white silky needles, m.p. 104~105°. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.84; H, 7.35. Found: C, 72.99; H, 7.4.

(4) *dl*-(6-Methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4'-methoxyphenyl)carbinol Methiodide (XXIX)—0.1 g. of the above carbinol was methylated in MeOH with MeI, and the methiodide was obtained as white plates, m.p. 160~161°. The infrared spectrum showed the presence of OH bands at 3.04 and 2.95 μ. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot CH_3I$: C, 52.76; H, 5.72. Found: C, 52.38, 52.34; H, 5.84, 5.78.

(5) First-Stage Hofmann Degradation of *dl*-(6-Methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4'-methoxyphenyl)carbinol Methiodide—0.1 g. of the methiodide was boiled with 10 cc. of 30% KOH. The depositing oil was extracted with ether, and the ether extract, after being dried over K_2CO_3, evaporated, yielding a residue having an odor like anisaldehyde.

Summary

Another one of the fragments obtained by the fission of cepharanthine with sodium in liquid ammonia, which has a composition of $C_{17}H_{19}O_2N$, m.p. 205~207°(decomp.), with two phenolic hydroxyl groups, was proved to be *d*-1-(4'-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline.

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35. Shigehiko Sugasawa and Makoto Kirisawa: Oxidation of 3-Substituted 1-Alkylpyridinium Salts. II.[1] Oxidation of 1-Methyl- and 1-Phenethyl-3-phenylpyridinium Salts.

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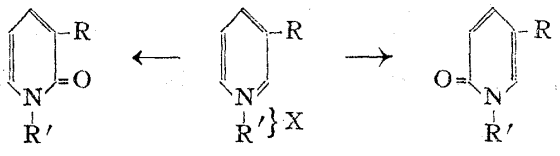
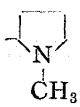
When oxidized with alkaline potassium ferricyanide, 3-substituted 1-alkylpyridinium salt (I) gives the corresponding 6- (II) and/or 2-pyridone (III). The orientation of this oxidation is exclusively governed by the nature of the substituent R in the 3-position, whereas that of R' seems to have scarcely any influence.

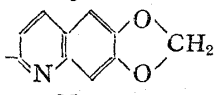


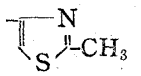
(III) (I) (II)

a: R'=-COOEt or $-CONH_2$

b: 

c: 

d: 

e: 

When R is an alkoxycarbonyl or a carbamyl[2], 3-pyridyl-,[3] N-methyl-2-pyrrolidyl-,[4] 6,7-methylenedioxy-2-quinolyl-,[5] or 2-methyl-4-thiazolyl-,[5] the corresponding 6-pyridone (II: a, b, c, d and e, respectively) is obtained as the main, if not the sole,

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1) Part I. S. Sugasawa, Y. Ban: J. Pharm. Soc. Japan, **72**, 1336(1952).
2) S. Sugasawa, K. Sakurai, T. Okayama: Ber., **74**, 537(1941).
3) S. Sugasawa, T. Saito: J. Pharm. Soc. Japan, **65 B**, 456(1945).
4) S. Sugasawa, T. Tatsuno: *Ibid.*, **72**, 248(1952).
5) T. Tatsuno: This Bulletin, **2**, 140(1954).

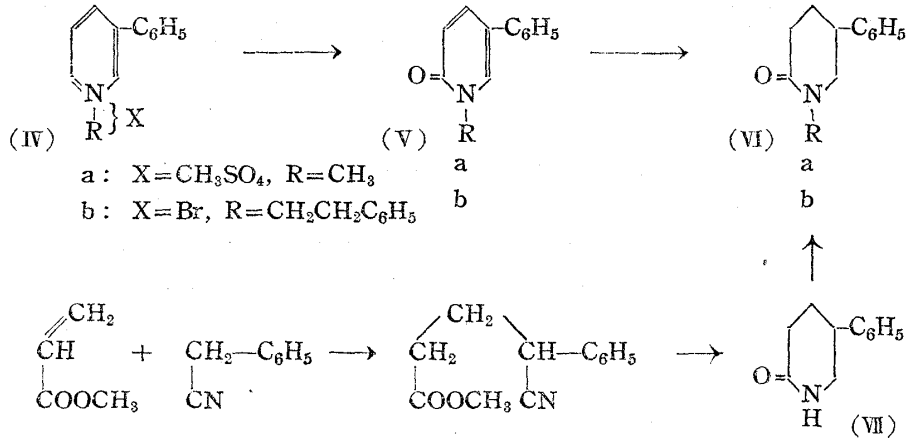
product whereas 2-pyridone (III) is produced exclusively when R is methyl,[6] ethyl,[1] bromo,[6] or carbamyl.[6] Therefore, in the last-mentioned case, the result is contradictory with ours, probably due to the difference in working conditions.

