Reaction of α-Phosphoryl Sulfoxide (1) with Benzoyl Chloride. General Procedure. Sulfoxide 1 (0.01 mol) and benzoyl chloride (5 mL) were stirred at room temperature for 5 h. An excess of benzoyl chloride was removed in vacuo and the residue was chromatographed to give chloro sulfide **4**.

Synthesis of α,α-Dichloro-α-phosphorylmethyl Alkyl(aryl) Sulfide (6). General Procedure. α-Phosphoryl sulfoxide (**6**) (0.01 mol) in methylene chloride (25 mL) was treated with sulfuryl chloride (0.022 mol) at 0 °C for 2 h. The solvent and hydrogen chloride were evaporated to give the crude dichloro sulfide (**6**) which was isolated by distillation.

Synthesis of *O,S*-Thioacetals of Formyl Phosphonates 7 and 8. General Procedure. α-Phosphoryl sulfoxide (1) (0.01 mol) was refluxed in an excess of alcohol in the presence of equimolar amounts of iodine. The optimal reaction time, as given in Table I, was estimated by ^{31}P NMR. After the reaction was complete excess alcohol was removed and chloroform was added. The organic solution was washed with thiosulfate solution followed by water, dried, and evaporated. The residue was fractionated or chromatographed to afford pure thioacetal **7** or **8**.

Registry No.—**1a**, 65915-23-3; **1b**, 63231-19-6; (+)-**1b**, 63231-19-6; **1c**, 65915-24-4; **1d**, 65915-25-5; (−)-**2b**, 65915-26-6; **5a**, 25508-32-1; **5c**, 28460-01-7; **5d**, 38066-16-9.

Supplementary Material Available: Table II including full ^{1}H- and ^{13}C-NMR data of **2**–' (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Part 16 of the series: Organosulfur Compounds. Part 15: J. Drabowicz and M. Mikołajczyk, *Synthesis*, 138 (1978). For a preliminary report of this work see: M. Mikołajczyk, B. Costisella, S. Grzejszczak, and A. Zatorski, *Tetrahedron Lett.*, 477 (1976).
(2) On leave of absence from the Institute of Organic Chemistry, Academy of Sciences of the German Democratic Republic, Berlin-Adlershof.
(3) R. Pummerer, *Ber.* **43**, 1401 (1910).
(4) T. Durst in "Advances in Organic Chemistry", Vol. 6 Interscience, New York, N.Y., 1969, p 356; S. Oae, *Khim. Org. Soedin. Siery (Russian Transl.)*, 239–244 (1975).
(5) M. Mikołajczyk and A. Zatorski, *Synthesis*, 669 (1973).
(6) M. Mikołajczyk, W. Midura, S. Grzejszczak, A. Zatorski, and A. Chefczynska, *J. Org. Chem.*, **43**, 473 (1978).
(7) For the Horner PO–olefination reactions of α-phosphoryl substituted organosulfur compounds see: M. Green, *J. Chem. Soc.*, 1324 (1963); J. Shahak and J. Almog, *Synthesis*. 170 (1969); J. Shahak and J. Almog, *ibid.*, 145 (1973); E. J. Corey and J. I. Shylman, *J. Org. Chem.*, **35**, 777 (1970); *J. Am. Chem. Soc.*, **82**, 5522 (1970); J. G. Popoff, J. L. Dever, and G. R. Leader, *J. Org. Chem.*, **34**, 1128 (1969); G. H. Posner and D. J. Brunelle, *ibid.*, **37**, 3547 (1972); M. Mikołajczyk, S. Grzejszczak, and A. Zatorski, *ibid.*, **40**, 1979 ([975(: M. Mikołajczyk, S. Grzejszczak, W. Midura, and A. Zatorski, *Synthesis*, 278 (1975); 396 (1976); J. I. Grayson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2263 (1977).
(8) After reporting our preliminary results on the Pummerer reaction of 1 Dinizo and Watt described some other examples of the 2-acyloxy-α-phosphoryl sulfides, S. E. Dinizo and D. S. Watt, *Synthesis*, 181 (1977).
(9) For activation of sulfoxides by trifluoroacetic anhydride see: A. Sharma and D. Swern, *Tetrahedron Lett.*, 1503 (1974); A. Sharma, T. Ku, A. Dawson, and D. Swern, *J. Org. Chem.*, **40**, 2758 (1975).
(10) B. Strindsberg and S. Allenmark, *Acta Chem. Scand., Ser. B*, **28**, 591 (1974); **30**, 219 (1976).
(11) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).
(12) T. Numata and S. Oae, *Tetrahedron Lett.*, 1337 (1977).
(13) Stereochemistry of the hydrogen–deuterium exchange in α-phosphoryl sulfoxides is under current study.
(14) H. Gross and H. Seibt, *J. Prakt. Chem.*, **312**, 475 (1970).
(15) B. Mjotkowska, H. Gross, B. Costisella, M. Mikołajczyk, S. Grzejszczak, and A. Zatorski, *J. Prakt. Chem.*, **319**, 17 (1977).
(16) M. Mikołajczyk, S. Grzejszczak, A. Zatorski, and B. Mjotkowska, *Tetrahedron Lett.*, 2731 (1976).
(17) T. L. Moore, *J. Org. Chem.*, **32**, 2786 (1967).
(18) This product was identical with that prepared from triethyl phosphite and ethyl chlorocarbonate by the Arbuzov reaction, $\delta_{^{31}P}$ −5.1 ppm.

Intramolecular Nonphenol Oxidative Coupling of Phenethylisoquinolines

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Anodic and chemical oxidative coupling of homolaudanosine (**6a**) in TFA–TFAA gave homoglaucine (**9a**) in moderate yield. Oxidative coupling of *N*-acyl nonphenolic phenethyltetrahydroisoquinolines **6c,e,f** using VOF_3–TFA–TFAA yielded homoproerythrinadienones **8a,c** as the primary products, in contrast to the results of oxidative coupling reactions of nonphenolic benzyltetrahydroisoquinoline precursors which yield morphinandienones as the primary products. Furthermore, the homoproerythrinadienone-type intermediates (e.g., **19**) and homoneospirenedienone-type intermediates (e.g., **20**) were shown to be in equilibrium in the reaction medium, and both spirodienone intermediates rearranged to homoaporphines. Thus the oxidative coupling of nonphenolic phenethyltetrahydroisoquinolines with VOF_3–TFA–TFAA provides an efficient synthetic route to homoproerythrinadienones, homoneospirenedienones, and homoaporphines. Diaryl derivatives such as **11a,b** were also obtained as byproducts, which could be transformed to dibenz[*d*,*f*]azecine (**14a**).

Intramolecular phenol oxidative coupling reactions as a mode of carbon–carbon bond formation hold a prominent position in the biosynthesis of many classes of natural products.[3–5] However, the synthetic potential of these reactions has been limited due to the low yields and the complex mixtures of products usually encountered when the coupling step is carried out in the laboratory.[6,7] Recent reports[8–16] have demonstrated that intramolecular nonphenol oxidative coupling reactions hold promise as effective synthetic methods for the preparation of certain alkaloids and other polycyclic compounds. The first practical synthesis of this type involved electrooxidative coupling of nonphenolic benzylisoquinolines to morphinandienones.[8–11] Chemical intramolecular coupling of nonphenolic benzylisoquinolines using vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) also proceeded via morphinandienone intermediates[13–15] to give aporphines and some other spirodienone products. The present paper describes, in detail, studies[17] on the intramolecular oxidative coupling of nonphenolic phenethyltetrahydroisoquinoline derivatives which represent efficient syntheses of homoproerythrinadienones, homoneospirenedienones, homoaporphines, and dibenz[*d*,*f*]azecine precursors.

On the basis of the results of oxidative couplings of nonphenolic benzyltetrahydroisoquinolines,[8,13,14] it seemed reasonable to assume that anodic coupling of nonphenolic phenethyltetrahydroisoquinolines would yield homomorphinandienones, and VOF_3–TFA oxidations would give homoaporphines and homoneospirenedienones (Scheme I). Thus, homolaudanosine (**6a**) seemed a reasonable starting material for initial studies. Preparation of homolaudanosine

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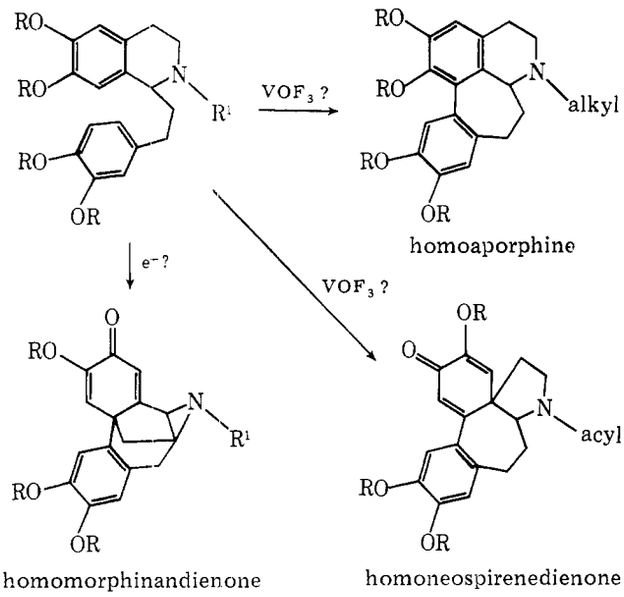
Scheme I[a]



[a] R = alkyl or benzyl; R¹ = alkyl or acyl.

