Electroanalytical Studies of Beta-adrenergic Blocking Agents; *N*-Isopropylethanolamine Derivatives; Procainamide

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The beta-adrenergic blocking agents metoprolol, oxprenolol, pindolol, practolol, propranolol and sotalol, and also the related procainamide, have been examined by anodic rotating disc electrode voltammetry in acidic media and in buffer media over the range of pH from 0 to 11.5. The best medium is 0.1 mol l^{-1} sulphuric acid, in which most of the compounds show obedience to the Levich relationship at platinum and gold electrodes. Rapid determinations of oxprenolol (up to 5×10^{-3} mol l^{-1}), practolol, propranolol and procainamide give very satisfactory results. Electrode kinetic parameters for mass and charge transfer have been determined for the latter four compounds. Reaction mechanisms have been elucidated and differ for each compound. Cyclic voltammetry has not proved to be particularly informative, and is illustrated for propranolol.

Keywords: *Beta-adrenergic blocking agents; procainamide; rotating disc electrode voltammetry; cyclic voltammetry; electrode kinetics and reaction mechanisms*

The beta-adrenergic blocking agents are competitive inhibitors of the effect of catecholamines at beta-adrenergic sites. Propranolol is the most prescribed for its antihypertensive, antianxiety, anticonvulsant and antianginal effects,[1,2] and has been proposed for disfunctional labour[3] and migraine.[4] The other antagonists differ in potency, beta-receptor selectivity, agonist activity and membrane stabilisation.[5] Despite their considerable history, and their known participation in biological electron-transfer systems, no electrochemical investigation has yet been reported. Fluorimetry[6,7] is commonly used for the determination of propranolol and its metabolites; spectrophotometry,[8] GLC,[9,10] HPLC,[11,12] TLC,[13] radioimmunoassay[14] and GC - MS[15] have also been used. Procainamide has a related use in cases of cardiac arrythmias,[16] and may conveniently be included. It has been determined polarographically,[17,18] as well as by other methods, but the common method of assay is by HPLC.[19,20]

Procainamide apart, the beta blocking agents are all *N*-isopropylethanolamine derivatives linked directly for sotalol, and via a methyl ether bridge in the rest, to a ring system which usually has another side chain, or second ring, as shown in Table 1. All have been investigated by direct anodic rotating disc electrode (RDE) voltammetry in aqueous media for analytical purposes and for reaction mechanisms and kinetics.

Experimental

The apparatus, instrumentation, electrode activation, solution manipulation and procedures have been described.[21] Oxprenolol, propranolol and procainamide were supplied as hydrochlorides, and were converted to sulphates.[21] Samples were of Drug Standard grade, and supplied by the manufacturers listed in Table 1. Normal scan speeds were 5 mV s^{-1}.

Results and Discussion

Voltammetry of Propranolol in Acidic Media

Although each compound displays a unique behaviour, propranolol, being the most frequently encountered, will alone be discussed in some detail. In 0.1 mol l^{-1} sulphuric acid at platinum, propranolol gives two waves, as in Fig. 1(*a*), the first being indistinct and merging with the second, which is well formed and obeys the Levich relationship with respect to square root of rotation speed and concentration. At the gold electrode a single wave appears [Fig. 1(*b*)], which also gives linear graphs of limiting current *versus* square root of rotation speed and *versus* concentration. In 1.0 mol l^{-1} sulphuric acid, the first wave is better defined at platinum [Fig. 2(*a*)] but does not obey the Levich relationship. The second wave does conform to the Levich relationship. At the gold electrode, Fig. 2(*b*), the first wave peaks at higher rotation speeds, and both waves show Levich dependence on rotation speed and concentration. An orange colour develops in the solution during voltammetry.

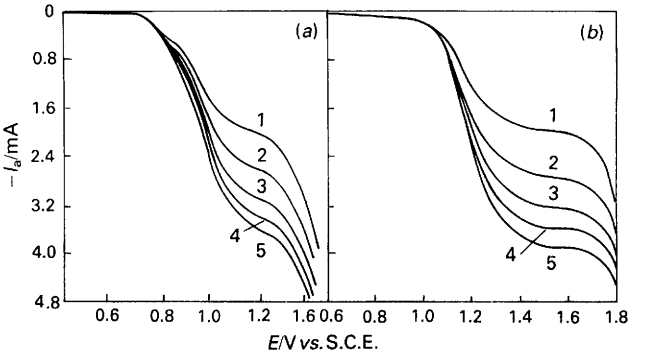

Fig. 1. Voltammetry of $4.999\ 8 \times 10^{-3}$ mol l^{-1} propranolol in 0.1 mol l^{-1} sulphuric acid at (*a*) platinum and (*b*) gold RDE. Conditions: nominal rotation speeds, (1) 10 Hz, (2) 20 Hz, (3) 30 Hz, (4) 40 Hz and (5), 50 Hz; scan speed, 5.0 mV s^{-1}; electrode area, 0.503 cm^2; temperature, 25 °C

