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Lactams. VI.¹⁾ Synthesis and Nuclear Magnetic Resonance Study of 1-Aralkyl-3-methyl- and -5-methyl-2(1H)-pyridones

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The alkaline ferricyanide oxidation of the quaternary pyridinium salts (Ia—g) furnished pairs of the isomeric 2-pyridones (IIa—g) and 6-pyridones (IIIa—g) in good total yields. In all cases, the oxidation at the 2-position was much favored over that at the 6-position. The effect of the aryl group in the N-aralkyl chain on the orientation of the oxidation seemed to be negligibly small regardless of the number of the methylene groups separating the aryl group from the nitrogen. The extent of the 6-oxidation was slightly increased as the alkyl group at the 3-position was changed from the methyl to the ethyl group.

The nuclear magnetic resonance spectra of these pyridones were measured in deuteriochloroform, carbon tetrachloride, and benzene-*d*₆. On the basis of the results summarized in Tables III—VI, the effects of the aryl group and the number of the methylene groups in the N-substituent on the chemical shifts for the pyridone-ring and neighboring group protons are discussed.

In the course of our recent study on the synthesis of the benzo[*a*]quinolizidine system from piperidine derivatives,^{1,3)} a few pairs of isomeric 3- and 5-alkyl-1-(2-arylethyl)-2(1H)-pyridones (types IIc and IIIc) (Chart 1) were prepared by the alkaline ferricyanide oxidation of the corresponding quaternary pyridinium salts (type Ic) and their structures were unequivocally established on the basis of spectral data.¹⁾ In the nuclear magnetic resonance (NMR) spectra of the 3-alkyl-2-pyridone derivatives (IIc, g) in CDCl₃, the H_α signal of the pyridone ring was found to resonate at higher field than does the H_γ signal by *ca.* 0.3 ppm, paralleling the experience of Kirisawa and Kawazoe^{4,5)} with the spectrum of 3-ethyl-1-methyl-2(1H)-pyridone (IIf) in CS₂. On the other hand, the H_α signal of 1,3-dimethyl-2(1H)-pyridone (IIa) has been reported to appear downfield from the H_γ signal by 0.10—0.13 ppm in CDCl₃.⁶⁾ In contrast, Elvidge and Jackman^{6a)} have reported that the H_α and the H_γ signals of 1,5-dimethyl-2(1H)-pyridone (IIIa) occur at 2.89 and 2.80 τ in the same solvent. This order of shifts, however, is opposite to that reported by Möhrle and Weber.^{6b)} Although it has been known that the chemical shifts of the α- and γ-protons of certain pyridone derivatives are influenced by the nature of solvent and concentration,⁷⁾ these two would not be the only

- 1) Paper V in this series, T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 2695 (1973).
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- 3) a) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972); b) T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, and S. Ikegami, *ibid.*, **23**, 144 (1975).
- 4) M. Kirisawa and Y. Kawazoe, private communication to Dr. H. Tomisawa, Tohoku College of Pharmacy. For details, see reference 5 cited in Ref. 5.
- 5) H. Tomisawa and H. Hongo, *Ann. Rept. Tohoku Coll. Pharm.* (Sendai), **10**, 39 (1963).
- 6) a) J.A. Elvidge and L.M. Jackman, *J. Chem. Soc.*, **1961**, 859; b) H. Möhrle and H. Weber, *Chem. Ber.*, **104**, 1478 (1971).
- 7) P.W. von Ostwalden and J.D. Roberts, *J. Org. Chem.*, **36**, 3792 (1971).

factors responsible for the considerably large upfield shift of the H α signals of the 1-(2-arylethyl) derivatives (IIc, g).

In the present work, we have synthesized several pairs of isomeric 1-aralkyl-3-methyl- and -5-methyl-2(1*H*)-pyridones (IIb—e and IIIb—e) by the ferricyanide oxidation of the 1-aralkyl-3-methylpyridinium salts (Ib—e) and explored the effect of the 3,4-dimethoxyphenyl group included in the N-substituent on the line positions (τ values) for protons attached directly to the pyridone ring and for those of the 3- and 5-methyl groups. In the oxidation of the quaternary pyridinium salts, the effect of the N-substituent on the orientation of the oxidation has also been studied.

Experimental

All melting points are corrected; boiling points, uncorrected. Spectra reported herein were measured with a Hitachi Model 323 UV spectrophotometer, a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a Varian HA-100 or a JEOL-JNM-PS-100 NMR spectrometer at 23° using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, d-m=doublet-of-multiplets, m=multiplet, q=quartet, s=singlet, t=triplet.

We are indebted to Mr. Y. Itatani and Misses S. Toyoshima and H. Hyuga at Kanazawa University for elemental analyses and NMR and mass spectral data.

Materials—Pure samples of 1-(3,4-dimethoxyphenethyl)-3-methyl- (IIc), -5-methyl- (IIIc), -3-ethyl- (IIg), and -5-ethyl-2(1*H*)-pyridone (IIIg) were obtained according to the procedure reported previously.¹⁾ Other compounds were prepared as described below.

1,3-Dimethylpyridinium Iodide (Ia: X=I)—The previously reported procedure⁸⁾ was slightly modified as follows. A solution of 3-methylpyridine (9.31 g, 0.1 mole) and methyl iodide (28.4 g, 0.2 mole) in dry benzene (40 ml) was stirred at room temperature for 8 hr. The pale yellowish precipitates that resulted were filtered off and dissolved in H₂O (20 ml). The aqueous solution was washed with three 10-ml portions of benzene and evaporated *in vacuo* to dryness to leave a brownish solid (23.1 g, 98%). Recrystallization of the solid from dry acetone produced Ia (X=I) as slightly yellowish plates, mp 90—91° (lit. mp 92°.^{9a)} mp 97—98°;^{9a)} mp 98—99°^{9b)}).

