

Substituted Oxindoles. Part VI.^{1a} Polarographic Reduction of Substituted *trans*-3-Benzylideneindol-2(3*H*)-ones

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The polarographic reduction of a number of substituted 3-benzylideneindol-2(3*H*)-ones in ethanol-water (3:2 v/v) has been studied. These exhibit one or two reduction waves depending on the supporting electrolyte and the pH of the solution. Changes in $E_{1/2}$ are discussed in terms of the Hammett σ values.

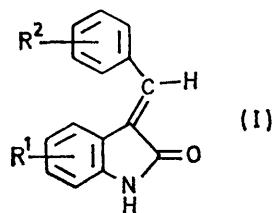
THE 3-benzylideneindol-2(3*H*)-ones (Ia—o) were prepared by the condensation of indol-2(3*H*)-one with the appropriate aromatic aldehyde in the presence of

piperidine. The products isolated were shown to exist in the *trans*-configuration from a study of their n.m.r. spectra and t.l.c. behaviour.¹

The polarographic reduction of 3-benzylideneindol-2(3*H*)-one (Ia) in ethanol-water (3:2 v/v) at a dropping mercury electrode using tetraethylammonium bromide

¹ (a) Part V, R. W. Daisley and J. Walker, *J. Chem. Soc. (C)*, 1971, 3357; (b) G. Tacconi and F. Marinone, *Ricerca sci.*, 1968, 38, 1239.

as supporting electrolyte gave one wave for buffered solutions in the relative pH range² 4–11. The wave height was independent of pH as was the half wave potential of 1.38 V above pH 9.2. Below pH 9.2 the



R ¹	R ²	R ¹	R ²
a; H	H	i; H	4-Cl
b; 5-MeO	H	j; H	4-HO
c; 6-MeO	H	k; H	3,4-OCH ₂ O
d; 7-MeO	H	l; H	4-F
e; 5-Br	H	m; H	4-MeO
f; 5-NO ₂	H	n; H	3-NO ₂
g; 6-Me	H	o; H	4-NO ₂
h; H	4-NMe ₂		

value for $\Delta E_{\frac{1}{2}}/\Delta\text{pH}$ was 0.038 V. The plot of $\log i/(i_a - i)$ against E gave two intersecting lines from which slopes in the range of 0.037 ± 0.002 V and 0.054 – 0.070 V were obtained for the pH range 4–11. These results indicate at least a two-stage electrode process which is dependent on hydrogen-ion concentration at $\text{pH} < 9.2$. The number of electrons transferred in the overall electrode processes was estimated as two by comparison with the wave heights of ethyl cinnamate and benzaldehyde. Confirmation of this result was obtained by the controlled potential reduction in which a value of $n = 1.75 \pm 0.05$ resulted for the different pH values using either tetraethylammonium bromide or lithium chloride as supporting electrolyte. Further support of this value was obtained by the isolation of 3-benzylindol-2(3H)-one (II) from the reduction mixtures, the isolated yields being *ca.* 50%. G.l.c. indicated this product was present in *ca.* 90–95% yield in the reduction mixture before work-up. Its structure was confirmed by comparison with an authentic specimen,³ prepared by the reduction of (Ia) with sodium borohydride. Other products found in the reduction mixture were indol-2(3H)-one (2–3%) by a retro-Knoevenagel reaction and 3-benzyl-3-hydroxyindol-2(3H)-one (III) by the rapid aerial oxidation of 3-benzylindol-2(3H)-one in alkaline solution. If after reduction the alkaline solutions were immediately neutralised the latter compound was not formed.

