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101. Yuichi Kanaoka, Miwako Ochiai, and Yoshio Ban: A Synthesis of Dibenzo(*a*, *h*)quinolizidine System by way of Immonium Salt Intermediate.

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A mixture of 3,4-dihydroisoquinoline derivative and 3,4-dimethoxyphenethyl bromide afforded dibenzo(*a*, *h*)quinolizidine derivative in one step by heating. This cyclization was interpreted in terms of electrophilic reactivity of immonium salt intermediate.

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The formation of pavine (IV) during the reduction of papaverine (I) with tin and hydrochloric acid was reasonably explained by Battersby, *et al.*[1a,b] by a mechanism which involves protonation of 1,2-dihydropapaverine (II) produced initially by partial reduction of I and the subsequent ring-closure of the resultant immonium salt (III) as shown in the equation. The important feature of this process is the electrophilic

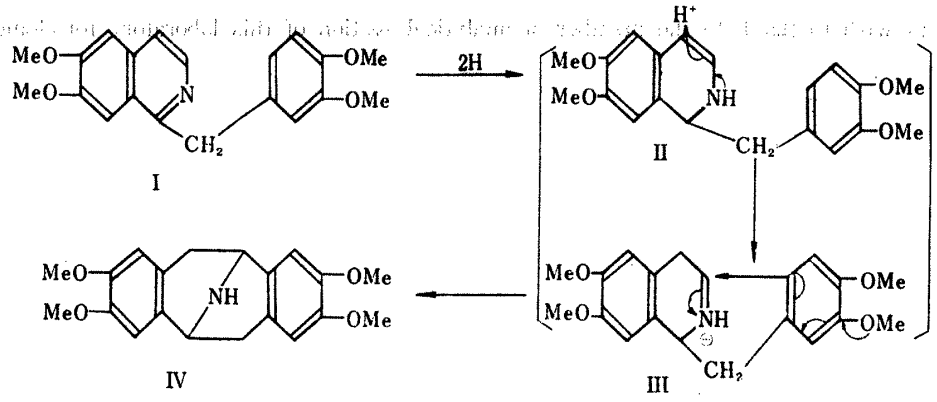

Chart 1.

reactivity of immonium carbon of 1,2-dihydroisoquinoline system, associated with the nucleophilicity of benzene ring activated by methoxyl group at *para* position.

With regard to the reactivity of dihydroisoquinolines, and analogous partially reduced pyridine derivatives, there are increasing reports describing the synthetic application in the field of isoquinoline,[2] and quinolizidine[3] including emetine derivatives. Reductive[4] and oxidative cyclization[5] in the synthesis of indole family arise also from this reactive immonium or protonated enamine system.

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1) *a*) A.R. Battersby, R. Binks: Chem. & Ind. (London), **1954**, 1455; *b*) *Idem.*: J. Chem. Soc., **1955**, 2888.

2) C. Szántay, J. Rohály: Chem. Ber., **98**, 557 (1965) and other papers cited therein.

3) T. Openshaw, N. Whittaker: J. Chem. Soc., **1963**, 1449; R.F.K. Meredith, A.C. Ritchie, T. Walker, K.D.E. Whiting: *Ibid.*, **1963**, 2672; M. Strandtmann, M.P. Cohen, J. Shavel: J. Org. Chem., **31**, 797 (1966); J.W. Huffman, E.G. Miller: J. Org. Chem., **25**, 90 (1960).

4) K.T. Potts, R. Robinson: J. Chem. Soc., **1955**, 2675; R.C. Elderfield, B.A. Fischer: J. Org. Chem., **23**, 332 (1958); J.W. Huffman: J. Am. Chem. Soc., **80**, 5193 (1958); J.H. Supple, D.A. Nelson, R.E. Lyle: Tetrahedron Letters, **1963**, 1645.

5) E. Wenkert, J. Kilzer: J. Org. Chem., **27**, 2283 (1962); E. Wenkert, B. Wickberg: J. Am. Chem. Soc., **84**, 4914 (1962).

In connection with the study of nitrogen-heterocyclic compounds, we had occasion to study chemical properties of immonium system, and we are in particular concerned with reaction of quaternary-type immonium salt without proton at a nitrogen atom. Attempted cyclization of a dihydroisoquinolinium salt (V) to a pavine-like product (VI) by Dyke and Sainsbury was unsuccessful.[6] However, Battersby, *et al.* synthesized (±) coreximine (VIII), a dibenzo(*a*, *g*)quinolizidine derivative, by acid-catalyzed cyclization of a 1,2-dihydroisoquinoline base (VII).[7] Their reaction course (VII→VIII) apparently involves a quaternary-type species (IX) as an intermediate. Formation of N-methylpavine from N-methyl-1,2-dihydropapaverine may also proceed by way of a similar step.[1b]

