was treated with lithium carbonate in dimethylformamide to afford 7-en-6-one (XIX) (mp 271—274°, $[\alpha]_{578}^{20}$ +20°, UV λ_{max}^{EtOH} (e) 244 mμ (14200)). A hydroxyl group was introduced at C-14 in XIX by a novel method developed in this laboratory,[9] that is, enol acetylation of XIX with acetic anhydride in the presence of a small amount of perchloric acid in ethyl acetate[10] afforded an enol acetate (XX) as an oily substance, which was oxidized with 1.3 equivalent of monoperphthalic acid in ether–tetrahydrofuran mixture to 14α-hydroxy-7-en-6-one (XXI) (mp 269—272°, $[\alpha]_{578}^{20}$ +70°, UV λ_{max}^{EtOH} (e) 240 mμ (12700)).

Hydrolysis and isomerization (at C-5) of XXI with 0.6% potassium carbonate in 90% methanol at reflux temperature for 30 minutes gave 2β,3β,14α-trihydroxy-7-en-6-ones as an equilibrium mixture. From this equilibrium mixture, which consisted of 5β- and 5α-compound at a ratio of 4:1,[11] 5β-isomer (XXII) (mp 264—266°, $[\alpha]_{578}^{20}$ +79°, UV λ_{max}^{EtOH} (e) 243 mμ (10600)) was isolated by preparative thin-layer chromatography. Grignard reaction of XXII with a large excess of methylmagnesium bromide in tetrahydrofuran at 0° for 30 minutes afforded ecdysone (I) (mp 238—239°, $[\alpha]_{578}^{20}$ +62°, UV λ_{max}^{EtOH} (e) 243 mμ (11600)) identical in all physical properties (melting point, optical rotation, UV, IR, NMR and MS) with those reported for the natural product.

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9) H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Chem. Pharm. Bull.* (Tokyo), to be submitted.
10) B.E. Edwards and P.N. Rao, *J. Org. Chem.*, **31**, 324 (1966).
11) Stereochemistry of this type of equilibrium was disccussed in detail in reference 8 and 9.

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UDC 547.833.3.04

Ferricyanide Oxidation of *dl*-N-Methylisosalsoline and Its Methiodide[1]

In connection with a preceding work,[2] ferricyanide oxidation of *dl*-N-Methylisosalsoline (I) and its methiodide (II) was examined.

To a stirred solution of I (1.56 g, 7.5 mmole) in dioxane (64 ml) and 2.8% aq. NH_4OH (160 ml) was added powdered $K_3Fe(CN)_6$ (5.6 g, 17.0 mmole). After two hr's agitation at room temperature followed by standing for 1 hr, the reaction mixture was treated with K_2CO_3 (powder) and the product was extracted with $CHCl_3$.

1) All melting points were uncorrected using a Yanagimoto micro melting point measuring apparatus. All nuclear magnetic resonance (NMR) spectra were taken with a JNR-C60S spectrometer and the chemical shifts were τ-value measured from DSS as internal standard. Mass spectrometory (MS) spectrum was measured with a Hitachi mass spectrometer Model RMU-6D. Gas liquid chromatography (GLC) was run with a Shimadzu GC-1C gaschromatograph (hydrogen flame ionization detector) on 1.5% OV-17 as stationary phase. Thin-layer chromatography (TLC) were carried out on silicagel G (Merck), developing solvents: *a*) conc. NH_4OH–MeOH (1:20) for tertiary and *b*) 10% HCl–MeOH (1:2) for quaternary amines.
2) B. Umezawa, O. Hoshino, H. Hara, and J. Sakakibara, *Chem. Pharm. Bull.* (Tokyo), **16**, 381 (1968).

Usual work-up gave a dark brown amorphous mass, which was converted to a dark brown amorphous hydrochloride (1.92 g, dry HCl in $CHCl_3$). The hydrochloride was chromatographed on silicic acid (Mallinckrodt) to give a small amount of I·HCl [elution with $CHCl_3$–MeOH (100:15)], A (199.5 mg, 1 spot on TLC)[3] and B (173 mg, 2 spots on TLC)[3] [elution with $CHCl_3$–MeOH (100:20)] successively.