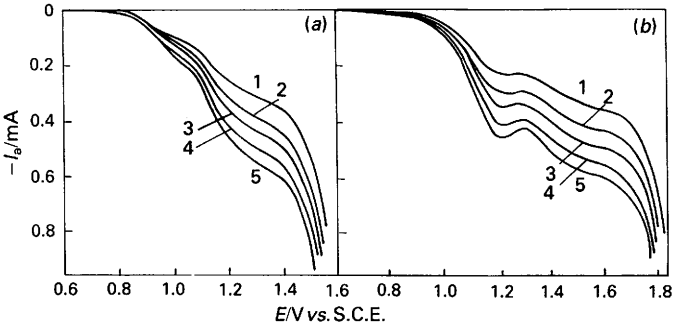

Fig. 2. Voltammetry of $9.999\ 6 \times 10^{-4}$ mol l^{-1} propranolol in 1.0 mol l^{-1} sulphuric acid at (*a*) platinum and (*b*) gold RDE. Conditions as in Fig. 1

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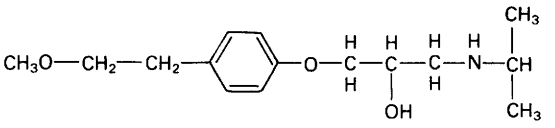
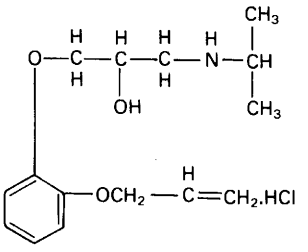
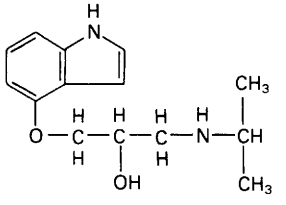
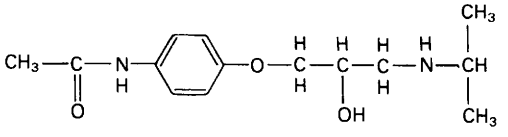
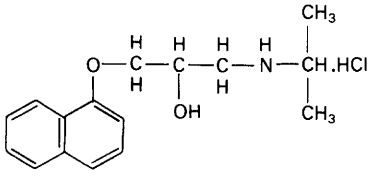
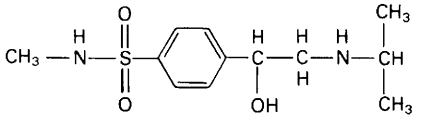
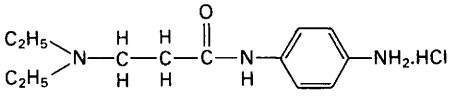
Table 1. Compounds examined

C.A. number	Generic name	Structure	Batch number	Supplier	Proprietary name
37350-58-6	Metoprolol		78 R 7 30	Geigy Pharmaceuticals	Lopresor
6452-71-71	Oxprenolol		71/78	Ciba Laboratories	Trasicor
13523-86-9	Pindolol		A/NO 81A313	Sandoz Products Ltd.	Visken
6673-35-4	Practolol		ADM 1072/73A	ICI	Eraldin
526-66-6	Propranolol		26851/79A	ICI	Inderal
3930-20-9	Sotalol		PO 149/022	Bristol Laboratories	Sotacor
51-06-9	Procainamide		02-655-4252	E. R. Squibb and Sons Ltd.	Pronestyl

Voltammetry of Propranolol in Buffer Media

There is a small but significant change in the half-wave potential, and a greater change in limiting current, which reaches a maximum in 0.1 mol l^{-1} sulphuric acid, as the pH of the medium is changed (Fig. 3). The first wave disappears at platinum at pH >1 and at gold at pH >2. The quality of the waves degrades with increasing pH at both activated and deactivated electrodes and the wave vanishes for deactivated electrodes at pH >4. The optimum condition is 0.1 mol l^{-1} sulphuric acid. The electrodes are not electrochemically deactivated in acidic media, but product adsorption at higher pH values leads to deactivation.

Voltammetry of Other Compounds

The remaining beta blockers have been examined in 0.1 mol l^{-1} sulphuric acid only. Practolol (Fig. 4) and oxprenolol (Fig. 5) both gave a single good wave at both platinum and gold electrodes; a light orange colour developed in the solutions. The limiting currents showed Levich dependence on square root of frequency and on concentration. Pindolol (Fig. 6) gave two overlapping waves at platinum and two waves plus a peak at gold; the peak limiting currents did obey the Levich relationship. For sotalol (Fig. 6) the waves merged with the background at platinum and became peaks at gold, which did show Levich dependence. Metoprolol (Fig. 6) revealed similar non-Levich behaviour at both platinum and gold.

Voltammetry of Procainamide

Procainamide gave a normal behaviour [Fig. 7(*a*)] at an activated platinum electrode with linear Levich dependences, but non-zero intercepts, and at an unactivated electrode the limiting current was diminished. At gold [Fig. 7(*b*)] the wave became a flat peak with a trough in it and the peak current gave linear graphs against square root of rotation speed and against concentration, but again with non-zero intercepts; unactivated electrodes revealed no deactivation effects. Despite the non-zero intercepts, the calibration graphs can be used in quantitative analysis.

