

THE ELECTROCHEMICAL REDUCTION MECHANISM OF 3-HYDROXYL-CONTAINING BENZODIAZEPINE DERIVATIVES

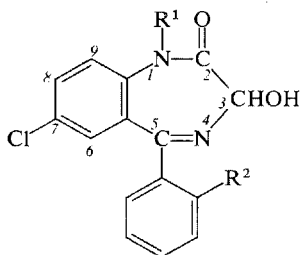
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From polarographic, controlled-potential coulometric and electropreparative experiments at mercury electrodes it was found that oxazepam (*I*), lorazepam (*II*) and temazepam (*III*) are reduced with an uptake of 4-electrons per molecule in acid media. In alkaline media, in all cases a lower amount of electrical charge has been consumed (in agreement with a decrease in height of the polarographic wave) and usually a mixture of two main products could be detected and isolated. One of them is always the same as in acid media (*e.g.* *IV*, *VI* and *VIII*), the other depends on the character of the substance to be studied. In *I* it is *V* ($n = 6$) which is obviously formed in chemical follow-up reactions from the reduction intermediate. In *II*, the secondary product *VII*, corresponding to a 2-electron reduction, probably has a double bond in position 3, 4 and is a tautomer of the intermediate formed after splitting off the 3-hydroxyl group.

Oxazepam (*I*), lorazepam (*II*) and temazepam (*III*), all of them containing a hydroxyl group in the position 3 of the seven-membered ring, form a special group among the more recent benzodiazepine tranquilizers.



I, $R^1 = H$, $R^2 = H$

II, $R^1 = H$, $R^2 = Cl$

III, $R^1 = CH_3$, $R^2 = H$

All have been studied with respect to their polarographic activity and analytical methods have been developed¹⁻⁴ for their determination in pharmaceutical preparations. The anomalous dependence of the limiting current of *I* on the applied potential at some pH-values has been studied and attributed⁵ to the adsorption of *I* on the D.M.E. up to the potential of its reduction. At potentials more negative than that of the maximum current on the polarographic wave a de-

sorption or reorientation of the reduction product occurs by which the conditions at the electrode are changed. Recently it has been found⁶ that *I* is reduced in acid buffers to 7-chloro-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine-2-one with the consumption of 4 electrons. In alkaline media *I* is assumed to be reduced to the 4,5-dihydro derivative. A similar mechanism² has been also confirmed with lorazepam.

We are convinced, however, that additional experimental work and more detailed interpretations are still necessary. The present paper, based on different techniques including preparative electrolysis, coulometric measurements, spectrophotometric methods of analysis and chromatographic separations, is intended to reach a deeper insight into the electrochemical reduction mechanisms, into the intermediates and final products.

EXPERIMENTAL

The polarographic measurements were carried out with an LP 60 polarograph of the firm Laboratorní přístroje, Prague, equipped with an electronic pen-recorder. Coulometric measurements were performed with an Amel 558 electronic current integrator (Apparechiature di misura elettronica, Milano). The hanging mercury drop used in some experiments was the AG CH — 9100 type produced by Metrohm AG, Herisau. For spectral measurements in the ultra-violet region a Unicam SP 800 spectrophotometer and in the infra-red region a Zeiss UR 10 spectrophotometer were made use of. The mass spectra were obtained making use of a mass-spectrometer MCH 1303 produced by the Development Workshops of the Soviet Academy of Sciences.

The thin-layer chromatography was carried out on silica gel plates (Silufol Kavalier, Votice, Czechoslovakia) with suitable solvent systems and with iodine vapour for visualisation of the spots. Chromatographic separation of the reduction products was performed with a column of 39 cm height and 10 mm diameter, filled with 20 g of silica gel (L 100/250 Lachema, Brno) and with a suitable solvent system for each mixture to be separated. The samples for elemental analysis were dried in a dessicator over phosphorus pentoxide.

