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Electroörganic Preparations

XXXII. Polarography and Reduction of Some 4-Substituted Quinazolines

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Some 4-substituted quinazolines have been investigated polarographically, by cyclic voltammetry, and by means of controlled potential reduction. The general scheme for the electrode reactions is in acid solution a reduction to the 3,4-dihydroderivative, followed by an elimination of the substituent and further reduction of the quinazoline thus formed.

3,4-Dihydro-4-methoxyquinazoline forms in alkaline solution a dimeric product, which easily is oxidized to 4,4′-biquinazoline; the reaction mechanism is suggested to be analogous to that of the benzoin condensation.

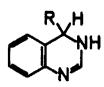
Quinazoline (Ia) derivatives react in many cases analogously to the corresponding purine derivatives. Adenine [1] and other biologically important 6-substituted purine bases [2–4] have been investigated polarographically and by controlled potential electrolysis; in the present investigation, 4-substituted quinazolines which, in comparison to the corresponding 6-substituted purine derivatives have certain advantages with respect to electrochemical behaviour, have been investigated by classical polarography, cyclic voltammetry at the hanging mercury drop electrode, and preparative controlled potential reduction.

In the study were included 4-aminoquinazoline (Ib), 4-diethylaminoquinazoline (Ic), 4-mercaptoquinazoline (Id), 4-(methylthio)quinazoline (Ie), 4-methoxyquinazoline (If), the 3,4-dihydroderivatives (IIa–f), 4,4′-biquinazoline (III), and its reduction product (IV). 4-Chloroquinazoline (Ig) has previously been investigated.[5]

RESULTS

4-Diethylaminoquinazoline (Ic). The polarographic behaviour of Ic is depicted in Fig. 1. In strongly acid solution, a single two-electron wave (wave

I a R=H
b R=NH_2
c R=$N(C_2H_5)_2$
d R=SH
e R=SCH_3
f R=OCH_3
g R=Cl



II a R=H
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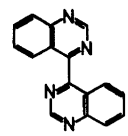
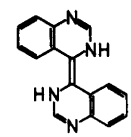
f R=OCH_3



III



IV

I) is found; between pH 0 and 2, it grows to the height of a four-electron wave. About pH 8, the height of wave I gradually diminishes with increasing pH, and another four-electron wave (wave II) grows up in the usual way for a transition from the reduction of a protonated molecule to a reduction of an unprotonated one. At about pH 6, a further reduction wave (wave III) appears at a potential, approximately the same as that of 3,4-dihydroquinazoline (IIa). The further polarographic reduction is similar to that of IIa.[5]

Cyclic voltammetry at the hanging mercury drop electrode (HME) of Ic in citric acid buffer indicated a reduction of Ia on the second sweep, but not on the first one.

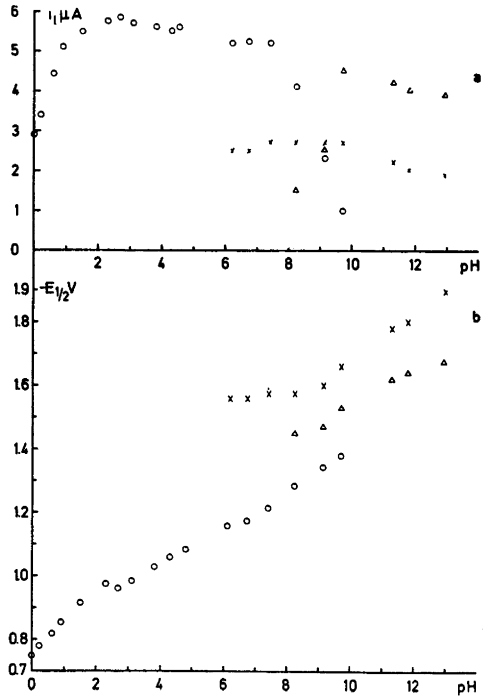


Fig. 1. (a) Limiting current (μA), and (b) half-wave potentials (V *vs.* SCE) of 4-diethylaminoquinazoline (Ic). ○, 1st wave (reduction of protonated Ic); △, 1st wave (reduction of unprotonated Ic); ×, 2nd wave of Ic. Concentration 4×10^{-4} M.

