Titanium(III) Chloride and Electrochemical Reduction of Pyrazine, Quinoxaline and Triazine Derivatives and of their Salts

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The reduction of pyrazine, quinoxaline and triazine derivatives by titanium(III) chloride leads to di- or tetrahydrogenated compounds. High yields of tetrahydro compounds are also obtained through the reduction of quinoxalinium salts. These results are compared with those obtained by electrochemical reduction.

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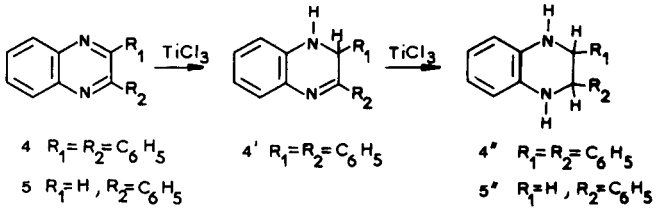
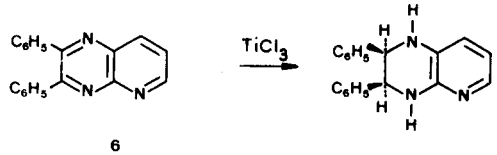
The reduction of organic molecules by titanium(III), chromium(II) and vanadium(II) has been known for a long time, but an upsurge of interest for these selective reagents arose a few years ago as shown in a recent review by Tse-Lok Ho (1). We have investigated the reactions of the commercially available aqueous solutions of titanium-(III) chloride with nitrogen heterocycles **1** to **10** in view of preparing reduced derivatives. The electrochemical reduction of compounds **1-7** has been published previously (2a,f); in this paper we shall described that of **8, 9** and **10**. Thus a comparison between the two methods of reduction will be possible.

The reduction with titanium(III) chloride was carried out according to two different procedures; in method A used in the case of the quaternized heterocycles, the reduced derivative is obtained directly in acidic medium; in method B the reduction takes place in acidic medium but the complex which is obtained is treated in alkaline medium to give the reduced derivative. Titanium(III) chloride does not react with compounds **1, 2** and **3**. Compound **4** gives the 1,2-dihydro-2,3-diphenylquinoxaline (**4'**) which can be reduced in its turn into the 1,2,3,4-tetrahydro-2,3-diphenylquinoxaline. 1,2,3,4-Tetrahydro-2-phenylquinoxaline is obtained directly from **5**, while **6** leads to *cis*-1,2,3,4-tetrahydro-2,3-diphenylpyrido[2,3-*b*]-pyrazine and **7** to 4,5-dihydro-5,6-diphenyl-*as*-triazin-3-one. In the case of the pyrazinium salt (**8**) the product which precipitates decomposes rapidly and only polymeric products can be recovered; on the contrary **9** and **10** lead to high yields of 1,2-dihydro derivatives.



4 $R_1=R_2=C_6H_5$ 4' $R_1=R_2=C_6H_5$ 4'' $R_1=R_2=C_6H_5$

5 $R_1=H, R_2=C_6H_5$ 5'' $R_1=H, R_2=C_6H_5$



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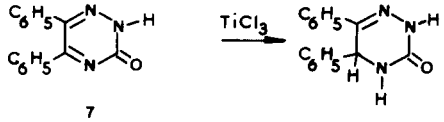

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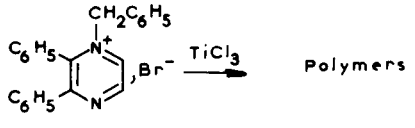

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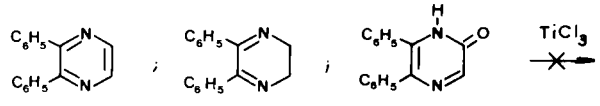
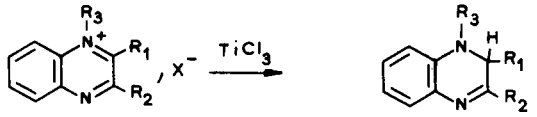


