HETEROCYCLES, Vol. 64, 2004, pp. 277 - 289
Received, 20th July, 2004, Accepted, 18th October, 2004, Published online, 19th October, 2004

STUDIES ON THE CONDENSATION PRODUCTS FROM *N*-PRIMARY 1,2-AMINO ALCOHOLS AND FORMALDEHYDE

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Abstract – The products of the condensation reactions of twenty-six different 1,2-amino alcohols with excess aqueous formaldehyde were identified, with the help of a simple and effective analytical technique based on mass spectroscopy. With a few exceptions, which arise from steric or solubility effects, most amino alcohols form bis(oxazolidine)methane adducts preferentially.

This paper is dedicated to Professor Pierre Potier on the occasion of his 70th birthday.

INTRODUCTION

The 1:1 condensation reaction of 1,2-amino alcohols with carbonyl compounds has been the major synthetic route to oxazolidines for over a century.[1] For several decades, it has been recognized that for *N*-primary 1,2-amino alcohols, the reaction with excess formaldehyde often leads to higher order adducts. Amongst these compounds are 2:3 adducts, for which bis(oxazolidine)methane structures are often reported,[2-7] including an intramolecular version.[8] Some specific examples of these compounds have recently been identified as useful therapeutic agents,[9] or as formaldehyde sources for use as biocides in industrial applications.[10]

From quite early on, though, it was evident that an isomeric 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane skeleton is also possible for a 2:3 adduct. Crabb and co-workers showed elegantly that such structures were obtained in the condensation of formaldehyde with *trans*-2-aminocyclopentanol and *trans*-2-aminocyclohexanol, arguing that ring fusion strain disfavored the bis(oxazolidine)methanes.[3] Thus, the epidoxorubicin-formaldehyde conjugate, a promising anti-tumor agent, possesses a 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane core.[11] Strain effects, however, are not the only determining factor for determining the nature of the 2:3 adduct; we[12] and subsequently others[7,13] have observed cases where no apparent strain was in evidence for the bis(oxazolidine)methane structures, yet the 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane isomers predominated. Recent articles by the respective research groups of Pavia[14] and Flores-Parra[15] concerning the relationships between the two possible structures prompt us to disclose and review our own results in this area. In this paper, we present the results of the condensation reactions of formaldehyde with twenty-six different *N*-primary 1,2-aminoalcohols under fixed conditions, in which we highlight the use of mass spectrometry as a simple tool for structural analysis.

RESULTS AND DISCUSSION

We selected a series of diversely substituted 1,2-aminoalcohols (**1a-z**) (Figure 1) to examine the scope of the 2:3 condensation reaction with formaldehyde. In some cases, these compounds are commercially available; in others, literature procedures or standard adaptations thereof were sufficient to obtain them. All chiral compounds were used as single enantiomers (with the exception of (±)-**1u**), in order to avoid problems arising from diastereoisomers mixtures in the condensation reactions. The reactivities of some of these compounds have been reported before (although not necessarily under the same conditions); we included them in our study for comparison purposes and to validate the mass spectrometric structural analysis technique which we have developed.

