Electrochemical Oxidation of Substituted Pyrroles. IV. The Influence of Soluble Bases

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The electrochemical oxidation of 4,5-diphenyl-2-(*p*-tolyl)pyrrole (**I**), 2,5-diphenyl-3-acetylpyrrole (**II**), and 4,5-diphenyl-2-mesitylylpyrrole (**III**), in the presence of pyridine is described. For these compounds the oxidation performed at the potential corresponding to the first cyclovoltammetric peak shows a charge consumption of 2 F/mole. Compound **III** leads to the formation of a monomeric oxidized species **III'** which by reduction with zinc again quantitatively leads to the starting material. Compounds **I** and **II** mainly lead to 2,3' dimers, with minor amounts of 3,3' dimers which, at the same potential undergo a further oxidation to a mixture of oxidized products, whose structures have been tentatively assigned on the basis of their chemical behavior. An overall reaction mechanism is proposed.

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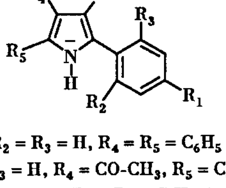
The electrochemical methodology has been successfully applied in our laboratories to the controlled oxidation of 2,4,5-trisubstituted pyrroles [1,2,3]. In particular our attention has been focused on the oxidation of some 2-aryl-substituted-pyrroles (Scheme 1) in which the *ortho* positions of the aryl group are substituted, **III** and **IV**, or unsubstituted, **I**, **II**, **V** and **VI**. For all these compounds, according to the behavior commonly observed for the oxidation of pyrroles, the first step of the anodic process results in the formation of the corresponding cation radicals whose stability and evolutions depend on the nature of the substituents on the pyrrole ring and on the position of the methyl groups on the 2-phenyl.

As an example, the cation radicals arising from **I**, **II**, **V**, and **VI**, after a fast 3,3' dimerization undergo, at the potential of formation, a further oxidation leading to the corresponding cation which evolves to a tetracyclic compound [1,3,4]. In the case of **II** the formation of the cyclic derivative was inhibited by the addition of substantial amounts of water; in this case the anodic oxidation of **II** leads to a dimeric hydroxylated derivative [3].

In contrast the radical cations arising from the oxidation of arylpyrroles bearing methyl substituents on the *ortho* position of the 2-aryl group, **III** and **IV**, undergo a different evolution, with formation of 2,3' dimers, sterically less hindered that the 3,3' dimers [2,4].

Scheme 1



I, $R_1 = CH_3, R_2 = R_3 = H, R_4 = R_5 = C_6H_5$ (ref [1])
II, $R_1 = R_2 = R_3 = H, R_4 = CO\text{-}CH_3, R_5 = C_6H_5$ (ref [3])
III, $R_1 = R_2 = R_3 = CH_3, R_4 = R_5 = C_6H_5$ (ref [2])
IV, $R_1 = R_2 = H, R_3 = CH_3, R_4 = R_5 = C_6H_5$ (ref [4])
V, $R_1 = R_2 = R_3 = H, R_4 = R_5 = C_6H_5$ (ref [4])
VI, $R_1 = R_2 = R_3 = H, R_4 = COC_6H_5, R_5 = CH_3$ (ref [4])

It was observed, in the course of these studies, that the cyclovoltammetric paths of all these pyrroles are deeply modified by the addition of soluble bases such as pyridine. Those observations prompted us to investigate which variations in the reactivity of these pyrroles are induced by the presence of pyridine in the reaction medium. As representative compounds **I**, **II**, and **III** were chosen, and the results obtained in this investigation are presented here.

Results.

Electroanalytical Investigations.

The cyclovoltammetric data related to the oxidation of **I**, **II**, and **III** are summarized in Table 1. The peak potentials of the oxidation waves are shifted towards less positive values by the addition of substantial amounts of

Table 1

Cyclovoltammetric Peak Potentials of **I**, **II**, and **III** in Neutral Medium and in the Presence of Pyridine

I	(neutral)	0.50 (i)	0.80 (p.r.)	1.28 (i.)
	(basic)	0.43 (i)	0.56 (i)	
II	(neutral)	0.74 (i)		
	(basic)	0.57 (i)	0.67 (i)	
III	(neutral)	0.62 (r)	1.14 (i)	
	(basic)	0.54 (i)		

S.S.E.:acetonitrile-Bu_4NClO_4 0.1*M*:[pyrrole] 5 x 10^{-3} *M*. Sweep rate 100 mV s^{-1}. Anode Pt disk (3.14 mm^2); cathode Pt wire; reference electrode Ag/Ag+ 0.1*M* in acetonitrile. Neutral: unbuffered acetonitrile; basic: pyridine 0.5 *M*.

