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65. Shigehiko Sugasawa and Kitaro Mizukami: Synthesis of *rac*-Dihydrorotundine.

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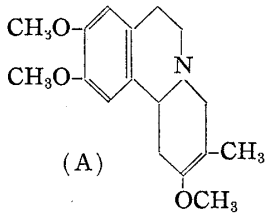
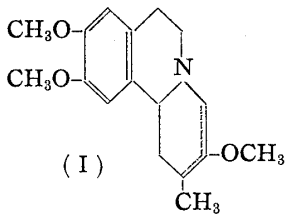
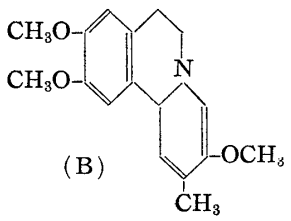
In the preceding paper of this series, one of us (K. M.) described a synthesis of *rac*-dihydroisorotundine (A).[1] In this paper we wish to report a synthesis of *rac*-dihydrorotundine (I), the dihydro derivative of rotundine (B).[2]


(A)


(I)


(B)

As a model experiment the synthesis of the nor compound (X) of (I) was first executed and for that purpose 3-oxobenzoquinolizine derivative (Ⅷ) was needed. Thus, 3,4-dimethoxyphenethylamine was treated with formaldehyde and potassium cyanide in aqueous solution to yield the acetonitrile (Ⅱ), which was converted to the corresponding ester (Ⅲ). The latter was now treated with succinic anhydride in benzene to furnish the amidic acid (Ⅳ), which was esterified to (Ⅴ). This was cyclized by treating with phosphoryl chloride, followed by hydrogenation to give the isoquinoline derivative (Ⅵ), from which the keto-ester (Ⅶ) was prepared by the method of Dieckmann.

The crude (Ⅶ) was obtained as a solid of m.p. 114~115°, which gave reddish purple coloration with ferric chloride concordant to its structure, but when purified repeatedly from ethanol this formed colorless needles of m.p. 127°, which now did not respond to ferric chloride. When the latter was dissolved in aqueous caustic soda solution and reprecipitated by saturating carbon dioxide, there separated a crystalline solid, which again gave a positive color test with ferric chloride.

In contrast to the isomeric keto-ester described in the preceding paper[1] this keto-ester (Ⅶ) was quite stable to boiling 10% hydrochloric acid and it was found necessary to boil with 18% hydrochloric acid for a long period of time to carry out the ketonic fission, when, however, a partial hydrolysis of the methoxyl groups also occurred and the ketone (Ⅷ) was obtained only in a poor yield. The structure of (Ⅷ) was proved beyond doubt by reducing this to the dimethoxybenzoquinolizine derivative (3), which was identified with an authentic specimen prepared according to the method of Sugasawa, as is shown by (1) → (2) → (3) in Chart 1.

The oxo derivative (Ⅷ) was then treated with methyl orthoformate in the presence of dry hydrogen chloride to yield the corresponding dimethyl ketal (Ⅸ), the structure of which was proved by methoxyl determination and also through the absence of CO-absorption in its infrared spectrum. When treated with dilute aqueous hydrochloric acid, (Ⅸ) readily yielded the original ketone (Ⅷ) in a good yield. The compound (Ⅸ), when distilled *in vacuo*, lost an element of methanol and furnished a compound corresponding to *rac*-dihydronorrotundine (X), which gave the correct analytical value of methoxyl groups for this substance. (X) could not be reduced with hydrogen activated over Adams' platinum catalyst under ordinary pressure.

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1) This Bulletin, **6**, 312(1958).
2) H. Kondo, T. Matsuno: Yakugaku Zasshi, **64B**, 113, 274(1944).

