UDC 547.836.3.07

26. Tetsuji Kametani and Yukio Nomura : Studies on the Syntheses of Heterocyclic Compounds. LXII.[1] Synthesis of *rac*-Tetrahydrorotundine.[2]

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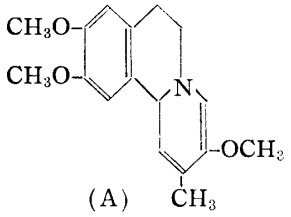
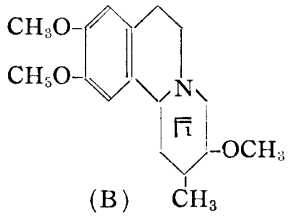
Attempts have been made in the past to synthesize rotundine, the main alkaloid of *Stephania rotunda* Loureilo, to which formula (A), 2-methyl-3,9,10-trimethoxy-6,7-dihydro-11b*H*-benzo[*a*]quinolizine, had been forwarded by H. Kondo and Matsuno.[3] Sugasawa and Mizukami[4] recently synthesized *rac*-dihydrorotundine (B). The corresponding 1,2,3,4-tetrahydrorotundine (XI) appeared to be a suitable intermediate to this end and partial dehydrogenation of 1, 2, 3, and 4 positions would be possible.

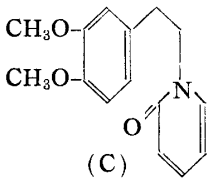


(A)

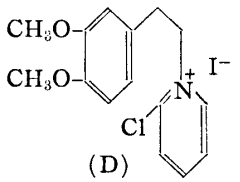


(B)

Many methods have hitherto been examined for this synthesis and the ring-closure of N-substituted pyridone (C) was first attempted as a model experiment.[5] However, contrary to expectations, the product obtained was N-substituted 2-chloropyridinium salt (D), which easily converted to the corresponding 2-pyridone derivative (C) on being treated with sodium hydroxide solution.[6]



(C)



(D)

Thus, conversion of pyridone derivative into benzoquinolizine by cyclization seemed to be comparatively difficult and the ester (IV) was prepared by cyclization of the 2-piperidone derivative (III), which was prepared by the condensation of 3,4-dimethoxyphenethyl bromide (I) and 4-methyl-5-ethoxycarbonyl-2-piperidone[7] (II) in the presence of sodium hydride. The use of metallic potassium[8] in place of sodium hydride did not give any better yield and the use of sodium amide as the condensation agent failed to give the objective piperidone. Further, attempt was made to prepare the piperidone derivative (III) by the reductive condensation of diethyl α-cyano-β-methylglutarate[7] with homoveratrylamine according to the

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1) Part LXI : Yakugaku Zasshi, **80**, 1127 (1960).
2) Paper presented at the monthly Meeting of the Pharmaceutical Society of Japan, Tokyo, March 18, 1960. This Bulletin, 8, 658 (1960).
3) H. Kondo, T. Matsuno : Yakugaku Zasshi, **64A**, 28 (1944); **64B**, 113, 274 (1944).
4) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 359 (1958).
5) T. Kametani, Y. Nomura : *Ibid.*, **8**, 741 (1960).
6) T. Kametani, Y. Nomura, K. Fukumoto : Yakugaku Kenkyu, **31**, 673 (1959).
7) T. Kametani, Y. Nomura : *Ibid.*, **31**, 687 (1959).
8) S. Fujii : This Bulletin, **6**, 591 (1958).