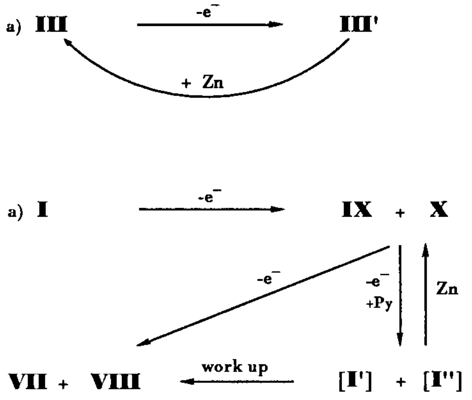
pyridine; furthermore the reversibility of the first oxidation peak, if any, disappears.

Controlled Potential Electrolyses.

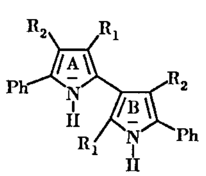
For the three pyrroles the oxidation performed in acetonitrile, in the presence of pyridine [0.5 *M*], at the potential corresponding to the first peak shows a charge consumption of 2 F/mole.

By oxidation of **III** a main derivative **III′** is obtained, which, by reduction with zinc and acetic acid, quantitatively leads to the starting pyrrole **III** (Scheme 2a). The ^{1}H nmr signals of **III′**, besides the CH ones attributable to the two phenyl and to the mesitylyl groups, indicate a singlet attributable to the pyrrole CH, and the characteristic CH signals of the pyridinium ring.

Scheme 2



The products of the oxidation of **I** ([I′], [I″] of Scheme 2b) have not been identified, as, in the course of the isolation, undergo chemical change towards two isomeric tetracyclic derivatives, **VII** and **VIII** ($M^+ = 614$) which were not present in the anolyte effluent. In order to get informations on the structures of the primary products of the electrolysis the effluents were directly acidified with acetic acid, and zinc powder was added until the complete reduction was attained. Following this procedure, two main products **IX** and **X** in a molar ratio 1:3 were recovered, which were isolated by column chromatography (see Scheme 2b). To these products, already obtained by oxidation with dichromate of the same pyrrole [5] respectively, the structures of 2,2′-di-*p*-tolyl-4,4′,5,5′-tetraphenyl-3,3′-dipyrryl (**IX**) and 2′,3-di-*p*-tolyl-4,4′,5,5′-tetraphenyl-2,3′-dipyrryl (**X**) were assigned. The presence of these compounds in the anolyte in the course of the electrolysis was confirmed by tlc. Taking into consideration the products recovered after workup of the effluent of the electro-oxidation of **I**, it was recognized that **VII** and **VIII** could respectively be obtained from **IX** and **X** by electro-oxidation in neutral unbuffered media. To **VII** the structure of 1,6a-dihydro-8-methyl-2,3,4,5-tetraphenyl-6a(*p*-tolyl)benzo[*g*]pyrrolo[3,2-*e*]indole had been already assigned [1,5]. To **VIII** the structure of 1,7b-dihydro-6-methyl-2,3,9,10-tetraphenyl-7b-(*p*-tolyl)benzo[*e*]pyrrolo[2,3-*g*]indole is tentatively assigned, considering that in all cases observed [1,2, 4-6] the ring closure of dimeric pyrroles involves the position 2 of one of the nuclei. On the other hand it has also been observed that the unsymmetrical dimer **X**, by treatment with dichromate, undergoes an oxidation selectively involving the nucleus **B** [5].



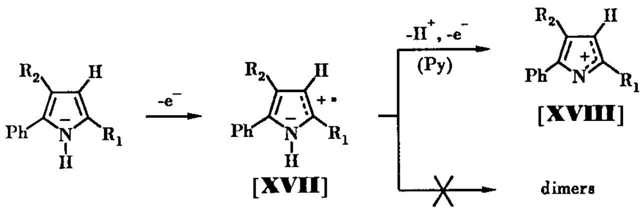
X

An analogous behavior is shown by **II**. The products of its primary oxidation undergo a change in the course of the workup leading to tetracyclic products, **XIII** and **XIV**, structurally analogous to those formerly described for **I**. Also in this case if the effluent of the anolyte is treated with zinc and acetic acid the two dimers, symmetrical **XV** and unsymmetrical **XVI** in a molar ratio 1:3, were obtained. All the products so obtained are electroactive at the same potential as the corresponding starting pyrroles.

Conclusions.

