Notes

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Phenolic Cyclization. IV.[1] The Mechanism of the Isoquinoline Formation (Studies on the Syntheses of Heterocyclic Compounds. CCCXXXVII[2])

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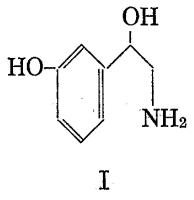
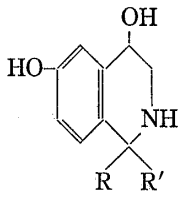
In a previous paper[4] we have reported that novel syntheses of 1-substituted and 1-spirocycloalkanoisoquinoline derivatives were achieved by condensation of 3-hydroxyphenethylamine derivatives, for instance, (I), with various aliphatic and aromatic carbonyl compounds having no basic functional group, and that application of this method led to the syntheses of various isoquinolines (II—VII) and total synthesis of (±)-coreximine.

The purpose of the present investigation was to study the condensation of 1-(3-hydroxyphenyl)-2-aminoethanol (I) with 1-benzyl-4-piperidone in order to expand this reaction to basic carbonyl compound. The Schiff base (XII) and the oxazolidine (XIV), which were thought to be the representative reaction intermediates in this type of reaction, were subjected to the cyclization in the same condition in order to reveal "the general mechanism" for the formation of 1-substituted-1,2,3,4-tetrahydro-4,6-dihydroxyisoquinolines. In the formation of the compounds (III and VI), the reaction was found to proceed through the Schiff base in aromatic carbonyl compounds and the oxazolidine in aliphatic ones, respectively.



I



II : R=CH_3, R'=CH_3
III : R=H, R'=C_6H_5
IV : R=CH_3, R'=C_2H_5
V : R=CH_3, R'=C_6H_5
VI : R+R'=$-CH_2(CH_2)_4CH_2-$
VII : R+R'=$-CH_2(CH_2)_3CH_2-$

Chart 1

First of all, 1-benzyl-4-piperidone was synthesized according to the literature.[5] Namely, the intramolecular cyclization of N,N-bis(2-ethoxycarbonylethyl)benzylamine, which was obtained by condensation of benzylamine with ethyl acrylate, with sodium ethoxide afforded 1-benzyl-3-ethoxycarbonyl-4-piperidone, which was heated with hydrochloric acid to give 1-benzyl-4-piperidone.

The condensation of the amine (I) with 1-benzyl-4-piperidone afforded our expected 1,2,3,4-tetrahydro-4,6-dihydroxy-1-spiro-(4-N-benzylpiperidino)isoquinoline (VIII) without using the acid. The compound (VIII) was very stable in an acidic medium and characterized as its hydrochloride, mp 250° (decomp.). Furthermore, acetylation of VIII with acetic anhyd-

1) Part III: T. Kametani, H. Agui, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1285 (1968).
2) Part CCCXXXVI: T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 2245 (1969)
3) Location: *a*) *Aobayama, Sendai*; *b*) *Shinmachi, Setagayaku, Tokyo.*
4) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (*C*), **1968**, 112.
5) S. Moresawa, *Bull. Chem. Soc. Japan*, **31**, 418 (1958).

ride afforded its acetyl-derivative (IX), whose infrared (IR) spectrum showed ester CO at 1760 and 1730 cm^{-1}, and amide CO at 1660 cm^{-1}, respectively. The nuclear magnetic resonance (NMR) spectrum of IX showed the reasonable patterns as the resonance of three acetyl signals at 2.09, 2.18 and 2.23 ppm. These facts reveal that the compound (VIII) is neither Schiff base (X) nor oxazolidine (XI), but cyclized product (VIII). In this case although each compound, X or XI, would be the intermediate for the formation of VIII, each could not be isolated.