Controlled-potential electrolysis: A 200 ml volume of a $2.5 \cdot 10^{-3}$ M solution of *I*, *II* or *III* (approx. 150 mg) in Britton–Robinson buffers containing 50% ethanol were electrolysed in a round-bottomed cell with a mercury pool cathode (for experimental details *cf.*⁷). A saturated Na_2SO_4 solution was used as anolyte. The anode was a platinum wire, and the reference electrode was a saturated mercurous sulphate electrode. The course of electrolysis was followed by means of a dme placed in the solution to be electrolysed. The reduction potential was kept constant manually making use of a simple circuit consisting of an electronic voltmeter and a variable dc source. The electrical charge that passed through the solution was measured with the Amel integrator in series.

The number of electrons *n*, consumed per molecule, was obtained by coulometry at a D.M.E. or at a mercury-pool electrode, following the wave-height at intervals after the consumption of a measured charge and plotting the percentage of the original wave-height *versus* consumed charge. In case of preparative electrolysis the values of *n* were obtained by taking into calculation the electric charge necessary for total electrolysis and the amount of starting material electrolysed.

RESULTS

dc Polarography

I, *II* and *III* are reduced in a similar manner over a wide pH-range in solutions containing 10% dimethylformamide. In all cases the shape of the obtained waves, their height and their half-wave potentials are strongly dependent on the pH of the electrolysed solution (Table I). In acid media a main wave can be observed which is diffusion-controlled up to pH about 6. Its height corresponds to the uptake of 4 electrons per molecule. This wave becomes affected by the adsorption of the electro-active species at pH > 6. Its height decreases with increasing pH of the base solution and attains the shape of an apparent maximum exhibiting special properties⁵. At pH 4–5 this wave is followed by a catalytic wave of hydrogen ion reduction. At pH > 10 the main wave becomes still lower with increasing pH, loses its conspicuous shape and finally its height corresponds to an uptake of slightly more than 2 electrons. This holds true for solutions containing 10% dimethylformamide. In base solutions with 10% dimethylsulphoxide the apparent maximum is less pronounced and above pH 11 the wave decreases further with increasing pH, becomes kinetic and is superseded by a more negative wave which finally corresponds to the uptake of more than 2 electrons. The reduction processes of *I*, *II* and *III* are at any conditions polarographically irreversible. The half-wave potentials of the three substances are a linear function of pH with an average slope of the $E_{1/2} = f(\text{pH})$ plot equal to $\sim 60 \text{ mV/pH}$ unit.

TABLE I

Change of $E_{1/2}$ (vs S.C.E.) and i_1 of Substances *I*, *II* and *III* with pH
 $5 \cdot 10^{-4} \text{ M}$ solutions in Britton–Robinson buffers containing 10% dimethylformamide.

pH	Oxazepam (<i>I</i>)		Lorazepam (<i>II</i>)		Temazepam (<i>III</i>)	
	$i_1, \mu\text{A}$	$-E_{1/2}, \text{V}$	$i_1, \mu\text{A}$	$-E_{1/2}, \text{V}$	$i_1, \mu\text{A}$	$-E_{1/2}, \text{V}$
2.17	4.2	0.60	4.9	0.60	4.62	0.60
2.91	4.69	0.66	4.55	0.69	4.69	0.67
4.52	4.83	0.78	4.41	0.80	4.83	0.74
5.1	4.62	0.80	4.27	0.84	4.62	0.82
6.0	4.2	0.86	3.47	0.88	3.64	0.91
7.0	3.22	0.92	2.9	0.91	2.81	0.94
8.92	2.8	0.98	3.15	1.02	2.6	0.98

Current-Voltage Curves with a Stationary Mercury Drop Electrode

Current-voltage curves with a hanging mercury drop electrode were recorded in order to get information about the possibility of carrying out coulometric measurements and preparative reductions for the elucidation of the reduction mechanisms. All three compounds give reduction peaks at this type of electrode. In repeated recordings without renewing the electrode surface the peak height only slightly decreases and the peak maximum potential E_p shifts to more negative values by less than 25 mV if the recording has been repeated five times. Characteristic E_p values for *I*, *II* and *III* are as follows: -0.97 V, -0.99 V and -0.93 V at pH 4.0, and -1.2 V, -1.16 V and -1.18 V at pH 8.6, respectively.