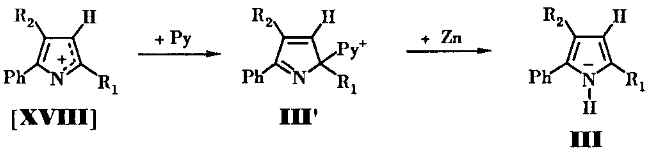
On the basis of the experimental data so far presented, we would propose the following hypotheses on reaction mechanism: a) As already observed in neutral unbuffered media, also in the case of the oxidation in the presence of pyridine, for all the pyrroles taken under consideration, the first oxidation step likely consists in the formation of the corresponding cation radical **XVII** (Scheme 3). b) In the presence of the base, the cation radical undergoes a fast deprotonation and the consequent oxidation to a mono cation **XVIII** (Scheme 3). c) **XVIII** in the case of **III**, is stabilized by a nucleophilic attack of a pyridine molecule, most probably on the position 2 (in fact, the attack of the pyridine molecule on the 3 position would very likely lead to the migration of the hydrogen to the pyrrole nitrogen). The resulting pyridinium perchlorate is easily reduced to the corresponding starting pyrrole (see Schemes 2 and 4). d) In contrast in the case of **I** and **II** the

Scheme 3



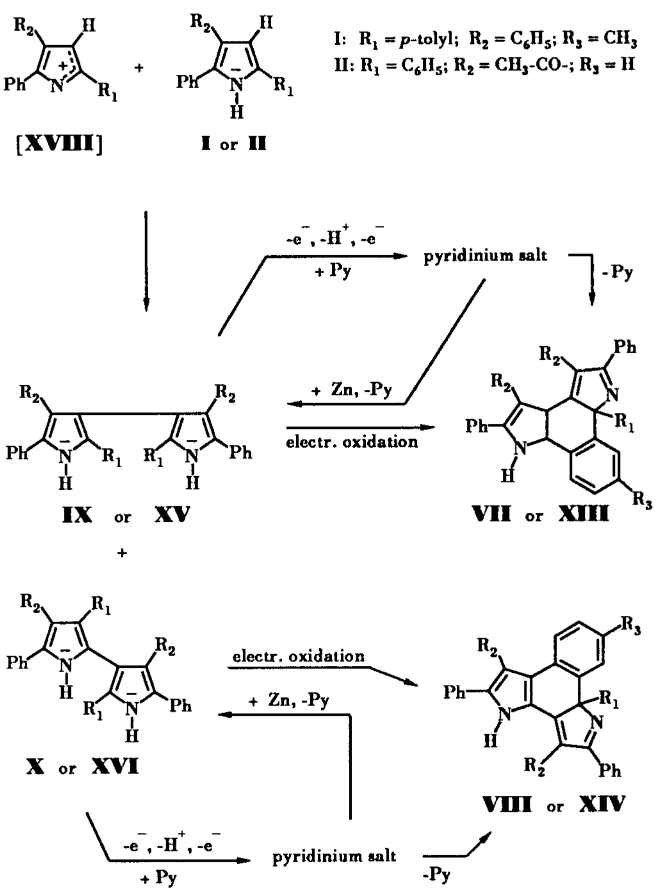
intermediate **XVIII** undergoes a reaction of its position **3** with the parent molecule on the 3′ position, thus leading to the symmetrical dimers, **IX** or **XIII**. The unsymmetrical dimers **X** or **XIV** arise from a competitive electrophilic reaction on the 2′ position of the parent molecule, followed by the migration of the aryl group from 2′ to the free 3′ position (see Schemes 2 and 4). The alternative hypothesis according to which the unsymmetrical structures should arise from a reaction pathway involving cation species **XVIII**, whereas the symmetrical ones could arise from a competitive radical-radical coupling involving **XVII** can be excluded on the basis of the experimental evidence that the ratio between symmetrical and unsymmetrical dimers is not affected by large variations of the pyridine concentration in the reaction medium (Scheme 3). We can therefore deduce that the reaction leading to the cation **XVIII** is faster than the hypothetical competitive radical-radical coupling, thus being **XVIII** the only intermediate to the formation of both symmetrical and unsymmetrical dimers. e) The dimers, at the potential of formation, undergo further oxidation leading to intermediates, which most probably are the same as those present in the course of the oxidation in unbuffered media [1,2]. Their cyclization is, in our case, hindered by the attack of pyridine on the cationic site with formation of complex species, indicated as pyridinium salts in Scheme 5. An analogous behavior has been already observed in the oxidation of **II** in the presence of water.