Recrystallization of A (*iso*-PrOH) afforded colorless prisms (III), mp 230—235° (decomp.) (152.5 mg). *Anal.* Calcd. for $C_{24}H_{32}O_4N_2 \cdot 2HCl \cdot 3H_2O$: C, 53.43; H, 7.42; N, 5.19. Found: C, 53.50; H, 7.65; N, 4.67. MS: 412 (parent peak). NMR τ(D_2O): 8.83, 8.76 (each d., two ArCH($\underline{CH_3}$)–, J=6.0 cps and J=6.5 cps), 7.08 (s., two –$\overset{+}{N}$H($\underline{CH_3}$)–), 6.06 (s., two O$\underline{CH_3}$), 2.92 (s., two aromatic ring protons); methiodide, mp 263—269° (decomp.) (MeOH), *Rf* 0.36. *Anal.* Calcd. for $C_{26}H_{38}O_4N_2I_2 \cdot 2H_2O$: C, 42.62; H, 5.74; N, 3.83. Found: C, 42.62; H, 5.70; N, 3.84. NMR τ (1N–NaOD–D_2O): 8.53 (d., two ArCH($\underline{CH_3}$)–, J=6.7 cps), 6.90, 6.79 (each s., two –$\overset{+}{N}$($\underline{CH_3}$)$_2$–), 6.19 (s., two O$\underline{CH_3}$), 3.20 (s., two aromatic ring protons).

The above elemental analysis, NMR and MS spectra supported the structure of III as *dl*-1,1′,2,2′-tetramethyl-6,6′-dimethoxy-7,7′-dihydroxy-1,1′,2,2′,3,3′,4,4′-octahydro-8,8′-bis-isoquinoline dihydrochloride (C–C dehydro compound).

Re-chromatography of B [silicic acid, elution with $CHCl_3$–MeOH (100:20)] furnished firstly a colorless amorphous substance (IV) (39 mg) [NMR τ (D_2O): 8.75 (d., two ArCH($\underline{CH_3}$)–, J=6.5 cps), 7.06 (s., two –$\overset{+}{N}$H($\underline{CH_3}$)–), 6.05 (s., two O$\underline{CH_3}$), 2.91 (s., two aromatic ring protons)] and secondly (V) (39 mg) [NMR τ (D_2O): 8.54, 8.49 (each d., two ArCH($\underline{CH_3}$)–, J=6.5 cps), 7.14, 7.08 (each s., two –$\overset{+}{N}$H(CH_3)–), 6.08, 6.03 (each s., two O$\underline{CH_3}$), 3.59, 3.03, 2.90 (each s., three aromatic ring protons)]; methiodide [NMR τ (1 N NaOD–D_2O): 8.52, 8.41 (each defused d., two ArCH($\underline{CH_3}$)–, J=6.0 cps), 7.02, 6.88 (each s., two –$\overset{+}{N}$($\underline{CH_3}$)$_2$–), 6.18, 6.00 (each s., two O$\underline{CH_3}$), 3.67, 3.23, 2.93 (each s., three aromatic ring protons)]; metho-picrate, mp 122—125° (H_2O). *Anal.* Calcd. for $C_{26}H_{38}O_4N_2 \cdot 2C_6H_2O_7N_3 \cdot H_2O$: C, 49.78; H, 4.80; N, 12.23. Found: C, 49.41; H, 4.78; N, 12.03.

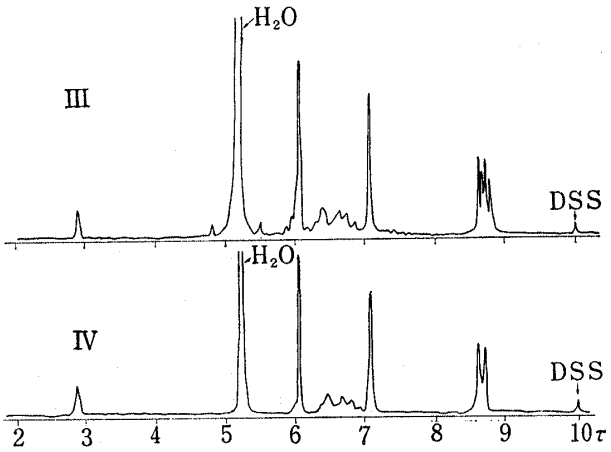


Fig. 1. NMR Spectra of III and IV

IV was recrystallized from *iso*-PrOH to give colorless prisms, mp 235—240° (decomp.), which was identical with III by comparisons of their IR (KBr), NMR (D_2O) and GLC retention time[4] (11.4 min, at 240°) respectively and therefore it was supposed that IV primarily formed was isomerized to III during the above procedure giving III as a major product.