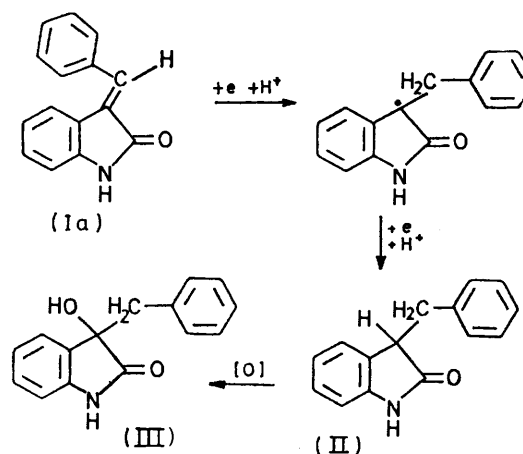
Further evidence for this two step process was obtained from polarographic studies involving lithium chloride as supporting electrolyte where two separate waves became discernible at $\text{pH} > 7.2$. The second wave increased in height at the expense of the first wave until both were of equal height at $\text{pH} 9.5$. The $E_{\frac{1}{2}}$ (1.65 V) of the second wave was pH independent as was the $E_{\frac{1}{2}}$ (1.42 V) for the first wave above $\text{pH} 7.2$. Below this pH a $\Delta E_{\frac{1}{2}}/\Delta\text{pH}$ of 0.61 V was obtained. The plots of E against $\log i/(i_a - i)$ for pH values below 7.2 gave

two intersecting lines with slopes in the ranges of 0.062 ± 0.02 V and 0.060 – 0.092 V. At higher pH values the two waves gave log plots with slopes of 0.053 ± 0.002 V and 0.090 – 0.120 V. Thus an $n : \text{H}^+$ ratio of 1 is indicated for the first wave or part of the wave.

Alternating current polarography gave a well defined first wave and a poorly defined second wave. The logarithmic analysis⁴ of these waves gave slopes of 0.112 and 0.490 V respectively indicating that the first wave could be reversible compared with the second wave. However, cyclic voltammetric studies up to sweep speeds of 1 V/s^{-1} at $\text{pH} 9.6$ and 4.2 using both supporting electrolytes gave only one cathodic peak. Thus any reversible electrode process must be followed very rapidly by proton addition.

The overall process would appear to be diffusion limiting since the plots of total i_d against $h_{\text{corr.}}^{\frac{1}{2}}$ and total i_d against concentration are both linear and pass through the origin.

The course of the electrode process thus follows the mechanism for an unsaturated compound⁵ involving the addition of two electrons and two protons (Scheme),



SCHEME

possibly in two steps with the proton addition being a rate-limiting step.

The second wave also depends on the supporting electrolyte present. An increase in the lithium concentration from 10^{-2} to 1.5 M had no effect on the i_d value of the second wave although a shift to more positive potentials for the $E_{\frac{1}{2}}$ value was obtained. Also, it was found that only one two electron wave was obtained if 10^{-4} M -tetraethylammonium bromide was present in a 0.2 M -lithium chloride solution of the compound.

The polarographic results expressed as $(E_{\frac{1}{2}} - E_{\frac{1}{2}})$ for $\text{pH} 4.2$, 9.40 (lithium chloride), and 9.40 (tetraethylammonium bromide) were 0.055 ± 0.015 ; 0.055 ± 0.005 , 0.11 ± 0.01 (two waves); and 0.06 ± 0.02 , and as i_d/c (Table 1) for the series of substituted 3-benzylideneindol-2(3H)-ones (Ia–o) agreed fairly well with respect

² R. G. Bates, M. Paabo, and R. A. Robinson, *J. Phys. Chem.*, 1963, **67**, 1833.

³ I. W. Elliott and P. Rivers, *J. Org. Chem.*, 1964, **29**, 2438.

⁴ A. M. Bond, *Analyt. Chem.*, 1972, **44**, 315.

⁵ P. G. Grodzka and P. J. Elving, *J. Electrochem. Soc.*, 1963, **110**, 225, 231.