Scheme 4



R_1 = mesitylyl, R_2 = C_6H_5

Scheme 5



I: R_1 = *p*-tolyl; R_2 = C_6H_5; R_3 = CH_3
II: R_1 = C_6H_5; R_2 = CH_3-CO-; R_3 = H

EXPERIMENTAL

Melting points were determined on a Buchi-Tottoly capillary apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer Infracord 137 and a Perkin Elmer 299 Spectrophotometers as nujol mulls unless otherwise specified. The ^1H nmr spectra were recorded on a Perkin Elmer EM-360 and Bruker SF 250 spectrometers, using tetramethylsylane as the internal standard. The mass spectra were measured with a Jeol 01SG-2 double focusing mass spectrometer at 65 eV (100A). The analyses of the products of the electrolyses were performed with a Perkin Elmer series 10 HPLC apparatus with a UV-Vis LC 95 detector. The tlc determinations were performed on Merck DC alufolien kieselgel 60 F254. Preparative chromatography was performed on columns of Fluka silica gel 60 F254. Cyclic voltammetric experiments were performed with an Amel apparatus, formed by a 552 potentiostat equipped with a 731 digital coulometer, a 566 function generator and a 863 xy recorder. A Nicolet 3091 oscilloscope was used in fast cyclovoltammetric determinations. Preparative controlled potential electrolyses were carried out in H shaped cells with a G4 glass fritt diaphragm. Platinum sheet (surface 4 cm^2) as anode, and platinum wire as cathode were used. Reagent grade acetonitrile was redistilled and stored over 4A molecular sieves.

4,5-Diphenyl-2-(*p*-tolyl)pyrrole (**I**), 2,5-Diphenyl-3-acetylpyrrole (**II**), and 4,5-Diphenyl-2-(mesitylyl)pyrrole (**III**) were prepared according to formerly described procedures [5,7,2].

Electrochemical Preparative Oxidation of I.

Compound **I** (0.31 g, 1 x 10^{-3} mole), dissolved in 30 ml of acetonitrile with 0.1 *M* tetrabutylammonium perchlorate was electrolyzed in the presence of pyridine (1.2 g, 1.5 x 10^{-2} mole) at the anodic potential of 0.40 V (Ag/Ag$^+$ 0.1 *M*). The current intensity drops from the initial value of 26 mA to the final one of 0.9 mA after the circulation of 182 C. The anolyte was evaporated under reduced pressure and the residue was chromatographed on a silica gel column. By elution with cyclohexane-ethylacetate 9:1 two main products were obtained: a) 0.20 g (65% yield) of 1,7b-dihydro-6-methyl-2,3,9,10-tetraphenyl-7b-(*p*-tolyl)benzo[*e*]-pyrrolo[2,3-*g*]indole **VIII**, as yellow crystals from ethanol, mp 237-238°; ir: ν 3440 cm^{-1} N-H; ^1H nmr (deuteriochloroform): δ 2.21 (3H, s, CH_3), 2.28 (3H, s, CH_3), 6.70-7.96 (27H, m, aromatic H), 8.10 (1H, b, pyrrole N-H, deuterium oxide-exchangeable); ms: (m/e) 614 (M$^+$).

Anal. Calcd. for $C_{46}H_{34}N_2$: C, 89.87; H, 5.58; N, 4.56. Found: C, 89.65; H, 5.48; N, 4.50.

b) In addition 0.06 g (20% yield) of the second product, 1,6a-dihydro-8-methyl-2,3,4,5-tetraphenyl-6a-(*p*-tolyl)benzo[*g*]pyrrolo-[3,2-*e*]indole **VII** was obtained as yellow crystals from ethanol, mp and mixed [1] mp 200-201°.

Reduction of the Primary Electrolysis Products from **I**.

A mixture of anolyte and 30 ml of acetic acid was stirred while 10 g of zinc dust (0.15 moles) was slowly added at room temperature. After 30 minutes the reaction mixture was filtered then quenched by addition of diluted aqueous ammonia and extracted with ether. The ethereal phase was dried on anhydrous sodium sulphate then evaporated to dryness. The residue was chromatographed on silica gel column. By elution with cyclohexane-ethyl acetate 9:1 two main products were recovered: a) 0.05 g (16% yield) of 2,2'-di-*p*-tolyl-4,4',5,5'-tetraphenyl-3,3'-dipyrryl **IX** as pale yellow crystals from ethanol, mp and mixed [1] mp 183-184°.

(b) In addition 0.15 g (48% yield) of the second product, 2',3-di-*p*-tolyl-4,4',5,5'-tetraphenyl-2,3'-dipyrryl **X** was obtained as pale yellow crystals from ethanol, mp and mixed [5] mp 220-221°.

Preparative Electrochemical Oxidation of **II**.