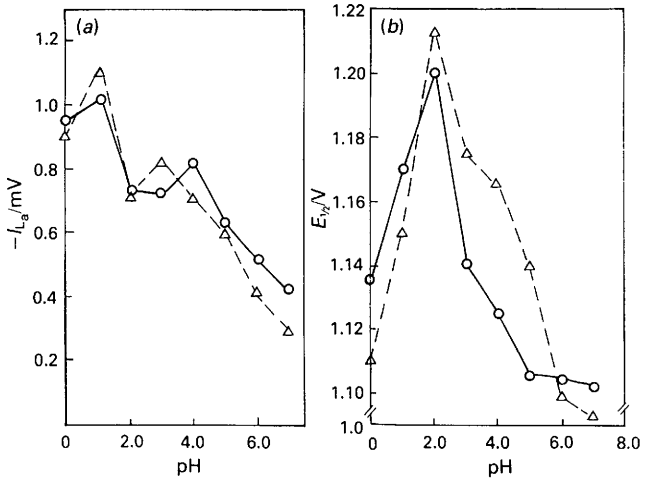


Fig. 3. Variation of (*a*) limiting current and (*b*) half-wave potential with pH for anodic voltammetry of 9.999 6 × 10^{-4} mol l^{-1} propranolol at platinum (solid line) and gold (broken line) RDE. Rotation speed, 50 Hz

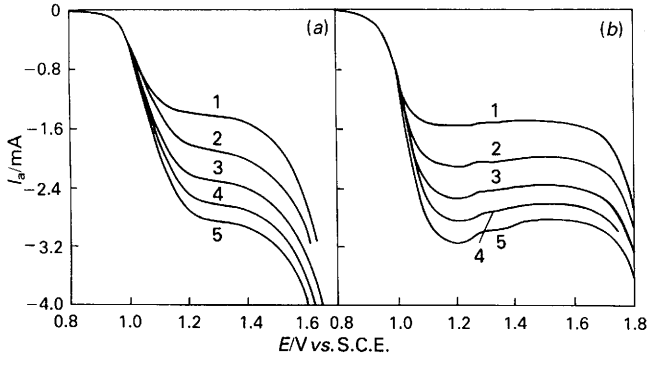


Fig. 4. Anodic voltammograms of 5 × 10^{-3} mol l^{-1} practolol in 0.1 mol l^{-1} sulphuric acid at (*a*) platinum and (*b*) gold RDE. Conditions as in Fig. 1

The influence of hydrogen ion concentration on the procainamide waves is illustrated in Fig. 8, over the pH range 0–11.5, maximum wave height is attained at both electrodes in 0.1 mol l^{-1} sulphuric acid. At platinum a single, well defined, wave appears from pH 0 to 5 at an activated electrode and also at an increasingly lower limiting current at an unactivated electrode. At the latter, the wave vanishes in more alkaline media, while at an activated electrode the wave is eclipsed, only to reappear, at a much more positive potential at pH >10. At an activated gold electrode the wave peaks at pH 7 and then becomes indistinct at pH >8 but does not reappear in more alkaline media. The wave becomes indistinct at an unactivated gold electrode at pH >2 and vanishes at pH >6.

Analytical Validity

Examples of calibration results for gold and platinum electrodes are given in Table 2. There is little to choose between the two electrode materials. Calibrations for oxoprenolol become non-linear (curvature towards the concentration axis) above 5 × 10^{-3} mol l^{-1}. To appraise the reliability of rapid determination, a series of four solutions of each of these drug standards was prepared and a single measurement of the limiting current was made at each of five rotation speeds. The concentration was calculated from slope and intercept, and the percentage relative standard deviations for each group of five determinations are given in Table 3. This involves the propagation of errors from five calibrations and small errors in rapid setting of rotation speed; the duration of each group of

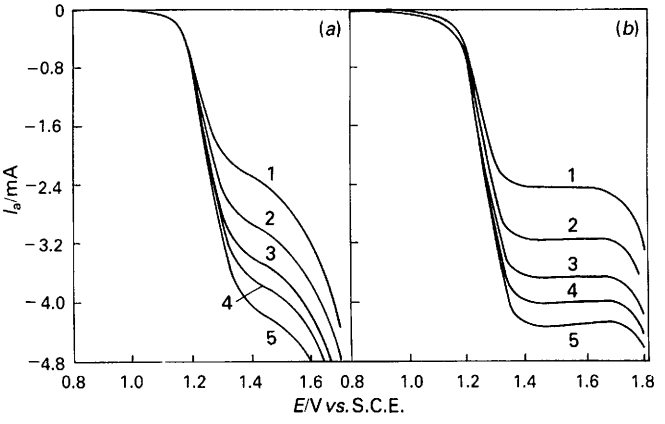


Fig. 5. Anodic voltammograms of 4.999 8 mol l^{-1} oxprenolol in 0.1 mol l^{-1} sulphuric acid at (*a*) platinum and (*b*) gold RDE. Conditions as in Fig. 1

five measurements is less than 10 min. Pindolol and sotalol can be determined at gold electrodes. Excipients in dosage forms encountered were electrochemically inert.