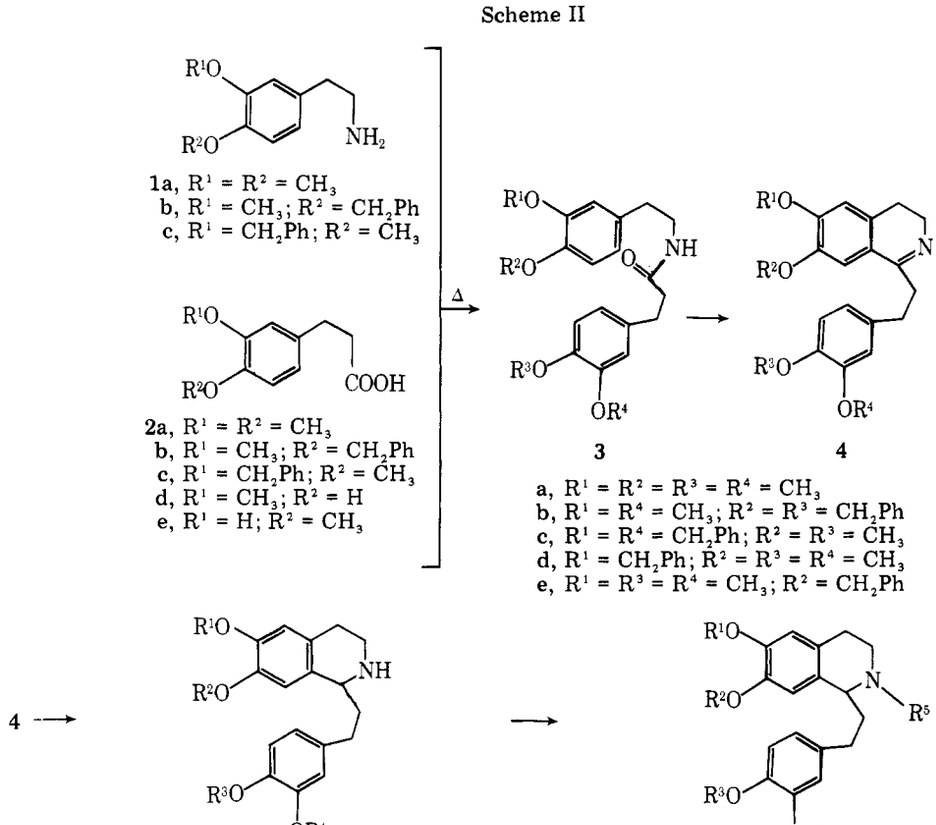
(**6a**) and other phenethyltetrahydroisoquinoline derivatives **6b–i** was achieved by the route shown in Scheme II.

Anodic oxidation of homolaudanosine (**6a**), under the reaction conditions which yield *O*-methylflavinantine from laudanosine in 94% yield,[15] did not yield any isolable product. However, anodic oxidation of **6a** in a mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) containing tetraethylammonium tetrafluoroborate as the supporting electrolyte at a constant potential of 1.3 V gave homoaporphine **9a** in 34% yield. The structure of the homoaporphine **9a** was assigned on the basis of its physical and spectral data and confirmed by an unambiguous synthesis.

Phenol oxidation of **6b** had previously been reported by several groups[18–21] to give a mixture of homoproaporphines **10a** and **10b** in yields of <40%. However, when **6b** was oxidized with VOF_3–TFA–TFAA at −10 °C, homoproaporphine **10a** and **10b** were obtained in 38 and 30% yield, respectively. Treatment of homoproaporphine **10a** with boron trifluoride etherate in CH_2Cl_2 afforded diphenolic homoaporphine[22] **9b** (87%), which, upon methylation with diazomethane, gave the tetramethoxyhomoaporphine **9a** in 70% yield as the hydrochloride salt, identical with the product obtained by anodic oxidation of **6a.**

Vanadium oxytrifluoride oxidation of a solution of homolaudanosine (**6a**) in a mixture of CH_2Cl_2, TFA, TFAA, and fluorosulfonic acid (FSO_2OH) also gave homoaporphine **9a** in 40% yield. FSO_2OH was used to ensure complete protonation of the nitrogen, since oxidation of **6a** in the absence of FSO_2OH yielded a dimer as indicated by mass spectrometry and the NMR spectrum.

Scheme II



1a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = CH_2Ph$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$

2a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = CH_2Ph$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$
d, $R^1 = CH_3$; $R^2 = H$
e, $R^1 = H$; $R^2 = CH_3$

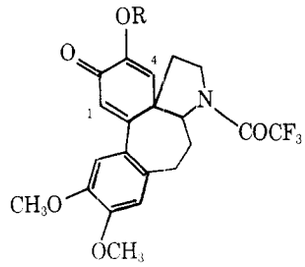
3

4

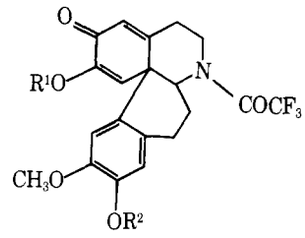
a, $R^1 = R^2 = R^3 = R^4 = CH_3$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = CH_2Ph$
c, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$
d, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$
e, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$

5a, $R^1 = R^2 = R^3 = R^4 = CH_3$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = CH_2Ph$
c, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$
d, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$
e, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$

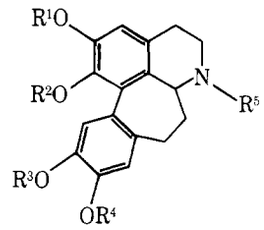
6a, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
b, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = H$
c, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$
e, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
f, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$; $R^5 = COCF_3$
g, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = CH_2Ph$
h, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$
i, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COOC_2H_5$



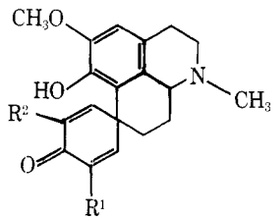
7a, R = CH_3
b, R = CH_2Ph



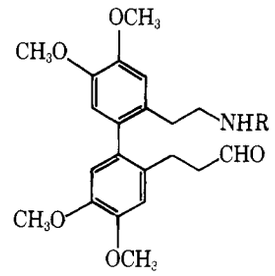
8a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = H$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$



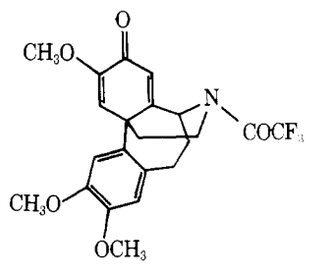
9a, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
b, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = H$
c, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$



10a, $R^1 = OCH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = OCH_3$



11a, R = $COCF_3$
b, R = $COOC_2H_5$



12

Table I. Calculation of the Chemical Shifts of the C-1 and C-4 Protons of 7a[23]

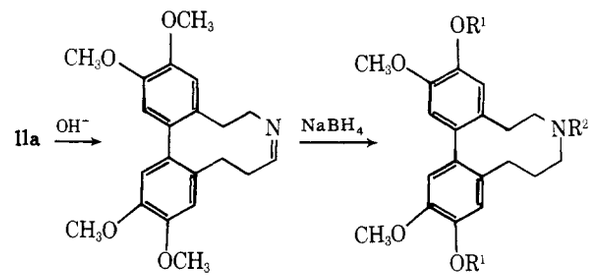
For the C-1 proton:

δ(C=CH) = 5.28 + 1.06 (*gem*-C=O, conjugated)
+ 0.37 (cis aromatic) − 0.30 (trans alkyl ring)
= δ 6.41

For the C-4 proton:

δ (C=CH) = 5.28 + 0.95 (*trans*-C=O, conjugated)
+ 0.71 (geminal alkyl ring) − 1.06 (*cis*-OMe)
= δ 5.88

Scheme III



13

14a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = R^2 = H$
c, $R^1 = R^2 = CH_3$

To study the effect of acylation of nitrogen, *N*-trifluoroacetylhomonorlaudanosine (**6c**) was prepared from tetrahydroisoquinoline **5a**. Treatment of (±)-*N*-trifluoroacetylhomonorlaudanosine (**6c**) with VOF_3–TFA–TFAA followed by aqueous workup gave homoneospirenedienone **7a** (64%), homoproerythrinadienone **8a** (5%), homoaporphine **9c** (2%), and aldehyde–amide **11a** (22%), respectively.

Homoneospirenedienone **7a** was assigned a molecular formula of $C_{22}H_{22}NO_5F_3$ on the basis of microanalysis and mass spectrometry (M^+ at *m/e* 437). The infrared spectrum showed typical dienone absorptions at 1690, 1653, and 1640 cm^{-1}, and the ultraviolet spectrum indicated a conjugated β-arylcyclohexadienone system in the structure. The NMR spectrum of **7a** in $CDCl_3$ showed peaks at δ 6.66 (s, 2 H, Ar**H**), 6.49 (s, 1 H, C-1 H), 5.75 (s, 1 H, C-4 H), 3.89, 3.87, and 3.72 (all s, 9 H, 3-OCH_3). The signals for the C-1 and C-4 protons were assigned in accordance with a calculation (Table I) of the expected chemical shifts by the method of Pascual, Meier, and Simon,[23] neglecting possible solvent and ring strain effects.