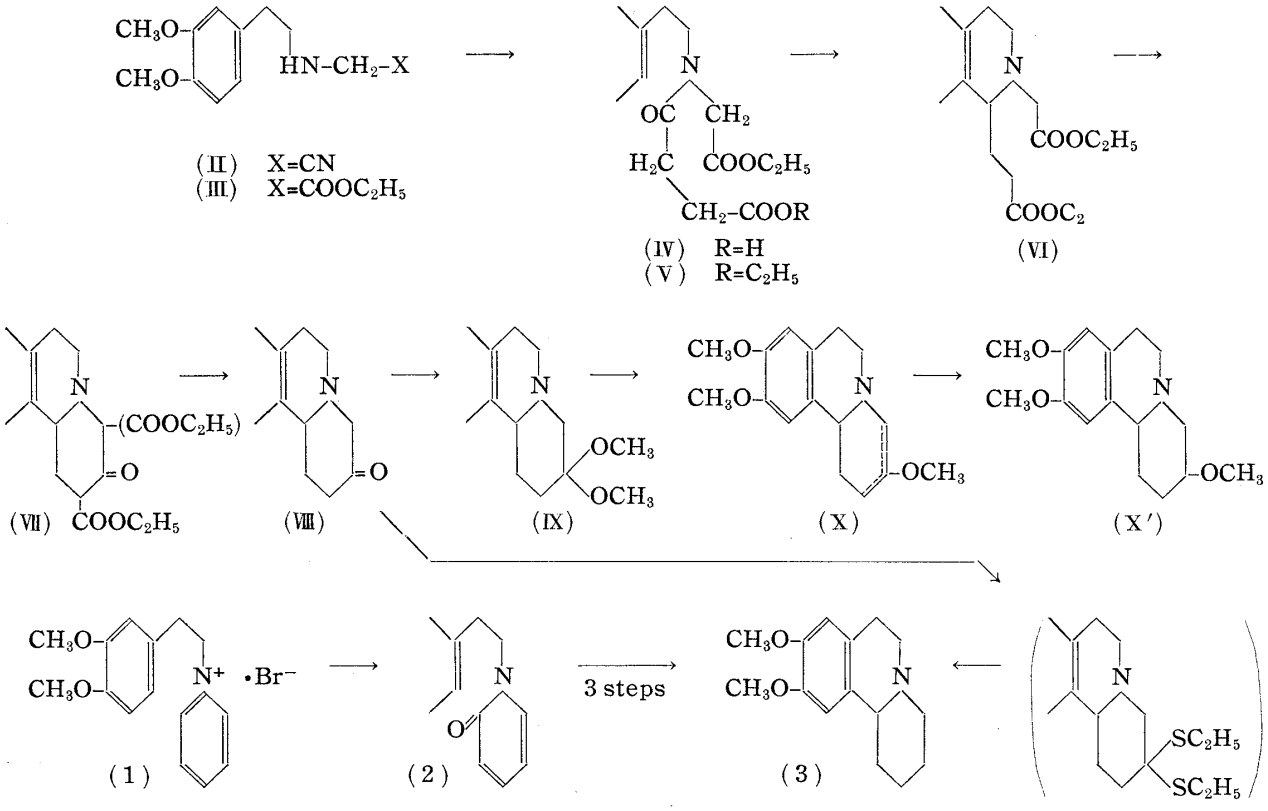


Chart 1.

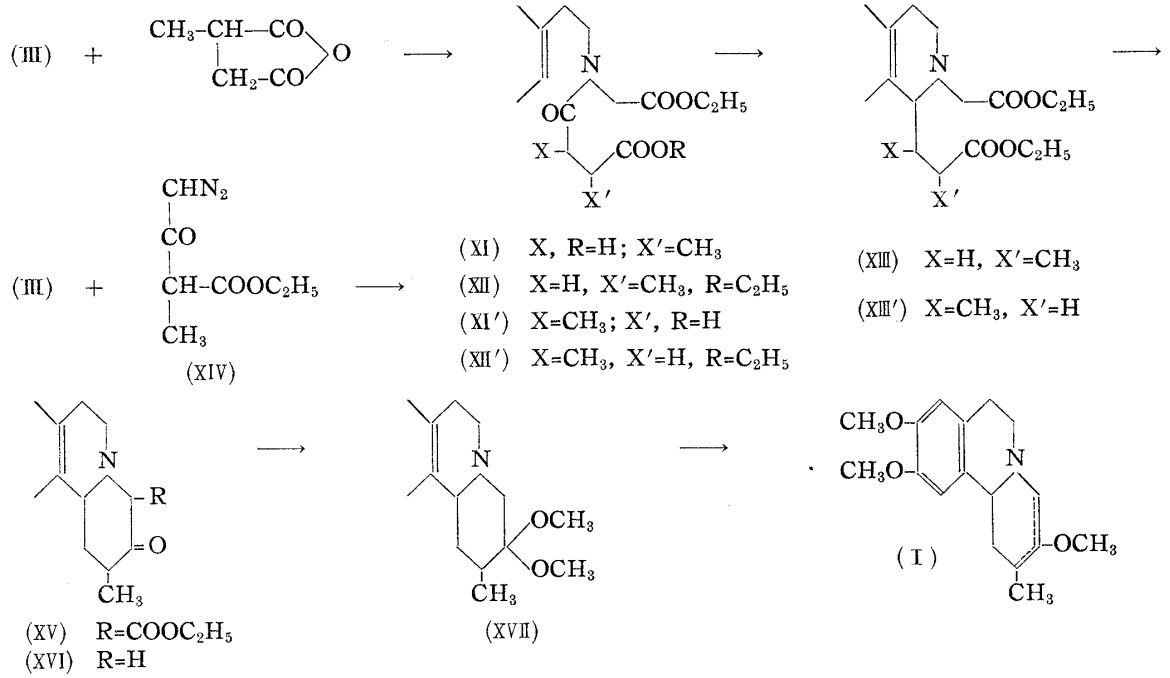
For the synthesis of *rac*-dihydrorotundine (I) the amino-ester (III) was condensed with methylsuccinic anhydride, when a single substance (XI or XI′) was obtained in an excellent yield. This was esterified to give (XII or XII′) and then cyclized by treating with phosphoryl chloride and hydrogenated. A viscous oil thus obtained was therefore (XIII or XIII′), which was characterized through its crystalline picrate of m.p. 113~114°.

