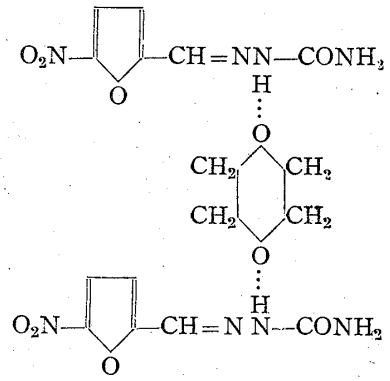
solution.*

4) Polarography can be applied to the quantitative analysis of Furacin in aqueous or hydrated alcoholic solution but not in dioxane soultion.

5) The nitro radical of Furacin is reduced to hydroxylamine by polarography and this reduction is an irreversible change.

(Received March 6, 1954)

* This reduction machanism may be caused by the dissociation of Furacin in dioxane where Furacin acts as a proton donor and dioxane acts as a proton acceptor as follows:



27. **Tadashi Sasaki**: Polarographic Study of Nitrofuran Derivatives. II[1]. Reduction Potential of Nirofuran Derivatives and Nitrobenzene Analogs.

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In Part I of this study[1], the reduction curve of Furacin was analyzed completely and the first wave was explained as being due to the reduction of the nitro radical. In the present series, experiments were enlarged to include several other nitrofuan derivatives and nitrobenzene analogs having a similar structure as Furacin in order to discover relationship, if any, between the reduction·potential of the nitro group in nitrofuran derivatives and their bactericidal action.

Experimental

Experiments were carried out essentially in a similar way as in Part I of this study[1]. The preparation of the sample to be electrolyzed was as follows: After dissolving 10^{-4} mole of the sample in 15 cc. of alcohol**, 1.5 cc. of this solution was mixed with a buffer solution to make a total volume of 10 cc. As a buffer solution McIlvain's citric acid-Na_2HPO_4 mixture[2], pH ranging from 4.0 to 8.0 was used. Electrolysis by using the dropping mercury cathode was carried out at a room temperature on nitrofurfural semicarbazone (Table I), nitrofuran (Table II), *p*-nitrobenzal semicarbazone (Table III), nitrofurfural aminoguanidine hydrochloride (Table IV), nitrofurfural phenylsemicarbazone (Table V), dinitrofuran (Table VI), *p*-nitrobenzal aminoguanidine hydrochloride (Table

* Yoshida-konoe-cho, Sakyo-ku, Kyoto (佐々木 正).

1) Part I: This Bulletin, 2, 99(1954). Part of the paper read before the Annual Meeting of the Pharmaceutical Society of Japan, June, 1950.

2) McIlvain: J. Biol. Chem., 49, 183(1921).

** When a sample did not dissolve completely in alcohol, a saturated soultion was used. Cf. References to Tables V, XXIII, XXIV, XXV, XXVII, and XXVIII.

VII), condensation products of nitrofurfural with aniline, toluidine, and phenylhydrazine (Table VIII), *o*-nitrobenzal semicarbazone (Table IX), *o*-nitrobenzal aminoguanidine hydrochloride (Table X), nitrofurfural aminoguanidine (Table XI), nitrofurfuraldoxime (Table XII), nitrobromofuran (Table XIII), nitrofurylacrylic acid (Table XIV), nitrofuroic acid (Table XV), furylacrylic acid (Table XVI), nitrofurfural (Table XVII), nitrofurylacrolein (Table XVIII), nitrofurylnitrile (Table XIX), ethyl nitrofuroate (Table XX), nitrofuroic amide (Table XXI), ethyl nitrofurylacrylate (Table XXII), nitrofuroic anilide (Table XXIII), nitrofuroic *p*-toluidide (Table XXIV), nitrofuroic *p*-nitroanilide (Table XXV), nitrofurfural semioxanazone (Table XXVI), nitrofurylacrolein semicarbazone (Table XXVII), nitrofurylacrolein aminoguanidine hydrochloride (Table XXVIII), and nitrofurylacrylic amide (Table XXIX).

E_i : Reduction potential vs. the standard calomel electrode in volt for i-th wave.
i_{di} : Diffusion current in 10^{-6} ampere for i-th wave.
0.02% aq. gelatine solution used.