Reduction of Ic in citric acid buffer at −1.1 V (SCE) consumed four electrons per molecule, and produced IIa. During the reduction, a small reduction wave of quinazoline (Ia) could be detected polarographically in the catholyte.

4-Aminoquinazoline (Ib). Ib behaves polarographically in a similar way as Ic. The two-electron wave (wave I) grows to the height of a four-electron wave between pH 2 and 4, and a further reduction wave (IIIa), nearly merging with the reduction of the hydrogen wave, is visible from about pH 3 to 5.5. The second wave (IIIb) appears again at pH > 6.5 at a potential corresponding to the reduction of IIa. The transition between the reduction of the protonated and the unprotonated molecule is not clearly visible, but about pH 8.5, the reduction waves merge to a composite wave with a height corresponding to a six-electron reduction; at pH > 11, the height of this wave diminishes somewhat.

Cyclic voltammograms of Ib showed similar features as those of Ic; a reduction wave of Ia was found on the second sweep, and not on the first one.

Controlled potential reduction of Ib in citric acid buffer at −1.2 V (SCE) produced 3,4-dihydroquinazoline (IIa) in a four-electron reduction; quinazoline, which is reduced at a less negative potential than Ib, could be detected

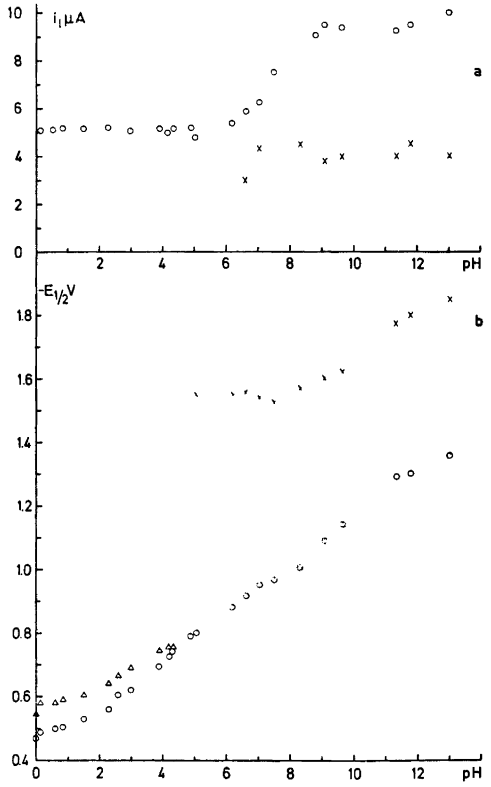


Fig. 2. (a) Limiting current (μA), and (b) half-wave potentials (V *vs.* SCE) of 4-(methylthio)quinazoline (Ie). (a) ○, 1st wave (in acid solution, the sum of the two one-electron waves); ×, 2nd wave. (b) ○, 1st wave; △, second one-electron wave); ×, 2nd wave in neutral and alkaline solution. Concentration 4×10^{-4} M.

polarographically as an intermediate in the catholyte during the reduction. IIa was also isolated from a reduction of Ib in 4 N hydrochloric acid.

A reduction of Ib in a solution of lithium chloride containing lithium hydroxide at −1.80 V (SCE) consumed between five and six electrons per molecule and produced 1,2,3,4-tetrahydroquinazoline; during the reduction, quinazoline (Ia) and biquinazoline (III) could be detected polarographically in the catholyte.

4-Mercaptoquinazoline (Id). Id is only slightly soluble in water and was investigated polarographically in a medium containing 40 % dimethylformamide (DMF). The polarographic behaviour of Id is very similar to that of Ib. The first wave of Ib grows from a two-electron wave to a four-electron wave between pH 2 and 4, and remains there constant between pH 4 and 10; at pH > 10, the wave diminishes, possibly due to the loss of a proton to form the anion. About pH 13, the first and the second wave merge. A small adsorption wave, due to the adsorption of either a mercapto derivative or hydrogen sulphide, is visible on the polarograms at pH > 1.

During a controlled potential reduction of Id in citric acid buffer hydrogen sulphide was evolved, and Ia could be detected polarographically in the catholyte.

