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ELECTROCHEMICAL STUDIES ON ß-LACTAMS. PART 4.[1] ELECTROACETYLATION OF ß-LACTAMS.

Maria Antonietta Casadei[①], Achille Inesi[①], Franco Micheletti Moracci[①]* and Donatella Occhialini[①]

① Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive - Università degli Studi di Roma "La Sapienza" P.le Aldo Moro, 5 - 00185 ROMA (Italy)

② Dipartimento di Ingegneria Chimica, dei Materiali, delle Materie Prime e Metallurgia - Università degli Studi di Roma "La Sapienza" - Roma

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Abstract. *Electroreduction of 3-bromo- and 3,3-dichloro-ß-lactams 1 carried out at the potential of the first voltammetric peak and in the presence of acetic anhydride gives 3-acetyl-ß-lactams 2. The electrosynthesis is highly stereoselective, as only the acetyl derivative with trans configuration is formed.*

Thienamycin and several related carbapenem derivatives are naturally occuring ß-lactams possessing biological activity as potent broad spectrum antibiotics or/and ß-lactamases inhibitors.[2] From a structural point of view a remarkable feature of these compounds is the presence of an 1-hydroxyethyl side chain at position 6, which has been shown important for biological activity to occur. After earlier attempts to directly achieve hydroxyethylation by reacting lithium enolate of a suitable bicyclic ß-lactam with acetaldehyde,[3] a better stereochemical control was later achieved by first introducing an acetyl group and then reducing it stereoselectively.[4]

Furthermore, it has been recently reported a facile, high yield conversion of 3-acetyl-ß-lactams into 3-amido--ß-lactams,[5] which makes α-acetyl-ß-lactams very attractive starting materials also for the synthesis of both "classical" (penicillins, cephalosporins) and "non classical" (nocardicins, monobactams) α-amido-ß-lactams.

From the foregoing it appears that, although a well established procedure is available for the synthesis of α-acetyl-ß-lactams (sequential treatment of the parent molecule with *i)* LDA in THF at -78°C and *ii)* acetylimidazole),[4] nevertheless, the search for new synthetic pathways involving more convenient reaction conditions and inexpensive reagents represents a goal to be usefully pursued. A good approach to solve this problem can be sought among the electrochemical methods. In fact, it is well known that electroreduction of organic halogeno compounds affords carbanions whose fate depends on the reaction conditions: inter alia, they can be trapped by electroinactive electrophiles purposely added to the solution, giving the corresponding coupling products. The electrochemical route to carbanions offers in principle a number of potential advantages over conventional chemical methods (*e.g* selectivity and the possibility of generating carbanions under neutral operating conditions): the method could therefore represent a worthwhile alternative to the chemical procedure, to the extent that the trapping reaction can be successfully achieved.

On this basis, we have attempted the electrosynthesis of α-acetyl-ß-lactams by reducing α-halogeno-ß-lactams, very easily accessible by conventional chemical routes, in the presence of acetic anhydride. In this paper we report the results obtained with a number of representative 1,4-disubstituted ß-lactams.

EXPERIMENTAL

General remarks.

Electrochemical apparatus as well as the cell and reference electrode used in the controlled-potential electrolyses (c.p.e.) have been already described.[6] Melting points were taken upon a Tottoli apparatus, and are uncorrected. IR spectra were recorded on a Perkin Elmer 281B grating spectrophotomer. NMR spectra were recorded for solution in $CDCl_3$, using a Varian EM-390 spectrometer and the chemical shift values are reported relative to Me_4Si as internal standard. The crude reaction mixtures were resolved either by column chromatography at ambient pressure (c.c.) carried out on Merck silica gel 60 (70-230 mesh) or by preparative h.p.l.c. carried out on Merck Lichroprep RP-18 (15-25 μm) with a chromatography system made up from a Jobin Yvon Miniprep column coupled with a Waters Prep LC/500A solvent delivery system and r.i. detector. Quantitative h.p.l.c. analyses were carried out on a Perkin Elmer system made up from a Series 4 LC, an LC 85B spectrophotometric detector, an LC Autocontrol, and a Sigma 15 chromatography data station using a Merck Hibar Lichrocart (250-4) RP-18 standard, with the method of the external standard. Mass spectra were recorded at 70 eV with a Hewlett Packard 5980A low-resolution spectrometer equipped with a Hewlett-Packard 5934A data system. Acetic anhydride was purified just before use.[7] Petroleum ether is referred to as the fraction with b.p. 40-60°C. All new compounds gave satisfactory elemental analyses. *cis* and *trans* configuration of 3,4-disubstituted ß-lactams were assigned by comparison of the J and ∂ values for the methine hydrogens with literature data.[8]