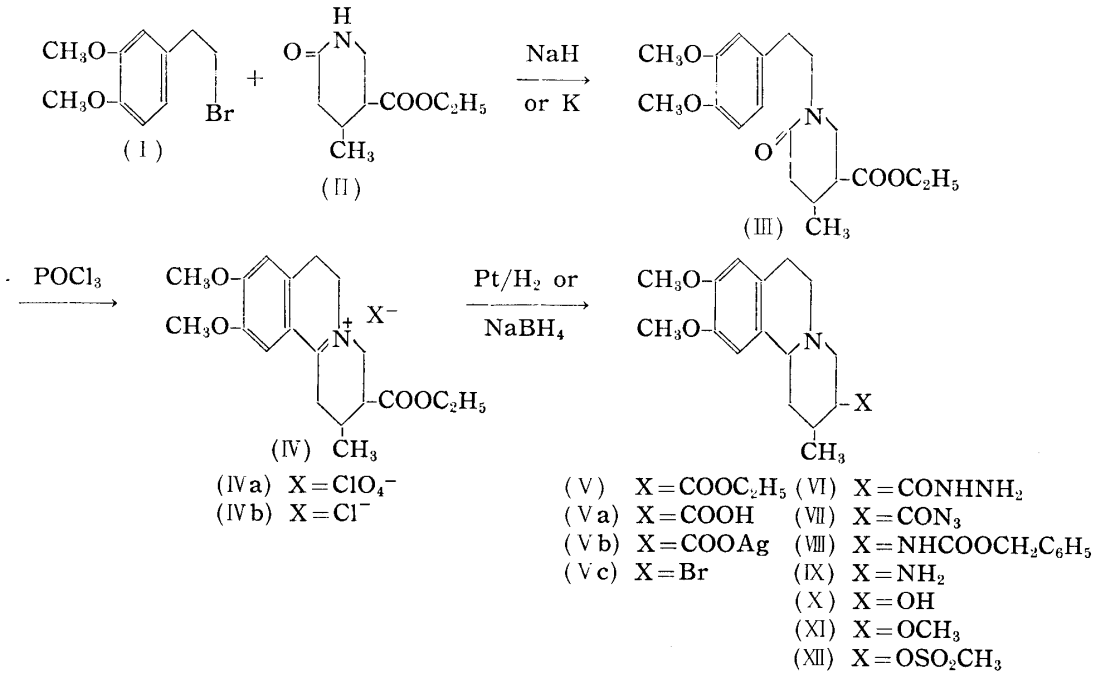
method of Preobrazhenski[9] but the objective piperidone was not obtained as a main product, various substances being formed.[10]

Therefore, benzoquinolizinium salt (IV) was converted to the corresponding compound (V) by catalytic hydrogenation of its chloride (IV), obtained through its free base, in the presence of Adams platinum, or by treatment with sodium borohydride in alcohol. The latter method was found to be more convenient and better than the former because the perchlorate (IVa) itself could be reduced without converting it to the chloride (IVb). Treatment with the ion exchanger, Amberlite IRA-400, was tried for obtaining the free base from the perchlorate (IVa) but the yield was not good.

The first attempt to prepare the objective compound (XI) via the carboxylic acid (Va), its silver salt (Vb), and bromo derivative (Vc) according to the method of Allen and Wilson[11] resulted in failure. It was expected that the silver salt (Vb) could be prepared by treatment of its potassium salt with silver nitrate after saponification of the ester (V) with alcoholic potassium hydroxide solution. However, the silver salt was very unstable and it turned black immediately, and this process had to be given up.

Attempt was then made to apply the Curtius reaction to prepare the amino derivative (IX) via the hydrazide (VI), azide (VII), and benzylurethan (VIII). Subsequently, the amino derivative (IX) was diazotized with sodium nitrite in acetic acid[12] and the carbinol base (X) was obtained as a viscous oily substance, which was purified as its methiodide.

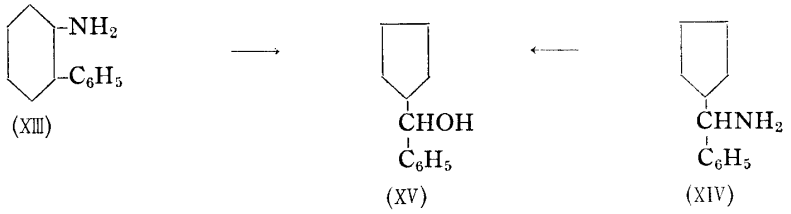
Noike[13] determined the configuration of the two diastereoisomers of 3-amino-9,10-methylenedioxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine, possessing a structure similar to the compound (VI), and examined the behavior of the two isomers to the Curtius degradation.[14] He revealed that the Curtius degradation progressed more smoothly with equatorial configuration at 3-position than the axial one. In the present series of work, two kinds of



