[Chem. Pharm. Bull. 32(4)1614—1618(1984)]

Studies on the Syntheses of Heterocyclic Compounds and Natural Products. MXVI.[1] Aziridine in Alkaloid Synthesis. (6). Alternative Synthesis of Isopavine-Type Alkaloid, (±)-Reframidine

TETSUJI KAMETANI,* KIMIO HIGASHIYAMA, TOSHIO HONDA, and HIROTAKA OTOMASU

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received August 5, 1983)

The isopavine alkaloid (±)-reframidine (**10**) was synthesized from deoxypiperoin (**1**) *via* a ring opening reaction of the quaternary aziridinium salt as a key step.

Keywords——synthesis; isopavine alkaloid; reframidine; aziridine; ring-opening reaction

We have recently reported syntheses of various types of isoquinoline alkaloids, such as a 2-benzylisoquinoline alkaloid, (±)-sendaverine,[2] a 4-phenylisoquinoline alkaloid, (±)-cherylline,[3] a phthalidylisoquinoline, hydrastine,[4] and γ-lycorane,[5] *via* a ring-opening reaction of quaternary aziridinium salts. The interest in the utilization of a quaternary aziridinium salt as a reactive intermediate stems not only from its high reactivity originating from the release of the strain energy inherent in a three-membered ring,[6] but also from the ease with which an ethylamine moiety can be introduced.

We have already indicated that the above procedure would provide a useful route to

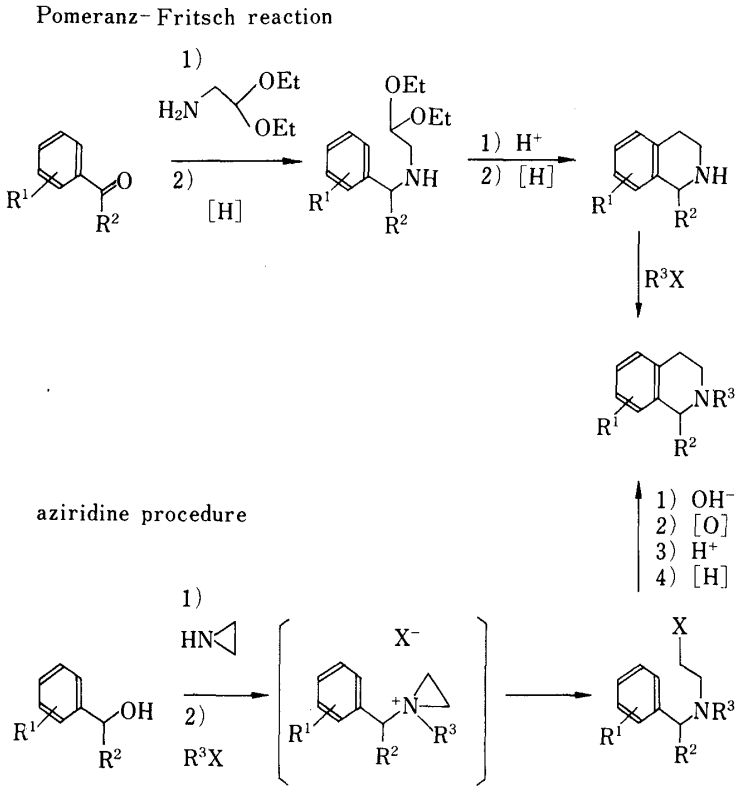


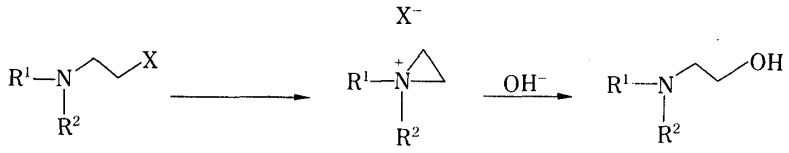
Chart 1

synthesize the 1,2,3,4-tetrahydroisoquinoline nucleus in a modified Pomeranz–Fritsch-type reaction,[2] shown in Chart 1.

