Studies on the Syntheses of Heterocyclic Compounds. Part DCXXXII (1). The Formation of the Benzimidazo[2,1-*a*]isoquinoline by Reaction of the 1,2,3,4-Tetrahydro-1-(2-nitrophenethyl)isoquinoline with Triethyl Phosphite

Tetsuji Kametani (2)

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Yasuo Fujimoto and Masakatsu Mizushima

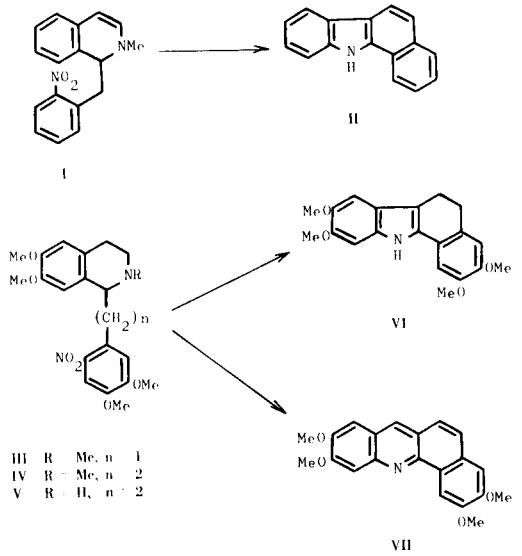
Research Laboratories, Nippon Chemiphar Co. Ltd., Komagome, Bunkyoku, Tokyo, Japan

Received July 1, 1975

Reductive cyclization of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (V) with triethyl phosphite gave 5,6-dihydro-2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline (IX), whose structure was identified by the spectroscopic analyses by an alternative synthesis.

Reductive cyclization of aromatic nitro compounds with triethyl phosphite has been hitherto investigated by many researchers (3-4) and a mechanism of this type reaction has been proposed to proceed through nitrene intermediate. Previously, we have reported the formation of the benzo[*a*]carbazoles (II) and (VI) by reductive cyclization of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (I) and 6′-nitrolaudanosine (III), respectively (5). Recently, we have found that the same reaction of the 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)-2-methylisoquinoline (IV) afforded the benzacridine derivative (VII) (6). As extension and generalization of this type reaction, we have been interested in effecting a similar reaction with *N*-desmethyl compound (V) of IV to afford the benzacridine, and here wish to report an unexpected but an interesting result.

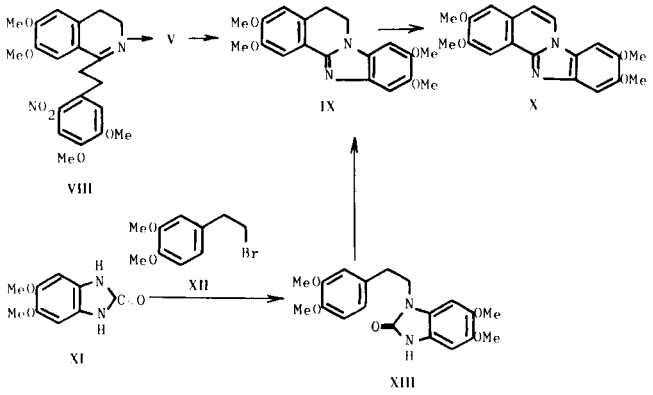
Chart 1



Reduction of 3,4-dihydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (VIII) with sodium borohydride gave the tetrahydroisoquinoline (V), whose nmr spectrum (δ in deuteriochloroform) showed NH group at 1.70 ppm as singlet in addition to four methoxyl groups (3.86, 3.88, 3.92, and 3.94) and four aromatic protons (6.58, 6.68, 6.78, and 7.60). Treatment of this tetrahydroisoquinoline with an excess of triethyl phosphite at 160-170° for 15 hours in a current of nitrogen gave an unexpected 5,6-dihydro-2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline (IX), m.p. 151-152°, in 12% yield, whose structure was determined as follows. The high resolution mass spectrum [M^+ (m/e), Calcd. 340.1422. Found: 340.1466] and microanalysis showed the molecular formula, $C_{19}H_{20}N_2O_4$, indicating an elimination of two carbons from the starting material, and the uv [λ max (methanol) 335 and 350 nm (log ϵ 4.39 and 4.55)] and ir spectra [ν max (potassium bromide) 1607 cm^{-1} (C = N)] suggested this product to have an Ar-N=C-Ar system. The nmr spectrum revealed an ethylene group to be located between an aromatic ring and nitrogen at 3.10 and 4.14 as each triplet having J = 7 Hz and four isolated aromatic protons at 6.66, 6.70, 7.24,

and 7.64 in addition to four methoxyl groups at 3.88, 3.90, 3.92 and 3.96. The presence of a deshielded aromatic proton at 7.64 showed that an electron-withdrawing group is located at the *ortho* position to this proton. The chemical shifts of the methylene and aromatic protons are similar to those of 5,6-dihydro--2,3,9,10-tetramethoxydibenz[*b*,*g*]indolizine (7). Heating of this product with 5% palladium on carbon in boiling decalin for 50 hours in a current of nitrogen afforded the dehydrogenated product (X), m/e 338 (M^+), whose nmr spectrum showed four isolated aromatic protons at 6.72, 6.96, 7.20 and 7.56, and two aromatic protons coupled each other at 6.56 and 7.68 as each doublet with J = 7 Hz, but no methylene and methine protons. On the basis of these data, we assigned the structure IX for this product. This was also proved by an alternative synthesis.