9) R. P. Evstigneeva, R. S. Livshits, L. I. Zakharkin, M. S. Bainova, N. A. Preobrazhenski : Doklady Akad. Nauk. S. S. S. R., **75**, No. 4, 539 (1950) (C. A., **45**, 7577 (1951)).
10) T. Kametani, Y. Nomura : Unpublished work.
11) C. F. H. Allen, C. V. Wilson : Org. Syntheses, **26**, 52 (1946).
12) S. Akiya, T. Ohsawa : This Bulletin, **7**, 277 (1959).
13) Y. Noike : Yakugaku Zasshi, **79**, 1520 (1959).
14) S. Sugasawa, H. Tomizawa : *Ibid.*, **72**, 804 (1952).

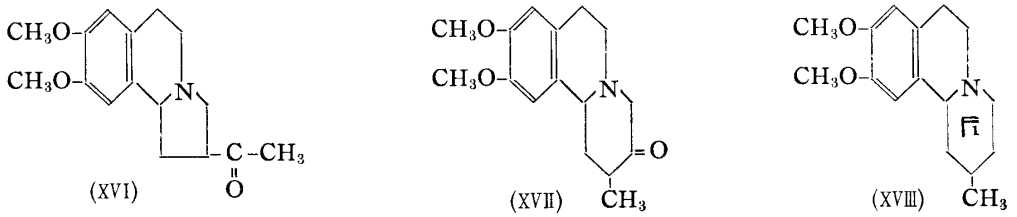
crystalline perchlorate (IVa) were obtained due to asymmetric carbon atoms in 2- and 3-positions, and one of them obtained as pure crystals of m.p. 219~220° was used as the starting material for the subsequent Curtius reaction.

The reaction of aliphatic primary amines with nitrous acid is known to yield a variety of products including those resulting from solvolysis, elimination, rearrangement, and ring contraction. For example, Streitwieser[15] reported the reaction mechanism in the diazotization of aliphatic amines. Smith, *et al.*[16] showed that the compound (XV) is obtained from either (XIII) or (XIV).



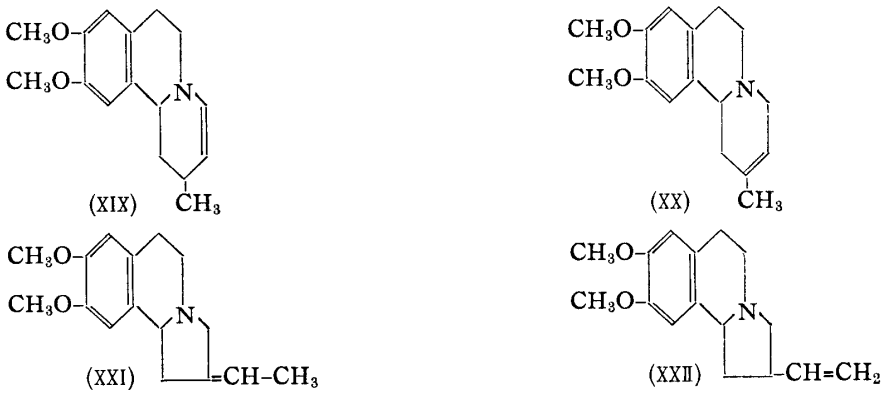
(XIII) (XV) (XIV)

In order to determine whether the oxidized product had the structure (XVI) or (XVII), attempt was made to oxidize the hydroxy base (X) with potassium *tert*-butoxide and benzophenone in benzene according to the modified Oppenauer procedure[17] but, contrary to expectations, a dehydrated compound (XVIII) was obtained in a poor yield. The compound was identified as its methiodide of m.p. 231~232°(decomp.), which showed no carbonyl absorption in its infrared spectrum.