1-(3,4-Dimethoxybenzyl)-3-methylpyridinium Chloride (Ib: X=Cl)—A solution of 3-methylpyridine (5.12 g, 55 mmoles) and 3,4-dimethoxybenzyl chloride¹⁰⁾ (9.33 g, 50 mmoles) in dry benzene (20 ml) was stirred at room temperature for 48 hr. The excess of the picoline and benzene was removed by evaporation under diminished pressure. The residue was recrystallized successively from ethanol and ethanol-ethyl acetate (1:2, v/v) to give Ib (X=Cl) as colorless prisms, mp 202—204° (decomp.). *Anal.* Calcd. for C₁₅H₁₈O₂NCl: N, 5.01. Found: N, 5.14.

1-[3-(3,4-Dimethoxyphenyl)propyl]-3-methylpyridinium Bromide (Id: X=Br)—A stirred solution of 3-methylpyridine (10.2 g, 0.11 mole) and 3-(3,4-dimethoxyphenyl)propyl bromide¹¹⁾ (25.9 g, 0.10 mole) in dry benzene (100 ml) was heated at reflux for 24 hr. The oily salt that formed was extracted with H₂O (150 ml). The aqueous solution was washed with three 50-ml portions of benzene and concentrated to dryness *in vacuo* to furnish crude Id (X=Br) (31.2 g, 89%) as a yellowish thick oil, which was directly used in the next oxidation reaction without further purification.

4-(3,4-Dimethoxyphenyl)-1-butanol—To a stirred and cooled (−10° to −5°) suspension of powdered LiAlH₄ (3.42 g, 90 mmoles) in dry ether (150 ml) was added dropwise a solution of ethyl 4-(3,4-dimethoxyphenyl)butyrate¹²⁾ (15.1 g, 60 mmoles) in dry ether (50 ml) over a period of 1 hr. After having been stirred at room temperature for 2.5 hr, the mixture was heated under reflux with stirring for 4 hr and worked up in the usual manner to produce the desired alcohol (11.6 g, 92%) as a colorless oil, bp 142—146° (1 mm Hg) [lit.¹³⁾ bp 155—157° (3 mm Hg)]; IR $\nu_{\text{max}}^{\text{film}}$ cm^{−1}: 3400 (b, OH), 2850 (CH₃O), 1060 (OH), 1030 (ArOCH₃); Mass Spectrum *m/e*: 210 (M⁺).

4-(4-Bromobutyl)-1,2-dimethoxybenzene—To a stirred and ice-cooled solution of the foregoing alcohol (10.5 g, 50 mmoles) in dry benzene (20 ml) was added dropwise a solution of PBr₃ (15.9 g, 59 mmoles) in dry benzene (20 ml) over a period of 1 hr. The mixture was stirred at room temperature for 24 hr, and then

8) a) H. Möhrle and H. Weber, *Tetrahedron*, **26**, 2953 (1970); b) R.A. Abramovitch and A.R. Vinutha, *J. Chem. Soc. (B)*, **1971**, 131.

9) a) E.A. Coulson and J.I. Jones, *J. Soc. Chem. Ind.*, **65**, 169 (1946); b) A.P. Phillips, *J. Am. Chem. Soc.*, **74**, 3296 (1952).

10) T. Fujii, Y. Ueno, and M. Mitsukuchi, *Chem. Pharm. Bull. (Tokyo)*, **19**, 1374 (1971).

11) G.H. Douglas, C.R. Walk, and H. Smith, *J. Med. Chem.*, **9**, 27 (1966).

12) E.C. Horning and J. Koo, *J. Am. Chem. Soc.*, **73**, 5828 (1951).

13) R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3114 (1957).

poured into ice-water (20 ml). The benzene layer was separated and the aqueous layer was extracted with two 50 ml- portions of benzene. The benzene solutions were combined, dried over anhyd. Na_2SO_4 , and evaporated to dryness *in vacuo*. The residue was distilled to give the desired bromide (7.11 g, 52%) as a colorless oil, bp 137° (1 mm Hg); IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2850, 1030 (ArOCH_3); NMR (10% in CDCl_3) τ : 7.9–8.9 (4H, m, two CH_2 's), 7.39 (2H, t, $J=6.5$ Hz, ArCH_2), 6.56 (2H, t, $J=6.5$ Hz, BrCH_2), 6.10 and 6.07 (6H, s each, two CH_3O 's), 3.0–3.5 (3H, m, aromatic protons).

1-[4-(3,4-Dimethoxyphenyl)butyl]-3-methylpyridinium Bromide (Ie: X=Br)—Prepared from 3-methylpyridine and 4-(4-bromobutyl)-1,2-dimethoxybenzene, obtained as above, in a manner similar to that described above for Id (X=Br). The resulting oily salt was directly used in the next oxidation step without further purification.

3-Ethyl-1-methylpyridinium Iodide (If: X=I)—3-Ethylpyridine and methyl iodide were allowed to react as described above for Ia (X=I), giving If (X=I) in 99% yield. It crystallized from acetone in pale yellowish, hygroscopic¹⁴) plates, mp 80 – 82° .

