OXIDATION OF 1,2,3,4,6-SUBSTITUTED PYRIDINIUM SALTS WITH FERRICYANIDE

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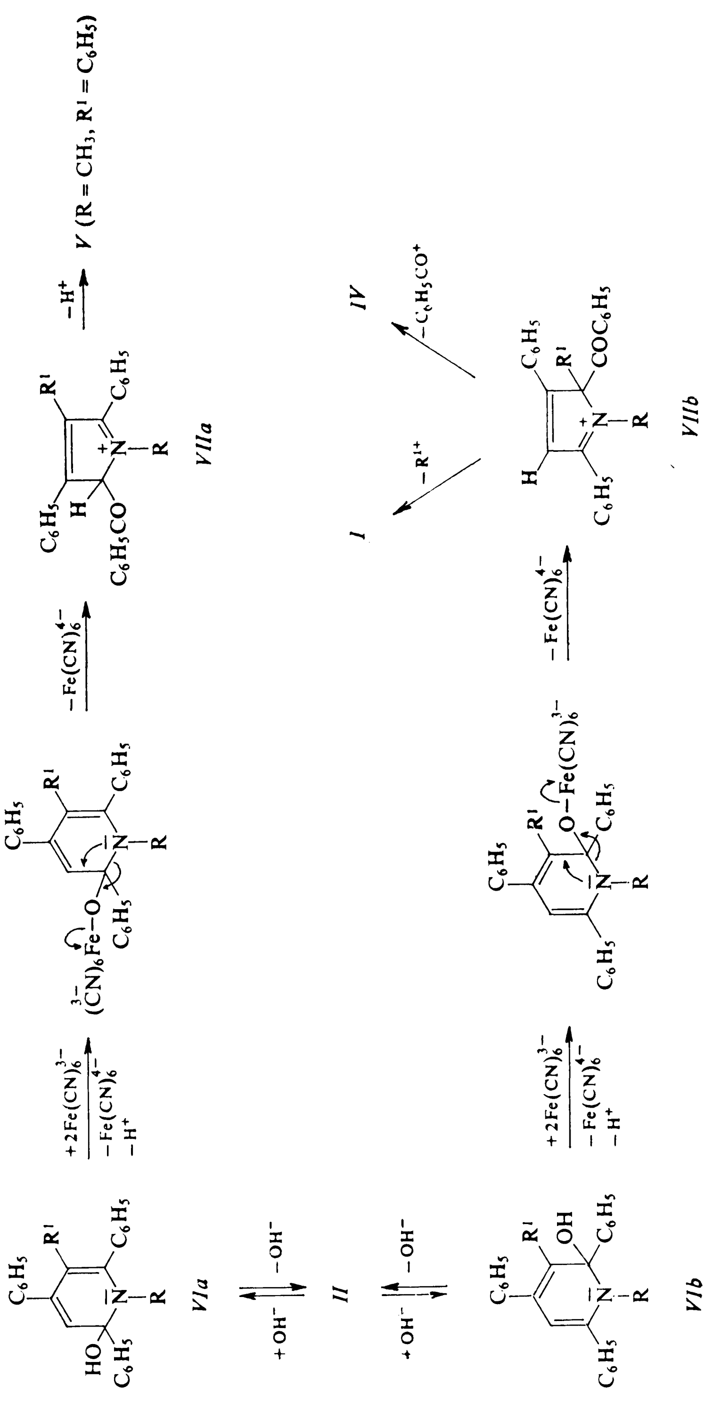
Received April 13th, 1982

Quaternary pyridinium salts *IIa—IId* are oxidized with alkaline solution of potassium ferricyanide to give a mixture of pyrrole derivatives *Ia—Ib* and *IVa—IVd*. The quaternary salt *IIe* under the same conditions affords a mixture of compounds *IVe* and *V* whereas *IId* gives only the pyrrole derivative *IVd*. The reaction mechanism is discussed and spectral characteristics of the products are interpreted.

