203. *Controlled-potential Electrolysis. Part IX.*[1] *Reduction of Two Nitro-indolyl-esters in Acid Solution.*

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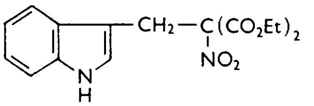
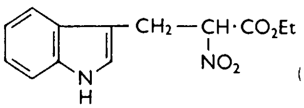
The reduction of ethyl α-nitro-β-indol-3-yl and ethyl α-ethoxycarbonyl-α-nitro-β-indol-3-yl-propionate has been investigated in order to see if the electrochemical reductive bond cleavage of the C–N bond, which is affected by strongly electronegative group(s) in aliphatic nitro-compounds, would take place. Our results have been compared with the chemical results obtained by Weisblat *et al.* The first compound was reduced to an amine and the second to a hydroxy-amine derivative by six- and four-electron reduction, respectively. The results are discussed.

In the electrochemical reduction of the *gem*-polynitroalkanes at a mercury electrode, it was found that, when the carbon atom linked to the nitro-groups has no hydrogen atom attached to it, then reductive bond cleavage of one of the C–N bonds occurred first, and this was facilitated by an increase in the number of nitro-groups.[1] The C–N bond fission is due to the large electron-attracting effect of the nitro-groups, and it was interesting to know if it takes place with compounds having other strongly electron-attracting groups in place of nitro-groups. For nitroalkanes having α-halogen substituents, C–halogen bond fission was stated to occur first,[2,3] and though this has not been proved experimentally it is plausible. Consequently, these observations give no information on the effect of the electronegativity of halogen on the reduction of $C-NO_2$ bonds. On the other hand, Weisblat *et al.*[4,5] stated that ethyl α-ethoxycarbonyl-α-nitro-β-indol-3-yl (I) and α-nitro-β-indol-3-yl propionate (II) behaved differently on chemical reduction. On catalytic reduction with Raney nickel, for instance, the former underwent C–N bond fission, whereas the latter formed an amine. On reduction with zinc and acetic acid, the former yielded a hydroxyamine derivative only.

(I)





(II)

In general an ethoxycarbonyl group resists reduction and has a large electron-attracting power. The present work was carried out in order to see whether the general rule governing the reduction of the *gem*-polynitroparaffins can be applied to nitroalkanes having an

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[1] Part VIII, Masui and Sayo, *J.*, 1962, 1733.

[2] Mairanowskii, Faĭnzil'berg, Movikov, and Klimova, *Doklady Akad. Nauk S.S.S.R.*, 1959, **125**, 351; *Chem. Abs.*, 1961, **55**, 8120.

[3] Glicksman and Morehouse, *J. Electrochem. Soc.*, 1959, **106**, 288.

[4] Weisblat and Lyttle, *J. Amer. Chem. Soc.*, 1949, **71**, 3079.

[5] Weisblat and Lyttle, *J. Amer. Chem. Soc.*, 1947, **69**, 2118.

electronegative group other than nitro in the α-position, and to compare the electrochemical and the chemical reductions.

Polarography.—The starting material (I) could be obtained only as a red-brown syrup which could not be purified completely,[4,5] and the polarographic studies of the two esters were carried out to find the correct conditions for controlled potential electrolysis. These and coulometric measurements showed that the syrup contained more than 90% of the malonate (I) and that none of the impurities was reducible.

The malonate (I) shows one reduction wave at pH 2·4—4·5 with a small but sharp maximum at pH 2·4, and two waves at pH 6·7—10·6 (cf. Fig. 1). From the dependence on pH of the half-wave potential and of the height of the first wave, and from the value of the diffusion current constant in acid solution, which is larger than that expected for a two-electron reduction, it seems that the reduction step must differ from that associated with the C–N bond fission observed with certain *gem*-polynitroalkanes.[1] The dependence of the diffusion current constant of the second wave on pH cannot be due to an equilibrium between a nitro- and an *aci*-form,[6] since the malonate cannot assume an *aci*-form. The marked decrease in wave height at pH 10·6 and above is probably to be explained by alkaline cleavage of the tertiary nitro-group,[7,8] but this was not investigated here. When tetraethylammonium iodide was used as supporting electrolyte, no further new wave was found in the more negative potential region, but the two waves obtained differed in the half-wave potentials and in the ratio of their wave heights from those obtained in Britton–Robinson's buffer solution in the near-neutral region. This difference seems to arise from either or both of the effects of tetraethylammonium iodide reported by Missan *et al.*[9] and the lack of buffer action. The final product may be assumed to be identical in the two cases because of the nearly equal total wave heights.