Table I. Nitrofurfural Semicarbazone

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.285	6.1	−1.515	5.5
5.0	−0.342	5.9	−1.312	4.2
6.0	−0.405	5.9	−1.475	2.9
7.0	−0.425	6.1	−1.410	2.6
8.0	−0.520	5.8	−1.500	0.6

10^{-4} mole in 15% alcoholic soultion.

Table II. Nitrofuran

E_1	i_{d_1}	
−0.732	13.0	This polarogram belongs to Fig. 3 ; only the first wave is described here.
−0.760	10.0	
−0.680	9.1	
−0.678	6.8	
−0.648	3.9	

Table III. *p*-Nitrobenzal Semicarbazone

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.480	5.1	−1.210	5.4
5.0	−0.480	5.1	−1.375	5.3
6.0	−0.530	4.7	−1.463	4.2
7.0	−0.580	4.7	−1.380	3.4
8.0	−0.680	4.4	−1.300	2.1

Table IV. Nitrofurfural Aminoguanidine-HCl

E_1	i_{d_1}	E_2	i_{d_2}
−0.265	6.4	−1.210	7.3
−0.340	6.7	−1.370	5.4
−0.380	6.2	−1.483	4.2
−0.400	6.4	−1.385	3.2
−0.500	7.3	−1.560	2.9

2 drops of aq. gelatine soln. was added.

Table V. Nitrofurfural Phenylsemicarbazone (saturated soln.)

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.185	0.57	−1.085	1.25
5.0	−0.225	0.48	−1.150	0.97
6.0	−0.250	0.41	−1.160	0.69
7.0	−0.310	0.32	−1.150	0.69
8.0	−0.382	0.31	−1.120	0.48
			−1.560	

Table VI. Dinitrofuran

E_1	i_{d_1}	E_2	i_{d_2}	E_3&E_4 (i_{d_3} & i_{d_4})	
−0.175	5.5	−0.990	7.1		
−0.185	4.2	—	—		
−0.180	2.9	—	—		
−0.160	2.4	−1.165	1.3		
−0.155	1.9	−1.210	1.1	−1.625	4.1
				−1.833	3.3

Table VII. *p*-Nitrobenzal Aminoguanidine-HCl

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.350	4.8	−1.120	4.3
5.0	−0.460	4.8	−1.350	3.5
6.0	−0.500	4.5	−1.440	3.0
7.0	−0.460	4.4	−1.320	3.4
8.0	−0.540	4.2	−1.450	2.6

Table VIII. Condensates with Aniline, Toluidine, and Phenylhydrazine

All the polarograms are shown in Fig. 3.

Table IX. *o*-Nitrobenzal Semicarbazone

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.520	1.7	−1.295	2.2
5.0	−0.450	0.5	−1.365	1.8
6.0	−0.490	1.8	−1.340	0.3
7.0	−0.550	1.8	−1.340	0.6
8.0	−0.600	1.7	−1.530	0.5

Table X. *o*-Nitrobenzal Aminoguanidine-HCl

E_1	i_{d_1}	
−0.463	3.3	Only the first wave described here.
−0.478	3.3	
−0.435	3.5	
−0.428	2.3	
−0.510	3.3	

Table XI. Nitrofurfural Aminoguanidine

pH	E_1	i_{d1}
4.0	−0.470	7.5
5.0	−0.470	7.3
6.0	−0.460	6.5
7.0	−0.475	7.7
8.0	−0.610	9.8

Maximum appeared even after the addition of aq. gelatine solution.

Table XII. Nitrofurfuraldoxime

E_1	i_{d1}	E_2	i_{d2}
−0.348	6.2	−1.575	5.6
−0.395	6.7	−1.550	4.2
−0.395	5.8	−1.410	3.8
−0.400	5.8	−1.400	2.7
−0.490	6.0	−1.570	2.1

One drop of aq. gelatine solution was added.

Table XIII. Nitrobromofuran

pH	E_1	i_{d1}
4.0	−0.352	1.8
5.0	−0.385	1.6
6.0	−0.350	1.9
7.0	−0.410	0.5
8.0	−0.440	0.5

One drop of aq. gelatine soln. was added.

Table XIV. Nitrofurylacrylic Acid.