Following a strictly analogous procedure to that already described for the oxidation of **I**, 0.26 g of **II** were electrolyzed at the anodic potential of 0.55 V (Ag/Ag$^+$ 0.1 *M*), with an overall circulation of 185 C. The anolyte was worked up as above described for **I** and chromatographed on a silica gel column. By elution with cyclohexane-ethyl acetate 9:1 two main products were obtained: a) 0.1 g (50% yield) of 1,7b-dihydro-2,7b,9-triphenyl-3,10-diacetylbenzo[*e*]pyrrolo[2,3-*g*]indole **XIV** as yellow orange crystals from acetone, mp 130° dec; ir: ν 3323 cm^{-1} N-H, 1660, 1680 (2 x C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.05 (3H, s, CH$_3$), 2.11 (3H, s, CH$_3$), 7.13-8.09 (15H, m, aromatic H), 10.71 (1H, b, pyrrole N-H, deuterium oxide-exchangeable); ms: (m/z) 518 (M$^+$).

Anal. Calcd. for $C_{36}H_{26}N_2O_2$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.45; H, 5.17; N, 5.22.

b) In addition 0.05 g (19% yield) of the second product, 1,6a-dihydro-2,5,6a-triphenyl-3,4-diacetylbenzo[*g*]pyrrolo[3,2-*e*]indole **XIII** was obtained as yellow crystals from ethanol, mp and mixed [3] mp 240-241°.

Reduction of the Primary Electrolysis Products from **II**.

A mixture of anolyte and 30 ml of acetic acid was stirred while 10 g of zinc dust (0.15 moles) was slowly added at room temperature. After 30 minutes the reaction mixture was filtered then quenched by addition of diluted aqueous ammonia and extracted with ether. The ethereal phase was dried on anhydrous sodium sulphate then evaporated to dryness. The residue was chromatographed on a silica gel column. By elution with cyclohexane-ethyl acetate 8:2 two main products were recovered: a) 0.16 g (61% yield) of 3,5,2',5'-tetraphenyl-4,4'-diacetyl-2,3'-dipyrryl **XIV** as pale yellow crystals from ethanol, mp 253-254°; ir (bromoform): ν 3381, 3223 cm^{-1} (2 x N-H), 1657, 1643 (2 x C=O); ^{1}H nmr (acetone-d$_6$): δ 1.90 (3H, s, CH$_3$), 1.96 (3H, s, CH$_3$), 6.90-7.80 (20H, m, aromatic H), 10.80 (1H, b, pyrrole N-H, deuterium oxide-exchangeable); ms: (m/z) 520 (M$^+$).

Anal. Calcd. for $C_{36}H_{28}N_2O_2$: C, 83.05; H, 5.42; N, 5.38. Found: C, 83.32; H, 5.61; N, 5.18.

b) In addition 0.06 g (23% yield) of the second product, 2,5,2',5'-tetraphenyl-4,4'-diacetyl-3,3'-dipyrryl **XIII** was obtained as pale yellow crystals from ethanol, mp and mixed [3] mp 150-151°.

Electrochemical Preparative Oxidation of **III**.

Following a strictly analogous procedure to that already described for the oxidation of **I**, 0.34 g of **III** was electrolyzed at the anodic potential of 0.50 V (Ag/Ag$^+$ 0.1 *M*), with an overall circulation of 180 C. The anolyte was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate and chromatographed on a silica gel column. By elution with methanol as the main product, 0.38 g (74% yield) of 4,5-diphenyl-2-mesitylyl-2-(*N*-pyridinium)-2*H*-pyrrole perchlorate was isolated as white needles, mp 165-166° from ethanol; ir: ν 1615 cm^{-1} C=N; ^{1}H nmr (DMSO-d$_6$): δ 2.15 (6H, s, 2 x CH$_3$), 2.28 (3H, s, CH$_3$), 6.98 (2H, s, H$_{3,5}$ mesitylyl), 7.35-7.60 (10H, m, aromatic H), 7.77 (1H, s, pyrrole H$_3$), 8.21 (2H, t, J = 7 Hz, H$_{3,5}$ pyridine), 8.77 (1H, t, J = 7.7 Hz, H$_4$ pyridine), 9.05 (2H, d, J = 6.2 Hz, H$_{2,6}$ pyridine).

Anal. Calcd.for $C_{30}H_{27}ClN_2O_4$: C, 69.96; H, 5.28; N, 5.44. Found: C, 69.70; H, 5.01; N, 5.70.

Reduction of the Primary Electrolysis Products from **III**.

Following a strictly analogous procedure as that already described for the reduction of the electrolysis products of **I**, 0.3 g (88% yield) of **III** was recovered.

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