On the other hand 2-ethoxycarbonylpropionyl chloride was treated with diazomethane to give the diazoketone (XIV), which was then reacted with (III) to yield the amido-ester (XII). The latter was now cyclized and reduced, giving an oily substance, the picrate of which melted at 114° and was found to be identical with the one obtained above. Thus the condensation of (III) with methylsuccinic anhydride was shown to produce the structure (XI) as the sole product.

The Dieckmann cyclization of (XIII) was executed by means of sodium hydride in boiling toluene to give a solid of m.p. 122.5°, which was soluble in caustic soda solution and therefore the structure of the condensation product can be represented by (XV), which did not give color reaction with ferric chloride.

The ketonic fission of this ester was again carried out with boiling 18% hydrochloric acid but with difficulty and the yield of the ketone (XVI) was poor. The dimethyl ketal (XVII) was prepared as usual, which on being distilled *in vacuo*, furnished a faint yellow viscous syrup, which responded distinctly to tetranitromethane and decolorized potassium permanganate solution instantaneously. That the compound (XVII) suffered a loss of a molecule of methanol on vacuum distillation to yield *rac*-dihydrorotundine (I) was verified by methoxyl determination of both of these compounds.

In parallel with the inertness of the double bond in dihydrorotundine prepared from the natural product towards catalytic hydrogenation, the compound (I) was also found quite resistant to hydrogen activated over Adams' platinum catalyst under ordinary pressure.



The authors are grateful to the Ministry of Education for a research grant in aid of this work. Their thanks are also due to Mr. N. Ito for his ardent and skilled technical assistance and also for methoxyl determination, and to Messrs. Ushioda and Tanikawa for infrared spectral measurements.

Experimental

3,4-Dimethoxyphenethylaminoacetonitrile (II)—3,4-Dimethoxyphenethylamine (36 g.), dissolved in 100 cc. of benzene, was mixed with HCl (72 cc. of 10%) with cooling and stirring, and to this mixture an aq. solution of KCN (24 g. in 90 cc. of H_2O) and of formaldehyde (9 cc. of 37%) were added dropwise with stirring, while the temperature of the mixture was kept around 5°. After being stirred for 2 hrs. at room temp., the reaction mixture was strongly basified with K_2CO_3 and the supernatant benzene layer was separated. The aq. layer was extracted thoroughly with benzene and the combined benzene solution was washed with NaCl solution, dried, and the solvent was distilled off, leaving a clear faint yellow syrup, which weighed 43.5 g. This could not be purified through distillation and was directly esterified, and characterized as the hydrogen oxalate, which formed colorless prisms of m.p. 163°(decomp.) from EtOH. *Anal.* Calcd. for $C_{14}H_{18}O_6N_2 \cdot \frac{1}{2}H_2O$: C, 52.7; H, 6.0; N, 8.8. Found : C, 53.2; H, 5.5; N, 8.6.

Ethyl Ester (III) of N-(3,4-Dimethoxyphenethyl)glycine—The crude (II) (22 g.) was dissolved in anhydr. EtOH (100 cc.), the solution was saturated with dry HCl gas and then warmed on a steam bath for 30 mins. The product was worked up as usual to yield a faint yellow oil of $b.p_{0.3}$ 172~175°. The yield was 15.5 g. The overall yield was 59% from 3,4-dimethoxyphenethylamine.

Picrate : Yellow prisms (from EtOH), m.p. 156.5~157°. *Anal.* Calcd. for $C_{20}H_{24}O_{11}N_4$: C, 48.4; H, 4.8; N, 11.4. Found : C, 48.3; H, 4.9; N, 11.2.

Ethyl N-(Ethoxycarbonylmethyl)-N-(3,4-dimethoxyphenethyl)succinamidate (V)—The foregoing ester (12 g.) in pure benzene (30 cc.) was mixed with succinic anhydride (5 g.) and the whole was refluxed on a steam bath for 2 hrs. On cooling the condensation product (IV) was extracted with aq. Na_2CO_3, filtered through a wet filter, and the filtrate was made Congo-acid with HCl with cooling, when a pasty mass separated. Since this did not solidify, it was collected in EtOAc, dried, and the solvent was evaporated, leaving an orange syrup, which was esterified as usual. The ester (V) was obtained as a colorless viscous syrup of $b.p_{0.1}$ 235°, which weighed 11.3 g. or 64% based on (III). *Anal.* Calcd. for $C_{20}H_{29}O_7N$: N, 3.5. Found : N, 3.45.

