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REARRANGEMENT OF DIALKYL-2-(AZETIDIN-3-YL)PROPANE-1,3-DIOATES – A STRUCTURAL REVISION

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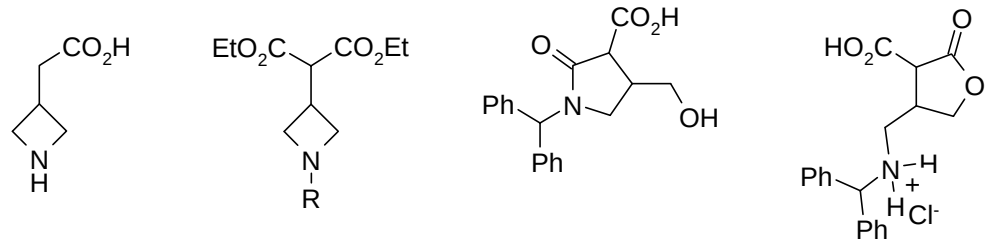
Abstract – The rearrangement reaction of dialkyl 2-[1-diphenylmethyl)azetidin-3-yl]propane-1,3-dioates during saponification was studied. Contrary to a previous report postulating the formation of a 4-(hydroxy-methyl)-2-oxo-pyrrolidine-3-carboxylic acid derivative, our analytical data showed that the rearrangement reaction led to a lactone ring. This structural revision is based on elemental analysis, IR and two-dimensional NMR studies.

INTRODUCTION

Cyclic amino acids have attracted considerable interest in the field of synthetic and medicinal chemistry due to their structural rigidity. As they induce conformational restrictions they were incorporated into peptides and peptidomimetics with the intention to create novel bioactive compounds and to perform structural and biomechanistic investigations.[1] Cyclic analogues of γ-amino butyric acid (GABA), such as nipecotic acid and guvacine, have been found to exhibit significant in vitro inhibitory affinity to the GABA transport proteins.[2] Since a low GABA concentration in the synaptic cleft is associated with the development of epilepsy it can be counteracted by inhibition of the GABA transport proteins. As part of an ongoing project directed towards the synthesis and biological evaluation of azetidine derivatives as conformationally constrained GABA uptake inhibitors we planned to employ azetidin-3-ylacetic acid (**1**) as a synthetic precursor.

In search of a preparative method, we found a procedure recently published by Carruthers *et al*.[3] The synthetic design employed therein started with N-protected diethyl 2-(azetidin-3-yl)propane-1,3-dioate derivatives **2**. The article describes how the saponification of **2a** - which contains a *tert*-butyloxycarbonyl group - followed by decarboxylation and subsequent cleavage of the ester and carbamate group by acidic

hydrolysis affords azetidin-3-ylacetic acid (**1**), as expected, in an overall yield of 18%.[3] Carruthers *et al.*[3] also used compound **2b**, incorporating a benzhydryl protection group, as starting material for the preparation of **1**. In contrast to the reaction employing **2a**, saponification of **2b** did not result in the formation of the corresponding free dicarboxylic acid of **1** as expected. Instead, a compound was produced by a rearrangement reaction which the authors, based on the structure of the product of a subsequent transformation reaction, identified as **3**. The outcome of this reaction was explained by the presence of a basic nitrogen atom in compound **2b**, which is absent in compound **2a**. This was thought to be the cause of an intramolecular acylation of the ring nitrogen by one of the ester functions present in the molecule which initiates a rearrangement reaction. However, analytical data we obtained when conducting this reaction demonstrate that the structural assignment of the rearrangement product **3** has to be revised. Based on our analytical investigations, we report in this article that though a rearrangement reaction does occur the product formed is not the lactam **3** but the lactone **4**.[4]

