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Synthesis of Alkaloids, (±)-Xylopinine and (±)-Tetrahydropalmatine, by a Photo-Induced Rearrangement of Spirobenzylisoquinolines in the Presence of Vitamin C

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The presence of vitamin C during the photo-induced rearrangement reaction of spirobenzylisoquinolines in ethanol suppressed the formation of the oxidation product, improving the yield of the berbinium compound, which yields the tetrahydroprotoberberine type compound on reduction with sodium borohydride. Synthesis of two alkaloids, (±)-xylopinine and (±)-tetrahydropalmatine, was accomplished by this method in fair yield.

Keywords——alkaloid; (±)-xylopinine; (±)-tetrahydropalmatine; rearrangement; spirobenzylisoquinoline; irradiation

Previously, we reported a synthesis of an alkaloid, (±)-xylopinine (**1**) (one of the tetrahydroprotoberberine alkaloids), from the spirobenzylisoquinoline (**2**) (ochotensine type base) by a photo-induced skeletal rearrangement followed by reduction with sodium borohydride.[1] However, repeated runs of the reaction revealed that the yield of the alkaloid (**1**) was not always reproducible because of the formation of the 8-oxo compound (**3**) even under a nitrogen atmosphere and in solvent boiled before use to remove oxygen. We have now found that the presence of vitamin C during the photo-rearrangement considerably reduces the formation of the oxo compound and results in an improvement of the yield of (±)-xylopinine, increasing the utility of the reaction, though the precise role of vitamin C is not yet clear. We report here the synthesis of (±)-xylopinine (**1**) and (±)-tetrahydropalmatine (**4**)[2] from spirobenzylisoquinolines by using this improved procedure.

Irradiation of the spirobenzylisoquinoline (**2**)[1] with a high-pressure mercury lamp (390 W) in ethanol at room temperature gave a mixture, which was, without further purification, subjected to reduction with sodium borohydride in methanol. The reaction products thus obtained were separated into a basic (60% yield) and a neutral portion (40% yield). The former consisted mainly of (±)-xylopinine (**1**) as determined by a thin layer chromatographic examination, and the latter gave the 8-oxo compound (**3**). On the other hand, addition of vitamin C to the solution of **2** caused a considerable decrease of formation of the 8-oxo compound (<4%) and an increase of the yield of (±)-xylopinine (>82%), the spectroscopic properties of which were identical with those of an authentic specimen.[1]

Based on the finding, a synthesis of (±)-tetrahydropalmatine (**4**) was undertaken. Treatment of 6,7-dimethoxyindan-1-one (**5**)[3] with isoamyl nitrite and concentrated hydrochloric acid in methanol gave the hydroxyimino-ketone (**6**) in fair yield.[3] We found that the hydroxyimino-ketone could be quantitatively prepared by treatment of a solution of the ketone (**5**) and isoamyl nitrite in ether with hydrogen chloride. Hydrolysis of **6** with aqueous 38% formaldehyde solution and concentrated hydrochloric acid for 150 s on a water bath gave the diketone (**7**) in 75% yield. Condensation of **7** and dopamine hydrochloride in ethanol gave the dihydroxy-spirobenzylisoquinoline (**8**) in 86% yield. Methylation of **8** with diazomethane

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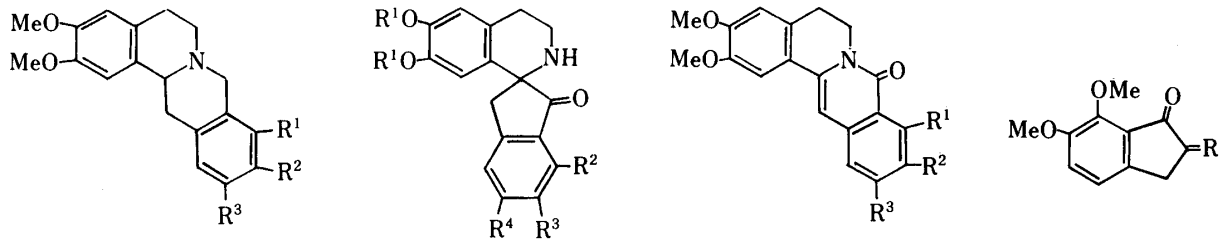

1: $R^1=H$, $R^2=R^3=OMe$ **2**: $R^1=Me$, $R^2=H$, $R^3=R^4=OMe$ **3**: $R^1=H$, $R^2=R^3=OMe$ **5**: $R=H_2$
4: $R^1=R^2=OMe$, $R^3=H$ **8**: $R^1=R^4=H$, $R^2=R^3=OMe$ **10**: $R^1=R^2=OMe$, $R^3=H$ **6**: $R=NOH$
9: $R^1=Me$, $R^2=R^3=OMe$, $R^4=H$ **7**: $R=O$

furnished the tetramethoxy-spirobenzylisoquinoline (**9**).