1-(2-Ethoxycarbonylethyl)-2-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI)—The ester (V) (17.8 g.) was mixed with $POCl_3$(50 g.) and the mixture was gently refluxed in an oil bath kept at 120~130° for 2 hrs. From the dark reaction mixture an excess of $POCl_3$ was removed *in vacuo*, the residue was decomposed with ice water, and was acidified by 5% HCl. The aq. solution was treated with carbon and the yellow fluorescent filtrate was directly reduced catalytically in the presence of Adams' Pt (0.3 g.), 650 cc. of H_2 being absorbed, and a faint yellow non-fluorescent solution resulted. This was evaporated to dryness *in vacuo*, and the resultant orange-yellow syrup was dissolved in anhydr. EtOH. This solution was saturated with dry HCl gas and then worked up as

usual, when a faint yellow viscous oil of b.$p_{0.2}$ 210～220° was obtained. The yield of the distilled product was 7.5 g. or 43.5% based on (V). For analysis this was redistilled and the fraction of b.$p_{0.01}$ 210° was analysed. *Anal.* Calcd. for $C_{20}H_{29}O_6N$: C, 63.3; H, 7.65; N, 3.7. Found : C, 63.5; H, 7.7; N, 3.7.

Picrate : Yellow scales (from EtOH), m.p. 123～124°. *Anal.* Calcd. for $C_{26}H_{32}O_{13}N_4$: C, 51.3; H, 5.3; N, 9.2. Found : C, 51.4; H, 5.4; N, 8.9.

Ethyl 3-Oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11*b*H-benzo[*a*]quinolizine-2 (or 4)-carboxylate (VII)—NaH(1 g.) was added to a toluene (50 cc.) solution of (VI) (7 g.) and the mixture was refluxed in an oil bath in N_2 atmosphere. After ca. 20 mins. there occurred a strong effervescence and the Na compound of (VII) began to separate out. After being refluxed for 3 hrs. ice water was added carefully to the cooled reaction mixture to decompose an excess of NaH and to dissolve the Na compound of (VII). The supernatant toluene layer was separated and extracted with aq. NaOH, which was combined with the original aq. layer and filtered through a wet filter. To the clear filtrate CO_2 was now introduced to saturation, separating a crystalline solid, which was taken up in benzene, washed, dried, and the solvent was evaporated. The residue solidified on standing, which melted at 114～115°, and gave a reddish purple coloration with $FeCl_3$ in EtOH solution. The yield was 4.5 g. or 65%. When this was purified from EtOH there was obtained colorless needles (3 g.) of m.p. 127°, which no longer gave a color test with $FeCl_3$. This compound was soluble in dil. aq. NaOH. I.R. ν_{max}^{Nujol} 1658 cm^{-1} (CO-CH_2-COOEt). *Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.7; H, 6.9; N, 4.2; C_2H_5O, CH_3O 32.1. Found : C, 64.6; H, 7.1; N, 4.3; C_2H_5O, CH_3O, 31.7.

3-Oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11*b*H-benzo[*a*]quinolizine (VIII)—A mixture of (VII) (1.5 g.) and HCl (15 cc. of 18%) was refluxed in an oil bath kept at 150～160° for 12 hrs., a slow evolution of CO_2 being observed. The reaction product was diluted with H_2O, treated with carbon, and the filtrate was evaporated to dryness *in vacuo*, leaving a caramel-like residue. This was dissolved in H_2O, strongly basified with K_2CO_3, and the base liberated was collected in ether. The ethereal solution was shaken with dil. aq. NaOH to remove the phenolic base, washed, dried, and the solvent was evaporated, when an orange-colored syrup (0.3 g.) was obtained, which showed I.R. ν_{max}^{Nujol} 1718 cm^{-1} for CO-group. Characterized as a crystalline methiodide, which separated in yellow grains from MeOH-ether, m.p. 212～213°(decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_3NI \cdot H_2O$: C, 45.6; H, 5.7; N,3.3. Found : C, 45.5; H, 6.1; N, 3.1.

9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-11*b*H-benzo[*a*]quinolizine (3)—i) The foregoing crude ketone (0.25 g.), EtSH(2 cc.), and freshly fused $ZnCl_2$(0.2 g.) were mixed and the mixture was saturated with dry HCl gas. The whole was allowed to stand in a stoppered bottle at room temp. for 48 hrs. The reaction product was then basified with 10% aq. NaOH and then thoroughly extracted with benzene. The benzene layer was washed with dil. aq. NaOH, dried, and evaporated, leaving the crude diethyl-thio compound as a reddish brown syrup (0.32 g.), which was directly desulfurized. Thus the foregoing compound (0.2 g.) was dissolved in EtOH(20 cc.) and the mixture was refluxed for 10 hrs. in the presence of Raney Ni (2 g.). From the filtrate the solvent was evaporated, the residue (0.1 g.) was dissolved in dehyd. benzene, and filtered through an Al_2O_3-column. The compound (3) was obtained as a yellow oil (0.05 g.) from the benzene filtrate, which formed a well-defined picrate of m.p. 169～170° and was not depressed on admixture with an authentic picrate of (3) prepared as described in (ii).