Ferricyanide Oxidation of the Pyridinium Salts (I)—The oxidation of the quaternary salts (Ia,b,d,e,f) was carried out according to the previously reported standard procedure.³⁾ Isolation of the isomeric pyridones (II and III) and determination of the isomer ratios were also performed in the same manner. In the cases of the N-methyl derivatives, the isomer ratios were obtained by gas-liquid chromatography (GLC) of the crude products. The GLC analyses were performed isothermally at 160° with helium as carrier gas on a Shimadzu GC-4BPT gas chromatograph equipped with a 1.5 m \times 3 mm column containing 5% diethylene glycol succinate on Shimalite W. The relative retention time of the 3-alkyl derivatives (IIa,f) to the corresponding 5-alkyl derivatives (IIIa, f) was 0.42–0.47.

The results of these experiments are summarized in Table I, and the physical properties of the pyridones are described in the following.

1,3-Dimethyl-2(1H)-pyridone (IIa)—Obtained as a yellowish oil, bp 96 – 97° (3 mm Hg) [lit. bp 86 – 88° (1.45 mm Hg);¹⁵) bp 78° (0.5 mm Hg)^{6a)}]; spectra (Tables II, III, and IV).

1,5-Dimethyl-2(1H)-pyridone (IIIa)—A light brownish oil, bp 83 – 84° (1.5 mm Hg) [lit.^{6a)} bp 98° (3.5 mm Hg)], crystallized in a hygroscopic solid^{6a)} on standing; spectra (Tables II, III, and IV).

1-(3,4-Dimethoxybenzyl)-3-methyl-2(1H)-pyridone (IIb)—Recrystallized from ether-pet. ether (bp 26 – 50°) (3:1, v/v) to colorless scales, mp 59 – 61° ; Mass Spectrum m/e : 259 (M^+); other spectra (Tables II, III, and IV). Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_3\text{N}$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.60; N, 5.32.

1-(3,4-Dimethoxybenzyl)-5-methyl-2(1H)-pyridone (IIIb)—Recrystallized from hexane-ethyl acetate (2:1, v/v) to slightly yellowish prisms, mp 107 – 108° ; Mass Spectrum m/e : 259 (M^+); other spectra (Tables II, III, and IV).

1-[3-(3,4-Dimethoxyphenyl)propyl]-3-methyl-2(1H)-pyridone (IIc)—Crystallized from hexane-ether (1:1, v/v) in colorless needles, mp 62 – 63° ; Mass Spectrum m/e : 287 (M^+); other spectra (Tables II, III, and IV). Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{O}_3\text{N}$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.98; H, 7.11; N, 4.82.

1-[3-(3,4-Dimethoxyphenyl)propyl]-5-methyl-2(1H)-pyridone (IIIc)—A pale yellowish thick oil, Mass Spectrum m/e : 287 (M^+); other spectra (Tables II, III, and IV).

1-[4-(3,4-Dimethoxyphenyl)butyl]-3-methyl-2(1H)-pyridone (IIe)—Obtained as a pale yellowish, thick oil, Mass Spectrum m/e : 301 (M^+); other spectra (Tables II, III, and IV).

1-[4-(3,4-Dimethoxyphenyl)butyl]-5-methyl-2(1H)-pyridone (IIIe)—A pale yellowish thick, oil, Mass Spectrum m/e : 301 (M^+); other spectra (Tables II, III, and IV).

3-Ethyl-1-methyl-2(1H)-pyridone (IIg)—A colorless oil, bp 72 – 73° (1.5 mm Hg) [lit.^{16a)} bp 122 – 123° (11 mm Hg)]; spectra (Tables II, III, and IV).

5-Ethyl-1-methyl-2(1H)-pyridone (IIIg)—Obtained as a colorless oil, bp 87 – 89° (1.5 mm Hg) [lit.^{16b)} bp 120 – 123° (6 mm Hg)]; spectra (Tables II, III, and IV).

Results

The alkaline ferricyanide oxidation of the quaternary pyridinium salts (Ia–g), prepared by quaternization of 3-methyl- or 3-ethylpyridine with methyl iodide or adequate aralkyl halides in benzene solution as delineated in Chart 1, was effected in the same manner as described previously¹⁾ and it furnished the results shown in Table I. It may be seen that in all cases the oxidation of the salt at the 2-position is much favored over that at the 6-position.

14) C. Stoehr, *J. Prakt. Chem.* [2], **45**, 20 (1892).

15) H.L. Bradlow and C.A. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951).

16) a) S. Sugawara and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **4**, 139 (1956); b) *Idem, ibid.*, **3**, 190 (1955).

