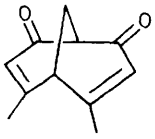
Synthesis of Substituted Barbaralanes by Electrochemical Reduction of Bridged 1,5-Benzodiazepines

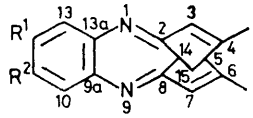
By **John M. Mellor,* B. Stanley Pons,** and **John H. A. Stibbard,** Department of Chemistry, The University, Southampton SO9 5NH

Electrochemical reduction of bridged 1,5-benzodiazepines, condensation products of *o*-phenylenediamines with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione, has been studied. Cathodic acylation of 4,6-dimethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecene (2) in the presence of acetic anhydride affords the substituted barbaralane 5,11-diacetyl-8,9-dimethyl-8,5a,10a-ethanylylidene-8*H*-cyclohepta[*b*]quinoxaline (6). Structures of the substituted barbaralanes have been established by ^{1}H n.m.r. analysis at +100 °C, at which temperature the complexities of conformational processes were avoided and the dominant valence isomers of the barbaralanes were recognised. At −2.35 V reduction proceeded in a single 2-electron wave. This behaviour is analogous to that of other Schiff bases and is contrasted with the electrochemical reduction of related heterocyclic systems.

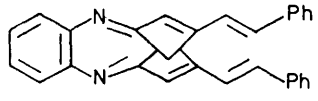
It has recently been noted [1] that in spite of extensive studies of the electrochemistry of simple heteroaromatic systems the electrochemistry of 1,5-benzodiazepines has been little studied. No product studies have been made, but limited polarographic data [2] are available for a series of simple 1,5-benzodiazepines. The electrochemistry of such 1,5-benzodiazepines may be expected to have two complicating features, at relatively low pH values the presence of mono- and di-protonated species and the possible presence of low concentrations of minor tautomeric species. We have recently described the preparation [3] of a series of bridged 1,5-benzodiazepines by condensation of *o*-phenylenediamines with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (1). These



(1)



(2) $R^1 = R^2 = H$
(3) $R^1 = H$; $R^2 = Cl$
(4) $R^1 = R^2 = Me$
(11) $R^1 = H$; $R^2 = NO_2$

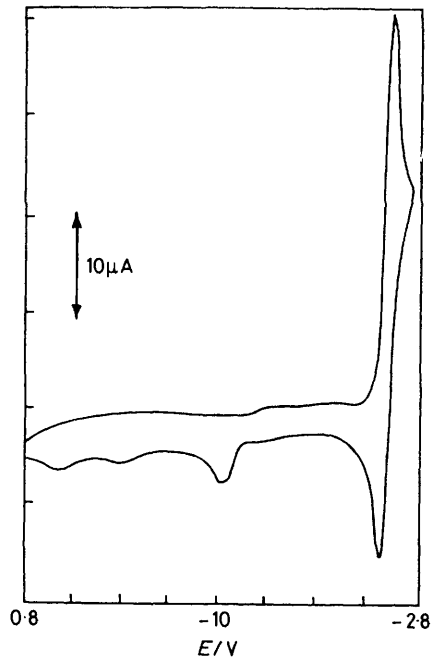


(5)

benzodiazepines, by virtue of their bridged structure are unable to tautomerise, and permit the study of the electrochemistry of the 1,5-benzodiazepine system uncomplicated by the problems of tautomerism. Here we describe the cathodic acetylation of compounds (2)—(4) to give novel barbaralanes.

RESULTS

Cyclic voltammograms were recorded for compounds (2)—(4) in acetonitrile. For each compound the first cathodic wave was observed at *ca.* 2.4 V [*versus* Ag/Ag^+ (0.01 M) electrode] (Figure). On the reverse sweep similar



Cyclic voltammogram of compound (2) in MeCN between +0.8 and −2.6 V at 0.5 V s^{-1}

behaviour was shown by compounds (2)—(4) and oxidation waves were observed at *ca.* −2.3 and −1.0 V. However faster sweep rates (20 V s^{-1}) were required to detect the reverse wave at −2.3 V for (3) than the rate (0.5 V s^{-1}) for compounds (2) or (4). Data for compounds (2)—(4) and related compounds is given in Table 1. Addition of t-butyl alcohol decreased the magnitude of the reverse wave at *ca.* −2.3 V but simultaneously increased the importance of the reverse wave at *ca.* −1.0 V. Similarly acetic anhydride quenched the reverse wave at *ca.* −2.3 V. On anodic oxidation of compounds (2)—(4) irreversible (sweep speed 20 V s^{-1}) waves were observed.