(ii) 3,4-Dimethoxyphenethylpyridinium bromide (1): Prepared in a good yield from the two components by heating in pure benzene. A hygroscopic solid of m.p. 185～186° and was characterized more conveniently through its O-picrate, which formed yellow prisms of m.p. 132～133° from EtOH. *Anal.* Calcd. for $C_{21}H_{20}O_9N_4$: C, 53.4; H, 4.2; N, 11.8. Found : C, 53.7; H, 4.65; N, 11.5.

1-(3,4-Dimethoxyphenethyl)-2(1*H*)-pyridone (2) : The foregoing bromide (2.7 g.) in H_2O(1.5 cc.) was mixed with aq. $K_3Fe(CN)_6$ (7 g. in 50 cc. of H_2O) and then was covered with 50 cc. of benzene. This mixture was cooled and added with KOH(7 g.) in small portions with stirring. After 3 hrs.' stirring the aq. layer was extracted with benzene, which was combined with the original benzene solution, washed, dried, and evaporated. The pyridone (2) was obtained as a yellow viscous syrup (1.4 g. or 72%), which is soluble in dil. HCl. Characterized as chloroplatinate, which formed orange yellow pillars of m.p. 178～179°(decomp.) from 10% HCl. *Anal.* Calcd. for $(C_{15}H_{17}O_3N_2)_2 \cdot H_2PtCl_6 \cdot H_2O$: C, 37.9; H, 4.4; N, 2.95, Pt, 20.8. Found : C, 37.7; H, 4.6; N, 2.5; Pt, 20.6.

1-(3,4-Dimethoxyphenethyl)-2-piperidone : For the best result in the preparation of (3) the foregoing pyridone was reduced to the corresponding piperidone prior to cyclization, and this was effected by treating the compound (2) with H_2 activated over Raney Ni in EtOH solution at 40°. The piperidone distilled at 215～218°(0.08 mm) as a viscous syrup. Yield, 88%.

Chloroplatinate : Orange red plates of m.p. 110°(decomp.) from EtOH acidified with HCl. *Anal.* Calcd. for $(C_{15}H_{21}O_3N)_2 \cdot H_2PtCl_6 \cdot 2H_2O$: C, 37.1; H, 4.9; N, 2.9; Pt, 20.1. Found : C, 37.5; H, 4.7; N, 2.75; Pt, 19.3.

The piperidone (1 g.) in 10 cc. of pure toluene was refluxed with $POCl_3$(5 cc.) for 1 hr., when the product separated into two layers. Toluene and an excess of $POCl_3$ was removed *in vacuo* and the

residue obtained was dissolved in EtOH and the solution was treated with carbon. The faint yellow fluorescent filtrate[3] was now catalytically reduced over Adams' Pt (0.1 g.), when a smooth and rapid uptake of H_2 (80 cc.) took place, furnishing a nearly colorless non-fluorescent solution, which was worked up as usual. The product (0.67 g.) formed a colorless syrup, which solidified when kept in an ice chest. On being purified form petr. ether this formed colorless plates of m.p. 57°[4](yield, 72%), whose picrate separated in faint yellow prisms of m.p. 171°[5] from EtOH, which remained unchanged when admixed with the one obtained as described under (i).

3,3,9,10-Tetramethoxy-1,2,3,4,6,7-hexahydro-11*b*H-benzo[*a*]quinolizine (IX)—The above-mentioned oxo compound (Ⅷ : 0.8 g.) was dissolved in 2 g. of methyl orthoformate, the resultant solution was saturated with dry HCl gas with cooling, and then gently refluxed on a steam bath for 2 hrs. On cooling benzene (20 cc.) was added and the mixture was basified with K_2CO_3, followed by addition of H_2O with cooling and stirring. The aq. layer was extracted with two 20-cc. portions of benzene, which was combined with the original benzene layer, dried, and the solvent was evaporated, yielding a yellowish brown syrup (0.7 g.). This was dissolved in hexane, filtered through an Al_2O_3-column, and the solvent was removed from the filtrate. A yellow viscous syrup was thus obtained in a yield of 0.6 g. or 69%, which did not contain the original oxo compound as was revealed by I. R. spectrum.

Picrate : Yellow needles (from EtOH), m.p. 167~168°(decomp.). *Anal.* Calcd. for $C_{15}H_{19}ON(OCH_3)_4$: C, 51.49; H, 5.22; N, 10.45; CH_3O, 23.1. Found : C, 51.46; H, 4.85; N, 10.24; CH_3O, 22.7.

