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OXIDATION OF 1-SUBSTITUTED 3-TERT-BUTYL- AND 3-ISOPROPYLPYRIDINIUM SALTS BY FERRICYANIDE ION[†]

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In the alkaline ferricyanide oxidation at 32° of 3-substituted 1-methylpyridinium ions (type IV), the isopropyl and the tert-butyl groups at the 3-position have been found to orient the oxidation to both the 2- (type V) and the 6-position (type VI) in ratios of 71 : 29 and 14 : 86. In the oxidation of the 3-tert-butyl derivative (IVi), replacement of the N-methyl group by the 3,4-dimethoxyphenethyl group resulted in the exclusive oxidation at the 6-position, suggesting the highest degree of steric hindrance to the approach of bulky ferricyanide ion to the 2-position.

Previous reports[1-4] from this laboratory described the results of the alkaline ferricyanide oxidation of 1,3-disubstituted pyridinium ions with particular emphasis on the effects of various 3-substituents on the orientation of oxidation in the nucleus. We have now extended the scope of the 3-substituent to include

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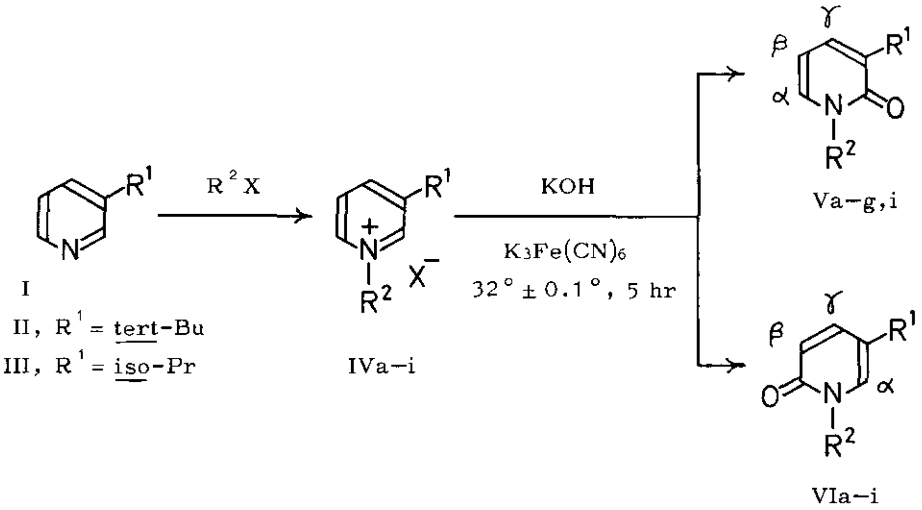
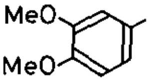
[†] Dedicated to Professor Dr. Adolf Butenandt on the occasion of his 75th birthday.



a, R^1 = Me; R^2 = $Ar(CH_2)_2$
b, R^1 = Me; R^2 = Me
c, R^1 = Et; R^2 = $Ar(CH_2)_2$
d, R^1 = Et; R^2 = Me
e, R^1 = n-Bu; R^2 = $Ar(CH_2)_2$
f, R^1 = iso-Pr; R^2 = $Ar(CH_2)_2$
g, R^1 = iso-Pr; R^2 = Me
h, R^1 = tert-Bu; R^2 = $Ar(CH_2)_2$
i, R^1 = tert-Bu; R^2 = Me

Ar =



the tert-butyl group, a highly branched, bulky hydrocarbon substituent.

Treatment of 3-tert-butylpyridine (II),[5,6] prepared from α-tert-butylacrolein as reported recently by us,[6] with an excess of methyl iodide in benzene (room temp., 36 hr) furnished the methiodide (IVi, X=I) (mp 169.5–170.5°; lit.[7] mp 168.2–169.4°) in 99% yield. The salt (IVi, X=I) was oxidized with potassium ferricyanide and potassium hydroxide (32° ± 0.1°, 5 hr) according to previously reported[1] standard procedure, providing the 2-pyridone (Vi) [mp 78.5–79.5°; ir $\nu_{max}^{CHCl_3}$ 1650 cm^{-1} (CO); uv $\lambda_{max}^{abs.\ EtOH}$ 233 nm (log ε 3.75), 302 (3.83); nmr