Oxidation of 1-substituted-2,4,6-triphenylpyridinium salts with alkaline solution of potassium ferricyanide affords[1,2] high yields of substituted pyrrole derivatives of the general formula *I*. On the other hand, 1-substituted-2,3,4,5,6-pentaphenylpyridinium salts under the same reaction conditions give 1-substituted-2,3,4,5-tetraphenylpyrroles[3]. The present communication concerns the outcome of oxidation of asymmetrically substituted pyridinium salts *IIa–IIf*.

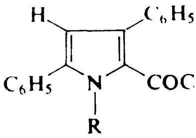
The starting quaternary salts *IIa–IIf* were prepared by reaction of methylamine or aniline with the described[4] pyrylium salts *IIIa–IIIc* (Table I). The oxidation products were isolated by column chromatography and identified by elemental analysis, ^{1}H NMR, IR and mass spectra (Table II).

It is generally assumed[5,6] that in ferricyanide oxidation of pyridinium quaternary salts the primarily oxidized substrate is the 2-hydroxy-1,2-dihydropyridine derivative (pseudo-base) arising by addition of OH^- ion into the α-position of the pyridinium cation. It our case, the oxidative transformations of this intermediate *VI*, leading to the pyrrole derivatives, can be described by the reaction mechanism depicted in Scheme 1. Accordingly, the asymmetrically substituted pyridinium cations *IIa–IIf* should afford oxidation products of both isomeric hydroxydihydropyridines *VIa,b*. From the fact that oxidation of salts *IIa–IId* gives only the pyrrole derivatives *Ia,b* and *IVa–IVd* we can deduce that the reaction proceeds preferentially *via* the intermediate *VIb*. The formation of mixture of the 2-benzoyl and 2-debenzoyl pyrrole derivatives (*I* and *IV*, respectively) can be explained by a common precursor *VIIb* which upon loss of the alkyl or benzyl cation affords the derivatives *I* or *IV*. In accord with the known difficult elimination of phenyl cation we did not find any derivative of the type *I* after oxidation of the salts *IIe,f*. On the contrary, the

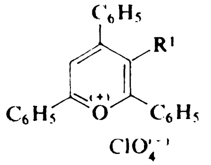

VIa
II
VIb
+OH⁻
−OH⁻
+2Fe(CN)₆³⁻
−Fe(CN)₆⁴⁻
−H⁺
−Fe(CN)₆⁴⁻
VIIa
VIIb
−H⁺
V (R = CH₃, R¹ = C₆H₅)
I
IV
−R¹⁺
−C₆H₅CO⁺
C₆H₅
R¹
R
HO
OH
C₆H₅CO
COC₆H₅
H

SCHEME 1

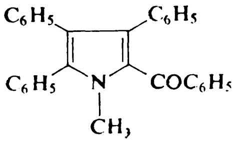
oxidation of *IIe* afforded 1-methyl-2-benzoyl-3,4,5-triphenylpyrrole *V* (40%) in addition to the 2,3,5-trisubstituted pyrrole *IVe*. Whereas the formation of compound *IVe* is explained by elimination of benzoyl cation from an intermediate of the type *VIIb*, the derivative *V* must arise by oxidation of the pseudo-base *VIa* and subsequent deprotonation of the intermediate *VIIa*. On the other hand, oxidation of *IIf* gave only the pyrrole *IVf*.



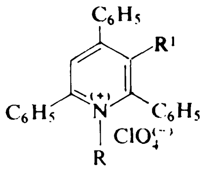
Ia, R = CH_3
Ib, R = C_6H_5



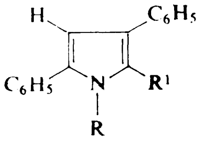
IIIa, $R^1 = CH_3$
IIIb, $R^1 = C_2H_5$
IIIc, $R^1 = C_6H_5$



V



IIa, $R = R^1 = CH_3$
IIb, $R = C_6H_5$, $R^1 = CH_3$
IIc, $R = CH_3$, $R^1 = C_2H_5$
IId, $R = C_6H_5$, $R^1 = C_2H_5$
IIe, $R = CH_3$, $R^1 = C_6H_5$
IIf, $R = R^1 = C_6H_5$