Coulometric Measurements and Preparative Reductions of I, II and III. Oxazepam (I)

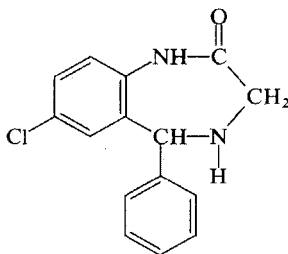
Coulometric measurements. The coulometric values of n in acid (Britton-Robinson, pH 4.0 50% ethanol; at -1.2 V) and in alkaline medium (the same buffer, pH 8.6; at -1.6 V) are as follows:

acid:	3.7	3.6	4.0	3
alkaline:	5.5	2→3	2→3.5	3.4

(the first data are theoretical values from the yields of products, second and third coulometric obtained at D.M.E. and mercury pool, respectively, the last ones from preparative electrolysis).

Both with the dropping mercury electrode and with the large-area mercury-pool electrode n -values in the vicinity of 4 were obtained if the total height of all waves appearing during the electrolysis was used for the calculation of n .

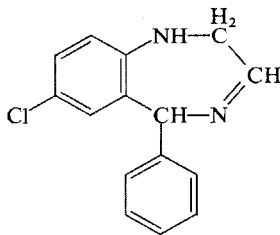
Products of electrolysis. Acid media: Thin-layer chromatography (10% ethanol by volume in chloroform) revealed that a single main product is formed (about 90%). This substance was purified by crystallisation from a water-ethanol mixture and the resulting solid product had a melting point between $186-187^\circ\text{C}$ in accordance with literature⁸ for *IV*. Spectral results for this product are summarised in Table II. The infra-red spectra proved the disappearance of the band with $\nu = 1600\text{ cm}^{-1}$ corresponding to the presence of $\text{C}=\text{N}$; a band appears at $2840-2920\text{ cm}^{-1}$ which reveals the presence of a CH_2 grouping after the loss of the OH group. These results point to the following structure for the compound *IV*:



IV

In the elemental analysis the following values were obtained which in comparison with the calculated values also point to structure *IV*: calculated: 66.06% C, 4.80% H, 10.27% N, 13.0% Cl; experimental: 66.44% C, 5.06% H, 9.71% N, 13.07% Cl.

Alkaline media. The thin-layer chromatographic identification (best with a solvent system composed of 15% ethanol by vol. in benzene) of the completely electrolysed solution showed the presence of two major products. Chromatographic separation was carried out on a silica gel column with ethanol and benzene (increasing concentrations from 5% to 20% of the polar solvent in 50 ml portions) as solvent system. The two major products were thus successfully separated (35% and 40% of the calculated theoretical yield). The first product was identical with that from the electrolysis in acid media, *i.e.* substance *IV*. This followed from the melting point, from the spectral properties and from elemental analysis. The second product has a melting point of 191–192°C with sublimation; its spectral properties are summarised in Table II. In the infra-red region very similar characteristics were found as those of the product of electrolysis in acid media, except for the disappearance of the band with $\nu_{\text{CO}} = 1700 \text{ cm}^{-1}$. With regard to the considerations in the next paragraph the following structure of *V* can be assumed:



V

The presence of two bands in the electronic spectra of *V* (Table II) is highly significant. In the spectra of *IV* after electrolysis in acid media, with a reduced 4,5 double bond and a split-off 3-hydroxyl group, a single band at $\lambda = 255 \text{ nm}$ can be observed.

Two bands can be only observed with the original substances *I* through *III*, possessing a 4,5-double bond in conjugation with the aromatic nuclei. The shift of λ to lower values in *V* in comparison with *I* can be only interpreted as due to breaking the conjugation between the aromatic nuclei and the double bond, *i.e.* to shifting the double bond into the position 3, 4.