4-(Methylthio)-quinazoline (Ie). Below pH 4, Ie shows two one-electron waves which merge about pH 4 (Fig. 2). Between pH 6.5 and 9, the wave grows to a four-electron wave; a two-electron reduction wave at more negative potentials corresponds to the reduction of IIa.

At pH > 4, the wave shows evidence of adsorption of Ie at the mercury cathode; the wave-form is similar to that found for 1-(2′-pyridyl)-2-(2′-pyridyl)-ethylene;[6] the current grows very steeply in dependence on potential. The explanation suggested [6] was that the depolarisator adsorbed to the electrode is more difficult to reduce than the free depolarisator; when the potential is reached where the adsorbed molecules are reduced, the adsorbed layer disappears, and at that potential the free depolarisator can be reduced and the limiting current is reached. The reduction and desorption of the depolarisator is evidenced on the electrocapillary curve, which shows a steep increase at the potential where the reduction of the depolarisator starts.

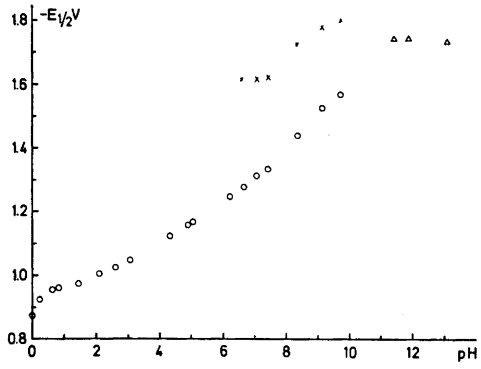


Fig. 3. Half-wave potentials (V *vs.* SCE) of 4-methoxyquinazoline. ○, 1st wave; ×, 2nd wave; △, composite wave.

4-Methoxyquinazoline (If). The polarographic reduction of If (Fig. 3) is like that of Ie, but no specific adsorption is indicated by the polarograms. The height of the first wave corresponds to a two-electron wave from pH 1.5 to 8; the wave of the protonated compound disappears between pH 8 and 11, and a composite reduction wave of the unprotonated compound is found at more negative potentials.

Controlled potential reduction of If in methanolic hydrochloric acid at −0.80 V (SCE) yielded a product which from its NMR-spectrum was assumed to be 3,4-dihydro-4-methoxyquinazoline (IIf). Attempts to purify the product were marred by its easy reoxidation or loss of methanol.

Reduction of If in aqueous hydrochloric acid also gave $n=2$; from the catholyte only 4-hydroxyquinazoline was isolated, which probably is formed in a coupled reoxidation and hydrolysis of the reduction product IIf. A similar result was obtained in acetate buffer.

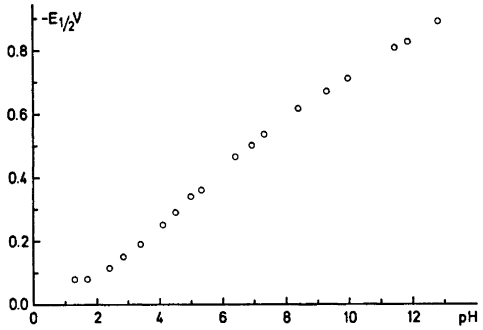


Fig. 4. Half-wave potentials (V *vs.* SCE) of 4,4′-biquinazoline.

A reduction of If in methanolic hydrochloric acid, followed by basification of the solution with solid potassium hydroxide, yielded three products, quinazoline, formed by loss of methanol from IIf, 4-methoxyquinazoline (If), from reoxidation of IIf, and 4,4′-biquinazoline; the formation of the latter will be discussed below.

4,4′-Biquinazoline (III). 4,4′-Biquinazoline and its reduction product IV form a redox system which according to certain criteria behaves reversibly in alkaline solution; in acid solution, the behaviour is complicated by a reversible hydration of the heterocyclic nuclei.

The half-wave potentials of III lie between pH 2 and 7 on a straight line with the slope 0.088 V/pH and between pH 8 and 13 on a line with the slope 0.059 V/pH (Fig. 4). The wave-height is constant at pH > 3, but lower in acid solution. At pH 0.4, the wave-height is about 15 % of the limiting current at pH 5 and is independent of the height of the mercury reservoir, which means that the limiting current is determined by the rate of a chemical reaction, whereas at pH 5, the limiting current is diffusion controlled.