IVa, $R = R^1 = CH_3$
IVb, $R = C_6H_5$, $R^1 = CH_3$
IVc, $R = CH_3$, $R^1 = C_2H_5$
IVd, $R = C_6H_5$, $R^1 = C_2H_5$
IVe, $R = CH_3$, $R^1 = C_6H_5$
IVf, $R = R^1 = C_6H_5$

The mentioned results show that key intermediates of the studied transformations are the cations *VIIa,b* which eliminate the secondary ions H^+, R^+ or $C_6H_5CO^+$ under formation of the pyrroles *I*, *IV* and *V*. According to the ratio of the products *I*, *IV* and *V* in the reaction mixtures, the propensity of these ions to be cleaved off decreases in the expected order $H^+ > C_6H_5CO^+ > C_2H_5^+ \geqq CH_3^+ \gg C_6H_5^+$.

EXPERIMENTAL

The temperature data are uncorrected. Melting points were determined on a Boetius block. ^1H NMR spectra were taken on a Varian XL-100 instrument, IR spectra on a Perkin-Elmer 325 spectrometer and mass spectra on an LKB 9000 mass spectrometer (at 70 eV). All analytical samples were crystallized from ethanol and dried over phosphorus pentoxide *in vacuo* at 78°C.

The quaternary salts *IIa*—*IIf* did not afford reproducible analysis data for C and H. An analogous behaviour, obviously due to the effect of the ClO_4^- anion on the combustion, was observed[7] for compound *IIe*.

Preparation of the Quaternary Salts

1,3-*Dimethyl*-2,4,6-*triphenylpyridinium perchlorate* (IIa): A 30% aqueous solution of methylamine (3 ml) was added to the pyrrylium salt *IIIa* (1·5 g) in methanol–ether (1 : 1; 20 ml). After standing overnight, the salt *IIa* was collected on filter and washed with ether; yield 1·5 g (97%).

3-*Methyl*-1,2,4,6-*tetraphenylpyridinium perchlorate* (IIb): Aniline (2 ml) was added to the pyrrylium salt *IIIa* (3·0 g) in methanol–ether (1 : 1; 40 ml). After refluxing for 3 h and standing overnight, the mixture was diluted with ether (300 ml) and the salt *IIb* (3·2 g; 91%) was filtered.

1-*Methyl*-3-*ethyl*-2,4,6-*triphenylpyridinium perchlorate* (IIc): The compound was prepared in 82% yield from the pyrrylium salt *IIIb* (1·5 g) as described for the compound *IIa*.

3-*Ethyl*-1,2,4,6-*tetraphenylpyridinium perchlorate* (IId): Aniline (1·5 ml) was refluxed with the pyrrylium salt *IIIb* (2·0 g) in ethanol (20 ml) for 2 h. After standing overnight and dilution with ether (200 ml), the product *IId* (1·5 g; 64%) was filtered.

1-*Methyl*-2,3,4,6-*tetraphenylpyridinium perchlorate* (IIe): The pyrrylium salt *IIIc* (0·5 g) was treated with a methylamine solution (1 ml) in the same manner as described for *IIa,c*, affording 0·5 g (97%) of *IIe*.