The course of the controlled-potential electrolysis of *I* both with the D.M.E. or with a large-area mercury pool electrode was checked by polarograms at regular intervals. However, during electrolysis in alkaline media some complications arise: there is not only a gradual decrease of the wave-height during electrolysis but, after the passage of a certain amount of charge, an additional prewave at -0.73 V appears which first increases at the expense of the original wave, and later also decreases with increasing consumption of charge.

In preparative electrolyses, the polarograms recorded during electrolysis showed a somewhat different situation with complications even in acid media. Here a small prewave and a postwave appear after the passage of a small amount of electric charge. The additional waves appear at about -0.55 V (shifted to -0.65 V during electrolysis) and at -1.6 V. All three reduction waves decrease then simultaneously with increasing amount of electric charge consumed, (Fig. 1).

In alkaline media a prewave at -0.92 V and an ill-defined postwave, as well as an anodic wave at -0.2 V appears after the consumption of a certain amount of charge. During electrolysis the main wave disappears at a certain stage and only the anodic wave and the cathodic prewave are to be seen. In contradistinction to the acid media the height of the main wave decreases with time without electrolysis whereas the prewave increases.

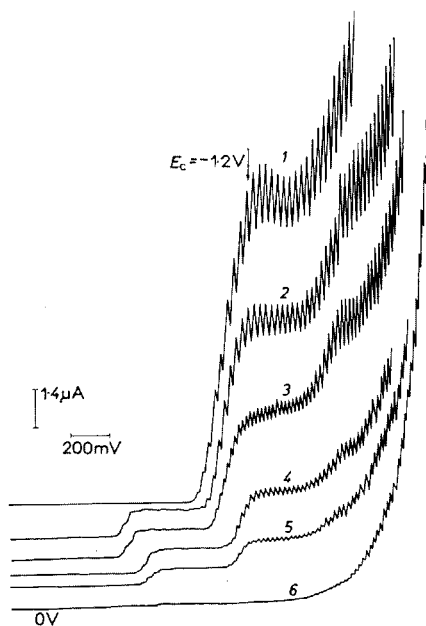


FIG. 1

Polarographic Control Curves During Preparative Electrolysis of $2.5 \cdot 10^{-3}$ M of Oxazepam (*I*) in Britton-Robinson Buffer pH 4.15 (50% ethanol)

Time (min) of electrolysis: 1 0; 2 9 (29C - consumed); 3 14 (58C); 4 28 (83C); 5 42 (122.5C); 6 150 (138C).

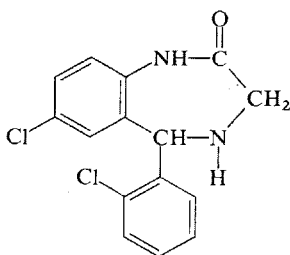
Lorazepam (II)

Coulometric measurements. The coulometric values of n , in acid (B.-R. buffer pH 4.0, 50% ethanol; at -1.1 V) and in alkaline medium (the same buffer, pH 8.9; at -1.6 V) are as follows (The sequence of data is the same as with oxazepam.)

acid:	3.7	3.85	4.0	5
alkaline:	2.5	2.2 \rightarrow 4 ^a	2 \rightarrow 3.3	1.5
		3.0 ^b		3.9

^a Values of n obtained from the original wave-height, ^b those from the sum of all waves appearing on the polarogram; the first method is obviously more correct.