As an extension of this work on the synthesis of isoquinoline alkaloids, we have investigated the synthesis of an isopavine alkaloid, (±)-reframidine.[7]

The known deoxypiperoin[8] (**1**) was converted into the chloride (**3**) *via* the alcohol (**2**) by reduction with sodium borohydride and subsequent chlorination with thionyl chloride. The requisite aziridine derivative (**4**) was prepared from the chloride (**3**) and ethyleneimine in the presence of potassium carbonate in benzene in 81.2% yield. Though the N-methylation of **4** with methyl iodide (from 1 to 10 mol) was used in an attempt to cleave the aziridine ring, none of the desired product was isolated. However, this was overcome by the reaction of **4** with ethyl chlorocarbonate, which could be transformed into a methyl group by reduction with lithium aluminum hydride, to yield the urethane (**5**).

Thus, the preparation of all the carbon frameworks required to synthesize (±)-reframidine was accomplished. We then focused our attention on the conversion of the chloride (**5**) into the corresponding alcohol (**6**). Though *N*,*N*-dialkyl-β-haloamines are readily transformed into the corresponding alcohols *via* quaternary aziridinium salts by passage through an alumina column, as shown in Chart 2, N-acylated derivatives, which do not give such reactive intermediates, resisted such conversion.



$R^1=R^2=H$, or alkyl X=halogen

Chart 2

Among various attempts, treatment of **5** with mercuric oxide and perchloric acid according to McKillop's procedure[9] afforded the desired alcohol (**6**) together with the oxazolidinone (**7**) in 47.8 and 25% yields, respectively. The former (**6**) was easily cyclized to the latter (**7**) by passing it through an alumina column using benzene as an eluant. Though the reduction of the urethane (**6**) with lithium aluminum hydride afforded none of the expected alcohol, **8** was obtained in good yield when the oxazolidinone (**7**) was subjected to reduction with lithium aluminum hydride. Swern oxidation[10] of the alcohol (**8**) furnished the aldehyde (**9**), which, without purification, was subjected to the ring closure reaction originally developed by Battersby,[11] to give (±)-reframidine (**10**). The synthetic material was identical with an authentic specimen.[12]

Thus, we achieved the synthesis of the isopavine alkaloid, (±)-reframidine, by employing a ring-opening reaction of a quaternary aziridinium salt as a key step.

This procedure should be available as an alternative synthetic route to various types of 1,2,3,4-tetrahydroisoquinolines.

Experimental

Infrared (IR) spectra were measured with a Hitachi 260-10 spectrophotometer, and nuclear magnetic resonance (NMR) spectra with JEOL PMS-60 SI and JEOL JNM-FX 100 spectrometers. Ordinary and accurate mass spectra (MS) were taken with a JEOL JMS-D 300 spectrometer.

Deoxopiperoin (2)——Sodium borohydride (1.51 g) was added to a stirred solution of deoxypiperoin (**1**) (5.68 g) in methanol (100 ml) in small portions at room temperature, and the resulting mixture was heated under reflux for