Mass spectrometry (M^+ at *m/e* 437) and microanalysis confirmed the formula $C_{22}H_{22}NO_5F_3$ for homoproerythrinadienone **8a**. The spectral data indicated that the structure was either **8a** or **12**. Therefore structure **8a** was confirmed by an unambiguous synthesis.

Marino has recently reported the oxidation of the diphenolic phenethyltetrahydroisoquinoline **6d** with vanadium oxytrichloride ($VOCl_3$) in CH_2Cl_2 to give homoproerythrinadienone **8b** in 35% yield. However, when **6d** was oxidized with VOF_3, homoproerythrinadienone **8b** was obtained in 78% yield. O-Methylation of **8b** with diazomethane then gave the homoproerythrinadienone **8a**, identical with a sample obtained by VOF_3 oxidation of **6c**.

The structure of homoaporphine **9c** was assigned on the basis of its physical and spectral data. This structure was confirmed by conversion to homoaporphine **9a** via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation (formaldehyde–$NaBH_4$). The *N*-methyltetramethoxyhomoaporphine **9a** thus obtained was identical with a sample obtained by electrooxidation of homolaudanosine (**6a**).

Aldehyde–amide **11a** was also characterized on the basis of its physical and, particularly, its spectral data, and the structure of **11a** was further supported by the following transformation (Scheme III).

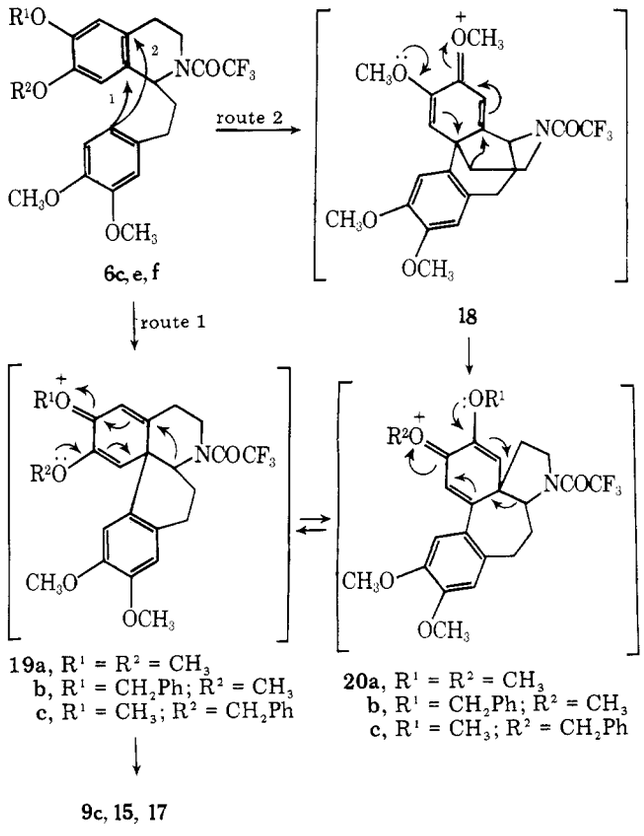
Treatment of **11a** with 1 N methanolic sodium hydroxide at room temperature resulted in hydrolysis of the amide and formation of the imine **13**, which was reduced with $NaBH_4$ to give tetramethoxydibenzazecine **14a**. The homoproerythrinadienone **8b** prepared previously was converted into diphenolic dibenzazecine **14b** by the procedure of Marino and Samanen.[25] Subsequent methylation of **14b** with diazomethane gave the tetramethoxydibenzazecine **14a**, identical with the product obtained from **11a**, along with some N-methylated product (**14c**).

In contrast to the acid-catalyzed rearrangement of proerythrinadienones to neospirenedienones,[26] homoproerythrinadienones rearrange to homoaporphines on treatment with boron trifluoride etherate.[24] Thus, treatment of **8a** with boron trifluoride etherate in CH_2Cl_2 at room temperature for 24 h afforded homoaporphine **15** which, upon methylation with diazomethane, gave the tetramethoxyhomoaporphine **9c**, identical with the homoaporphine obtained by VOF_3 oxidation of *N*-trifluoroacetylhomonorlaudanosine (**6c**).

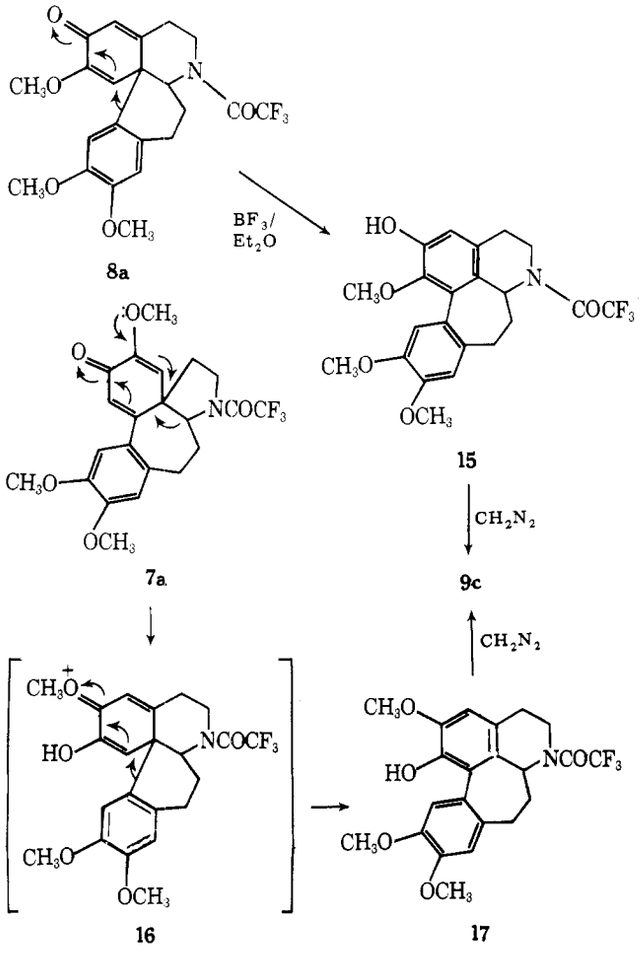
Interestingly, the homoneospirenedienone **7a** also rearranged to a monophenolic homoaporphine upon treatment with boron trifluoride etherate. The monophenolic homoaporphine product was different from homoaporphine **15** yet, upon methylation with diazomethane, gave the same tetramethoxyhomoaporphine **9c** as obtained by methylation of **15**, indicating that the structure of this monophenolic homoaporphine must be **17**. The formation of **17** from **7a** may be rationalized if homoneospirenedienone **7a** first rearranged to a homoproerythrinadienone-type intermediate **16**, which then rearranged to the homoaporphine **17** (Scheme IV).

Homoneospirenedienone **7a** could not be formed directly by oxidative coupling from *N*-trifluoroacetylhomonorlaudanosine (**6c**). Rather, the formation of **7a** must result from the rearrangement of either a homoproerythrinadienone-type intermediate (route 1, Scheme V) as in the acid-catalyzed rearrangement of proerythrinadienones to neospirenedienones,[26] or a homomorphinandienone-type intermediate (route 2, Scheme V) as in the conversions of (±)-*N*-acylnorlaudanosines to (±)-*N*-acylmorphinandienones and thence to (±)-*N*-acylneospirenedienones in nonphenol oxidative coupling of benzyltetrahydroisoquinolines.[14]

Scheme V



Scheme IV



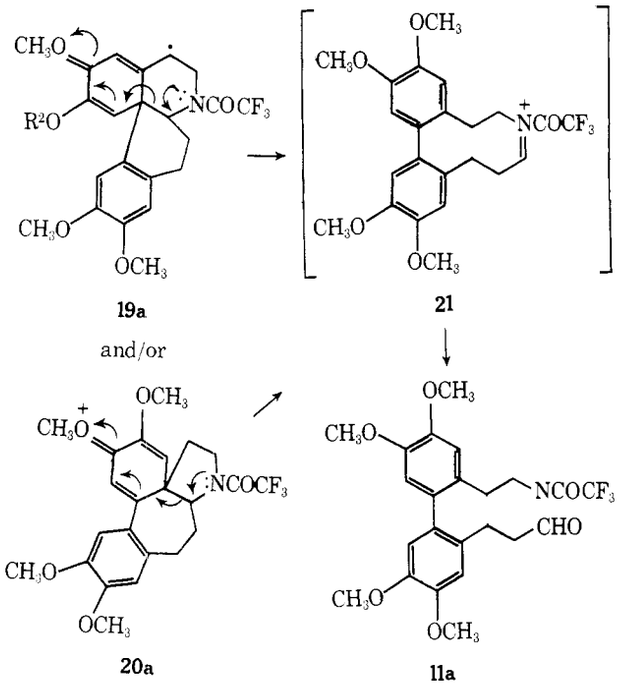
Evidence for determining the operative carbon rearrangement was obtained by oxidation of 6- and 7-benzyloxyphenethyltetrahydroisoquinolines **6e** and **6f**, respectively. Oxidation of **6e** with VOF_3 yielded homoproerythrinadienone **8a** (50%) and homoneospirenedienone **7b** (42%), the benzyloxy analogue of homoneospirenedienone **7a**. Oxidation of **6f** yielded homoneospirenedienone **7a** (60%), identical with the product obtained by oxidation of **6c**, and homoproerythrinadienone **8c** (3%), the benzyloxy analogue of homoproerythrinadienone **8a**.