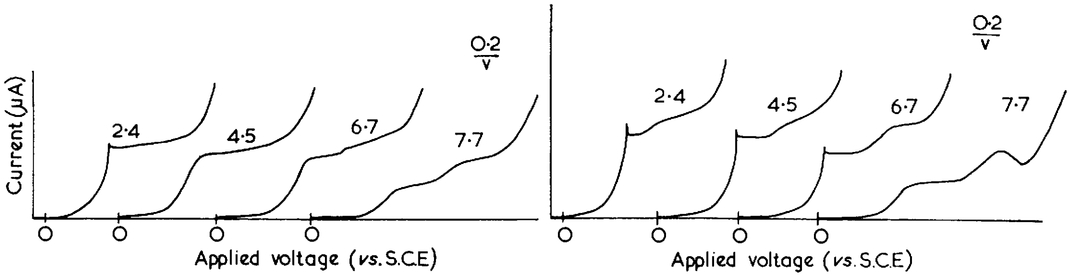

FIG. 1. FIG. 2.

Polarograms of the (Fig. 1; cf. Table 1) malonate (I) and (Fig. 2; cf. Table 2) propionate (II). Numerals on the curves denote pH.

The propionate (II) shows two waves at pH 2·4—7·7 (see Fig. 2). The first wave has a more pronounced maximum than that of the malonate (I) at pH 2·4—6·7. The second wave is observed at pH 2·4—7·7, and shows a broad maximum (or minimum) at pH 6·7—7·7. From the wave form, and the fact that some of the reduction product was adsorbed on a mercury electrode, as shown by a controlled-potential electrolysis, it seems that adsorption occurs to some extent at this stage. These waves disappear in alkaline solution. In this case also, the simple *aci*-nitro-equilibrium is not sufficient to explain all the polarographic behaviour.

The slightly lower value of the height of the first wave at pH 2·4 compared with that at pH 4·5 can be understood by considering the instability of the compounds in very acid solution.[4] The similarities of the half-wave potentials and of their dependence on pH,

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[6] Miller, Arnold, and Astle, *J. Amer. Chem. Soc.*, 1949, **71**, 3971.
[7] Seager and Elving, *J. Amer. Chem. Soc.*, 1950, **72**, 3241.
[8] Kleinfeller, *Ber.*, 1929, **62**, 1582.
[9] Missan, Becker, and Meites, *J. Amer. Chem. Soc.*, 1961, **83**, 58.

TABLE 1.

Half-wave potentials and diffusion-current constants of ester (I) in buffer solutions containing 30% of ethanol.

pH	2·4	4·5	6·7	7·7	8·7	10·6	12	0·1M–NEt_4I
$E_{\frac{1}{2}}$ (v)	$-0·48$	$-0·58$	$-0·67$	$-0·65$	$-0·67$	$-0·71$	—	$-0·71$
$i_d/cm^{\frac{2}{3}}t^{\frac{1}{6}}$	3·16	3·22	2·82	1·94	1·79	0·39	—	1·80
$E_{\frac{1}{2}}$ (v)	—	—	$-1·08$	$-1·15$	$-1·18$	$-0·9$	—	$-1·52$
$i_d/cm^{\frac{2}{3}}t^{\frac{1}{6}}$	—	—	0·23	0·75	0·98	0·15	—	1·40

TABLE 2.

Half-wave potentials and diffusion-current constants of ester (II) in buffer solutions containing 30% of ethanol.

pH	2·4	4·5	6·7	7·7	8·7	10·6
$E_{\frac{1}{2}}$ (v)	$-0·48$	$-0·60$	$-0·67$	$-0·69$	$-0·71$	—
$i_d/cm^{\frac{2}{3}}t^{\frac{1}{6}}$	3·86	3·91	3·32	1·21	0·22	—
$E_{\frac{1}{2}}$ (v)	$-0·77$	$-1·10$	$-1·27$	$-1·33$	—	—
$i_d/cm^{\frac{2}{3}}t^{\frac{1}{6}}$	0·40	0·52	1·03	—*	—	—

* Immeasurable.

for the two compounds, suggest that the reductions proceed with the participation of protons, and that their mechanisms may not be very different at the rate-determining step.