($CDCl_3$) δ : 1.36 (9H, s, tert-Bu), 3.52 (3H, s, NMe), 6.04 (1H, t, Hβ), 7.16 (1H, d-d, Hγ), 7.20 (1H, d-d, Hα) ($J\alpha\beta$ = $J\beta\gamma$ = 6.6 Hz, $J\alpha\gamma$ = 2.0 Hz)][8] and the 6-pyridone (VIi) [mp 91.5–92.5°; ir $\nu_{max}^{CHCl_3}$ 1663 cm^{-1} (CO); uv $\lambda_{max}^{abs.EtOH}$ 230 nm (log ε 3.96), 309 (3.75); nmr ($CDCl_3$) δ: 1.24 (9H, s, tert-Bu), 3.54 (3H, s, NMe), 6.53 (1H, d, Hβ), 7.09 (1H, d, Hα), 7.42 (1H, d-d, Hγ) ($J\alpha\beta$ = 0 Hz, $J\alpha\gamma$ = 3.0 Hz, $J\beta\gamma$ = 9.5 Hz)][8] in a combined yield of 89%. The assignment of the two pyridone structures was based on the above spectral data, which fulfilled the previously described criteria[1–3] for distinguishing between 1,3-dialkyl-2- (type V) and -6-pyridones (type VI). By column chromatographic analysis as reported previously[1–4] or by high performance liquid chromatographic analysis [Corasil II, $CHCl_3$—EtOH (98 : 2, v/v), 250 p.s.i.], the isomer ratio of the pyridones thus formed was determined to be Vi : VIi = 14 : 86.

On the other hand, a similar ferricyanide oxidation of 1-(3,4-dimethoxyphenethyl)-3-tert-butylpyridinium bromide (IVh, X = Br), prepared by quaternization of II with 3,4-dimethoxyphenethyl bromide (boiling benzene, 52 hr), was found to give only one pyridone isomer, namely, the 6-pyridone (VIh) [57% overall yield from II; ir $\nu_{max}^{CHCl_3}$ 1660 cm^{-1} (CO); uv $\lambda_{max}^{abs.EtOH}$ 230 nm (log ε 4.18), 286 (3.70), 312 (3.76); nmr ($CDCl_3$) δ : 1.06 (9H, s, tert-Bu), 6.52 (1H, d, Hα), 6.56 (1H, d, Hβ), 7.38 (1H, d-d, Hγ) ($J\alpha\beta$ = 0 Hz, $J\alpha\gamma$ = 3.0 Hz, $J\beta\gamma$ = 9.5 Hz)], and no 2-pyridone isomer (Vh) was detected in crude product. This change in the isomer ratio seemed significant since we had already observed[1,2] that in similar oxidations of 1-substituted 3-methyl- and 3-ethylpyridinium ions the effect of a slender N-alkyl or N-aralkyl group on the regioselectivity in the nucleus oxidation was negligibly small (see Table 1). Therefore, we next carried out the oxidation of 1-methyl-3-isopropylpyridinium iodide (IVg, X = I) with ferricyanide ion in order to compare its result with that reported[3] for the corresponding 1-(3,4-dimethoxyphenethyl)pyridinium salt (IVf, X = Br).

TABLE 1. The Alkaline Ferricyanide Oxidation of 3-Substituted Pyridinium Salts

Pyridinium salt (IV)				Product[a]		
No.	R^1	R^2[b]	X	Combined yield (%)	% 2-Pyridone (V)	% 6-Pyridone (VI)
IVa	Me	Ar(CH$_2$)$_2$	Br	76	94 (Va)	6 (VIa)
IVb	Me	Me	I	82	93 (Vb)[c]	7 (VIb)[c]
IVc	Et	Ar(CH$_2$)$_2$	Br	71	88 (Vc)	12 (VIc)
IVd	Et	Me	I	86	87 (Vd)[c]	13 (VId)[c]
IVe	*n*-Bu	Ar(CH$_2$)$_2$	Br	44[d]	74 (Ve)	26 (VIe)
IVf	*iso*-Pr	Ar(CH$_2$)$_2$	Br	79[d]	71 (Vf)	29 (VIf)
IVg	*iso*-Pr	Me	I	88[d]	71 (Vg)[e]	29 (VIg)[e]
IVh	*tert*-Bu	Ar(CH$_2$)$_2$	Br	57[d]	0 (Vh)	100 (VIh)
IVi	*tert*-Bu	Me	I	89	14 (Vi)[e]	86 (VIi)[e]