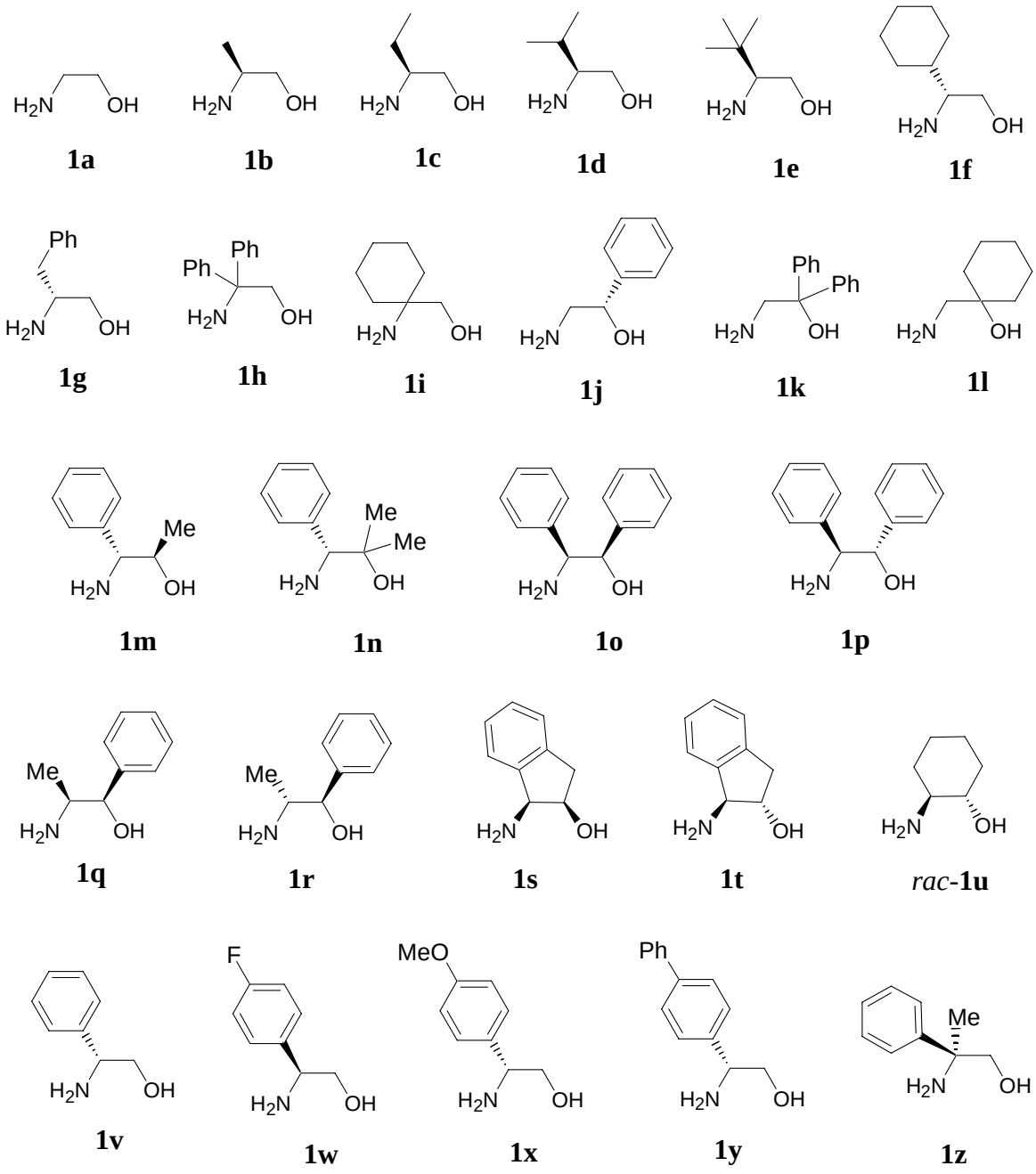
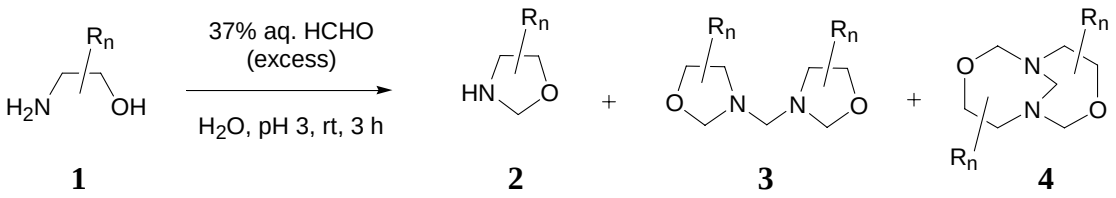


Figure 1. Amino alcohols studied in this work.

The reaction conditions for the condensation reaction with formaldehyde vary considerably in the literature. Our own work in this field, which began over a decade ago,[12] involved the treatment of an slightly acidic aqueous solution of the 1,2-amino alcohol with an excess of 37% aqueous formaldehyde at room temperature for 3 hours; we decided to retain these conditions as standard for this study (Scheme 1). Results are presented in Table 1. In some cases, where mixtures of products were obtained, it was not easy to isolate pure material; however, sufficient spectroscopic data were always obtained to satisfy structural attributions.



1 **2** **3** **4**

Scheme 1.

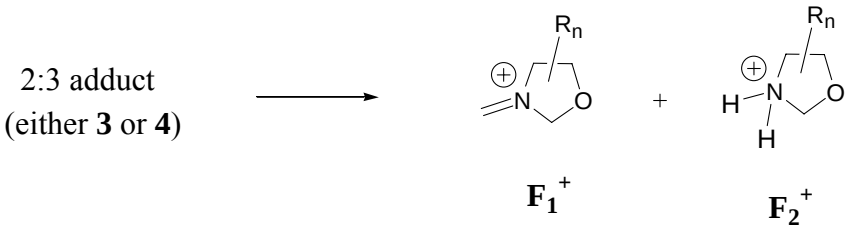
Table 1. Yields (%) of condensation reaction products.[a]