Products of electrolysis. Acid media: Thin-layer chromatography (best with 10% ethanol in chloroform) of the electrolysed solution revealed again a single main product which was isolated by column chromatography on silica gel with ethanol, and chloroform (5, 10, 15% by vol. of the polar solvent in successive 50 ml portions) and purified by crystallisation from a water-ethanol mixture; the resulting solid had a melting point of $231-232^{\circ}\text{C}$ (product VI), and showed spectral results as summarized in Table II, which point to the following structure for compound VI, analogous to that of product IV from oxazepam (I):

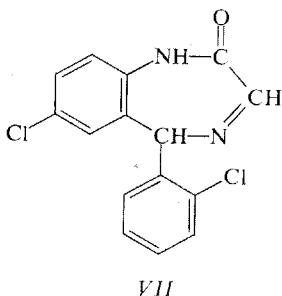


VI

This structure was confirmed by elemental analysis: calculated: 58.63% C, 3.90% H, 9.12% N, 23.12% Cl; experimental: 58.66% C, 4.09% H, 8.97% N, 23.28% Cl.

Alkaline media. As with oxazepam (I), thin-layer chromatographic analysis after electrolysis pointed to the formation of two major reduction products. Column chromatographic separation was successful with ethanol-chloroform as solvents and a silica gel column. The separated two products were recrystallized from an ethanol-water mixture and had the following melting points: 222°C (i.e. product VI); the other product, VII, has no sharp melting point and melts between $125-130^{\circ}\text{C}$.

The identity of the first product (19.0% yield) with *VI* from electrolyses in acid media was confirmed by ultra-violet, infra-red and mass spectra and by TLC. Product *VII* (29% yield) showed spectral results as summarised in Table II. Basing on similar reasoning as in case of *V* and making use of these results, one can possibly ascribe to *VII* the following formula with a 3,4 double bond:



Temazepam (III)

Coulometric measurements. The coulometric values of n for different experimental conditions are as follows: B.R.-buffer (50% ethanol), pH 3.3, at -1.1 V, $n = 4$ (D.M.E) and 5.5 (preparative electrolysis); pH 8.15, at -1.65 V, $n = 2 \rightarrow 3$ (D.M.E.) and 1.6 (preparative electrolysis).

Products of electrolysis. Acid media: After an electrolysis carried out at the potential of the limiting current of the reduction wave with a mercury-pool electrode as in the above cases the reaction mixture was analysed by means of thin-layer chromatography (10% ethanol by vol. in chloroform). This procedure revealed the presence of more than one component. A column-chromatographic separation, however, on silica gel, with ethanol-chloroform as solvent system yielded only one product (77% yield) which, crystallized from ethanol-water, had a melting point $136-137^\circ\text{C}$. Spectral results of this main isolated product are summarised in Table II, and all point to the following structure *VIII*:

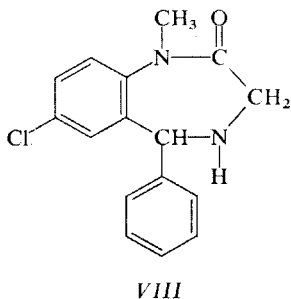


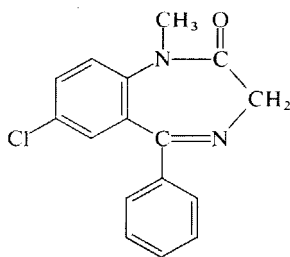
TABLE II
Spectral Data for the Separated Reaction Products of Compounds I—III

Isolated product	Ultra-violet	Infra-red (bands, cm^{-1})	Mass spectra (ionic peaks, m/e)
IV	Only one maximum at λ 255 nm	(KBr tab.) 3 425 (w), 3 260 (m), 3 200 (w), 2 915 and 2 945 (w), 1 675 (s), 1 485 (s), 1 455 (w), 1 400 (m), 1 380 (m), 1 350 (w)	272, 243, 229, 216, 195
V	Two new peaks at λ 233 nm and a diffuse one at λ 285—290 nm	(KBr tab.) 3 125 (w), 3 040 (w), 2 800 (w), 2 000 (w), 1 750 (m), 1 650 (m), 1 625 (m), 1 575 (w), 1 490 (w), 1 400 (s)	258, 243, 230, 207, 195
VI	Only one maximum at λ 253 nm	(KBr tab.) 3 290 (s), 3 020 and 3 080 (w), 2 850 (m), 1 675 (s), 1 485 (s), 1 435, 1 420 and 1 400 (m)	306, 277, 272, 250, 219
VII	Two distinctive absorption maxima at λ 235 and λ 285 nm	(KBr tab.) main diffusion band at 2 850—3 140 (s), 1 650 (m), 1 580 (m), 1 490 (s), 1 400 (m)	304, 195, 177, 150
VIII	One maximum at λ 243 nm	(CHCl_3) 3 010 (s), 2 920 (w), 1 660 (s), 1 590 (w), 1 480 (s), 1 445 (w), 1 365 (m), 1 300 (w), 1 210 (s)	286, 270, 257, 242, 229
IX	Two maxima at λ 250 nm and λ 315 nm	(KBr tab.) 3 000 (m), 1 500 (m), 1 430 (w), 1 200 (s), 1 270 (w), 820 (w)	284, 257, 242, 228, 215, 205