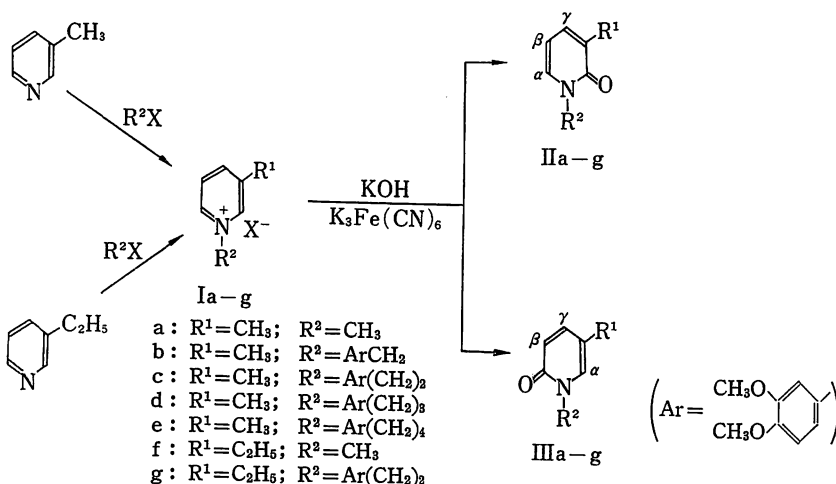


Chart 1

TABLE I. The Ferricyanide Oxidation of 3-Substituted Pyridinium Salts

Pyridinium salt	Substituent ^{a)}		Product ^{b)}		
	R ¹	R ²	Combined yield (%)	% 2-Oxidation (II)	% 6-Oxidation (III)
Ia (X=I)	CH ₃	CH ₃	82 70 ^{d)} 53.1 ^{e)}	93 (IIa) ^{e)} 90 (IIa) ^{c,d)} 96.6 (IIa) ^{c,e)}	7 (IIIa) ^{e)} 10 (IIIa) ^{c,d)} 3.4 (IIIa) ^{c,e)}
Ib (X=Cl)	CH ₃	ArCH ₂	68	92 (IIb)	8 (IIIb)
Ic (X=Br)	CH ₃	Ar(CH ₂) ₂	76 ^{f)}	94 (IIc) ^{f)}	6 (IIIc) ^{f)}
Id (X=Br)	CH ₃	Ar(CH ₂) ₃	50 ^{g)}	92 (IId)	8 (IIId)
Ie (X=Br)	CH ₃	Ar(CH ₂) ₄	50 ^{g)}	91 (IIe)	9 (IIIe)
If (X=I)	C ₂ H ₅	CH ₃	86	87 (IIf) ^{e)}	13 (IIIf) ^{e)}
If (X=CH ₃ OSO ₃)			76—84 ^{h)}	(IIIf) : (IIIIf) = 8 : 1 ^{h)}	
Ig (X=Br)	C ₂ H ₅	Ar(CH ₂) ₂	71 ^{f)}	88 (IIg) ^{f)}	12 (IIIg) ^{f)}

a) The abbreviation Ar stands for 3,4-dimethoxyphenyl group.

b) Unless otherwise noted, all isomer ratios were determined by column chromatographic analysis.

c) Determined by gas-liquid chromatographic analysis.

d) From ref. 8a; the oxidation conditions used were not identical with the present ones.

e) From ref. 8b; the reaction conditions used were slightly different from the present ones.

f) From ref. 1.

g) Overall yield based on the aralkyl bromide employed in the preceding quaternization of 3-methylpyridine.

h) From ref. 16a. The isomer ratio was obtained by separating both isomers in the form of the picrates.

The effect of the aryl group in the N-aralkyl chain on the orientation of the oxidation seems to be negligibly small regardless of the number of the methylene groups separating the aryl group from the nitrogen. The extent of the 6-oxidation was slightly increased as the substituent at the 3-position was changed from the methyl to the ethyl group.

Table II assembles the ultraviolet (UV) and the infrared (IR) spectra of the pyridones thus obtained. 2-Pyridones IIa—g had the long-wavelength UV absorption band at 300—303 nm, and 6-pyridones IIIa—g, at 311—315 nm. In the IR spectra IIa—g exhibited the CO stretching vibration in the range 1650—1653 cm⁻¹, and IIIa—g, in the 1667—1673 cm⁻¹ region. For the reasons described in a previous paper,¹⁾ such marked differences in spectra served as good criteria for distinguishing between the isomeric pyridones. The assigned structures were also supported by the NMR spectral data summarized in Tables III and IV. The assignment of the signals was based on our previous experience¹⁾ as well as the following consideration.

TABLE II. Ultraviolet and Infrared Spectra of Pyridones

Compound	UV spectrum ^{a)}						IR spectrum ^{b)} ν_{CO} (cm ⁻¹)
	Short-wavelength band		Medium-wavelength band		Long-wavelength band		
	λ_{max} (nm)	log ϵ	λ_{max} (nm)	log ϵ	λ_{max} (nm)	log ϵ	
2-Pyridones							
IIa	232	3.72	—	—	300	3.80	1653
IIb	231	4.11	286	3.83	300	3.81	1653
IIc ^{c)}	231	4.12	286	3.84	302	3.83	1651
II d	230	4.11	282 ^{d)}	3.82	300	3.80	1652
			286	3.84			
IIe	230	4.12	282 ^{d)}	3.83	300	3.81	1651
			286	3.85			
II f	232	3.74	—	—	300	3.82	1652
IIg ^{c)}	232	4.08	286	3.81	303	3.81	1650
6-Pyridones							
IIIa	232	3.89	—	—	312	3.73	1673
IIIb	231	4.21	285	3.63	315	3.71	1670
IIIc ^{c)}	231	4.17	284	3.66	314	3.74	1667
III d	230	4.16	282	3.65	314	3.69	1670
			286	3.65			
III e	230	4.18	281	3.67	313	3.71	1670
			286	3.67			
III f	232	3.92	—	—	311	3.73	1669
IIIg ^{c)}	232	4.19	284	3.68	313	3.76	1668

a) Measured in abs. ethanol.

b) Determined in chloroform solution at 0.2M concentration.

c) From ref. 1.

d) Shoulder.

