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One-step synthesis of a new heterocyclophane family

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ABSTRACT

New macrocyclic compounds having two benzoxazine subunits joined by two ethylene bridges have been prepared by Mannich condensation of the appropriate 4-hydroxyphenylethylamine with an excess of formaldehyde. This is a general method for synthesising a new family of heterocyclophanes.

The Pictet–Spengler reaction involves adding an aldehyde to a phenylethylamine to form an iminium ion; this electrophile is suitable for aromatic substitution and ring-closure.[1–4]

During the course of our research, the L-tyrosine ethyl ester (ethyl (*S*)-2-amino-3-(4-hydroxyphenyl)propanoate) **1a** reaction was carried out with some carbonyl compounds (such as 4-methoxybenzaldehyde acetophenone and formaldehyde); this was directed towards obtaining new isoquinoline alkaloids which might be potentially useful in controlling plague insects and extending the usefulness of the Pictet–Spengler reaction in obtaining isoquinolines with substituents at carbon position 3.

The 4-methoxybenzaldehyde and benzophenone reaction led to hydrolysis of the starting ester and to the formation of resinous and insoluble compounds, which could not be characterised. The reaction with formaldehyde in aqueous medium presented a different pattern, and led to the formation of a new cyclophane produced by condensing two L-tyrosine ethyl ester units with four of formaldehyde.

The results showed that when the phenylethylamine being used has a hydroxyl group at aromatic ring carbon position 4, then the reaction with formaldehyde leads to a new pentacyclic product containing two 3,4-dihydro-2*H*-1,3-benzoxazine units joined by two ethylene bridges forming the (5*S*,14*S*)-5,14-diethoxycarbonyl-2,11-dioxa-4,13-diazapentacyclo[11.5.3.3.^{4,16}0.^{10,23}0.^{1,20}]tetracosa-1(18),7,9,16,20,23-hexaene **2a** (Scheme 1).

This new cyclophane **2a** was isolated as an amorphous solid (88–90 °C mp). Its EIMS (*m*/*z* 466.24) suggested a $C_{26}H_{30}N_2O_6$ molecular formula. Cyclophane **2a** structure was unambiguously determined by 1D (^{1}H, ^{13}C) and 2D (COSY, HMQC, HMBC, NOESY) NMR spectroscopy and mass spectrometry.

The ^{1}H NMR spectrum for **2a** revealed a 1,2,4-trisubstituted ring and ethyl ester group signals in the aromatic region, a hydrogen signal at carbon α and diasterotopic hydrogen signal in the aliphatic region. Differently to the starting ester, no different displacements for diasterotopic hydrogens were observed in **2a;** four signals originated by N–CH_2–ph and N–CH_2–O– units were observed (Fig. 1).

The simplicity of ^{1}H and ^{13}C NMR spectra in $CDCl_3$ indicated the molecule's high symmetry. Correlations in the HMBC spectrum (Fig. 2) between the hydrogen group at carbon α with carbon 2 (N–CH_2–ph) and carbon 4 (N–CH_2–ph) from the benzoxazine unit confirmed obtaining a macrocyclic molecule formed by two L-tyrosine units produced by Mannich condensation with four formaldehyde molecules.[5,6]

The NOESY spectrum showed correlations between the hydrogen group at carbon α with hydrogens from the NCH_2Ph group, the NCH_2O group and aromatic hydrogen group in benzoxazine unit position 5. NCH_2Ph group hydrogen correlated with aromatic hydrogen in position 5. The foregoing correlations led to conclude that **2a** is a cyclophane compound where the two benzoxazine nuclei were found in parallel. This formation was corroborated by the couplings between benzyl hydrogens with NCH_2Ph and NCH_2O groups, couplings which can only be present if the hydrogen atom of chiral carbon is in a pseudo-axial position and the ethyloxycarbonyl group in a pseudo-equatorial position (Fig. 3).