Kinetics

Conditional potentials are not accessible for these systems, so kinetic parameters are calculated with reference to the half-wave potentials. The half-wave potentials are similar for gold and platinum electrodes and show a small increase with increasing mass-transfer rate, that is with increasing rotation speed and concentration. The range for propranolol and oxprenolol is 1.10–1.26 V *versus* S.C.E.; practolol gives potentials about 100 mV smaller, while procainamide is intermediate. The electrode reactions are of moderate[22] speed. The charge-transfer rate constants range from 2.83 to 7.68 × 10^{-6} l cm^{-2} s^{-1} for practolol and about half of these values for the other compounds, showing modest increases with increasing rotation speeds and decreases with increasing concentration. The charge-transfer coefficients, β, lie in the range 0.07–0.22 for propranolol, oxprenolol and procainamide and 0.22–0.62 for practolol, decreasing with increasing mass-transfer rate. Tabulations of the results of definitive sets of measurements for the four compounds, calculated by pattern theory,[22] are available from the authors. The small differences in half-wave potential mean that the compounds cannot be resolved in mixtures by normal voltammetry, but practolol can be resolved from the others by differential-pulse voltammetry.

Coulometry and Reaction Mechanisms

An attempt to examine the first, indistinct, wave of propranolol in 0.1 mol l^{-1} sulphuric acid by potentiostatic coulometry yielded no useful information. Amperostatic coulometry engaged both waves and showed that the over-all reaction involved four electrons. For example, passage of a charge equal to one half of an electron equivalent caused a decrease in limiting current of 13%, and a further similar charge led to a decrease of 25%, which accords with four electrons. Continued scanning of the latter solution showed that the limiting current gradually increased until it regained the 13% level, when subsequent scans superimposed. Thus the product of the four-electron oxidation is unstable, and undergoes chemical reaction to regenerate the stable product of a two-electron process corresponding to the first wave. The solution became dark orange and a fine precipitate settled out. Practolol, however, showed a simple two-electron step, with no further oxidation or regeneration. Passage of, for example, charge equivalent to half an electron gave a reduction of limiting

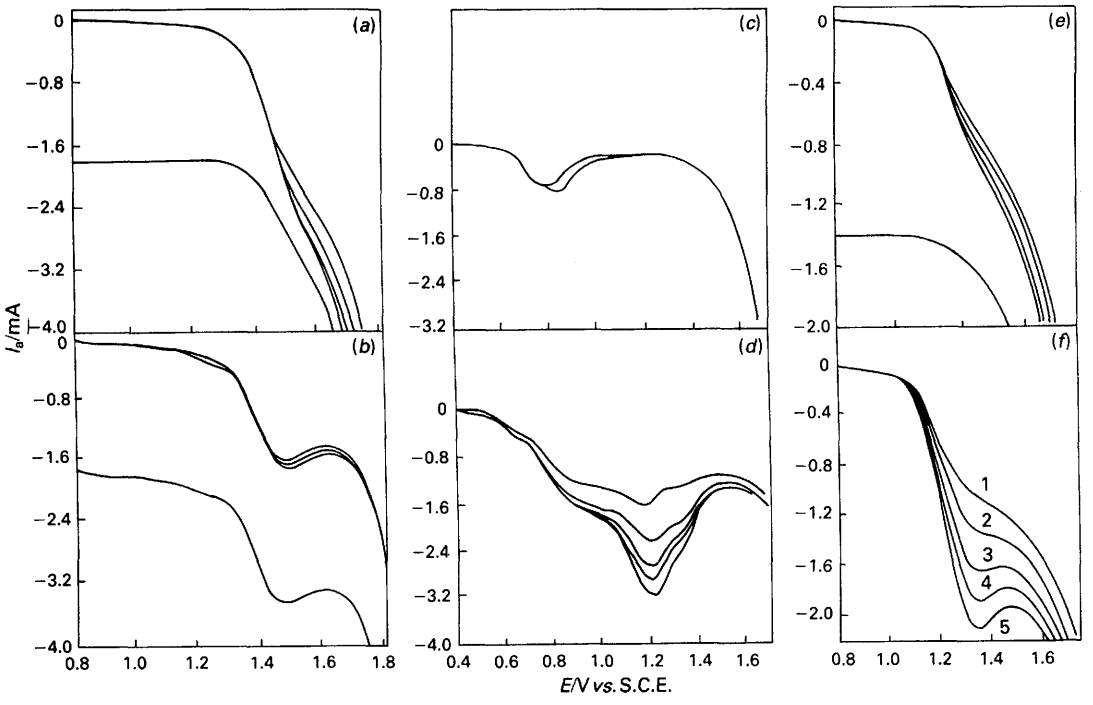


Fig. 6. Anodic voltammograms in 0.1 mol l^{-1} sulphuric acid of (*a* and *b*) metoprolol, (*c* and *d*) pindolol and (*e* and *f*) sotalol at (*a*, *c* and *e*) platinum and (*b*, *d* and *f*) gold RDE. Conditions as in Fig. 1. Detached line in *a*, *b* and *e*, unactivated electrode