TABLE 1

Effect of different supporting electrolytes on i_a/c values for substituted *trans*-3-benzylideneindol-2(3*H*)-ones

Compound	$(i_a/c)/\mu\text{A mm}^{-1}$		
	LiCl pH 4.2	LiCl pH 9.40	Et ₄ NBr pH 9.40
(Ia)	5.85	7.10	6.25
(Ib)	7.58	5.86	7.50
(Ic)	6.68	6.01	6.68
(Id)	6.88	5.10	7.10
(Ie)	5.59	6.45	6.83
(If)	6.70	7.88	6.70
(Ig)	5.80	5.89	6.29
(Ih)	7.20	6.86	7.13
(Ii)	5.66	4.87	6.45
(Ij)	3.86	6.11	6.34
(Ik)	4.69	7.25	
(Il)	5.03	6.62	7.35
(Im)	5.70	6.87	7.05
(In)	1.62	1.50	1.75
(Io)	1.80	3.08	

to each other with the exception of the nitro-compounds a similar overall mechanism of reduction is indicated.

The experimental changes in half-wave potential as a function of structure may be compared with Hammett σ values (Figures 1 and 2).⁶

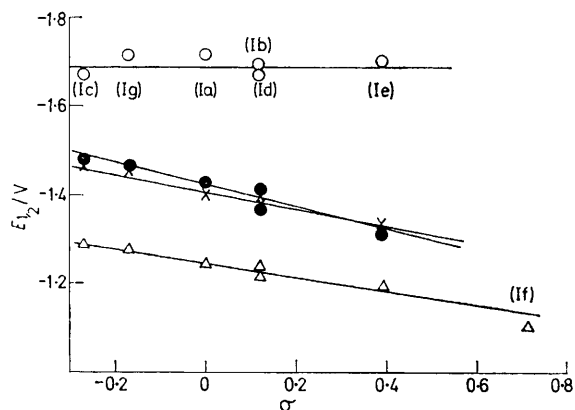


FIGURE 1 Hammett σ values for R¹ substituted *trans*-3-benzylideneindol-2(3*H*)-ones (Ia—g) as a function of $E_{1/2}$: Δ LiCl, pH 4.2, $r = 0.98$; \bullet LiCl, pH 9.4 (1st wave), $r = 0.97$; \circ LiCl, pH 9.4 (2nd wave), $r = -0.084$; \times Et₄NBr, pH 9.4, $r = 0.98$

A good correlation was obtained for the first wave in all cases of pH and supporting electrolyte. $\rho_{\pi, R}$ Values⁷ are given in Table 2 using σ_m for 5- and 7-substituents and σ_p for 6-substituents of the indol-2(3*H*)-one ring.

TABLE 2

Variation of $\rho_{\pi, R}$ values for a series of substituted *trans*-3-benzylideneindol-2(3*H*)-ones

Compound	$\rho_{\pi, R}/V$			
	LiCl pH 4.2	LiCl pH 9.40 1st wave	LiCl pH 9.40 2nd wave	Et ₄ NBr pH 9.40
(Ia—g) (R ¹)	-0.15	-0.25	+0.007	-0.20
(Ia), (Ih—o) (R ²)	-0.18	-0.18	-0.20	-0.26

⁶ D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420; H. H. Jaffé, *J. Chem. Phys.*, 1952, **20**, 1554.

⁷ C. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1940, p. 184.

In the case of the second wave no obvious correlation could be observed with respect to the Hammett function. Two opposite effects occurred in the $E_{1/2}$ values depending on whether the substituent was in position R¹ or R².

