Notes

Synthesis of an Isopavine Alkaloid. (±)-*O*-Methylthalisopavine

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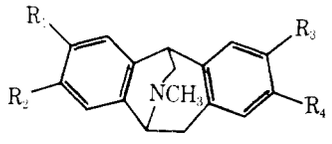
Isopavine alkaloids (**1**) have only recently been recognized as a class of natural products, and their identification fills a gap in the array of compounds biogenetically derived from the 1-benzylisoquinolines (**2**).[1,2] From a purely structural standpoint, the isopavine system could be formed from **2** by oxidative coupling between the 6′ position of the benzyl group and the 4 position of the isoquinoline ring. Dyke and Ellis have proposed that 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines may be biogenetic precursors of isopavine alkaloids.[3]



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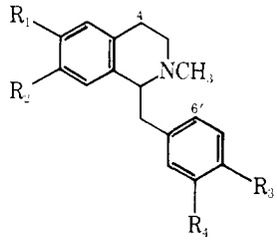

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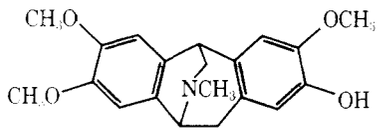
In our program to synthesize isoquinoline alkaloids from 6-homoveratroylhomoveratic acid (**3**),[4] we had found earlier that anodic oxidation of the 3-isochromanone derivative **4** in acetonitrile afforded a bridged lactone (**5**) and noted that **5** provided a close oxygen analogue of an isopavine alkaloid (Scheme I).[5] At that time, however, we were unsuccessful in preparing a comparable bridged lactam (**7**) by electrochemical oxidation of the corresponding 3-isoquinolone derivative (**6**). In the prior work we had observed that oxidation of **4** in dichloromethane–trifluoroacetic acid (DCM–TFA) solution gave the identical spiro dienone **8**, either by reaction at a platinum anode or by VOF_3. In like fashion, the lactam **6** was converted to **9** electrolytically or chemically in DCM–TFA. Based on these parallel results in DCM–TFA solutions, we subsequently decided to investigate the behavior of **4** toward VOF_3 in acetonitrile and now wish to report that from this system the same bridged lactone (**5**) is obtained in 71% yield.



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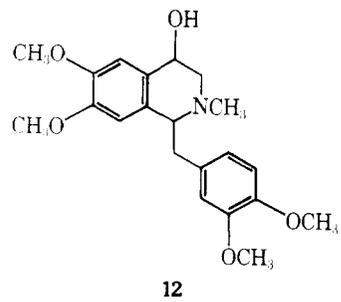

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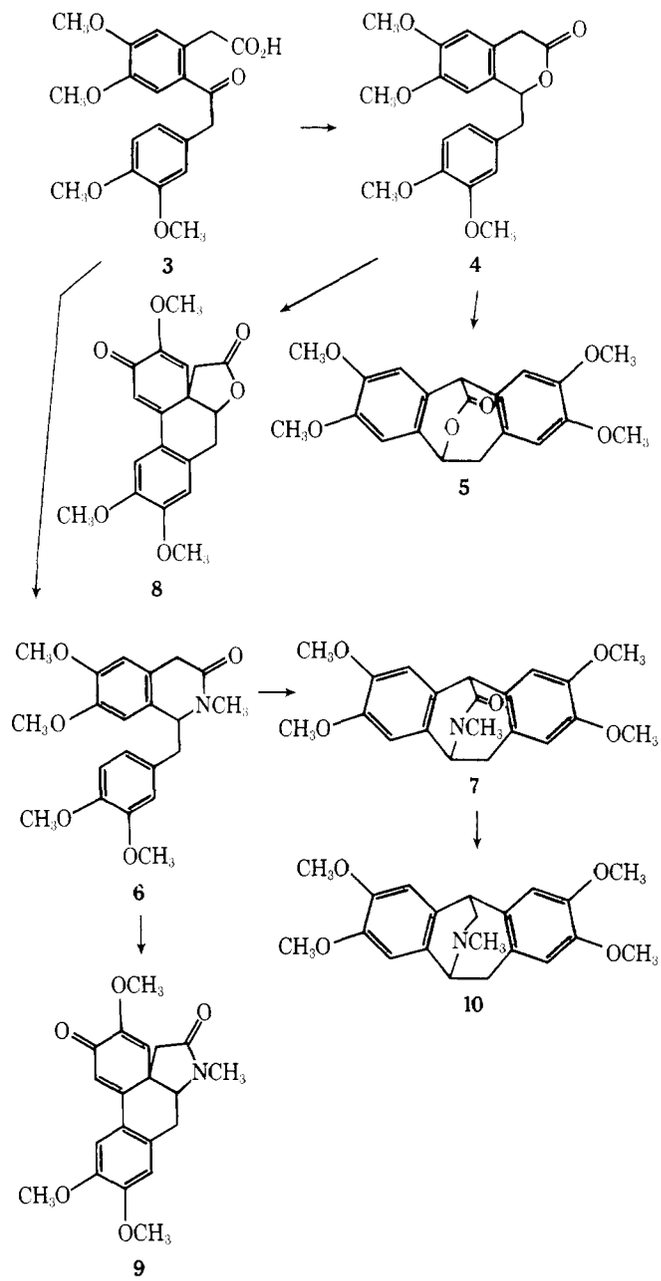
Scheme I