TABLE 1

Voltammetric data for benzodiazepines (2)—(5) and related compounds in MeCN

Compd.	Reduction wave $E_p^{\frac{1}{2}}$/V [a]	First reverse oxidation wave	Second reverse oxidation wave
(1)	−1.71 and −2.71	−1.61	
(2)	−2.42	−2.34	−0.99
(3)	−2.38	−2.22	−1.11
(4)	−2.54	−2.46	−1.03
(5)	−1.88 [b] and −2.36 [b]		
(11)	−1.51 [c] and −2.26	−1.35	−0.56 and −1.11 [c]
Phenazine [d]	−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] Irreversible. [c] Extra waves associated with reduction of nitro-group. [d] See D. K. Root, R. O. Pendarvis, and W. H. Smith, *J. Org. Chem.*, 1978, **43**, 778.

+100 °C. At this temperature the possible complexities are due to nitrogen inversion and restricted rotation associated with the amide groups is avoided. At +100 °C a single resonance (Ψ 7.80) is associated with the methyl groups of the amide function. Only one further signal associated with methyl groups is observed at Ψ 8.16. This defines unequivocally the product as (6a). The alternative valence isomer (6b) can be rejected on the grounds of the chemical shift observed, which is characteristic of a vinylic methyl group. The remaining signals of the spectrum of (6a) accord with this assignment. Structures were assigned to the diamides (7) and (8) in a similar manner. Features of their spectra are more fully discussed below and are shown in Table 2. ^{13}C N.m.r. data are given in Table 3 for spectra recorded at ambient temperatures. Complex spectra result from the hindered rotation.

TABLE 2

^1H N.m.r. data for cathodic reduction products (6)—(8)

Compound	Solvent * and temp. (°C)	H-8	H-6 and H-10	H-1 and H-4	H-2 and H-3	H-12	H-13	Amide Me	Me
(6)	HCBD, +100	7.47	4.69	2.56	2.96	7.60	8.60	7.80	8.18
	HCBD, +31	7.36	4.58	2.29	2.80	7.56	8.45	7.67	8.08
			4.69	2.36			8.64	7.78	
							8.70		
							8.77		
	CS_2, −90	7.48	4.62	2.47	2.80	7.54	8.42	7.68	
							8.58	7.79	8.08
							8.76	7.85	
	$CDCl_3$, +31	7.43	4.60	2.28	2.83	7.50	8.46		
				2.33			8.60	7.71	8.14
							8.74	7.82	
(7)	$CDCl_3$, +31	7.42	4.63	2.31	2.88	7.46	8.34		
				2.44			8.48	7.73	8.12
							8.60	7.86	
(8)	$CDCl_3$, +31	7.45	4.61	2.63		7.50	8.35	7.73	8.13
				3.00			8.48	7.82	
							8.62		

* HCBD = hexachlorobutadiene.

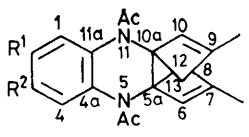
Chronoamperometric results were obtained on 5 mmol solutions of compounds and related to the behaviour of phenazine known to be reduced by successive one-electron transfers. Appropriate plots were made of I *vs* $t^{-\frac{1}{2}}$ from the I-t transient data. The gradient of the linear plot for phenazine was related to similar plots for (2), and the styryl derivative (5) obtained at the cathode potential corresponding to the first reduction wave. Similar gradients were observed for phenazine and for compound (5) and it was concluded that a single electron transfer was associated with the cathodic reduction in the first wave of compound (5). In contrast, the gradient for compound (2) indicated that two electrons were associated with the first wave reduction of (2).