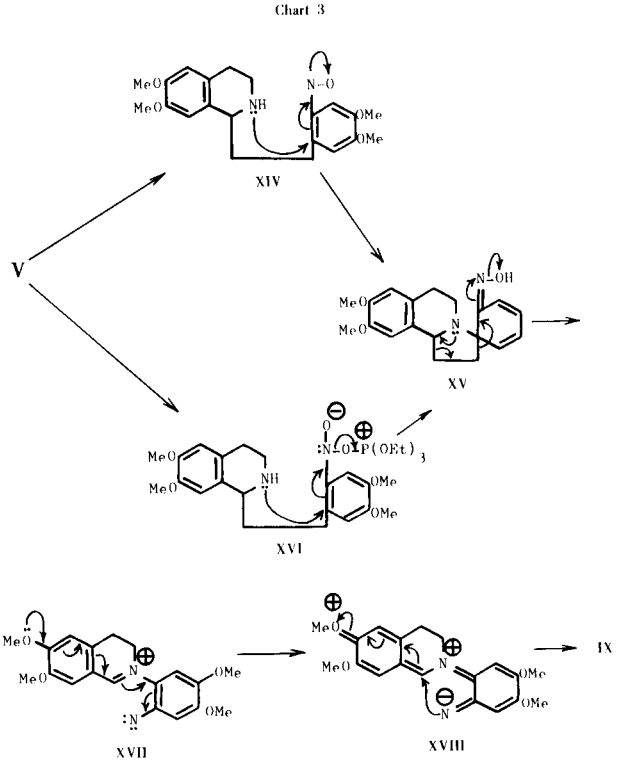
Chart 2



The condensation of 5,6-dimethoxy-2(3*H*)benzimidazolone (XI) (8) with 3,4-dimethoxyphenethyl bromide (XII) in the presence of potassium carbonate gave 5,6-dimethoxy-1-(3,4-dimethoxyphenethyl)-2(3*H*)benzimidazolone (XIII), which was treated with phosphoryl chloride and phosphorous pentoxide to give the benzimidazo-[2,1-*a*]isoquinoline (IX), which was identical with the above sample in mixed melting point test and ir, nmr and mass spectral comparisons.

The formation mechanism of the compound (IX) would be presumed as shown in Chart 3. Thus, the nitroso compound (XIV), derived from V by reduction with triethyl phosphite, was attacked by a basic nitrogen to form the spiro type intermediate (XV), whose fragmentation afforded the nitrene (XVII) by heating. The oxime intermediate (XV) may be formed by another mechanism through the intermediate (XVI). The nitrene (XVII) then isomerized to the anion (XVIII), which was cyclized to give 5,6-dihydro-2,3,9,10-tetramethoxybenzimidazo-[2,1-*a*]isoquinoline (IX).

Chart 3



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with Hitachi EPI-G2 and JASCO IRA-1 recording spectrophotometers, uv spectra with a Hitachi 124 recording spectrophotometer, nmr spectra with a JEOL NH-100 spectrometer (tetramethylsilane as an internal standard), and mass spectra with JMS-OSG-2 spectrometer.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (V).

To a stirred solution of 5 g. of 3,4-dihydro-6,7-dimethoxy-1-(4,5-dimethoxy-2-nitrophenethyl)isoquinoline (VIII) hydrochloride in 180 ml. of methanol and 20 ml. of chloroform, 2 g. of sodium borohydride was added in small portions during 20 minutes. After stirring for 3 hours, the solvent was evaporated off to give a residue which was diluted with water and extracted with 100 ml. of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave 4.1 g. of a syrup; nmr (deuteriochloroform): δ 1.70 (NH, disappeared with deuterium oxide, 1H, s), 3.86, 3.88 3.92 3.94 (4 x OMe, 12H, each s), which was characterized as its hydrochloride, mp. 225-226°, after recrystallization from methanol-ether.

Anal. Calcd: for $C_{22}H_{26}N_2O_6 \cdot HCl \cdot 0 \cdot 5H_2O$: C, 56.31; H, 6.08; N, 6.25. Found: C, 56.46; H, 5.96; N, 6.22. Mass (m/e), 402 (M^+-HCl), 400, 356, 354.

5,6-Dihydro-2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline (IX).

a) By Reductive Cyclization.

