AN UNUSUAL TRANSANNULAR REARRANGEMENT OF A [2.2]PARACYCLOPHANE DERIVATIVE TO YIELD THE FIRST [6.2.2]CYCLOPHANE

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A unique transannular interaction in the [2.2]paracyclophane series that involves the disruption of an oxazoline on one of the aromatic rings by a ψ-geminal carboxyl group on the adjacent ring is described. The result is the linking of the two benzene rings by the formation of a new interannular ring containing an ester and a secondary amide linkage leading to the first [6.2.2]cyclophane.

Keywords: Transannular rearrangements; Cyclophanes; [2.2]Paracyclophane; [6.2.2]Cyclophane; Oxazoline ring opening; Interannular bridging.

A recent report[1] of an unusual deacylation that occurred on reduction of 4,12-dihydroxy-5-pentanoyl[2.2]paracyclophane was ascribed in large part to a transannular interaction between the 5-pentanoyl group and the ψ-geminal[2] 12-hydroxy group.

In the course of a rational preparation[3] of 4-amino-13-carboxy[2.2.]paracyclophane (**1**), a unique amino acid of planar chirality[4,5], we had occasion to prepare compound **2** and to subject it to both direct and indirect Curtius reactions in order to prepare the corresponding amine **3**. It is interesting to note that **2** itself is a unique, planarly chiral imino acid which should exist as a zwiterion (Fig. 1) and possibly be particularly susceptible to intramolecular interactions.

We report here that in a variety of the Curtius reactions, of which some examples are given in Scheme 1, along with the expected products **3**, **5**,

or **6**, an unusual by-product was isolated. Physical data for the unknown product, to which we have assigned structure **4**, are given in the Experimental (*vide infra*) together with the corresponding data for **2** and **3** for comparison. Compound **4** is formed by a unique transannular interaction.

The by-product was not soluble either in aqueous 2 M HCl or in 10% (w/w) KOH and is therefore neither an amine nor a carboxylic acid. Accurate mass measurements (see Experimental) show that the unknown is an isomer of **2**. From its ^{13}C and ^{1}H NMR spectra it is clear that in **4** the disubstituted [2.2]paracyclophane unit of **2** has been left intact as all four bridge methylene groups are present as are the usual six quaternary aromatic carbon atoms and six aromatic methine atoms for a disubstituted [2.2]paracyclophane. However, while all the aliphatic carbons of the oxazoline ring are present, there are major changes in δ_C (all comparisons for the $CDCl_3$ spectra of all three compounds) for the aliphatic carbons for the unknown substance as compared with **2** and **3** or, indeed, any of the other oxazolines that we have in hand. Thus the quaternary $C(CH_3)_2$ in the unknown has moved upfield by *ca* 5 ppm as compared with either **2** or **3**. Unlike the case of the oxazolines, signals for the methyl groups of the unknown are well separated (by 4.56 ppm), suggesting that are being held in very different electronic environments from each other. The OCH_2 signal in the ^{13}C NMR spectrum has been displaced by 8.44 ppm in the unknown as compared with **2** and 8.46 ppm as compared with **3**. Clearly the substituted