1 →	2	3	4	1 →	2	3	4
a	-	-	-	**n**	-	65	-
b	-	-	-	**o**	-	86	-
c	-	-[b]	-	**p**	-	75	-
d	-	96	-	**q**	-	82	-
e	-	91	-	**r**	-	85	-
f	-	72	-	**s**	-	94	-
g	-	89	-	**t**	-	-	74
h	27	63	-	**u**	-	-	72
i	46	-	-	**v**	-	18	71
j	-	94	-	**w**	-	27[c]	63
k	-	97	-	**x**	19[c]	36[c]	22
l	-	68	-	**y**	33[c]	33[c]	22
m	-	81	-	**z**	14	66	-

a: Yields are given for NMR-pure material isolated from the reaction mixture; single-product reactions give samples of high purity. Analytical samples were obtained by recrystallisation (often repeated), resulting in an inevitable loss of material to a variable extent. *b*: Detected in the crude reaction mixture but not isolated. *c*: These products were not isolated in pure form, but their presence was inferred from spectral data.

Structural identification of oxazolidines (**2**) on the basis of NMR and MS spectral data was straightforward. Differentiation between the isomeric 2:3 adducts, on the other hand, is not a trivial affair; Crabb and co-workers[3] showed that the geminal coupling constants observed for the OCH_2N signals in the ^1H NMR spectrum can be diagnostic, since this value is around 2-6 Hz for bis(oxazolidine)methanes, and 10-13 Hz for 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecanes. This approach is convenient, but limited to cases where coupling is in fact observed; it fails completely for achiral bis(oxazolidine)methanes and has been inconclusive in other chiral cases.[12,14] Single-crystal X-Ray diffraction is a reliable alternative, but of course requires crystalline samples, and is somewhat onerous. We recently reported a simple, convenient method of differentiation between the test cases (**3v**) and (**4v**) based on the fragmentation pattern observed in the chemical ionization MS spectrum using NH_3 as the reagent gas.[16] This technique turns out to be general, and allows rapid differentiation of all examples of **3** and **4**, whatever the nature of the substituents. Regardless of its molecular structure (**3** or **4**), under CI/NH_3 conditions the protonated

2:3 adduct $[MH]^+$ gives rise to two fragments $\mathbf{F_1}^+$ and $\mathbf{F_2}^+$ (Scheme 2). In the case of a bis(oxazolidine)methane (**3**), $[MH]^+$ is of weak-to-moderate abundance, $\mathbf{F_1}^+$ is the base peak, and $\mathbf{F_2}^+$ is of variable intensity. In the case of a 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane **4**, $[MH]^+$ is the base peak, while $\mathbf{F_1}^+$ and $\mathbf{F_2}^+$ are of low intensity (a few percent at most). It was possible to validate this technique by corroborating structural attributions based thereupon with NMR spectral data (when geminal OCH_2N is observed) and/or X-Ray diffraction data (available for adducts **3j,**[17] **3q,**[18,19] **3s,**[7] **4v**,[7,12]), and we consider it to be sufficiently reliable for structural attribution to made with confidence on its basis alone.



Scheme 2.

As an illustrative example, we consider the single 2:3 adduct obtained in the condensation of formaldehyde with **1o**. The CI/NH_3 MS spectrum shown peaks at *m/z* 463 (6%), 238 (100%) and 226 (15%), which suggests a bis(oxazolidine)methane structure (**3o**). This attribution was corroborated by an observed geminal coupling constant of 2.6 Hz for the OCH_2N protons, and confirmed by an X-Ray diffraction study (Figure 2).