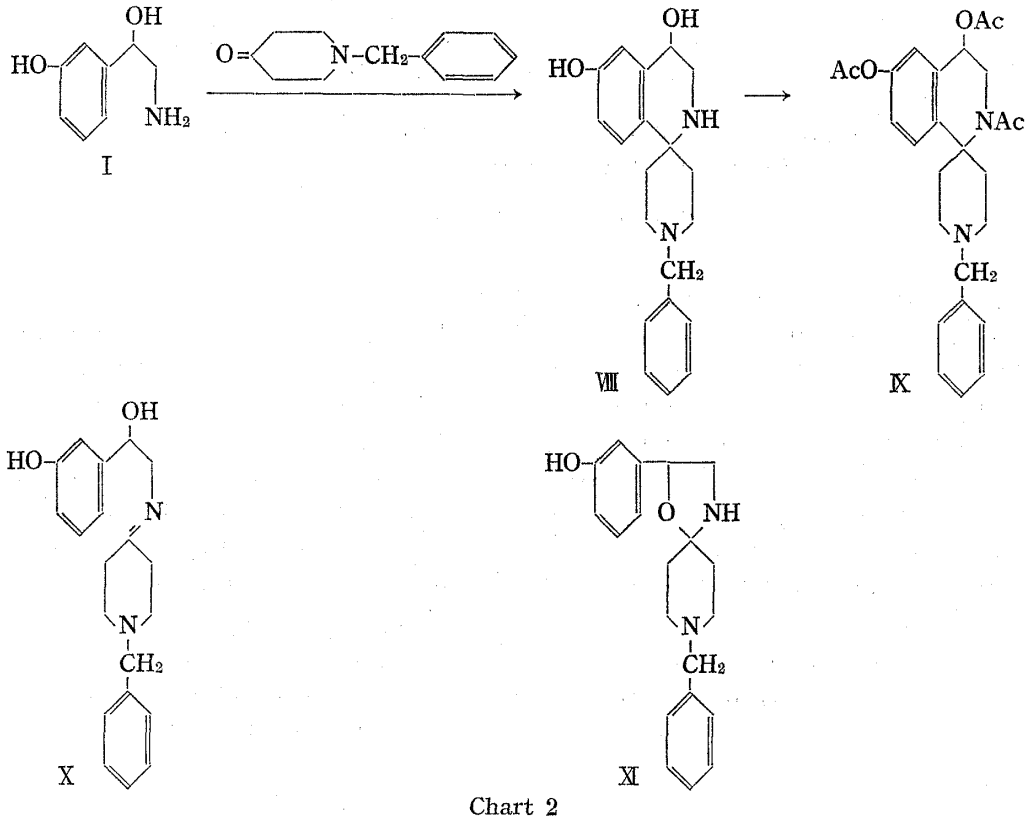


Chart 2

Secondly, we have reported previously the formation of two diastereoisomers (IIIa and IIIb) by refluxing the amine (I) with benzaldehyde in ethanol, but on being allowed to stand at room temperature, a mixture of I and benzaldehyde afforded solely the Schiff base (XII), mp 147°, which was identical with D'amico's sample.[6]

In this case D'amico reported the formation of oxazolidine derivative (XIII) by refluxing the above Schiff base in ethanol, but two diastereoisomers (IIIa and IIIb) were obtained in our trial by the same treatment as above. Accordingly, the formation of the 1,2,3,4-tetrahydroisoquinolines (IIIa and IIIb) would proceed *via* Schiff base (XII).

On the other hand, condensation of the amine (I) with cyclohexanone by refluxing in ethanol gave 5-(3-hydroxyphenyl)-2-spirocyclohexanooxazolidine (XIV), whose structure was confirmed by the absence of C=N absorption band in its IR spectrum. Furthermore, benzoylation of XIV by Schotten–Baumann reaction afforded the tribenzoyl-derivative of I. The heating of XIV at 150° gave our expected 1,2,3,4-tetrahydroisoquinoline (VI), which was identical with an authentic sample[4] by a mixed melting point test and IR spectral comparison. These facts show that the formation of VI would proceed *via* the oxazolidine (XIV) as an intermediate.