TABLE I

Quaternary pyridinium salts *IIa*—*IIf*

Compound	M.p., °C	Formula (mol.wt.)	Calculated/Found % N	δ, ppm[a]
IIa	307—308	$C_{25}H_{22}ClNO_4$ (435·9)	3·21 3·33	2·0 s (CH_3), 3·58 s (CH_3), 7·4 to 7·9 m (3 × C_6H_5), 7·94 s (1 H)
IIb	157—159	$C_{30}H_{24}ClNO_4$ (498·0)	2·81 2·85	2·1 s (CH_3), 6·9—7·8 m (4 × C_6H_5), 8·1 s (1 H)
IIc[b]	228—231	$C_{26}H_{24}ClNO_4$ (449·9)	3·11 3·39	0·75 t (CH_3), 2.57 q (CH_2), 3·82 s (CH_3), 7·5—7·9 m (3 × C_6H_5), 8·37 s (1 H)
IId	153—155	$C_{31}H_{26}ClNO_4$ (512·0)	2·74 2·63	1·0 t (CH_3), 3·36 q (CH_2), 6·6 to 6·8 m (4 × C_6H_5), 8·06 s (1 H)
IIe	155—158	$C_{30}H_{24}ClNO_4$ (498·0)	2·81 3·10	3·64 s (CH_3), 6·8—7·9 m (4 × C_6H_5), 8·1 s (1 H)
IIf	310—315	$C_{35}H_{26}ClNO_4$ (560·0)	2·50 2·29	6·9—7·5 m (5 × C_6H_5), 8·34 s (1 H)

[a] In hexadeuteriodimethyl sulfoxide, internal standard tetramethylsilane; [b] in hexadeuterioacetone.

1,2,3,4,6-*Pentaphenylpyridinium perchlorate* (IIf): A mixture of the pyrrylium salt *IIIc* (3·0 g), ethanol (40 ml) and aniline (2·0 ml) was refluxed for 2 h. After standing overnight and dilution with ether (200 ml), the salt *IIf* was filtered; yield 2·5 g (72%).

Oxidation of Salts *II*

IIa: A solution of potassium ferricyanide (7·5 g) and potassium hydroxide (2·5 g) in water (100 ml) was added to a solution of *IIa* (2·5 g) in ethanol (100 ml). After refluxing for 3 h, the mixture was diluted with water (1 l), and extracted with chloroform (3 × 100 ml). The chloroform layer was taken down, the residue was dissolved in ether (100 ml) and the unreacted salt (0·75 g) was removed by filtration. Evaporation of ether and chromatography of the residue

TABLE II

Pyrrole derivatives

Compound	M.p., °C (reported, °C)	Formula (mol.wt.)	Calculated/Found			δ, ppm[a]
			% C	% H	% N	
Ia	163–165 (163–165)[1]	$C_{24}H_{19}NO$ (337·4)	85·43 85·41	5·67 5·59	4·15 4·13	3·8 s (CH_3), 6·3 s (1 H), 6·9–7·6 m (3 × C_6H_5)
Ib	177–178 (177–178)[1]	$C_{29}H_{21}NO$ (399·5)	87·19 87·36	5·30 5·57	3·51 3·59	6·65 s (1 H), 7·0–7·75 m (4 × C_6H_5)
IVd[b]	160–161 (160–162)[8]	$C_{18}H_{17}N$ (247·3)	87·41 87·33	6·93 7·03	5·66 5·96	2·40 s (CH_3), 3·54 s (CH_3) 6·3 s (1 H), 7·2–7·6 m (2 × C_6H_5)
IVb	172–173	$C_{23}H_{19}N$ (309·5)	89·27 89·15	6·19 6·48	4·54 4·29	2·23 s (CH_3), 6·55 s (1 H), 7·1–7·6 m (3 × C_6H_5)
IVc	oil	$C_{19}H_{19}N$ (261·4)	87·31 87·12	7·33 7·10	5·36 5·40	1·29 t (CH_3), 2·78 q (CH_2), 3·55 s (CH_3), 6·29 s (1 H), 7·1–7·6 m (2 × C_6H_5)
IVd	84–86	$C_{24}H_{21}N$ (323·4)	89·12 89·58	6·54 6·55	4·33 4·19	0·90 t (CH_3), 2·69 q (CH_2), 6·51 s (1 H), 7·0–7·6 m (3 × C_6H_5)
IVe	177–178 (178–179)[8]	$C_{23}H_{19}N$ (309·5)	89·27 89·31	6·19 6·34	4·54 4·52	3·42 s (CH_3), 6·46 s (1 H), 7·0–7·6 m (3 × C_6H_5)
IVf	201–202 (201)[9]	$C_{28}H_{21}N$ (371·5)	90·51 90·64	5·69 5·89	3·78 3·66	6·68 s (1 H), 6·9–7·3 m (4 × C_6H_5)
V	186–188	$C_{30}H_{23}NO$ (413·5)	87·14 87·02	5·61 5·55	3·39 3·49	3·74 s (CH_3), 6·6–7·6 m (4 × C_6H_5)

[a] In deuteriochloroform, internal standard tetramethylsilane; [b] in hexadeuteriobenzene.

on a column of silica gel in chloroform afforded 0·84 g (59%) of the pyrrole *IVa* and 0·45 g (23%) of the benzoylpyrrole *Ia*.

