[Chem. Pharm. Bull. 32(10)4154—4156(1984)]

Studies on Tetrahydroisoquinolines. XXII.[1] A Stereospecific Synthesis of (±)-Srilankine and (±)-Cataline

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(Received March 2, 1984)

Lead tetraacetate oxidation of (±)-predicentrine (**4**) in acetic acid and in CH_2Cl_2 gave (±)-4-*O*-acetylsrilankine (**11**) and the *o*-quinol acetate (**6**), respectively. The latter (**6**) was transformed into (±)-*O*,*O*-diacetylsrilankine (**13**) under Thiele's conditions. Hydrolysis of **11** or **13** afforded (±)-srilankine (**1**), methylation of which yielded (±)-cataline (**2**).

Keywords——lead tetraacetate oxidation; *o*-quinol acetate; 4-hydroxyaporphine; stereospecificity; biomimetic reaction

Recently, Philipov *et al.*[2] reported a novel synthesis of (+)-srilankine (**1**) and (+)-cataline (**2**) starting from either (+)-glaucine (**3**) or (+)-predicentrine (**4**). A common intermediate for the reaction was proved to be glaucine-quinol (**5**).

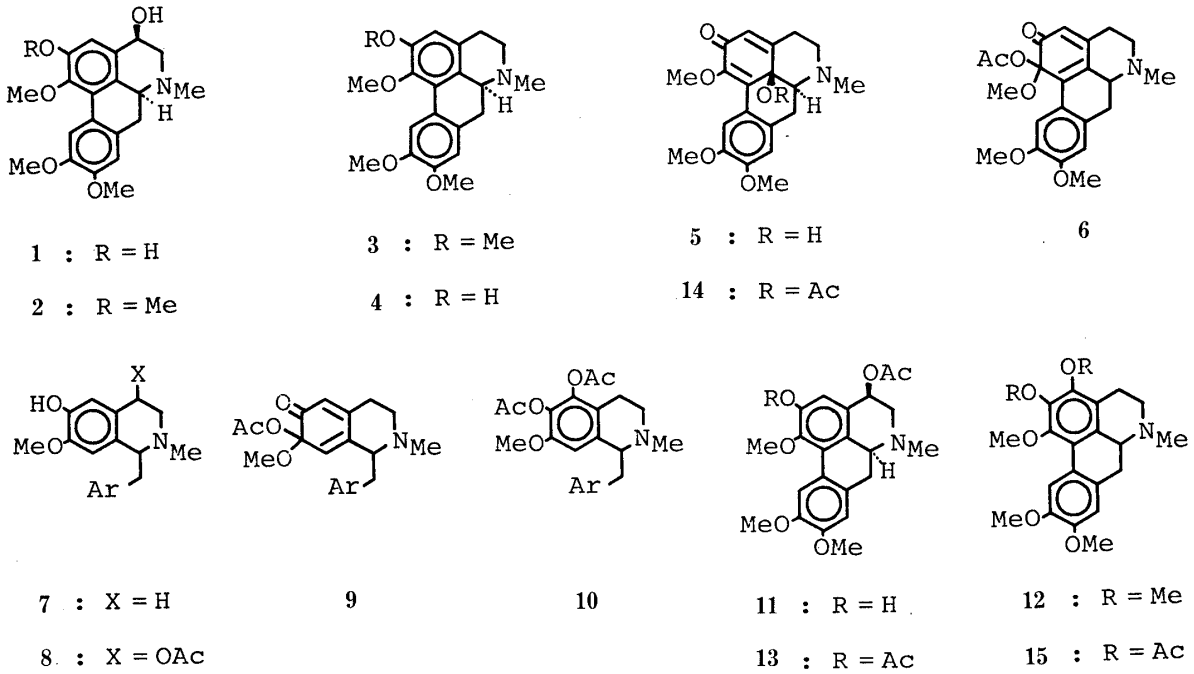
Since we have developed lead tetraacetate oxidation of phenolic 1,2,3,4-tetrahydroisoquinolines, we were interested in an alternative synthesis of the alkaloids based on our own methodology, *i.e.* by way of an appropriate *o*-quinol acetate (**6**), which was derivable from (±)-predicentrine (**4**).