This formula is also in accordance with the results of elemental analysis: calculated: 67.13% C, 5.24% H, 9.78% N, 12.41% Cl; experimental: 67.77% C, 5.51% H, 9.08% N, 12.50% Cl.

Alkaline media: The thin-layer chromatographic analysis of the product of electrolysis showed the same pattern as that in acid media. The column-chromatographic separation of this mixture (using a silica gel column and a solvent system of ethanol in n-heptane in an increasing ratio of the polar solvent from 5 to 30% in 50 ml portions) gave only one product with a melting point of 135°C. Spectral investigations such as ultra-violet, infra-red and mass spectrometry, proceed this product to be identical with that in acid solutions, *i.e.* VIII. Owing to the very bad separation on the column no other products (possibly with a reduced CO grouping) were isolated.

In order to be able to make a decision which electronegative group is first reduced in substances from *I* to *III* the intermediate in the reduction of temazepam (*III*) was isolated. An electrolysis of *III* was performed in alkaline media (Britton–Robinson buffer pH 8.1, 50% ethanol); the electrolysis — otherwise under the same conditions as in the above case — was continued until one half of the electric charge necessary for the total, 4-electron reduction has been consumed. This procedure was followed by column chromatography on silica gel with n-heptane and ethanol as solvent (5, 10, 15 and 20% of ethanol in 50 ml portions) which led to the separation of a product. The spectral data of this product are summarized in Table II, and they point to the structure *IX*, without the hydroxyl group.

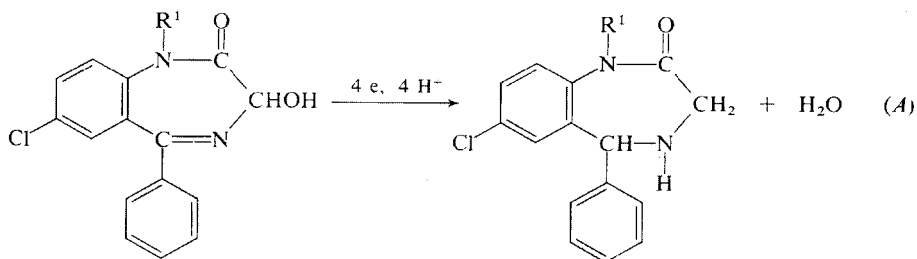


IX

Moreover, the physical properties of the isolated product were compared with diazepam, a substance having the structure *IX*. Chromatographic thin-layer analysis revealed that the two substances have the same R_F -values under the same conditions. The polarographic activity of these two substances has been also compared and in the same supporting electrolyte the half-wave potentials were virtually identical.