The above-mentioned results show that a ring substituent in the 3-position directs the oxidation to occur at 6-position and our present investigation of the oxidation of 3-phenylpyridinium salts forming the corresponding 3-phenyl-6-pyridones is another such example. The exact reason for this orientation is not clear to us, but it probably is due chiefly to the steric influence of the ring substituent.

3-Phenylpyridine, prepared according to Rapoport, *et al.*,[7] was treated with dimethyl sulfate to form the corresponding N-methyl-methosulfate (IVa). The oxidation of the latter was carried out as usual, giving an oily product (Va) of $b.p_2$ 167~169° in 66% yield, which gave a single picrate of m.p. 131~133° in 89% yield, showing the unique nature of this oil. The recovered base was obtained crystalline (m.p. 73~74°). The corresponding piperidone (VIa) was prepared by catalytic hydrogenation of the pyridone (Va), forming a crystalline solid of m.p. 104~106°.

On the other hand, 3-phenyl-6-piperidone (VII) was prepared by the known method of Koelsch[8] and N-methylated to give a crystalline substance of m.p. 104~106°, which was found to be identical with the above-mentioned piperidone of the same melting point by direct comparison. The pyridone prepared by oxidation was thus proved to be 1-methyl-3-phenyl-6-pyridone (Va).

The oxidation of 1-phenethyl-3-phenylpyridinium bromide (IVb) gave a similar result.



We thank Mrs. Hisamichi, Mr. Yoda, and members of the analysis room of this Institute for microanalytical data.

Experimental

1-Methyl-3-phenyl-6-pyridone (Va)—3-Phenylpyridine (0.7 g., 0.0045 mole) was mixed with freshly purified Me_2SO_4 (0.8 g., 0.0063 mole) with evolution of heat, separating colorless needles. The mixture was heated at 80° in a water bath for 30 mins. On cooling, the whole solidified to a white mass (1-methyl-3-phenylpyridinium methosulfate, IVa), which was dissolved in 6 cc. of H_2O and mixed with aq. $K_3Fe(CN)_6$ solution (4.5 g. of the salt, 0.0137 mole, in 18 cc. of H_2O) with stirring and cooling, separating a yellow solid. NaOH pellets (3.8 g., 0.068 mole) were then added in 15 mins., during which time the temperature of the mixture was maintained at 5~10°; separation of brownish oil was observed. Benzene (10 cc.) was added and the whole was kept stirring at 5° for 1 hr., and then at room temp. for additional 1.5 hrs. The aq. layer was extracted with benzene and this was combined with the original benzene layer, washed, dried, and evaporated, leaving a dark brown oil,

6) Bradlaw, Vanderwerf : J. Org. Chem., **16**, 73(1951).
7) J. Am. Chem. Soc., **74**, 6293(1952).
8) *Ibid.*, **65**, 437, 2093(1943).

which distilled at 167~169°/2 mm. Yield of colorless very viscous oil was 0.55 g. or 66%. This was mixed with EtOH solution of picric acid, giving a single picrate in 89% yield. The oil recovered from the picrate solidified (m.p. 73~74°) on standing.

Picrate: Yellow needles from EtOH, m.p. 131~133°. *Anal.* Calcd. for $C_{18}H_{14}O_8N_4$: C, 52.2; H, 3.4; N, 13.5. Found: C, 52.5; H, 3.9; N, 13.4.