1 2 3

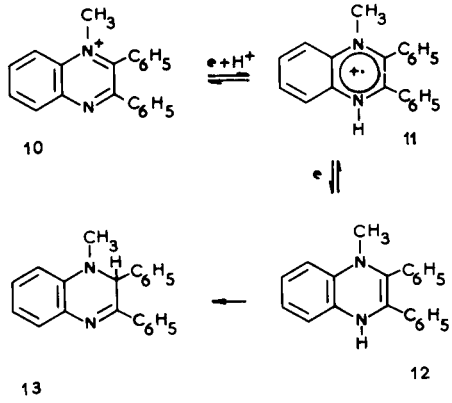


9 $R_1=H$; $R_2=C_6H_5$; $R_3=CH_2C_6H_5$; $X^-=Br^-$

10 $R_1=R_2=C_6H_5$; $R_3=CH_3$; $X^-=FSO_3^-$

0022-152X/80/061237-04$02.25

The electrochemical reduction of **8, 9** and **10** has been carried out both in aqueous and aprotic medium. In acidic solution (*p*H 0.5) the three compounds present two one-electron waves the half wave potentials ($E_{1/2}$) of which are *p*H dependent as shown in Table 1. The voltammograms in acidic medium evidences two reversible peaks (figure 1). In the case of **10** an electrolysis carried out at a potential corresponding to the plateau of the first wave (E = −0.2 V, *p*H = 1.5) gives after consumption of 1F/mole a solution presenting a one-electron anodic wave. The $E_{1/2}$ of this anodic wave is close to that of the first cathodic wave of **10**. Besides a one-electron cathodic wave is observed at the potential of the second cathodic wave of **10**. Under argon the solution of this compound is stable several hours and its esr spectrum can be recorded. As this radical is unstable in aprotic medium (see below) it is most likely a protonated radical **11** as in the electrochemical reduction of pyrazine itself (5). The electrochemical reduction of **11** (E = −0.5 V/sce) give the 1,2-dihdyro derivative **13**. The voltammogram of **10** (Figure 1) shows that the primary two electron reduction product of **10** presents two anodic peaks; as the voltammogram of **13** does not evidence such anodic peaks, it cannot be the primary two electron reduction product of **10**. The similarity between the voltammogram of **10** and that of pyrazine itself leads to assign a 1,4-dihydro structure to this primary two electron product.



In aprotic medium (acetonitrile) the cyclic voltammogram of **10** recorded at 200 mVs^{-1} on a vitreous carbon electrode shows a reversible monoelectronic peak at Ep = −0.80 V followed by a second irreversible monoelectronic peak at Ep = −1.63 V, this second peak became reversible by increasing the sweep rate up to 2 Vs^{-1}. An electrolysis of a dilute solution of **10** performed on the plateau of the first wave (E = −1.0 V) leads to the appearance of an anodic wave the half wave potential of which is close from that of **10**. This anodic wave which decreases rapidly is that of the neutral radical of **10** which is unstable in this medium. Under the same conditions **9** presents an irreversible one-electron peak at Ep = −0.68 V: the scan rate must be increased up to 120 Vs^{-1} in order to observe the reversibility of this peak. Correspondingly, no anodic wave is observed during the electrolysis of **9** showing that its neutral radical is very unstable. Preparative electrolysis of **8, 9** and **10** in acetonitrile only leads to gummy products.

Table 1

Half Wave Potentials (volts/sce) as a function of *p*H for the First (first line) and Second (second line) Waves (50% methanol c = $10^{-3}M$)

*p*H	1	2	3	4
8	−0.22	−0.31	−0.36	−0.41
	−0.37	−0.46	−0.52	−0.57
9	−0.09	−0.14	−0.19	−0.23
	−0.39	−0.40	−0.40	−0.41
10	−0.09	−0.15	−0.22	−0.28
	−0.30	−0.37	−0.44	−0.46

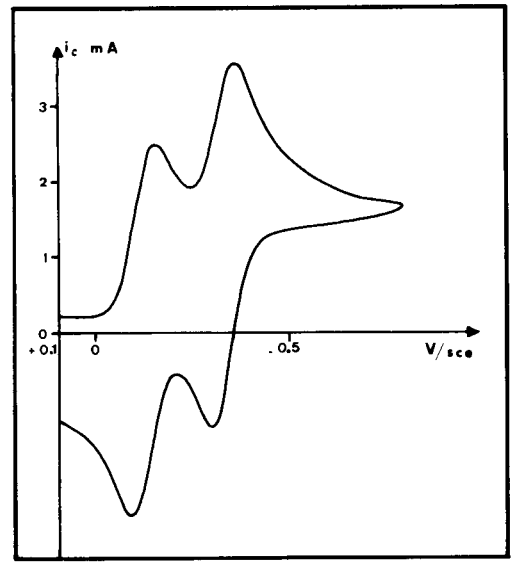


Figure 1. Voltammogram of **10** in acidic medium (c = $10^{-3}M$, 50% methanol, *p*H 1.5, mercury electrode, reference: saturated calomel electrode, scan rate: 0.2 Vs^{-1}).