Formation of **7b** via oxidation of **6e** and **7a** via oxidation of **6f** confirms that rearrangement of **6c**, **6e**, and **6f** to form homoneospirenedienones **7a** and **7b** takes place via homoproerythrinadienone-type intermediates **19a**, **19b**, and **19c**, respectively. If a homomorphinandienone intermediate had been involved, **6e** would have given **7a** and **6f** would have afforded **7b**.

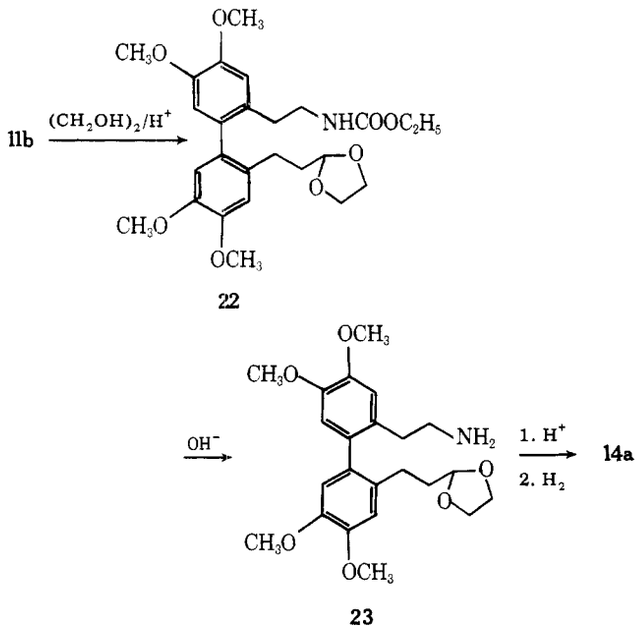
The formation of homoneospirenedienone **7a** via homoproerythrinadienone-type intermediate **19a**, and the demonstrated facile acid-catalyzed rearrangement of homoproerythrinadienone **8a** and homoneospirenedienone **7a** to homoaporphines **15** and **17**, respectively, suggested that homoproerythrinadienone-type intermediates (e.g., **19**) and homoneospirenedienone-type intermediates (e.g., **20**) exist in equilibrium in the reaction medium. In the oxidation of **6e**, cleavage of the benzyl group from the homoproerythrinadienone-type intermediate (**19b**) should shift the equilibrium toward the homoproerythrinadienone-type intermediate (**19b**), and, after a certain period of time, homoproerythrinadienone **8a** would be isolated as the major product. In the oxidation of **6f** cleavage of the benzyl group from **19c** should shift the equilibrium toward homoneospirenedienone-type intermediate **20c** and homoneospirenedienone **7a** would be the major product.

Indeed, when 6-benzyloxyphenethylisoquinoline **6e** was oxidized with VOF_3 and the reaction worked up after 1 h and

Scheme VI



Scheme VII



25 min, homoproerythrinadienone **8a** was obtained in 71% yield. Oxidation of 7-benzyloxyphenethyltetrahydroisoquinoline **6f** with VOF_3 and workup after 1 h afforded homoneospirenedienone **7a** in 65% yield. This evidence thus supports the proposed equilibrium of homoproerythrinadienone-type and homoneospirenedienone-type intermediates in the reaction mixture.

The equilibrium of homoproerythrinadienone-type and homoneospirenedienone-type intermediates and the demonstrated facile acid-catalyzed rearrangement of homoproerythrinadienone **8a** and homoneospirenedienone **7a** to 1,2,10,11-tetrasubstituted homoaporphines **15** and **17**, respectively, suggested that homoaporphines might be obtained directly from phenethyltetrahydroisoquinolines if enough time were allowed for rearrangement of the intermediates formed. Indeed, phenethyltetrahydroisoquinolines **6c**, **6e**, and **6f** gave homoaporphines **9c** (84%), **15** (80%), and **17** (67.5%), respectively, upon oxidation with VOF_3 for 3, 24, and 24 h, respectively. The difference in the reaction times can be rationalized on the basis of the difference in the rates of rearrangement of the corresponding homoproerythrinadienone-type and/or homoneospirenedienone-type intermediates. In the case of **6c**, the methoxonium ions **19a** and **20a** rearrange to homoaporphine **9e**, whereas in the case of **6e** and **6f**, cleavage of the benzyl group from intermediates **19b** and **20c** results in the formation of homoproerythrinadienone **8a** and homoneospirenedienone **7a**, which, as demonstrated earlier, undergo acid-catalyzed rearrangement to homoaporphines **15** and **17** in 24 h at room temperature.

Oxidation of **6c** with VOF_3–TFA–TFAA over 3 h resulted in the formation of only homoaporphine **9c** (84%) and no aldehyde–amide **11a**. Thus, **11a** could not be formed via direct oxidative coupling but must have resulted from rearrangement of intermediate(s) **19a** and/or **20a** during the workup procedure (Scheme VI). This requires the participation of the amide function which would be unexpected due to the strong withdrawing property of the acyl moiety.

If the proposed mechanism is correct, oxidation of *N*-carbethoxyhomonorlaudanosine (**6i**) should give a high yield of aldehyde–urethane **11b** because the nitrogen will retain a higher electron density. Consequently, *N*-carbethoxyhomonorlaudanosine (**6i**) was prepared by treatment of **5a** with ethyl chloroformate and pyridine, and oxidized with VOF_3 according to the procedure described earlier. Aldehyde–urethane **11b** was obtained in 62% yield, thus supporting the proposed mechanism.

The structure of aldehyde–urethane **11b** was confirmed by heating **11b** under reflux with ethylene glycol and *p*-toluenesulfonic acid using a Dean–Stark trap for azeotropic removal of water to give ketal **22** (Scheme VII). Heating ketal **22** with 20% aqueous sodium hydroxide then gave amine **23**. Hydrolysis of amine **23** with 5% aqueous HCl gave imine **13**, which was catalytically reduced to tetramethoxydibenzazecine (**14a**), identical in melting point, mixture melting point, NMR, TLC, IR, and mass spectrum with the product obtained from aldehyde–amide **11a**.

Experimental Section

General. Melting points were determined on a Mettler FP2 melting point apparatus and are uncorrected. UV and IR spectra were determined on Beckman DK-2A and Perkin-Elmer 337 spectrophotometers, respectively. NMR spectra were recorded on a JEOL PS-100p FT NMR spectrometer interfaced to a Texas Instruments JEOL 980A computer with Me_4Si as the internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E and AEI MS-902 spectrometers. All thin-layer chromatography was carried out on commercially prepared plates (E. M. Laboratories); silica gel 60 F-254 plates (2, 0.5, or 0.25 mm thickness 20 × 20 cm) were used for preparative TLC. Visualization of the alkaloids was performed by means of ultraviolet light and/or by spraying the entire analytical plate, or the edges of the preparative plate, with an aqueous solution of iodoplatinic acid reagent (1.0 g in 250 mL of water containing 15 g of potassium iodide). Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Ga. Column chromatography was carried out on silica gel 60 (70–230 mesh ASTM) obtained from E. M. Laboratories. Anhydrous sodium sulfate was used as the drying agent exclusively. The phenethyltetrahydroisoquinolines **6a–i** were prepared by standard methods,[32,33] i.e., condensation of phenethylamines and acids to the corresponding amides followed by Bischler–Napieralski cyclization, $NaBH_4$ reduction, N-acylation, N-methylation, or N-carbethoxylation, and subsequent debenzylation by hydrogenolysis where required. Anodic oxidations were conducted in a three compartment cell (which separated the anode, cathode, and reference electrode solutions by glass frits) in conjunction with a Princeton Applied Model 376 potentiostat. The anode was a platinum mesh and a stainless steel spatula served as the cathode. The anode compartment had an ap-

proximate 120 mL volume in which the solution was agitated by means of a magnetic stir bar. A 0.1 N $AgNO_3$ solution in acetonitrile in contact with an Ag wire served as the reference.

3-Benzyloxy-4-methoxyphenylpropionic Acid (2c). A mixture of 24.0 g (122 mmol) of 3-hydroxy-4-methoxyphenylpropionic acid,[30] 10.6 g of sodium hydroxide, and 50 mL of methanol was heated until a clear solution was obtained. Following the addition of 30.0 mL of benzyl chloride, the solution was heated at 72 °C for 3 h, then 5.3 g of sodium hydroxide dissolved in 5.3 mL of water was added and the solution heated at reflux for an additional 6 h. The methanol was distilled off and the residue suspended in 300 mL of water, acidified with 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried, and evaporated to a semisolid residue. Crystallization from ethanol gave 22.0 g (62%) of **2c:** mp 120–122 °C; NMR ($CDCl_3$) δ 9.5 (br s, 1 H, COO**H**), 7.35 (s, 5 H, Ar**H**), 6.75 (s, 3 H, Ar**H**), 5.10 (s, 2 H, OCH_2), 3.83 (s, 3 H, OCH_3), 2.7 (m, 4 H, CH_2); mass spectrum *m/e* 286 (M^+), 195 ($M^+ - PhCH_2$).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.38; H, 6.37.