As to the oxidation of 1-substituted 1,2,3,4-tetrahydroisoquinolin-6-ols (**7**) in general, two distinctive features have been uncovered so far in our laboratory: 1) the oxidation in acetic acid gives 4-acetoxy derivatives (**8**),[3] 2) that in CH_2Cl_2 furnishes *o*-quinol acetates (**9**), acid treatment of which under Thiele's conditions (Ac_2O–conc. H_2SO_4) provides 5,6-diacetates (**10**).[4] Accordingly, it was anticipated that the former oxidation would give (±)-srilankine (**1**) as its 4-acetate (**11**), while the latter would give (±)-thalicsimidine (**12**).

Lead tetraacetate oxidation of (±)-predicentrine (**4**)[5] in acetic acid at room temperature, as expected, gave (±)-4-*O*-acetylsrilankine (**11**) [IR: 3500 cm^{-1} (OH) and 1730 cm^{-1} (OAc); NMR: δ 5.75 (br s, 4-H)] stereospecifically. The stereospecificity of this reaction was a result of attack of acetic acid from the lone pair side of nitrogen as shown in the scheme.[6] Without purification, **11** was hydrolyzed with 10% hydrochloric acid to give (±)-srilankine (**1**) in 20% yield from **4**. The nuclear magnetic resonance (NMR) spectrum of **1** was superimposable on that of Prof. Philipov's authentic sample.[2] Acetylation of **1** afforded the diacetate (**13**), which gave NMR data coincident with those reported in the literature.[2] Thus, our expectation was validated.

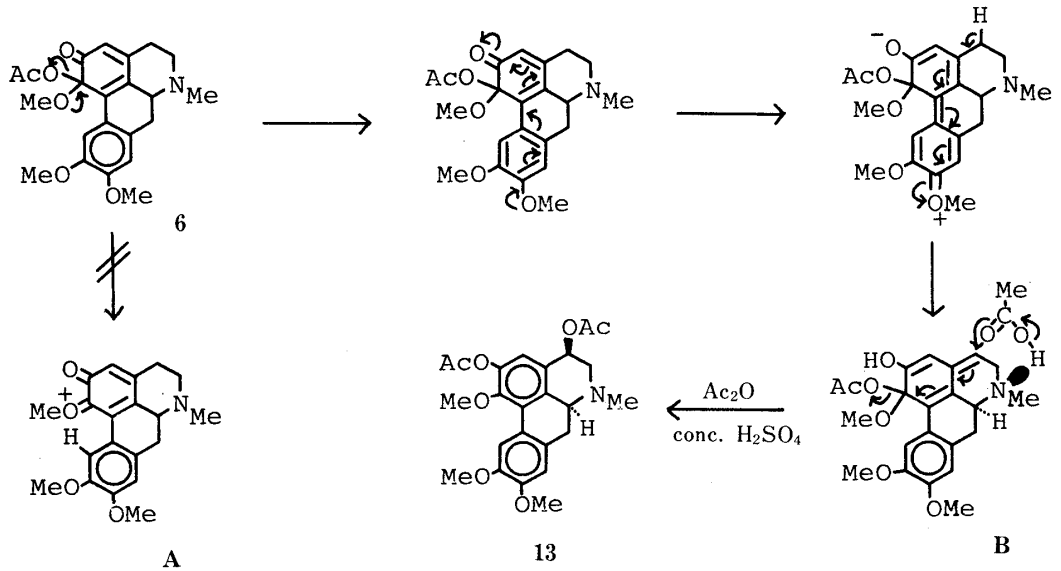
Next, (±)-predicentrine (**4**) was oxidized in CH_2Cl_2 at 0 °C for 1 min to give rise to the *o*-quinol acetate (**6**) as a mixture of two diastereomers. The NMR spectrum of **6** showed two signals due to an aliphatic methoxyl group [δ 3.34 and 3.46 (3:2)], which unequivocally supported the *o*-quinol acetate structure (**6**), excluding the *p*-quinol acetate (**14**). Without purification, **6** was treated with Ac_2O–conc. H_2SO_4 at room temperature to afford (±)-*O*,*O*-diacetylsrilankine (**13**) in 70% yield. The reaction again proceeded stereospecifically. No formation of 2,3-diacetoxy-1,9,10-trimethoxyaporphine (**15**) was observed, contrary to our