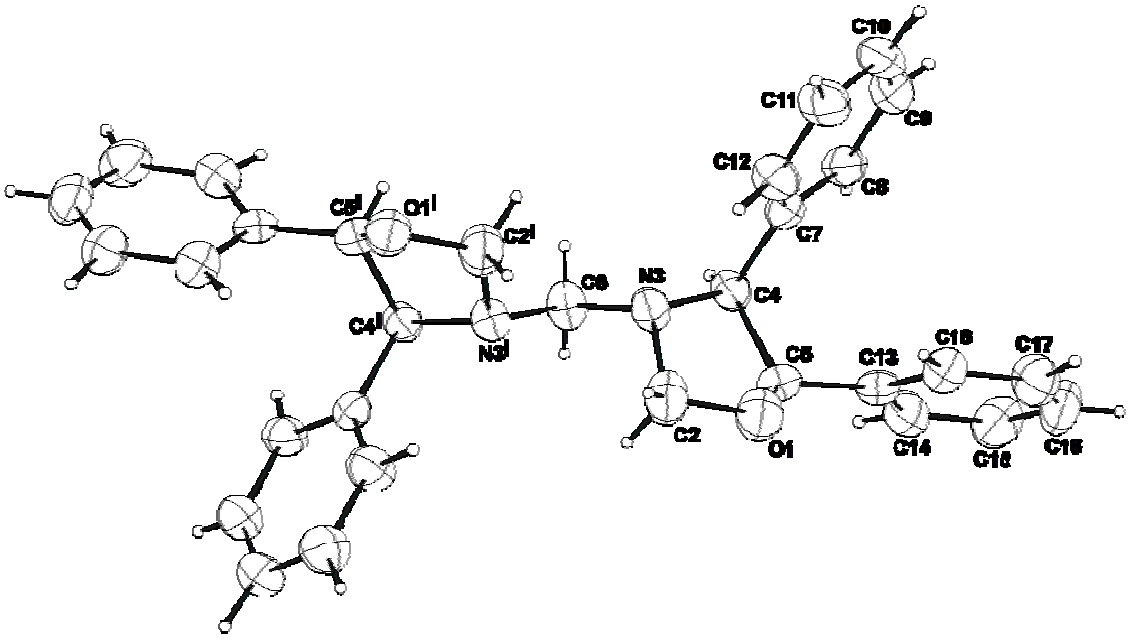


Figure 2. Crystal structure of compound (**3o**).

Using this technique, compound (**3l**), an oil showing no homonuclear coupling constants in its ^{1}H NMR spectrum, could be assigned a bis(oxazolidine)methane structure solely on the basis of its CI/NH_3 MS: *m/z* 295 (7%), 154 (100%) and 142 (46%). Similarly, adducts (**4w**, **4x** and **4y**) (like **4v** previously[12]) showed only singlets for their ^{1}H NMR OCH_2N signals, but were attributed 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane skeletons on the basis of the observation of $[MH]^+$ ions as base peaks in their CI/NH_3 MS spectrum.

The first point to emerge from the results is that the scope for formation of a 2:3 adduct under the present conditions is quite large. Amino alcohols of an "intermediate" degree of substitution generally give single products. Compounds (**1**) having minimal or no substitution (**1a**, **1b**, **1c**) provide more complex reaction mixtures, from which isolation of a 2:3 adduct is not easy; higher-order condensation products and ill-defined oligomers cannot be ruled out. Bolm and co-workers also observed that alaninol (**1b**) did not provide a 2:3 adduct when treated with aqueous formaldehyde.[7] Minimally-substituted bis(oxazolidine)methanes, including **3a**, **3b** and bis(5-methyloxazolidin-3-yl)methane (Grotan OX, a commercial product), are well-known compounds, but are usually prepared from the amino alcohol by heating with formaldehyde or paraformaldehyde in organic solvent or neat.[13,14,15] To obtain such examples of **3**, non-aqueous conditions are therefore preferred. At the other end of the scale, amino alcohols (**1**) which are highly sterically-hindered next to the nitrogen have difficulty in forming a 2:3 adduct; in such cases, the condensation progresses as far as the 1:1 oxazolidine adduct (**2**). This tendency is nicely demonstrated in the series **1v** < **1z** < **1h**, while the absence of a spiro- 2:3 adduct from **1i** marks the upper limit for steric congestion. In contrast, a high degree of substitution can be accommodated next to the oxygen atom (as shown for **1k** and **1l**).

The second feature of note is that, as a general rule, the preferred structure for the 2:3 adduct is a bis(oxazolidine)methane (**3**). There are two exceptions to this, the first of which is where *trans*-fused ring strain precludes formation of **3**. This was already noted by Crabb and co-workers[3] and explains why **1s** gives **3s** but **1t** gives **4t**; similarly, **1u** gives only **4u**. The second exception is rather more intriguing, and concerns the reactivity of phenylglycinol (**1v**). This compound, and its ring substituted derivatives (**1w**, **1x** and **1y**), furnish significant amounts of the corresponding 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecanes (**4**), although there is no apparent obstacle to formation of **3** (which, furthermore, appears less strained than **4** upon examination of models). In contrast, derivatives of phenylglycinol bearing substituants on the aminoalcohol backbone (**1h**, **1m**, **1n**, **1o**, **1p**, **1z**) produce adducts (**3**) invariably. The explanation for this, for which clues appeared a few years ago,[20,21] is probably the existence of a dynamic equilibrium between structures (**3**) and (**4**), which can be displaced in either direction depending on the prevailing conditions. If one structure precipitates or crystallizes out from the reaction medium quicker than the interconversion, then its formation may predominate, even if it is not the thermodynamically favored product. This process,

and its reversal upon dissolution of certain compounds of type **4** which isomerize to **3** under appropriate conditions, was recently demonstrated by Pavia[14] and Flores-Parra.[15] In the aqueous medium adopted for the condensation reaction studied here, phenylglycinol (**1v**) and a few of its close derivatives behave in such a fashion. The observation of non-negligible amounts of oxazolidines (**2**) at the end of the usual reaction time in the cases of **1x** and **1y** is consistent with a border-line situation for these aminoalcohols, since **2** is the probable intermediate in the interconversion of **3** and **4**.