IIb: A solution of potassium ferricyanide (3·0 g) and potassium hydroxide (0·5 g) in water (40 ml) was added to a solution of the salt (1·0 g) in ethanol (40 ml). After refluxing for 2 g and dilution with water (200 ml), the mixture was extracted with chloroform (2 × 50 ml). Chromatography on a column of silica gel in chloroform gave 0·33 g (53%) of the pyrrole *IVb* and 0·05 g (6%) of the benzopyrrole *Ib*.

IIc: A solution of potassium ferricyanide (6·0 g) and potassium hydroxide (1·0 g) in water (80 ml) was added to a solution of the salt (2·0 g) in ethanol (80 ml). After refluxing for 6 h and dilution with water (1 litre) the mixture was extracted with chloroform (3 × 100 ml). Chromatography on a column of silica gel yielded 0·35 h (30%) of the pyrrole *IVc* and 0·5 g (33%) of the benzoylpyrrole *Ia*.

IId: Similarly as described for the compound *IIc*, the salt *IId* (2·0 g) afforded (after chromatography) 0·80 g (63%) of *IVd* and 0·55 g (35%) of *Ib*.

IIe: A solution of potassium ferricyanide (4·5 g) and potassium hydroxide (0·75 g) in water (60 ml) was added to a solution of the salt (1·5 g) in ethanol (60 ml). The mixture was refluxed for 5 h, diluted with water (1 litre) and extracted with chloroform (3 × 100 ml). After removal of chloroform, the residue was chromatographed on silica gel in chloroform, affording 0·2 g (21%) of compound *IVe* and 0·5 g (40%) of the benzoyl derivative *V*. For compound *V*: IR spectrum (chloroform): ν(C=O) 1 625 cm^{-1}; mass spectrum, m/e (% rel. int.): 413 (100), 412 (71), 396 (9), 336 (13), 264 (7), 105 (16), 77 (21).

IIf: A solution of potassium ferricyanide (3·0 g) and potassium hydroxide (1·0 g) in water (40 ml) was added to a solution of the salt (1·0 g) in ethanol (40 ml). After refluxing for 2 h, the mixture was diluted with water (200 ml) and extracted with chloroform (3 × 50 ml). Chromatography on silica gel gave 0·4 g (60%) of the pyrrole *IVf*.

We are indebted to the staff of the Central Laboratories of this Institute for carrying out the elemental analyses and spectral measurements.

REFERENCES

1. Nesvadba P., Kuthan J.: Tetrahedron Lett. *21*, 3727 (1980).
2. Nesvadba P., Kuthan J.: This Journal *47*, 1494 (1982).
3. Kuthan J.: Unpublished results.
4. Van Allan J. A., Reynolds G. H.: J. Org. Chem. *33*, 1102 (1968).
5. Meislich H. in the book: *Pyridine and Its Derivatives* (M. Klinsbeerg, Ed.), Part 3, p. 596. Interscience, New York 1962.
6. Tieckelmann H.: *Pyridine and Its Derivatives*, Vol. 14, Supplement (R. A. Abramovitch, Ed.), Part 3, p. 706. Interscience, New York 1974.
7. Libert M., Caullet C.: Bull. Soc. Chim. Fr. *1974*, 800.
8. Huisgen R., Gotthardt H., Bayer H. O., Schaefer F. C.: Chem. Ber. *103*, 2611 (1970).
9. Stetter H., Schreckenberg M.: Chem. Ber. *107*, 2453 (1974).

Translated by M. Tichý.