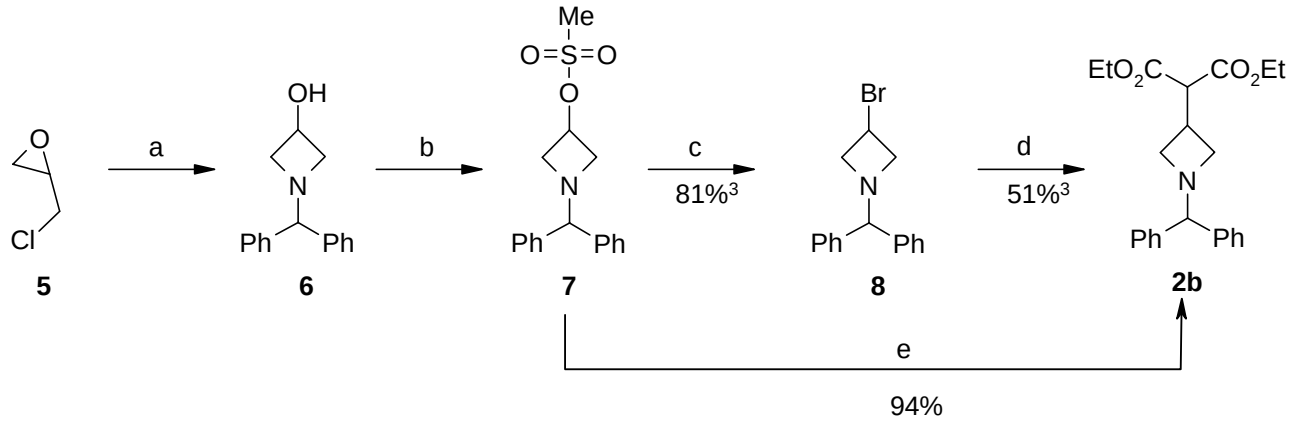


1 **2a**: R = Boc; **2b**: R = $CHPh_2$ **3** **4**

Scheme 1

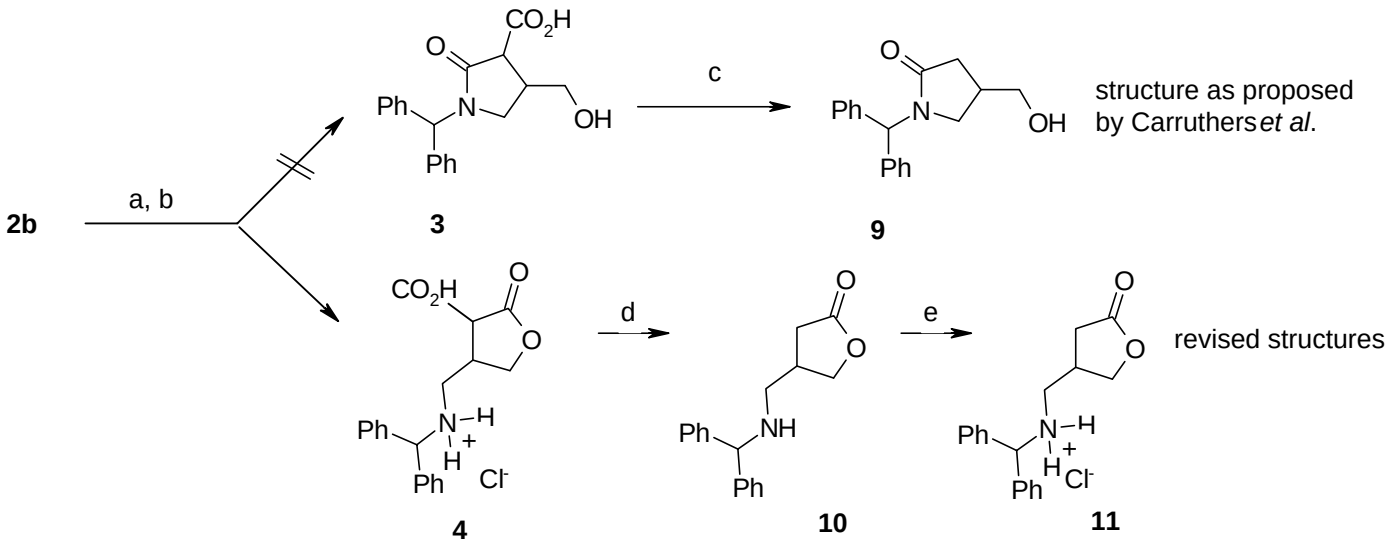
RESULTS AND DISCUSSION

For this study we prepared the required compound **2b** starting with epichlorhydrin **5** (Scheme 2). Following the procedure published by Carruthers *et al*.[3] reacting **5** with diphenylmethanamine yielded the benzhydryl protected azetidine **6** in one step. Compound **6** was then subjected to a mesylation reaction to afford compound **7** still following the synthetic route described in literature.[3] However, instead of the nucleophilic substitution of the mesyl group using LiBr and displacement of the bromine with the diethyl malonate anion described there (Scheme 2) we attempted to simplify and optimise this procedure by directly treating mesyl compound **7** with the diethyl malonate anion (generated by deprotonation of diethyl malonate with NaH). This way, we did indeed obtain diethyl 2-[1-(diphenylmethyl)azetidin-3-yl]propane-1,3-dioate (**2b**) in a 94% yield (Scheme 2).