The ratio of the total wave heights of the malonate (I) and the propionate (II) at pH 4·5, where they have their maxima, is 1:1·4. Applying Riecke's rule[10] to calculate the relative electron numbers involved in these reductions gave $n = 4·7$ for (I) if n for (II) was assumed to be 6. In general, $n = 6$ denotes $-NO_2 \longrightarrow -NH_2$ and $n = 4$ denotes $-NO_2 \longrightarrow -NH{\cdot}OH$.

Studies by Controlled-potential Electrolysis.—Electrolysis of the propionate (II). Electrolysis was carried out at pH $\sim$2·5, after consideration of the polarographic results. Electrolysis, at a potential between the upper plateau of the first wave and the shoulder of the second wave, was prevented by adsorption of some of the reduction products which made the mercury electrode disperse into droplets after the current had passed for a few minutes. The electrolysis carried out at a more negative potential on the second-wave plateau proceeded without trouble and consumed electricity corresponding to 6·1 electrons per molecule. A hydrochloride was isolated from the electrolysed solution and identified as the hydrochloride of the tryptophan ethyl ester. Paper-chromatographic investigation of this solution showed also that the electrolysis yielded mainly tryptophan ethyl ester.

Electrolysis of the malonate (I). Electrolysis at a cathode potential of $-1·1$ volt and pH $\sim$2·5 consumed electricity corresponding to 3·9 electrons per molecule. From this solution colourless crystals were obtained in good yield which were identical with ethyl α-ethoxycarbonyl-α-hydroxyamino-β-indol-3-yl propionate prepared by a known method.[4] Investigation of the electrolysed product by paper chromatography showed no spot with the ninhydrin test.

Electrolysis of the Malonate (I) *with Uncontrolled Potential.*—It was proved as above that the nitro-group of the ester (I) was not reduced by the mercury cathode to an amine, but only to a hydroxyamine. In order to examine the effect of active hydrogen generated at an electrode on the reduction of this ester, a solution of it was electrolysed, at a lead cathode, with an applied voltage which caused violent generation of hydrogen gas, until the solution had lost the polarographic waves ($\sim$6 hours). The hydroxyamine derivative was the main product in this case also.

Discussion.—These results prove that electrolytic reduction of the malonate (I) in acid solution caused the process $-NO_2 \longrightarrow -NH{\cdot}OH$, requiring four electrons per molecule. With the propionate (II) the nitro-group was reduced to amino, six electrons per molecule

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[10] Cf. Riehl and Wirths, *Z. phys. Chem.*, 1944, **194**, 97.

being needed. The results are identical with those obtained by the chemical methods of Weisblat *et al.*,[4] except for catalytic reduction of the malonate with Raney nickel. It has been shown that the total effect of the two ethoxycarbonyl groups of the malonate on the C–NO_2 bond is not large enough to cause predominantly C–N bond fission at the electrode, unlike that of a nitro-group in 2,2-dinitropropane. Substituent constants for the inductive effect (σ' or σ_I) of a nitro-group are about twice those of an ethoxycarbonyl group,[11] and the experimental results are therefore rather unexpected. If, however, electrons from the electrode are to attack the carbon atom α to the nitro-group, and thus cause C–N bond fission, the latter must approach the electrode closely. It is possible that, for our esters (I) and (II), this close approach is prevented by the steric effects of the other three groups linked to this carbon atom. This is not the case for 2,2-dinitropropane. The more negative values of the half-wave potential of the malonate (I) than of 2,2-dinitropropane at the same pH values do not contradict this view, since this shows that the attack of electrons takes place at a point where electron-donation is more difficult than at the carbon atom, namely, at the neighbouring nitrogen atom.

The difference between the effects of two and of one ethoxycarbonyl group on the reduction of the nitro-groups is quite small in neutral and acid regions, as is shown by the half-wave potentials, and it might be supposed that the reduction mechanisms are not very different. Formation of hydroxyamine from the more easily reduced malonate (I), and of an amine from ester (II), can however scarcely be understood by considering simply the inductive effect of the ethoxycarbonyl groups or the steric effects of the neighbouring groups. It may be attributed to the absence or otherwise of an α-hydrogen atom, and further study on this point will be reported later.