***N*-(3-Benzyloxy-4-methoxyphenethyl)-3-benzyloxy-4-methoxyphenylpropionamide (3c).** From 21.85 g (85 mmol) of 3-benzyloxy-4-methoxyphenethylamine[29] and 24.05 g (85 mmol) of **2c** there was obtained 39.0 g (88%) of **3c:** NMR ($CDCl_3$) δ 7.34 (m, 10 H, Ar**H**), 6.72 (m, 6 H, Ar**H**), 5.10 (s, 4 H, OCH_2), 3.85 and 3.84 (both s, 6 H, OCH_3), 3.3–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.28; H, 6.77; N, 2.61.

***N*-(3-Benzyloxy-4-methoxyphenethyl)-3-(3,4-dimethoxyphenyl)propionamide (3d).** From 7.45 g (29 mmol) of 3-benzyloxy-4-methoxyphenethylamine[29] and 6.1 g (29 mmol) of 3,4-dimethoxyphenylpropionic acid (**2a**) there was obtained 11.0 g (84%) of **3d** as colorless crystals: mp 88.3–89.8 °C (ether); NMR ($CDCl_3$) δ 7.35 (m, 5 H, Ar**H**), 6.71 (m, 6 H, ArH), 5.11 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3), 2.35 (t, 2 H, $COCH_2CH_2$, J = 7.5 Hz), 2.64 (t, 2 H, CH_2CH_2NH, J = 7.0 Hz), 2.88 (t, 2 H, $COCH_2CH_2$, J = 7.5 Hz), 3.38 (t, 2 H, CH_2CH_2NH, J = 7.0 Hz).

Anal. Calcd for $C_{27}H_{31}NO_5 \cdot \frac{1}{2}H_2O$: C, 70.72; H, 7.03; N, 3.05. Found: C, 70.70; H, 6.98; N, 2.92.

1-(3-Benzyloxy-4-methoxyphenethyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (4c). From 39.0 g (74.5 mmol) of **3c** and 10.0 mL of $POCl_3$ in 800 mL of toluene there was obtained, after heating at 100 °C for 1 h and usual workup, 32.3 g (80%) of **4c:** mp 113–115 °C (ethyl acetate); NMR ($CDCl_3$) δ 7.38 (m, 10 H, Ar**H**), 6.95 and 6.71 (both s, 2 H, Ar**H**), 6.81 (s, 3 H, Ar**H**), 5.17 and 5.1 (both s, 4 H, OCH_2), 3.86 (s, 6 H, OCH_3), 2.89 (s, 4 H, CH_2), 3.6 (t, 2 H, CH_2, J = 7 Hz), 2.53 (t, 2 H, CH_2, J = 7 Hz).

Anal. Calcd for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 77.95; H, 6.50; N, 2.72.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (4d). From 8.03 g (17.9 mmol) of **3d** and 18 mL of $POCl_3$ in 130 mL of toluene there was obtained, after heating at 110 °C for 1 h and usual workup, 6.56 g (78.6%) of **4d** as the hydrochloride salt: mp 173.8–174.7 °C (ethanol–ether); IR ($CHCl_3$) 1645 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 7.40 (s, 5 H, Ar**H**), 7.09, 6.88, 6.82 (each s, 3 H, ArH), 6.70 (s, 2 H, ArH), 5.26 (s, 2 H, OCH_2), 3.90, 3.87, 3.82 (all s, 9 H, OCH_3), 3.7–2.81 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{29}NO_4 \cdot HCl$: C, 69.29; H, 6.46; N, 2.99. Found: C, 69.23; H, 6.60; N, 2.97.

1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a). From 6.2 g (17.5 mmol) of 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[27] (**4a**) by $NaBH_4$ reduction in methanol there was obtained 6.0 g (98%) of **5a** as the hydrochloride salt: mp 186.7–187.7 °C; NMR ($CDCl_3$) δ 6.95 (s, 1 H, Ar**H**), 6.78 (br s, 2 H, Ar**H**), 6.49 and 6.48 (both s, 2 H, Ar**H**), 4.33 (hump, 1 H, NH), 3.85 (s, 9 H, OCH_3), and 3.81 (s, 3 H, OCH_3).

Anal. Calcd for $C_{21}H_{27}NO_4 \cdot HCl$: C, 64.19; H, 7.18; N, 3.56. Found: C, 64.02; H, 7.20; N, 3.53.

1-(3-Benzyloxy-4-methoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5c). From 29.0 g (57.2 mmol) of **4c** by $NaBH_4$ reduction in methanol there was obtained 30.0 g of the crude product. Treatment with methanolic HCl gave 27.0 g (87%) of **5c** as the hydrochloride salt: mp 186.5–188 °C; NMR ($CDCl_3$) δ 7.38 (m, 10 H, Ar**H**), 6.98 (s, 1 H, Ar**H**), 6.78 (s, 2 H, Ar**H**), 6.58, 6.45 (both s, 2 H, ArH), 5.09 and 5.08 (both s, 4 H, OCH_2), 3.82 and 3.78 (both s, 6 H, OCH_3), 3.5–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{33}H_{35}NO_4 \cdot HCl$: C, 72.58; H, 6.65; N, 2.56. Found: C, 72.61; H, 6.47; N, 2.56.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5d). From 6.42 g (13.8 mmol) of the hydrochloride salt of **4d** by $NaBH_4$ reduction in methanol there was obtained 6.0 g of a yellow oil. Treatment with methanolic HCl gave 6.05 g (94%) of **5d** as the hydrochloride salt: mp 132.6–133.7 °C; NMR ($CDCl_3$) δ 7.39 (br s, 5 H, **Ph**CH_2), 6.95 (s, 1 H, ArH), 6.77 (s, 2 H, Ar**H**), 6.62, 6.50 (both s, 2 H, ArH), 5.10 (s, 2 H, O**C**H_2), 3.84 (s, 6 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.25–2.4 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{31}NO_4 \cdot HCl$: C, 68.99; H, 6.86; N, 2.98. Found: C, 68.84; H, 6.82; N, 2.96.

1-(3,4-Dimethoxyphenethyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5e). From 3.71 g (8.6 mmol) of 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[31] (**4e**) by $NaBH_4$ reduction in methanol there was obtained 3.5 g of a brown oil. Treatment with methanolic HCl and crystallization from methanol–ether gave 3.12 g (77%) of **5e** as the hydrochloride salt: mp 183.4–184.4 °C; NMR ($CDCl_3$) δ 7.35 (m, 5 H, ArH), 6.90 (s, 1 H, ArH), 6.73 (s, 2 H, ArH), 6.60, 6.49 (both s, 2 H, ArH), 5.08 (s, 2 H, OCH_2). 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3), 3.5–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{31}NO_4 \cdot HCl$: C, 68.99; H, 6.86; N, 2.98. Found: C, 68.85; H, 6.81; N, 2.96.

***N*-Trifluoroacetylhomonorlaudanosine (6c).** From 8.93 g (25 mmol) of **5a,** 7.5 mL of TFAA, and 1.00 mL of pyridine in 25 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 9.00 g of the crude product. Crystallization from ethanol gave 8.75 g (77%) of **6c:** mp 89–90 °C; UV λ_{max}(EtOH) (log ε) 228 (sh, 4.30), 282 (3.84), 286 (sh, 3.83) nm; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.77 (s, 3 H, ArH), 6.59 and 6.53 (both s, 2 H, Ar**H**), 5.56 (t, 1 H, CH, J = 7 Hz), 3.87 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.85–2.20 (m, 8 H, CH_2); mass spectrum *m/e* 453 (M^+), 288.

Anal. Calcd for $C_{23}H_{26}NO_5F_3$: C, 60.92; H, 5.78; N, 3.09. Found: C, 60.91; H, 5.88; N, 3.13.

1-(3-Hydroxy-4-methoxyphenethyl)-6-hydroxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6d). From 6.16 g (12 mmol) of **5c,** 7.5 mL of TFAA, and 1.0 mL of pyridine in 70 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 7.0 g of **6h** as a colorless foam. Hydrogenolysis of **6h** over 1.5 g of 10% Pd/C at atmosphere temperature and pressure of hydrogen gave, after crystallization from ether, 3.9 g (76%) of **6d:** mp 131.5–132.2 °C (lit.[24] 129–130 °C); NMR ($CDCl_3$) δ 6.73 (br s, 3 H, Ar**H**), 6.65 and 6.52 (both s, 2 H, Ar**H**), 5.62 (s, 2 H, OH), 3.84 (s, 6 H, OCH_3); mass spectrum *m/e* 425 (M^+), 274.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6e). From 4.6 g (10.6 mmol) of **5d,** 7.5 mL of TFAA, and 1.0 mL of pyridine in 70 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 5.45 g (97%) of **6e** as colorless foam: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.38 (m, 5 H, ArH), 6.77 (br s, 3 H, ArH), 6.61, 6.56 (s, 2 H, ArH), 5.57 (t, 1 H, CH, J = 7 Hz), 5.10 (s, 2 H, OCH_2), 3.95, 3.94, 3.93 (each s, 9 H, O**C**H_3), 3.8–2.5 (m, 8 H, CH_2).