(XVI) (XVII) (XVIII)

With regard to the position of the double bond in (XVIII), which was formed by dehydration of (X), two locations are possible, as in (XIX) and (XX), and examination was made in the infrared spectrum of (XVIII). The weak absorption of -C=C- at 1650 cm^{-1} appearing in dihydrorotundine[4] was not observed in the spectrum of (XVIII), probably due to overlapping of other bands, but an absorption of a *cis*-form double bond appeared at 685 cm^{-1} and another at 827 cm^{-1} in the finger-print region. The absorption band at 685 cm^{-1} would not appear in the case of a trisubstituted double bond, such as in (XX) and (XXI). There was



(XIX) (XX) (XXI) (XXII)

15) A. Streitwieser : J. Org. Chem., **22**, 861 (1957).
16) P. A. Smith, D. R. Bier, S. N. Ege : J. Am. Chem. Soc., **76**, 4514 (1954).
17) R. S. Woodward, N. L. Wendler, F. J. Brutschy : *Ibid.*, **67**, 1425 (1945).

also no absorption in (XVIII) which might be due to the vinyl-type double bond like that in (XXII), which is generally found in the region of 890~910 and 1780~1820 cm^{-1}.[18] Accordingly, the dehydrated compound (XVIII) probably has the structure of the type (XIX) and further detailed examinations are being made.

Catalytic hydrogenation of (XVIII) over platinum resulted in absorption of one mole of hydrogen and infrared spectrum of the product showed the absence of the characteristic absorption band at 685 cm^{-1}.

Even if the oxidized product (XVII) were formed, besides a small amount of the dehydrated compound (XVIII), it would probably have become a resinous substance due to its lability as revealed by Sugasawa and Mizukami.[4] Consequently, only the dehydrated compound (XVIII) was isolated as its methiodide, besides a large amount of resinous substance.

Since the conversion of the hydroxy base (X) to the corresponding cyclic ketone (XVII) by the Oppenauer method was not successful, a milder oxidation was attempted, either with chromium trioxide-pyridine[19] or chromium trioxide-*tert*-butanol.[20] The former oxidation procedure finally afforded the six-membered ketone (XVII), having an absorption band at 1728 cm^{-1} in its infrared spectrum and identified as its methiodide of m.p. 234~236° (decomp.). If this compound is the expected product, the oxidation product should have the same structure (XVII).

In addition, the fact that the oxidized ketone showed a negative haloform reaction indicated that the diazotized product did not have the contracted five-membered ring (XVI), since the latter should show positive haloform reaction characteristic to aliphatic ketones.

The hydroxy derivative (X) was then methylated with diazomethane in the presence of fluoroboric acid in chloroform after the free base (X) was changed to its fluoroborate[21] and the objective methyl ether (XI), *rac*-tetrahydrorotundine, was obtained as its methiodide of m.p. 240~241° (decomp.). The methanesulfonate[22] (XII) of (X) was also prepared in order to confirm the presence of the hydroxyl group.

Experimental*2

1-(3,4-Dimethoxyphenethyl)-4-methyl-5-ethoxycarbonyl-2-piperidone (III)—a) Condensation with NaH : NaH (1.9 g.) was added to a mixture of 4-methyl-5-ethoxycarbonyl-2-piperidone[7] (13.4 g.) and toluene (200 cc.), and the mixture was refluxed gently in an oil bath for 3.5 hr. A solution of 3,4-dimethoxyphenethyl bromide (I) (17.5 g.) in toluene (50 cc.) was added to the foregoing solution and the mixture was again refluxed for 3 hr. with stirring. The mixture was filtered while warm to remove NaBr that separated during the reaction, NaBr was washed with hot toluene on the filter, and the filtrate was combined with the hot toluene mother liquor. The combined toluene solution was concentrated in a reduced pressure and the residual reddish orange, viscous oil was distilled *in vacuo*, affording 11.0 g. of (III), b.$p_{0.06\sim0.07}$ 195~205°, besides 5.95 g. of the starting material recovered as the initial distillate. Yield, 77.8% of the theoretical if the lactam (II) recovered by distillation is taken into account. (III) is a yellowish-white, viscous oil, which could not be crystallized.

The yield of the lactam (III) was not improved even when the reaction mixture was refluxed for a longer time in the presence of Cu powder as a catalyst.

b) Condensation with K : To a benzene solution of powdered K, prepared from metallic K (1 g.) and benzene (30 cc.), a mixture of the lactam (II) (4.7 g.) and toluene (150 cc.) was added dropwise with stirring at 20° during 15 min. During this addition, K salt of (II) began to separate, evolving H_2, and the solution colored orange. After stirring this mixture for 1 hr. at room temperature and heating for 30 min., a solution of 3,4-dimethoxyphenethyl bromide (6.2 g.) in xylene (20 cc.) was added and the whole mixture was refluxed at 110~115°, when KBr began to separate out after a few minutes.