Preparative electrolyses of compounds (2)—(4) and of (5) were carried out at the potential corresponding to the first reduction wave in the presence of acetic anhydride. Conventional work-up led to the isolation of products (fully described in the Experimental section) and their spectroscopic characterisation. Structural assignment for compound (6) followed from microanalytical data and observation of a parent ion in the mass spectrum at 334. Formation of a diamide was suggested by i.r. spectroscopy ($\nu_{max.}$ 1 665 cm^{-1} and absence of bands at 1 700 cm^{-1}). Although the ^1H n.m.r. spectrum was complex at ambient temperatures a much simpler spectrum of (6) was obtained at

TABLE 3

^{13}C N.m.r. data for cathodic reduction products (6)—(8)

Carbon	Compounds (6)	(7)	(8)
8	40.16	40.02	40.20
7	138.66	139.07	138.50
6	117.92, 117.02	117.52, 116.64	118.02, 117.09
5a	54.21, 54.04	52.90, 53.37	54.55, 54.30, 53.90
4a	137.29, 136.11, 134.5	136.44, 135.29, 134.57	137.16, 134.48, 133.28
4	126.00, 125.23, 124.75	126.06, 125.24, 124.77	126.78, 125.96, 125.51
3	126.00	137.56	133.82
2	126.00	125.24	133.82
1	126.00, 125.23, 124.75	126.81, 126.06, 125.24	126.78, 125.96, 125.51
11a	137.29, 136.11, 134.5	133.41, 131.18, 129.79	137.16, 134.48, 133.28
10a	54.21, 54.04	53.90, 53.37	54.55, 54.30, 53.90
10	117.92, 117.02	117.52, 116.64	118.02, 117.09
9	138.66	139.07	138.50
12	34.40, 33.90	34.35, 33.92	34.50, 34.03
13	16.77, 16.14	16.64, 15.99	16.84, 16.22
Me's	22.83	22.77	22.81
CO	171.22, 170.24	171.06, 170.25, 169.82	171.05, 170.16
Others			19.61



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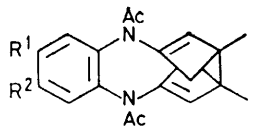
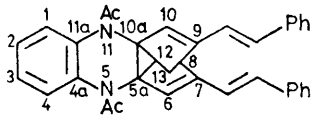


(b)

(6) $R^1 = R^2 = H$
(7) $R^1 = H$, $R^2 = Cl$
(8) $R^1 = R^2 = Me$



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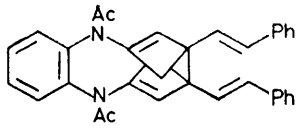

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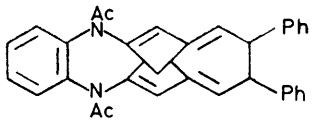

(c)

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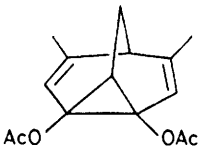

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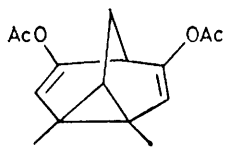

(b)

(10)

DISCUSSION

The observation [4] that the diketone (1) underwent reduction in the second cathodic wave to give a barbaralane had suggested the extension of this cathodic acylation to the 1,5-benzodiazepines (2)—(5). A reduction similar to that observed with compound (1) might lead to substituted barbaralanes (6)—(8) from compounds (2)—(4). These barbaralanes could exist either as the more conjugated isomers (6b)—(8b) or by analogy with extended simibullvalenes recently studied by Paquette *et al.*[5] as the less-conjugated and possibly less-strained isomers (6a)—(8a).

In the case of compound (5) a more complicated set of equilibria are possible in the equivalent cathodic acylation product (9). In addition to the two equilibrating barbaralane structures (9a) and (9b) a further divinylcyclopropane rearrangement can lead to formation of (9c). Formation of compound (9c) would provide an attractive route to the synthesis of benzodiaza[14]-annulenes.

Preparative cathodic acylation of (2a—c) in the first cathodic wave led smoothly to the desired barbaralanes (6)—(8) by a two-electron reduction. This behaviour contrasts markedly with the reduction of the ketone (1) where only dihydro-dimeric products were obtained in the first cathodic wave, and where reduction in the second wave was required to give barbaralane products. This distinction stems from the differing behaviour of the anion radicals. In the reduction of compound (1) in the first wave, dimerisation of the anion radical is favoured over nucleophilic attack on either solvent or acetic anhydride. In the reduction of compounds (2)—(4) two possible routes to the diamide products (6)—(8) can be envisaged. Attack by the more nucleophilic anion radicals derived from compounds (2)—(4) on either solvent or acetic anhydride can give a radical then further reduced at the potential of the first wave. Alternatively, disproportionation of the anion radical to give compounds (2)—(4) and dianions, can lead by direct acetylation to compounds (6)—(8). The reduction of imines,[6] is distinguished from that of ketones by the typical observation of two well separated one-electron waves for ketones but either a single two-electron wave or two narrowly separated one-electron waves for imines. This behaviour of imines can be explained either by an e.c.e. reaction scheme or by disproportionation. Our results with compounds (2)—(4) indicate typical imine behaviour. Although we have not distinguished between the e.c.e. or disproportionation mechanisms, the electrochemical reduction of the 1,5-benzodiazepines (2)—(4) is to be distinguished from that of phenazine and other aromatic heterocyclic systems where a one-electron first-wave reduction is typical.