a) Unless otherwise noted, all isomer ratios were determined by column chromatographic analysis as reported previously.[1] The results with IVa–d are taken from ref. 2; those with IVe,f, from ref. 3.

b) The abbreviation Ar stands for the 3,4-dimethoxyphenethyl group.

c) Determined by gas-liquid chromatographic analysis.

d) Overall yield from the corresponding pyridine base (I) used in the preceding quaternization.

e) High performance liquid chromatographic analysis gave identical results.

Quaternization of 3-isopropylpyridine (III)[5] with an excess of methyl iodide in benzene (room temp., 5 hr) yielded the methiodide (IVg, X = I) as a hygroscopic solid (lit.[9] mp 85°). On oxidation in the same manner as described above, the crude methiodide produced the 2-pyridone (Vg) [bp 106° (5 mmHg); ir $\nu_{max}^{CHCl_3}$ 1646 cm^{-1} (CO); uv $\lambda_{max}^{abs. EtOH}$ 234 nm (log ε 3.74), 303 (3.83); nmr ($CDCl_3$) δ: 1.18 (6H, d, $\underline{J}$ = 7.0 Hz, $CH\underline{Me}_2$), 3.22 (1H, septet, $C\underline{H}Me_2$), 3.55 (3H, s, NMe), 6.11 (1H, t, H_β), 7.16 (1H, d-d, H_α), 7.16 (1H, d-d, H_γ) ($\underline{J}_{\alpha\beta} = \underline{J}_{\beta\gamma}$ = 6.8 Hz, $\underline{J}_{\alpha\gamma}$, unmeasurable)] together with the 6-pyridone (VIg) [bp 124° (5 mmHg); ir $\nu_{max}^{CHCl_3}$ 1665 cm^{-1} (CO); uv $\lambda_{max}^{abs. EtOH}$ 231 nm (log ε 3.92), 310 (3.72); nmr ($CDCl_3$) δ: 1.16 (6H, d, $\underline{J}$ = 7.0 Hz, $CH\underline{Me}_2$), 2.66 (1H, septet, $C\underline{H}Me_2$), 3.52 (3H, s, NMe), 6.54 (1H, d, H_β), 7.04 (1H, d, H_α), 7.28 (1H, d-d, H_γ) ($\underline{J}_{\alpha\beta}$ = 0 Hz, $\underline{J}_{\alpha\gamma}$ = 2.6 Hz, $\underline{J}_{\beta\gamma}$ = 9.5 Hz)] in a combined overall yield of 88% from III. The ratio of isomer formation was determined to be Vg : VIg = 71 : 29, in agreement with that reported for the N-(3,4-dimethoxyphenethyl) analog[3] (Vf : VIf = 71 : 29).

The present results are summarized in Table 1, which also includes some of previous results for comparison. It may be seen that in the alkaline ferricyanide oxidation of the quaternary pyridinium ions (IV), which carry a $\underline{n}$-alkyl or isopropyl group at the 3-position, the oxidation at the 2-position is much favored over that at the 6-position. A higher and/or bulkier 3-alkyl group, however, tends to increase the extent of the 6-pyridone formation, and the 3-$\underline{tert}$-butyl group eventually brings about a reversal of the regioselectivity. The utmost of such a reversal is the case of the 1-(3,4-dimethoxyphenethyl)-3-$\underline{tert}$-butyl derivative (IVh, X = Br), where the highest degree of steric hindrance to the approach of bulky ferricyanide ion to the 2-position of the intermediate 2-alkoxide[3,4,10,11] should be produced by both substituents.

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