1-(3,4-Dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6f). From 2.68 g (6.2 mmol) of **5e,** 3.75 mL of TFAA, and 0.5 mL of pyridine in 30 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and workup, 3.0 g (94%) of **6f:** mp 115.7–117 °C (methanol); IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.35 (m, 5 H, **Ph**CH_2O), 6.76, 6.55 (both s, 2 H, ArH), 6.70 (S= 2 H, ArH), 5.45 (t, 1 H, CH, J = 8 Hz), 5.09 (s, 2 H, OCH_2), 3.87 (s, 3 H, O**C**H_3), 3.85 (s, 6 H, OCH_3), 3.5–2.5 (m, 8 H, CH_2).

Anal. Calcd for $C_{29}H_{30}NO_5F_3$: C, 65.77; H. 5.71; N, 2.65. Found: C, 65.72; H, 5.62; N, 2.65.

***N*-Carbethoxyhomonorlaudanosine (6i).** From 2.3 g (6.4 mmol) of **5a,** 1.2 mL of ethyl chloroformate, and 0.6 mL of pyridine in 45 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 2.5 g (94%) of **6i** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.78 (s, 3 H, ArH), 6.59 and 6.56 (both s, 2 H, ArH), 5.13 (mound, 1 H, CH), 4.19 (q, 2 H, $COOCH_2CH_3$, J = 7.1 Hz), 3.87 (s, 3 H, OCH_3), 3.85 (s, 9 H, OCH_3), 3.25–2.10 (m, 8 H, CH_2), 1.29 (t, 3 H, $COOCH_2CH_3$, J = 7.1 Hz); mass spectrum *m/e* 429 (M^+), 264.

Anodic Oxidation of Homolaudanosine (6a). Homolaudanosine perchlorate[27] (300 mg; 0.636 mmol) was added to the anode compartment containing 120 mL of a mixture of TFA–TFAA (20:1 by weight). Tetraethylammonium tetrafluoroborate (3.0 g) was added as a background electrolyte to the anode and to the cathode (1.0 g) compartments. The electrolysis was carried out at a constant potential of 1.3 V for 130 min. The anodic solution was evaporated to an oil; water was added and the solution made alkaline with 58% ammonium hydroxide. At this point there were two layers, one aqueous and the other a heavy syrupy red liquid. Addition of 50 mL of benzene to this

Table II. Oxidation of Phenethyltetrahydroisoquinolines with VOF_3 in CH_2Cl_2–(TFA–TFAA)

Substrate	Registry No.	Temp, °C	Time	Products	Registry No.	Yield, %
6a		−10	40 min	**9a**		40
6b	56114-05-7	−10	6 min	**10a**		38
				10b		30
6c	61659-99-2	−10	10 min	**9c**	61660-02-4	2
				11a	61660-03-5	22
				7a	61660-01-3	64
				8a	61660-00-2	5
6c		−10 → 30	3 h	**9c**		84
6d	65899-32-3	−10	5 min	**8b**	52418-69-6	78
6e	61660-07-9	−10	10 min	**8a**		50
				7b	61660-09-1	42
		−10 → 30[a]	15 h	**8a**		71
		−10 → 30[a]	24 h	**15**	61660-04-6	80
6f	61660-08-0	−10	10 min	**7a**		60
				8c	61660-10-4	3
		−10 → 30[a]	1 h	**7a**		65
		−10 → 30[a]	24 h	**17**	61659-92-5	67.5
6i	65899-33-4	−10	10 min	**11b**	65899-34-5	60

[a] The reaction mixture was slowly allowed to attain room temperature (30 °C).

resulted in three layers with benzene being at the top. Successive extraction with benzene, followed by drying and evaporation of the combined benzene extracts, gave a pale yellow oil which was chromatographed on four 0.5-mm preparative silica gel plates using 5% methanol in chloroform as eluent. The major band was collected to give 110 mg of a slightly yellow glass which was dissolved in methanolic HCl and evaporated to dryness, and the residue was crystallized from methanol–ether giving 90.0 mg of the homoaporphine **9a** as the hydrochloride salt: mp 242–244 °C dec; UV λ_{max}(EtOH) (log ϵ) 266 (4.11), 289 (3.95); NMR ($CDCl_3$) δ 7.05 (s, 1 H, C-12 H), 6.77 (s, 1 H, ArH), 6.74 (s, 1 H, ArH), 3.94, 3.93, 3.87, and 3.48 (all s, 12 H, OCH_3), 2.75 (s, 3 H, NCH_3); mass spectrum *m/e* 369 (M^+), 354, 338.

Anal. Calcd for $C_{22}H_{28}NO_4Cl \cdot \frac{1}{2} \cdot CH_3OH$: C, 64.04; H, 7.16; N, 3.32. Found: C, 64.22; H, 7.06; N, 3.42.

VOF_3 Oxidation. General Procedure. In a typical oxidation 0.25–1.0 mmol of the substrate [0.05 M solution in CH_2Cl_2 containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)] at −10 °C (ice–salt bath) and the resulting dark red (in case of nonphenolic substrates) or dark blue (in case of phenolic substrates) solution was stirred for various lengths of time (see Table II). The reaction was quenched with 10% citric acid solution and the pH adjusted to ~7.5 with 58% NH_4OH. The solution was extracted with CH_2Cl_2 and the extract washed with brine, dried, and evaporated under reduced pressure to give the crude product.

VOF_3 Oxidation of Homolaudanosine (6a). Oxidation of 118 mg (0.25 mmol) of homolaudanosine perchlorate[27] (**6a**) in the presence of 0.1 mL of FSO_2OH gave 120 mg of a dark brown residue. Preparative TLC ($CHCl_3$–5% methanol) and crystallization from methanol–ether yielded 41 mg (40%) of **9a** as the hydrochloride salt: mp 243–245 °C. The melting point, mixture melting point, TLC, UV, NMR, and MS were identical with those of a sample prepared by anodic oxidation of **6a**.

VOF_3 Oxidation of 1-(4-hydroxy-3-methoxyphenethyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (6b). Oxidation of 297.0 mg (0.78 mmol) of **6b**[19] gave 218 mg of a pale yellow gum. Preparative TLC ($CHCl_3$–12% methanol) yielded 218 mg of a yellow gum which was crystallized from benzene to give 100.5 mg (38%) of **10a**. A sample was purified by crystallization from acetonitrile–ether: mp transition at 150–153 °C, melts at 193–194 °C dec (lit.[19] 193–195 °C); NMR ($CDCl_3$) δ 6.84 (q, 1 H, H_B, J_{AB} = 2.5 Hz, J_{BX} = 10 Hz), 6.66 (s, 1 H, ArH), 6.34 (d, 1 H, H_X, J_{BX} = 10 Hz), 6.08 (d, 1 H, H_A, J_{AB} = 2.5 Hz), 3.85 (s, 3 H, OCH_3 aromatic), 3.58 (s, 3 H, OCH_3 olefinic), 2.42 (s, 3 H, NCH_3), 2.0–4.0 (m, 9 H, CH, CH_2).

The mother liquor was evaporated and then crystallized from benzene–hexane (1:2) to give 80.0 mg (30%) of **10b**: mp 198–200 °C (lit.[28] mp 202 °C dec); NMR ($CDCl_3$) δ 6.99 (q, 1 H, H_B, J_{AB} = 2.6 Hz, J_{BX} = 10 Hz), 6.54 (s, 1 H, ArH), 6.25 (d, 1 H, H_X, J_{BX} = 10 Hz), 5.81 (d, 1 H, H_A, J_{AB} = 2.6 Hz), 3.8 (s, 3 H, OCH_3 aromatic), 3.64 (s, 3 H, OCH_3 olefinic), 2.4 (s, 3 H, NCH_3), 1.5–3.5 (m, 9 H, CH, CH_2).

VOF_3 Oxidation of (±)-*N*-Trifluoroacetylhomonorlaudanosine (6c). Oxidation of 227.0 mg (0.5 mmol) of **6c** yielded 270 mg of a yellow glass. Separation of the mixture by preparative TLC (ether–2% acetone) afforded 4 mg (2%) of homoaporphine **9c**, 51 mg (22%) of the aldehyde–amide **11a**, 10 mg (5%) of dienone **8a**, and 140 mg (64%) of the dienone **7a**.

Homoaporphine **9c**: mp 167–169 °C (ether); UV λ_{max}(EtOH) (log ϵ) 267 (4.07), 289 (3.98) nm; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.05 (s, 1 H, C-12 H), 6.78, 6.68 (both s, 2 H, ArH), 3.95, 3.90, 3.85, and 3.45 (all s, 12 H, OCH_3), 3.1–2.3 (m, 8 H, CH_2); mass spectrum *m/e* 451 (M^+), 420 ($M^+ - OCH_3$).

Anal. Calcd for $C_{23}H_{24}NO_5F_3$: C, 61.19; H, 5.36; N, 3.10. Found: C, 60.92; H, 5.45; N, 2.94.

Aldehyde–amide **11a**: mp 143–144 °C (ether); UV λ_{max}(EtOH) (log ϵ) 285 (3.84), 235 (sh, 4.25); mass spectrum *m/e* 469 (M^+), 298.

Anal. Calcd for $C_{23}H_{26}NO_6F_3$: C, 58.84; H, 5.58; N, 2.98. Found: C, 58.96; H, 5.76; N, 2.83.