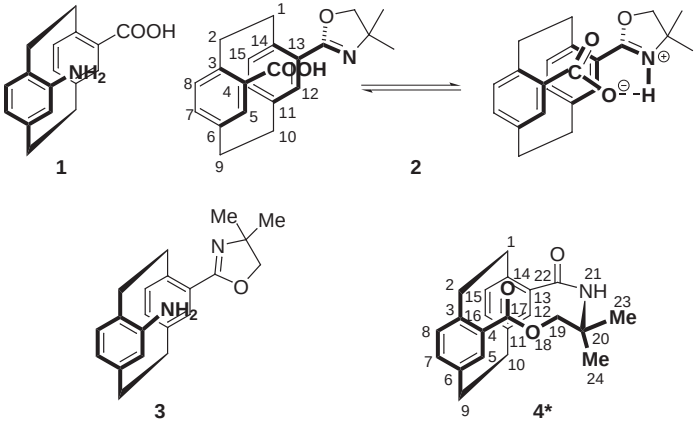
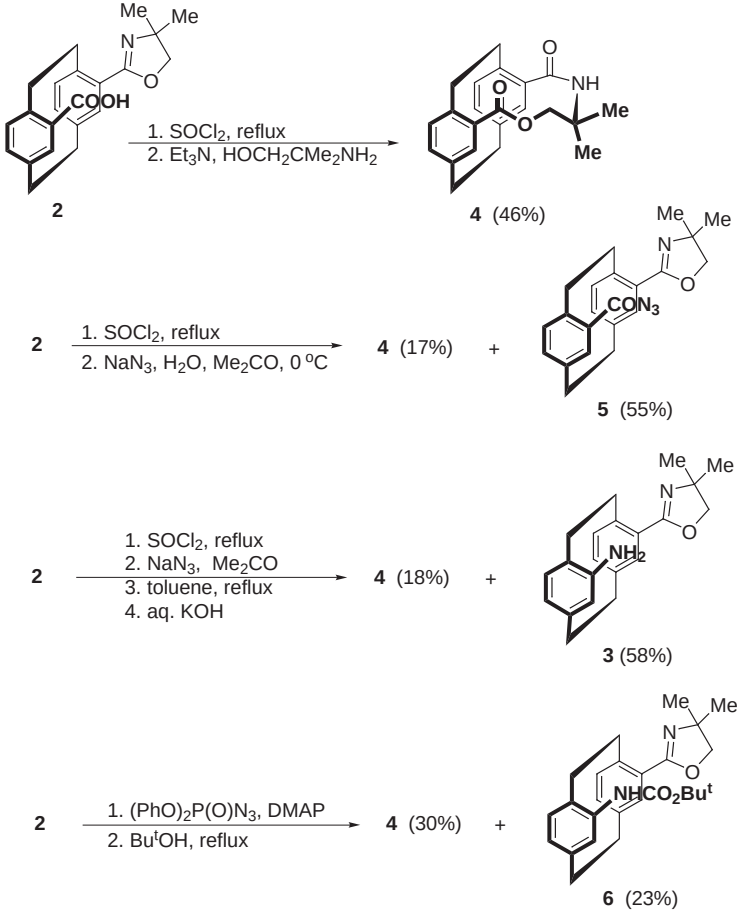


FIG. 1
Structures of compounds **1–4**. * The numbering used is not the IUPAC numbering but is chosen so that the [2.2]paracyclophane portion of **3** and **4** it is numbered in the same manner as the starting material **2**

2-aryloxazoline ring of the starting material **2** is no longer present in the new product. However, as the by-product is isomeric with the starting material, a new ring or extra unsaturation must have been formed. There was no evidence for the latter and so we assumed that in some fashion a new ring was formed as the oxazoline ring was opened.

In the ^{1}H NMR spectrum run in $CDCl_3$, because of the closeness of the chemical shifts in each of the aromatic AB systems, we observed extreme intensity redistribution and in those systems, the outer line of each doublet could only be seen in the expanded spectrum. The situation was better in the spectrum run in C_6D_6 as the two AB doublets are better separated. The two expected ABX systems are readily discerned thus confirming that no



SCHEME 1

change in the pattern of ring substitution had occurred in the isomerisation. The two methyl groups are separated by 0.44 ppm which again emphasises their different environments and contrasts with all of our oxazolines.

In both the IR and the ^{13}C NMR spectra, signals due to the C=N of the oxazoline and the C=O and OH of the carboxyl group of **2** are absent and are replaced by signals due to two new carbonyl groups. The fact that a carbonyl group is present with ν_{max} 1 721 cm^{-1} suggests that the unknown contains a newly formed ester group. The NH signals in the IR and ^1H NMR spectra together with the carbonyl signals in the IR and ^{13}C NMR spectra show that the other carbonyl group is present as part of a secondary amide grouping.

To satisfy all the data, we proposed structure **4** for the new product and this was fully confirmed by an X-ray structure determination (Fig. 2). Compound **4** is to our knowledge the first [6.2.2]paracyclophane. It is also unusual in that although extra ethano bridging of [2.2]paracyclophanes is well known[6] and indeed "superphane" has six ethano bridges[6,7], the new bridge of compound **4** contains an ester and an amido group.

There are many possibilities for the mechanism of formation of **4**, produced as it is in a variety of reaction conditions. A general mechanism (Scheme 2) is that the nitrogen atom of the oxazoline ring is quaternised by an electrophile[8–12] and that the positively charged ring is then attacked intramolecularly by the adjacent carboxyl group in a manner which has precedent in the intermolecular attack by a chloride anion[9]. The nature of the electrophile will vary with the particular reaction being considered.

