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SYNTHESIS OF GALANTHAMINE: INTRAMOLECULAR PARA-ORTHO-COUPLING OF DIARYL ETHERS BY ANODIC OXIDATION.

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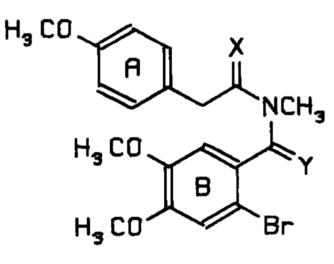
Abstract: Intramolecular para-ortho-coupling of the amide **4** to **7** was achieved by anodic oxidation in acetonitrile solution (containing 2% of methanol) in eighty % yield.

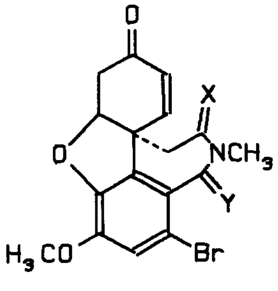
As is known from literature[1] the potential-controlled anodic oxidation of diaryl compounds containing an amide group in the bridge connecting the two aromatic rings which may be further substituted by methoxy groups takes place only then intramolecularly if the amide moiety is tertiary, otherwise intermolecular coupling is observed. The coupling occurs most probably by an "e.e.c."-mechanism[2,3]. Whether intramolecular coupling or intermolecular dimerization occurs depends not only on the electronic properties of the two substituted rings but also on the possibility to adopt a favourable geometry in the transition state. In this way e.g. Kotani et al.[4] obtained high yields during a para-para cyclization step in the synthesis of rac. oxomaritidine.

As already reported[5] we could achieve para-ortho coupling with the amides **1a** or **1b**; the p-position to the one methoxy group was blocked by Br in order to direct the bond formation at ring B into the o-position, obtaining thus a mixture of rac. enones **2a** or **2b** and **3a** or **3b**, in which the unstable dienones **3a** or **3b** dominated; the enones **2a** or **2b** were isolated only in minute amounts.

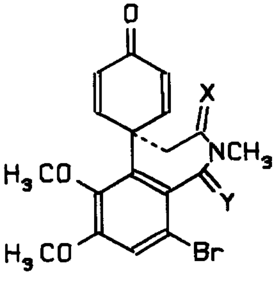
Taking into account the aforementioned factors we modified the structure of the starting material for the electrochemical oxidation and report here on the cyclization of **4**. Ring A contains still the methoxy group which is para-directing, and stabilizes best intermediate radical cations. In ring B the directing methoxy group has been replaced by the similarly acting benzoyloxy grouping which after the cyclization can very easily be transformed into the phenolic OH which later forms the ether bridge in these alkaloids. In order to be independent on any E/Z equilibrium the oxofunction was eliminated from the connecting chain and the trifluoroacetate of a secondary amine is used instead.



1a X = H_2, Y = O
1b X = O, Y = H_2



2a X = H_2, Y = O
2b X = O, Y = H_2



3a X = H_2, Y = O
3b X = O, Y = H_2

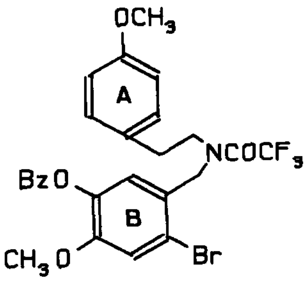
Preparative runs with 500 mg (0.9 mmol) **1a** were electrolyzed in a three-compartment-cell with a platinum gauze (19.6 cm²) as anode and a platinum sheet (3.1 cm²) as cathode with currents of 45 to 8 mA at 0° C. As solvent had to be used acetonitrile containing 2% of methanol, the solution was 0.01 molar in **1a.** The supporting electrolyte was dry lithium perchlorate in 0.1 molar concentration, and finely powdered sodium carbonate was added to avoid acidic conditions which would cause apogalanthamine rearrangement of the coupled product. The working potential of the anode was maintained at 1.15 V with reference to an Ag-electrode in 0.1 molar solution of $AgNO_3$ in acetonitrile.

The yield of oily endproduct **7** was 80% after purification by filtration through a short column of silicagel. Its structure was determined by spectroscopic methods. From the FD-MS ($M^{+\cdot}$ at 611 and 613 mu and from isotope pattern) the elemental composition follows as $C_{28}H_{29}BrF_3NO_6$; the presence of traces of compounds with higher relative molar mass was, however, also indicated.