Scheme 2. [a]Ph_2CHNH_2, MeOH [b]MsCl, pyridine [c]LiBr, Li_2CO_3, THF [d,e]NaH, $CH_2(CO_2Et)_2$

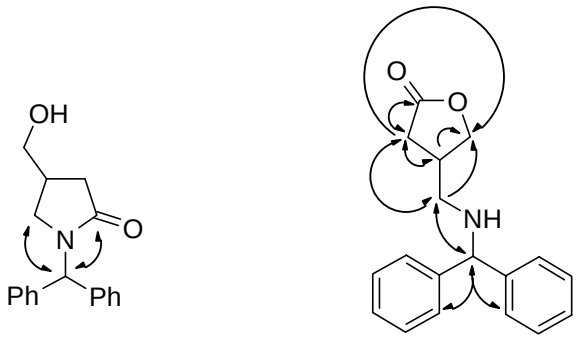
The next step, the saponification of compound **2b**, was performed exactly as described by the experimental procedure of Carruthers *et al.*[3] The product obtained this way was characterized by IR, elemental analysis and one- and two-dimensional NMR experiments. However, to our surprise the data obtained by us, though identical with those reported by Carruthers *et al.*, were not in accord with the structure of the cyclic amide **3**.



Scheme 3. [a]KOH, EtOH, H_2O [b]acidification to pH 4.5 (1 M HCl) [c]130 °C, 2 x 10^{-3} bar, 120 min [d](1) 130 °C, 2 x 10^{-3} bar, 2 h; (2) CC (*n*-heptane/EtOAc = 80/20 + 0.5% ethyldimethylamine) [e]HCl

The IR spectrum of the product shows an absorbance at 1768 cm^{-1} and 1715 cm^{-1}, whereas the absorption of a lactam group in a five-membered ring and a carboxylic group should only show absorbance at