*2 All m.p.s and b.p.s are uncorrected.

18) K. Nakanishi : Kagaku-no-Ryoiki, **13**, 69 (1959); cf. L. J. Bellamy : "The Infra-red Spectra of Complex Molecules," 50 (1959). John Wiley & Sons, Inc., New York.
19) C. Djerassi, L. E. Geller, A. J. Lemin : J. Am. Chem. Soc., **76**, 4089 (1954).
20) A. Leo, F. H. Westheimer : *Ibid.*, **74**, 4383 (1952).
21) M. Neeman, M. C. Casero, J. D. Roberts, W. S. Johnson : Tetrahedron, **6**, 36 (1959).
22) H. Irie, Y. Tsuda, S. Uyeo : J. Chem. Soc., **1959**, 1446.

The reaction mixture was heated for 9 hr., the inorganic salts were removed, and the solvent was evaporated. The residual orange syrup was distilled *in vacuo* and 2.7 g. (79.4%) of (III) was obtained as the fraction of b.$p_{0.06\sim0.07}$ 190～205°, with recovery of 2.8 g. of the starting material as the initial fraction. Infrared spectrum of (III) revealed the presence of ester (1724 cm^{-1}) and lactam (1639 cm^{-1}) (in Nujol).

2-Methyl-3-ethoxycarbonyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizinium Salt (IVa or IVb)—A mixture of the foregoing piperidone (III) (3.3 g.) and $POCl_3$ (11 cc.) in pure toluene (22 cc.) was refluxed for 2.5 hr., toluene and excess $POCl_3$ were removed *in vacuo*, and the residue was dissolved in 10% HCl. The acid solution was treated with conc. $HClO_4$ until no more precipitate separated. The perchlorate separated as an oil at first but gradually solidified on standing for several hours. The crude perchlorate (IVa) was obtained as colorless needles, m.p. 98～195°, which melted at 219～220° after recrystallization from MeOH. Yield, 2.7 g. (66.3%). *Anal.* Calcd. for $C_{19}H_{26}O_8NCl$: C, 52.84; H, 6.07; N, 3.24. Found : C, 52.58; H, 5.92; N, 3.21.

From the mother liquor, a low-melting substance and another perchlorate separated as yellowish orange crystals, m.p. 208～209° (decomp.). Repeated recrystallization failed to raise the m.p., though the substance was purified to yellowish white needles. *Anal.* Calcd. for $C_{19}H_{26}O_8NCl$: C, 52.84; H, 6.07; N, 3.24. Found : C, 53.02; H, 5.99; N, 3.12.

Ethyl 2-Methyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-3-carboxylate (V)—a) Catalytic hydrogenation over Pt : The perchlorate (IVa) (2.2 g.) was treated with 10% NaOH (30 cc.) by warming on a water bath and the free base was extracted thoroughly with Et_2O. Et_2O was extracted with 10% HCl and evaporation of HCl to dryness *in vacuo* furnished 1.7 g. of a viscous reddish chloride (IVb).

MeOH solution (150 cc.) of (IVb) was catalytically reduced over Adams Pt (62 mg.) and 117.7 cc. of H_2 was absorbed. The bluish green, fluorescent solution was worked up as usual and the product was obtained as a crude hydrochloride of yellowish orange syrup. The objective ester (V) was obtained by basification of the hydrochloride with $NaHCO_3$ and purified from Et_2O to yellowish white needles, m.p. 128～129°. Yield, 1.2 g. (70.6%). *Anal.* Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.13; N, 4.20. Found : C, 68.80; H, 8.18; N, 4.15.

Picrate : Faint yellow prisms (from EtOH), m.p. 169～170°. *Anal.* Calcd. for $C_{19}H_{27}O_4N \cdot C_6H_2O_7N_3$: C, 53.76; H, 5.38; N, 9.91. Found : C, 53.15, 53.11; H, 5.09, 5.29; N, 9.96.