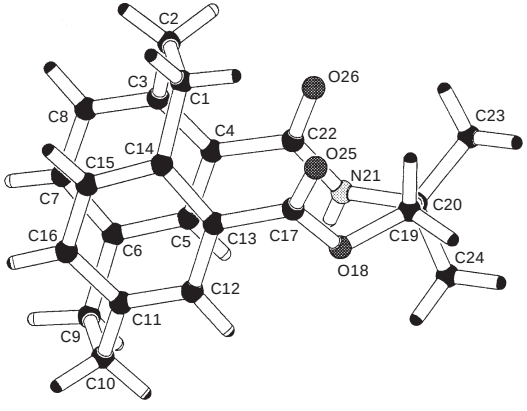
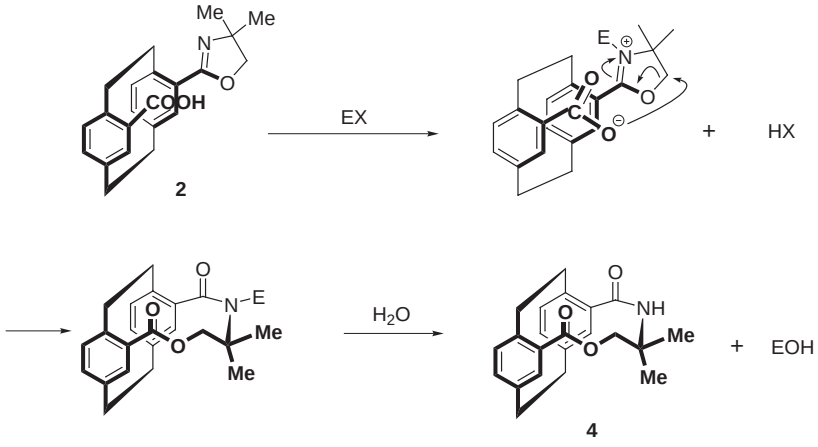


FIG. 2
Molecular structure of compound **4**



SCHEME 2

We have not attempted to optimise the yields of **4** and indeed our efforts were spent in attempting to minimize its production. That it was produced in such a variety of conditions and in some cases competed as the main product suggests a strong driving force in its formation. Both molecular models and the bond angles found in the X-ray analysis suggest that there is little strain associated with the extra ring of **4**. The models show that the ring could be flexible but it appears that it is held in one favoured conformation. This is probably due to a combination of electronic factors, particularly those of two ψ-geminal carbonyl groups held closely together, plus steric factors. In particular the interactions of one of the geminal methyl groups with the ethylene bridge protons if the conformation were to flip and hydrogen bonding interactions (donor–acceptor distance C–H···O is 3.250(4) Å). In the favoured conformation, one of the methyl groups is much closer (1.221 Å) to the C-22 carbonyl group than is the other and this explains the differences noted previously in the positions of the signals in the ^{13}C NMR spectrum of the methyl groups.

To summarise, we have serendipitiously made and then characterised compound **4** which, to our knowledge, is the first [6.2.2]paracyclophane[6]. Very unusually, the extra bridge is formed across two functional groups.

EXPERIMENTAL

General Comments

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument at 400.1 and 100.6 MHz, respectively. All spectra used tetramethylsilane as internal standard and were run in $CDCl_3$ unless otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling

constants (*J*) in Hz. Mass spectra were recorded either on a VG 12-250 quadrupole instrument or on a VG Micromass Quattro II instrument. Accurate mass measurements were made using either a ZAB-E high resolution double focussing instrument or a Finnegan Mat 900 instrument. IR spectra (ν_{max} in cm^{-1}) were recorded as films on NaCl plates using a Perkin–Elmer transform 1725X spectrometer. UV spectra were recorded on a Perkin Elmer Lamda 9 spectrometer. Melting points were recorded on a Gallenkamp microscope block and are uncorrected. Thionyl chloride was heated under reflux with zinc powder before distillation and direct usage. Other solvents were purified by standard means[13]. Chromatography was carried out on silica gel (30–70 micron mesh) under medium pressure using chromatographically pure solvents. Sodium azide was used as purchased.

