UDC 547.837.2.07

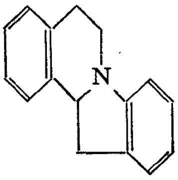
108. **Yuichi Kanaoka** : Application of the Robinson Dehydrogenation Reaction. III.[1] Synthesis of 2,3,9,10-Tetramethoxy-5,6,6a,7,12,13-hexahydro-13-methyldibenzo[*b,f*]quinolizinium Iodide.

(*Pharmaceutical Institute, Medical School, University of Hokkaido**)

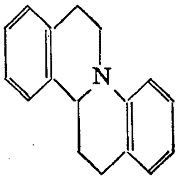
Of alicyclic nitrogen compounds to which the Robinson dehydrogenation reaction had been applied, tertiary amines of tetrahydroisoquinoline type submitted most successfully to result in the formation of several dibenzo-quinolizine[2] and indolizine[3] derivatives, ring systems of which are shown by formulae (I) to (III).

It became possible, therefore, that suitable 3-substituted tetrahydroisoquinoline might be cyclized to form dibenzo-quinolizine derivative.

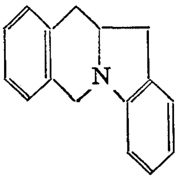
Now this was examined and the compound (IV) mentioned in the title was obtained. Synthesis of (IV) had been described by Sugasawa *et al.*[4] many years before in their synthetic study by another route.



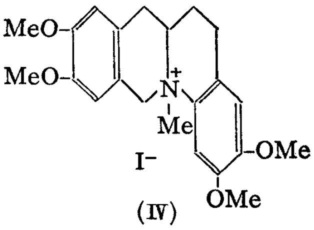
(I)



(II)



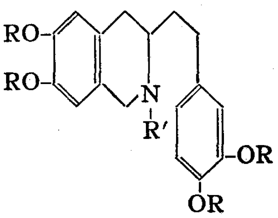
(III)



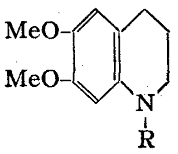
(IV)

3-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V)[5] was formylated to give (VI), which was reduced with lithium aluminum hydride to the N-methyl derivative (VII).

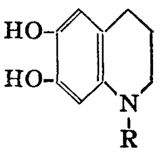
Oxidation of (V; R=H) proceeded with color-deepening but gave no definite result. On oxidation (VII; R=H) afforded the cyclized base (IV) in a good yield after methylation while showing the color change characteristic to the favored Robinson dehydrogenation reaction.[1]



(V); R'=H
(VI) =CHO
(VII) =Me



(VIII)



(IX)

It should be noted that the secondary and tertiary amines behaved in such a different manner upon application of this oxidation reaction. In the hope of clarifying this, some tetrahydroquinolines (VIII), their demethylated derivatives (IX), and methiodide (X) of

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

1) Part II : This Bulletin, **7**, 589(1959).

2) S. Sugasawa, Y. Yoshikawa : J. Chem. Soc., **1934**, 1538.

3) R. Robinson, S. Sugasawa : *Ibid.*, **1932**, 789; S. Sugasawa, K. Kodama : Proc. Imp. Acad. (Tokyo), **17**, 102(1941).

4) S. Sugasawa, K. Kodama, K. Inagaki : Yakugaku Zasshi, **61**, 491(1941).

5) Y. Kanaoka, M. Terashima, T. Kimura : This Bulletin, **7**, 648(1959).

(IX) were qualitatively compared by exposure to the air or treatment with chloranil.

Although (VIII) and (X) did not show any change on exposure to air in ethanol solution, (IX; R=H, Me) was unstable in the air becoming immediately reddish violet and formed a resinous precipitate. In addition, (VIII; R=H) was susceptible to oxidation with chloranil to form quinoline derivative, in contrast to the relative stability of isoquinoline derivatives.

Based on this preliminary examination, the most probable explanation for the above difference is as follows: The system of (IX)-type formed from the secondary amine as the result of cyclization is so unstable that the product cannot be isolated owing to some secondary oxidation. On the other hand, the system of (X)-type from the tertiary amine is rather stable thus resulting in a good yield of a product. This observation is also in agreement with the observation of Sugasawa who had pointed out the relative unstability of dibenzoquinolizine compounds containing tetrahydroquinoline system in their structure.[6)]

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 encouragement, to Messrs. M. Terashima and T. Kimura for technical cooperation, and to Mr. K. Narita of this Institute and members of Analytical Room of Tokyo Research Laboratory, Tanabe Seiyaku Co. Ltd., for microanalytical data.