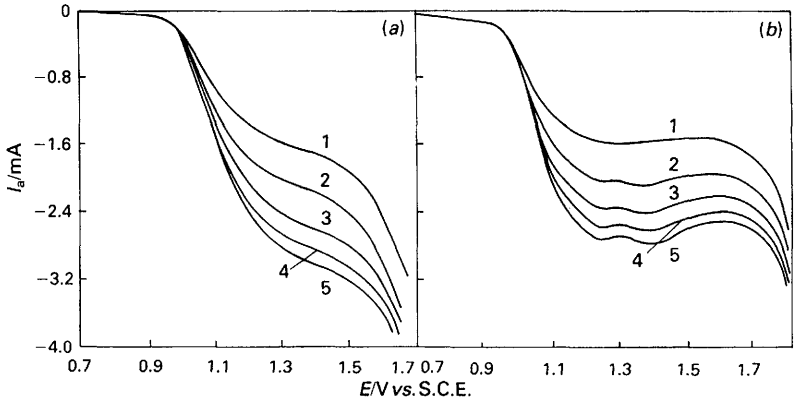


Fig. 7. Anodic voltammograms of 5.0002 × 10^{-3} mol l^{-1} procainamide in 0.1 mol l^{-1} sulphuric acid at (*a*) platinum and (*b*) gold RDE. Conditions as in Fig. 1

current of 25%, an additional similar charge decreased the limiting current by 50%, and repetitive scans of these solutions simply superimposed. The primary reaction product is therefore stable. Oxprenolol, on the other hand, displayed an *n*-value of six electrons, with regeneration to the product of a four-electron step: thereafter subsequent scans superimposed, indicating that this product was stable. Amperostatic coulometry of procainamide revealed a simple single-step four-electron oxidation, producing a red colour turning brown, and a stable product that neither decomposed nor underwent further oxidation.

That a group of compounds so closely related in functional structure should display such a diversity of behaviour is intriguing and puzzling. Sufficient information about the three members that underwent orderly quantitative anodic oxidation has been gleaned to state the mechanisms with clarity. The *N*-alkylethanolamine group is the common active site (Fig. 9). The hydroxyl function is oxidised by two sequential one-electron steps, I and II, of which the second is rate determining, via the radical to the ketone, which is the stable product in all instances, and is the origin of the first wave of propranolol, which is more marked in 1 mol l^{-1} sulphuric acid (Fig. 2). The practolol molecule does not accommodate any further reaction.

Propranol, by virtue of current sinking in the naphthol residue, permits a further two-electron step to the dication diradical, III, which is not stable, and reacts quickly with the solvent to regenerate the stable ketone by step IV. For oxprenolol, the side chain in the 2-position is oxidised to the dieneoxy group by a two-electron step, so transferring four electrons and giving the stable diene ketone. The *N*-alkylethanal side chain can also undergo oxidation to the dication diradical, III, so giving a total of six electrons. But again the radical is unstable, and reacts by step IV, regenerating the stable ketone, so that the product of the primary amperostatic process decays to the stable four-electron stage. Procainamide reacts through the 4-amino group to give straightforward oxidation to the nitroso compound, VI. This resists further oxidation to the nitro compound, a situation for which there is precedent,[23] although the survey of the effect of pH variation suggests that in 0.1 mol l^{-1} sodium carbonate the nitro compound may be formed at platinum electrodes.