Chemistry.

Halogenated ß-lactams **1** used as starting materials have been prepared through the classical "acid chloride-imine" cycloaddition route to ß-lactams.

N-Benzylideneaniline, m.p. 48-50°C (lit.,[9] m.p. 48-49°C), *N-benzylidene-p-anisidine*, m.p. 69-71°C (lit.,[10] m.p. 72°C), *N-benzylidenebenzylamine*,[11] *ethyl N-benzylideneaminoacetate*,[12] and *N-cinnamylideneaniline*, m.p. 107--108°C (lit.,[13] m.p. 109°C) have been prepared according to standard procedures. ß-lactams **1a-f** have been prepared by reacting the appropriate acid chloride and Schiff's base in dichloromethane as solvent, according to a procedure previously described.[14] In the case of ß-lactam **1g**, the Schiff's base was allowed to react with bromoacetyl bromide in benzene as solvent under heating at reflux for 4 h. The crude reaction mixtures were resolved by c.c., using a mixture chloroform/petroleum ether either 95:5 (in the case of **1a-d**, **f**) or 75:25 (in the case of **1e**, **g**) as eluant.

3,3-Dichloro-1,4-diphenyl-2-azetidinone (**1a**), m.p. 151-152°C (cyclohexane) (lit.,[15] m.p. 150°C).

3,3-Dichloro-1-p-methoxyphenyl-4-phenyl-2-azetidinone (**1b**), m.p. 108-110°C (petroleum ether) (lit.,[11] m.p. 110.5-112°C).

1-Benzyl-3,3-dichloro-4-phenyl-2-azetidinone (**1c**), m.p. 45-47°C (petroleum ether) (lit.,[11] m.p. 45-46°C).

3,3-Dichloro-1-ethoxycarbonylmethyl-4-phenyl-2-azetidinone (**1d**), m.p. 58-59°C (petroleum ether) has been previously described as an oily compound.[16]

3,3-Dichloro-1-phenyl-4-styryl-2-azetidinone (**1e**), m.p. 96-97°C (cyclohexane); IR (nujol): ν 1785, 1640, 1590 and 1500 cm^{-1}; NMR: ∂ 7.7-7.2 (m,10H,aromatic), 7.02 (d,1H,CH-Ph,J=15Hz), 6.20 (dd,1H,CH=,J_{CH-CH}=15Hz, J_{CH-H-4}=9Hz) and 5.10 ppm (d,1H,H-4,J=9Hz); *m/z*: 317 ($^{35}ClM^+$) and correct pattern of isotopic abundances.

trans-3-Bromo-1,4-diphenyl-2-azetidinone (**1f**), m.p. 93-94°C (cyclohexane) (lit.,[6] m.p. 93-94°C).

trans-3-Bromo-1-p-methoxyphenyl-4-phenyl-2-azetidinone (**1g**), m.p. 79-80°C; IR (nujol): ν 1750, 1600, 1580 and 1500 cm^{-1}; NMR: ∂ 7.45 (s,5H,aromatic), 7.4-7.2 (m,2H,aromatic), 6.9-6.7 (m,2H,aromatic), 5.10 (d,1H,H-4, J=2Hz), 4.65 (d,1H,H-3,J=2Hz) and 3.75 ppm (s,3H,OCH_3); *m/z*: 331 ($^{79}BrM^+$) and correct pattern of isotopic abundances.