Irradiation of **9** in ethanol without addition of vitamin C gave (±)-tetrahydropalmatine (**4**) and 8-oxypalmatine (**10**) in 35% and 14% yields, respectively, after reduction of the irradiation product with sodium borohydride. On the other hand, addition of vitamin C to the reaction mixture increased the yield (45%) of (±)-tetrahydropalmatine and decreased the yield of 8-oxypalmatine (**10**) (less than 1%).

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-G2 infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were taken on Hitachi R-600 and JEOL FX-90Q spectrometers with tetramethylsilane as an internal standard in $CDCl_3$. Mass spectra (MS) were recorded with a JEOL JMS-OlSG spectrometer. Preparative thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) with appropriate solvents.

Photo-Rearrangement of the Spirobenzylisoquinoline (2)——a) Without vitamin C. A solution of the spirobenzylisoquinoline (**2**) (200 mg) in EtOH (350 ml) (EtOH as a solvent gave slightly better and more reproducible results than tetrahydrofuran[1]) was irradiated with a 390 W mercury lamp at 25—30 °C for 2.5 h, then concentrated to dryness under reduced pressure to leave a residue, which was taken up in MeOH (18 ml). Sodium borohydride (150 mg) was added portionwise to the solution at room temperature. The mixture was stirred for 4.5 h, a few drops of AcOH were added, and the whole was concentrated under reduced pressure to leave a residue, which was dissolved in benzene. The solution was extracted with dil. HCl, and water, and dried over Na_2SO_4. Removal of the solvent gave the 8-oxo compound (**3**) (54 mg), mp 195—197 °C, after purification by column chromatography. This product was identical with an authentic sample.[1] The foregoing dil. HCl extract was basified with K_2CO_3 and extracted with benzene. The extract was washed with water and dried over K_2CO_3.Removal of the solvent gave a residue, which was chromatographed over silica gel in $CHCl_3$. Elution with $CHCl_3$ gave an additional crop of **3** (20 mg). Subsequent elution with the same solvent gave (±)-xylopinine (**1**) (60 mg) mp 152—152.5 °C,[4] after recrystallization from EtOH.

b) In the presence of vitamin C. The irradiation reaction of **2** (400 mg) was carried out in the presence of vitamin C (380 mg) followed by reduction with $NaBH_4$ in the same manner as above to give (±)-xylopinine (314 mg, 82%) and the 8-oxo compound (**3**) (16 mg, 4%).

6,7-Dimethoxy-1*H*-indene-1,2(3*H*)-dione 2-Oxime (6)——A solution of the ketone (**5**) (2.39 g) and isoamyl nitrite (4.0 g) in ether was treated with hydrogen chloride to give the 2-oxime (**6**) as an immediate precipitate (95%), mp 220—223 °C (from EtOH) (lit.[3] mp 208—209.5 °C). *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.51; H, 5.05; N, 6.20. IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO).

6,7-Dimethoxy-1*H*-indene-1,2(3*H*)-dione (7)——A mixture of the 2-oxime (**6**) (1.94 g), 38% aqueous formaldehyde solution (8 ml), and conc. HCl (2 ml) was stirred on a water-bath for 150 s and filtered to give the diketone (**7**) (1.35 g, 75%), mp 137—139 °C (from benzene). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.84; H, 4.86. IR ν_{max}^{Nujol} cm^{-1}: 1768, 1725 (CO). ^{1}H-NMR δ: 7.28, 7.14 (1H each, d, J=8Hz), 4.07, 3.90 (3H each, s, OMe), 3.53 (2H, s).