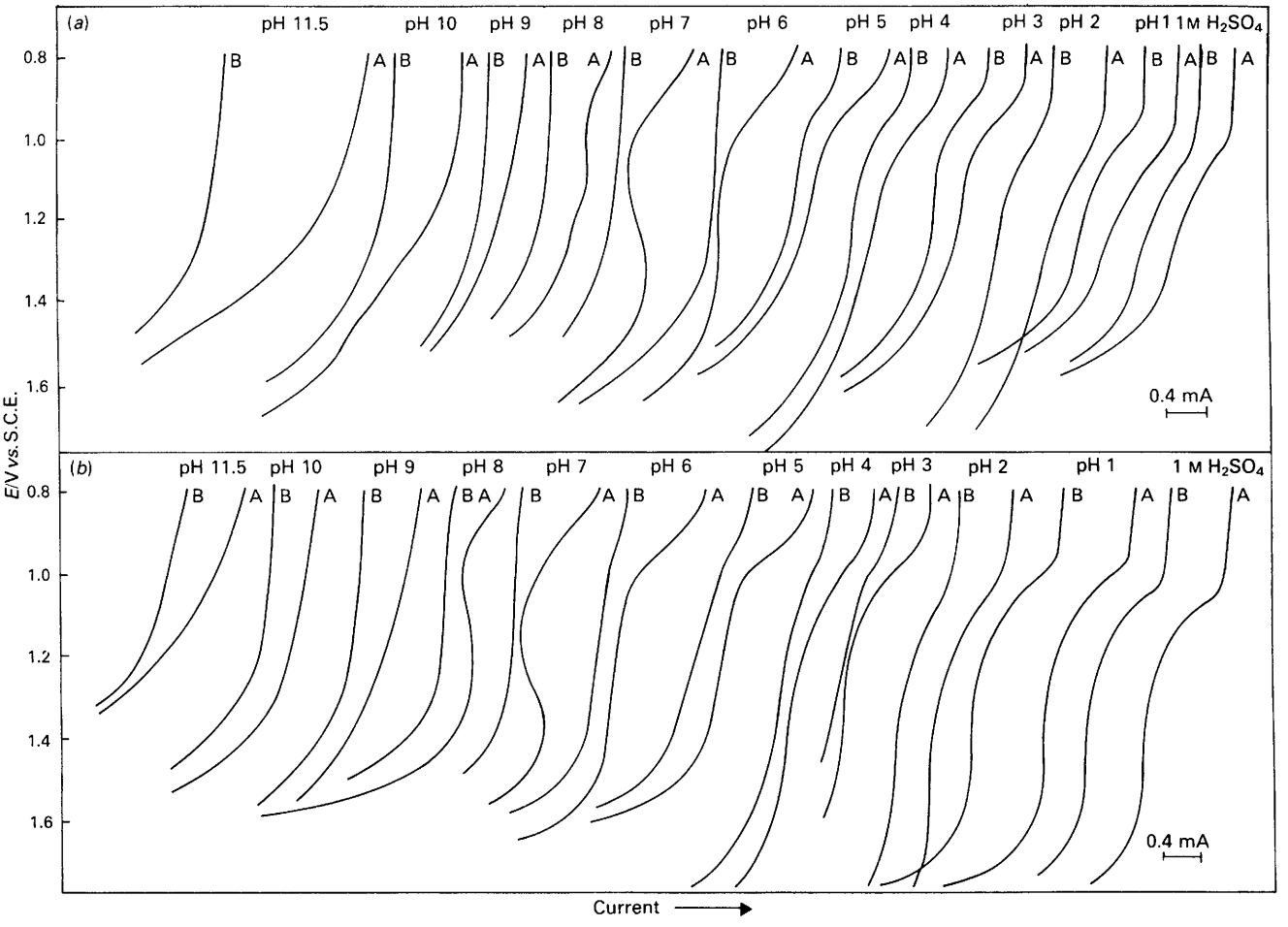


Fig. 8. Effect of pH on the anodic wave of 10^{-3} mol l^{-1} procainamide at (*a*) platinum and (*b*) gold RDE. Rotation speed, 50 Hz; media, sulphuric acid (pH = 0, 1), citrate - phosphate buffer (pH = 2–8), sodium carbonate (pH = 9–11.5) adjusted to exact pH value at 25 °C, Curves: A, activated electrode; B, unactivated electrode

Table 2. Example calibration results for RDE voltammetry. Electrode area, 0.503 cm^2; medium, 0.1 mol l^{-1} sulphuric acid; temperature, 25 °C; and $n = 4$

Sample	Nominal frequency/Hz	Slope/mA l mmol^{-1}	Intercept/ mA	Correlation coefficient	S.d. of residuals/ mA	S.d. of slope/mA l mmol^{-1}	R.s.d. of slope, %
Oxprenolol (0–5 × 10^{-3} mol l^{-1}, gold)	10	0.471 58	0.006 32	0.999 94	0.009 18	0.002 58	0.55
	20	0.619 74	0.003 95	0.999 99	0.005 74	0.001 61	0.26
	30	0.719 74	0.003 95	0.999 99	0.005 74	0.001 61	0.22
	40	0.789 47	0.007 89	0.999 97	0.011 47	0.003 22	0.41
	50	0.846 84	0.017 37	0.999 86	0.025 24	0.007 09	0.84
Practolol (0–10^{-2} mol l^{-1}, platinum)	10	0.275 00	0.095 00	0.999 89	0.008 66	0.002 04	0.74
	20	0.370 00	0.123 33	0.999 32	0.028 87	0.006 80	1.84
	30	0.495 79	0.161 05	0.999 99	0.004 59	0.001 29	0.26
	40	0.543 68	−0.09 158	0.999 97	0.006 88	0.001 93	0.36
	50	0.597 89	−0.130 53	1.000 00	0.002 30	0.000 65	0.11
Propranolol (0–10^{-2} mol l^{-1}, platinum)	10	0.366 68	0.146 67	0.999 01	0.034 64	0.008 16	2.23
	20	0.471 68	0.198 33	0.999 30	0.037 53	0.008 83	1.88
	30	0.548 85	0.248 33	0.999 56	0.026 36	0.007 41	1.49
	40	0.610 00	0.250 00	0.999 19	0.059 16	0.012 23	2.08
	50	0.660 02	0.246 67	0.999 46	0.046 19	0.010 89	1.65
Procainamide (0–12^{-2} mol l^{-1}, gold)	10	0.269 77	0.249 17	0.999 97	0.004 33	0.001 02	0.34
	20	0.335 77	0.351 54	0.999 94	0.011 09	0.001 88	0.56
	30	0.390 58	0.386 16	0.999 96	0.009 71	0.001 65	0.42
	40	0.423 65	0.412 31	1.000 00	0.001 39	0.000 24	0.06
	50	0.448 65	0.426 31	1.000 00	0.001 39	0.000 24	0.05

Table 3. Precision of determinations by RDE voltammetry. Each result arises from measurement of the limiting current at each of five rotation speeds. Electrode area, 0.503 cm²; medium, 0.1 mol l⁻¹ sulphuric acid; temperature, 25 °C

Electrode type	Oxprenolol*		Practolol		Propranolol		Procainamide	
	Concentration/ mmol l⁻¹	R.s.d., %	Concentration/ mmol l⁻¹	R.s.d., %	Concentration/ mmol l⁻¹	R.s.d., %	Concentration/ mmol l⁻¹	R.s.d., %
Platinum	1.999 91	2.22	1.999 70	3.61	1.999 94	0.86	2.000 08	3.41
	4.999 79	0.67	4.999 26	0.45	4.999 86	0.76	5.000 20	3.60
	7.999 66	0.47	7.998 81	0.31	7.999 77	0.98	8.000 32	1.28
	9.999 58	4.23	9.998 52	1.39	9.999 72	1.43	10.000 40	2.72
Gold	1.999 91	1.58	1.999 70	2.26	1.999 94	0.92	2.000 08	4.64
	4.999 79	2.50	4.999 26	0.17	4.999 86	3.08	5.000 20	0.25
	7.999 66	0.75	7.998 81	0.51	7.999 77	1.76	8.000 32	1.37
	9.999 58	3.13	9.998 52	0.98	9.999 72	0.16	10.000 40	0.56

* Calibration graphs non-linear above 5×10^{-3} mol l⁻¹.