Preparation of 5,5-Dimethyl-3-oxa-6-aza-1,8(2,1,4)dibenzenabicyclo-[6.2.2]dodecaphane-2,7-dione (**4**)

Purified thionyl chloride (6 ml) was distilled directly into a round bottomed flask containing dry **2** (0.3 g, 0.86 mmol)[3] and the resultant reaction mixture was stirred at room temperature for 4 h. The excess thionyl chloride was distilled off and any traces left were removed by distillation with toluene (3 × 20 ml). The solid residue was dissolved in acetone, cooled to 0 °C and the solution added *via* a cannula to stirred sodium azide (0.296 g, 4.56 mmol) dissolved in acetone–water (10 ml, 1 : 1 vol.) also at 0 °C. The reaction mixture was left at room temperature for 15 h, then extracted with dichloromethane (3 × 15 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated to give a light brown solid (0.35 g) which was dissolved in toluene (20 ml) and then heated under reflux for 2 h. Aqueous potassium hydroxide (10 ml, 10% w/v) was added and the mixture heated under reflux for 3 h.

The mixture was cooled to room temperature, brought to pH 8 by addition of 2 M HCl and then concentrated almost to dryness. The residue was taken into CH_2Cl_2 (30 ml) and extracted with 2 M HCl (3 × 50 ml). The organic layer was separated, dried and concentrated to give an orange oil (0.11 g). The acidic aqueous layer was brought to pH 9 and re-extracted with dichloromethane (4 × 75 ml). Concentration gave almost pure 13-amino-4-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)[2.2]paracyclophane[3] (**3**) as an off-white solid (0.159 g, 58%). The neutral fraction was purified by column chromatography on silica using gradient elution between light petroleum (100%) to light petroleum–ethyl acetate (70 : 30). The major fraction **4** (0.053 g, 18%) was produced as crystals on allowing the eluate to evaporate overnight. Analytical and spectral data:

Compound **2** (ref.[3]): m.p. 180–181 °C. IR: 3 469 (COOH), 1 681 (C=O), 1 635 (C=N). ^{1}H NMR ($CDCl_3$): 1.22 (3 H, s, CH_3); 1.26 (3 H, s, CH_3); 3.07 and 4.25 (6 H and 2 H as two multiplets, H-1a, 1b, 2a, 2b, 9a, 9b, 10a, 10b); 3.91 (1 H, *J* = 15.3, OCH); 3.93 (1 H, d, *J* = 15.3, OCH); 6.61 (1 H, dd, *J* = 1.6, 7.7, H-16); 6.66, 6.67 (2 H, 2d, *J* = 7.7, H-8 and H-15); 6.74 (1 H, dd, *J* = 1.6, 7.7, H-7); 7.01 (1 H, d, *J* = 1.6, H-12); 7.37 (1 H, d, *J* = 1.6, H-5). ^{13}C NMR (all carbons other than those designated are C-H): 27.8, 28.1 (2 × CH_3); 34.2, 34.7, 35.0 (C-1, 2, 9, 10); 67.4 s ($C(CH_3)_2$); 78.3 (OCH_2); 128.7 s, 128.8 s, 132.6, 134.8, 134.9, 135.5, 136.3, 137.2, 139.0 s, 139.7 s, 140.7 s, 144.0 s, 161.8 (C=N); 171.8 (C=O). CI MS (*m/z*): 350 ($M + 1^+$, 100). EI MS (*m/z*): 349 (M^+, 32), 305 (50), 201 (100), 146 (23), 131 (20), 105 (41). HRMS: for $C_{22}H_{23}NO_3$ calculated 349.1678; found 349.1678. UV (CH_2Cl_2; λ_{max}, nm (intensity)): 245.5 (18 552).