From the isomerization,[5] NMR spectra (Fig. 1) of III and IV and inspection of a molecular model, III and IV were assumed to be diastereoisomeric with each other.[6]

3) Elution orders on column chromatography were not parallel to behaviors on TLC: the first eluent (A) *Rf* 0.28 and the second (B) *Rf* 0.28 and 0.48.

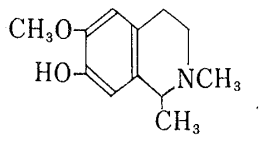
4) Methyl ethers of each free base were used for GLC. Authors are indebted to Dr. N. Ikekawa for supplying silicone polymer OV-17.

5) An acid-catalyzed isomerization of oxyacanthine-repandine is reported by Knabe, *et al.* [J. Knabe and P. Horn, *Arch. Pharm.*, **300**, 726 (1967) and references cited therein.] The present irreversible isomerization of IV to III seemed rather specific.

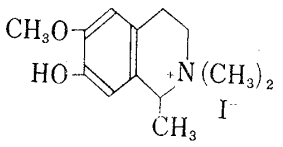
6) As shown in Fig. 1, NMR spectra of III and IV showed the same resonance forms excluding two methyl groups at 1- and 1′-positions, which were two doublets in III and a sharp doublet in IV. From the different resonance forms of two methyl groups, those of III were non-equivalent and the fact was supported by inspection of a molecular model. Therefore those of III were assigned to be different in their configuration and those of IV the same.

The structure of V, though unable to crystallize by itself, was assigned as *dl*-1,1',2,2'-tetramethyl-6,6'-dimethoxy-7'-hydroxy-1,1',2,2',3,3',4,4'-octahydro-7,8'-bisisoquinolyl ether dihydrochloride (C–O dehydro compound) on the basis of elemental analysis as its metho-picrate, and of NMR spectra of both V and its methiodide.

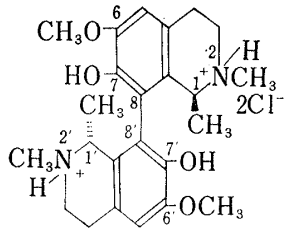
Formation of C–O dehydro compound (V), though in low yield, in the oxidation of I was suggestive of possible high yield production of a C–O dehydro compound (generally believed to be derived from a quaternary amine) from a tertiary amine, if suitable conditions were employed.



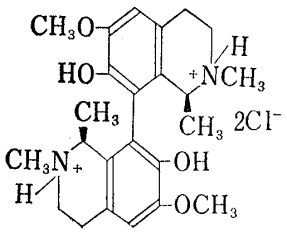
I



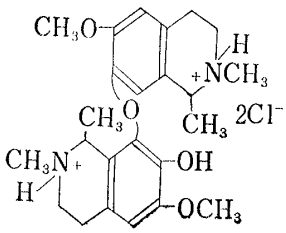
II



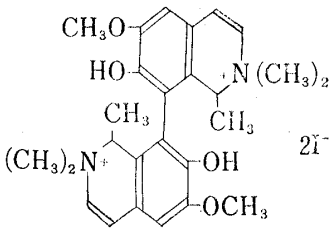
III



IV



V



VI

Chart 1

On the other hand, stirring a solution of II (1.84 g, 5.3 mmole) and $K_3Fe(CN)_6$ (4.77 g, 14.5 mmole) in 0.08 N aq. Na_2CO_3(300 ml) for 5 hr gave a crude product, which was then converted to its picrate by addition of Na–picrate.