Table 4. Cyclic voltammetry of propranolol. Concentration, 5×10^{-3} mol l⁻¹ in 0.1 mol l⁻¹ sulphuric acid; gold electrode, 0.503 cm²; temperature, 25 °C; potentials *versus* S.C.E.

Scan rate (v)/ mV s⁻¹	Anodic						Cathodic	
	i_{pA_1}/ mA	i_{pA_2}/ mA	i_{pA_3}/ mA	E_{pA_1}/ V	E_{pA_2}/ V	E_{pA_3}/ V	i_{pC}/ mA	E_{pC}/ V
200	0.575	0.675	0.575	−0.10	0.10	1.0	1.25	0.475
400	1.00	1.00	1.00	−0.08	0.25	0.91	1.25	0.475
588	1.35	1.25	1.275	−0.072	0.28	0.95	1.75	0.450
769	1.75	1.525	1.575	−0.060	0.45	0.95	1.75	0.450
1 000	2.075	1.75	1.775	−0.055	0.45	0.95	1.75	0.375
1 176	2.2	1.95	2.025	−0.04	0.50	0.95	1.50	0.375
1 369	2.35	2.1	2.225	−0.025	0.46	0.95	2.25	0.350
1 579	2.65	2.425	2.55	−0.020	0.48	0.95	1.65	0.350
1 765	2.85	2.80	—	−0.09	0.50	—	1.75	0.350
2 000	3.02	3.125	—	0.06	0.55	—	2.50	0.30
2 105	4.45	3.75	—	0.10	0.70	—	2.65	0.32
2 384	4.65	4.25	—	0.125	0.75	—	2.75	0.29

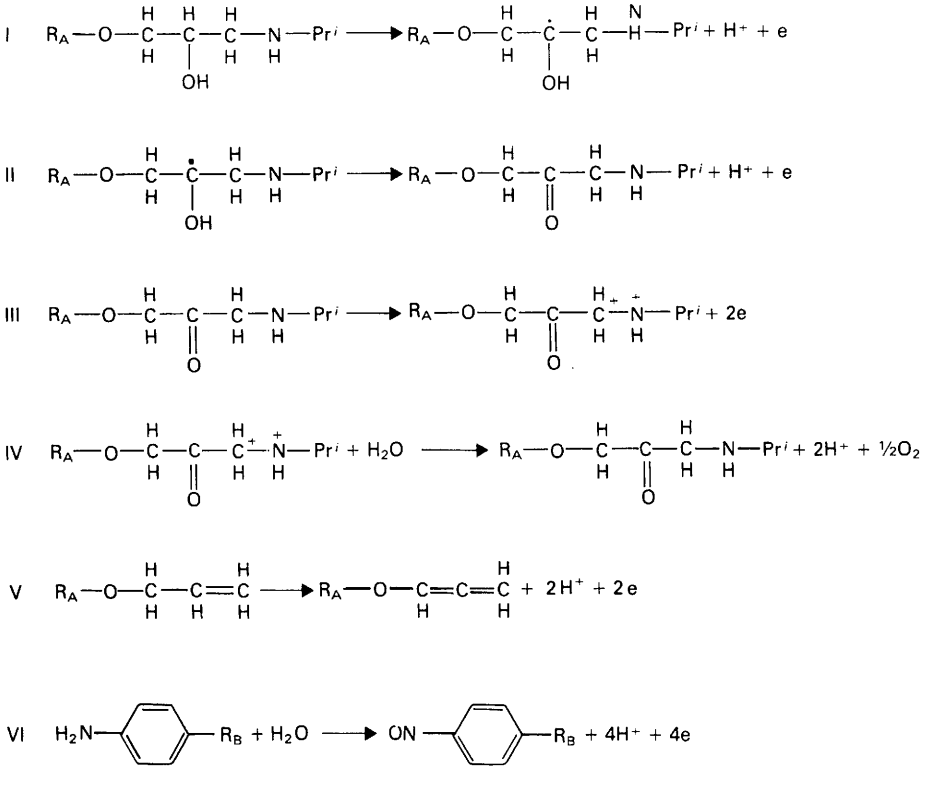


Fig. 9. Reaction mechanisms: R_A in I–V = residue of molecule of beta blocking agent; R_B in VI = residue of procainamide side chain, *cf.* Table 1