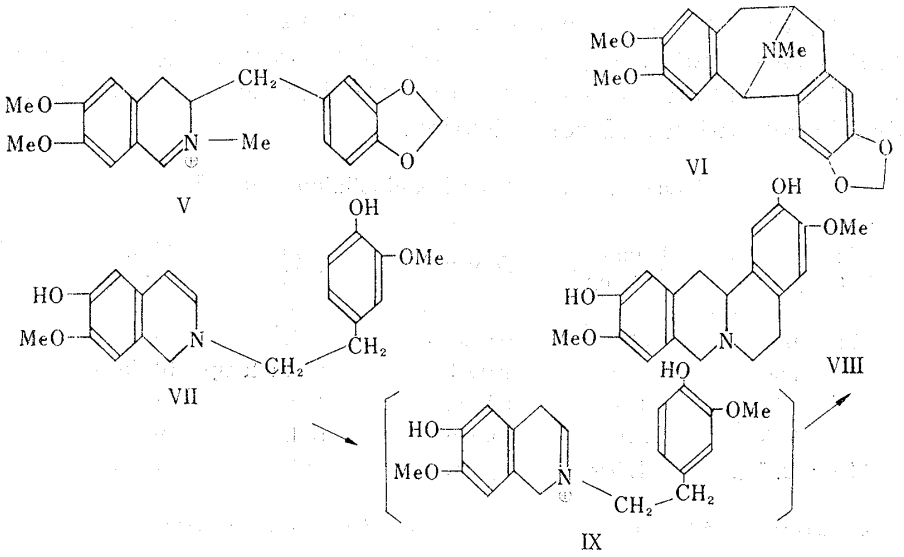


Chart 2.

Based on the foregoing discussion, N-(3,4-dimethoxyphenethyl)-3,4-dihydroisoquinolinium salt (XII), an isomeric dihydroisoquinolinium salt of IX, was chosen as our potential substrate of quaternary-type for desired cyclization. This compound (XII; R =MeO) had been prepared by Sugasawa, *et al.* in their extensive study on syntheses of dibenzoquinolizine groups.[8] According to the described procedure, 6,7-dimethoxy-3,4-dihydroisoquinoline (X; R=MeO) and 3,4-dimethoxyphenethyl bromide (XI) were

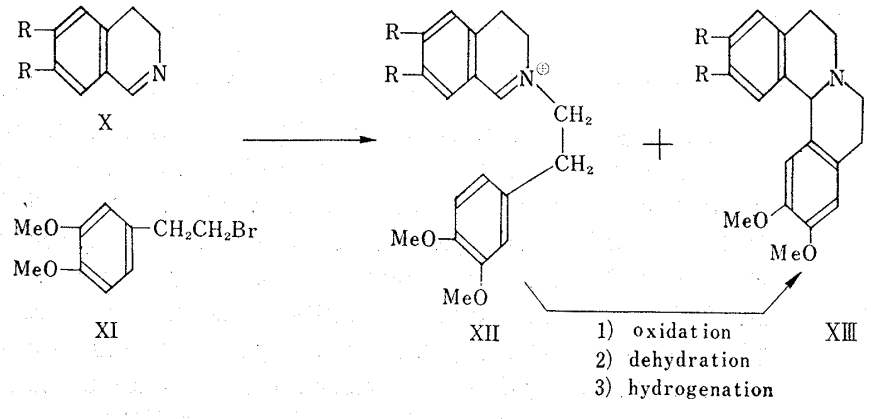


Chart 3.

6) S. F. Dyke, M. Sainsbury : Tetrahedron, **21**, 1907 (1965).
7) A. R. Battersby, D. J. LeCount, S. Garratt, R. I. Thrift : *Ibid.*, **14**, 46 (1961).
8) S. Sugasawa, N. Sugimoto : Proc. Imp. Acad. Tokyo, **18**, 658 (1942) and papers cited therein.

refluxed in xylene solution to afford (XII; R=MeO) in 53% yield. As expected, a small amount (*ca.* 1%) of a base was isolated from the xylene solution after the separation of XII. Its structure was confirmed to be the desired product (XIII; R=MeO) as the result of direct cyclization, by showing that the same base was obtained when (XII; R =MeO) was subjected to the sequence of reactions; *i.e.*, oxidation with potassium ferricyanide, dehydrating cyclization with phosphoryl chloride and catalytic hydrogenation.[9]

In an attempt to find an optimum condition for the cyclization, reaction of 3,4-dihydroisoquinoline (X; R=H) and XI was examined and the results are listed in Table I. In analogy with the methoxyl analog, a dibenzo(*a*, *h*)quinolizidine derivative (XIII; R=H) was isolated. Under usual conditions for salt formation, however, yield of cyclization was again very low. Direct heat treatment of XII under various conditions with or without solvent failed to give XIII, probably because high melting points of XII often required high reaction temperature for realizing homogeneous conditions, which led to undesirable coloration and resinification.