E_1	i_{d1}
−0.510	6.4
−0.512	6.0
−0.480	5.5
−0.450*	4.9
−0.535*	4.7

*) Polarographic maximum appeared, so aq. gelatine soln. was added.

Table XV. Nitrofuroic Acid

pH	E_1	i_{d1}
4.0	−0.248	2.0
5.0	−0.310	1.8
6.0	−0.390	1.3
7.0	−0.455	1.1
8.0	−0.550	1.3

Table XVI. Furylacrylic Acid

There was no wave in this pH range.

Table XVII. Nitrofurfural

pH	E_1	i_{d1}
4.0	−0.161	
	−0.370	4.6
5.0	−0.225	
	−0.510	4.1
6.0	−0.285	
	−0.580	3.7
0.7	−0.330	
	−0.580	3.2
0.8	−0.380	
	−0.650	3.4

The first wave divided into two. The polarogram belongs to Fig. 3. One drop of aq. gelatine soln. was added.

Table XVIII. Nitrofurylacrolein

E_1	i_{d1}
−0.390	5.1
−0.350	4.7
−0.305	4.4
−0.350	3.1
−0.400	3.1

This polarogram belongs to Fig. 3. Only the first wave is described here. One drop of aq. gelatine soln. was added.

Table XIX. Nitrofurylnitrile

pH	E_1	i_{d1}
4.0	−0.242	4.8
5.0	−0.305	5.4
6.0	−0.310	4.4
7.0	−0.355	4.2
8.0	−0.420	4.2

One drop of aq. gelatine soln. was added.

Table XX. Ethyl Nitrofurylcarboxylate

E_1	i_{d1}
−0.255	4.8
−0.310	4.9
−0.345	4.6
−0.415	4.6
−0.455	4.2

One drop of aq. gelatine soln. was added.

Table XXI. Nitrofuroic Amide

pH	E_1	i_{d1}
4.0	−0.320	5.3
5.0	−0.335	5.8
6.0	−0.380	5.8
7.0	−0.482	5.6
8.0	−0.582	5.4

One drop of aq. gelatine soln. was added.

Table XXII. Ethyl Nitrofurylacrylate

E_1	i_{d1}
−0.225	3.2
−0.325	3.9
−0.350	2.1
−0.370	2.2
−0.425	1.3

Table XXIII. Nitrofuroic Anilide (saturated soln.)

pH	E_1	i_{d_1}
4.0	−0·160	2.9
5.0	−0.220	1.9
6.0	−0.250	1.7
7.0	−0.325	1.9
8.0	−0.400	1.7

Table XXIV. Nitrofuroic *p*-Toluidide (saturated soln.)

E_1	i_{d_1}
−0.135	0.6
−0.170	0.6
−0.220	0.6
−0.270	0.6
−0.335	0.6

Table XXV. Nitrofuroic *p*-Nitroanilide (saturated soln.)

pH	E_1	i_{d_1}	E_2	i_{d_2}
4.0	−0.100	0.45	−0.345	0.23
5.0	−0.120	0.38	−0.400	0.13
6.0	−0.180	0.23	−0.450	0·13
7.0	−0.250	0.32	−0.500	0.13
8.0	−0.280	0.32	−0.580	0.09

Table XXVI. Nitrofurfural Semioxanazone

E_1	i_{d_1}	E_2	i_{d_2}
−0.200	2.2	−1.270	1.5
−0.230	2.2	−1.240	1.5
−0.300	2.4	−1.350	1.3
−0.350	2.2	−1.340	1.4
−0.410	2.4	−1.430	1.4

Table XXVII. Nitrofurylacrolein Semicarbazone (saturated soln.)

pH	E_1	i_{d_1}
4.0	−0.275	2.2
5.0	−0.320	2.2
6.0	−0.340	2.4
7.0	−0.370	2.2
8.0	−0.465	2.5

One drop of aq. gelatine soln. was added.
Only the first wave is described.

Table XXVIII. Nitrofurylacrolein Aminoguanidine-HCl (saturated soln.)

E_1	i_{d_1}
−0.185	1.5
−0.225	1.2
−0.270	1.3
−0.340	1.8
−0.440	2.0

One drop of aq. gelatine soln. was added.
Only the first wave is described.

