Summary

Digipronin, a digitanol glycoside, and its aglycone, γ-digiprogenin, were respectively converted to isodigipronin and its aglycone, α-digiprogenin, by treatment with dilute alkali or acid. On refluxing with acid, α-digiprogenin lost an element of water and formed β-digiprogenin. The structure of the Δ^4-3-oxo compound, obtained from β-digiprogenin by reduction with acetic acid and zinc dust followed by Oppenauer oxidation, was established as 14β,17α-pregn-4-ene-3,11,15,20-tetrone by comparison with the product of isomerization of pregn-4-ene-3,11,15,20-tetrone with alkali or acid. Consequently, the structure of β-digiprogenin was presumed as 3β-hydroxy-14β-pregna-5,16-diene-11,15,20-trione and the tertiary hydroxyl group in α- and γ-digiprogenin would be located at 17-position. In view of the stability of α-digiprogenin to dilute alkali or acid and its negative contribution to optical rotation compared to γ-digiprogenin, it would be appropriate to give the structure of 3β,17α-dihydroxy-14β-pregn-5-ene-11,15,20-trione and 3β,17α-dihydroxypregn-5-ene-11,15,20-trione to α- and γ-digiprogenin, respectively. Digipronin is a monodigitaloside of γ-digiprogenin.

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9. **Masatomo Hamana and Motoyoshi Yamazaki**: Studies on Tertiary Amine Oxides. X.[*1] Alkaline Ferricyanide Oxidation of Some Aromatic N-Oxides.

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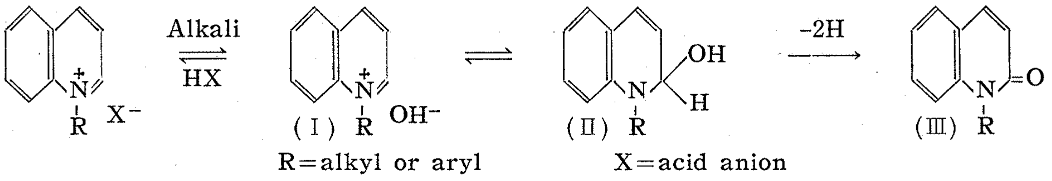
It is well known that quaternary salts of aromatic nitrogen heterocycles, such as N-substituted pyridinium and quinolinium salts, are oxidized by alkaline ferricyanide to N-substituted α-oxo compounds.[1,2] This reaction is generally assumed,[1,2] for example in a quinoline series, to proceed through isomerization of the corresponding quaternary hydroxide (I) to a pseudobase (II), which is subsequently dehydrogenated by ferricyanide to an 2(1*H*)-quinolone (III).



In a previous paper of this series,[3] it was shown that 1-benzoyloxy-2-hydroxy-1,2-dihydroquinoline (IV) was isolated as an unstable intermediate in the reaction of quinoline 1-oxide with benzoyl chloride and sodium carbonate solution, which was derived to

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[*1] Part IX. Yakugaku Zasshi, **81**, 574 (1961).

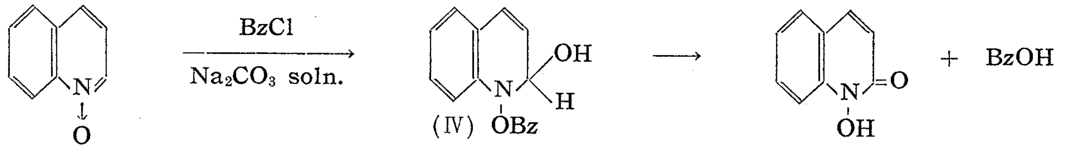
[*2] Katakasu, Fukuoka (浜名政和, 山崎企善).

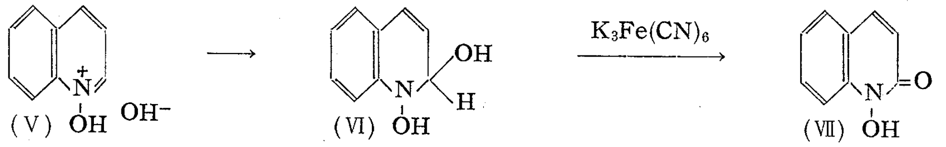
1) F. Krönke, K. Ellegast: Ann., **600**, 176 (1957).

2) B. S. Thyagargjan: Chem. Revs., **58**, 439 (1958).