approximately 1720 cm^{-1} and 1700 cm^{-1},[5] respectively. The absorption of five-membered cyclic lactones, however, is generally observed at a wave number of approximately 1770 cm^{-1}. To further verify the structure of the product obtained we performed an elemental analysis. Since the lactone derivative **4** bears a secondary amine functionality, we expected to obtain the corresponding ammonium salt following acidification to pH 4.5 with 1 M HCl. In contrast, structure **3** is naturally not able to form a hydrochloride. We found that the elemental analysis for the compound isolated is in accordance with the empirical formula of hydrochloride **4**. Furthermore, decarboxylation of the rearrangement product following the procedure of Carruthers *et al.*[3] led to a product (**10**) which after purification by column chromatography (*n*-heptane/EtOAc = 80/20 + 0.5% ethyldimethylamine) and subsequent treatment with hydrogen chloride was also found, according to elemental analysis, to form a hydrochloride **11**. Compound **10** also spotted on a TLC plate gave a positive response with Dragendorff's reagent,[6] which further proves the presence of a basic nitrogen atom. Most importantly, the IR spectrum of **10** shows an absorbance at 1752 cm^{-1}. This clearly points to the presence of a lactone moiety in compound **10** just as it is present in its precursor **4**. Next, we performed a multidimensional NMR analysis of compounds **4** and **10**. The data for **4** were also in accord with the lactone structure proposed by us. However, the NMR spectra contained two sets of signals, one with high the other with very low intensity. This is likely to be a result of the presence of the two diastereomeric forms compound **4** can take. For simplicity's sake we therefore decided to analyze the NMR spektra of **10** which does not have diastereomeric forms. In the ^{1}H NMR spectrum of compound **10** the ring methylene hydrogen atoms were observed at 4.13 ppm and 4.44 ppm. These chemical shift values correspond to a structure with a methylene group located next to a lactone moiety and not to a lactam functionality. The hydrogen atoms of a methylene group bound to a lactam moiety are expected to be at a higher field. Furthermore, the coupling constants, ^{3}J = 9.1/4.8 and 9.1/6.7, respectively, are evidence of a methylene group as part of a ring system and not of an aliphatic side chain. Analysis of $^{1}H,^{13}C$-HMBC corroborates our structural assignment (Scheme 4). In theory, for compound **9** long range correlation (^{3}J) would be observed between the aliphatic hydrogen atom of Ph_2CH and both, the lactam carbon atom as well as the carbonyl atom of NCH_2 in addition to the signals to be attributed to coupling with the aromatic ring carbons. However, only one signal resulting from the coupling of the hydrogen atom of Ph_2CH (δ = 4.78 ppm) with the carbon atom of $NHCH_2$ (δ = 50.5 ppm) was detected besides the aromatic ring correlations. Likewise, a cross-peak between the aliphatic carbon atom of Ph_2CH (δ = 67.6 ppm) and the hydrogens attached to the carbon of the $NHCH_2$ moiety (δ = 2.57–2.75 ppm) was seen. In summary, based on our findings the compound formed from by a rearrangement and subsequent decarboxylation reaction must be **10** whereas **9** proposed by Carruthers *et al*. has to be ruled out.

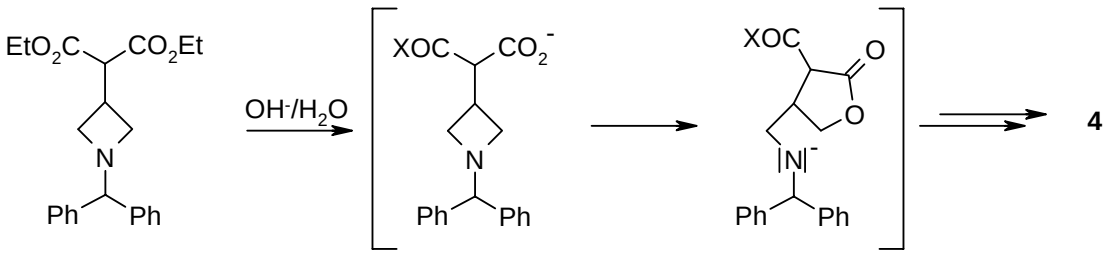


hypothetical $^{1}H,^{13}C$-HMBC coupling of **9**

observed $^{1}H,^{13}C$-HMBC coupling of **10**

Scheme 4. Expected and observed $^{1}H,^{13}C$-HMBC couplings for compounds **9** and **10**, respectively.

Carruthers suggested that the ring expansion to lactam **3** may occur due to the presence of a basic nitrogen which is attacked by a carbonyl group of the malonate moiety. The charged bicyclic intermediate subesquently fragments to lactam **3**. However, since we found that the rearrangement product is the lactone **4**, it seems safe to assume that under the saponification conditions the ester functions are cleaved. Then, in the next step, as soon as one of the carboxylate groups has formed, it attacks the C-2 position of the azetidine ring. As a result of this intermolecular substitution reaction the azetidine ring is cleaved and a γ-lactone moiety formed. From there it takes only a reprotonation step and a further ester hydrolysis, if one of the ester functions should still be intact, to get to the isolated compound **4**.



2b

X = O^{-} or OEt

Scheme 5. Postulated mechanism for the formation of lactone derivative **4**

CONCLUSION

In this article we present a structural revision of the product obtained after saponification of diethyl 2-[1-diphenylmethyl)azetidin-3-yl]propane-1,3-dioate (**2b**) which appears to be the lactone **4** and not the

lactam **3**. In addition, we describe a straightforward, optimized synthesis of diethyl 2-[1-diphenylmethyl)azetidin-3-yl]propane-1,3-dioate (**2b**) in three steps starting from epichlorhydrin (overall yield: 46%).