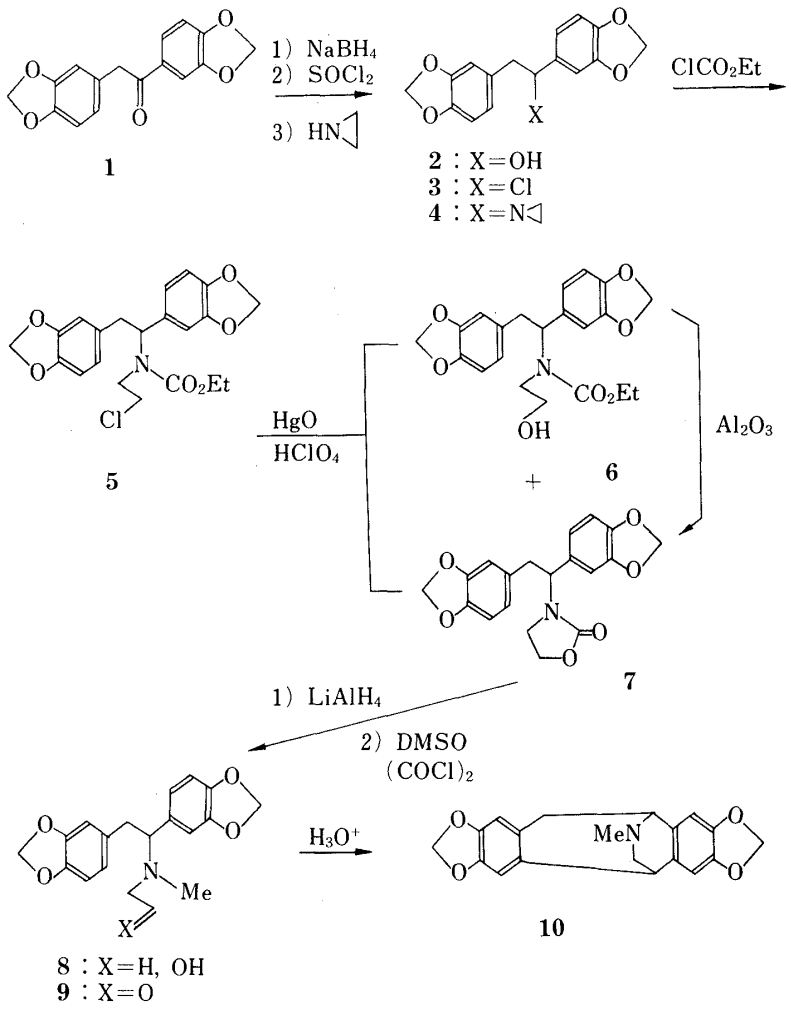


Chart 3

1.5 h. After evaporation of the solvent, the residue was treated with water and the solid precipitate was collected by filtration. Recrystallization from methanol–benzene afforded the alcohol (**2**) (5.65 g, 98.8%) as colorless prisms, mp 163—164 °C. *Anal.* Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 66.99; H, 4.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1610 (C=C). NMR ($CDCl_3$) δ: 1.92 (1H, s, OH), 2.88 (2H, d, J=6.8 Hz, CH_2), 4.74 (1H, t, J=6.8 Hz, CH), 5.92 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O), 6.56—6.87 (6H, m, ArH). MS (*m/e*): 286 (M^+).

***N*-[Bi(3,4-methylenedioxybenzyl)-α-yl]aziridine (4)**——A mixture of the alcohol (**2**) (5.72 g), phosphorus trichloride (2.2 g) and dry benzene (100 ml) was stirred at ambient temperature for 5 h. The resulting mixture was then poured into ice-water and extracted with benzene. The organic layer was washed with 10% aqueous sodium carbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded the chloride (**3**) as an oil [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600 (C=C). NMR ($CDCl_3$) δ: 3.24 (2H, d, J=7.5 Hz, CH_2), 4.90 (1H, t, J=7.5 Hz, CH), 5.91 (2H, s, OCH_2O), 5.96 (2H, s, OCH_2O), 6.58—6.88 (6H, m, ArH). MS (*m/e*) 304 (M^+)] which, without purification, was used for the next reaction. Ethyleneimine (40 ml) was added to a stirred solution of the chloride (**3**) obtained above in benzene (50 ml) in the presence of potassium carbonate (5 g) at ambient temperature and the resulting mixture was further stirred for 12 h at the same temperature. After evaporation of the solvent and excess reagent, the residue was diluted with water and extracted with benzene. The benzene layer was washed with water, dried over Na_2SO_4 and concentrated to give the residue, which was subjected to column chromatography on neutral alumina. Elution with methylene chloride gave the aziridine (**4**) (5.05 g, 81.2%) as a colorless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}· 1610 (C=C). NMR ($CDCl_3$) δ: 1.09 (2H, m, aziridine protons), 1.71 (2H, m, aziridine protons), 2.27 (1H, t, J=6.6 Hz, CH), 2.91 (1H, dd, J=6.6 and 14.4 Hz, C<H/H), 3.03 (1H, dd, J=6.6 and 14.4 Hz, C<H/H), 5.89 (2H, s, OCH_2O), 5.93 (2H, s, OCH_2O), 6.45—6.86 (6H, m, ArH). MS (*m/e*): 311 (M^+); Found: *m/e* 311.1160. Calcd for $C_{18}H_{17}NO_4$ (M^+), *m/e* 311.1158.