When activated Amberlite IRA-400 (15 cc.) was used in order to obtain the free base (IV) from its perchlorate (IVa) (1.5 g.), it was catalytically hydrogenated over Adams Pt as described above and the objective ester (V) was obtained as crystals of m.p. 125～128°, in only 27.4% yield (105.8 mg.).

b) Reduction with $NaBH_4$: $NaBH_4$ (4 g.) was added in small portions to a suspension of the perchlorate (IVa) (2 g.) in 99% MeOH (250 cc.) with stirring at 5～7°. After standing overnight, the reaction mixture was neutralized with AcOH and concentrated to dryness *in vacuo*. The residue was extracted with 5% HCl, the acid extract was filtered, and the filtrate was basified with 10% NaOH. The precipitate thereby produced was extracted with Et_2O, the extract was evaporated to dryness, and the residue was recrystallized from Et_2O to white needles (1.2 g.), m.p. 126～127°. Further crop (0.1 g.) was obtained from its mother liquor. Total yield, 1.3 g. (85.1%). This substance showed no depression of m.p. on admixture with the product obtained by the foregoing procedure (a).

2-Methyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-3-carbohydrazide (VI)—A mixture of the above ester (V) (1.5 g.) and 80% $NH_2NH_2 \cdot H_2O$ (25 cc.) was refluxed for 16 hr. at 130～145° and allowed to stand overnight. The white precipitate that formed was collected to 1.4 g. (98%) of the crude hydrazide (VI) and recrystallized from EtOH to colorless needles, m.p. 220～221°. *Anal.* Calcd. for $C_{17}H_{25}O_3N_3 \cdot \frac{1}{2}H_2O$: C, 62.17; H, 7.98; N, 12.80. Found : C, 61.68, 62.25; H, 7.73, 8.31; N, 13.33.

2-Methyl-3-benzyloxycarbonylamino-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (VIII)—A clear solution of the hydrazide (VI) (690 mg.) in 10% HCl (6 cc.) was mixed with benzene (50 cc.) and the solution of $NaNO_2$ (212 mg) in H_2O (2 cc.) was added in drops during 10 min., with cooling and stirring. After 2 hr. of stirring, the reaction mixture was basified with Na_2CO_3 and extracted with benzene. The azide (VI) so obtained was dried over $CaCl_2$ for 2 hr.

Freshly distilled benzyl alcohol (2 g.) was added to the benzene solution of (VII) and the mixture was evaporated to 50 cc. After refluxing for 1 hr., benzene and benzyl alcohol were evaporated *in vacuo* and the residual viscous syrup was kept in an ice chest, from which benzylurethan (VIII) was obtained on addition of a small quantity of EtOH. Yield, 0.7 g. (78%). Recrystallization from EtOH gave 490 mg. of colorless needles, m.p. 207～208°. *Anal.* Calcd. for $C_{24}H_{30}O_4N_2$: C, 70.22; H, 7.37; N, 6.82. Found : C, 69.70; H, 7.19; N, 7.28.

2-Methyl-3-amino-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (IX)—A solution of (VIII) (490 mg.) dissolved in a mixture (35 cc.) of 20% HCl and AcOH (1:1) was refluxed gently at 130～140° for 1 hr. and decarboxylation was completed in 30 min. Excess of HCl and AcOH were removed *in vacuo* and the residual hydrochloride of (IX) (389.4 mg. or 93.3%) was recrystallized from

EtOH-Et_2O to colorless prisms, m.p. 302~303° (decomp.). *Anal.* Calcd. for $C_{16}H_{24}O_2N_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 53.63; H, 7.51; N, 7.82. Found : C, 53.25; H, 7.67; N, 7.99.

Attempted catalytic hydrogenation of (VIII) over PtO_2, in the presence of KOH, ended in recovery of the starting material.