Cyclic voltammetry at the hanging mercury drop electrode indicated that between pH 9 and 12, using a sweep rate of 63 mV/sec, the redox system was reversible, according to the criterion Ep 3/4 = E 1/2 (DME) for both the cathodic (Epc) and the anodic peak potentials (Epa). The values of the peak

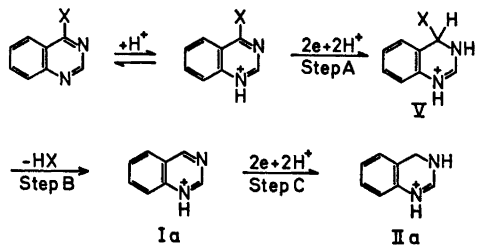
potentials and half-peak potential (Ep 1/2) indicated a reversible two-electron reaction according to $Ep - Ep\ 1/2 = 0.059/n$, and $Epc - Epa = 0.059/n$.

Controlled potential reduction at -0.8 V (SCE) of III in an acetate buffer containing 70 % *N*,*N*-dimethylformamide gave $n = 2$ *F*/mol; the reduced solution was then reoxidized at -0.5 V (SCE) with the consumption of 2 *F*/mol. Attempts to isolate the reduction product IV failed due to its easy reoxidation to III and/or hydrolysis to quinazoline.

DISCUSSION

The polarographic behaviour and the preparative results from the electrolysis of the 4-substituted quinazolines Ib – If can be explained if the following general reaction mechanism is assumed in acid solution:

SCHEME I



In neutral and alkaline solution, a reduction of IIa to 1,2,3,4-tetrahydroquinazoline occurs if the potential is sufficiently negative.

The rate of step B is dependent on pH and the nature of X, a.o. the properties of X as a leaving group. No quantitative investigations on the rates have been made here; the qualitative finding is that the rate grows with pH. In acid solution, the height of the polarographic wave of Ib, Ic, Id, and Ie corresponds to $n = 2$, whereas a preparative reduction indicates $n = 4$. The rate of step B is too slow at the dropping mercury cathode (DME), so the primarily formed product V diffuses away from the electrode before the reducible Ia is formed; at higher pH, the rate of step B is faster, and Ia is formed near the electrode surface. The duration of a preparative reduction is so long that the elimination can occur, even if the rate is relatively low.

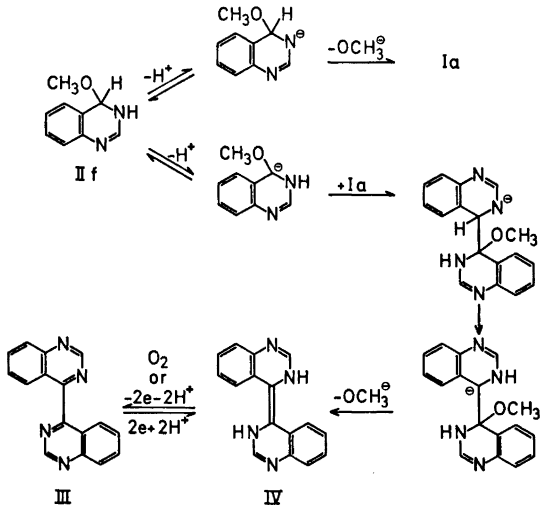
The 3,4-dihydroderivatives (IIb – f) are analogous to the covalent hydrated quinazoline, in which case only the protonated quinazoline is appreciably hydrated. For the compounds IIb – IIf, the reversal of step B is unimportant; a reversible hydration of the quinazoline cation formed in step B could account for the two-electron wave observed in the reduction of Ib – If, if the rate of hydration was high enough; the polarographic results of 4-chloroquinazoline (Ig) show,[5] however, that this explanation can be ruled out, as Ig even at pH 1 exhibits two two-electron polarographic waves.

The results from cyclic voltammetry are also in accordance with Scheme I; the dihydrocompound formed in the first sweep eliminated HX to Ia, which shows a reduction peak on the second, but not on the first sweep.

A direct proof of the existence of a dihydro derivative as V was obtained in the reduction of If from the NMR-spectrum of the product. On the basis of this and the above mentioned evidence, it is suggested that Scheme I is valid for all the compounds Ib – If; it seems reasonable to expect that the reduction of adenine follows a similar route.

