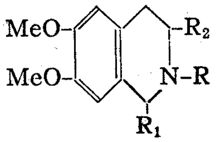
i) Amines : Phenethylamine and 3,4-dimethoxyphenethylamine colored dark reddish and soon formed a deeply colored precipitate; aniline, light purple; N-methylaniline, deep blue; N,N-dimethylaniline, light blue; diphenylamine, faint blue.

ii) Tetrahydroisoquinolines : Color changed from light brown to greenish brown, but no appreciable consumption of chloranil.

Isoquinolines tested :



R	Me	H	H	Me	H	Me
R_1	H	H	$ArCH_2$	$ArCH_2$	H	$ArCH_2CH_2$
R_2	H	H	H	H	$ArCH_2CH_2$	H

iii) Tetrahydroquinolines : Chloranil disappeared (Ⅷ; R=H, Me). UV of (Ⅷ; R=H) showed blue-shift, λ_{max}^{EtOH} 314, 327 mμ.

b) EtOH solution of hydroxyl derivatives : 6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline and its N-methyl derivative were nearly unchanged on exposure. (Ⅸ; R=H, Me) became immediately reddish purple and formed a deeply colored precipitate. (Ⅹ) nearly unchanged.

UV absorption spectra of 6,7-Dimethoxy-1,2,3,4-tetrahydroquinoline derivatives : UV λ_{max}^{EtOH} mμ (log ε) : (Ⅷ; R=H), 242(3.91), 304(3.60); (Ⅷ; R=Me), 251(3.77), 309(3.40). Hydrochloride of (Ⅷ; R=Me), 250.5(3.91), 307(3.53). Methiodide of (Ⅷ), 280(3.66).

Summary

3-Substituted tetrahydroisoquinoline (Ⅶ) was oxidatively cyclized to form dibenzoquinolizine derivative (Ⅳ). Some related aspects of the Robinson dehydrogenation reaction were discussed.

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109. **Yuichi Kanaoka** : Application of the Robinson Dehydrogenation Reaction. IV.[1] Oxidation of Some Tetrahydro-β-carboline Derivatives.

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In the preceding paper of this series,[1] the application of this oxidative cyclisation on several cyclic and non-cyclic amines was reported.

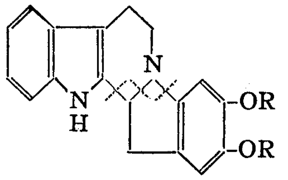
Reports concerning the Robinson dehydrogenation reaction,[1,2] including the one cited above, all have dealt with aliphatic amines, both cyclic and non-cyclic, and none of aromatic or heteroaromatic amines being shown to be used successfully. It is likely, therefore, that this reaction is applicable most satisfactorily to compounds containing an aliphatic nitrogen atom.

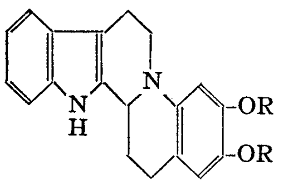
In the course of extensive study of this reaction, some 2-substituted tetrahydro-β-carbolines (Ⅲ, Ⅴ, Ⅵ, Ⅶ) were selected for examination. Since these compounds were regarded as aliphatic amine derivatives, they were expected to lead to (Ⅰ) and (Ⅱ) by the oxidative cyclisation.

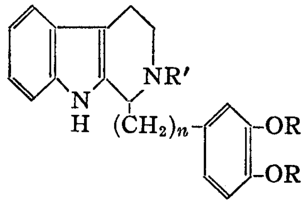
[*1] Kita-12-jo, Nishi-5-chome, Sapporo (金岡祐一).

[1] Part Ⅲ : Y. Kanaoka : This Bulletin, **7**, 595 (1959).

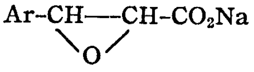
[2] Y. Kanaoka : This Bulletin, **7**, 589 (1959), and many works cited therein.