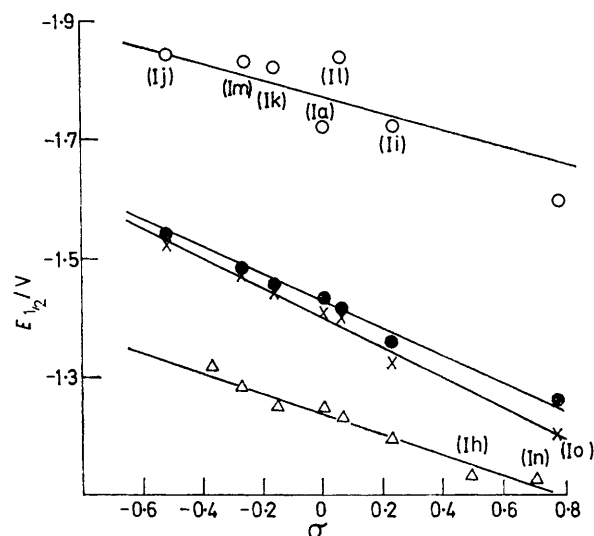


FIGURE 2 Hammett σ values for R² substituted *trans*-3-benzylideneindol-2(3*H*)-ones (Ia), (Ih—o) as a function of $E_{1/2}$: Δ LiCl, pH 4.2, $r = 0.98$; \bullet LiCl, pH 9.4 (1st wave), $r = 0.98$; \circ LiCl, pH 9.4 (2nd wave), $r = 0.89$; \times Et₄NBr, pH 9.4, $r = 0.99$

In the case of R¹ substituents a shift of the half-wave potential to more positive values occurred showing facilitation of the addition of the second electron. For those compounds with R² substituents the shift in $E_{1/2}$ was negative, indicating a reduction in the ease of addition of the second electron, except in the case of (In) and (Io), where R² was a nitro-group.

Further studies are being undertaken to see how these substituents influence the stability of the intermediate free radical.⁸

EXPERIMENTAL

Preparation of Compounds. The preparation of compounds (II)³ and (III)⁹ has already been described.

Benzylidene derivatives. The appropriate indol-2(3*H*)-one¹⁰ (0.01 mol) and the appropriate aromatic aldehyde (0.012 mol) in ethanol (10 ml) were boiled under reflux with a few drops of piperidine for 1 h or until solid material separated in substantial amount from the solution. After being left at 0° overnight, the product was filtered off and recrystallised from ethanol [several crystallisations were required for (If) and (Ig)]. The isolated products (Table 3) were shown to exist in the *trans*-configuration from a study of their n.m.r. spectra and t.l.c. behaviour.^{1,2} The small amounts of *cis*-products formed remained in the mother liquors.

Polarography.—Polarographic measurements were made using a Cambridge polarographic analyser. Half-wave

⁸ A. Streitwieser, jun., and C. Perrin, *J. Amer. Chem. Soc.*, 1964, **86**, 4938.

⁹ B. Mills and K. Schofield, *J. Chem. Soc.*, 1961, 5558.

¹⁰ A. H. Beckett, R. W. Daisley, and J. Walker, *Tetrahedron*, 1968, **24**, 6093.

potentials and diffusion currents were measured against a saturated calomel electrode and a mercury pool counter electrode. The automatic drop time of the analyser was set at 3 s with $m = 21.6 \text{ mg s}^{-1}$. The alternating current polarograms were obtained using the analyser set at 10 mV rms and 38 Hz. Cyclic voltammetry was also carried out using the analyser with sweep rates up to 1 V s^{-1}

samples were degassed for 10 min with oxygen-free nitrogen immediately prior to recording the polarogram. Correlation coefficients (r) for all the $\log i/i_a - i$ against voltage plots were >0.999 , and the variance about the regression line <0.001 .

Controlled-potential Reductions.—These were carried out using a mercury pool cathode at a fixed potential measured

TABLE 3
trans-3-Benzylideneindol-2(3*H*)-ones (Ia—o)

Compound (Ia)	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Analysis * (%)					
				Requires			Found		
				C	H	N	C	H	N
(Ia)	69	181—183	181—183 ^{10,11} 176—177 ¹²						
(Ib)	79	184—185		76.5	5.2	5.6	76.8	5.2	5.6
(Ic)	64	177—178	177—178 ¹²						
(Id)	75	171	171 ¹²						
(Ie)	80	214	214 ¹² 197—199 ¹³						
(If)	42	259—261		67.7	3.8	10.5	67.6	3.7	10.4
(Ig)	33	178—179		81.7	5.6	5.9	81.7	5.5	5.8
(Ih)	58	197	194—195 ¹⁷						
(Ii)	84	183—184	188—189 ¹⁵ 184 ¹⁶						
(Ij)	81	299	300 ¹⁷						
(Ik)	55	232	228—229 ¹⁴						
(Il)	74	196—197	194—196 ¹¹						
(Im)	73	163	157 ¹⁷						
(In)	73	227—228	227 ¹⁶ 255—257 ¹⁷	67.7	3.8	10.5	67.5	3.7	10.6
(Io)	63 †	254—255	224—225 ¹⁸ 229 ¹⁶	67.7	3.8	10.5	67.6	3.7	10.5

* Microanalyses are by Dr. J. Baker and Mr. R. Turner, School of Pharmacy, Brighton. † Recryst. from glacial acetic acid.