Compound **3** (ref.[3]): m.p. 160–161 °C. IR: 3 418, 3 312 (NH), 1 624 (C=N). ^{1}H NMR ($CDCl_3$): 1.30 (3 H, s, CH_3); 1.31 (3 H, s, CH_3); 2.64 (1 H, ddd, *J* = 6.4, 10.6, 16.4, H-2a); 2.88 (5 H, m, H-1b, 9a, 9b, 10a, 10b); 3.06 (1 H, m, H-2b); 3.30 (2 H, br, NH_2); 3.94 (1 H, d, *J* = 8.0, OCH); 4.00 (1 H, d, *J* = 8.0, OCH); 4.18 (1 H, ddd, *J* = 6.4, 9.4, 16.4, H-1a); 5.43 (1 H, d, *J* = 1.7, H-5); 6.01 (1 H, dd, *J* = 1.7, 7.7, H-7); 6.27 (1 H, d, *J* = 7.7, H-8); 6.31 (1 H, d, *J* = 7.7, H-15); 6.50 (1 H, dd, *J* = 1.9, 7.7, H-16); 7.06 (1 H, d, *J* = 1.9, H-12). ^{13}C NMR: 28.2 (2 × CH_3); 30.9, 32.3 (C-1, 2); 34.6, 34.8 (C-9, 10); 67.4 s ($C(CH_3)_2$); 78.5 (OCH_2); 121.4, 122.4, 124.2 s, 125.5 s, 132.1, 134.4, 134.8, 136.0, 138.3 s, 140.0 s, 140.6 s, 146.5 s, 163.4 s (C=N). EI MS (*m/z*): 320 (M^+, 65), 201 (100), 119 (42). HRMS: for $C_{21}H_{24}N_2O$ calculated 320.18885; found 320.18890. UV (CH_2Cl_2; λ_{max}, nm (intensity)): 226 (19 192), 249 (12 808).

Compound **4**: m.p. 203–205 °C. IR: 3 428 (NH stretch), 1 721 (CO-O), 1 698, 1 654 (CONH). ^{1}H NMR (C_6D_6): 1.02 (3 H, s, H-23); 1.46 (3 H, s, H-24); 2.51 (2 H, m, H-9b, 10b); 2.74 (4 H, m, H-9a, 10a, 1b, 2b); 3.66 (1 H, d, *J* = 10.8, OCH); 4.57 (2 H, m, H-1a, 2a); 5.35 (1 H, d, *J* = 10.8, OCH); 5.43 (1 H, br s, NH); 6.21 (1 H, dd, *J* = 1.7, 7.9, H-7); 6.25 (1 H, dd, *J* = 1.6, 7.9, H-16); 6.27 (1 H, d, *J* = 7.9, H-15); 6.31 (1 H, d, *J* = 7.9, H-8); 6.60 (1 H, d, *J* = 1.6, H-12); 7.03 (1 H, d, *J* = 1.7, H-5). ^{13}C NMR: 24.8 (C-23); 29.4 (C-24); 34.8, 35.1, 35.2 (C-1, 2, 9, 10); 55.9 s (C-20); 69.9 (C-19); 131.3, 131.6 s, 132.9, 134.9 s, 135.5, 136.0, 136.5, 136.9, 139.2 s, 139.5 s, 142.6 s, 142.7 s, 168.7 s (C-22); 169.4 s (C-17). CI MS (*m/z*): 367 (M + NH_4^+, 9), 350 (M + 1^+, 100). EI MS (*m/z*): 350 (M^+ + 1, 9), 349 (M^+, 37), 304 (8), 290 (7), 278 (19), 260 (9), 249 (15), 202 (13), 189 (11), 157 (24), 147 (63), 146 (28), 131 (100), 103 (83), 77 (77). HRMS: for $C_{22}H_{24}NO_3$ calculated 350.1756; found 350.1753. UV (CH_2Cl_2; λ_{max}, nm (intensity)): 242 (14 409), 306 (1 652).

X-Ray Crystallography

A suitable crystal was selected and data collected on a Nonius KappaCCD area detector at the window of a Nonius FR591 rotating anode ($\lambda_{MoK\alpha}$ = 0.71073 Å). Data were corrected for absorption effects using the program SORTAV (ref.[14]). The structure was solved and refined using the SHELX (ref.[15]) suite of programs. Two chemically identical and crystallographically similar molecules crystallise in the asymmetric unit, however, only one is used as an example for this discussion. Hydrogen atoms were placed in idealised positions and their parameters tied to the values of the parent atom. Publication material was prepared using the PLATON (ref.[16]) software.

Crystal data: $C_{22}H_{23}NO_3$. *M* = 349.41, *T* = 150(2) K, monoclinic, space group $P2_1/c$, *a* = 13.288(3) Å, *b* = 16.032(3) Å, *c* = 16.484(3) Å, β = 99.03(3)°, *V* = 3 468.2(12) Å^3, ρ_{calc} = 1.338 g cm^{-3}, μ = 0.089 mm^{-1}, *Z* = 8; reflections collected: 50 016; independent reflections: 6 087 (R_{int} = 0.1276); final *R* indices [$I > 2\sigma I$]: R_1 = 0.0743, wR_2 = 0.1740; *R* indices (all data): R_1 = 0.1006, wR_2 = 0.1889.

CCDC 179686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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