By a similar procedure, VOF_3 in acetonitrile is shown to oxidize 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-3-isoquinolone (**6**) to a bridged lactam (**7**) in 40% yield.[6] The constitution **7** is assigned to the oxidation product on the basis of its properties, including spectral characteristics closely related to **5**, and the reduction of **7** to (±)-*O*-methylthalisopavine (**10**) with borane–THF complex. Although **10** is not among the known isopavine alkaloids, it was prepared earlier by Kupchan[7] by methylation of the alkaloid thalisopavine (**11**) and also by Dyke and Ellis[3] from a synthetic sequence in which the penultimate compound was the 4-hydroxyisoquinoline derivative **12**. The properties of our isopavine compound **10** agreed with those in the literature, and, finally as a proof of structure an alternate synthesis of **10** was accomplished by a more traditional approach from deoxyveratroin (**13**) (Scheme II).[8]

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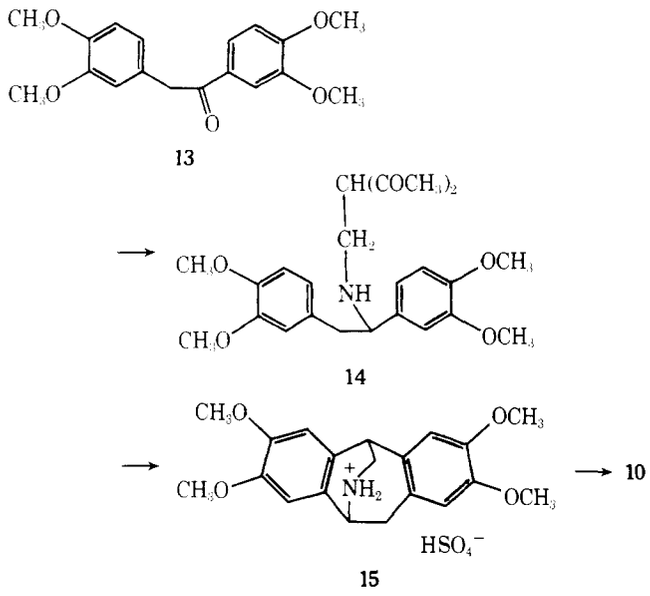
Scheme II. Alternative Synthesis of (±)-*O*-Methylthalisopavine



Experimental Section[9]

2,3,7,8-Tetramethoxy-13-oxo-10,5-(epoxymethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (5). A solution of the lactone **4** (1.8 g) in CH_3CN (100 mL) was stirred mechanically and cooled in an ice bath, and a slurry of VOF_3 (3.5 g) in CH_3CN (15 mL) was added over a 2-min period. After stirring for 3 h, the mixture was diluted with CH_2Cl_2 (100 mL) and poured into water (300 mL) containing citric acid (10 g). The layers were separated, and the CH_2Cl_2 solution was evaporated. The crude product was recrystallized from EtOH–C_6H_6, and the bridged lactone **5** (1.27 g, 71%) was obtained in two crops, mp 247–249 °C. This oxidation product was identified as **5** by infrared and mass spectral comparison with a sample prepared by anodic oxidation.[5]

2,3,7,8-Tetramethoxy-12-methyl-13-oxo-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane (7). By the procedure described for the preparation of **5**, the 3-isoquinolone **6** (1.5 g) was oxidized by VOF_3 (2.9 g) in CH_3CN (50 mL). The crude product recrystallized very slowly from aqueous MeOH in three crops: 0.6 g; mp 231–233 °C; MS *m/e* 369 (M^+); UV λ_{max} (EtOH) 290 nm (log ϵ 4.0). Anal. Calcd for $C_{21}H_{23}NO_5 \cdot 0.5H_2O$: C, 66.69; H, 6.39; N, 3.71. Found: C, 66.96; H, 6.29; N, 3.60.