expectation. Hydrolysis of the diacetate (**13**) gave (±)-srilankine (**1**) in 79% yield. The overall yield from **4** amounted to 55%. Methylation of (±)-**1** with diazomethane provided (±)-cataline (**2**) [mp 148—152 °C (dec.)] in 83% yield. Admixture of **2** with an authentic sample[6] did not depress the melting point. Thus, (±)-srilankine (**1**) and (±)-cataline (**2**) were stereospecifically and biomimetically synthesized. However, transformation of the *o*-quinol acetate (**6**) into the 3-oxygenated aporphine (**15**) has not been achieved yet. Failure to obtain **15** seems to suggest that no cation such as **A** was formed initially because of inherent steric strain in the molecule and that the conjugation of the C-9 methoxy group to the enone system in **6** resulted in electron movement as shown in the scheme, leading to an enol **B**, which would be readily susceptible to stereoselective vinylogous allylic substitution by the hydrogen-bonded acetic acid.[6]



1 : R = H
2 : R = Me
3 : R = Me
4 : R = H
5 : R = H
14 : R = Ac
6
7 : X = H
8 : X = OAc
9
10
11 : R = H
13 : R = Ac
12 : R = Me
15 : R = Ac

Fig.



6
A
13
B

Chart

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. NMR spectra were taken with a JEOL JNX-FX-100 (100 MHz) or Hitachi R-24B instrument in $CDCl_3$ solution with Me_4Si as an internal standard. Infrared (IR) spectra were run on a Hitachi model 260 spectrometer in $CHCl_3$ solution, unless otherwise noted. Mass spectral (MS) data were measured with a Hitachi RMU-6E mass spectrometer. Preparative thin layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} plates (Merck) 2.0 mm thick.

Oxidation of 4 in AcOH and the Synthesis of (±)-Srilankine (1) (Method A)——Lead tetraacetate (115 mg, 1.2 eq) was added to a stirred AcOH (4 ml) solution of (±)-predicentrine (**4**)[5] (73 mg) in one portion. The mixture was stirred at room temperature for 5 min, and usual work-up[6] gave (±)-4-*O*-acetylsrilankine (**11**) [89 mg, oil; IR (cm^{-1}): 3500 (OH), 1730 (OAc); NMR δ: 2.08 (3H, s, OAc), 2.47 (3H, s, NMe), 3.55, 3.82, 3.86 (each 3H, s, OMe), 5.75 (1H, br s, 4-H), 6.63, 6.69, 7.70 (each 1H, s, ArH)]. Without purification, **11** (89 mg) was hydrolyzed with 10% HCl at room temperature for 1 h. Work-up as usual gave an oil (80 mg), which was purified by preparative TLC (development with $CHCl_3$: MeOH = 10 : 1) to afford (±)-srilankine (**1**) [15 mg (20% yield from **4**), oil, IR (cm^{-1}): 3500 (OH); NMR δ: 2.56 (3H, s, NMe), 3.58, 3.90, 3.92 (each 3H, s, OMe), 4.45 (1H, br s, 4-H), 6.75, 6.89, 7.87 (each 1H, s, ArH); MS *m/z*: 357 (M^+), 356, 314 (base peak)]. The spectral data of **1** were consistent with those of an authentic sample.[2]