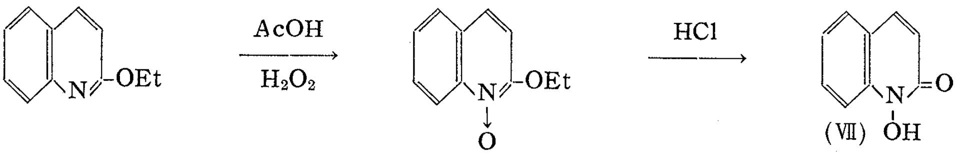
3) M. Hamana, K. Funagoshi: Yakugaku Zasshi, **80**, 1031 (1960).

carbostyril.[4] (IV) may be regarded as N, O-benzoate of the pseudo-base (VI) derived from quinoline 1-oxide hydrate (V). This fact suggests the possibility that quinoline 1-oxide would be converted through (V) into the pseudo-base (VI) in an alkaline solution and (VI) might be oxidized to 1-hydroxycarbostyril (VII) by alkaline ferricyanide. The present investigation was undertaken in order to examine this possibility and some aromatic N-oxides were oxidized with alkaline ferricyanide.

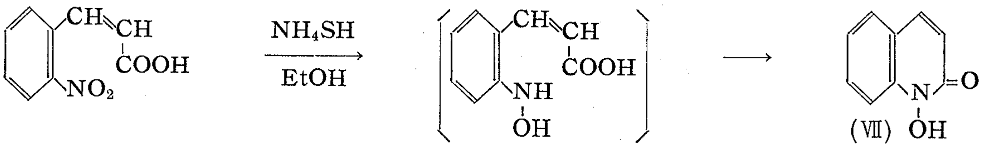




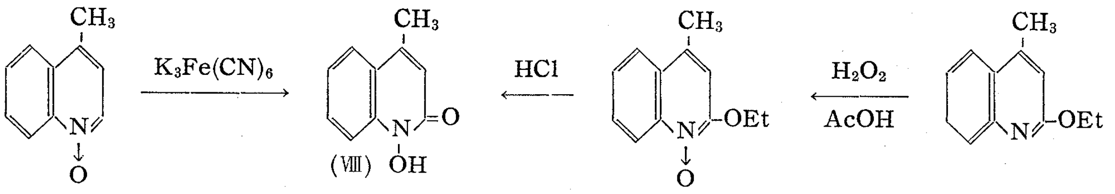
When quinoline 1-oxide was oxidized with concentrated potassium ferricyanide solution in the presence of strong alkali at room temperature, 1-hydroxycarbostyril (VII) was obtained in 75% yield. It crystallized from hydrous methanol as faintly brownish scales of m.p. 188~191°, and its structure was determined from elementary analysis and mixed fusion with an authentic specimen prepared by the method of Newbold and Spring[5] as shown below.



The method of Newbold and Spring[5] was rather circuitous and the yield from N-oxidation of 2-ethoxyquinoline was poor. As an alternative approach, a ring closure reaction[6] has been reported, but it was also found unsatisfactory because of the difficulty of availability of the starting material and the poor yield of the reaction. Therefore, this oxidation procedure seems to be most convenient and a better one for preparing 1-hydroxycarbostyril (VII).



Similarly, lepidine 1-oxide gave 1-hydroxy-4-methylcarbostyril[7] (VIII) of m.p. 222~224°, but its yield was only 20%. This low yield may be attributed to the electron-releasing effect of 4-methyl group, which would decrease the electrophilic character of the carbon atom at 2-position of the quinoline ring and attack of the hydroxide ion on the carbon atom, that is, the formation of the pseudo-base, would be hindered to some extent.



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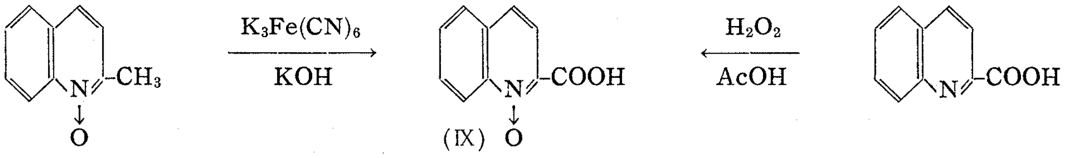
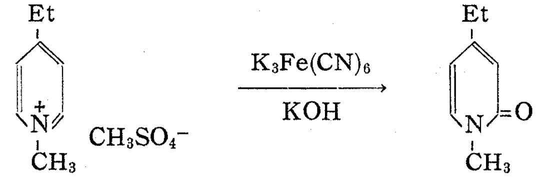
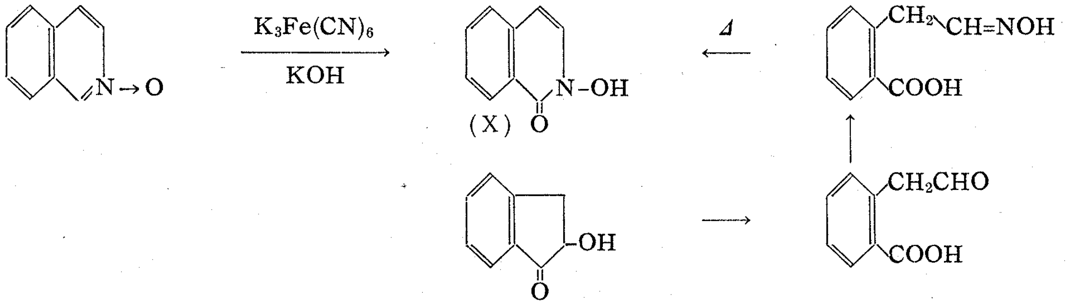
[4] M. Henze: Ber., **69**, 1566 (1936).
[5] G. T. Newbold, F. S. Spring: J. Chem. Soc., **1948**, 1864.
[6] P. Friedländer: Ber., **14**, 1916 (1881); **15**, 332 (1882).
[7] K. G. Cunningham, G. T. Newbold, F. S. Spring, J. Stark: J. Chem. Soc., **1949**, 2091.