Methiodide : Colorless pillars (from MeOH), m.p. 246~247°(decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_{11}N_4 \cdot H_2O$: C, 46.25; H, 5.99. Found : C, 46.29; H, 5.99.

3,9,10-Trimethoxy-1,4,6,7(or 1,2,6,7)-tetrahydro-11*b*H-benzo[*a*]quinolizine (X)— The foregoing compound (0.5 g.) was heated in an oil bath kept at 200~210° for 2 hrs. The product was now distilled *in vacuo*, when a yellow viscous syrup came over at 210~215°(bath temp.) under 0.01 mm. This was dissolved in hexane and purified through an Al_2O_3-column. When the solvent was evaporated from the filtrate there remained 0.2 g. of yellow viscous syrup (yield, 44.7%).

Methiodide : Recrystallized from MeOH-ether in the cold. Colorless plates of m.p. 236~237° (decomp.). *Anal.* Calcd. for $C_{14}H_{15}NI(OCH_3)_3 \cdot 1\frac{1}{2}H_2O$: C, 45.95; H, 6.08; N, 3.15; CH_3O, 20.95. Found: C, 45.58; H, 5.98; N, 3.03; CH_3O, 21.90.

This compound (50 mg.) was dissolved in dil. HCl(20 cc. of 5%) and the solution was submitted to distillation. In the distillate the presence of MeOH was proved by the standard method using chromotropic acid. The residue in the flask was evaporated to dryness and its I. R. spectrum revealed the presence of CO-group ($\nu_{max}^{CHCl_3 \cdot EtOH}$ 1724 cm^{-1}).

3,9,10-Trimethoxy-1,2,3,4,6,7-hexahydro-11*b*H-benzo[*a*]quinolizine (X′)—The foregoing compound (X : 100 mg.) in MeOH(40 cc.) was reduced over Raney Ni (100 mg.) under 100 atm. pressure at 40~50° for 4 hrs. The filtrate from the catalyst was evaporated, the residue was dissolved in benzene, and filtered through an Al_2O_3-column. On distilling off the solvent there remained a colorless syrup, which solidified on standing and melted at 38~42°. This was readily soluble in most of the solvents and was difficult to purify through recrystallization. For characterization the methiodide was prepared, which formed colorless needles of m.p. 218° from MeOH-ether. *Anal.* Calcd. for $C_{14}H_{17}NI(OCH_3)_3$: C, 48.69; H, 6.20; CH_3O, 22.19. Found : C, 48.31; H, 6.15; CH_3O, 21.94,

A small portion of the compound (X′) was treated with 5% HCl as in the above case, but the presence of MeOH was not traced in the distillate. The residual solution in the flask was basified and a syrupy substance was recovered, which gave a methodide of m.p. 216~217°, identical with the one of the original compound (X′).

Ethyl 2-Methyl-N-ethoxycarbonylmethyl-N-(3,4-dimethoxyphenethyl)succinamidate (XII)—i) The compound (Ⅲ : 45.5 g.) in 200 cc. of dehyd. benzene was mixed with methylsuccinic anhydride (21 g.) and the whole was refluxed on a steam bath for 4 hrs. The reaction product was worked up as in the above case to yield an orange viscous syrup (Ⅺ), which could not be induced to crystallize. The yield was 52.1 g. When this was esterified as usual there was obtained a viscous liquid of $b.p_{0.02}$ 230~240°; yield, 35.7 g. or 52% based on (Ⅲ). For analysis this was redistilled, $b.p_{0.02}$ 218°. *Anal.* Calcd. for $C_{21}H_{31}O_7N$: C, 61.3; H, 7.8; N, 3.4. Found : C, 61.2; H, 7.6; N, 3.5.

ii) 2-Ethoxycarbonylpropionyl chloride (3.4 g.) in 30 cc. of pure ether was mixed with an ethereal solution of diazomethane, which was generated from 17 g. of nitrosomethylurea as usual. The reaction proceeded with evolution of N_2 and after being allowed to stand for 3 hrs., AcOH (2 cc.) was added to the reaction mixture in order to decompose the excess of CH_2N_2. The ethereal solution containing ethyl 2-diazoacetylpropionate (XIV) was now washed with aq. NaCl solution, dried, and directly used in the next step. Thus the compound (Ⅲ : 10.5 g.) and Et_3N (5 g.) were added to this solution, fol-

3) Gave O-picrate of 184~185°, which tallies with the description of Child and Pyman (J. Chem. Soc., **1931**, 36).

4) m.p. 61° according to Child and Pyman (*loc. cit*).