In conclusion, this work suggests that a wide range of substituted 1,2-amino alcohols form 2:3 adducts upon treatment with excess aqueous formaldehyde, although upper and lower limits of substitution are identified. The preferred 2:3 adduct is a bis(oxazolidine)methane (**3**), with the exception of (a) *trans*-aminoalcohols and (b) certain cases, such as with phenylglycinol (**1v**), in which kinetic/solubility factors intervene; in these cases, the 2:3 adducts are 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane. In the course of this work, mass spectrometry proved to be a simple yet powerful tool for structural analysis.

EXPERIMENTAL

General Remarks. Melting points were recorded on a Kofler hotplate and are uncorrected. Optical rotations were obtained using a Perkin-Elmer 141 MC polarimeter. NMR spectra were recorded as $CDCl_3$ solutions on a Bruker AC-300 spectrometer operating at 300 MHz for ^1H and at 75 MHz for ^{13}C; chemical shifts (δ) are given in ppm and were measured with reference to TMS as an internal standard. CIMS spectra were recorded on a triple quadrupole Nermag 30-10 instrument operating at a potential of 100eV using ammonia as the reactant gas. Elemental analyses were carried out in the Microanalysis Laboratory of the Institut de Chimie des Substances Naturelles du CNRS (Gif-sur-Yvette, France).

Standard procedure for condensation reactions. The 1,2-amino alcohol (**1**) (or its hydrochloride) (about 1 g) was dissolved in water and the solution was adjusted to pH 3 by addition of 10% aqueous citric acid solution. A 37% aqueous solution of formaldehyde (4 mL) was added dropwise over 10 min, and the reaction mixture was stirred at room temperature for 3 h. The solution was then made pH 9 by addition of solid sodium carbonate. One of two procedures was then followed:

- if a solid precipitated (usually around pH 5) then it was isolated by simple filtration, washed with water, then dried *in vacuo* over phosphorus pentoxide.
- if no precipitation was observed, the mixture was extracted with dichloromethane (3 × 15 mL). Combined extracts were dried over magnesium sulfate, the solvent was evaporated, and the residue dried *in vacuo* over phosphorus pentoxide.

Samples were then analyzed by NMR and MS spectrometry. Analytical samples were obtained by flash chromatography on silica gel or recrystallisation. In some cases (see Table 1), mixtures of products were obtained, from which single pure substances were not easily isolated.

4,4-Diphenyloxazolidine (2h)

Isolated by repeated fractional crystallisation from cyclohexane to remove **3h**. mp 87 °C (cyclohexane); δ_H 2.80 (br s, 1 H), 4.39 (s, 2 H), 4.63 (s, 2 H), 7.35 (m, 10 H); δ_C 75.1, 76.1, 82.0, 126.4, 127.2, 128.6, 144.8; CIMS: *m/z* 226 $[MH]^+$; Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.86; H, 7.01; N, 6.29.

4,4-Diphenyloxazolidine (2i)[22]

oil; δ_H 1.52 (m, 10 H), 2.12 (s, 1 H), 3.40 (s, 2 H), 4.44 (s, 2 H); δ_C 23.3, 25.5, 35.5, 61.6, 74.6, 84.2; CIMS: *m/z* 142 $[MH]^+$.

(*S*)-4-Methyl-4-phenyloxazolidine (2z)

oil, obtained after flash chromatography (EtOAc/cyclohexene 1/4); δ_H 1.26 (s, 3 H), 2.95 (br s, 1 H), 3.79 (d, 1 H, *J* = 7.5 Hz), 3.92 (d, 1 H, *J* = 7.5 Hz), 4.46 (d, 1 H, *J* = 5.9 Hz), 4.66 (d, 1 H, *J* = 5.9 Hz), 7.17-7.47 (m, 5 H); δ_C 20.6, 66.0, 81.7, 84.9, 125.5, 127.0, 128.6, 145.7; CIMS: *m/z* 164 $[MH]^+$.

Bis[(*S*)-4-isopropyloxazolidin-3-yl]methane (3d)[7]

oil; CIMS: *m/z* (%) 243 (15), 128 (100), 116 (3); other data as in the literature.[7]

Bis[(*S*)-4-*tert*-butyloxazolidin-3-yl]methane (3e)[7]

mp 60 °C (hexane); CIMS: *m/z* (%) 271 (21), 142 (100), 130 (2); other data as in the literature.[7]

Bis[(*R*)-4-cyclohexyloxazolidin-3-yl]methane (3f)

mp 102 °C (heptane); $[\alpha]_D^{20} = -56°$ (*c* = 0.94, $CHCl_3$); δ_H 0.80-2.05 (m, 22 H), 2.58 (td, 2 H, *J* = 7.1, 7.5 Hz), 3.24 (s, 2 H), 3.41 (dd, 2 H, *J* = 7.5, 8.0 Hz), 3.91 (dd, 2 H, *J* = 7.5, 8.0 Hz), 4.13 (d, 2 H, *J* = 6.6 Hz), 4.77 (d, 2 H, *J* = 6.6 Hz); δ_C 26.2, 26.8, 29.8, 30.8, 41.6, 67.2, 68.2, 84.4; CIMS: *m/z* (%) 323 (11), 168 (100), 156 (11); Anal. Calcd for $C_{19}H_{34}N_2O_2$: C, 70.96; H, 10.63; N, 8.69. Found: C, 70.97; H, 10.61; N, 8.29.