A doublet was observed at 1.21 ppm in the ^{1}H NMR spectrum of **2a** originated by the methyl groups in the isopropyl alcohol molecule. A methyne hydrogen signal was not observed due to overlapping with signals from **2a**; the presence of isopropyl alcohol was probably due to a host–guest interaction between the cyclophane so obtained and the solvent used for the reaction (Fig. 4a). Two signals at 1.01 and 1.27 ppm corresponding to methyls from the ethyloxycarbonyl group were also observed in this spectrum (Fig. 4a). These hydrogens correlated with a single carbon at 13.9 ppm in the HMQC spectrum, indicating that only methyl hydrogens are found in different settings, possibly by conformational equilibrium.

Variable-temperature ^{1}H NMR experiments (35 °C and 50 °C) for **2a** in $CDCl_3$ were carried out for observing possible conformational changes. No changes regarding Figure 4a were observed in these spectra. A sample was later subjected to heating at a temperature higher than its fusion point (100 °C) for 6 h; partial disappearance of the isopropyl alcohol signal in ^{1}H NMR was observed, but the general spectroscope pattern showed no changes

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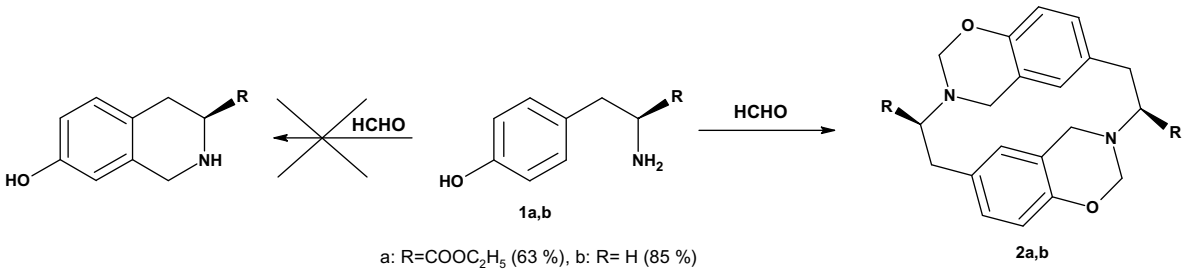

Scheme 1. 4-Hydroxyphenylethylamine reaction with formaldehyde.

(Fig. 4b). This experiment showed high stability of **2a** at temperatures higher than its fusion point, and no evidence of conformational changes was observed.

The reaction between tyramine **1b** and formaldehyde was carried out in the same experimental conditions, aimed at extending this reaction for synthesising new heterocyclic systems of interest in supramolecular chemistry. This reaction presented a similar pattern and produced the respective cyclophane **2b** having high yields (204–208 °C mp (with decomposition)) (Fig. 5). The presence of the solvent used for the reaction in **2b** was not observed, differently to **2a**.

1a initially reacted with formaldehyde in the usual Pictet–Spengler condensation conditions in isopropyl alcohol as dissolvent and 10% acetic acid. An insoluble resinous mixture and a small amount of **2a** (5–6%) was obtained in these conditions; **2a** was obtained with good yield when the reaction was carried out in basic media by adding a small amount of NaOH. Such cyclisation was probably favoured by the amphoterous nature of the starting reagent, since this would lead to interactions via hydrogen bonds allowing molecule organisation forming a template, thereby impeding condensation of lineal products.

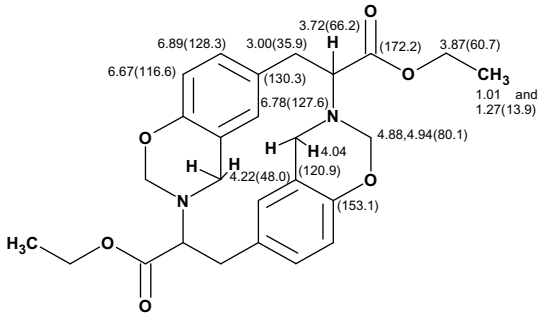

Figure 1. ^{1}H NMR (^{13}C) ppm spectroscopic data for **2a** in $CDCl_3$.