A solution of 2.5 g. of the isoquinoline (V) in 25 g. of triethyl phosphite was refluxed at 160-170° in an oil-bath for 15 hours under a current of nitrogen. After removal of a lower

boiling substance by distillation under reduced pressure, the resulting brown syrup was chromatographed on silica gel, and evaporation of the chloroform eluate, followed by recrystallization from methanol, afforded 360 mg. of the benzimidazoisoquinoline (IX) as a colorless powder, m.p. 151-152°; ir ν max (chloroform): 1607 cm^{-1} (C=N); uv λ max (methanol): (log ϵ) 335 (4.39) and 350 nm (4.45); nmr (deuteriochloroform): δ 3.10 ($ArCH_2CH_2N$, 2H, t, J = 7 Hz), 4.14 ($ArCH_2CH_2N$, 2H, t, J = 7 Hz), 3.88, 3.90, 3.92, 3.96, (4 x OMe, 12H, each s), 6.66, 6.70, 7.24, 7.64, (4 x ArH, 4H, each s).

Anal. Calcd. for $C_{19}H_{20}N_2O_4 \cdot 0 \cdot 25H_2O$: C, 66.17; H, 5.92; N, 8.12. Found: C, 66.29; H, 5.86; N, 7.88. Mass (m/e) Calcd. for $C_{19}H_{20}N_2O_4$, 340.1422 (M^+). Found: 340.1466.

b) By An Alternative Synthesis.

A mixture of 80 mg. of the benzimidazolone (XIII), 10 ml. of phosphoryl chloride, and 2 g. of phosphorus pentoxide was refluxed for 3 hours with stirring, and the solvent was then evaporated off, giving a residue which was basified with 10% sodium hydroxide and extracted with 100 ml. of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give a brown oil, which was chromatographed on silica gel. Evaporation of the chloroform-ethanol (v/v 100:1) eluate, followed by recrystallization from methanol, afforded 5 mg. of the benzimidazoisoquinoline (IX) as a colorless powder, m.p. 151-152°, identical with the sample obtained by reductive cyclization in ir, uv, nmr and mass spectral comparisons.

5,6-Dimethoxy-1-(3,4-dimethoxyphenethyl)-2(3*H*)benzimidazolone (XIII).

A mixture of 500 mg. of 5,6-dimethoxy-2(3*H*)benzimidazolone (XI), 500 mg. of 3,4-dimethoxyphenethyl bromide (XII), 200 mg. of potassium carbonate, and 50 ml. of *N,N*-dimethylformamide was heated under reflux in an oil-bath for 18 hours. After removal of inorganic substance by filtration, the filtrate was evaporated to leave a dark brown oil, which was chromatographed on silica gel. Evaporation of the chloroform-ethanol (v/v 100:1) eluate, followed by recrystallization from methanol, afforded 120 mg. of the benzimidazolone (XIII) as a pale yellow powder, m.p. 171°; ir ν max (chloroform): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.00 ($ArCH_2CH_2N$, 2H, t, J = 8 Hz), 4.80 ($ArCH_2CH_2N$, 2H, t J = 8 Hz), 3.48 br (NH, 1H, s), 3.78 (2 x OMe, 6H, s), 3.80 (OMe, 3H, s), 3.84 (OMe, 3H, s), 6.28, 6.70 (ArH, 2H, each s), 6.76 (ArH, 2H, s), 6.78 (ArH, 1H, s).

Anal. Calcd. for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.54; H, 6.24; N, 7.75. Mass (m/e) 358 (M^+).

2,3,9,10-Tetramethoxybenzimidazo[2,1-*a*]isoquinoline (X).

A mixture of dihydrobenzimidazoisoquinoline (IX) (200 mg.), 40% palladium-carbon (800 mg.), and decalin (30 ml.) was refluxed in an oil bath for 24 hours under a current of nitrogen and then filtered in order to remove the catalyst. The solvent was evaporated off to give a residue, which was chromatographed on silica gel. Evaporation of the chloroform eluate gave the starting material (30 mg.), and then chloroform-ethanol (v/v 100:1) eluate afforded a solid, which was recrystallized from acetone-*n*-hexane to give the benzimidazoisoquinoline (X) [17 mg., 10% based on a recovery of starting material (30 mg.)] as a powder, m.p. 155-157°; ir ν max (chloroform): 1615 (C=N); uv λ max (methanol); 356, 338, 295 nm; nmr δ (perdeuteriomethanol): 3,80, 3.84, 3.92, 3.95 (4 x OCH_3, 12H, each s), 6.44, 7.56 (C*H* : C*H*, 2H, each d, J = 7 Hz), 6.64, 6.92, 6.98, 7.54 (Ar*H*, 4H, each s); m/e (M^+). Found: 338.1296. $C_{19}H_{18}N_2O_4$ requires 338.1265.

Anal. Calcd. for $C_{19}H_{18}N_2O_4 \cdot 0 \cdot 25H_2O$: C, 66.56; H, 5.44; N, 8.17. Found: C, 66.44; H, 5.82; N, 8.22.

Acknowledgement.

We thank President A. Yamaguchi, Nippon Chemiphar Co. Ltd., for his encouragement. We also thank Dr. K. Fukumoto, for his kind suggestions, Miss R. Kato, Miss R. Suenaga, Miss Y. Yokohama, and Miss E. Nagaoka, Pharmaceutical Institute, Tohoku University, and the Analytical Center of Nippon Chemiphar Co. Ltd., for spectral measurements and microanalyses.

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