Acetylation of 1——Acetylation of crude **1** (71 mg) with Ac_2O (1 ml) and pyridine (2 ml), followed by purification by preparative TLC (development with pet. ether : $CHCl_3$: acetone : MeOH = 16 : 16 : 2 : 1) gave (±)-*O*,*O*-diacetylsrilankine (**13**) [24 mg (26% yield from **4**), oil; IR (cm^{-1}): 1770, 1725 (OAc)[7]; NMR δ: 2.15, 2.36 (each 3H, s, OAc), 2.58 (3H, s, NMe), 3.61, 3.89, 3.93 (each 3H, s, OMe), 5.86 (1H, br s, 4-H), 6.76, 7.00, 7.90 (each 1H, s, ArH)]. Methiodide of **13**: mp 240—243 °C (dec.) (MeOH); *Anal.* Calcd for $C_{25}H_{29}INO_7 \cdot 0.5H_2O$ (m.w. = 591.408): C, 50.77; H, 5.11; N, 2.37; Found: C, 50.78, H, 5.07, N, 2.36. IR and NMR spectral data of **13** were consistent with those reported in the literature.[2]

Oxidation of 4 in CH_2Cl_2 and the Synthesis of 13 and (±)-Srilankine (1) (Method B)——Lead tetraacetate (57 mg, 1.1 eq) was added into an ice-cooled solution of **4** (40 mg) in CH_2Cl_2 (2 ml), and the mixture was stirred at the same temperature for 1 min. The resulting precipitate was removed by filtration and a few drops of water were added to the filtrate with stirring. The filtrate was dried over K_2CO_3, and the solvent was removed under reduced pressure at below 30 °C to give the *o*-quinol acetate (**6**) [oil; IR (cm^{-1}): 1710 (OAc), 1660 (dienone); NMR δ: 1.89, 2.10 (3H, 2 × s (2 : 3), OAc), 2.48, 2.52 (3H, 2 × s (2 : 3), NMe), 3.34, 3.46 (3H, 2 × s (3 : 2), OMe), 3.85 (6H, br s, 2 × OMe), 5.92 (1H, br s, olefinic H), 6.62 (1H, s, 8-H), 7.30, 7.51 (1H, 2 × s (2 : 3)]. Without purification, **6** was dissolved in Ac_2O (1 ml), and a mixture of Ac_2O (0.5 ml) and conc. H_2SO_4 (0.1 ml) was added to the ice-cooled solution. The mixture was stirred at room temperature for 30 min, and usual work-up gave an oil (44 mg), which was purified by preparative TLC (development with $CHCl_3$: MeOH = 15 : 1) to afford the diacetate (**13**) [36 mg (70% yield from **4**), oil]. **13** was identical with an authentic sample reported above. Hydrolysis of the diacetate (**13**) (23 mg) with 10% HCl (8 ml) yielded (±)-srilankine (**1**) [15 mg (79%), oil], which was identical with the authentic sample reported above.

The Synthesis of (±)-Cataline (2)——Methylation of **1** (23 mg) in MeOH (1 ml) with diazomethane–ether solution (excess) gave (±)-cataline [20 mg (83%), mp 148—152 °C (dec.) (ether); IR (cm^{-1}): 3520 (OH); NMR δ 2.53 (3H, s, NMe), 3.63, 3.86 (each 3H, s, OMe), 3.89 (6H, s, 2 × OMe), 4.43 (1H, br s, 4-H), 6.70, 6.81, 7.99 (each 1H, s, ArH)], which was identical with an authentic sample (mp 149—150 °C[6]) on the basis of mixed melting point determination and NMR and TLC comparisons.

Acknowledgement The authors gratefully acknowledge the financial support of this work by a Grant-in-Aid for scientific research (No. 58570890) from the Ministry of Education, Science and Culture, Japan. They are indebted to Prof. S. Philipov of the Bulgarian Academy of Sciences for providing NMR charts of (+)-srilankine and its diacetate, and to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for providing the starting vanillin. Thanks are also due to Sankyo Co., Ltd. for elemental analysis, and to Miss N. Sawabe, Miss N. Takagi, and Miss K. Kim of this Faculty for NMR and MS measurements.

References and Notes

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