Electrochemistry.

Preparative c.p.e. have been carried out at a mercury pool cathode by stepwise addition of a DMF solution of the substrate to 50 mL of a DMF-0.1 M TEAP solution of acetic anhydride ($E'_{1/2}$=-2.3 V *vs* sce). The molar ratio substrate/Ac_2O was 1:5 and the applied potential was as reported in every case. The electrolyses were stopped when the current had dropped from its initial value of 0.2 A to 10 mA. The n_{app} value is referred to as the number of Faraday × $mole^{-1}$, and was obtained by coulometry. At the end of the electrolysis the cathode was discharged, a small amount (0.5 mL) of the solution was taken off to perform quantitative h.p.l.c. analysis on the crude reaction mixture without any loss due to the work-up. The solvent was removed from the bulk of the solution by heating at 40-45°C under reduced pressure, the residue was extracted with Et_2O (5×50 mL), the insoluble solid was dissolved in H_2O and extracted with $CHCl_3$ (3×50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by c.c. or preparative h.p.l.c. Parameters concerning the various electrolyses and analytical data of the new ß-lactams prepared are given below.

3,3-Dichloro-1,4-diphenyl-2-azetidinone (**1a**) ($E'_{1/2}$=-1.4 V; 0.53g) was reduced at -1.5 V. The measured value of n_{app} is 3.5. C.c. (CH_2Cl_2-petroleum ether 9:1 as eluant) of the residue gave *cis*-**4a** (0.05 g, 10% yield), m.p. 188-190°C (EtOH) (lit.,[17] m.p. 192°C), and a mixture of *trans*-**2a** and **3a**. Preparative h.p.l.c. (CH_3CN-H_2O 47:53 as eluant) allowed the isolation of pure samples of both components: *trans*-**2a**, m.p. 96-98°C (lit.,[18] 98-99°C); **3a**, m.p. 149--151°C (cyclohexane); IR (nujol): ν 1760, 1725, 1590 and 1490 cm^{-1}; NMR: ∂ 7.5-7.2 (m,10H,aromatic), 5.40 (s,1H,H-4), 2.25 (s,3H,CH_3CO) and 1.85 ppm (s,3H,CH_3CO); *m/z*: 307 (M^+). The yields of compounds **2a** and **3a** were determined by quantitative h.p.l.c. analysis (CH_3CN-H_2O 47:53) of the crude reaction mixture. **2a**: 55% yield; **3a**: 12% yield.

3,3-dichloro-1-p-methoxyphenyl-4-phenyl-2-azetidinone (**1b**) ($E'_{1/2}$=-1.4 V; 0.52 g) was reduced at -1.5 V. The measured value of n_{app} is 3.5. C.c. (CH_2Cl_2-petroleum ether 9:1 as eluant) of the residue gave *cis*-**4b** (0.05 g, 10% yield) and a mixture of *trans*-**2b** and **3b**. Preparative h.p.l.c. (CH_3CN-H_2O 47:53 as eluant) allowed the isolation of pure samples of **2b** and **3b**. *trans*-**2b**, IR (film): ν 1745, 1710, 1600, 1580 and 1500 cm^{-1}; NMR: ∂ 7.45 (s,5H,aromatic), 7.4-7.2 (m,2H,aromatic), 6.9-6.7 (m,2H,aromatic), 5.45 (d,1H,H-4,J=2Hz), 4.15 (d,1H,H-3, J=2Hz), 3.75 (s,3H,OCH_3) and 2.38 ppm (s,3H,CH_3CO); *m/z*: 295 (M^+). **3b**, m.p. 124-125°C (cyclohexane); IR (nujol): ν 1760, 1725, 1580 and 1500 cm^{-1} ; NMR: ∂ 7.40 (s,5H,aromatic), 7.4-7.2 (m,2H,aromatic), 6.9-6.7 (m,2H,aromatic), 5.35 (s,1H,H-4), 3.75 (s,3H,OCH_3), 2.25 (s, 3H, CH_3CO) and 1.85 ppm (s,3H,CH_3CO); *m/z*: 337 (M^+). *cis*-**4b**, m.p. 156-158°C (EtOH) (lit.,[19] m.p. 159-161°C); IR (nujol): ν 1750, 1590 and 1520 cm^{-1}; NMR: ∂ 7.6--7.2 (m,7H,aromatic), 6.9-6.7 (m,2H,aromatic), 5.40 (d,1H,H-4,J=6Hz), 5.25 (d,1H,H-3,J= 6Hz) and 3.75 ppm (s,3H,OCH_3). The yields of compounds **2b** and **3b** were determined by quantitative h.p.l.c. analysis (CH_3CN-H_2O 4:6) of the crude reaction mixture. **2b**: 55% yield; **3b**: 15% yield.