Bis[(*R*)-4-benzyloxazolidin-3-yl]methane (3g)[7]

oil; CIMS: *m/z* (%) 339 (43), 176 (100), 164 (38); other data as in the literature (for the antipode).[7]

Bis(4,4-diphenyloxazolidin-3-yl)methane (3h)

Isolated by repeated fractional crystallisation from benzene/heptane to remove **2h**. mp 147 °C (benzene/heptane); δ_H 2.62 (s, 2 H), 4.28 (s, 4 H), 4.91 (s, 4 H), 7.17 (m, 20 H); δ_C 65.3, 72.0, 78.8, 85.5, 127.2, 127.6, 128.0, 140.9; CIMS: *m/z* (%) 463 (3), 238 (100), 226 (30); Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.16; H, 6.58; N, 5.81.

Bis[(*S*)-5-phenyloxazolidin-3-yl]methane (3j)[5,17]

mp 108 °C (cyclohexane); $[\alpha]_D^{21}$ = +63° (*c* = 0.99, $CHCl_3$);δ_H 2.87 (dd, 2 H, *J* = 7.9, 11.7 Hz), 3.53 (s, 2 H), 3.57 (dd, 2 H, *J* = 6.8, 11.8 Hz), 4.67 (d, 2 H, *J* = 5.8 Hz), 4.71 (d, 2 H, *J* = 5.7 Hz), 4.92 (t, 2 H, *J* = 7.3 Hz), 7.32 (m, 10 H); δ_C 59.0, 74.9, 76.3, 86.2, 127.5, 127.6, 128.6, 142.1; CIMS: *m/z* (%) 311 (10), 162 (100), 150 (92); Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.72; H, 6.69; N, 8.83.

Bis(5,5-diphenyloxazolidin-3-yl)methane (3k)

mp 110 °C (cyclohexane); δ_H 3.21 (s, 2 H), 3.71 (s, 4 H), 4.67 (s, 4 H), 7.23-7.46 (m, 20 H); δ_C 62.6, 74.3, 85.2, 85.4, 125.8, 127.0, 128.3, 146.1; CIMS: *m/z* (%) 463 (9), 238 (100), 226 (46); Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.27; H, 6.79; N, 6.19.

Bis(1-oxa-3-azaspiro[4.5]decan-3-yl)methane (3l)

oil; δ_H 1.20-1.73 (m, 20 H), 2.77 (s, 4 H), 3.45 (s, 2 H), 4.40 (s, 4 H); δ_C 23.8, 25.4, 36.9, 61.2, 75.5, 80.2, 83.4; CIMS: *m/z* (%) 295 (7), 154 (100), 142 (46); Anal. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.84; H, 10.05; N, 9.20.

Bis[(4*R*,5*R*)-5-methyl-4-phenyloxazolidin-3-yl]methane (3m)

mp 76 °C (EtOAc/cyclohexane); $[\alpha]_D^{23}$ = –232° (*c* = 0.59, CH_2Cl_2); δ_H 1.20 (d, 6 H, *J* = 6.0 Hz), 3.11 (d, 2 H, *J* = 8.2 Hz), 3.30 (s, 2 H), 3.78 (m, 2 H), 4.35 (d, 2 H, *J* = 3.7 Hz), 4.92 (d, 2 H, *J* = 3.7 Hz), 7.30 (m, 10 H); δ_C 17.5, 71.4, 72.9, 82.0, 86.2, 127.6, 127.8, 128.6, 139.2; CIMS: *m/z* (%) 339 (6), 176 (100), 164 (7); Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.25; H, 7.86; N, 8.01.

Bis[(4*R*)-5,5-dimethyl-4-phenyloxazolidin-3-yl]methane (3n)

mp 110 °C (EtOAc/cyclohexane); $[\alpha]_D^{23}$ = –242° (*c* = 0.50, $CHCl_3$); δ_H 0.86 (s, 6 H), 1.29 (s, 6 H), 3.25 (s, 2 H), 3.32 (s, 2 H), 4.29 (d, 2 H, *J* = 3.0 Hz), 5.09 (d, 2 H, *J* = 3.0 Hz), 7.32 (m, 10 H); δ_C 23.4, 26.5, 71.0, 74.4, 82.8, 84.8, 127.7, 127.9, 128.3, 138.1; CIMS: *m/z* (%) 367 (3), 190 (100), 178 (27); Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 76.37; H, 8.25; N, 7.64. Found: C, 76.03; H, 8.11; N, 7.29.