In CDCl₃ solution the pyridone-ring protons of IIa displayed the spectrum of an A₂X-type and a decrease in concentration from 0.4M to 0.2M or to 0.1M did not alter the spectrum. The accidental equivalence of the α - and γ -protons, confirmed by spin-decoupling experiments, was not preserved when the solvent was changed from CDCl₃ to CCl₄ or benzene-*d*₆. The results are also included in Table IV. The α - and γ -protons of IIb and II f also behaved similarly. In the other cases including those of the 6-pyridones (III), the pyridone-ring protons approximate to ABX systems. However, difference in chemical shift between strongly coupled protons was sufficiently large to allow a first-order analysis. It should be noted that the criterion used for distinguishing between the H α and H γ signals of the 2-pyridone derivatives was the multiplicity of the latter due to long-range coupling between H γ and the methyl or methylene protons at the 3-position. For example, spin-decoupling experiments with IIc in CCl₄ revealed that $J_{H\gamma,CH_3}$ is *ca.* 1 Hz and $J_{H\alpha,CH_3}$, *ca.* 0.7 Hz. Additional evidence for the identification of the H γ signal was an 18% nuclear Overhauser effect observed between H γ and 3-methyl protons. Similarly, saturation of the methylene protons of the 3-ethyl group in IIg gave an 11% nuclear Overhauser effect for H γ , demonstrating the proximity of H γ and the methylene group.

It may be seen from Table IV that in CDCl₃ solutions all 2-pyridones exhibited their H γ signals in the range 2.79—2.82 τ ; H β signals, in the range 3.89—3.93 τ with the exception of that of IIc; H α signals, in the range 2.80—2.88 τ with the exception of that of IIc. The 6-pyridones displayed H γ signals in the same solvent in the 2.76—2.81 τ region; H β signals, in the 3.43—3.49 τ region; H α signals, in the 2.93—2.98 τ region with the exception of that of IIIc. 3-methyl signals, in the 7.93—7.96 τ region with the exception of that of IIIc. The

TABLE III. Chemical Shifts for Protons Other than Those Attached to Pyridone Ring

Com- pound	Sol- vent	Concen- tration (M)	Chemical shift (τ) ^{a)}							Aromatic protons	
			Methyl protons			Methylene protons					
			CCH ₃	NCH ₃	OCH ₃	CH ₃ CH ₂	CCH ₂ C	ArCH ₂	NCH ₂		ArCH ₂ N
2-Pyridones											
IIa	CDCl ₃	0.4	7.85 (s)	6.46 (s)	—	—	—	—	—	—	—
	CCl ₄	0.4	7.95 (s)	6.54 (s)	—	—	—	—	—	—	—
	C ₆ D ₆	0.4	7.85 (s)	7.03 (s)	—	—	—	—	—	—	—
IIb	CDCl ₃	0.2	7.82 (s)	—	6.13(s)	—	—	—	—	4.91 (s)	3.02— 3.15(m)
IIc	CDCl ₃	0.2	7.81 (s)	—	6.16(s) 6.12(s)	—	—	6.98 (t)	5.85 (t)	—	3.16— 3.33(m)
	CCl ₄	0.2	7.92 (s)	—	6.30(s) 6.27(s)	—	—	7.12 (t)	6.01 (t)	—	3.28— 3.50(m)
	C ₆ D ₆	0.2	7.79 (s)	—	6.57(s)	—	—	7.11 (t)	6.12 (t)	—	3.41 (s)
II d	CDCl ₃	0.2	7.84 (s)	—	6.12(s) 6.10(s)	—	7.72— 8.10(m)	7.32 (t)	6.01 (t)	—	3.08— 3.30(m)
IIe	CDCl ₃	0.33	7.85 (s)	—	6.13(s) 6.11(s)	—	8.02— 8.62(m)	7.39 (t)	6.04 (t)	—	3.10— 3.40(m)
II f	CDCl ₃	0.4	8.82 (t) ^{b)}	6.45 (s)	—	7.41 (q) ^{b)}	—	—	—	—	—
	CCl ₄	0.4	8.87 (t) ^{b)}	6.53 (s)	—	7.53 (q) ^{b)}	—	—	—	—	—
	C ₆ D ₆	0.4	8.84 (t) ^{b)}	7.00 (s)	—	7.34 (q) ^{b)}	—	—	—	—	—
II g	CCl ₄	0.2	8.84 (t) ^{b)}	—	6.29(s) 6.26(s)	7.49 (q) ^{b)}	—	7.11 (t)	6.00 (t)	—	3.26— 3.48(m)
6-Pyridones											
IIIa	CDCl ₃	0.4	7.93 (s)	6.48 (s)	—	—	—	—	—	—	—
	C ₆ D ₆	0.4	8.45 (s)	7.02 (s)	—	—	—	—	—	—	—
IIIb	CDCl ₃	0.2	7.96 (s)	—	6.13(s)	—	—	—	—	4.94 (s)	3.08— 3.16(m)
IIIc	CDCl ₃	0.2	8.01 (s)	—	6.15(s) 6.11(s)	—	—	7.00 (t)	5.89 (t)	—	3.10— 3.34(m)
	C ₆ D ₆	0.2	8.51 (s)	—	6.56(s) 6.54(s)	—	—	7.11 (t)	6.14 (t)	—	3.30— 3.55(m)
III d	CDCl ₃	0.2	7.94 (s)	—	6.12(s) 6.11(s)	—	7.74— 8.12(m)	7.34 (t)	6.06 (t)	—	3.10— 3.34(m)
III e	CDCl ₃	0.33	7.93 (s)	—	6.11(s) 6.10(s)	—	8.06— 8.65(m)	7.39 (t)	6.08 (t)	—	3.10— 3.35(m)
III f	CDCl ₃	0.4	8.85 (t)	6.47 (s) ^{b)}	—	7.60 (q) ^{b)}	—	—	—	—	—
	C ₆ D ₆	0.4	9.16 (t)	6.98 (s) ^{b)}	—	8.09 (q) ^{b)}	—	—	—	—	—

a) The letter in parentheses refers to the multiplicity or shape of the signal with the abbreviations appeared at the head of Experimental part. Unless otherwise stated, t designates triplet with $J=7.0$ Hz.

b) $J=7.5$ Hz.

exceptions observed for IIc and IIIc, pyridones of an N-phenethyl type, trend toward upfield shifts. Similar exceptions were also observed in CCl₄ solutions.