1-benzyl-3,3-dichloro-4-phenyl-2-azetidinone (**1c**) ($E'_{1/2}$=-1.65 V, 0.52 g) was reduced at -1.7 V. The measured value of n_{app} is 3.3. C.c. ($CHCl_3$-AcOEt 95:5 as eluant) of the residue gave *cis*-**4c** (0.10 g, 20% yield) and a mixture of *trans*--**2c** and **3c**, which was resolved into pure components by preparative h.p.l.c. (CH_3CN-H_2O 1:1 as eluant). *trans*-**2c**, IR (film): ν 1755, 1705, 1600, 1580 and 1490 cm^{-1}; NMR: ∂ 7.5-7.0 (m,10H,aromatic), 4.86 (d,1H,H-4,J=2Hz), 4.80 (d,1H,CH-Ph,J=15Hz), 4.10 (d,1H,H-3,J=2Hz), 3.85 (d,1H,CH-Ph,J=15Hz) and 2.30 ppm (s,3H,CH_3CO); *m/z*: 279 (M^+). **3c**, IR (film): ν 1760, 1740, 1600 and 1490 cm^{-1}; NMR: ∂ 7.5-7.1 (m,10H,aromatic), 4.86 (d,1H,CH-Ph, J=15Hz), 4.83 (s,1H,H-4), 3.85 (d,1H,CH-Ph,J=15Hz), 2.25 (s,3H,CH_3CO) and 1.75 ppm (s,3H,CH_3CO); *m/z*: 321 (M^+). *cis*-**4c**, IR (film): ν 1760, 1605, and 1500 cm^{-1}; NMR: ∂ 7.6-7.0 (m,10H,aromatic), 5.05 (d,1H,H-4,J=6Hz), 4.92 (d,1H,CH-Ph,J=15Hz), 4.75 (d,1H,H-3,J=6Hz) and 3.90 ppm (d,1H,CH-Ph,J= 15Hz); *m/z* (recorded in CH_4C.I.): 272 ($^{35}ClM^+$+1) and correct pattern of isotopic abundances. The yields of compounds **2c** and **3c** were determined by quantitative h.p.l.c. analysis (CH_3CN-H_2O 4:6) of the crude reaction mixture. **2c**: 40% yield; **3c**: 20% yield.