Less conclusive evidence is available for the reduction in alkaline solution where the unprotonated, substituted quinazoline is reduced. The presence of Ia as an intermediate was shown during the reduction of If and Ib in methanol, containing lithium methoxide, and in the absence of contradicting evidence, the general validity of a scheme will be assumed, in which the elimination occurs after the first two-electron reduction. 4-Hydroxyquinazoline (VI) is, however, in alkaline solution reduced in a two-electron reaction to 4-oxo-1,2,3,4-tetrahydroquinazoline,[7,8] but VI is found predominantly at the keto-form (an amide) and is thus only formally an analog to the compounds discussed above.

3,4-Dihydro-4-methoxyquinazoline (IIf) reacts in alkaline solution in two ways; in one, Ia is formed, and in another, III is the product; the yield of III is higher at higher concentrations of IIf; IIb reacts in a similar manner. The following reaction mechanism for the formation of III from IIf is suggested:

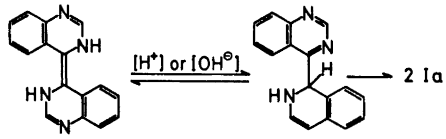


A similar condensation of quinazoline to 4,4′-biquinazoline can be effected on addition of cyanide ions [9] or Grignard reagents [10] to quinazoline.

Compound III is formally an α-diimine, and IV an enediamine; the redox system III⇌IV is, however, more reversible than systems as 5,6-dihydropyrazine-1,2,3,4-tetrahydropyrazine [11] or other α-diimine-enediamine systems,[12]

where the anodic wave of the enediamine occurs at less negative potentials than the cathodic wave of the α-diimine.

IV may tautomerize to 4-(4′-quinazolyl)-3,4-dihydroquinazoline (VII) which, as the other 4-substituted 3,4-dihydroquinazolines studied here, may easily eliminate the substituent, in this case quinazoline; these reactions may influence the reversibility of the redox system III – IV.



IV VII

EXPERIMENTAL

Apparatus. The potential control was made with a transistorized potentiostat (Tage Juhl Electronics, Copenhagen); the amount of electricity consumed was measured with an electromechanical integrator. For the cyclic voltammetry, a Heathkit Polarograph Module EUA-19-2 with an operational amplifier EUW-19B and X-Y-recorder (Hewlett Packard 7035B) was used. The hanging drop electrode was obtained from Radiometer, Copenhagen.

Materials. 4-Aminoquinazoline (Ib) and 4-diethylaminoquinazoline (Ic) were prepared according to Tomisek and Christensen,[13] 4-mercapto- (Id) and 4-(methylthio)-quinazoline (Ie) according to Leonard and Curtis,[14] and 4-methoxyquinazoline (If) according to Bogert and May.[15] Quinazoline and 3,4-dihydroquinazoline were prepared as previously described.[5]

Reduction of 4-aminoquinazoline (Ib). Ib (0.2 g) was reduced in a citric acid buffer, pH 2.9, at −1.20 V (SCE). The reduction consumed 4 *F*/mol. On polarograms obtained from the catholyte during the reduction, two polarographic waves of equal height at −0.175 and −0.65 V (SCE) were visible; reduction waves at these potentials in this medium point to the presence of quinazoline. The reduction completed, the catholyte was made alkaline (pH 13), and a polarographic wave at −1.80 V (SCE) indicated that the product was 3,4-dihydroquinazoline (IIa).

Reduction of Ib in 4 N hydrochloric acid at −0.80 V (SCE) also consumed 4 *F*/mol; evaporation of the catholyte after completion of the reduction left a residue of ammonium chloride and 3,4-dihydroquinazoline hydrochloride; the latter was identified by its IR- and NMR-spectrum (CF_3COOH; $\delta = 4.92$ (singlet), $\sum H = 2$; $\delta = 7.0 - 7.5$ (multiplet), $\sum H = 4$; $\delta = 9.5 - 10.0$ (multiplet), $\sum H = 1$), identical with that of authentic IIa.