In CCl₄ or benzene-*d*₆ solutions all protons of both the 2- and 6-pyridones resonated at higher field than did in CDCl₃ solutions. The effect of benzene-*d*₆ on the line positions of the pyridone-ring protons is documented in more detail in Table V. When measured in a mixture

TABLE IV. Pyridone-Ring Proton Resonances

Compound	Solvent	Concentration (M)	Chemical shift (τ^a)			Coupling constant (Hz)		
			H α	H β	H γ	J $\alpha\beta$	J $\alpha\gamma$	J $\beta\gamma$
2-Pyridones								
IIa	CDCl ₃	0.4	2.82(d-d) ^b	3.93(t)	2.82(d-m) ^b	6.6	—	6.6
	CCl ₄	0.4	2.86(d-d) ^b	4.11(t)	2.94(d-m)	6.6	2.0	6.6
	C ₆ D ₆	0.4	3.71(d-d) ^b	4.51(t)	3.31(d-m)	6.7	2.0	6.7
IIb	CDCl ₃	0.2	2.80(d-d) ^b	3.92(t)	2.80(d-m) ^b	7.0	—	7.0
IIc	CDCl ₃	0.2	3.12(d-d) ^b	4.02(t)	2.79(d-m)	6.7	2.0	6.7
	CCl ₄	0.2	3.20(d-d) ^b	4.23(t)	2.96(d-m)	6.7	2.0	6.7
	C ₆ D ₆	0.2	3.73(d-d) ^b	4.57(t)	3.27(d-m)	6.6	2.0	6.6
II d	CDCl ₃	0.2	2.88(d-d) ^b	3.91(t)	2.79(d-m)	6.8	2.0	6.8
IIe	CDCl ₃	0.33	2.87(d-d) ^b	3.92(t)	2.80(d-m)	6.8	2.0	6.8
II f	CDCl ₃	0.4	2.82(d-d) ^b	3.89(t)	2.82(d-m) ^b	6.7	—	6.7
	CCl ₄	0.4	2.87(d-d) ^b	4.08(t)	2.98(d-m)	6.7	2.0	6.7
	C ₆ D ₆	0.4	3.67(d-d) ^b	4.44(t)	3.25(d-m)	6.7	2.0	6.7
II g	CCl ₄	0.2	3.18(d-d) ^b	4.19(t)	2.99(d-m)	6.8	2.0	6.8
6-Pyridones								
IIIa	CDCl ₃	0.4	2.93(m)	3.49(d)	2.80(d-d)	... ^c	2.5	9.4
	C ₆ D ₆	0.4	3.86(m)	3.54(d)	3.39(d-d)	... ^c	2.4	9.2
III b	CDCl ₃	0.2	2.95(m)	3.43(d)	2.81(d-d)	0.8	2.5	9.2
III c	CDCl ₃	0.2	3.15—3.28 ^d	3.43(d)	2.78(d-d)	... ^c	2.5	9.1
	C ₆ D ₆	0.2	3.85(m)	3.3—3.55 ^d	3.3—3.55 ^d	... ^c
III d	CDCl ₃	0.2	3.01(m)	3.47(d)	2.80(d-d)	... ^c	2.5	9.7
III e	CDCl ₃	0.33	2.98(m)	3.47(d)	2.80(d-d)	... ^c	2.5	9.5
III f	CDCl ₃	0.4	2.93(m)	3.47(d)	2.76(d-d)	... ^c	2.5	9.1
	C ₆ D ₆	0.4	3.76(m)	3.51(d)	3.33(d-d)	... ^c	2.5	9.1

a) The letter in parentheses designates the multiplicity or shape of the signal with the abbreviations appeared at the top of Experimental part.

b) Observed as a doublet of dull doublets.

c) Unmeasurably small.

d) Overlapped with the signals of the aryl protons.

of CDCl₃ and benzene-*d*₆, most signals shifted upfield as the concentration of benzene-*d*₆ was increased. Among the pyridone-ring protons and the neighboring methyl or methylene protons, H α was the one most profoundly affected by the aromatic solvent. In contrast, the 3-methyl protons of IIa, c and the H β protons of IIIa, c were virtually unaffected, whereas the other protons were moderately influenced.

Finally, the effect of temperature on the chemical shifts of these protons is visualized in Table VI. It may be pointed out that the H α signal of IIc alone shifted upfield as the temperature became lower, while the other protons shifted downfield.