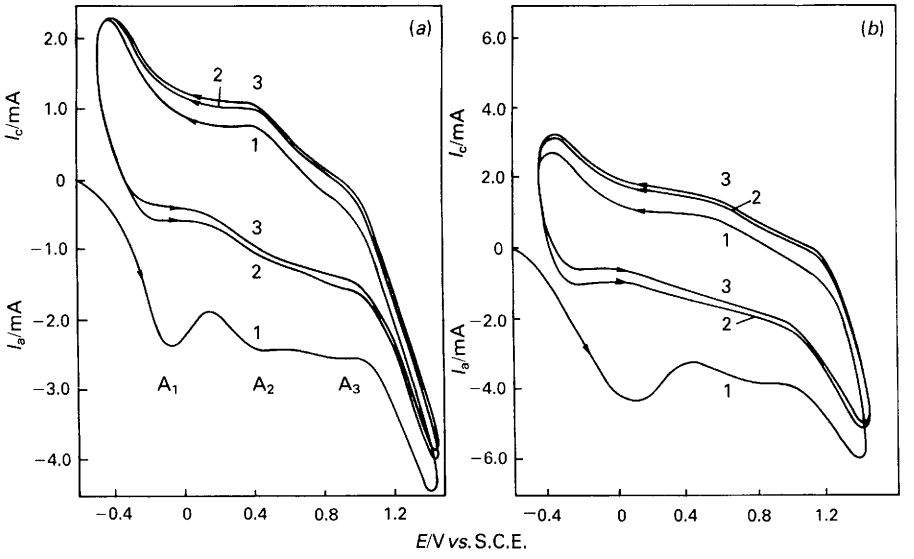


Fig. 10. Cyclic voltammograms of 5 × 10^{-3} mol l^{-1} propranolol in 0.1 mol l^{-1} sulphuric acid at a stationary 0.503 cm^2 gold electrode. Scan speeds: (*a*) 1579 mV s^{-1}; (*b*) 2384 mV s^{-1}. A_1, A_2 and A_3, anodic peaks; 1, 2 and 3, first, second and third cycle

Cyclic Voltammetry

Cyclic voltammograms of propranolol, practolol and oxprenolol were examined for information about adsorption and fast reverse radical reactions, but were not fruitful. The behaviour of propranolol is exemplified in Fig. 10 and Table 4. The first anodic half cycle is alone informative, and gave essentially a single broad peak broken up into a peak (A_1), a plateau (A_2) and a small after-peak (A_3). The peak A_3 disappears at higher scan rates. There is a single cathodic wave. Peak currents and potentials are scan rate dependent, but do not accurately conform to the conventional relationships. In the example illustrated, an unactivated gold electrode gave a similar result to an activated electrode, suggesting that reaction and product species did not affect electrode activity.

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References

1. Shand, D. G., *N. Engl. J. Med.*, 1975, **293**, 280.
2. Harner, J., Grandjean, T., Melendey, L., and Gowton, G., *Br. Med. J.*, 1965, **2**, 720.
3. Mitrani, A., Oettinger, M., Alunader, E. G., Sharf, M., and Klein, A., *Br. J. Obstet. Gynaecol.*, 1975, **82**, 651.
4. Weber, R. B., and Reinmuth, O. M., *Neurology*, 1972, **22**, 366.
5. Pendleton, R. G., Newman, D. J., Sherman, S. S., Brawn, E. G., and Maya, W. E., *J. Pharmacol. Exp. Ther.*, 1972, **180**, 647.
6. Black, J. W., Duncan, W. A. M., and Shanks, R. G., *Br. J. Pharmacol.*, 1965, **25**, 577.
7. Kraml, M., and Robinson, W. T., *Clin. Chim. Acta*, 1978, **24**, 171.
8. Shaw, R. F., *in* Sunshine, I., *Editor*, "Methodology for Analytical Toxicology," CRC Press, Cleveland, Ohio, 1975.
9. Disale, E., Baker, K. M., Bareggi, S. R., Watkins, W. D., Cidsey, C. A., Frigero, A., and Morselli, P. L., *J. Chromatogr.*, 1973, **24**, 347.
10. Hackett, L. P., and Dusci, L. J., *Clin. Toxicol.*, 1979, **15**, 63.
11. Pritchard, J. F., Schneck, D. W., and Hayes, A. H., *J. Chromatogr.*, 1979, **162**, 47.
12. Walle, T., *Pharmacologist*, 1975, **17**, 262.
13. Kawashima, K., Levy, A., and Specter, S., *J. Pharmacol. Exp. Ther.*, 1976, **196**, 517.
14. Garteiz, D. W., and Aqwalle, T., *J. Pharm. Sci.*, 1972, **61**, 1720.
15. Ehrsson, H., *J. Pharmacol.*, 1976, **28**, 662.
16. Kayden, H. J., Steele, J. M., and Mark, L. C., *Circulation*, 1951, **4**, 13.
17. Burghardt, H., *Deut. Apoth.-Ztg.*, 1968, **108**, 115.
18. Kiseleva, L. A., and Orlov, Yu. E., *Farmatsiya*, 1977, **26**, 38.
19. Schmidt, G., Vandemark, F. L., and Adam, R. F., *Chromatogr. Newsl.*, 1976, **4**, 32.
20. Griffiths, W. C., Dextraze, P., Hayes, M., and Dimond, T., *Clin. Toxicol.*, 1980, **16**, 51.
21. Bishop, E., and Hussein, W., *Analyst*, 1984, **109**, in the press.
22. Bishop, E., *Analyst*, 1972, **97**, 761.
23. Sidgwick, N. V., Taylor, T. W. J., and Nevil, I., "Organic Chemistry of Nitrogen," Third Edition, Oxford University Press, London, 1966, p. 339.

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