3′,4′-Dihydro-6′,7′-dihydroxy-6,7-dimethoxy-spiro[2*H*-indene-2,1′(2′*H*)-isoquinolin]-1(3*H*)-one (8)——A mixture of the diketone (**7**) (0.76 g), dopamine hydrochloride (1.06 g), and EtOH (20 ml) was heated under reflux with stirring for 2.5 h and concentrated to dryness under reduced pressure to leave a residue, which was taken up in 0.1% HCl (20 ml). The solution was filtered and the filtrate was washed with ether and basified to pH 8 with 28% NH_4OH to deposit the spirobenzylisoquinoline (**8**) (1.18 g, 86%), mp 222—223 °C (from EtOH). *Anal.* Calcd for $C_{19}H_{19}NO_5 \cdot 1/4\ H_2O$: C, 65.98; H, 5.68; N, 4.05. Found: C, 66.08; H, 5.69; N, 3.99. IR ν_{max}^{Nujol} cm^{-1}: 3520—3350 (OH), 1712 (CO).

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3',4'-Dihydro-6,6',7,7'-tetramethoxy-spiro[2*H*-indene-2,1'(2'*H*)-isoquinolin]-1(3*H*)-one (9)——A solution of the foregoing spirobenzylisoquinoline (**8**) (0.43 g) in MeOH was treated with excess diazomethane etherate in a refrigerator for 2 d. After addition of AcOH, the solution was concentrated to leave a residue which was taken up in $CHCl_3$. Usual work-up gave the tetramethoxyspirobenzylisoquinoline (**9**) (0.44 g, 84%) as a base, which crystallized as its ethanol solvate from EtOH mp 73—75 °C. *Anal* Calcd for $C_{21}H_{23}NO_5 \cdot C_2H_5OH$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.37; H, 7.11; N, 3.43. MS: M^+ 369. IR ν_{max}^{Nujol} cm^{-1}: 1708 (CO). ^{1}H-NMR δ: 7.23, 7.08 (1H each, d, J=8 Hz), 6.60 (1H, s), 6.16 (1H, s), 4.01, 3.90, 3.83 3.63 (3H each, s), 1.22 (3H, t, CH_3 of EtOH).

Photo-Rearrangement of the Spirobenzylisoquinoline (9) into (±)-Tetrahydropalmatine (4)——a) Without vitamin C. The reaction was carried out in the same manner as in the case of **2**. Spirobenzylisoquinoline ethanol solvate (**9**) (200 mg) gave (±)-tetrahydropalmatine (**4**) (60 mg, 35%), mp 147—148 °C (from EtOH–ether) (lit.[2] mp 147.5—148.5 °C), the IR spectrum of which was identical with that of an authentic specimen of (±)-tetrahydropalmatine,[5] and 8-oxypalmatine (**10**) (24 mg, 14%), which crystallized from EtOH, mp 185—186 °C. *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.63; H, 5.76; N, 3.81. Found: C, 68.50: H, 5.83; N, 3.74. ^{1}H-NMR δ: 7.31 (2H, s), 7.22 (1H, s), 6.75 (1H, s), 6.72 (1H, s), 4.32 (2H, t, J=5.3 Hz), 4.01, 3.98, 3.95, 3.93 (3H each, s) 2.91 (2H, t, J=5.3 Hz), after preparative TLC.

b) In the presence of vitamin C. The same reaction sequence on **9** (200 mg) as above in the presence of vitamin C (190 mg) in EtOH (350 ml) gave (±)-tetrahydropalmatine (**4**) (75 mg, 45%) after preparative TLC. 8-Oxypalmatine (**10**) was detected very faintly on a thin layer chromatogram.

References

1) H. Irie, K. Akagi, S. Tani, K. Yabusaki, and H. Yamane, *Chem. Pharm. Bull.*, **21**, 855 (1973).
2) J. S. Glasby, "Encyclopedia of the Alkaloids," Vol. 2, Plenum Press, New York, 1975, p. 1298 and references cited therein.
3) S. O. deSilva, I. Ahmad, and V. Snieckus, *Can. J. Chem.*, **57**, 1598 (1979).
4) The melting point of 189—190 °C for (±)-xylopinine reported in our previous paper[1] was incorrect, and should be revised to 152—152.5 °C based on a re-investigation of the melting point of the synthetic compound.
5) We are indebted to Emeritus Professor M. Tomita (Kyoto University) for providing a sample of (±)-tetrahydropalmatine.

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