Dienone **8a**: mp 125 °C, solidifies and remelts at 161–162 °C (ether); UV λ_{max}(EtOH) (log ϵ) 243 (4.33), 286 (3.67); mass spectrum *m/e* 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.53; H, 5.13; N, 3.40.

Dienone **7a**: mp 171.5–172.0 °C (ethanol); UV λ_{max}(EtOH) (log ϵ) 235 (4.23), 259 (4.07), 284 (3.88), 340 (3.73) nm; mass spectrum *m/e* 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.52; H, 5.49; N, 2.96.

VOF_3 Oxidation of 6d. Oxidation of 213 mg (0.5 mmol) of **6d** yielded 250 mg of a pale yellow foam. Preparative TLC (ether–5% acetone) and crystallization from ether gave 165 mg (78%) of **8b**: mp 202–203.5 °C (lit.[24] 198–200 °C); NMR ($CDCl_3$) δ 6.74, 6.46 (both s, 2 H, ArH), 6.29 (s, 1 H, C-1 H), 5.94 (s, 1 H, C-4 H), 5.67 (s, 1 H, OH), 3.74, 3.62 (both s, 6 H, OCH_3).

VOF_3 Oxidation of 6e. Oxidation of 133 mg (0.25 mmol) of **6e** yielded 150 mg of a yellow glass. Separation of the mixture by preparative TLC (ether–5% acetone) afforded 55 mg (50%) of **8a** and 54 mg (42%) of **7b**: mp 109.5 °C, solidifies and remelts at 169–170 °C; UV λ_{max}(EtOH) (log ϵ) 235 (4.23), 258 (4.07), 285 (3.85), 342 (3.74) nm; IR ($CHCl_3$) 1690 (C=O), 1665, and 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.36 (s, 5 H, $PhCH_2O$), 6.64 (s, 2 H, ArH), 6.48 (s, 1 H, C-1 H), 5.76 (s, 1 H, C-4 H), 5.03 (s, 2 H, OCH_2Ph), 3.88 and 3.86 (each s, 6 H, OCH_3); mass spectrum *m/e* 513 (M^+), 485, 422, 394.

Anal. Calcd for $C_{28}H_{26}NO_5F_3$: C, 65.49; H, 5.10; N, 2.73. Found: C, 65.54; H, 5.30; N, 2.90.

VOF_3 Oxidation of 6f. Oxidation of 133 mg (0.25 mmol) of **6f** gave 110 mg of a yellow residue. Separation of the mixture by preparative TLC ($CHCl_3$–2% methanol) afforded 58.4 mg (60%) of **7a** and 5.5 mg (3%) of **8c**: mp 134–134.5 °C (ether); UV λ_{max}(EtOH) (log ϵ) 243 (4.37), 285 (3.72) nm; IR ($CHCl_3$) 1688 (C=O), 1668, and 1645 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.31 and 6.62 (both s, 2 H, ArH), 6.27 (s, 1 H, C-1 H), 5.99 (s, 1 H, C-4 H), 4.87 (s, 2 H, $ArCH_2O$), 3.89 and 3.77 (both s, 6 H, OCH_3); mass spectrum *m/e* 513 (M^+), 422.

Anal. Calcd for $C_{28}H_{26}NO_5F_3$: C, 65.49; H, 5.10; N, 2.73. Found: C, 65.56; H, 5.09; N, 2.73.

VOF_3 Oxidation of *N*-Carbethoxyhomonorlaudanosine (6i). Oxidation of 215 mg (0.5 mmol) of **6i** gave 230 mg of a yellow glass.

Preparative TLC (ether–5% acetone) afforded 134 mg (60%) of **11b** as colorless crystals: mp 139.5 –140.5 °C (ether); IR ($CHCl_3$) 3465 (NH), 2830 and 2710 (CHO), 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.25 (s, 1 H, CHO), 6.80 (s, 1 H, ArH), 6.76 (s, 1 H, ArH), 6.65 (s, 2 H, ArH), 4.05 (q, 2 H, $COOCH_2CH_3$, J = 7.1 Hz), 3.92 (s, 6 H, OCH_3), 3.84 (s, 6 H, OCH_3), 1.26 (t, 3 H, $COOCH_2CH_3$, J = 7.1 Hz), 3.58–2.53 (m, 8 H, CH_2); mass spectrum m/e 445 (M^+), 299.

Anal. Calcd for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.79; H, 6.94; N, 3.19.

Methylation of Diphenolic Homoaporphine 9b to 1,2,10,11-Tetramethoxyhomoaporphine (9a). A solution of 20.0 mg of **9b** in 5.0 mL of methanol was treated with an excess of an ether solution of diazomethane, and the solution was kept at room temperature for 4 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in 2 mL of methanol, made acidic with concentrated HCl, and evaporated to leave a yellow residue. Crystallization from methanol–ether gave 15.6 mg (70%) of **9a** as the hydrochloride salt: mp 242–244 ° dec; the melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those described earlier for **9a.**

Rearrangement of 10a with Boron Trifluoride Etherate. A mixture of 80.0 mg of dienone **10a,** 5.0 mL of CH_2Cl_2, and 1.5 mL of boron trifluoride etherate was stirred at room temperature for 24 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water and 10% ammonia and water, dried, and evaporated to give 90.0 mg of a yellow glass. Preparative TLC ($CHCl_3$–15% methanol) gave 69.5 mg (87%) of **9b:** mp 185–187 °C (methanol–ether) (lit.[22] 185–187 °C); NMR ($CDCl_3$) δ 7.03 (s, 1 H, C-12 H), 6.74 (s, 1 H, ArH), 6.61 (s, 1 H, ArH), 5.41 (s, 2 H, OH), 3.89 (s, 6 H, OCH_3), 2.37 (s, 3 H, NCH_3).

2,10,11-Trimethoxy-*N*-trifluoroacetylhomoproerythrinadienone (8a). A solution of 52 mg of **8b** in 5 mL of methanol was treated with an excess of an ether solution of diazomethane and kept at room temperature for 1 h. Evaporation of the solvent and crystallization of the residue from ether gave 50 mg (94%) of **8a:** mp 125.5 °C, solidifies and remelts at 161–162 °C. The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of a sample obtained by oxidation of **6c.**

Conversion of *N*-Trifluoroacetyl-1,2,10,11-tetramethoxyhomoaporphine (9c) to *N*-Methyl-1,2,10,11-tetramethoxyhomoaporphine (9a). A solution of 100 mg of **9c** in 25 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 2 h, at which time the solution was evaporated to dryness and the residue was suspended in 10 mL of water and extracted with three 20-mL portions of ether. The ether solution was washed with water, dried, and evaporated to give 78 mg of a colorless glass. The glass was taken up in 3 mL of methanol and treated with 0.3 mL of 37% formaldehyde solution, and the mixture was stirred at room temperature for 3 h. The reaction was diluted with 10 mL of methanol; 50 mg of $NaBH_4$ was added at room temperature, portionwise, with stirring, over 10 min and the reaction was stirred for an additional 0.5 h. The methanol was evaporated and the residue was suspended in 15 mL of water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 85 mg of a yellow oil. Preparative TLC ($CHCl_3$–5% methanol) and crystallization of the residue as the hydrochloride salt from methanol–ether gave 67 mg (75%) of **9a:** mp 242–244 °C dec. The melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those of a sample obtained by anodic oxidation of **6a.**

Conversion of Aldehyde–Amide 11a to Tetramethoxydibenzazecine 14a. A solution of 20.0 mg of **11a** in 5 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 6 h, at which time 200 mg of $NaBH_4$ was added and the reaction was stirred for an additional 0.5 h. The methanol was evaporated and the residue was suspended in water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 15 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol) and crystallization of the residue as the hydrochloride salt from methanol–ether gave 7.3 mg of **14a:** mp 166–168 °C; NMR ($CDCl_3$) δ 6.77, 6.73, 6.60, and 6.55 (all s, 4 H, ArH), 3.94, 3.92, 3.85, and 3.83 (all s, 12 H, OCH_3), 3.30–2.30 (m, 10 H, CH_2); mass spectrum m/e 357 (M^+), 342, 325, 299.

Anal. Calcd for $C_{21}H_{28}NO_4Cl \cdot 2.5H_2O$: C, 57.46; H, 7.57; N, 3.19. Found: C, 57.17; H, 7.31; N, 3.19.

Conversion of Homoproerythrinadienone 8b to Tetramethoxydibenzazecine 14a. A solution of 60 mg of **8b** in 5 mL of 1 N methanolic sodium hydroxide was stirred at 0 °C for 24 h, at which time 50 mg of $NaBH_4$ was added, in portions, over 10 min, and stirring was continued for 4 h. The reaction mixture was evaporated to dryness and the residue was suspended in water, the pH adjusted to 7.5, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried, and evaporated to leave 35 mg of a yellow glass. Preparative TLC ($CHCl_3$–15% methanol) gave 15 mg of **14b** as a colorless glass which was dissolved in 5 mL of methanol and treated with an excess of an ether solution of diazomethane. The reaction mixture was allowed to stand at room temperature for 2 h and then evaporated to give 15 mg of a yellow glass. Separation of the mixture by preparative TLC ($CHCl_3$–15% methanol: two elutions) afforded the following products. **14a,** 5 mg: mp 165–167.5 °C; the melting point, mixture melting point, IR, NMR, and mass spectrum were identical with those of the product obtained from aldehyde–amide **11a. 14c,** 8 mg: NMR ($CDCl_3$) δ 6.80, 6.74, 6.60, and 6.56 (all s, 4 H, ArH), 3.95, 3.92, 3.86, and 3.82 (all s, 12 H, OCH_3), 2.45 (s, 3 H, NCH_3); mass spectrum m/e 371 (M^+).