Further confirmation comes from the comparison of the UV-spectra of the products. Compound (I) shows the absorption maximum at 277 mμ, and oxazolidine derivative (XIV)

6) A. D'amico, L. Bertolini, et C. Monreale, *La chimica e L'industria*, **38**, 93 (1956).

at 277 mμ, both bands of which are compared with that of *m*-cresol at 276.4 mμ. On the other hand, tetrahydroisoquinoline derivatives (III) and (VI) represent the absorption maximum at 284.5 mμ and 282 mμ, respectively. In case of 3,4-dimethylphenol a similar shift at 281 mμ is observed. The maximum bands in the *para*-substituted phenols as compound (I) were found to show bathochromic shift compared with those of the phenols which had no substituent at *para*-position. Therefore, this observation may be applied to differenciate the cyclized isoquinolines from noncyclized compound, namely, Schiff base or oxazolidine derivatives.

Perhaps the route in this phenolic cyclization would involve the formation of isoquinoline *via* the oxazolidine because of no stabilization by conjugation of double bonds in case of alicyclic or aliphatic carbonyl compounds and *via* the Schiff base because of stabilization by conjugation of the azomethine group in case of aromatic carbonyl compounds.

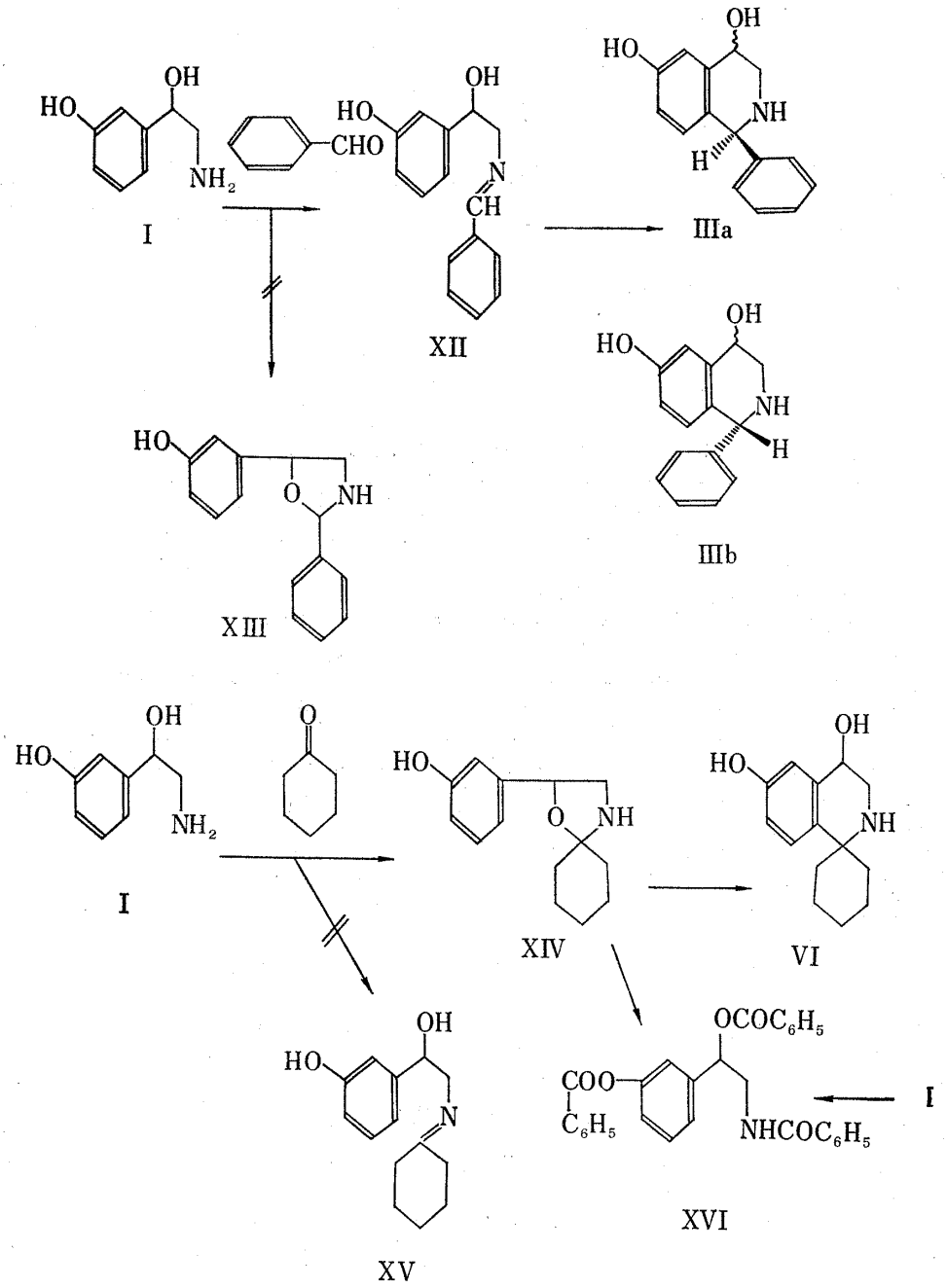


Chart 3

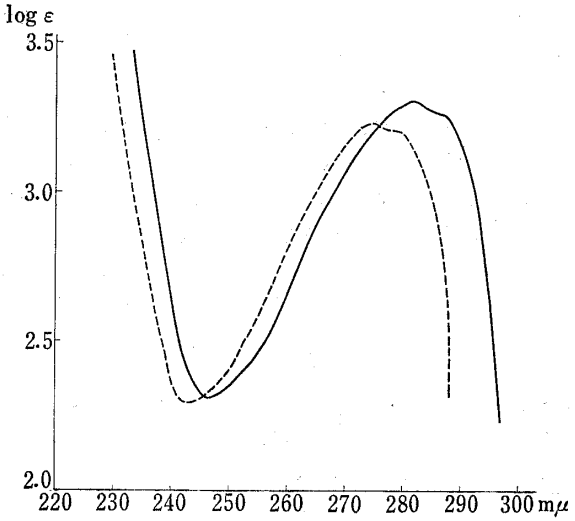


Fig. 1. UV Spectra of *m*-Cresol and 3,4-Dimethylphenol in EtOH

------: *m*-cresol ——: 3,4-dimethylphenol

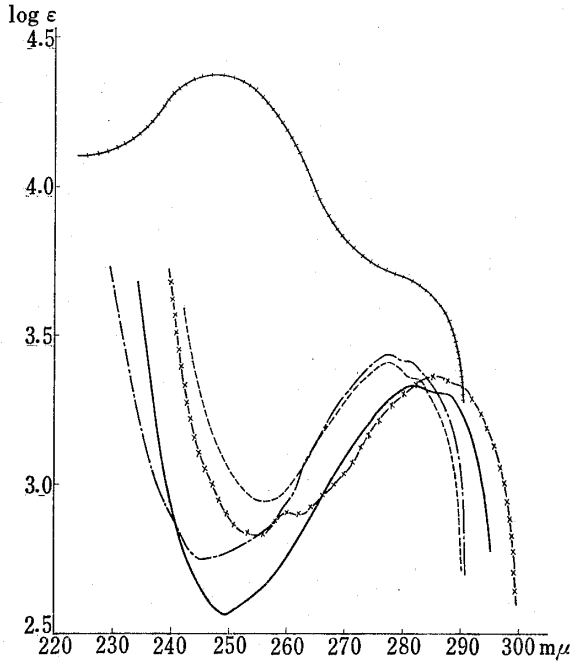


Fig. 2. UV Spectra of I, III, VI, XII, and XIV in EtOH

I: ---------- III: —×—×—
XIV: —·—·— VI: ————
XII: —|—|—

Experimental[7]