It would be interesting to be able to predict whether a given heterocyclic compound or its salt can be reduced by titanium(III) chloride. Titanium(III) chloride is a one-electron reduction product, so a connection between the potentials involved should exist. The compounds which are reduced (**4-10**) have (at *p*H 1) $E_{1/2}$ more anodic than −0.15 V, whereas those not reduced (**1-3**) have $E_{1/2}$ more cathodic than −0.40 V. The oxidation wave of titanium III to titanium IV has an $E_{1/2}$ at −0.20 V in 0.1*N* hydrochloric acid (8). There is thus some evidence that heterocyclic compounds have $E_{1/2}$ more anodic than about −0.25 V should be reduced, whereas those with $E_{1/2}$ more cathodic than about −0.40 V should be reduced slowly or not at all. However such conclusions should be taken with

care as in other cases different mechanisms involving for example the formation of complexes may be operative. This is the case of maleic acid and its diethylester which both have reduction potentials at about −0.6 V at *p*H 1, *i.e.*, more cathodic than −0.4 V, even though the acid can be reduced by titanium(III) chloride but not its diester (9).

Discussion.

The selectivity of the different reduction methods is clearly evidenced by the following results.

In the case of heterocycles **1**, **2** and **3** no reaction is observed with titanium(III) chloride while the electrochemical reduction allows one to obtain dihydro derivatives (2a-c). Thus **1** gives the 1,2-dihydro derivative, **2** gives the 1,2,3,4-tetrahydro derivative and **3** the 3,6-dihydro derivative. The reaction of titanium(III) chloride with quinoxalines **4** and **5** leads in both cases to the tetrahydro compounds **4″** and **5″** as a mixture of *cis*- and *trans*- in the case of **4″** through an intermediate 1,2-dihydro compound (**4′**) which could be isolated only in the case of **4**. These same tetrahydro derivatives can be obtained by lithium aluminium hydride (3) or by electrochemical reduction (2d), but in these cases the reaction is stereospecific, yielding only the *cis*-**4″**. Dihydro derivatives (1,4-dihydro in the case of **4**, 1,2- or 1,4-dihydro in the case of **5**), can be prepared by electrochemical reduction (2d). The *cis*-tetrahydro derivative is obtained by reduction of **6** by titanium(III) chloride but the intermediate dihydro compound could not be isolated; the electrochemical reduction in an alkaline water methanol medium leads to the 3,4-dihydro or to the 5,6,7,8-tetrahydro 6-methoxy derivatives while lithium aluminium hydride furnishes the above *cis*-tetrahydro compound (4). As in the case of quinoxalinium salts, **8** gives only polymeric material upon reduction with titanium(III) chloride, while **9** and **10** lead to 1,2-dihydro compounds in good yields. The one-electron reduction of **10** in aqueous medium leads to a stable protonated radical while the 1,2-dihydro compound **13** is obtained after 2F/mole (10). In aprotic medium the three salts give only gummy products. The reduction of pyrazinium and quinoxalinium salts by sodium borohydride allows one to obtain tetrahydro derivatives (6,7).

The above results evidence clearly the selectivity of each of the reduction methods and the interest of titanium(III) chloride as a reagent for the reduction of heterocyclic systems.

EXPERIMENTAL

The melting points were determined on a Kofler apparatus, nmr spectra were recorded on a Varian A/60 instrument with tetramethylsilane as internal reference and esr spectra were recorded on a Varian CSE 109 instrument. The different compounds under investigation have been prepared by standard methods. Titanium(III) chloride was used as a molar solution of Prolabo. All the reactions were carried out with deoxygenated solutions and under a nitrogen atmosphere.

Method A.

The quinoxalinium salts (200 mg.) were dissolved in 50 ml. of water. The titanium(III) chloride solution (5 ml.) is then added. A precipitate appeared rapidly; after one hour this precipitate was filtered, washed with water and dried.

1,2-Dihydro-1-benzyl-3-phenylquinoxaline.

This compound was obtained from **9**. The yield was 185 mg. (92%), m.p. 100°; nmr (deuteriochloroform): δ ppm C-CH_2-C 4.27 (singlet, 2H), N-CH_2- 4.42 (singlet, 2H), aromatic protons 6.4-8 (multiplet, 10H).

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.56; H, 6.04; N, 9.40. Found: C, 84.50; H, 6.15; N, 9.31.