TABLE 4
Controlled potential reductions of *trans*-3-benzylideneindol-2(3*H*)-one (Ia)

Wt. reduced (mg)	pH	Supporting electrolyte	No. of electrons	Cathode potential (V)	% of (II) in crude reduction mixture *	Wt. of pure (II) isolated (mg)
22.0	4.4	LiCl	1.8	-1.5	92	11.1
22.0	9.6	LiCl	1.8	-1.75	85	12.1
22.0	4.6	Et ₄ NBr	1.8	-1.5	95	16.5
22.0	9.6	Et ₄ NBr	1.8	-1.5	89	10.3

* Estimated by g.l.c.; error $\pm 7\%$.

using a hanging drop of mercury as the working electrode and a Byrans 24000XY recorder.

For direct and alternating current polarography and coulometric measurements a Telsec 700 recorder was used. The electrolytes used consisted of 0.25*M*-tetraethylammonium bromide or 0.25*M*-lithium chloride in ethanol-water (3:2 v/v) with the solutions buffered by using mixtures of acetic acid and the appropriate hydroxide, tris-(hydroxymethyl)methylamine and hydrochloric acid, or by substituting lithium chloride and lithium hydroxide or tetraethylammonium bromide and tetraethylammonium hydroxide in Clark and Lubs borate buffer (0.01*M* solutions used instead of 0.1*M*). The pH was checked before and after each polarographic run using a Vibret pH meter. A depolariser concentration of 10^{-3} *M* was generally employed. All measurements were carried out at $21 \pm 0.5^\circ$ and all

against a saturated calomel electrode with a platinum gauze as counter electrode. After reduction the catholyte was neutralised, evaporated under reduced pressure to remove ethanol, and extracted with CH_2Cl_2 . The extract was washed with water, dried (MgSO_4), and evaporated. The residue was examined by g.l.c. and purified by recrystallisation from EtOH-H₂O to yield compound (II), m.p. 129—130° (lit.,³ 129—131°). Details are reported in Table 4.

G.l.c. analyses were carried out using a Varian Aerograph series 1520 with a stainless steel column (6 ft \times 1/16 in) packed with 15% SE30 on acid-washed hexamethyldisilazane, treated Chromosorb W at 250°, detection temp. 275°, injection temp. 275°, N₂ 35 ml min⁻¹, H₂ 25 ml min⁻¹, air 4 lb in⁻². Retention times were indol-2(3*H*)-one 1.7, 3-benzyl-3-hydroxyindol-2(3*H*)-one (III) 6.3, 3-benzylindol-

¹¹ G. N. Walker, R. T. Smith, and B. W. Weaver, *J. Medicin. Chem.*, 1965, **8**, 626.

¹² R. W. Daisley and J. Walker, *J. Chem. Soc. (B)*, 1969, 146.

¹³ R. A. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1954, 1697.

¹⁴ A. Wahl and P. Bagard, *Compt. rend.*, 1909, **148**, 716.

¹⁵ E. L. May and E. Mosettig, *J. Org. Chem.*, 1946, **11**, 435.

¹⁶ P. W. Neber and E. Rocker, *Ber.*, 1923, **56B**, 1710.

¹⁷ A. Wahl and P. Bagard, *Compt. rend.*, 1910, **149**, 132.

¹⁸ D. H. Hey and J. M. Osbond, *J. Chem. Soc.*, 1949, 3172.

2(3*H*)-one (II) 9.0, and 3-benzylideneindol-2(3*H*)-one (Ia) 15.6 min.

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