Bis[(4*S*,5*R*)-4,5-diphenyloxazolidin-3-yl]methane (3o)

mp 109 °C (heptane/cyclohexane); $[\alpha]_D^{21}$ = +240° (*c* = 1.11, $CHCl_3$); δ_H 3.36 (s, 2 H), 3.92 (d, 2 H, *J* = 7.4 Hz), 4.33 (d, 2 H, *J* = 2.6 Hz), 5.19 (d, 2 H, *J* = 7.4 Hz), 5.47 (d, 2 H, *J* = 2.6 Hz), 6.87-7.11 (m, 20 H); δ_C 68.4, 69.2, 83.7, 87.2, 126.5-128.4 (several non-resolved signals), 136.4, 138.7; CIMS: *m/z* (%) 463 (6), 238 (100), 226 (15); Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.31; H, 6.51; N, 5.88.

Bis[(4*S*,5*S*)-4,5-diphenyloxazolidin-3-yl]methane (3p)

mp 88 °C (heptane/cyclohexane); $[\alpha]_D^{23}$ = +119° (*c* = 1.00, $CHCl_3$); δ_H 3.40 (s, 2 H), 3.45 (d, 2 H, *J* = 8.1 Hz), 4.63 (d, 2 H, *J* = 3.5 Hz), 4.72 (d, 2 H, *J* = 8.1 Hz), 5.18 (d, 2 H, *J* = 3.5 Hz), 7.07-7.35 (m, 20 H); δ_C 70.8, 73.9, 87.3, 87.8, 126.4, 127.8, 128.0, 128.3, 128.6, 138.2, 139.1; CIMS: *m/z* (%) 463 (11), 238 (100), 226 (30); Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.35; H, 6.32; N, 5.91.

Bis[(4*S*,5*R*)-4-methyl-5-phenyloxazolidin-3-yl]methane (3q)[7,15,18,19,21]

mp 98 °C; CIMS: *m/z* (%) 339 (4), 176 (100), 164 (20); other data as in the literature.[7,15,21]

Bis[(4*R*,5*R*)-4-methyl-5-phenyloxazolidin-3-yl]methane (3r)

oil, purified by repeated flash chromatography (EtOAc/cyclohexane 1/9); $[\alpha]_D^{21}$ = –89° (*c* = 1.06, $CHCl_3$); δ_H 1.24 (d, 6 H, *J* = 6.4 Hz), 2.82 (qd, 2 H, *J* = 6.4, 7.2 Hz), 3.52 (s, 2 H), 4.41 (d, 2 H, *J* = 7.2 Hz), 4.68 (d, 2 H, *J* = 5.1 Hz), 4.73 (d, 2 H, *J* = 5.1 Hz), 7.26-7.39 (m, 10 H); δ_C 17.2, 65.3, 73.2, 85.7, 86.2, 126.0, 127.7, 128.5, 140.7; CIMS: *m/z* (%) 339 (11), 176 (100), 164 (22); Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.44; H, 7.53; N, 7.98.

Bis[(4*S*,5*R*)-3-aza-1-oxabenzocyclopentyl[1,2-*d*]cyclopentan-3-yl]methane (3s)[3b,7]

mp 191 °C; CIMS: *m/z* (%) 335 (12), 174 (100), 162 (8); other data as in the literature.[3b,7]

Bis[(*R*)-4-phenyloxazolidin-3-yl]methane (3v)[7,15,16,20]

We have already reported on this compound.[16,20] CIMS: *m/z* (%) 311 (7), 162 (100), 150 (84); other data as in the literature.[7,15,20]

Bis[(*S*)-4-methyl-4-phenyloxazolidin-3-yl]methane (3z)

oil obtained after flash chromatography (EtOAc/cyclohexane 1/4); δ_H 1.30 (s, 6 H), 3.16 (s, 2 H), 3.69 (d, 2 H, *J* = 4.7 Hz), 3.71 (d, 2 H, *J* = 4.7 Hz), 4.34 (d, 2 H, *J* = 2.6 Hz), 4.96 (d, 2 H, *J* = 2.6 Hz), 7.17-7.47 (m, 10 H); δ_C 17.3, 60.8, 63.9, 81.2, 85.5, 126.5, 127.3, 128.4, 143.4; CIMS: *m/z* (%) 339 (8), 176 (100), 164 (20); Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.44; H, 7.53; N, 7.98.