1-Methyl-3-phenyl-6-piperidone (VIa)—i) By reduction of (Va): The foregoing pyridone (0.33 g. 0.0018 mole) in 20 cc. of EtOH was reduced with Adams' Pt (prepared from 0.1 g. of PtO_2), absorbing ca. 10 cc. of H_2 after 3 hrs. PdO (0.05 g.) was then added and the reduction was continued, absorbing another 40 cc. of H_2 in 7 hrs. The catalyst was filtered and the filtrate was reduced over Raney Ni (ca. 0.5 g.), additional 40 cc. of H_2 being absorbed in 4 hrs. Thus, about 90 cc. of H_2, which corresponds to approximately 110% of the theoretical volume, was fixed. The reduction product was isolated as colorless plates of m.p. 102~104° (yield, 83%), which was purified from ether, forming colorless pillars of m.p. 104~106°. *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.1; H, 8.0; N, 7.4. Found: C, 76.05; H, 7.8; N, 7.1.

This compound does not form a picrate, is readily soluble in 10% HCl, EtOH, and benzene, but sparingly so in ether, and not soluble in ligroine.

ii) By methylation of 3-phenyl-6-piperidone: 3-Phenyl-6-piperidone (0.16 g., 0.0009 mole) prepared according to the method of Koelsch in pure xylene (10 cc.) was mixed with K dust (ca. 0.05 g.), forming a white K-salt with evolution of H_2. The reaction was completed by heating on a steam bath for 5 hrs. Freshly purified Me_2SO_4 (0.16 g., 0.0013 mole) was then added and the mixture was refluxed for 15 hrs. The filtrate from some undissolved substance left a crystalline solid of m.p. 95~100° (0.16 g., 93%) on being evaporated *in vacuo*, which, when purifed from ether, formed colorless pillars of m.p. 104~106°, which was not depressed on admixture with the sample obtained above.

1-Phenethyl-3-phenyl-6-pyridone (Vb)—1-Phenethyl-3-phenylpyridinium bromide (IV b) was obtained as a brownish viscous syrup, which was oxidized in a similar fashion. The oxidation product was a brown syrup, which was characterized as a well-defined picrate, obtained in 53% yield, based upon 3-phenylpyridine used.

Picrate: Yellow needles from EtOH, m.p. 132~134°, which was proved to be a dipicrate by analysis. *Anal.* Calcd. for $C_{31}H_{23}O_{15}N_7$: C, 50.75; H, 3.2; N, 13.4. Found: C, 51.15; H, 3.3; N, 13.4.

1-Phenethyl-3-phenyl-6-piperidone (VI b)—i) By reduction of (Vb): The foregoing pyridone (Vb) in EtOH was reduced over Raney Ni and the hydrogenation proceeded smoothly. The reduction product recovered from the filtrate solidified on standing (m.p. 100~102°; yield, 93%). Purified from ether forming colorless needles of m.p. 101~103°. *Anal.* Calcd. for $C_{19}H_{21}ON$: C, 81.7; H, 7.6; N, 5.0. Found: C, 81.1; H, 7,2; N, 5.3.

ii) By alkylation of 3-phenyl-6-piperidone: K-Salt of 3-phenyl-6-piperidone (prepared from 1.1 g., 0.0063 mole of the piperidone and 0.28 g. K dust in xylene as usual) was refluxed with phenethyl bromide (1.33 g., 0.0072 mole) for 24 hrs. in the presence of a little Cu powder. The filtrate left a brown solid on being evaporated, which was dissolved in benzene and purified through an alumina column. The benzene solution left a colorless solid of m.p. 99~101° on evaporation, which after repeated crystallization from ether formed colorless needles of m.p. 101~103°, not depressed when admixed with the piperidone obtained above.

Summary

In accordance with the experimental results hitherto obtained in our laboratories that a ring-substituent group in the 3-position of 1-alkylpyridinium salt directs the oxidation to occur at 6-position to give solely the corresponding 3-substituted 6-pyridone, 1-methyl- and 1-phenethyl-3-phenylpyridinium salts furnished the corresponding 3-phenyl-6-pyridones as the only oxidation product by means of alkaline potassium ferricyanide in fair yields.

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