The IR spectrum shows in the carbonyl region only the band for the trifluoroacetate but not for a crossed conjugated dienone; in the ^1H NMR spectrum only one single aromatic proton signal is visible besides signals of four methyl, three methylene and one phenyl group, one proton at C-10 and an AB-quartet integrating for altogether four olefinic protons. From this information follows that the expected coupling had indeed taken place and that the carbonyl of the dienone moiety had been transformed into its dimethyl acetal. The same information is evident from the ^{13}C NMR spectrum of **7** if one counts the number of signals corresponding to sp^2 hybridized methine carbons.

Besides the ring coupling an additional methoxy group must have been introduced into the molecule during the anodic oxidation. Its position is at C-10 (the C atom between the nitrogen and ring B) as can be deduced from the position of the signal of its geminal proton and from its form as a singlet as well as from the corresponding ^{13}C signal. It should be noted that the ^{13}C signals have been assigned unambiguously by selective ^1H decoupling. Since **7** is actually a mixture of two epimeric methoxy derivatives at C-10 the NMR spectra are superpositions of two similar spectra for both nuclei, one for each stereomer.

The following mechanism is proposed for the electrochemical coupling process, which also takes into account the important role of the methanol. The first step may be the abstraction of one electron from ring A leading to a radical cation, which suffers nucleophilic attack by methanol at C-4 and concomitant loss of a proton; a second electron is then abstracted from ring B ("e.e.c."-mechanism) leading to the cyclized ion **5** which loses again a proton. At which stage the extra methoxy group is introduced cannot be deduced from the isolation of the endproduct **7**. The formation of this compound is, however, evidence for the existence of another active centre against anodic oxidation under the conditions used by us, namely the benzylic methylene C-10 connected to the amide moiety.



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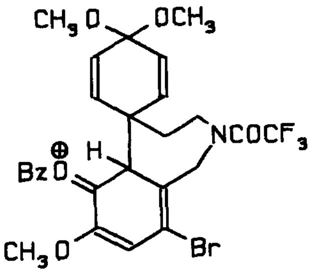

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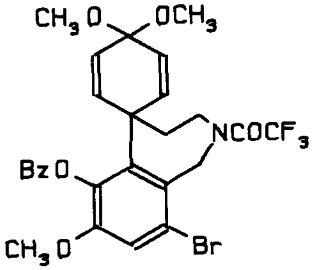

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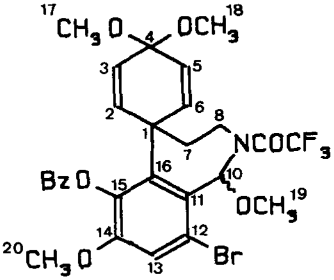

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Spectral data of 7. IR: 1690 cm^{-1} (C=O st). - ^{1}H NMR: δ = 7.30 -7.35 (m, 5H), 6.85 and 7.09 (two AB-quartets, H-2/H-6 and H-3/H-5), 6.48 (2s, 1H, H-13 of E/Z-mixture), 5.63 and 5.79 (2s, 1H, H-10), 4.72 (m, 2H, $PhC\underline{H}_2$), 3.80 (s, 3H, methyl C-20), 3.51 (m, 2H, methylene C-8), 3.38 - 3.48 (4s, 9H, methyls C-17, C-18, C-19), 2.83 (m, 2H, methylene C-7). - ^{13}C NMR: δ = 138.8 (s), 128.3 (d), 127.4 (d), 127.2 (d) (C_6H_5), 133.4/133.2 (d, C-13 of E/Z-mixture), 131.7, 131.2, 130.2, 129.0, 128.8 (all s, C-11, C-12, C-14 - C-16), 129.8/129.7 (d, C-3 and C-5 of E/Z-mixture), 120.2/119.5 (d, C-10 of E/Z-mixture), 114.3/114.2 (d, C-2 and C-6 of E/Z-mixture), 101.1/100.0 (s, C-4 of E/Z-mixture), 65.7/65.5 (t, C-8 of E/Z-mixture), 55.3 (q, C-20), 51.6 - 51.2 and 48.8/48.7 (q, C-17 - C-19), 49.6 (s, C-1), 34.6/32.1 (t, C-7 of E/Z-mixture).

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