(±)-*O*-Methylthalisopavine. (a) By Reduction of 7. The lactam **7** (0.9 g) was added to BH_3–THF complex (100 mL), and the solution was allowed to stand 18 h. Addition of cold water and evaporation of the THF left a gum that, after unsuccessful attempts to purify as the HCl salt, was finally converted back to the base with aqueous NaOH and recrystallized from MeOH–H_2O as a colorless solid, 0.1 g, mp 163–165 °C, after drying over KOH pellets: MS *m/e* 355 (30), 354 (28), 312 (39), 204 (100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.80; H, 6.95; N, 3.77.

(b) From Deoxyveratroin. Deoxyveratroin (5 g) was condensed with aminoacetaldehyde dimethyl acetal (20 g) and immediately hydrogenated to the amine acetal (**14**) by the procedure of Battersby and Yeowell.[8a] Compound **14** was cyclized by sulfuric acid, and thalisopavine sulfate (1.0 g), mp 185–188 °C, was isolated. A solution of the salt (0.8 g) in 40% HCHO (3 mL)–EtOH (5 mL) was treated after 5 min with $NaBH_4$ (0.3 g). The reaction mixture was diluted with water (15 mL) after 3 h, and a colorless solid (0.3 g) was collected. The isopavine **10** was recrystallized from aqueous MeOH, mp 165–166 °C (lit.[3] mp 165–166 °C); this compound proved to be identical with the product from part a by melting point, IR, and MS comparisons.

Acknowledgments. This work was supported by National Institutes of Health Grant SO6-RR0862.

Registry No.—**4**, 68890-14-2; **5**, 68890-15-3; **6**, 30048-23-8; **7**, 68890-17-5; **10**, 33579-95-2; **13**, 4927-55-3; **14**, 68890-18-6; **15**, 68907-93-7; aminoacetaldehyde dimethyl acetal, 22483-09-6.

References and Notes

(1) S. F. Dyke, "Rodd's Chemistry of Carbon Compounds", Vol. 4H, S. Coffey, Ed., Elsevier, New York, N.Y., 1978, p 1.
(2) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972); I. D. Spenser, "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand Reinhold, New York, N.Y., 1970, p 669.
(3) S. F. Dyke and A. C. Ellis, *Tetrahedron*, **27**, 3803 (1971).
(4) (a) I. W. Elliott, *J. Heterocycl. Chem.*, **7**, 1229 (1970) (b) *ibid.*, **9**, 453 (1972).
(5) I. W. Elliott, *J. Org. Chem.*, **42**, 1090 (1977).
(6) These yields are reproducible under the conditions described but not necessarily optimized. A mechanism was suggested in ref 5 for the mode of oxidative coupling represented by the conversion of **4** to **5** or of **6** to **7**. The effects of solvent and of activation of the benzylic positions in **4** or **6** by the adjacent carbonyl groups are probably the same for oxidation by VOF_3 as for anodic oxidation.
(7) S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969).
(8) (a) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958); (b) E. Waldmann and C. Chwala, *Justus Liebigs Ann. Chem.*, **609**, 125 (1957); (c) D. A. Guthrie, A. W. Frank, and C. B. Purves, *Can. J. Chem.*, **33**, 729 (1955).
(9) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Spectra were recorded on the following instruments: Perkin-Elmer 337 IR; Cary 14 UV, LKB 2091 MS, and Varian XL100 NMR.

Stereospecific Synthesis of (*R*)- and (*S*)-Isophosphamide

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Isophosphamide (**1**) is a constitutional isomer of the clinically established anticancer drug cyclophosphamide (**2**, "Cytoxan"),[1] and **1** has been found to elicit therapeutic response in human breast, ovarian, and lung cancer.[2] The chirality of **1** and **2** necessitates consideration of stereochemical factors within the mechanisms of action for these drugs and, moreover, the clinical significance thereof. Recent progress in this direction has been achieved only in the case of **2**,[3-5] as the *R* and *S* enantiomers of **1** have been heretofore unavailable except as the racemate. We now wish to report the stepwise construction of separable diastereomers which serve as precursors to (*R*)- and (*S*)-**1** via a hydrogenolysis reaction that is unquestionably stereospecific according to ^{31}P NMR data.

By analogy to the previously reported[3d,4a] catalytic conversion of $(S)_C(R)_P$-**3** to (*S*)-**2** (eq 1) and of diastereomer $(S)_C(S)_P$-**3** to (*R*)-**2**, $(S)_C(S)_P$-**4** represented the logical precursor to (*R*)-**1** (eq 2), while its $(S)_C(R)_P$-**4** diastereomer was