When quinaldine 1-oxide was employed, the reaction resulted in the formation of a small amount (18%) of quinaldic acid 1-oxide (IX) with a 35.3% recovery of the starting material. (IX) was characterized by comparing with an authentic sample prepared by oxidation of quinaldinic acid with 30% hydrogen peroxide and acetic acid in the usual manner. Sugasawa and Kirisawa[8] reported that methyl methosulfate of 4-ethylpyridine is oxidized by an excess of potassium ferricyanide to 1-methyl-2-oxo-1,2-dihydroisonicotinic acid in a poor yield. Except for this example, no such oxidation of alkyl group by means of ferricyanide has been reported in the case of N-substituted pyridinium salts and similar compounds.[*3]





Further, 2-hydroxyisocarbostyril (X), m.p. 185~187°, was obtained in 59% yield from isoquinoline 2-oxide. The structure of (X) was deduced from its conversion to isocarbostyril by catalytic hydrogenation over Raney nickel in methanol.[9] So far, 2-hydroxyisocarbostyrils have been prepared by ring closure reactions[10] through several steps and therefore, this ferricyanide oxidation may be better for preparing 2-hydroxyisocarbostyrils.



Finally, attempt was made to oxidize pyridine 1-oxide and nicotinic acid 1-oxide by this reaction, but only the starting material was recovered. Comparing these results with the ready formation of 2(1*H*)-pyridones in the ferricyanide oxidation of N-alkylpyridinium salts, it may be concluded that the ability of aromatic N-oxides to form the pseudo-base is considerably smaller than that of N-alkylpyridinium salts; that is, for the initiation of the reaction, activation of heterocyclic ring by means of naphthoid structure seems to be necessary in addition to N-oxidation of the ring nitrogen atom.

Experimental

Potassium Ferricyanide Oxidation of Quinoline 1-Oxide——To a vigorously stirred solution of

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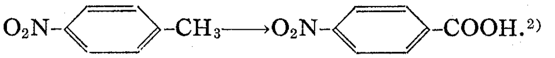
[*3] In benzene derivatives, oxidation of the active methyl group has been observed, e.g.



$O_2N-C_6H_4-CH_3 \longrightarrow O_2N-C_6H_4-COOH.^{2)}$

8) S. Sugasawa, M. Kirisawa : This Bulletin, **6**, 615 (1958).
9) E. Hayashi, H. Yamanaka, T. Higashino : *Ibid.*, **7**, 149 (1959).
10) C. Schöpf, R. Kühne : Chem. Ber., **83**, 390 (1950); M. M. Robison, B. L. Robison : J. Am. Chem. Soc., **80**, 3443 (1958).

quinoline 1-oxide (dihydrate, 1.8 g.) in H_2O (15 cc.), solutions of $K_3Fe(CN)_6$ (13 g.) in H_2O (30 cc.) and of KOH (6 g.) in H_2O (10 cc.) were separately added dropwise at 5~10°, the rate of addition being regulated so that the addition of both solutions was finished at the same time (ca. 1 hr.). After further 1 hr.'s stirring and standing overnight at room temperature, the solution was separated from the precipitate, extracted with $CHCl_3$, and afforded quinoline 1-oxide, b.p$_4$ 150~180° (bath temp.), (0.24 g.). The residual alkaline solution from $CHCl_3$-extraction was acidified with AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, evaporated, and the residue was sublimed at 200~220°/4 mm. Hg (bath temp.), giving crystals (VII) (1.2 g., 75%). Recrystallization from MeOH-H_2O gave faintly brownish scales, m.p. 188~191°, alone and on admixture with a specimen prepared by Newbold's method.[5] *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.39; N, 8.72. Found: C, 67.33; H, 4.60; N, 8.90.