(I)

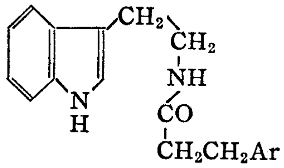

(II)

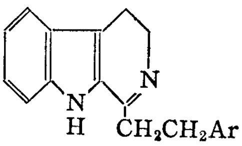


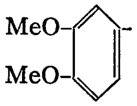
	n	R'
(III)	1	H
(IV)	1	CHO
(V)	1	Me
(VI)	2	H
(VII)	2	Me


$\mathrm{Ar{-}}\underbrace{\mathrm{CH{-}CH}}_{\mathrm{O}}\mathrm{{-}CO_2Na}$

(VIII)


(IX)


(X)

Ar =


(III) was prepared according to the method of Robinson,[3] but was also obtained by the reaction of tryptamine hydrochloride and sodium glycidate (VIII). The latter was expected to offer a new route for synthesis of 1-substituted tetrahydro-β-carbolines.

(III) was formylated to (IV) and this was reduced to (V). (IX), obtained by heating the corresponding salt, was cyclized as usual to (X). This and its methiodide were respectively reduced to (VI) and (VII).

Attempted cyclization of (III; R=H) or (V; R=H) to produce (I) was unsuccessful in spite of the biogenetic possibility that (I) might be led *in vivo* from one mole each of tryptophan and phenylalanine equivalent, as shown dissected by dotted lines in (I).

However, oxidation of (VI; R=H) and (VII; R=H) gave smoothly the same methiodide (XI). Ultraviolet absorption spectral data revealed that (XI) was not the expected meth-

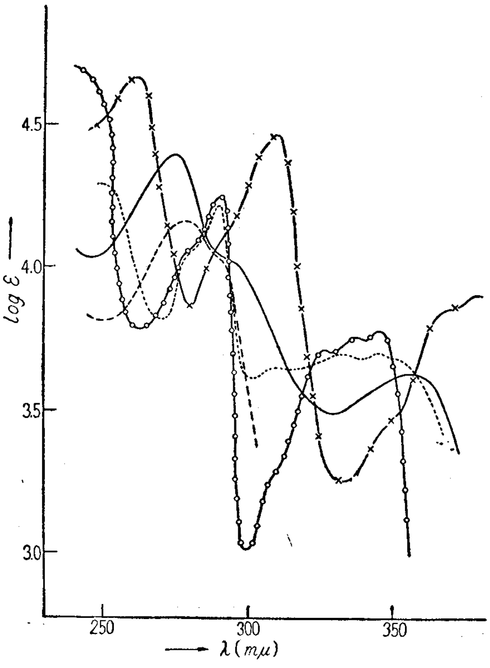


Fig. 1.

Ultraviolet Absorption Spectra (in 95% EtOH)

—o—o— (XII)
—x—x— Methochloride of (XII)
············ Dehydration product of (X)
------ Methiodide of (VII)
———— (XI) in a), b), c)
(see Experimental section)

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[3] K. T. Potts, R. Robinson: J. Chem. Soc., **1955**, 2675.

[4] cf. R. Robinson: "The Structural Relations of Natural Products" (1955). Clarendon Press, Oxford University.

iodide of the base (II), arising from the simple oxidative cyclization, but had some additional unsaturation in its molecule as shown in Fig. 1.

The possibility that the base (VI or VII) should suffer alternative oxidation apart from normal cyclization to form the dihydro- or true β-carboline derivatives was discounted from the following facts : First, ultraviolet absorption spectrum of (XI) remained unchanged when it was measured alone in ethanol, in 0.01*N* KOH-ethanol solution, or after treatment with sodium borohydride, thereby showing that the pyridine-nitrogen atom in (IX) was not involved in unsaturation. Second, the above spectrum of (XI) was clearly different from that of methochloride of yobyrine (XII),[5] whose spectrum is similar to that of crude dehydrogenation product of (X). The one of methiodide of (X) also differed from that of (XI) as shown in Fig. 1. Third, when treated with chloranil, (VI; R=Me) did not react appreciably, most of the reagent being recovered. It was shown, therefore, that free hydroxyl groups in (VI or VII; R=H) are likely to participate in the reaction to form (XI). Finally, the color change in the course of oxidation of (VI) or (VII) proceeded along the characteristic mode of the oxidative cyclization.[6]

On the above basis, (XI) was proposed to be methiodide of (II) involving more unsaturation in it as the result of initial cyclization and successive dehydrogenation. The location and number of double bond were yet inconclusive.

