Short Communication

Electrochemical Reduction of a 5*H*-2,3-Benzodiazepine

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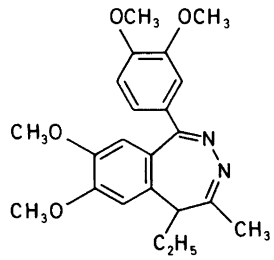
7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine (**1**) (Tofisopam®) may be determined polarographically in slightly acidic solution.[1] The electrode reaction consumes four electrons per molecule and the product has been suggested to be a 1,2,3,4-tetrahydro derivative of **1**.[1]

A 2,3-benzodiazepine may be regarded as an unsymmetrical azine of a derivative of benzophenone and an aliphatic ketone. It is generally found that compounds of the type RR'C=N–Y, where Y is a heteroatom, are reduced in aqueous acidic solution after protonation with cleavage of the N–Y bond followed by saturation of the carbon–nitrogen double bond.[2,3] In most cases the compounds give a single 4-electron polarographic wave, but in some cases[4] two two-electron waves are observed; it has been shown that the first reduction in the latter cases involves cleavage of the N–Y bond.

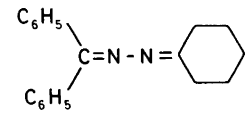
The electrode reaction suggested for **1** would be an exception from the general behaviour of such azomethine compounds, and the electrochemical reduction of **1** and of a model compound, benzophenone cyclohexanone azine (**2**), under different conditions was therefore undertaken.

Results and discussion

Polarography of **2** in 40 % aqueous DMF at pH 1 gave two two-electron waves, at $E_{1/2}(1) = -0.55$ V (SCE) and $E_{1/2}(2) = -0.70$ V. The polarograms were run immediately after mixing of the stock solution with the supporting electrolyte to avoid acid hydrolysis of the compound. At pH 5 a single 4-electron wave was observed, and a preparative reduction consumed approximately 4 F mol^{-1} and gave benzhydrylamine and cyclohexanone. These results may be explained on the basis of the general behaviour of such compounds;[2,3] cyclohexanone imine is not reducible at the potential used for the reduction, and is hydrolyzed to cyclohexanone and ammonia.



1



2

At higher pH the wave for the protonated compound disappears and a wave close to that for the reduction of the supporting electrolyte was observed; however, the electrode reaction was not investigated. Attempts to establish the nature of the first wave at low pH failed for two reasons: at higher concentrations the two waves for **2** coalesced and the acid hydrolysis was too fast for reliable results to be obtained.

Compound **1** was reduced in 0.2 M hydrochloric acid (pH = 0.8), with $n = 4.3$. After the reduction the catholyte was treated with an excess of potassium hexacyanoferrate(III) to ox-

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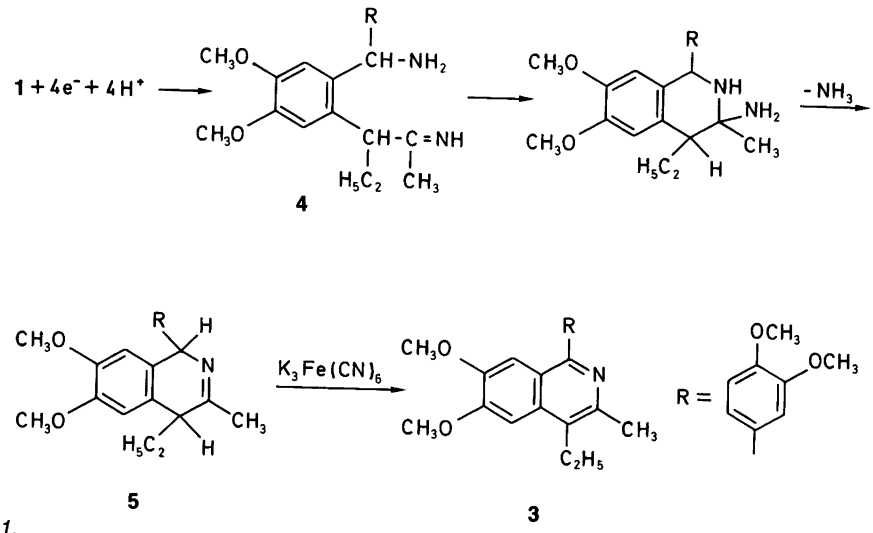
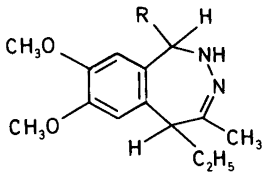


Scheme 1.

idize a possible tetrahydro derivative of **1** to **1** and any dihydro heterocyclic compounds to the aromatic derivatives. During the oxidation a product precipitated and extraction produced a further crop; the combined yield was 74 %. The product was assigned the structure 4-ethyl-3-methyl-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)isoquinoline (**3**). The compound is proposed to be formed by the route shown in Scheme 1.

The first step is assumed to be two-electron cleavage of the nitrogen–nitrogen bond; of the two azomethine groups, that corresponding to the derivative of benzophenone imine is reducible and compound **4** is formed; the aliphatic imine is not reducible at the potential employed. Attack of the amine on the aliphatic imine (or ketone, if the imine is hydrolyzed) followed by loss of ammonia (water) gives the dihydroisoquinoline **5**, or one of its isomers. Oxidation of **5** produces the isolated compound **3**. The formation of **3** on reduction of **1** is thus analogous to the reduction of cinnolines to indoles,[5] phthalazines to isoindoles,[6] and pyridazines to pyrroles.[7]



6

In DMF, **1** gave an irreversible peak at −1.85 V (vs. Ag/AgI, 0.1 M I^-); reduction of **1** in DMF in the presence of phenol as proton donor gave a product mixture which according to the MS and ^{1}H NMR spectrum mainly consisted of a 5:2 mixture of two diastereomers (α and β) of 1,2-dihydro-7,8-dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine (**6**); one of the diastereomers has the 5-ethyl group and the 1-(3,4-dimethoxyphenyl) group *cis*, and the other one has the groups *trans*; an assignment of *cis* and *trans* to the isomers has not been made.