EXPERIMENTAL

Methods and Materials. Anhydrous reactions were carried out in vacuum dried glassware under nitrogen atmosphere. THF and Et_2O were distilled from sodium metal/benzophenone ketyl prior to use. Other common solvents for column chromatography were freshly distilled before use. Purchased chemical reagents were used without further purification. TLC plates were made from silica gel 60 F_{254} on aluminum sheets (Merck). Compounds were stained with 5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0.2% $Ce(SO_4)_2\cdot 4H_2O$ and 5% conc. H_2SO_4. Unless otherwise stated, Merck silica gel (mesh 230-400) was used as stationary phase for flash chromatography (CC). Melting points: mp (uncorrected) were determined with a Büchi 510 Melting Point apparatus. Elementary analysis: Elementaranalysator Rapid (Heraeus). IR spectroscopy: FT-IR Spectrometer 1600 and Paragon 1000 (Perkin Elmer). Mass spectrometry: Mass Spectrometer 5989 A with 59980 B particle beam LC/MS interface (Hewlett Packard). NMR spectroscopy: NMR spectra were recorded on JNMR-GX (Jeol, 400 MHz and 500 MHz) with TMS as internal standard and integrated with the program of NMR-software Nuts (2D Version 5.097, Acorn NMR, 1995).

Diethyl 2-[1-(diphenylmethyl)azetidin-3-yl]propane-1,3-dioate (2b). Diethylmalonat (21 mL, 139 mmol, 2.2 equiv.) was added to a slurry of NaH (3.0 g, 126 mmol, 2.0 equiv.) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 15 min. Following addition of compound **7**[3] (20.0 g, 63 mmol) in THF (30 mL), the reaction mixture was refluxed for 18 h. Subsequently, the reaction was quenched by pouring the reaction mixture into ice. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo.
2b: 22.6 g (94%). Analytical data were in accord with those reported in literature.[3]

4-[(Diphenylmethylamino)methyl]-2-oxotetrahydrofuran-3-carboxylic acid hydrochloride (4). KOH (8.64 mmol, 4.4 equiv.) was added to a solution of compound **2b** (748 mg, 1.96 mmol) in EtOH (7 mL) and H_2O (1.5 mL). The reaction mixture was stirred for 16 h. Following acidification to pH 4.5 using 2 N HCl, the solvent was evaporated. The resulting residue was washed with water (3 x 5 mL) and dried in vacuo. (yield: 511 mg; 72%).

4: 511 mg (72%); colorless crystals, mp 106°C. ^{1}H NMR (DMSO-d_6): δ = 2.58 ppm (d, *J* = 6.8 Hz, 2 H, NH_2CH_2), 2.93–3.05 (m, 1 H, $CHCH_2$), 3.47 (d, *J* = 8.1 Hz, 1 H, CHCO), 4.03 (t, *J* = 8.1 Hz, 1 H, OCH_2), 4.43 (t, *J* = 8.1 Hz, 1 H, OCH_2), 4.83 (s, 1 H, $CHPh_2$), 7.16-7.23 (m, 2 H, CH_{ar}), 7.26-7.34 (m, 4 H, CH_{ar}), 7.38-7.46 (m, 4 H, CH_{ar}). ^{13}C NMR (DMSO-d_6): δ = 40.1 ppm ($CHCH_2$), 49.8 (NCH_2), 51.0 ($CHCO$), 66.4 ($CHPh_2$), 70.1 (OCH_2), 126.6 (CH_{ar}), 126.9 (CH_{ar}), 128.2 (CH_{ar}), 143.9 (C_q), 169.3 (CO), 173.1 (CO). IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1}, 3031, 2965, 2869, 2586, 1768, 1715, 1610, 1455, 1374, 1159, 1024, 749, 700. MS (CI, CH_5^+); *m/z* (%): 282 [M^++1-HCl-CO_2] (45), 167 (100); MS (EI, 70eV); *m/z* (%): 281 [M^+-HCl-CO_2] (5), 204(35), 167 (100). Anal. Calcd for $C_{19}H_{20}ClNO_4$ (361.8): C, 63.07; H, 5.57; N, 3.87. Found. C, 63.01; H, 5.42; N, 3.86.