1,2-Dihydro-1-methyl-2,3-diphenylquinoxaline.

This compound was obtained from **10**. The yield was 181 mg. (90%), m.p. 60° dec.; nmr (deuteriochloroform): δ ppm N-CH_3 2.93 (singlet, 3H), C_6H_5-C-*H* 5.60 (singlet, 1H), aromatic protons 6.5-8.5 (multiplet, 10H).

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.56; H, 6.04; N, 9.40. Found: C, 84.41; H, 6.13; N, 9.45.

Method B.

The heterocycles (500 mg.) were dissolved in 75 ml. of ethanol, x ml. of titanium(III) chloride was added under nitrogen and the reaction mixture was allowed to stand at room temperature for y hours. Ethanol was evaporated, the residue was dissolved in 50 ml. of methanol and z ml.of a 10*N* sodium hydroxide solution was added. The solution was then stirred until a thin titanium dioxide precipitate appears (5-10 minutes). This precipitate was filtered and washed with methanol, 50 ml. of water was added to the filtrate and the solution was concentrated. The reduced derivative which precipitated was filtered, washed with water and dried under vacuum.

Compounds **1**, **2** and **3** (x = 7, y = 5, z = 4) did not react.

1,2-Dihydro-2,3-diphenylquinoxaline (**4′**).

This compound was obtained from **4** (x = 7, y = 18, z = 4), after recrystallization from ethanol. The yield was 350 mg. (70%), m.p. 147° (lit. (11) m.p. 147-148°).

1,2,3,4-Tetrahydro-2,3-diphenylquinoxaline **4″**.

This compound was obtained from **4′** (x = 7, y = 18, z = 4) (320 mg., 64%), as a mixture of the *cis*- and *trans*-derivatives as shown by the nmr spectrum (3).

1,2,3,4-Tetrahydro-2-phenylquinoxaline.

This compound was obtained from **5** (x = 15, y = 18, z = 8) (260 mg., 52%) after recrystallization from ethanol, m.p. 77° (lit. (12) 77°). If x was smaller than 15, a mixture of **5**, its dihydro and tetrahydro derivatives was obtained as shown by the nmr spectrum.

Cis-1,2,3,4-Tetrahydro-2,3-diphenylpyrido[2,3-*b*]pyrazine.

This compound was obtained from **6** (x = 15, y = 18, z = 8) and recrystallized from ethanol (300 mg., 60%), m.p. 206° (lit (4) m.p. 206°). As in the preceding case, if x was smaller than 15, a mixture of the starting compound and its dihydro and tetrahydro derivative was obtained.

4,5-Dihydro-5,6-diphenyl-*as*-triazin-3-one.

This compound was obtained from **7** (x = 8, y = 18, z = 5) according to method B or more easily by making the reaction mixture alkaline, filtering and diluting the filtrate with water. The compound was recrystallized from ethanol (400 mg., 80%), m.p. 275° (lit. (13) m.p. 274-276°).

Electrochemical Reactions.

The polarograms in aqueous medium were recorded on a Radiometer PO4, the reference electrode was a saturated calomel electrode. In acetonitrile the voltammograms were recorded with a system composed of a Tacussel PRG 3 signal generator and a potentiostat provided with an

ohmic drop compensation device (14). The electrode was of vitreous carbon and used either as a stationary or as a rotating (1000 ppm) electrode. The reference was a silver/silver(I) 0.01*M* electrode and the supporting electrolyte was tetrabutylammonium tetrafluoborate (0.1*M*). Acetonitrile was purified by distillation over calcium hydride. The cathodic compartment of the electrolytic cell used for preparative experiments was a glass cylinder of 85 mm diameter and the anodic compartment which was fitted in the cathodic compartment was a glass cylinder of 50 mm diameter closed at its lower end by a fine fritted glass. The potential was set at the desired value by a Tacussel ASA 100-1 potentiostat and the number of coulombs was measured with a Tacussel IG4 10000 integrator. The reduction (E = −0.2 V/sce) at *p*H 1.5 of **10** was carried out on 100 ml. of a $4 \times 10^{-3}M$ solution (50% methanol) and the esr spectrum was recorded by withdrawing a small amount of the solution under argon into the tube of the esr spectrometer.

1-Methyl-1,2-dihydro-2,3-diphenyl quinoxaline (**13**).

This compound was obtained by reduction of **11** prepared from 159 mg. of **10** at *p*H 1.5; **13** precipitated after partial evaporation of the solution (66 mg., 55%).

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