The author wishes to express his deep gratitude to Prof. S. Sugasawa of the University of Tokyo for his unfailing guidance throughout this work. He is also grateful to Prof. Y. Ban for his encouragement, to Mr. M. Terashima for his kind cooperation, and to Messrs. T. Kimura, T. Ohishi, and O. Yonemitsu for the measurement of ultraviolet and infrared spectra. He is also indebted to Mr. K. Narita of this Institute, and to the members of Analytical Room of Tokyo Research Laboratory, Tanabe Seiyaku Co. Ltd., for microanalytical data. This work was supported partly by a Grant-in-Aid for Developmental Scientific Research from the Ministry of Education, to which the author is indebted.

Experimental

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-β-carboline (III; R=Me)—a) From 3,4-dimethoxyphenylpyruvic acid : Tryptamine hydrochloride[7] and pyruvic acid were heated according to the method of Robinson[3][*2] to give hydrochloride of (III) as colorless needles (from MeOH-Et_2O), m.p. 235~236° (reported,[3] m.p. 236°). *Anal.* Calcd. for $C_{20}H_{22}O_2N_2 \cdot HCl$: C, 66.94; H, 6.42; N, 7.80. Found : C, 66.8, 67.0; H, 6.4, 6.3; N, 8.15, 7.7. UV $\lambda^{\mathrm{EtOH}}_{\mathrm{max}}$ mμ($\log \varepsilon$) : 278(4.04), 287.5(3.89).

This salt was dissolved in a large amount of hot water, cooled quickly, and basified with dil. NH_4OH. The separated white precipitate was collected and washed. (III), colorless prisms (from benzene-hexane), m.p. 130~131° (reported,[3] m.p. 91° (from Et_2O-petr. ether), m.p. 98° (from water); m.p. 98°[8]). *Anal.* Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found : C, 74.8, 74.5; H, 6.95, 7.0; N, 9.0, 8.7. UV $\lambda^{\mathrm{EtOH}}_{\mathrm{max}}$ mμ($\log \varepsilon$) : 280(4.15), $\lambda^{\mathrm{EtOH}}_{\mathrm{min}}$: 250(3.55) (reported,[3] $\lambda^{\mathrm{MeOH}}_{\mathrm{max}}$ mμ($\log \varepsilon$) : 225 (4.49), 280(4.04), $\lambda^{\mathrm{MeOH}}_{\mathrm{min}}$: 245(3.52)).

b) From sodium 3,4-dimethoxyphenylglycidate : The glycidate[10] (4.2 g.) was dissolved quickly in

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[*2] Though m.p. of the base was different from that of the reported one, there were several evidences indicating that the base had the structure (III). This was concluded from the following facts : i) Analytical data, UV data, and the nature of the hydrochloride which were in accordance with those reported by Robinson.[3] ii) By treating with HCHO, the hydrochloride (m.p. 257~262°) corresponding to benzindolopyridocoline derivative was obtained (reported,[3] m.p. 276°; in a crude state, m.p. 263°). iii) The base was identical with the sample liberated from the hydrochloride kindly supplied by Mr. M. Kawanishi[9] who had followed the method of Robinson.[3] IV) The same base was obtained from another route described in b).