2-Methyl-3-hydroxy-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (X)—Anhyd. AcONa (475.0 mg.) and 50% AcOH (6 cc.) were added to the faint yellow solution of (IX) (451.5 mg.) dissolved in H_2O (2 cc.) and a solution of $NaNO_2$ (132.8 mg.) in H_2O (1 cc.) was added to it during 10 min., while chilling with ice and NaCl to −7° to −10°. The mixture was stirred at this temperature for 6 hr., allowed to stand overnight at 7°, and the dark reddish reaction mixture was added dropwise into conc. alkali solution covered with Et_2O, with stirring and cooling. The free base that separated was extracted with Et_2O, the extract was dried over K_2CO_3, and the solvent was evaporated, leaving 340.7 mg. (98%) of reddish orange syrup.*3

Methiodide : Colorless sandy crystals (from EtOH-Et_2O), m.p. 223~225°. *Anal.* Calcd. for $C_{16}H_{23}O_2N \cdot CH_3I \cdot 1\frac{1}{2}H_2O$: C, 45.74; H, 6.50; N, 3.14. Found : C, 45.77; H, 6.48; N, 4.80.

2-Methyl-3-mesyloxy-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XII)—The reddish orange solution of the crude hydroxy derivative (X) (93 mg.) dissolved in dehyd. pyridine (1 cc.) was treated with a solution of methanesulfonyl chloride (58 mg.) in pyridine for 5 min., with chilling to −10°, the reddish solution was allowed to stand in an ice chest for 32 hr., and poured into ice and water. This mixture was extracted with $CHCl_3$, the extract was washed with Na_2CO_3 solution and H_2O and dried over anhyd. K_2CO_3. Evaporation of $CHCl_3$ *in vacuo* left an orange viscous syrup and addition of dehyd. Et_2O to it gave 26 mg. (21%) of slightly pink powder, m.p. 155~192°.

Methiodide : Colorless granular crystals (from Et_2O-MeOH), m.p. 255~257° (decomp.). *Anal.* Calcd. for $C_{17}H_{25}O_5NS \cdot CH_3I \cdot H_2O$: C, 41.94; H, 5.83. Found : C, 41.99; H, 6.04.

2-Methyl-3,9,10-trimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XI) (*rac*-Tetrahydrorotundine)—A mixture of the foregoing (X) (120 mg.), benzene, MeOH, and aqueous solution of 8.28*N* HBF_4*4 (159.5 mg.) was evaporated to dryness *in vacuo* and the fluoroborate (159.5 mg.) was obtained as a hygroscopic, faintly brown powder.

The fluoroborate was dissolved in MeOH (50 cc.) to form a pale reddish orange clear solution, 2 drops (0.04 cc.) of 15*N* HBF_4 solution*5 were added as a catalyst, and CH_2N_2, prepared from N-methyl-N-nitroso-*p*-toluenesulfonamide (13 g.), was added with chilling to −18° during 5 hr., evolution of N_2 being observed immediately. The reaction mixture was kept in an ice chest overnight, extracted with 10% HCl (7 cc.), and the orange-colored acid extract was added dropwise into a mixture of 10% NaOH and $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and evaporated *in vacuo*, leaving a faintly brown, amorphous powder (51.8 mg.). This residue was dissolved in benzene and filtered through a column of alumina, giving a purified brown powder (43.6 mg. or 33.7%).

Methiodide (XI) : Prepared in cold Me_2CO and recrystallized from MeOH-Et_2O to colorless cubic crystals, m.p. 240~241° (decomp.). Yield, 13.4 mg. *Anal.* Calcd. for $C_{17}H_{25}O_3N \cdot CH_3I \cdot \frac{1}{2}H_2O$: C, 48.87; H, 6.56; N, 3.17. Found : C, 48.56; H, 6.29; N, 3.34.

2-Methyl-9,10-dimethoxy-1,2,6,7(or 1,4,6,7)-tetrahydro-11b*H*-benzo[*a*]quinolizine (XVIII) (Attempted Oxidation of the Hydroxy Base (X) by the Modified Oppenauer Procedure)—A yellowish orange mixture of the crude hydroxy base (X) (186.7 mg.), benzophenone (500 mg.), and dehyd. benzene (70 cc.) was added to the white powder of *tert*-BuOK, prepared by mixing metallic K (107 mg.), dehyd. *tert*-BuOH (20 cc.) freshly distilled over metallic Na, and dehyd. benzene (30 cc.). The resultant pink solution containing a small amount of colloidal substance was heated at 95~100° for 3.5 hr. The dark reddish solution so formed was extracted with 10% HCl, the acid solution was extracted with benzene to remove insoluble substance, and the aqueous orange layer was basified with K_2CO_3. The alkaline solution was extracted with benzene, the extract was dried over K_2CO_3, and benzene was evaporated *in vacuo* in N_2 atmosphere, leaving 48.3 mg. (26.1%) of a dark reddish syrup.