4-[(Diphenylmethylamino)methyl]-4,5-dihydrofuran-2(3*H*)-one (10). Compound **4** (391 mg, 1.08 mmol) was heated to 130 °C at 2 x 10^{-3} bar for 120 min. Purification by CC (*n*-heptane/EtOAc = 80:20 + 0.5% ethyldimethylamine) .

10: 275 mg (91%); colorless crystals, mp 109 °C. R_f = 0.24 (*n*-heptane/EtOAc = 80:20 + 0.5% ethyldimethylamine). ^{1}H NMR ($CDCl_3$): δ = 1.72 ppm (s br, 1 H, NH), 2.32 (dd, *J* = 16.4, 4.8 Hz, 1 H, CH_2CO), 2.57-2.75 (m, 4 H, NCH_2, $CHCH_2$, CH_2CO), 4.13 (dd, *J* = 9.1, 4.8 Hz, 1 H, OCH_2), 4.44 (dd, *J* = 9.1, 6.7 Hz, 1 H, OCH_2), 4.78 (s, 1 H, $CHPh_2$), 7.20-7.40 (m, 10 H, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ = 32.6 ppm (CH_2CO), 35.8 ($CHCH_2$), 50.5 (CH_2N), 67.6 ($CHPh_2$), 71.9 (OCH_2), 127.1 (CH_{ar}), 127.2 (CH_{ar}), 127.3 (CH_{ar}), 128.6 (CH_{ar}), 143.4 (C_q), 143.6 (C_q),177.0 (CO). IR (KBr): $\tilde{\nu}$ = 3312 cm^{-1}, 3024, 2918, 2849, 1752, 1492, 1451, 1193, 1000, 747, 705. MS (CI, CH_5^+); *m/z* (%): 282 [M^++1] (100), 167 (60); MS (EI, 70eV): *m/z* (%): 281 [M^+] (3), 204 (39), 167 (100). Anal. Calcd for $C_{18}H_{19}NO_2$ (281.4): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.61; H, 6.72; N, 4.87.

4-[(Diphenylmethylamino)methyl]-4,5-dihydrofuran-2(3*H*)-one hydrochloride (11). Compound **10** (102 mg, 0.36 mmol) in Et_2O/CH_2Cl_2 (50:50, 5 mL) was treated with anhydrous, gaseous HCl. The resulting compound **11** was dried in vacuo.

11: 115 mg (~100%); colorless crystals, mp 223°C. ^{1}H NMR ($CDCl_3$): δ = 2.00 ppm (dd, *J* = 21.1, 1 H, 10.7 Hz, CH_2CO), 2.58 (dd, *J* = 21.1, 9.0 Hz, 1 H, CH_2CO), 2.51-2.63 (m, 1 H, $CHCH_2$), 2.81 (m, 2 H, CH_2N), 3.77 (dd, *J* = 9.7, 6.0 Hz, 1 H, OCH_2), 4.21 (dd, *J* = 9.7, 7.0 Hz, 1 H, OCH_2), 5.08 (s, 1 H, $CHCPh_2$), 7.34-7.66 (m, 10 H, CH_{ar}), 10.53 (s br, 2 H, NH_2^+). IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1}, 2743, 1788, 1576, 1497, 1454, 1172, 1031, 748, 703, 564. MS (EI, 70eV); *m/z* (%): 281 [M^+-HCl] (3), 204 (30), 167 (100); MS (CI, CH_5^+); *m/z* (%): 282 [M^++1-HCl] (100), 167 (47). Anal. Calcd for $C_{18}H_{20}NO_2Cl$ (317.8): C, 68.03; H, 6.34; N, 4.41; Cl, 11.16. Found: C, 67.82; H, 6.44; N, 4.28; Cl, 10.93.

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