The structures of the diamide products (6)—(8) from reduction of compounds (2)—(4) are most easily established by analysis of the ^1H n.m.r. spectra at +100 °C. Below this temperature the spectrum is complicated by hindered rotation associated with the amide groups. The spectrum of the diamide (6) shows that the equilibrium between compounds (6a) and (6b) lies heavily in favour of (6a). The different position of this equilibrium by comparison with the preference for (10b) in equilibration of (10a) and (10b) could be attributed to either a differing substituent effect (comparison of AcNR with AcO) or the stereochemical constraint of the fused benzene ring. Models indicate that compound (6b) is much more strained than (6a) and we therefore conclude that steric factors control the position of equilibrium in (6). We note that in some extended semibullvalene analogues [5] a similar equilibrium is observed, but since even change of remote substituents can profoundly influence the position of equilibrium, further studies are required to

determine the factors controlling the position of the equilibrium in compounds (6)—(8).

The di-imine (5) was prepared by Aldol condensation of compound (2) with benzaldehyde. Although cyclic voltammetry with compound (5) suggested no unusual features, on preparative cathodic acylation it gave a complex mixture of products from which no discrete products could be isolated. Chronoamperometry indicated that a single-electron transfer is associated with the first-reduction wave. Failure to isolate the desired compound (9) could be explained by dimerisation of the more-stable anion-radical intermediates formed from (5). Dimerisation of such a less-nucleophilic anion radical has analogy in the behaviour of the anion radical in the reduction of compound (1). However in contrast to the successful second-wave reduction of compound (1) reduction of compound (5) in the second cathodic wave failed to give products which could be identified.

EXPERIMENTAL

General experimental details were as reported in a previous paper.[4] Methods for cyclic voltammetry and chronoamperometry have been described.[4]

Preparation of Substrates.—Preparations of 4,6-dimethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecene (2), 11-chloro-4,6-dimethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecene (3), 4,6,11,12-tetramethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecene (4), 4,6-dimethyl-11-nitro-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecene (11) are described elsewhere.[3]

4,6-*Di*-(E)-*styryl*-5,2,8-*ethanylylidene*-5H-1,9-*benzodiazacycloundecene* (5).—The benzodiazacycloundecene (2) (2.03 g) and benzaldehyde (2.1 ml) were dissolved in methanol (120 ml) containing potassium hydroxide (1.22 g) in water (7 ml). The solution was heated under nitrogen under reflux for 140 h. On cooling the title compound (5) was precipitated. This was filtered off and crystallised (ethyl acetate); the product had m.p. 151—153 °C (Found: C, 87.2; H, 5.9; N, 6.4. $C_{31}H_{24}N_2$ requires C, 87.7; H, 5.7; N, 6.6%), *m/e* 424 (M^+), $\nu_{max.}$ (Nujol) 1 600 and 1 580 cm^{-1}; $\lambda_{max.}$ 243 (ε 35 000), 266 (24 000) 332 (12 700), and 390 nm (ε 35 000); τ, 2.36 (2 H, m, H-10 and H-13), 2.65 (12 H, m, other ArH), 2.82 (2 H, d, *J*, 18 Hz, H-α-styryl), 3.1br (2 H, d, *J*, 18 Hz, H-β-styryl), 3.40 (2 H, s, H-3 and H-7), 5.88 (1 H, m, H-5), 7.84 (2 H, t, *J* 3 Hz, H-15), and 8.49 (1 H, m, 14-H); ^{13}C n.m.r. (p.p.m.) 146.23 (s, C-2 and C-8), 143.04 (s, C-4 and C-6), 139.37 (s, C-9a and C-13a), 135.89 (s, C-1), 133.36 (d, C-α-styryl) 128.60 (d, C-3′, C-5′ and C-β-styryl), 128.13 (d, C-4), 127.99 (d, C-10 and C-13), 126.66 (d, C-2 and C-6), 125.00 (d, C-11 and C-12), 123.44 (d, C-3 and C-7), 39.28 (d, C-14), 33.04 (d, C-5) and 26.48 (t, C-15).