A methochloride from the picrate by a usual manner was chromatographed on silicic acid to afford an amorphous substance [198 mg, elution with $CHCl_3$–MeOH (100:70), *Rf* 0.37], whose methiodide, mp 230—235° (decomp.), colorless prisms (VI) (144 mg, MeOH–*iso*-PrOH). *Anal.* Calcd. for $C_{26}H_{34}O_4N_2I_2 \cdot H_2O$: C, 43.94; H, 5.07; N, 3.94. Found: C, 44.12; H, 5.31; N, 3.97. NMR τ (1 N NaOD–D_2O): 8.81, 8.79 (each d., two ArCH($\underline{CH_3}$)–, J=6.5 cps), 6.86, 6.79, 6.67 (each s., two $-\overset{+}{N}(CH_3)_2$–), 6.14[7] (s., two O$\underline{CH_3}$), 4.09, 3.20 (defused AB quartet, two Ar$\underline{CH}$=CH–$\overset{+}{N}(CH_3)_2$– and two ArCH=$\underline{CH}$–$\overset{+}{N}(CH_3)_2$–, J=6.0 cps), 3.13 (s., two aromatic ring protons) and another amorphous substance (VII) [375 mg, elution with $CHCl_3$–MeOH (1:1), *Rf* 0.28]. NMR τ (1 N NaOD–D_2O): 8.57 (broad t., three ArCH($\underline{CH_3}$)–), 6.81 (broad s., three $-\overset{+}{N}(\underline{CH_3})_2$–), 6.44, 6.19, 6.17 (each s., three O$\underline{CH_3}$), 3.27, 3.07 (each broad s., three aromatic ring protons); metho-picrate, yellow prisms, mp 147—150° (H_2O). *Anal.* Calcd. for $C_{39}H_{56}O_6N_3 \cdot 3C_6H_2O_7N_3 \cdot 2H_2O$: C, 49.49; H, 4.78; N, 12.16. Found: C, 49.58; H, 4.79; N, 12.17.

7) NMR spectrum of VI at 100 Mc showed the resonances of two methoxyl groups as each singlet at τ 6.10 and 6.09. Authors are thankful to Dr. T. Hino for the NMR spectral measurement.

Provided that this oxidation products were C–O dehydro compounds, VI or VII would be identical with a metho–salt of V. Comparisons of their NMR spectra (1 N NaOD–D_2O), however, revealed that they were all different.

Thus, the foregoing fact and investigation of NMR spectra of VI and VII were probably indicative of the structure of VI as 1,1′,2,2′–tetramethyl–6,6′–dimethoxy–7,7′–dihydroxy–1,1′,2,2′–tetrahydro–8,8′–bisisoquinolinium dimethiodide, though contrary to the common belief that such an oxidation gave C–O dehydro compounds, and VII was assumed to be a trimer, whose structure was still obscure.

From the above–mentioned results, although ferricyanide oxidation products were susceptible to a kind of substituents at 1–position, they were largely dependent on both oxidants and solvents, which would have controlling effect upon the product ratio, namely C–C dehydro and C–O dehydro compounds.

Further research on this problem and the syntheses of bis–coclaurine alkaloids having bis–diphenyl ether linkage from corresponding tertiary amines as an extention of the oxidation are currently undertaken.

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Syntheses of Ten-membered Ring Amines from Quinolizidine[1,2]

The structural relation of the ten–membered ring alkaloids to the corresponding quinolizidine alkaloids has led us to develope syntheses of medium–sized ring amines from 1–azabicycloalkanes. This paper deals with the syntheses of ten–membered ring amines from quinolizidine.

The iminium salt[3] (II) (perchlorate: mp 233—234° (decomp.), picrate: mp 105.5—106°) obtained by mercuric acetate oxidation of quinolizidine (I) was treated with potassium cyanide to give cyanoquinolizidine (III),[4] which was neutralized with perchloric acid or picric acid to give back the iminium salt (II). Methiodide (IV), mp 242—243° (decomp.) (*Anal.* Calcd. for $C_{11}H_{19}N_2I$: C, 43.14; H, 6.26; N, 9.15. Found: C, 43.16; H, 6.27; N, 9.33) of III, when treated with silver oxide, gave an amide (V), which was neutralized with hydrobromic acid into a methobromide (VI), mp 286—289° (decomp.) (IR cm^{-1}: 3200, 3350 (NH_2),

1) Presented at the Hokuriku branch meeting of the Pharmaceutical Society of Japan, November, 1967.
2) All melting points were measured with a micro–melting point apparatus, the Yanagimoto Mfc. Co.
3) N.J. Leonald, A.S. Hay, R.W. Fulmer, and V.W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).
4) N.J. Leonald and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).