3,3-dichloro-1-ethoxycarbonylmethyl-4-phenyl-2-azetidinone (**1d**) ($E'_{1/2}$=-1.7 V, 0.52 g) was reduced at -1.8 V. The measured value of n_{app} is 3.0. C.c. ($CHCl_3$-AcOEt 95:5 as eluant) of the residue allowed the isolation of pure samples of *trans*-**2d**, **3d** and *cis*-**4d**. *trans*-**2d**, IR (film): ν 1765, 1740, 1710 and 1490 cm^{-1}; NMR: ∂ 7.40 (s,5H,aromatic), 5.25 (d,1H,H-4,J=2Hz), 4.30 (d,1H,N-CH-CO,J=18Hz), 4.16 (q,2H,CH_2-O), 4.06 (d,1H,H-3,J=2Hz), 3.53 (d,1H,N-CH-CO,J=18Hz), 2.33 (s,3H,CH_3CO) and 1.25 ppm (t,3H,CH_3-CH_2); *m/z*: 275 (M^+). **3d**, IR (film): ν 1760, 1740, 1730, 1490 and 1450 cm^{-1}; NMR: ∂ 7.6-7.3 (m,5H,aromatic), 5.30 (s,1H,H-4), 4.5-4.0 (group of signals,3H,N--CH-CO+CH_2-O), 3.55 (d,1H,N-CH-CO,J=17Hz), 2.25 (s,3H,CH_3-CO), 1.80 (s,3H,CH_3-CO) and 1.25 ppm (t,3H,CH_3-CH_2); *m/z*: 274 (M^+-CH_2CO). *cis*-**4d** (0.18 g, 40% yield), IR (film): ν 1775, 1740, 1590 and 1490 cm^{-1}; NMR (CCl_4): ∂ 7.5-7.2 (m,5H,aromatic), 5.3-5.1 (group of signals,2H,H-3 + H-4), 4.45 (d,1H,N-CH-CO,J=18Hz), 4.16 (q,2H,CH_2-O), 3.46 (d,1H,N-CH-CO,J=18Hz) and 1.25 ppm (t,3H,CH_3-CH_2); *m/z*: 232 (^{35}Cl M^+-Cl). The yields of compounds **2d** and **3d** were determined by quantitative h.p.l.c. analysis (CH_3CN-H_2O 58:62) of the crude reaction mixture. **2d**: 25% yield; **3d**: 25% yield.

3,3-dichloro-1-phenyl-4-styryl-2-azetidinone (**1e**) ($E'_{1/2}$=-1.35 V, 0.52 g) was reduced at -1.4 V. The measured value of n_{app} is 3.2. C.c. ($CHCl_3$-petroleum ether 7:3 as eluant) of the residue allowed the isolation of *trans*-**2e** (0.24 g, 50% yield), *trans*-**4e** (0.06 g, 13% yield) and *cis*-**4e** (0.14 g, 30% yield). *trans*-**2e**, IR (film): ν 1750, 1710, 1645, 1595 and 1495 cm^{-1}; NMR: ∂ 7.7-7.1 (m,10H, aromatic), 6.95 (d,1H,CH=C*H*-Ph, J=16Hz), 6.30 (dd,1H,C*H*=CH-Ph, J= =16Hz,J=7.5Hz), 5.20 (dd, 1H,H-4,J=7.5Hz,J=2Hz), 4.15 (d,1H, H-3,J= 2Hz) and 2.40 ppm (s,3H,CH_3-CO); *m/z*: 291 (M^+). *trans*-**4e**, IR (film): ν 1760, 1650, 1595 and 1495 cm^{-1}; NMR: ∂ 7.6-7.1 (m,10H,aromatic), 6.95 (d,1H,CH=C*H*-Ph,J=16Hz), 6.15 (dd,1H,C*H*=CH-Ph,J=16Hz,J=7Hz) and 4.8-4.6 ppm (m,2H,H-3 + H-4, J=7Hz,J=1.5Hz). *cis*-**4e**, m.p. 156-157°C; IR (nujol): ν 1770, 1650, 1595 and 1495 cm^{-1}; NMR: ∂ 7.6-7.1 (m,10H,aromatic), 6.92 (d,1H,CH=C*H*-Ph,J=16Hz), 6.30 (dd,1H,C*H*=CH-Ph,J=16Hz,J=7.5Hz), 5.20 (d,1H,H-3, J=5.5Hz) and 4.97 ppm (dd,1H,H-4,J=7.5Hz,J=5.5Hz); *m/z*: 283 (^{35}Cl M^+) and correct pattern of isotopic abundances.

trans-3-bromo-1,4-diphenyl-2-azetidinone (**1f**) ($E'_{1/2}$=-1.0 V, 0.50 g) was reduced at -1.3 V. The measured value of n_{app} is 1.6. C.c. ($CHCl_3$-petroleum ether 9:1 as eluant) of the residue allowed the isolation of **4f** (0.15 g, 40% yield), m.p. 152-153°C (MeOH) (lit.,[20] m.p. 153-154°C) and *trans*-**2a** (0.13 g, 30% yield). Quantitative h.p.l.c. analysis (CH_3CN-H_2O 47:53) of the crude reaction mixture confirmed the values of the yield for both compounds.