The reduction of **1** to **6** is analogous to the reduction of benzalazine to benzaldehyde benzylhydrazone in alkaline solution;[2] **6** may be regarded as a benzhydrylhydrazone of an aliphatic ketone. The reduction of the conjugated C(1)–N(2) double bond in preference to the unconjugated C(4)–N(3) double bond is in accordance with the reduction of **2** in DMF to the benzhydrylhydrazone of cyclohexanone.

It can thus be concluded that **1** behaves as an unsymmetrical azine; it might be expected that other 5*H*-2,3-benzodiazepines will behave similarly.

Experimental

Apparatus. The NMR spectra were recorded on a Varian XL-300 spectrometer, and MS spectra were obtained with a Micromass 7070 F instrument.

Materials. Tofisopam was a gift from Egis Pharmaceuticals, Budapest, Hungary. Benzophenone cyclohexanone azine (**2**) was prepared by dissolving benzophenone hydrazone and cyclohexanone in methanol containing a few drops of acetic acid. After several hours the precipitate was filtered off and recrystallized from methanol; m.p. 79–80 °C.

Reduction of **1** *in dilute hydrochloric acid.* Tofisopam (0.5 g) was reduced in 0.2 M hydrochloric acid (80 ml) containing 0.5 M potassium chloride at −1.2 V (vs. SCE), with $n = 4.3$. The reduction completed, an excess of potassium hexacyanoferrate(III) (1 g) was added and the solution heated to boiling for 10 min. After cooling, the solution was extracted with 50 ml of a 20:1 mixture of diethyl ether and 2-propanol to remove any non-basic product; the organic phase did not extract any material. The aqueous phase was made alkaline, and on addition of a mixture of diethyl ether and 2-propanol (20:1) a precipitate (**A**) was formed which was filtered off. The organic phase was dried (A4 molecular sieves) and evaporated, leaving a slightly impure crop of product **A**; combined yield 74 %. ^{1}H NMR: δ 1.227 (3H, t, *J* 7.5 Hz), 2.632 (3H, s), 2.954 (2H, q, *J* 7.5 Hz), 3.760 (3H, s), 3.833 (3H, s), 3.866 (3H, s), 3.969 (3H, s), 6.908 (1H, d, *J* 8.67 Hz), 7.11–7.14 (3H, m), 7.27 (1H, s). MS [70 eV, *m/e*(%)]: 367 (3.7), 352 (34), 336 (15), 321 (11), 202 (21), 201 (14), 200 (16), 199 (16), 166 (47), 149 (73).

Reduction of **1** *in DMF.* Tofisopam (0.50 g, 1.3 mmol) was reduced in 60 ml of DMF/0.10 M TBAI containing an excess of phenol (5 mmol) at −1.85 V (vs. Ag/AgI, 0.1 M I^-); the reduction consumed 2.1 F mol^{-1}. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether which was then washed with 0.1 M sodium hydroxide to remove the phenol, with 0.01 M hydrochloric acid and finally with phosphate buffer (pH 7). The organic layer was dried and the solvent removed. The ^{1}H NMR spectrum of the residue showed the presence of a 5:2 mixture of two diastereomeric 1,2-dihydro-7,8-dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5*H*-2,3-benzodiazepines. α-Isomer: ^{1}H NMR ($CDCl_3$): δ 1.06 (3H, t, *J* 7.5 Hz), 2.08 (3H, s), 2.20 (1H, m, *J* 7.5 Hz), 2.75 (1H, m, *J* 7.5 Hz), 3.23 (1H, dd, *J* 7.6, 7.4 Hz), 3.57 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 4.53 (2H, s), 5.09 (1H, s), 6.20 (1H, s), 6.55 (1H, s), 6.81 (1H, d, *J* 1.93 Hz), 6.86 (1H, s), 6.90 (1H, d, *J* 1.92 Hz). The chiral centre at C(5) caused the appearance of two signals from the methylene protons at δ 2.20 and 2.75; no attempts have been made to extract the geminal coupling constant from the multiplet. ^{13}C NMR ($CDCl_3$): δ 12.72 (Et−CH_3), 26.04 (4-CH_3), 27.71 (CH_2), 55.02 (5-CH), 55.45, 55.55, 55.57, 55.59 (4 × OCH_3), 64.06 (1-CH), 110.64, 111.82, 112.96, 113.07, 121.25, 128.50, 132.79, 135.93, 146.94, 147.00, 148.33, 148.76 (12 arom. C), 169.15 (C4). Ms [70 eV, *m/e* (%)]: 384 (21), 383 (66), 354 (31), 325 (25), 247 (27), 246 (100), 217 (12), 151 (16).

The assignment of the spectrum of the β-isomer is less certain, as some of the signals are probably obscured by the lines of the major isomer. ^{1}H NMR ($CDCl_3$): δ 1.04 (3H, t, *J* 7.5 Hz), 2.00 (3H, s), (CH_2 ~ α-isomer), (5-CH ~ α-isomer), 3.63, 3.84, 3.88, 3.88 (4 × 3H, s), (2NH and 1-CH ~ α-isomer), 6.25 (1H, s), 6.63 (1H, s), (3 arom. CH ~ α-isomer).

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