***N*-β-Chloroethyl-*N*-ethoxycarbonyl-[α-(3,4-methylenedioxybenzyl)]-3,4-methylenedioxybenzylamine (5)**——Ethyl chlorocarbonate (2.17 g) was added to a stirred solution of the aziridine (**4**) (6.22 g) in benzene (100 ml) over a period of 15 min at room temperature, and the mixture was further stirred for 12 h at the same temperature. After

evaporation of the solvent, the solidified residue was recrystallized from *n*-hexane to afford the ring-opened product (**5**) (7.70 g, 91.8%) as colorless prisms, mp 79—80 °C. *Anal.* Calcd for $C_{21}H_{22}ClNO_6$: C, 60.07; H, 5.28; N, 3.34. Found: C, 60.37; H, 5.26; N, 3.05. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (C=O), 1600 (C=C). NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.1 Hz, CH_2CH_3), 2.75—3.58 (6H, m, 3×CH_2), 4.07 (2H, q, J=7.1 Hz, CH_2CH_3), 5.36 (1H, t, J=8.0 Hz, NCH), 5.89 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O), 6.65—6.85 (6H, m, ArH); MS (*m/e*): 419 (M^+).

***N*-Ethoxycarbonyl-*N*-β-hydroxyethyl-[α-(3,4-methylenedioxybenzyl)]-3,4-methylenedioxybenzylamine (6) and *N*-[Bi(3,4-methylenedioxybenzyl)-α-yl]-1,3-oxazolidin-2-one (7)**——The chloride (**5**) (4.2 g) was added to a stirred suspension of mercuric oxide (2.15 g) in 1,2-dimethoxyethane (25 ml), 60% aqueous perchloric acid (2.5 ml) and water (2 ml) at room temperature according to McKillop's procedure.[9] After stirring for 12 h at room temperature, the mixture was concentrated to half-volume and diluted with water (50 ml). The resulting mixture was extracted with methylene chloride and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent afforded the residue, which was subjected to column chromatography on neutral alumina. Elution with methylene chloride yielded the alcohol (**6**) (1.92 g, 47.8%) as a colorless oil. *Anal.* Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.70; H, 5.73; N, 3.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1740 (C=O), 1610 (C=C). NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz, CH_2CH_3), 1.69 (1H, s, OH), 2.61—2.80 (4H, m, 2×CH_2), 3.72 (1H, t, J=7.4 Hz, NCH), 4.03—4.15 (2H, m, CH_2OH), 4.16 (2H, q, J=7.4 Hz, CH_2CH_3), 5.91 (2H, s, OCH_2O), 5.93 (2H, s, OCH_2O), 6.57—6.85 (6H, m, ArH). MS (*m/e*): 266 ($M^+ - 135$).

Further elution with methylene chloride afforded the oxazolidinone (**7**) (0.89 g, 25.0%) as colorless needles, mp 146—147 °C (from benzene). *Anal.* Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.21; H, 4.75; N, 3.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 1600 (C=C). NMR ($CDCl_3$) δ: 3.16 (2H, d, J=8.1 Hz, CH_2Ar), 3.24 (1H, dd, J=7.9 and 14.8 Hz, NC$\overset{H}{\underset{H}{<}}$), 3.50 (1H, dd, J=7.9 and 14.8 Hz, NC$\overset{H}{\underset{H}{<}}$), 5.90 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O), 6.68—6.87 (6H, m, ArH). MS (*m/e*): 355 (M^+).

The oxazolidinone (**7**) was easily obtained from the alcohol (**6**) by passing **6** through a neutral alumina column using benzene as an eluant (73.4% yield).