trans-3-bromo-1-p-methoxyphenyl-4-phenyl-2-azetidinone (**1g**) ($E'_{1/2}$=-1.0 V, 0.71 g) was reduced at -1.3 V. The measured value of n_{app} is 1.7. C.c. ($CHCl_3$-petroleum ether 8:2 as eluant) of the residue allowed the isolation of **4g** (0.27 g, 50% yield), m.p. 95-97°C (cyclohexane) (lit.,[21] m.p. 94-96°C) and *trans*-**2b** (0.19 g, 30% yield). Quantitative h.p.l.c. analysis (CH_3CN-H_2O 4:6) of the crude reaction mixture confirmed the values of the yield for both compounds.

Table 1.
Products and yields of the electrochemically promoted acetylation of ß-lactams **1**.

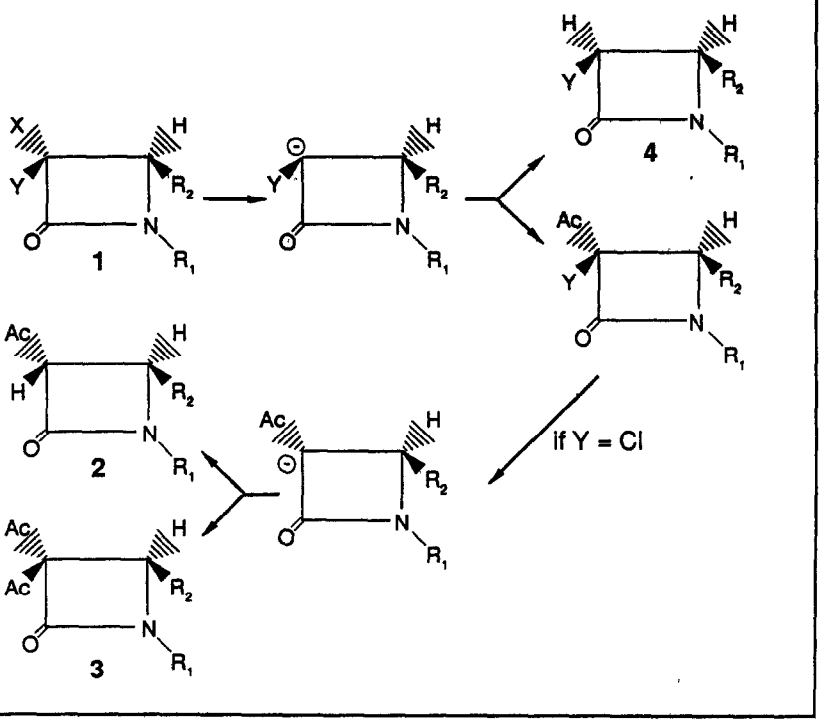
Substrate	X	Y	R_1	R_2	2,%	3,%	4,%
1a	Cl	Cl	C_6H_5	C_6H_5	55	12	10
1b	Cl	Cl	$C_6H_4OCH_3$ (p)	C_6H_5	55	15	10
1c	Cl	Cl	$CH_2C_6H_5$	C_6H_5	40	20	20
1d	Cl	Cl	$CH_2CO_2C_2H_5$	C_6H_5	25	25	40
1e	Cl	Cl	C_6H_5	$CH=CHC_6H_5$	50	-	43[a]
1f	Br	H	C_6H_5	C_6H_5	30	-	40
1g	Br	H	$C_6H_4OCH_3$ (p)	C_6H_5	30	-	50

[a] As a mixture of 30% *cis* and 13% *trans* isomers.