1,2,3,4-Tetrahydro-4,6-dihydroxy-1-spiro-(N-benzyl-4-piperidino)isoquinoline (VIII)——A mixture of 1.5 g of I and 1.9 g of N-benzyl-4-piperidone[5] was heated at 170° for 3 hr and, after cooling, 3 g of an amorphous powder was obtained. HCl gas was introduced into a solution of the above powder in EtOH to give the hydrochloride, whose recrystallization from MeOH gave 2.2 g of the HCl salt of VIII as a colorless powder, mp 250° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_2N_2 \cdot 2HCl \cdot H_2O$: C, 57.83; H, 6.79; N, 6.75. Found: C, 57.61; H, 7.00; N, 6.43. UV λ_{max}^{EtOH}: 282 mμ (log ε 3.26).

2,4,6-Triacetyl-1,2,3,4-tetrahydro-1-spiro-(N-benzyl-4-piperidino)isoquinoline (IX)——A mixture of 350 mg of VIII, 500 mg of AcONa and 5 ml of Ac_2O was refluxed at 160° for 1 hr. Removal of the excess of Ac_2O gave a viscous syrup, which was basified with 10% NaOH aq. solution and extracted with ether and then $CHCl_3$. Both extracts were combined, washed with water, and dried on Na_2SO_4. Removal of the solvent gave 360 mg of IX as a pale yellow oily substance. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1760, 1730 (ester); $\nu_{C=O}$ 1660 (amide). NMR (ppm) (in $CDCl_3$): 2.09, 2.18, 2.23 (3H, singlets, $COC\underline{H}_3$), 3.49 (2H, singlet, $C\underline{H}_2$–C_6H_5), 3.92 (2H, triplet, C_3–$\underline{H}$), 5.82 (1H, triplet, C_4–$\underline{H}$), 6.90—7.50 (8H, multiplet, aromatic protons), 1.20—3.42 (8H, broad, methylene protons).

2-N-Benzylidene-1-(3-hydroxyphenyl)-2-aminoethanol (XII)——A mixture of 3.1 g of 1-(3-hydroxyphenyl)-2-aminoethanol (I), 2.1 g of benzaldehyde, and 30 ml of EtOH was allowed to stand at room temperature. Collection of the crystals precipitated and recrystallization from EtOH afforded 3.7 g of the Schiff base (XII) as colorless plates, mp 147°, which were identical with an authentic sample[5] on mixed melting point test and IR spectral comparison. IR cm^{-1} (KBr): $\nu_{-C=N-}$ 1650. UV λ_{max}^{EtOH}: 248.5 mμ (log ε 4.38).

1,2,3,4-Tetrahydro-4,6-dihydroxy-1-phenylisoquinoline (IIIa) and (IIIb)——A mixture of 3 g of XII and 30 ml of EtOH was refluxed for 5 hr. After cooling, the crystals were collected by filtration. Recrystallization from MeOH afforded 2 g of IIIa as colorless plates, mp 214—215°, which were identical with one of the authentic samples.[4] UV λ_{max}^{EtOH}: 284.5 mμ (log ε 3.37).

To the above filtrate in case of recrystallization was added $CHCl_3$, causing the precipitation of crystals. Collection and recrystallization from EtOH afforded 0.6 g of IIIb, mp 177—180°, which was also identical with the other authentic sample[4] on mixed melting point test and IR spectral comparison.

5-(3-Hydroxyphenyl)-2-spirocyclohexanooxazolidine (XIV)——A mixture of 1.5 g of I, 1 g of cyclohexanone and 30 ml of EtOH was refluxed for 3 hr. After the solvent had been distilled, the residue was

7) All melting points were not corrected.

poured into water and the crystals were precipitated. Recrystallization from EtOH–H_2O afforded 2 g of XIV as colorless plates, mp 132°. *Anal.* Calcd. for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.27; H, 7.93; N, 5.85. UV λ_{max}^{EtOH}: 277 mμ (log ε 3.43).