Reduction of Ib in an alkaline solution (lithium chloride and lithium hydroxide) at −1.80 V (SCE) consumed 6 *F*/mol; the reduction completed, the catholyte was extracted with ether which was dried (Na_2SO_4) and evaporated. The residue was treated with ethanolic hydrogen chloride and the hydrochloride precipitated with ether. It was identified as 1,2,3,4-tetrahydroquinazoline from the NMR-spectrum (CF_3COOH; $\delta = 4.82$ (singlet), $\sum H = 2$; $\delta = 5.33$ (singlet), $\sum H = 2$; $\delta = 7.2 - 8.0$ (multiplet), $\sum H = 4$). The methylene group of 1,2,3,4-tetrahydro-4-oxo-quinazoline exhibits a singlet at $\delta = 5.35$.

4-Diethylaminoquinazoline (Ic), 4-mercaptoquinazoline (Id), and 4-(methylthio)-quinazoline (Ie) were reduced in citric acid buffer; they all consumed 4 *F*/mol, and the product was IIa, which was shown by polarography of the reduced solution, after pH was raised to 13. During the reduction of Id, hydrogen sulphide was evolved.

Reduction of 4-methoxyquinazoline (If). If was reduced in anhydrous methanol containing hydrogen chloride (2 N) at −0.80 V (aq. SCE); the reduction consumed 2 *F*/mol. The reduction completed, the catholyte was evaporated *in vacuo*, and the residue washed with dry ether. The product was assumed to be 3,4-dihydro-4-methoxy-quinazoline from the NMR-spectrum (CF_3COOH; $\delta = 3.25$ (singlet), $\sum H = 3$; $\delta = 4.88$

(singlet), $\sum H = 1$; $\delta = 7.9 - 8.7$ (multiplet), $\sum H = 4$; $\delta = 9.2$ (singlet), $\sum H = 1$. The same compound was obtained in citric acid buffer pH 3; it was isolated by extraction with ether.

During the reduction of If in anhydrous methanol containing lithium methoxide at -1.70 V, the presence of Ia, IIa, and III could be detected by polarography.

4,4'-Biquinazoline (III). If was reduced in anhydrous methanol containing hydrogen chloride as described above; the reduction completed (2 F/mol), the catholyte was made strongly alkaline with solid potassium hydroxide, and the methanol evaporated *in vacuo;* after addition of water, the solution was left overnight. The aqueous solution was extracted with chloroform, which was then dried (Na_2SO_4), and the chloroform was removed *in vacuo*. The residue was chromatographed on alumina with a 2:3 mixture of ether and benzene as eluent. Isolated were If, m.p. 35°C (34.5°C),[15] Ia, m.p. 48°C (48.5°C),[16] and III, m.p. 230–232°C (208–209°C,[10] 246–247°C [9]). (Found: C 73.75; H 3.69; N 22.73. Calc. for $C_{16}H_{10}N_4$: C 74.41; H 3.90; N 21.60.) Mass spectrum showed a.o. the molecular ion *m/e* 258. IR-spectrum (KBr): 1620(m), 1560(s), 1535(m), 1495(s), 1377(s), 1330(s), 1150(m), 1090(m), 970(m), 760(s), 630(m). UV-spectrum (cyclohexane, nm): 223 (log ε 4.56), 242 (log ε 4.19), 284 (log ε 3.61), 320 (log ε 3.87). NMR-spectrum ($CDCl_3$): $\delta = 8.3 - 7.25$ (multiplet), $\sum H = 8$; $\delta = 9.50$ (singlet), $\sum H = 2$. The spectra were identical to those obtained from III, prepared according to Amarego and Willette.[9]

Reduction of 4,4'-biquinazoline (III). III (0.2 g) was reduced at -0.80 V (SCE) in 70 % aqueous *N,N*-dimethylformamide, containing sodium perchlorate and an acetate buffer pH 5. The reduction consumed 2 F/mol; the cathodic wave disappeared, and an anodic one appeared with the same half-wave potential. The reduced compound was then reoxidized at an anode potential of -0.50 V (SCE); the oxidation also consumed 2 F/mol, and III was obtained.

Attempts to isolate the reduced compound IV were unsuccessful, only III and Ia were isolated. If a solution of IV was allowed to stand under nitrogen at 0°C, Ia was formed gradually.

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