Experimental

2-Formyl-3-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI)—(V)[5)] (5 g.) was refluxed with formamide (8 g.) at 175~185° (oil-bath temp.) for 4 hr. After cool, water was added to the reaction mixture, the separated oil was taken up in $CHCl_3$, washed with dil. HCl and then water, and evaporated. (VI) was obtained as colorless prisms (from hydr. MeOH), m.p. 116~117°; yield, 4.2 g. *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 68.55; H, 7.57; N, 3.63. Found: C, 68.0; H. 7.0; N, 3.4. IR: 1652 cm^{-1} (NC=O).

2-Methyl-3-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII)—To a solution of (VI) (4 g.) in tetrahydrofuran (150 cc.) $LiAlH_4$ (0.8 g.) suspended in dehyd. Et_2O (50 cc.) was added under cooling and stirring. After 7 hr.'s refluxing, calculated amount of water was added, the solvent removed *in vacuo*, and the residue was taken up in Et_2O. The Et_2O layer was extracted with dil. HCl, aqueous layer was basified (NaOH), K_2CO_3 added, and extracted with a large amount of Et_2O (3×100 cc.). Crystals that separated on removal of Et_2O were collected and purified from Et_2O or benzene-hexane, forming colorless needles, m.p. 87~88°; yield, 3.9 g. or 96%. *Anal.* Calcd. for $C_{22}H_{29}O_4N$: C, 71.11; H, 7.86; N, 3.76. Found: C, 71.1; H, 7.8; N, 4.0. UV λ_{max}^{EtOH} mμ(log ε): 280.5 (3.90), 285(3.86). Hydrochloride: hygroscopic.

Methiodide: Colorless needles (from EtOH-Et_2O), m.p. 217~218°. *Anal.* Calcd. for $C_{23}H_{32}O_4NI$: C, 53.78; H, 6.29; N, 2.72. Found: C, 53.7; H, 6.2; N, 2.5.

Oxidation of (V)—(V; R=H) was demethylated as usual and this was oxidized. Reddish violet coloration appeared and kept deepening (negative), giving no definite product after methylation.

Oxidation of (VII; R=H); 2,3,9,10-Tetramethoxy-13-methyl-5,6,6a,7,12,13-hexahydrodibenzo-[*b,f*]quinolizinium Iodide (IV)—(VII; R=Me) was demethylated as usual giving the hydrobromide of (VII; R=H) as colorless needles (from water), m.p. 180~181°. *Anal.* Calcd. for $C_{18}H_{22}O_4NBr \cdot H_2O$: C, 52.20; H, 5.84; N, 3.33. Found: C, 52.3; H, 5.9; N, 3.7.

This salt (2.2 g.) was mixed with AcOK (0.5 g.) and EtOH (90 cc.), warmed, and filtered. To this solution was added a suspension of chloranil (1 g.) in EtOH (250 cc.) under stirring over a period of 1.5 hr. Reddish brown coloration appeared and disappeaed readily. Separation of the product commenced when about 1/5 of the reagent had been introduced and towards the end of the addition the coloration was more persistent, finally giving a reddish solution. After 4 hrs.' standing, the gray precipitate was collected (2.1 g.) and this was methylated with Me_2SO_4 as usual to form the methiodide as pale-yellow fine needles (from MeOH-Et_2O), m.p. 194~195°(decomp.), with an over-all yield of 47% (reported[4)] m.p. 197~198°(decomp.)). *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.11; H, 5.67; N, 2.82. Found: C, 52.7; H, 5.8; N, 2.9. UV λ_{max}^{EtOH} mμ(log ε): 281(3.93).

Preliminary Tests of Amines—a) With chloranil: To a solution of the amine (0.2 g.) in EtOH (10 cc.), AcOH (0.2 g.) and then a suspension of chloranil (0.14 g.) in EtOH (50 cc.) were added.

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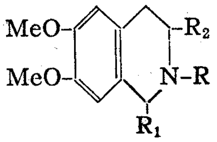
6) S. Sugasawa, N. Sugimoto: Proc. Imp. Acad. (Tokyo), **18**, 658(1942).

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.