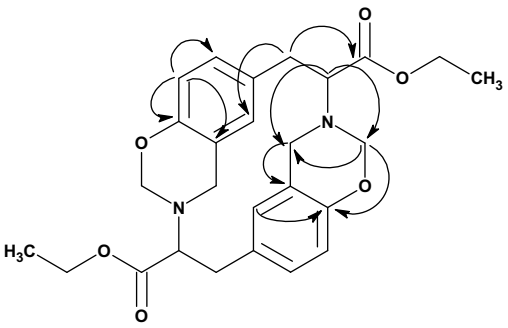

Figure 2. Selected key **2a** HMBC correlations (H→C).

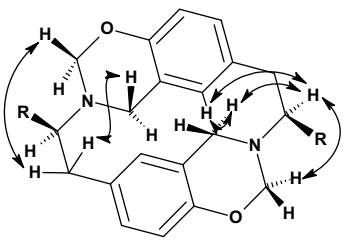

Figure 3. Selected key **2a** NOESY correlations.

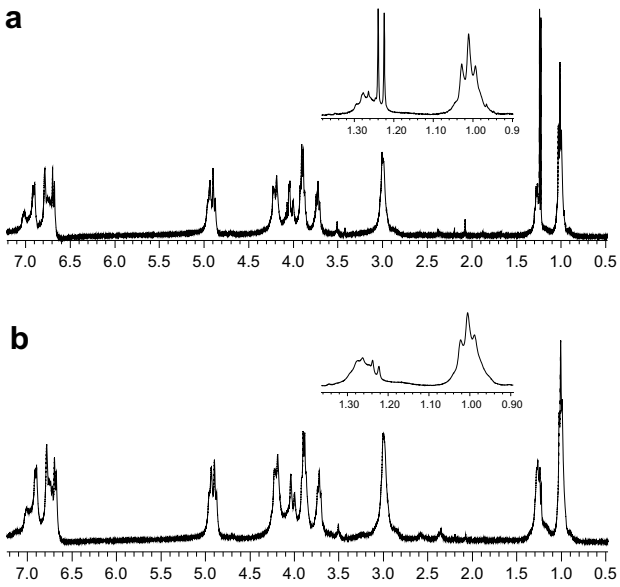

Figure 4. (a) ^{1}H NMR spectra in $CDCl_3$ for **2a**, (b) ^{1}H NMR spectra in $CDCl_3$ for **2a** after heating at 100 °C.

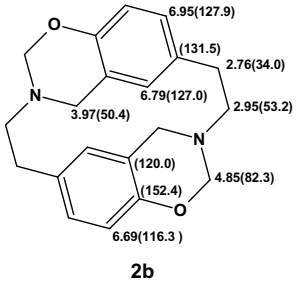

Figure 5. ^{1}H NMR (^{13}C) ppm spectroscopic data for **2b** in $CDCl_3$.

This work has thus presented the synthesis of a new family of cyclophanes in a single step by means of Mannich-type condensation between tyrosine derivates and formaldehyde. This is a novel application of the Mannich reaction with phenols for obtaining new heterocyclophanes having good yields; this method has several advantages, such as its easy preparation, easy handling, stability, easy recovery, readily available starting materials, high yield and operational simplicity.

Typical procedure for heterocyclophane synthesis: 37% formaldehyde in excess and a few drops of 5% KOH were added to 4-hydroxyphenylethylamine dissolved in isopropyl alcohol. The resulting mixture was shaken for 3 h; once this time had elapsed, the dissolvent was evaporated, and the solid so obtained was suspended in water, filtered and washed with ethanol.

Spectroscopic data of ethyl (S)-2-amino-3-(4-hydroxyphenyl)propanoate ***1a****:*

^{1}H NMR (MeOD): 1.3 (3H, t, *J* = 7.2 Hz), 2,8 (1H, *c*, J = 7.6 Hz), 3.0 (1H, c, *J* = 8.7), 3.7 (1H, c, *J* = 5.2 Hz), 4.2 (2H, c, *J* = 7.24 Hz), 6.7 (2H, d, *J* = 8.5), 7.0 (2H, d, *J* = 8.48).

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