Table XXIX. Nitrofurylacrylic Amide

pH	E_1	i_{d_1}
4.0	−0.275	5.2
5.0	−0.320	5.3
6.0	−0.345	5.2
7.0	−0.400	5.6
8.0	−0.450	5.8

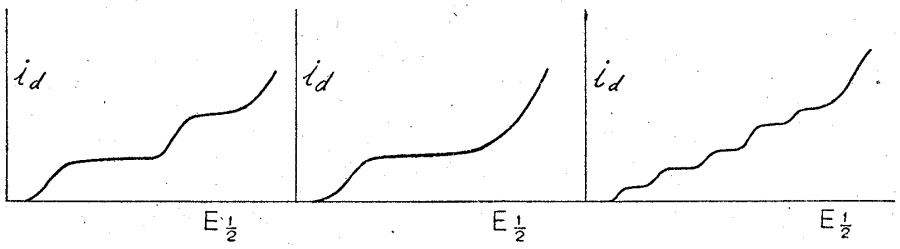

Fig. 1. Fig. 2. Fig. 3.

Discussion

The results obtained from the polarograms of these compounds show that there are three types of reduction waves as shown in Figs. 1, 2, and 3. Fig. 1 shows two reduction waves which are the reduction of the nitro radical and of the unsaturated bond at the side chain. Fig. 2 has only one wave which is the reduction of the nitro radical, and acids and their derivatives belong to this group. Fig. 3 shows a multi-waved shape and these polarograms are comparatively labile to the variation of pH and to the passage of time. The compounds belonging to this group have no remarkable bactericidal action.

Concerning the relation between the reduction potential of the nitro group and its bactericidal action, the following can be concluded:

(1) Nitrofuran compounds generally have a more positive reduction potential than the corresponding nitrobenzene compounds, though their waves are similar in shape.

(2) Among the nitrofuran compounds the introduction of an ethylenic bond between the furan nucleus and the side chain makes the reduction potential more positive than those having no such bond. In other words, the introduction of a conjugated bond with furan nucleus makes the reduction potential of the nitro radical more positive.

(3) Nitrofuran compounds belonging to Fig. 1 generally have a more positive reduction potential than those of Fig. 2 for the same reason as for (2).

(4) There is no bactericidal compound that shows a labile polarogram.

Generally speaking, it can be said that with the reduction potential more positive, the bactericidal action becomes stronger. Nevertheless, the proposal that only the lowering of the reduction potential of the nitro radical is an essential factor for the compounds to be bactericidal seems to be an extreme argument, for the introduction of a positive radical, such as methyl, to the side chain lessened the reduction potential of the nitro radical but did not show any marked bactericidal action*. Furthermore, if the reduction of the nitro radical is the most essential factor for the bactericidal action, a more marked difference in the reduction potential should be observed among nitrofuran derivatives in accordance with their bactericidal action but this difference is experimentally within a very narrow range and no difference can be observed.

Indeed, the reduction of the nitro group in nitrofuran derivatives will proceed in a different way from such an electrochemical reduction as polarography in the human body in which the enzymic reduction seems to play an important part. In this sense, the redox potential[3] should be measured by a proper method under proper conditions. It seems true, however, that the important requirements for any nitrofuran compound to be bactericidal are the lessening of the reduction potential and showing of a stable polarogram to the variation of pH and the passage of time.

The author is grateful to Prof. H. Saikachi of Kyushu University for his kind advices and criticism. This study was supported by a Grant from the Ministry of Education, for which he wishes to express his gratitude.

Summary

The reduction potential given by the polarography of antibacterial nitrofuran derivatives is more positive than the corresponding nitrobenzene derivatives and as a whole, the requirements for any nitrofuran compound to be bactericidal seem to be the lessening of the reduction potential of a nitro radical and the showing of a stable polarogram. These facts show that the reduction of a nitro radical plays an important part in its bactericidal mechanism, though not clear in detail.

(Received March 6, 1954)

* Author's unpublished data. This polarogram gave a labile wave.

3) O. Dann, E.F. Möller: Ber., 82, 76(1949); H. Kubo: "Oxidation-Reduction Potential," Nanjo Shoten, 25(1947).