RESULTS AND DISCUSSION

Electroreduction of α-halogeno-ß-lactams **1** carried out at the potential of the first voltammetric peak and in the presence of acetic anhydride gives α-acetyl-ß-lactams **2**. Dehalogenated ß-lactams **4** are also formed as by-products in all cases along with diacetylated ß-lactams **3** in the case of dihalogeno-ß-lactams **1a-d**, thus preventing the yields of the desired products to exceed 50-55% (Table 1). In spite of this drawback, the electroacetylation of ß-lactams offers the advantage of an high degree of stereoselectivity. In fact, only *trans*-3-acetyl-ß-lactams **2** (and *cis*-3-chloro-ß-lactams **4**) are formed. The nature of the isolated products suggest that the electroreduction of ß--lactams **1** is likely to take place following the reaction pathway outlined in Scheme 1.

Scheme 1



Two-electron reduction of a carbon-halogen bond preferentially involves the less hindered halogen atom trans with respect to the substituent at position 4. The resulting carbanion undergoes coupling reaction with the electrophile and, competitively, protonation to the corresponding dehalogenated ß-lactam **4**. When Y=Cl, the activating effect of the carbonyl group makes more easily reducible the geminal C-Cl bond in the intermediate 3--acetyl-3-chloro-ß-lactam,[22] which is further reduced at the working potential. As a consequence, a new acetylated carbanion is formed, which undergoes protonation to *trans*-**2** or, competitively, further acetylation to **3**. According to this general picture: i) the reduction of *trans*-3-bromo-ß-lactams **1f, g** gives 3-acetyl-ß-lactams **2a, b** exclusively with trans configuration, showing that inversion of configuration does not occur in the intermediate carbanions; ii) the measured n_{app} value is always lower than 2 in the case of monohalogeno ß-lactams **1f, g** and always higher than

2 (and lower than 4) in the case of dihalogeno ß-lactams **1a-e**, showing that in the latter compounds also the reduction of the second C-Cl bond takes place, even if partially; iii) the reduction of dichloro-ß-lactams **1a-d** gives 3-acetyl--ß-lactams **2a-d** exclusively with trans configuration and 3-chloro-ß-lactams **4a-d** exclusively with cis configuration, confirming that there is not inversion of configuration at the stage of both the intermediate carbanions and showing that the first C-Cl bond to be reduced lies on the opposite side with respect to the substituent at position 4; iv) the higher the availbility of protons in the medium, the higher the amount of dehalogenated products formed. Accordingly, higher yields of dehalogenated products **4** are observed when "acidic" hydrogens are present in the starting ß-lactam, either in the nucleus (as at position 3 of **1f, g**) or in a side-chain substituent (as in **1d**), which should therefore be considered a potential proton source, in addition the usually considered solvent-electrolyte-electrophile system.

4-styryl-ß-lactam **1e** behaves somewhat differently from the others members of the serie. As evidenced in Table I, its reduction yields *trans*-**2e** and a mixture of cis and trans dehalogenated products. It was presumed, but not proven, that the different nature of the substituent at position 4 cannot alter the ability of the carbanion at position 3 to totally retain its configuration, as observed in the other cases. If this is true, the formation in the reduction of **1e** of only one stereoisomeric monoacetylated derivative (as well as the absence of detectable amounts of diacetylated derivative) on one hand and of a cis-trans mixture of dehalogenated products on the other, should be ascribed to steric factors with divergent effects upon the heterogeneous and homogeneous reaction. In fact, no more complete stereoselectivity is observed in the electrodic reaction, even if the products arising from the cleavage of the C-Cl bond trans to the styryl substituent (*trans*-**2e** + *cis*-**4e**) are still largely predominant in the reaction mixture. On the contrary, there is experimental evidence (no formation of **3e** and/or *cis*-**2e**) that an acetyl group cannot enter at all the molecule from the same side of the substituent, which can be easily done by a proton. Inspection of molecular models shows that the different steric hindrance of the styryl and phenyl groups allows different ease of access to the adjacent position 3 of the ß-lactam nucleus. However, it is quite surprising, and we are unable at present to explain why, that the same substituent can induce different selectivity on the heterogeneous and homogeneous reaction.

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