Discussion

The ratio of the isomeric 1,3- and 1,5-dimethyl-2-pyridones formed by the ferricyanide oxidation of Ia (X=I), shown in Table I, may be compared with that reported by other workers⁹ for the same reaction but under slightly different conditions. The fact that replacement of the methyl group attached to the nitrogen of Ia by ω -(3,4-dimethoxyphenyl)alkyl group, even by 3,4-dimethoxybenzyl group, does not cause any appreciable change in the orientation of the oxidation is probably attributed to the almost equal effects of the steric bulk of the N-substituent on both the 2- and the 6-positions. The results of the oxidation of If (X=I) also compare favorably with those^{16a)} reported for If (X=CH₃OSO₃) and those¹⁾ for Ig (X=Br). As pointed out previously,¹⁾ the slight increase in the 6-oxidation observed

TABLE V. Effect of Aromatic Solvent on Chemical Shifts for Pyridone-Ring Protons and Neighboring Methyl or Methylene Protons

Com- pound	Proton	Chemical shift (τ)								$\tau(\text{C}_6\text{D}_6)$ - $\tau(\text{CDCl}_3)$	
		In CDCl_3 - C_6D_6 Molar ratio ($\text{C}_6\text{D}_6/\text{pyridone}$)							In C_6D_6^a		
		0 ^{b)}	1	2	4	8	16	32			64
IIa	H $_{\alpha}$	2.82	2.89	2.94	3.03	3.11	3.30	—	—	3.71	+0.89
	H $_{\beta}$	3.93	3.98	4.00	4.07	4.12	4.24	—	—	4.51	+0.58
	H $_{\gamma}$	2.82	2.85	2.87	2.93	2.96	3.03	—	—	3.31	+0.49
	NCH $_3$	6.46	6.48	6.50	6.56	6.63	6.74	—	—	7.03	+0.57
	CCH $_3$	7.85	7.85	7.86	7.86	7.88	7.89	—	—	7.85	0.00
IIc	H $_{\alpha}$	3.12	3.14	3.15	3.18	3.24	3.26— 3.40 ^{e)}	—	—	3.73	+0.61
	H $_{\beta}$	4.02	4.03	4.05	4.07	4.13	4.18	—	—	4.57	+0.55
	H $_{\gamma}$	2.79	2.79	2.81	2.83	2.89	2.91	—	—	3.27	+0.48
	NCH $_2$	5.85	5.87	5.88	5.90	5.92	5.96	—	—	6.12	+0.27
	CCH $_3$	7.81	7.81	7.82	7.82	7.83	7.83	—	—	7.79	+0.02
IIIa	H $_{\alpha}$	2.93	2.96	3.00	3.09	3.22	3.40	3.64	3.80	3.86	+0.93
	H $_{\beta}$	3.49	3.50	3.50	3.51	3.53	3.56	3.58	3.58	3.54	+0.05
	H $_{\gamma}$	2.80	2.82	2.85	2.89	2.97	3.09	3.22	3.32	3.39	+0.59
	NCH $_3$	6.48	6.50	6.53	6.58	6.65	6.75	6.90	7.00	7.02	+0.54
	CCH $_3$	7.93	7.95	7.97	8.02	8.07	8.17	8.30	8.40	8.45	+0.52
IIIc	H $_{\alpha}$	3.15— 3.28 ^{e)}	3.17— 3.32 ^{e)}	3.17— 3.38 ^{e)}	3.27— 3.38 ^{e)}	3.34— 3.44 ^{e)}	3.47	3.60	—	3.85	+0.57— +0.70
	H $_{\beta}$	3.43	3.45	3.45	3.45	3.47	3.47	3.49	—	3.3— 3.55 ^{e)}	-0.13— +0.12
	H $_{\gamma}$	2.78	2.80	2.81	2.85	2.91	2.97	3.09	—	3.3— 3.55 ^{e)}	+0.52— +0.77
	NCH $_2$	5.89	5.91	5.92	5.96	5.98	6.02	6.08	—	6.14	+0.25
	CCH $_3$	8.01	8.03	8.04	8.07	8.12	8.19	8.28	—	8.51	+0.50

a) From Tables III and IV.

b) At 0.2M concentration with respect to the pyridones examined.

c) Overlapped with signals of the aryl protons.

for the 3-ethyl analogs may be owing to the steric bulk of the ethyl group at the 3-position unfavorable, relative to the methyl group, for the oxidation at the 2-position.¹⁷⁾

The spectral data collected in Tables II, III, and IV have definitely confirmed the structures of the pyridones thus prepared. It is particularly noteworthy that the previously reported^{1,6b)} four criteria for distinguishing between 1,3-dialkyl-2- and -6-pyridones, namely, isomer ratio, long-wavelength UV absorption band position, CO stretching vibration band position, and splitting pattern of pyridone-ring proton resonances, were found to be reliable also in the present work.

In the interpretation of the NMR spectra of the 2-pyridone derivatives (II), it would be difficult in principle to draw a distinction between the signals for H $_{\alpha}$ and H $_{\beta}$ without recourse to prediction of their chemical shifts since coupling constants $J_{\alpha\beta}$ and $J_{\beta\gamma}$ are usually equal, producing a pair of virtually identical splitting patterns for the two protons. Although it has been reported that in CDCl_3 the H $_{\alpha}$ signal of IIa appears downfield from the H $_{\gamma}$ signal by 0.10—0.13 ppm,⁹⁾ our present work has revealed that both protons resonate in such a manner that their signals overlap each other in the same solvent in the concentration range studied. In the cases of IIc—e, the H $_{\alpha}$ and H $_{\gamma}$ signals appeared separately. However, the assignment as shown in Table IV became feasible when long-range coupling between H $_{\gamma}$ and the 3-methyl protons was found to be larger than that between H $_{\alpha}$ and the 3-methyl protons.