DISCUSSION

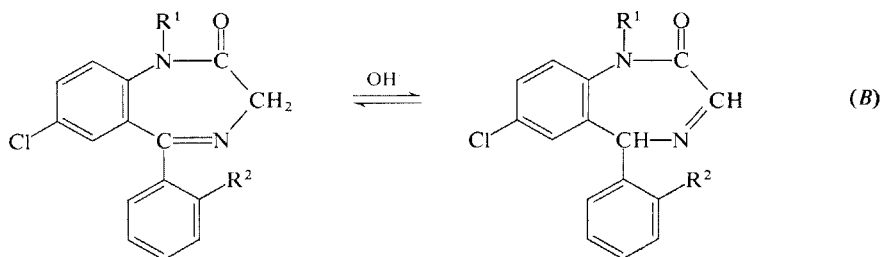
In the combined polarographic, coulometric and electrolytical experiments the basic reduction mechanisms of the substances *I*, *II* and *III* at mercury electrodes of different types have been found. In essence they are in accordance with the results given *e.g.* in papers^{1,5,6}. The prevailing reduction course in acid media can be generally described as follows:



If this over-all mechanism has to be described in more detail the ECE mechanism suggested by Oelschläger and coworkers¹¹ must be considered. According to our interpretation, in acid media the starting substance (*I*, *II* or *III*) is protonated on the nitrogen atom in the position 4 (*e.g.*⁹, $pK = 1.7$ for oxazepam (*I*)). This protonation makes the reduction of the 4,5 double bond easier. In alkaline buffers this protonation process probably is no more operative. However, Oelschläger¹¹ takes into account a protonation of the 3-hydroxyl group in the intermediate of the first, two-electron step in which only the 4,5 double bond has been reduced. This protonation would be necessary for the abstraction of water in a chemical follow-up reaction (*cf.* the general scheme in¹¹). This ECE mechanism is in agreement with our findings in solutions up to pH 4. Unfortunately, it cannot be deduced from Oelschläger's data in which pH region this elimination of water occurs and at what rate. According to Smyth and Clifford's⁹ equilibria no ionized species play a role in the reduction mechanism in alkaline media. Oelschläger¹⁰ also experimentally excluded a participation of diketo tautomers in the electroreduction in alkaline media.

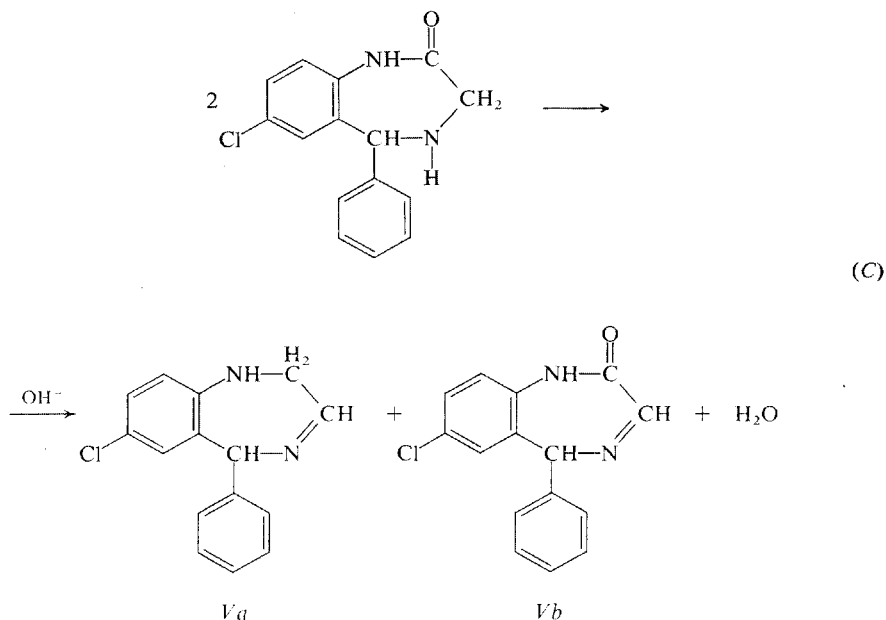
As a whole the mechanism of electrolysis of *I*, *II* and *III* in alkaline media remains obscure. It is a strange fact that in spite of the complicated polarographic behaviour no other products have been isolated here than those obtained from acid solutions. In some investigations¹¹ two further products have been postulated but they have not been isolated. The low and non-stoichiometric value of n obtained from coulometric measurements is explained here by a 2-electron reduction leading to an intermediate containing a reduced 4,5 double bond and the original hydroxyl group in position 3 preserved. Accordingly, the elimination would not occur. However, the authors of the present paper were unable to obtain such a product from the electrolysis. There is another possibility of interpretation of the low values of n in alkaline solutions, namely a complex of chemical reactions of the dihydro derivatives giving rise to polarographically inactive products as those proposed by the Frankfurt school. Our interpretation is somewhat different: in alkaline media we succeeded in isolating the substance *VII*, containing a 3,4 double bond, as the secondary reduction product of lorazepam (*II*). We assume that *VII* is polarographically inactive because the 3,4 double bond is isolated from the benzene nuclei. The loss of conjugation causes a shift of the absorption band in the electronic spectra to shorter wave lengths. This hypsochromic effect is important in investigating the product structure. An unambiguous proof for the position of the double bond in the 7-membered ring would be a NMR spectrum. However, owing to a small quantity of the product isolated, we were unable to apply this technique.