EXPERIMENTAL

Apparatus.—The instruments and techniques used for polarographic study, controlled potential electrolysis, examination of infrared spectra, and measurements of pH values were the same as those described in a previous paper.[1] The saturated calomel electrode was used as a reference electrode. The dropping mercury electrode had a value of $m^{2/3}t^{1/6} = 1{\cdot}39$ mg.$^{2/3}$ sec.$^{-1/2}$ on open circuit. The temperature of the polarographic cell was $25° \pm 0{\cdot}1°$, but electrolyses were carried out at 15—30°. 0·005% of gelatin was used as a maxima suppressor for polarographic studies.

Materials.—The esters (I) and (II) were synthesised as described by Weisblat *et al.*[4,5] The latter was obtained from the former in 65% yield (calculated after recrystallisation of the product from benzene–acetone).

Ethyl α-ethoxycarbonyl-α-hydroxyamino-β-indol-3-yl propionate, prepared by Weisblat's method (35·5%), had m. p. 132—133°. The hydrochloride of DL-tryptophan ethyl ester, prepared according to the standard method,[12] had m. p. 225—227° (decomp.) (lit., 226—227°).

Paper Chromatography.—Toyo-roshi No. 51 filter paper and t-butyl alcohol–formic acid–water and butan-2-ol–acetic acid–water systems [13] were used.

Controlled-potential Electrolysis of the Propionate (II).—This ester (127·5 mg.) was dissolved in a small portion of ethanol and added to about 200 ml. of an aqueous-ethanolic solution 0·1M in phosphoric acid and 0·1M in potassium chloride which had previously been electrolysed. The final solution contained about 30% of ethanol and its pH value was ~2·5. Electrolysis at −1·1 v was continued for 1 hr., by which time the current had decreased to its background value. If necessary, ethanol was added during the electrolysis, but its content did not exceed about 50% (pH ~3). Electricity passed was 284 coulombs ($n = 6{\cdot}05$). The electrolysed solution was brought to pH 6—7 with dilute sodium hydroxide solution. Evaporation under reduced pressure, extraction with ether, and evaporation of the ether yielded a thick syrup, which gave a precipitate when dissolved in anhydrous ether and treated with ethanolic 10% w/v hydrochloric acid. Recrystallisation (once) from ethanol–ethyl acetate gave colourless crystals,

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[11] Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956.

[12] Snyder and Katz, *J. Amer. Chem. Soc.*, 1947, **69**, 3140.

[13] Underwood and Rockland, *Analyt. Chem.*, 1954, **26**, 1553.

m. p. 222—225° (decomp.), identical in infrared spectrum with the hydrochloride of DL-tryptophan ethyl ester described above. A portion of the syrup was treated with aqueous sodium hydroxide and examined on paper chromatograms by comparing its behaviour with that of various samples, including authentic DL-tryptophan. A brown substance observed at the edge of the solvent on the paper was not investigated, since it was found only in small quantities and appeared to be a decomposition product.

Controlled Potential Electrolysis of the Malonate of (I).—Procedures were the same as above. From the electrolysis of 117·8, 135·5, and 162·6 mg. of the ester, the electron number *n* was calculated to be 3·86 ± 0·05. The red-brown solid obtained from ether extracts after evaporation was recrystallised from ethanol. Colourless crystals, m. p. 133—134°, obtained in good yield, were identical (mixed m. p. and infrared spectrum) with ethyl α-ethoxycarbonyl-α-hydroxyamino-β-indol-3-ylpropionate. Paper chromatography was carried out on the red-brown solid as described above. A brown substance at the edge of the solvent was also observed.

Electrolysis of the Malonate (I) *with a Lead Cathode.*—A lead cathode (16 × 8·5 × 0·2 cm.) and a graphite anode were used. The anode solution was 0·1M in both phosphoric acid and potassium chloride, which was separated from the catholyte by a glass filter and a potassium chloride–agar salt bridge, having a large contacting area. The malonate (500 mg.) was dissolved in solution (~500 ml.) 0·1M in phosphoric acid and 0·1M in potassium chloride, and was electrolysed with a current of 1—2 amp. (20—30 v) for 6 hr. During the electrolysis the pH of the solution was maintained at pH 2·7—3·0 by addition of phosphoric acid solution, and the degree of the reduction was observed by taking polarograms of the solution from time to time. Treatment of the electrolysed solution was as described above.

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