5) Also was not depressed on admixture with the specimen prepared by S. Sugasawa, S, Akaboshi, and M. Yamada (Yakugaku Zasshi, **71**, 1341(1951)).

lowed by an addition of dry silver benzoate (1 g.), and the whole was allowed to stand at room temp. for 10 mins., during which time evolution of N_2 was observed and the content became dark brown due to the separation of Ag_2O. This was refluxed for 1 hr., the ether was replaced with benzene, and was again refluxed for an additional 1 hr. Charcoal (0.5 g.) was added to the reaction mixture, filtered together with Ag_2O, and the filtrate was washed successively with 5% HCl, 10% Na_2CO_3, and H_2O, dried, and the solvent was evaporated. The residue distilled at 228~230°(0.2 mm.), forming a viscous oil, which weighed 5.3 g. or 63% based on 2-ethoxycarbonylpropionyl chloride.

1-(2-Ethoxycarbonylpropyl)-2-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIII)—The syrup (XII : 50 g.) obtained under i) was mixed with $POCl_3$(150 g.) and the mixture was refluxed in an oil bath at 120~130° for 2 hrs., resulting in a formation of a dark brown mixture. This was worked up as in the above-mentioned case and an orange red fluorescent solution was obtained. Adams' Pt (1 g.) was added to this solution and the whole was shaken in H_2 atomosphere at 50°, when 2050 cc. of H_2 was absorbed, giving a faintly colored non-fluorescent solution. The filtrate from the catalyst was evaporated to dryness *in vacuo* and the residue was esterified. A faint yellow syrup of $b.p_{0.05}$ 215~225° was obtained in a yield of 23.5 g. or 51%.

Picrate : Yellow prisms (from EtOH), m.p. 114°. *Anal.* Calcd. for $C_{27}H_{34}O_{13}N_4$: C, 52.1; H, 5.5; N, 9.0. Found : C, 51.8; H, 5.5; N, 8.8.

From the substance obtained under ii) the same compound was obtained in a like manner.

Ethyl 2-Methyl-3-oxo-9,10-dimethoxy-1.2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine-4-carboxylate (XV)—The foregoing compound (XIII : 9.8 g.) in pure toluene (60 cc.) was mixed with NaH(1.5 g.) and the whole was refluxed for 2 hrs. in an oil bath kept at 120°. After about 15 mins. a strong effervescence took place, followed by separation of Na compound of (XV). The reaction product was worked up as in the model case and thus the crude (XV) was obtained as a solid in a yield of 4.4 g. or 50.7%. This was purified from EtOH, forming colorless needles of m.p. 122.5°. I.R. ν_{max}^{Nujol} 1649 cm^{-1}(CO-CH_2-COOEt). *Anal.* Calcd. for $C_{19}H_{25}O_5N$: C, 65.6; H, 7.2; N, 4.0, Mol. wt., 347.5. Found : C, 65.7; H, 7.2; N, 4.1; Mol. wt., 343.5 (Micro-Rast.).

2-Methyl-3-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine (XVI)—A mixture of the keto-ester (XV : 7 g.) and 50 cc. of 18% HCl was refluxed in an oil bath kept at 170~180° for 25 hrs., and was worked up as was mentioned before. Yellow caramel-like residue thus obtained was dissolved in H_2O, basified with K_2CO_3, and the base that separated was collected in benzene, which was shaken thoroughly with dil. NaOH to remove the phenolic base. From the benzene solution there was obtained an orange caramel-like residue in a yield of 1.4 g. I.R. ν_{max}^{Nujol} 1722 cm^{-1}(-CO group). Characterized as a crystalline methiodide, which formed faint yellow prisms of m.p. 230~231°(decomp.) from MeOH-hexane. *Anal.* Calcd. for $C_{17}H_{24}O_3NI$: C, 48.9; H, 5.7; N, 3.4, CH_3O, 14.75. Found : C, 48.9; H, 6.0; N, 3.1; CH_3O 14.9.

2-Methyl-3,3,9,10-tetramethoxy-1,2,3,4,6,7-hexahydro-11*bH*-benzo[*a*]quinolizine (XVII)—A mixture of the foregoing ketone (0.3 g.), methyl orthoformate (1 g.), and 1 cc. of dehyd. MeOH was saturated with dry HCl gas. The whole was now kept in a stoppered bottle for 24 hrs. and then warmed at 50~60° for 3 hrs. The reaction mixture was worked up as in the model case and thus there was obtained a yellowish viscous syrup in a yield of 0.2 g., whose methiodide came in faint yellow grains of m.p. 242°(decomp.) from MeOH-hexane and showed no CO absorption in its I.R. spectrum. *Anal.* Calcd. for $C_{19}H_{24}O_4NI \cdot \frac{1}{2}H_2O$: C, 48.2; H, 6.55; N, 3.0. Found : C, 48.5; H, 5.9; N, 2.8.