5) E. Schlittler, *et al.* : Helv. Chim. Acta, **32**, 415(1949); **34**, 629(1951); **35**, 29(1952); Ann., **554**, 129 (1943).
6) Y. Kanaoka : This Bulletin, **7**, 589(1959).
7) J. Thesing, F. Schulde : Ber., **85**, 324(1952).
8) G. Hahn : *Ibid.*, **71**, 2192(1938).
9) M. Onda, M. Kawanishi : Yakugaku Zasshi, **76**, 966(1956).
10) Y. Ban, T. Oishi : This Bulletin, **6**, 574(1958).

water (200 cc.). To the solution, solution of tryptamine hydrochloride (3 g.) in water (50 cc.), then 10% HCl (7 cc.) and AcOH (7 cc.) were added immediately. CO_2 evolved and the mixture became turbid. The whole was decanted from a small amount of resinous substance and kept at 36° overnight, then in a refrigerator for 24 hr. Separated yellowish white solid was collected (2.9 g.) and purified from MeOH-Et_2O to the salt as colorless needles, m.p. 235°. This salt and the base liberated from it were identical with the hydrochloride of (III) and (III), respectively, by mixed m.p. test.

1-(3,4-Dimethoxybenzyl)-2-formyl-1,2,3,4-tetrahydro-β-carboline (IV)—(III) (3 g.) was heated with formamide (12 g.) at 180° (oil-bath temp.) for 5 hr. After cool, hydr. MeOH was added and the separated crystals were purified from 50% EtOH to colorless needles of m.p. 184~185° (2.4 g.) *Anal.* Calcd. for $C_{21}H_{22}O_3N_2$: C, 71.98; H, 6.33; N, 8.0. Found : C, 71.9; H, 6.4; N, 7.5. IR ν_{Nujol} 1645 cm^{-1}(NC=O).

1-(3,4-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline (V)—To a solution of (IV) (1.9 g.) in dehyd. tetrahydrofuran (100 cc.) a suspension of $LiAlH_4$ (0.4 g.) in dehyd. tetrahydrofuran (50 cc.) was added under cooling and stirring. After refluxing for 7 hr., calculated amount of water was added carefully, the solvent removed *in vacuo*, and the residue was taken up in $CHCl_3$. On removal of $CHCl_3$ (V) was obtained as faintly colored syrup (1.5 g.).

Methiodide : A mixture of crude (V) (0.1 g.) and MeI (2 moles) in acetone was allowed to stand in a sealed tube at a room temp. for 2 days. Separated crystals were collected and purified from MeOH-Et_2O forming colorless needles of m.p. 180°. *Anal.* Calcd. for $C_{22}H_{27}O_2N_2I$: N, 5.85. Found : N, 5.5.

Oxidation of (III: R=H) and (V: R=H)—Hydrobromides of (III: R=H) and (V : R=H) were obtained as usual by means of 48% HBr. On oxidation color of the reaction mixture deepened without any fading, but there was nothing definite formed in spite of much elaboration. From (III; R=H), minor amount of reddish crystals of m.p. 198~202°(decomp.) were obtained, but this was not examined further.

N-[2-(3-Indolyl)ethyl)]-β-(3,4-dimethoxyphenyl)propionamide (IX)—A solution of tryptamine (3.6 g.) in benzene (50 cc.) was added to a solution of 3-(3,4-dimethoxyphenyl)propionic acid (5.2 g.) in hot benzene (150 cc.) and the whole was warmed for 10 min. on a steam bath. After cool, separated crystals were collected (7.1 g.). The salt, purified from MeOH, formed colorless pillars of m.p. 161~163°. *Anal.* Calcd. for $C_{10}H_{12}N_2 \cdot C_{11}H_{14}O_4$: N, 7.56. Found : N, 7.2.

The above crude salt (5 g.) was heated at 180° (oil-bath temp.) for 30 min., and *in vacuo* for 5 min. After cool, the mixture was extracted with $CHCl_3$, washed with dil. HCl, dil. NaOH, and water, dried, and evaporated. (IX) formed colorless needles (from aq. EtOH), m.p. 84~86° (4.1 g.). *Anal.* Calcd. for $C_{21}H_{24}O_3N_2 \cdot \frac{1}{2}H_2O$: C, 69.80; H, 6.92; N, 7.96. Found : C, 70.1; H, 6.8; N, 7.65. IR ν_{Nujol} 1626 cm^{-1} (NC=O).