***N*-β-Hydroxyethyl-*N*-methyl-[α-(3,4-methylenedioxybenzyl)]-3,4-methylenedioxybenzylamine (8)**——A solution of the oxazolidinone (**7**) (1.78 g) in dry tetrahydrofuran (20 ml) was added to a stirred suspension of lithium aluminum hydride (0.38 g) in dry tetrahydrofuran (30 ml) at ambient temperature. The mixture was then heated under reflux for 1 h. After the reaction had been quenched by addition of water, the precipitates formed were filtered off. The filtrate was concentrated to give the residue, which was subjected to column chromatography on silica gel. Elution with methylene chloride–methanol (99 : 1, v/v) gave the alcohol (**8**) (1.50 g, 87.2%) as a colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (OH), 1610 (C=C). NMR ($CDCl_3$) δ: 2.18 (3H, s, NMe), 2.37—2.74 (3H, m, NCH_2 and OH), 2.89 (1H, dd, J=7.6 and 13.7 Hz, $ArCH_2$), 3.10 (1H, dd, J=7.6 and 13.7 Hz, $ArCH_2$), 3.49 (2H, t, J=5.2 Hz, CH_2OH), 3.72 (1H, t, J=7.6 Hz, NCH), 5.87 (2H, s, OCH_2O), 5.92 (2H, s, OCH_2O), 6.51—6.78 (6H, m, ArH). MS (*m/e*): 208 ($M^+ - 135$), which was crystallized as its picrate, mp 159—160 °C (from ethanol). *Anal.* Calcd for $C_{25}H_{24}N_4O_{12}$: C, 52.45; H, 4.23; N, 9.79. Found: C, 52.53; H, 4.19; N, 9.91.

(±)-Reframidine (10)——A solution of dimethylsulfoxide (0.94 g) in methaylene chloride (2.6 ml) was added to a stirred solution of oxalyl chloride (0.7 g) in methylene chloride (12.5 ml) at −60 °C over a period of 5 min, and the resulting mixture was further stirred at the same temperature for 15 min. A solution of the alcohol (**8**) (1.4 g) in methylene chloride was then added to the above solution at −60 °C over a period of 5 min and the resulting mixture was stirred for 0.5 h at the same temperature. After the addition of trifluoroacetic acid (2.53 g) at −60 °C, the mixture was warmed up to room temperature, and treated with water. The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated to give the aldehyde (**9**), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O). NMR ($CDCl_3$) δ: 2.34 (3H, s, NMe), 2.50—3.75 (5H, m, 2×CH_2 and CH), 5.85 (2H, s, OCH_2O), 5.90 (2H, s, OCH_2O), 6.38—6.77 (6H, m, ArH), 9.55 (1H, t, J=1.8 Hz, CHO). MS (*m/e*): 206 ($M^+ - 135$), which, without further purification, was used for the next reaction. A solution of the aldehyde (**9**) obtained above in ethanol (3 ml) and concentrated hydrochloric acid (30 ml) was allowed to stand at ambient temperature for 5 d. After the solution had been basified with ammonium hydroxide, the mixture was extracted with chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and concentrated to give the residue, which was subjected to column chromatography on silica gel. Elution with methylene chloride–methanol (99 : 1, v/v) afforded (±)-reframidine (**10**) (0.64 g, 46.3%) whose spectral data and thin-layer chromatographic behavior were identical with those of an authentic specimen.

Acknowledgement We thank Mrs. T. Ogata, Mrs. M. Yuyama, Miss T. Tanaka, Mrs. A. Kumazawa, and Miss M. Moriki of Hoshi University for spectral measurements and for preparation of the manuscript.

References and Notes

1) Part MXV: M. Ihara, F. Konno, K. Fukumoto, and T. Kametani, *Heterocycles*, **20**, 2181 (1983).
2) H. Otomasu, K. Higashiyama, T. Honda, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2399.
3) T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1935.

4) T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1221.
5) K. Higashiyama, T. Honda, H. Otomasu, and T. Kametani, *Planta Med.*, **48**, 268 (1983).
6) D. R. Crist and N. J. Leonard, *Angew. Chem. Int. Ed. Engl.*, **8**, 962 (1969).
7) S. F. Dyke and A. C. Ellis, *Tetrahedron*, **27**, 3803 (1971).
8) I. Allen and J. S. Buck, *J. Am. Chem. Soc.*, **52**, 310 (1930).
9) A. McKillop and M. E. Ford, *Tetrahedron*, **30**, 2647 (1974).
10) A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
11) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, **1958**, 1988.
12) T. Kametani, S. Hirata, and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1466.