Potassium Ferricyanide Oxidation of Lepidine 1-Oxide——Freshly distilled lepidine 1-oxide (0.8 g. in 10 cc. of H_2O) was oxidized as described above, using $K_3Fe(CN)_6$ (7 g. in 15 cc. of H_2O) and KOH (3 g. in 5 cc. of H_2O). Similar treatment of the reaction mixture gave 0.17 g. (26%) of 1-hydroxy-4-methylcarbostyril (VIII) with 35.25% recovery of the starting material. (VIII) sublimed at 140~160°/0.1 mm. Hg (bath temp.) and formed faintly brownish, short prisms, m.p. 223~225°, from MeOH-benzene, which was identical with an authentic specimen prepared by the method of Cunningham, Newbold, and co-workers.[7] *Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.57; H, 5.14; N, 8.00. Found : C, 68.89; H, 4.47; N, 7.995.

Potassium Ferricyanide Oxidation of Quinaldine 1-Oxide——To a vigorously stirred suspension of quinaldine 1-oxide (3.4 g.) in H_2O (20 cc.), solutions of $K_3Fe(CN)_6$ (26 g. in 60 cc. of H_2O) and of KOH (12 g. in 10 cc. of H_2O) were separately added dropwise at 5~10°. The reaction mixture was stirred for 2 hr. and kept overnight at room temperature. On treatment of the reaction mixture as above, 1.2 g. (35.3%) of the starting material was recovered and 0.67 g. (18%) of quinaldinic acid 1-oxide (IX) was obtained as the fraction extractable with $CHCl_3$ from AcOH-acidic solution. Recrystallization from MeOH gave (IX) as faintly brownish needles of m.p. 173~174°. It did not depress the melting point of an authentic sample prepared as described below. *Anal.* Calcd for $C_{10}H_7O_3N$: C, 63.49; H, 3.70; N, 7.41. Found : C, 63.75; H, 4.06; N, 7.60.

Quinaldinic Acid 1-Oxide——A mixture of quinaldinic acid (0.2 g.) in AcOH (2 cc.) and 30% H_2O_2 (5 cc.) was warmed on a water bath at 70~80° for 12 hr. The solvent was evaporated in a reduced pressure and the residual solid was recrystallized from MeOH to 0.3 g. (36%) of pale brownish needles, m.p. 172~177° (decomp.). *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.70; N, 7.41. Found : C, 63.71; H, 3.98; N, 7.45.

Potassium Ferricyanide Oxidation of Isoquinoline 2-Oxide——Isoquinoline 2-oxide (1.64 g. of hemihydrate in 15 cc. of H_2O) was oxidized with $K_3Fe(CN)_6$ (13 g. in 30 cc. of H_2O) and KOH (6 g. in 10 cc. of H_2O) and 0.4 g. of the starting material, b.p$_4$ 180~200° (bath temp.), was recovered and 0.95 g. (59%) of 2-hydroxyisocarbostyril was obtained, which sublimed at 170~190°/4 mm. Hg (bath temp.). Recrystallization from MeOH afforded faintly yellow, short needles of m.p. 185~187°. *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.39; N, 8.72. Found : C, 67.02; H, 4.56; N, 8.84.

Catalytic Reduction of 2-Hydroxyisocarbostyril over Raney Nickel——A solution of 2-hydroxyisocarbostyril (0.5 g.) in MeOH (30 cc.) was shaken with Raney Ni catalyst (prepared from 1 g. of Ni alloy) in H_2 stream at atmospheric pressure and room temperature. After absorption of 72 cc. of H_2, the catalyst was filtered off, the filtrate was concentrated to a small volume, basified with K_2CO_3, and extracted with $CHCl_3$. Sublimation of the extract gave 0.4 g. of crystals and its recrystallization from MeOH-H_2O afforded colorless scales of m.p. 207~210°, which did not depress the melting point of an authentic sample of isocarbostyril.

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Summary

Alkaline ferricyanide oxidation of some aromatic N-oxides was examined. Quinoline 1-oxide, lepidine 1-oxide, and isoquinoline 2-oxide were smoothly oxidized to the corresponding N-hydroxy-carbostyrils or -isocarbostyrils. From quinaldine 1-oxide, only a small amount of quinaldinic acid 1-oxide was obtained. In contrast, pyridine and nicotinic acid 1-oxide were not affected by this oxidation procedure.

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