(4*S*,5*S*,9*S*,10*S*)-5,5a,13,13a-Hexahydrodiindeno[1,2-*d*:1'2'-*i*]-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4t)[3b]

mp 210 °C (EtOAc/cyclohexane); $[\alpha]_D^{21}$ = +283° (*c* = 0.84, CH_2Cl_2); δ_H 2.97 (dd, 2 H, *J* = 9.8, 14.6 Hz), 3.10 (dd, 2 H, *J* = 7.3, 14.6 Hz), 4.36 (td, 2 H, *J* = 7.3, 9.7 Hz), 4.55 (d, 2 H, *J* = 11.2 Hz), 4.63 (s, 2 H), 4.67 (d, 2 H, *J* = 9.6 Hz), 4.90 (d, 2 H, *J* = 11.2 Hz), 7.15-7.23 (m, 8 H); δ_C 36.3, 67.4, 72.1, 85.3, 87.0, 122.5, 124.7, 127.1, 127.3, 138.1, 142.5; CIMS: *m/z* (%) 335 (100), 162 (7); Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.75; H, 6.46; N, 8.01.

(4*RS*,5*RS*,9*RS*,10*RS*)-(4,5),(9,10)-Bis(tetramethylene)-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4u)[3a]

mp 153 °C ; CIMS: *m/z* (%) 267 (100); other data as in the literature.[3a]

(5*R*,10*R*)-5,10-Diphenyl-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4v)[7,12,15,16]

We have already reported on this compound.[12,16] CIMS: *m/z* (%) 311 (100), 162 (16), 150 (1); other data as in the literature.[7,12,15]

(5*S*,10*S*)-5,10-Bis(4-fluorophenyl)-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4w)

Isolated by repeated crystallisation from cyclohexane. mp 198 °C (cyclohexane); δ_H 3.79 (d, 4 H, *J* = 4.6 Hz), 4.13 (s, 4 H), 4.55 (dd, 2 H, *J* = 4.8, 7.1 Hz), 4.77 (s, 2 H), 6.98 (t, 4 H, *J* = 8.4 Hz), 7.35 (t, 4 H, *J* = 8.2 Hz); δ_C 65.2, 71.1, 74.5, 86.2, 115.4 (d, *J* = 19.8 Hz), 129.0 (d, *J* = 7.5 Hz), 137.1, 162.4 (d, *J* = 216 Hz); CIMS: *m/z* (%) 347 (100), 180 (17), 168 (8).

(5*R*,10*R*)-5,10-Bis(4-methoxyphenyl)-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4x)

Isolated after flash chromatography (EtOAc/cyclohexene 1/4). mp 203 °C (EtOAc/cyclohexane); $[\alpha]_D^{22}$ = –121° (*c* = 1.02, CH_2Cl_2); δ_H 3.80 (s, 6 H), 3.84 (m, 4 H), 4.18 (s, 4 H), 4.55 (dd, 2 H, *J* = 4.4, 8.4 Hz), 4.80 (s, 2 H), 6.86 (d, 4 H, *J* = 8.7 Hz), 7.32 (d, 4 H, *J* = 8.7 Hz); δ_C 55.4, 65.3, 71.1, 74.6, 86.2, 114.0, 128.6, 128.7, 121.7; CIMS: *m/z* (%) 371 (100), 192 (11); Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.92; H, 7.07; N, 7.31.

(5*R*,10*R*)-5,10-Bis(4-phenylphenyl)-1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane (4y)

Isolated after flash chromatography (EtOAc/cyclohexene 1/1). mp 202 °C (EtOAc/cyclohexane); δ_H 3.94 (d, 4 H, *J* = 6.3 Hz), 4.26 (s, 4 H), 4.68 (t, 2 H, *J* = 6.2 Hz), 4.91 (s, 2 H), 7.32-7.61 (m, 18 H); δ_C 65.7, 71.1, 74.6, 86.4, 127.2, 127.4, 128.1, 128.9, 132.6, 140.7; CIMS: *m/z* (%) 463 (100), 238 (16), 226 (13); Anal. Calcd for $C_{31}H_{30}N_2O_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.02; H, 6.53; N, 5.77.

X-Ray diffraction study on compound 3o.

Data were collected on a Siemens *P*3 diffractometer, using graphite-monochromated Mo-K_α radiation. Unit cell parameters: a = 8.750 Å, b = 5.661 Å, c = 25.673 Å, α = 90.00°, β = 106.26°, γ = 90.00°, V = 1220.7 Å^3, Z = 4, space group *A*2. The structure was solved from 956 reflections in accord with $I > 2\sigma(I)$ using SIR97, and refined with SHELXL97. The molecule was drawn (Figure 2) using CAMERON. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as document CCDC-226084.

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