17) A more detailed study on the effect of the steric bulk of the alkyl group at the 3-position will be reported in sequential papers in preparation.

TABLE VI. Influence of Temperature on Chemical Shifts for Pyridone-Ring Protons and Neighboring Methyl or Methylene Protons

Compound	Proton	Chemical shift (τ) in CDCl_3 Temperature ($^\circ\text{C}$)				$\tau(-50^\circ)$ $-\tau(23^\circ)$
		23	0	-30	-50	
IIa ^{a)}	H _{α}	2.82	2.80	2.77	2.76	-0.06
	H _{β}	3.93	3.92	3.89	3.87	-0.06
	H _{γ}	2.82	2.80	2.77	2.76	-0.06
	NCH ₃	6.46	6.42	6.41	6.41	-0.05
	CCH ₃	7.85	7.85	7.83	7.83	-0.02
IIc ^{b)}	H _{α}	3.12	3.14	3.14	3.14	+0.02
	H _{β}	4.02	4.01	3.99	3.98	-0.04
	H _{γ}	2.79	2.76	2.75	2.74	-0.05
	NCH ₃	5.85	5.86	5.85	5.85	0.00
	CCH ₃	7.81	7.80	7.80	7.79	-0.02
IIIa ^{a)}	H _{α}	2.93	2.90	2.88	2.87	-0.06
	H _{β}	3.49	3.48	3.47	3.47	-0.02
	H _{γ}	2.80	2.78	2.76	2.75	-0.05
	NCH ₃	6.48	6.46	6.46	6.45	-0.03
	CCH ₃	7.93	7.91	7.90	7.89	-0.04
IIIc ^{b)}	H _{α}	3.15-3.28 ^{c)}	3.15-3.28 ^{c)}	3.15-3.28 ^{c)}	3.15-3.28 ^{c)}	—
	H _{β}	3.43	3.42	3.39	3.39	-0.04
	H _{γ}	2.78	2.75	2.73	2.71	-0.07
	NCH ₃	5.89	5.89	5.89	5.88	-0.01
	CCH ₃	8.01	8.01	8.01	7.99	-0.02

a) Measured on 0.4M solution.

b) Measured on 0.2M solution.

c) Overlapped with the signals of the aryl protons.

Probably the most salient feature of the present proton resonance study is that the 2- and 6-pyridones of an N-phenethyl type behave in a manner different from that of the other homologs. The upfield shifts observed for H _{α} and H _{β} of IIc and for H _{α} and the 3-methyl protons of IIIc may be interpreted in terms of contributions of conformers IV and V as shown in Chart 2, which are folded in such a manner that these protons lie above the plane of the benzene ring. The obvious analogy can be drawn with the results of the study of the effect of solvent benzene-*d*₆ on chemical shifts for the pyridone-ring protons and the neighboring methyl or methylene protons (Table V). Resonance structures for 1,3-dialkyl-2- and -6-pyridones are shown in VI and VII (Chart 2) with the benzene ring in a plane parallel to the

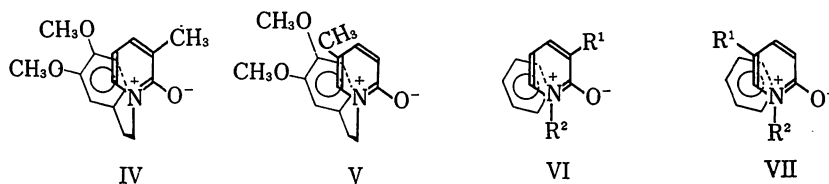


Chart 2

pyridone ring. On the analogy of the proposed specific interaction between the benzene ring and N,N-disubstituted amides,¹⁸⁾ the aromatic ring is presumably attracted by the partial positive charge on the nitrogen of resonance structures VI and VII, but repelled by the negative charge of the carbonyl oxygen. The proximity of the benzene ring and H _{α} as well as the

18) a) J.V. Hatton and R.E. Richards, *Mol. Phys.*, 3, 253 (1960); b) *Idem, ibid.*, 5, 139 (1962).

neighboring protons of VI or VII in such an association would cause upfield shift of these proton signals as seen in Table V. The upfield shift for $H\alpha$ of IIc recorded in Table VI is suggestive of an increase in population of conformer IV at lower temperature and may support the contribution of conformers IV and V as assumed above.

Inspection of molecular models indicated that in the cases of IIb and IIIb the methylene group separating the intramolecular benzene ring from the nitrogen is insufficient in number to allow conformers of IV- and V-types to exist. This appears to be a reason for the striking similarities in pyridone-ring proton resonances between IIb and IIa as well as between IIIb and IIIa. On the other hand, elongation of the N-alkyl group by insertion of three or more methylene groups as in IIId, e or IIIId, e would make the N-substituent chain more flexible than that of IIc or IIIc, giving in $CDCl_3$ a spectrum similar to that of IIa or IIIa in $CDCl_3$ solution containing one equivalent mole of benzene- d_6 . The results shown in Tables IV and V are in accord with these expectations.

In conclusion, it should be noted that in $CDCl_3$ solutions the α -protons of 2- and 6-pyridones of II- and III-types are more (or at least similarly) shielded than the γ -protons. The observed order of chemical shifts for $H\alpha$ and $H\gamma$ of 6-pyridone IIIa is in agreement with that reported by the British workers^{6a)} and opposite to that assigned by the German workers.^{6b)} It is hoped that the present study will prove of general utility in interpretation of the NMR spectra of related compounds.

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