Methiodide : Prepared in Me_2CO and crystallized form MeOH-benzene to white prisms, m.p. 231~232° (decomp.). Yield, 8.8 mg. A large amount of the product remained as a resinous substance during preparation of the methiodide. The infrared spectrum of this methiodide showed no absorption of a ketone. *Anal.* Calcd. for $C_{16}H_{21}O_2N \cdot CH_3I$: C, 50.89; H, 6.29. Found : C, 50.41; H, 6.09.

*3 This hydroxy base was comparatively labile and a fair amount of resinous substance insoluble in majority of solvents formed unless used immediately after preparation.

*4 Concentration of commercial HBF_4 was determined by titration of 1 cc. of its solution with *N* NaOH (F=0.986), with Phenolphthalein as the indicator. Consumption of 8.4 cc. of *N* NaOH showed this to be 8.28*N*.

*5 To prepare this HBF_4 reagent, commercial HBF_4 solution was evaporated as much as possible in reduced pressure (5 mm. Hg) at 50~60° and concentration of the residual solution was found to be 14.98*N* by titration with *N* NaOH (F=0.986).

This dehydrated compound (XVIII) was also obtained by heating (X) in benzene with *tert*-BuOK, without the use of benzophenone.

2-Methyl-3-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XVII)—CrO_3 (160 mg.) was added to pyridine (2 cc.) gradually, while chilling with ice and NaCl, and orange complex separated to form an orange mixture. The dark brown solution of the hydroxy base (X) (152.3 mg.) in pyridine (1 cc.) was added to the above solution, chilled to $-5°$ to $-10°$, and the mixture was shaken for 20 min. The mixture was allowed to stand in an ice chest overnight, poured into ice-water, and extracted repeatedly with benzene. The emulsified benzene layer was centrifuged and pyridine was removed from the yellowish green benzene solution by washing with 1% AcOH and H_2O. The benzene layer was dried over Na_2SO_4 and the solvent was evaporated to leave 34 mg. (22.5%) of a green oil. This substance seemed to be considerably unstable, particularly in alkaline state, and was therefore converted immediately into its methiodide.

Methiodide : Prepared with MeI in Me_2CO and recrystallized from MeOH-Et_2O to white cubic crystals (5.5 mg.), m.p. 234~236° (decomp.), undepressed on admixture with the sample of m.p. 233~234° (decomp.), prepared by Sugasawa, *et al.*[4] The infrared spectra of these two samples were almost similar, except for a very small difference in the finger-print region and the presence of a carbonyl absorption at 1728 cm^{-1} in the present sample, while this absorption appeared at 1726 cm^{-1} in Sugasawa's sample.[4] This methiodide formed a product of somewhat lower melting point when recrystallized from a warm solvent. It was negative to the haloform reaction. *Anal.* Calcd. for $C_{16}H_{21}O_3N \cdot CH_3I \cdot H_2O$: C, 46.91; H, 6.02. Found : C, 46.71; H, 5.96.

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Summary

2-Methyl-3-ethoxycarbonyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizinium salt was prepared by cyclization of the piperidone compound synthesized by the condensation of 3,4-dimethoxyphenethyl bromide and 4-methyl-5-ethoxycarbonyl-2-piperidone in the presence of sodium hydride. Its amino derivative was prepared by the Curtius degradation, via the hydrazide, azide, and benzylurethan. The amino compound was diazotized with sodium nitrite in acetic acid and converted to the hydroxyl derivative, which was purified as its methiodide. In order to prove the presence of this hydroxyl group, the compound was led to its methanesulfonate. The hydroxy base was methylated with diazomethane, in the presence of fluoroboric acid in chloroform, and the objective methyl ether, i.e. *rac*-tetrahydrorotundine, was obtained as its methiodide. Some discussions were made on the reaction of aliphatic primary amines with nitrous acid.

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