Table I. 3,4-Dihydroisoquinolinium Salt (XII)

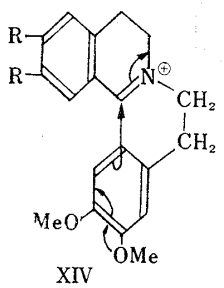
Amine (X; mg.)	Bromide (XI; mg.)	Solvent	Temp. (°C)	Time (hr.)	Yield (%)
R=H; 600	324	benzene	refl.	8	0
360	156	EtOH	room temp.	10 days	38
250	149	toluene	100	4	33
735	370	toluene	refl.	9	47[a]
R=MeO; 2.5 g.	1.9 g.	xylene	100	4	53[b]

a) accompanied by XIII (4%) *b*) accompanied by XIII (1%)

Table II. Cyclization to Dibenzo(*a*, *h*)quinolizidine (XIII)

Amine (X; mg.)	Bromide (XI; mg.)	Solvent	Temp. (°C)	Time (hr.)	Yield[a] (%)
R=H; 735	370	toluene	refl.	4	4
100	104	toluene	refl.	17	16
100	108	dioxane	refl.	24	12
107	104	none	140~150[b]	1.5	20
300	300	none	140~150[b]	0.5	19
R=MeO; 137	157	none	140~150[b]	1.75	8

a) Yields of purified hydrochloride *b*) bath-temp.



XIV

Chart 4.

Finally, when a mixture of (X; R=H) and XI was heated in toluene for 17 hr., (XIII; R=H) was obtained in 16% yield. Heating a mixture without solvent raised a yield up to 20%. Likewise, (XIII; R=MeO) was obtained in 8% yield by heating a mixture of (X; R=MeO) and XI without solvent. Experimental data are listed in Table II. The above results thus demonstrate that, though yield is low, certain quaternary-type 3,4-dihydroisoquinolinium salt such as XII is capable of cyclization, as interpreted in terms of electrophilic reactivity of immonium salt (XIV).

This approach is expected to find some application in syntheses of nitrogen-heterocyclic compounds.

9) S. Sugasawa, K. Kakemi : Proc. Imp. Acad. Tokyo, **15**, 52 (1939).

Experimental*2

N-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Bromide (XII; R=MeO)——A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (X; R=MeO)[10] (1.9 g.) and 3,4-dimethoxyphenethyl bromide (XI) (2.5 g.) in abs. xylene (30 ml.) was warmed in water-bath for 4 hr.[9] After cooling, deposited crystalls were collected and recrystallized from EtOH-ether to give XII as pale yellow plates of m.p. 196~199° (lit.,[9] m.p. 192°); 2.3 g. or 53%. UV λ_{max}^{EtOH} mμ (log ε): 251.5 (4.30); 288 (3.66); 315 (4.05); 375 (4.06).

2,3,11,12-Tetramethoxy-5,6,8,9-tetrahydrodibenzo(*a*,*h*)quinolizine (XIII; R=MeO)——The foregoing xylene solution was shaken with 10% HCl after separation of (XII; R=MeO) and the aq. extract was made alkaline with 10% NaOH and extracted with benzene. The basic fraction (689 mg.), obtained on removal of the solvent, was applied to alumina column and eluted with benzene-acetone (20:1). Solvent was evaporated *in vacuo* and the basic residue was purified as hydrochloride in usual manner to give the hydrochloride of (XIII; R=MeO) as faintly yellow plates of m.p. 231~235° from EtOH-EtOAc; 37 mg. or 1%. UV λ_{max}^{EtOH} mμ (log ε): 282.5 (3.85). The m.p. of this compound showed no depression on admixture with the authentic specimen prepared from (XII; R=MeO) following the published procedure.[9] Their IR spectra were superimposable and thin-layer chromatography (silica gel; benzene-acetone (9:1)) showed same spots.

N-(3,4-Dimethoxyphenethyl)-3,4-dihydroisoquinolinium Bromide (XII; R=H)——Prepared from X and XI as given in Table I. Pale yellow plates from EtOH-ether of m.p. 194~196°. UV λ_{max}^{EtOH} mμ (log ε): 286 (4.23). *Anal.* Calcd. for $C_{19}H_{22}NO_2Br$ (XII; R=H): C, 60.64; H, 5.89; N, 3.72. Found: C, 60.52; H, 5.81; N, 3.74.

2,3-Dimethoxy-5,6,8,9-tetrahydrodibenzo(*a*,*h*)quinolizine (XIII; R=H)——The toluene solution, after separation of (XIII; R=H), was worked up as in the case of (XIII; R=MeO) to give the hydrochloride of (XIII; R=H) as colorless plates of m.p. 212~214° from EtOH-ether; 40 mg. or 4%. UV λ_{max}^{EtOH} mμ (log ε): 281 (3.52). *Anal.* Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$ (hydrochloride of XIII; R=H): C, 68.77; H, 6.68; N, 4.22. Found: C, 68.59; H, 7.04; N, 4.25.

Cyclization to Dibenzo(*a*,*h*)quinolizidines (Table II)——For a typical example, a mixture of (X; R=H) (300 mg.) and (XI) (300 mg.) was heated at 140~150° (bath temp.) for 30 min. Water was added and the whole was extracted with benzene, and the extract was washed with water and dried (K_2CO_3). An oily residue (167 mg.), obtained on removal of the solvent, was applied to alumina column and eluted with benzene-acetone (50:1). Solvent was evaporated *in vacuo* and the basic product was purified as hydrochloride in usual manner; 77 mg. or 19%.

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*2 All melting points are uncorrected.

10) E. Spath, N. Polgar: Monatshefts f. Chem., **51**, 190 (1929).