1,2,3,4-Tetrahydro-4,6-dihydroxy-1-spirocyclohexanoisoquinoline (VI)——Fusion of 1.5 g of XIV at 150° for 3 hr afforded a solid, which was recrystallized from EtOH to give 1.2 g of VI as colorless prisms, mp 178—180°, whose IR spectrum was identical with an authentic sample.[4] UV λ_{max}^{EtOH}: 282 mμ (log ε 3.34).

N-benzoyl-[β-(benzoyloxy)-β-(3-benzoyloxyphenyl)]ethylamine (XVI)——a) Benzoylation of XIV: A solution of 25 mg of XIV in $CHCl_3$ was benzoylated with 5 ml of benzoyl chloride in the presence of 10% NaOH aq. solution by Schotten–Baumann reaction. The $CHCl_3$ layer was separated, washed with 10% HCl aq. solution and dried on K_2CO_3. Evaporation of the solvent gave a solid which was recrystallized from benzene–cyclohexane to give 30 mg of colorless needles, mp 128—131°, whose IR spectrum was identical with that of the tribenzoyl compound (XVI) described below, and this compound also showed no depression of melting point on admixture with the tribenzoyl compound (XVI) described later.

b) Benzoylation of I: A solution of 40 mg of I in $CHCl_3$ was benzoylated with 5 ml of benzoyl chloride in the presence of 10% NaOH aq. solution by Schotten–Baumann reaction. The solvent layer was separated, washed with 10% HCl aq. solution and dried on K_2CO_3. Evaporation of the solvent gave a solid which was recrystallized from benzene–cyclohexane to give 48 mg of colorless needles, mp 128—131°. *Anal.* Calcd. for $C_{29}H_{23}O_5N$: C, 74.82; H, 4.98; N, 3.01. Found: C, 74.30; H, 5.05; N, 2.99. IR cm^{-1} (KBr): $\nu_{C=O}$ 1720 (ester): $\nu_{C=O}$ 1630 (amide).

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Synthesis of Mercaptoquinazolinone Derivatives as Potential Antimalarials[1]

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Many quinazolines possessing a wide variety of biological activities are known. The antimalarial activity of febrifugine,[3,4] an alkaloid having 3-substituted 4(3*H*)quinazolinone structure, spurred the preparation and testing of a number of quinazolines[5] and quinazolinones[6] and several patent claims have been made on quinazolinones as intermediates for potential antimalarials.[7] Wolf[8] has reported that 2- and 4-sulphanilamidoquinazolines are

1) The major part of the paper was presented before the 55th session of the Indian Science Congress held at B.H.U., Varanasi-5 (India) in January, 1968.
2) Location: *Varanasi-5, India.*
3) J.B. Koepfli, J.F. Mead and J.A. Brockman, *J. Am. Chem. Soc.*, **69**, 1837 (1947); **71**, 1048 (1949); **72**, 3323 (1950).
4) B.R. Baker, F.J. McEvoy, R.E. Schaub, J.P. Joseph and J.H. Williams, *J. Org. Chem.*, **18**, 178 (1953).
5) F.W. Wiselogle, "Survey of Antimalarial Drugs 1941—1945," Edward Bros., Ann. Arbor, Michigan (U.S.A.), 1946.
6) B.R. Baker, R.E. Schaub, J.P. Joseph, F.J. McEvoy and J.H. Williams, *J. Org. Chem.*, **17**, 164 (1952).
7) B.R. Baker and M.V. Querry, U.S. Patent 2796417 (1957); *C.A.*, **52**, 459 (1958); B.R. Baker, U.S. Patent 2811524 (1957); *C.A.*, **52**, 5488 (1958).
8) F.J. Wolf, U.S. Patent 2473931 (1949); *C.A.*, **43**, 7042 (1949).