[(s)-α-Phenylethyl]-3-methylazethidinone (−)VB. A solution of 0.5 mmole lithium diisopropylamide, prepared from 0.5 ml 1.1 N solution of butyllithium in hexane and 0.07 ml (0.5 mmole) diisopropylamine, in 0.5 ml THF was treated dropwise in a stream of argon at −78° by a solution of 94.5 mg (0.05 mmole) of the individual diastereomer (−)-Vb, and after 5 min by 1 mmole water in 2.5 ml THF. The reaction mixture was stirred for 30 min at −78°, treated with a saturated solution of ammonium chloride, extracted with ether, dried with magnesium sulfate, and the ether stripped off. The obtained yellow oil was separated on a column packed with silica gel (L40/100, benzene–ethyl acetate 2:1), and the chromatographically uniform fractions evaporated. Yield 32.9 mg (−)-Vb and 16.9 mg of a mixture of diastereomers (−)-Va and (−)-Vb 1:1 (according to the PMR spectrum taken on an XL-100 spectrometer).

Enantiomers of 3-Methylazethidinone-2. A solution of 50 mg (2 mmoles) metallic sodium in 10 ml liquid ammonia was treated dropwise with a solution of 1.3 mmole of azethidinone

(−)-Va in 3 ml absolute ether at −78°. The reaction mixture was stirred for 1.5 h. The excess sodium was decomposed with dry ammonium chloride and the reaction mixture allowed to warm up to room temperature (until complete removal of ammonia); the residue was then extracted with absolute ether. After stripping of the solvent the yellow oil was purified on a column (SiO_2, L40/100, benzene–acetone 1:1). Yield 42 mg (38%) (+)-VIIIa, R_f 0.48 (Silufol UV-254; benzene–acetone 1:1). IR spectrum: 1760 cm^{-1} (CO of β-lactam). PMR spectrum: 1.30 (3H, d, $CH_3C_{(3)}$); 2.90 (1H, m, 4-H; 3.08 (1H, m, 4-H); 3.42 (1H, M, 3-H). Mass spectrum: M^+ 85, M_{calc} 85; $[\alpha]_{300}^{20}$+54.1° (c 0.17, CCl_4). The analogous procedure gave from 1.3 mmoles (−)-Vb 43 mg (39%) (−)-VIIIb; the R_f value, IR and PMR spectra were identical to those of the compound (+)-VIIIa, $[\alpha]_{300}^{20}$-45.4° (c 0.15, CCl_4), however the course of the CD curve is antipodic (see Fig. 1).

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AZO COUPLING AND AMINOMETHYLATION OF 2,5-DIPHENYLPYRROLE AND ITS DERIVATIVES

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The azo coupling of 2,5-diphenylpyrrole with arenediazonium chlorides has given previously unknown 3-arylazopyrroles and 4-phenylazo-3-phenylhydrazono-3H-pyrrole. The methylation and reductive acetylation of the anylazo derivatives have led to N-methylarylazo and acetylamino derivatives of 2,5-diphenylpyrrole. 3-Amino-2, 5-diphenylpyrrole has been obtained by the reduction of 3-p-chlorophenylazo-2,5-diphenylpyrrole. The aminomethylation of 2,5-diphenylpyrrole and its derivatives with bis(dialkylamino)methanes had led to aminomethyl derivatives.

Continuing investigations in the pyrrole series [1] with the aim of finding biologically active compounds, we have studied the azo coupling of 2,5-diphenylpyrrole with aryldiazonium chlorides. It has been established that, depending on the pH of the medium during azo coupling, either monoarylazo- (Ia, b) or 4-phenylazo-3-phenylhydrazono-2,5-diphenyl-3H-pyrroles (II) are formed. The methylation of compounds (Ia) and (II) takes place in each case at the nitrogen atom of the pyrrole ring with the formation of compounds (Ic) and (III), respectively.

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