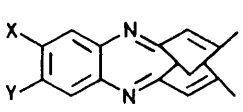
Synthesis of Substituted Barbaralanes by Electrochemical Reduction of Bridged 1,5-Benzodiazepines†

By JOHN M. MELLOR,* B. STANLEY PONS, and JOHN H. A. STIBBARD
(*Department of Chemistry, The University, Southampton* SO9 5NH)

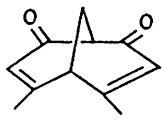
Summary Bridged 1,5-benzodiazepines, products of condensation of *o*-phenylenediamines with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione, give barbaralanes on electrochemical reduction; the mechanism of the reduction has been elucidated and the valence isomerisation of the barbaralanes has been shown by variable temperature ^{1}H n.m.r. analysis.

THE bridged 1,5-benzodiazepines (**1**) are readily available by the efficient condensation[1] of *o*-phenylenediamines with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (**2**). We report here their electrochemical reduction to give novel barbaralanes, whose structures have been investigated by variable temperature n.m.r. spectroscopy.

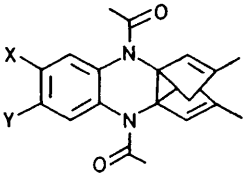


(1)

a; X = Y = H
b; X = H, Y = Cl
c; X = Y = Me
d; X = H, Y = NO_2

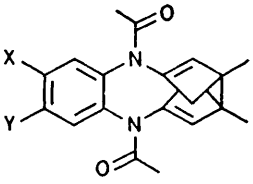


(2)



(3)

a; X = Y = H
b; X = H, Y = Cl
c; X = Y = Me



(4)

a; X = Y = H
b; X = H, Y = Cl
c; X = Y = Me

In spite of their pharmacological interest no preparative electrochemical and only limited polarographic studies[2] have been made with 1,5-benzodiazepines. By contrast, the reductive acylation of quinoxaline with acetic anhydride[3] to give *NN'*-diacetyldihydroquinoxalines and the more recent reductive alkylation of phenazine to give 5,10-dihydro-5,10-dialkylphenazines[4] are well described.

Reduction of the benzodiazepine (**1a**) in acetonitrile at −2·35 V with passage of 2·3 Faradays per mole, and a conventional work up afforded the diamide (**3a**) isolated by preparative t.l.c. in 40% yield. The two possible barbaralane structures (**3a**) and (**4a**) were considered on the basis of microanalytical data, mass spectroscopy (M^+ 334), and i.r. spectroscopy (ν_{max} 1665 cm^{-1}). The ^{1}H n.m.r. spectrum at +100 °C in hexachlorobutadiene had resonances at τ 2·56 (2H), 2·96 (2H), 4·69 (2H), 7·47 (1H), 7·60 (1H), 7·80 (6H), 8·16 (6H), and 8·60 (2H), which established that the product had a symmetry plane. From the above chemical shift data the equilibrium between (**3a**) and (**4a**) lies heavily in favour of (**3a**). In particular the methyl resonances (τ 8·16) are in good agreement with the value (τ 8·21) observed[5] in methylsemibullvalene. Models show that structure (**3a**) is much less strained than structure (**4a**). The preference for structure (**3a**) accords well with related equilibria[6] in extended semibullvalenes.

Similar reductions of (**1b**) and (**1c**) afforded (**3b**) and (**3c**) in 45 and 88% yields respectively, based on recovered starting materials. Structures were assigned on similar spectroscopic evidence. At lower temperatures both ^{1}H and ^{13}C n.m.r. spectra of the series (**3a**—**c**) are highly complex. At ambient temperatures in addition to possible isomerisation by divinylcyclopropane rearrangement characteristic of barbaralanes, restricted rotation associated with the amide groups increases the conformational complexity. As expected a multiplicity of signals associated with the amide methyl groups is observed at −90 °C in CS_2. The coalescence temperatures (T_c *ca.* 50 °C) are in good agreement[7] with data for other heterocyclic amides. At +100 °C the conformational complexities associated with hindered amide rotation are removed, and although this temperature is well above that required to equilibrate (**3**) and (**4**) by rearrangement, only the spectrum of (**3**) is observed. The contribution of (**4**) to the time-averaged spectrum is low because of its low thermodynamic stability relative to (**3**).

TABLE. Cyclic voltammetry data for the benzodiazepines (**1a**—**c**) and related compounds in MeCN

Compound	Reduction wave $E_{p/2}$/V[a]	First reverse oxidation wave	Second reverse oxidation wave
(**1a**)	−2·42	−2·34	−0·99
(**1b**)	−2·38	−2·22	−1·11
(**1c**)	−2·54	−2·46	−1·03
(**1d**)	−1·51[b] and −2·26	−1·35	−0·56 and −1·11[b]
Phenazine[c]	−1·60 and −2·41	—	—

[a] Sweep rate 0·1 V s^{-1}; [substrate] 10 mM; electrolyte Bu_4NBF_4; reference 10^{-2} M-$AgNO_3$–Ag; platinum electrode. [b] Extra waves associated with reduction of nitro-group. [c] See ref. 4.

In the case of the only 1,5-benzodiazepines studied polarographically[2] proton transfer steps complicating the analysis are readily envisaged. Indeed the paucity of data concerning the electrochemistry of 1,5-benzodiazepines has been attributed[8] 'to their relative instability in aqueous

† No reprints available.

solution which makes it difficult to determine whether observed values are due to the compound under examination or to decomposition products.' Although (**1a**—**c**) are 3*H*-1,5-benzodiazepines, similar proton transfers from the 3-position are improbable (Bredt's rule) and hence reduction of a single tautomer is expected. Comparison of the position of the reduction wave with that for phenazine (Table) and of the number of electrons passed in the first wave [1 for phenazine and 2 for (**1a**) determined by chronoamperometry relative to phenazine] is interesting. For phenazine reduction at a lower potential leads to a stable radical anion which is further reduced only at a more cathodic potential. For (**1a**) no such stable radical anion is observed. The electrochemical behaviour resembles more that of a Schiff's base where the separation between first and second reduction waves is small (*e.g.* benzylideneaniline[9] with waves at −2·15 and −2·35 V in dimethylformamide).

The successful application of reductive acylation to formation of novel barbaralanes (**3a**—**c**) from bridged 1,5-benzodiazepines suggests the technique might also be used more generally with non-bridged 1,5-benzodiazepines.

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