2-Methyl-3,9,10-trimethoxy-1,4,6,7(or 1,2,6,7)-tetrahydro-11*bH*-benzo[*a*]quinolizine (*rac*-Dihydrorotundine) (I)—The compound (XVII : 0.15 g.) was submitted to distillation *in vacuo*, giving a faint yellow oil, which came over at 185~195° under 0.02 mm. (bath temp.). The yield was 0.08 g. This gave a distinct orange yellow coloration with $C(NO_2)_4$ and decolorized $KMnO_4$ in acetone immediately. I.R. ν_{max}^{Nujol} 1656 cm^{-1}(weak)(-C=C-). *Anal.* Calcd. for $C_{14}H_{14}N(OCH_3)_3$: CH_3O, 32.1. Found : CH_3O, 30.9.

Methiodide : Colorless prisms of m.p. 246~247°(decomp.) from MeOH-benzene. *Anal.* Calcd. for $C_{15}H_{17}NI(OCH_3)_3 \cdot \frac{1}{2}H_2O$: C, 49.1; H, 6.1; N, 3.2; CH_3O, 21.2. Found : C, 48.8; H, 6.1; N, 3.2; CH_3O, 21.6.

Summary

A synthesis of *rac*-dihydrorotundine (I) was described. Methylsuccinic anhydride was condensed with ethyl 3,4-dimethoxyphenethylaminoacetate to yield a single methylsuccinamic acid (XI), having the methyl substituent β to the amido group. This was esterified, cyclized, and reduced, and thus the tetrahydroisoquinoline base (XIII) was obtained. Dieckmann cyclization of the latter by means of sodium hydride in boiling toluene gave a fair yield of the keto-ester (XV), but its ketonic fission proceeded with difficulty and thus the ketone (XVI) was produced only in a low yield. When dimethyl

ketal (XVII) of (XVI) was submitted to distillation *in vacuo* a loss of one molecule of methanol took place and *rac*-dihydrorotundine (I) was collected as a viscous distillate, which was characterized as its crystalline methiodide. *rac*-Dihydro-norrotundine (X) was also prepared as a model substance and its behavior towards catalytic hydrogenation was studied.

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66. Torizo Takahashi und Fumio Yoneda: Über die Synthese der heterozyklischen Verbindungen mit Stickstoff. CXII.[1] Synthese der Derivate des Oxypyridins.

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Seit Pechmann und Baltzer[2] berichtet haben, dass sich 2-Methoxypyridin neben N-Methyl-2-pyridon beim Schütteln des 2-Pyridon-silbersalzes (I) mit ätherischer Jodmethyllösung ergibt und dass sich nur 2-Äthoxypyridin aus (I) und Jodäthyl analogerweise wie oben erhalten lässt, finden sich über die Reaktion des Silbersalzes des Pyridons in der Literatur keine weiteren Unterlagen.

In der vorliegenden Mitteilung berichten wir nun über die Ergebnisse, die wir bei der Reaktion von aktivierten Halogenverbindungen mit 2- sowie 4-Pyridon-silbersalz erhalten haben.

Das nach dem Pechmann'schen Verfahren[2] hergestellte 2-Pyridon-silbersalz (I) lieferte in der Äthanollösung durch Einwirkung von Phenacylbromid das 2-Phenacyloxy-pyridin (II) in guter Ausbeute. Das so erhaltene (II) unterscheidet sich von dem in der Literatur beschriebenen N-Phenacyl-2-pyridon (III)[3] im Schmelzpunkt sowie auch deutlich bezüglich seines UV-Spektrums. Auf Grund der Untersuchung der Absorptions-spektren des Pyridons durch Specker[4] wird im allgemeinen angenommen, dass das Maximum des langwelligen Bandes vom Äther-typus um etwa 30 mμ kurzwelliger ist als das vom Pyridon-typus und dass auch die gesamte Kurve vom Äther-typus schmaler erscheint.

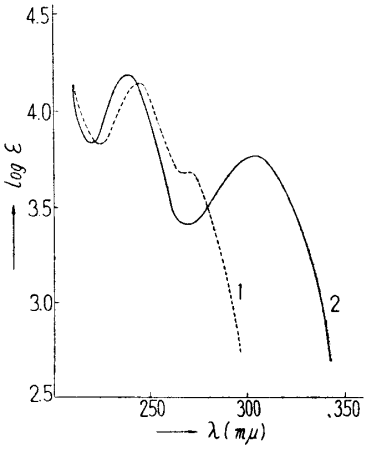

Fig. 1.

1. 2-Phenacyloxy-pyridin
2. N-Phenacyl-2-pyridon (in abs. EtOH)

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1) CXI. Mitt.: Yakugaku Zasshi, **78**, 467(1958).
2) H. von Pechmann, O. Baltzer: Ber., **24**, 3144(1891).
3) F. Kröhnke, W. Heffe: *Ibid.*, **70**, 877(1937).
4) H. Specker, H. Gawrosch: *Ibid.*, **75**, 1341(1942).