1-(3,4-Dimethoxyphenethyl)-3,4-dihydro-β-carboline (X)—(IX) (5 g.) was dissolved in hot dehyd. benzene (60 cc.), $POCl_3$ (25 cc.) was added, and the whole was warmed on a steam bath for 1.5 hr. Solvent was removed *in vacuo*, the residue was treated with dil. NH_4OH, extracted with $CHCl_3$, and evaporated, leaving a brownish oil (5 g.). Methiodide : A mixture of (X) (4 g.) and MeI (3.5 g.) in acetone (20 cc.) was allowed to stand for 1 day. Separated methiodide was collected and washed with acetone to 3.6 g. of yellow needles (from MeOH-Et_2O), m.p. 225~226°(decomp.). *Anal.* Calcd. for $C_{22}H_{25}O_2N_2I$: C, 55.45; H, 5.29; N, 5.89. Found : C, 55.7; H, 5.4; N, 6.4. UV $\lambda_{\max}^{\text{EtOH}}$ mμ(log ε) : 250.5 (4.05), 275(3.54), 355(4.35).

1-(3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydro-β-carboline (VI)—To a solution of (X) (6 g.) in MeOH (40 cc.) a solution of $NaBH_4$ (5 g.) in MeOH (80 cc.) was added under ice-cooling and stirring. The color of the reaction mixture changed to faint yellow with evolution of H_2. After stirring for 1 hr. at room temp., it was warmed on a steam bath for 0.5 hr., the solvent was removed *in vacuo*, and taken up in $CHCl_3$. The extract was washed with water and dried. On removal of $CHCl_3$, (VI) was obtained as slightly colored syrup (5.1 g.). Colorless needles (from benzene-hexane), m.p. 103~106°. *Anal.* Calcd. for $C_{21}H_{24}O_2N_2$: N, 8.33. Found : N, 8.35.

Hydrochloride : Colorless needles (from MeOH-Et_2O), m.p. 240~242°. *Anal.* Calcd. for $C_{21}H_{24}O_2N_2 \cdot HCl$: C, 66.45; H, 6.65; N, 7.51. Found : C, 67.0; H, 6.7; N, 7.45. UV $\lambda_{\max}^{\text{EtOH}}$ mμ(log ε) : 279(4.09), 288(3.92).

1-(3,4-Dimethoxyphenethyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline (VII)—A suspension of the methiodide of (X) (3.5 g.) in MeOH (80 cc.) was reduced with a solution of $NaBH_4$ (3.5 g.) in MeOH (30 cc.) as in the case of (VI) to give 2.8 g. of (VII) as slightly yellow prisms (from benzene-hexane), m.p. 142~143°. *Anal.* Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.40; H, 7.48; N, 7.99. Found : C, 75.25; H, 7.4; N, 8.0. UV $\lambda_{\max}^{\text{EtOH}}$ 280 mμ(log ε 4.11).

Methiodide : Faintly yellow prisms (from MeOH-Et_2O), m.p. 174~175°. *Anal.* Calcd. for $C_{23}H_{29}O_2N_2I$: C, 56.09; H, 5.9; N, 5.70. Found : C, 56.05; H, 5.9; N, 5.6. UV $\lambda_{\max}^{\text{EtOH}}$ mμ : 279, 288.