Electroreduction of the Benzodiazacycloundecene (2).—Compound (2) (248 mg) in dry acetonitrile containing acetic anhydride was reduced at −2.35 V. An initial current of 50 mA was observed, which fell after passage of 2.3 F mol^{-1} to a final current of 10 mA. Work-up by method A followed by preparative t.l.c. using ether as eluant afforded two major fractions; unchanged starting material (2) (65 mg) R_F 0.85 was recovered and at R_F 0.4 5,11-diacetyl-8,9-dimethyl-8,5a,10a-ethanylylidene-8*H*-cyclohepta[*b*]quinoxaline (6) (97 mg), m.p. 242—244 °C (Found: C, 75.2; H, 6.6; N, 8.2. $C_{21}H_{22}N_2O_2$ requires C, 75.4; H, 6.6; N, 8.4%), *m/e* 334 (M^+), $\nu_{max.}$ ($CHCl_3$) 1 665, 1 400, and 1 355 cm^{-1}; $\lambda_{max.}$ 226 (ε 15 300), 254 (9 180), and 285 nm (585); for ^{1}H and ^{13}C n.m.r. data see Tables 2 and 3.

Electroreduction of the Benzodiazacycloundecene (3).—Compound (3) (282 mg) was similarly reduced at −2.50 V. An initial current of 150 mA was observed, which fell after passage of 2.8 F mol^{-1} to a final current of 10 mA. Work-up by method A followed by preparative t.l.c. using ether as eluant afforded two major fractions; unchanged starting material (3) (69 mg) R_F 0.9 was recovered and at R_F 0.3 5,11-diacetyl-2-chloro-8,9-dimethyl-8,5a,10a-ethanylylidene-8*H*-cyclohepta[*b*]quinoxaline (7) (128 mg), m.p. 250—253 °C (Found: C, 68.2; H, 5.7; N, 7.9. $C_{21}H_{21}ClN_2O_2$ requires C, 68.4; H, 5.7; N, 7.6%), *m/e* 370 and 368 (ratio 1 : 3) (M^+) $\nu_{max.}$ (Nujol) 1 670, 1 400, and 1 350 cm^{-1}; $\lambda_{max.}$ 223 (ε 17 700), 237 (16 600), 255 (12 300), 285 (1 400), and 294 nm (995); for ^{1}H and ^{13}C n.m.r. data see Tables 2 3.

Electroreduction of the Benzodiazacycloundecene (4).—Compound (4) (167 mg) was similarly reduced at −2.61 V. An initial current of 180 mA was observed, which fell after passage of 2.5 F mol^{-1} to a final current of 6 mA. Work-up by method B followed by preparative t.l.c. using ether as eluant afforded two major fractions; unchanged starting material (4) (29 mg) R_F 0.7 was recovered and at R_F 0.3 5,11-diacetyl-2,3,8,9-tetramethyl-8,5a,10a-ethanylylidene-8*H*-cyclohepta[*b*]quinoxaline (8) (160 mg), m.p. 245—248 °C (Found: C, 75.9; H, 7.4; N, 7.4. $C_{23}H_{26}N_2O_2$ requires C, 76.2; H, 7.2; N, 7.7%), *m/e* 362, $\nu_{max.}$ (Nujol) 1 670 and 1 400 cm^{-1}; $\lambda_{max.}$ 227 (ε 19 500), 251 (12 500), 280 (1 600), and 290 nm (1 200); for ^{1}H and ^{13}C n.m.r. data see Tables 2 and 3.

Electroreduction of the Benzodiazacycloundecane (5).—Compound (5) (330 mg) was similarly reduced at 2.1 V. An initial current of 233 mA was observed, which fell after passage of 1.92 F mol^{-1} to a final current of 10 mA. Work-up by method A gave a complex mixture of products (n.m.r. and t.l.c.). Similar reduction in the second wave at −2.4 V again led after passage of 2.5 F mol^{-1} and work-up by method A to a complex product mixture.

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