The formation of *VII* is given by the tautomeric equilibrium:



and is a part of Oelschläger's ECE mechanism taking place at $\text{pH} > 4$. The equilibrium is shifted to the right with increasing concentration of hydroxyl ions. Under such circumstances a part of the starting substance is deactivated by a chemical reaction like (B) after the uptake of only 2 electrons per molecule, and the value of n becomes non-stoichiometrical.

The electrolysis in neutral and alkaline solutions is accompanied also by some other chemical reactions of the products. We came to this conclusion by following polarographically the composition of the solution during electrolysis. This assumption is supported by the finding of the product *V* and this reaction can be for oxazepam (I) described by the following chemical disproportionation:



The final elucidation of all reactions involved in the electrolytical reduction of *I*, *II* and *III* will require the isolation of all products, even of the minor ones and their

investigation, in particular by spectral methods. Here, we should like to emphasize that the position of the double bonds in the seven-membered ring cannot be reliably determined by infra-red spectra (in particular with chloroform-insoluble substances where potassium bromide techniques are used) or mass spectra. Only NMR spectra are reliable. In addition to this one will have to take into account the tautomers of the starting substances in sense of the equilibria suggested by Bell and coworkers^{12,13} for *I* or *II*; and these equilibria should be in future considered when deciding which form of *I*, *II* or *III* enters the electrochemical reaction.

REFERENCES

1. Oelschläger H., Volke J., Lim G. T., Spang R.: Arch. Pharm. (Weinheim) 302, 946 (1969).
2. Oelschläger H., Sengün F. J.: Pharmazie 29, 770 (1974).
3. Fazzari F. R., Riggleman O. H.: J. Pharm. Sci. 58, 1530 (1969).
4. Goldsmith J. A., Jenkins H. A., Grant J., Smyth W. F.: Anal. Chim. Acta 66, 427 (1973).
5. Volke J., Oelschläger H., Lim G. T.: J. Electroanal. Chem. Interfacial Electrochem. 25, 307 (1970).
6. Oelschläger H., Volke J., Lim G. T., Bremer U.: Arch. Pharm. (Weinheim) 303, 364 (1970).
7. Hlavatý J., Volke J., Manoušek O.: This Journal, in press.
8. Fryer R. I., Winter D., Sternbach L. H.: J. Heterocycl. Chem. 4, 355 (1967).
9. Clifford J. M., Smyth W. F.: Fresenius' Z. Anal. Chem. 264, 149 (1973).
10. Oelschläger H., Oehr H. P.: Pharm. Acta Helv. 49, 179 (1974).
11. Oelschläger H., Sengün F. J.: Chem. Ber. 108, 3303 (1975).
12. Bell S. C., Childress S. J.: J. Org. Chem. 27, 1691 (1962).
13. Bell S. C., Caulty R. J., Childress S. J.: J. Med. Chem. 11, 172 (1968).

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