Oxidation of (VI : R=H) and (VII : R=H); 2,3-Dimethoxy-5-methyl-5,6,7,12b,13,14-heyahydro-12*H*-benz[*f*]indolo[2,3-*a*]quinolizinium Iodide (VIII); Methiodide of the Derivative of (II)—(VI : R=H) and (VII : R=H) were prepared as usual. i) Hydrobromide of (VI : R=H) (pale yellow fine needles, m.p. ca. 310°(decomp.); 1.6 g.) was mixed with AcOK (0.5 g.) and EtOH (40 cc.), warmed, and filtered. To this clear solution a suspension of chloranil (0.75 g.) in EtOH (250 cc.) was added under stirring. Reddish brown coloration appeared on addition and disappeared readily (positive color change).[6] Addition was continued until a permanent reddish coloration was realized. After standing for 1 hr., 10% HCl (5 cc.) was added and the solvent was evaporated *in vacuo*. The residue was extracted with water (15 cc., 3 times), filtered, and evaporated *in vacuo* to leave a solid (1.5 g.). The residue (0.8 g.) was suspended in water (10 cc.), KOH solution (5 cc., 33%) was added, and the mixture shaken until a clear solution resulted. Me_2SO_4 (2 cc.) was then added and the whole was shaken vigorously. After this procedure (aq. K_2CO_3 4 cc., 33% and Me_2SO_4, 2 cc.) was repeated twice, K_2CO_3 solution (10 cc., 33%) was added, shaken and warmed on a steam-bath for 5 min. After cool, the separated product was taken up in $CHCl_3$, $CHCl_3$ layer was extracted with water (30 cc., 3 times), and the combined aqueous layer was filtered. KI (3 g.) was added to this and kept in a refrigerator overnight to separate an amorphous solid. This was collected, washed with water, dried in a desiccator, and recrystallized from $MeOH-Et_2O$ to pale yellow prisms of m.p. 188~191°(decomp.) (0.4 g.) (over-all yield of oxidation, 44%).

Methiodide of (II : ╒). *Anal.* Calcd. for $C_{22}H_{23}O_2N_2I$ (╒$_1$) : C, 55.58; H, 4.85; N, 5.91. Found : C, 55.1; H, 4.9; N, 6.0. UV λ_{max}^{EtOH} mμ(log ε) : 273(4.40), 296(4.01), 355(3.60).

ii) Hydrobromide of (VII : R=H) (1.2 g.) was treated with AcOK (0.5 g.) and chloranil (0.6 g.) as in the case of (VI : R=H), whereby the color change was positive. After methylation, the methiodide was obtained as pale yellow prisms (from $MeOH-Et_2O$), m.p. 189~192°(decomp.), in 37% yield (0.45 g.). *Anal.* Found : C, 55.9; H, 5.35; N, 5.5. This methiodide was shown to be identical with the one obtained above by mixed m.p. test and comparison of IR and UV spectra.

UV absorption of the methiodide—a) In 95% EtOH. b) The methiodide (2.4 mg.) was dissolved in 95% EtOH (10 cc.). To this was added $NaBH_4$ (5 mg.) and the whole was allowed to stand for 30 min. and diluted (20 ×). c) In 0.01*N* KOH-EtOH solution.
All UV absorption spectra measured in different solutions of a), b), and c), gave almost entirely the same curve.

Preliminary test of (VI : R=Me)—To a mixture of (VI : R=Me) (0.2 g.), EtOH (10 cc.), and AcOH (0.2 g.), a suspension of chloranil (0.14 cc.) in EtOH (50 cc.) was added under stirring. After 30 min.'s stirring, unreacted chloranil was recovered by filtration (89%).

Dehydrogenation of (X)—An intimate mixture of powdered (X) (0.2 g.) and Pd-black (0.2 g.) was heated at 200° (oil-bath temp.) for 30 min. A small amount of EtOH was added, filtered, and evaporated *in vacuo* to leave a crude dehydrogenated product. UV λ_{max}^{EtOH} mμ(log ε) : 250(4.28), 282(4.06), 288.5(4.17), 334(3.70).

Summary

In the course of extensive studies on the Robinson dehydrogenation reaction, 1-(3,4-dihydroxybenzyl)- and 1-(3,4-dihydroxyphenethyl)-1,2,3,4-tetrahydro-β-carbolines (III and VI) and their N-methyl derivatives (V and VII) were oxidized. Though (III) and (V) failed in giving any definite result, (VI) and (VII) gave the same oxidation product (XI), to which was assigned the structure (II) involving additional unsaturation.

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