Rearrangement of 8a with Boron Trifluoride Etherate. A mixture of 30 mg of dienone **8a,** 5 mL of CH_2Cl_2, and three drops of boron trifluoride etherate was stirred at room temperature for 24 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water and 10% ammonia and water and dried over $NaSO_4$. Evaporation of the solvent and crystallization of the residue from ether gave 26 mg (87%) of **15:** mp sintering at 198 °C, melts at 221–222 °C; UV λ_{max}(EtOH) (log ϵ) 267 (4.09), 289 (3.99); NMR ($CDCl_3$) δ 7.07 and 7.03 (each s, 1 H, ArH), 6.80 (s, 1 H, ArH), 6.75 (s, 1 H, ArH), 5.87 (s, 1 H, OH), 3.95, 3.87, and 3.31 (each s, 9 H, OCH_3); mass spectrum m/e 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.47; H, 5.11; N, 3.27.

1,2,10,11-Tetramethoxy-*N*-trifluoroacetylhomoaporphine (9c). A solution of 11.0 mg of **15** in 5 mL of methanol was treated with an excess of an ether solution of diazomethane and kept at room temperature for 1 h. Evaporation of the solvent and crystallization from ether gave 10.0 mg (88%) of the product (**9c**): mp 166–168 °C. The melting point, mixture melting point, IR, NMR, TLC, UV, and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **6c.**

Rearrangement of 7a with Boron Trifluoride Etherate. A mixture of 100 mg of dienone **7a,** 10 mL of CH_2Cl_2, and three drops of boron trifuloride etherate was stirred at room temperature for 22 h. After the solution had been diluted with CH_2Cl_2 to 50 mL, the solution was washed with water and 10% ammonia and water, and dried. Evaporation of the solvent and crystallization of the residue from ether gave 83 mg (84%) of **17:** mp 200–201 °C; UV λ_{max}(EtOH) (log ϵ) 265 (4.05), 296 (3.93) nm; IR ($CHCl_3$) 3550 (OH), 1690 cm^{-1} (C=O); mass spectrum m/e 437 (M^+); NMR ($CDCl_3$) δ 7.12 and 7.08 (each s, 1 H, ArH), 6.79 and 6.63 (each s, 2 H, ArH), 5.74 (s, 1 H, OH), 3.93 (s, 6 H, OCH_3), 3.86 (s, 3 H, OCH_3).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.50; H, 5.17; N, 3.18.

1,2,10,11-Tetramethoxy-*N*-trifluoroacetylhomoaporphine (9c). A solution of 30 mg of **17** in 3 mL of methanol was methylated according to the procedure given for the methylation of **15,** yielding 25.5 mg (87%) of the product (**9c**): mp 167–169 °C. The melting point, mixture melting point, TLC, IR, UV, NMR, and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **6c.**

Treatment of 11b with Ethylene Glycol in the Presence of *p*-Toluenesulfonic Acid. A mixture of 75 mg of **11b,** 50 mL of benzene, 1 mL of ethylene glycol, and 50 mg of *p*-toluenesulfonic acid was heated at reflux with azeotropic removal of water. After 7 h the mixture was poured into aqueous sodium carbonate and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give a residue. Preparative TLC (ether–10% acetone) afforded 70 mg of **22** as a colorless glass: NMR ($CDCl_3$) δ 6.81 and 6.79 (both s, 2 H, ArH), 4.71 [t, 1 H, J = 4.7 Hz, c-(–$CHOCH_2CH_2O$)], 4.64 (mound, 1 H, NH), 4.05 (q, 2 H, J = 7.0 Hz, CH_3CH_2O), 3.92 (s, 6 H, OCH_3), 3.84 (s, 10 H, 2-OCH_3 and OCH_2CH_2O), 2.17 (m, 2 H, $CH_2NHCOOEt$), 2.45 (m, 4 H, $ArCH_2$), 1.80 (m, 2 H, CH_2CH), 1.19 (t, 3 H, CH_3CH_2O, J = 7.0 Hz).

Conversion of Acetal–Urethane (22) into Tetramethoxydibenzazecine (14a). A mixture of 60 mg of **22,** 5 mL of 20% aqueous sodium hydroxide, and 5 mL of methanol was heated at reflux on a steam bath for 48 h. The methanol was evaporated and the aqueous solution was extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give 50 mg of **23** as a colorless glass: mass spectrum m/e 417 (M^+); IR 3490 cm^{-1} (NH_2). The glass was treated with 5 mL of 5% aqueous HCl and heated on a steam bath for 10 min. The acidic solution was neutralized with powdered sodium bicarbonate and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to leave 50 mg of a yellow glass. The glass was dissolved in 5 mL of methanol containing 10 mg

of PtO_2 and 5 drops of concentrated HCl. Hydrogenation was carried out under 1 atm of pressure of hydrogen for 5 h. The solution was filtered through Celite and the solvent removed in vacuo to leave a colorless oil. Crystallization from methanol–ether gave 30 mg of the hydrochloride salt of **14a**: mp 166–168 ° C; NMR and IR identical with those of **14a** obtained from aldehyde–amide **11a**.

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Registry No.—**1c**, 36455-21-7; **2a**, 2107-70-2; **2c**, 36418-96-9; **2e**, 1135-15-5; **3c**, 20872-69-9; **3d**, 65899-35-6; **4a**, 20944-14-3; **4b**, 30034-51-6; **4c**, 65899-36-7; **4d** HCl, 65899-37-8; **4e**, 65899-38-9; **5a**, 65899-28-7; **5a** HCl, 32487-02-8; **5c**, 65899-29-8; **5c** HCl, 65899-19-6; **5d**, 65899-30-1; **5d** HCl, 65899-20-9; **5e**, 65899-31-2; **5e** HCl, 65899-21-0; **6a** perchlorate, 65899-22-1; **6h**, 65899-23-2; **9a** HCl, 61660-06-8; **9b**, 61660-05-7; **10** isomer I, 51744-25-3; **10** isomer II, 30040-57-4; **14a** HCl, 65899-24-3; **14b**, 58141-98-3; **14c**, 65899-25-4; **22**, 65899-26-5; **23**, 65899-27-6.

References and Notes

(1) Deceased October 18, 1976.
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(3) W. I. Taylor and A. R. Battersby, Ed., "Oxidative Coupling of Phenols", Marcel Dekker, New York, N.Y., 1967.
(4) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972).
(5) A recent review of biosynthesis of isoquinoline alkaloids is found in: H. R. Schutte, "Biosynthese der Alkaloide", K. Mothes and H. R. Schutte, Ed., VEB Deutscher Verlag der Wissenchaften, Berlin, 1969, p 367.
(6) T. Kametani, K. Fukumoto, and F. Satoh, *Bioorg. Chem.*, **3**, 430 (1974).
(7) T. Kametani and K. Fukumoto, "Phenolic Oxidation", Gihodo, Tokyo, 1970, p 121.
(8) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **93**, 5941 (1971); **95**, 2651 (1973).
(9) E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
(10) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974).
(11) J. R. Falck, L. L. Miller, and F. R. Stermitz, *J. Am. Chem. Soc.*, **96**, 2981 (1974).
(12) M. Sainsbury and R. F. Shinazi, *J. Chem. Soc., Chem. Commun.*, 718 (1972).
(13) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973).
(14) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Am. Chem. Soc.*, **97**, 5622 (1975).
(15) C.-K Kim and S. M. Kupchan, *J. Am. Chem. Soc.*, **97**, 5623 (1975).
(16) M. A. Schwartz, B. F. Rose, R. A. Holton, S. W. Scott, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **99**, 2571 (1977).
(17) A portion of this work has been reported as a communication: S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, **41**, 4047 (1976).
(18) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).
(19) R. E. Harmon and B. L. Jensen, *J. Heterocycl. Chem.*, **7**, 1077 (1970).
(20) A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 934 (1967).
(21) A. Brossi, J. O. Brlen, and S. Teitel, *Helv. Chim. Acta*, **52**, 678 (1969).
(22) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc. C*, 1003 (1968).
(23) L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", Vol. 5, Pergammon Press, Oxford, 1969, pp 184–185.
(24) J. P. Marino and J. M. Samanen, *Tetrahedron Lett.*, 4553 (1973).
(25) J. P. Marino and J. M. Samanen, *J. Org. Chem.*, **41**, 179 (1976).
(26) T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **20**, 1793 (1972).
(27) F. R. Sternmitz and D. K. Williams, *J. Org. Chem.*, **38**, 2099 (1973).
(28) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **24**, 1921 (1976).
(29) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).
(30) N. J. McCorkindale, A. W. McCulloch, and D. S. Magrill, *Tetrahedron*, **25**, 5475 (1969).
(31) O. Hoshino, T. Toshioka, K. Ohyama, and B. Umezawa, *Chem. Pharm. Bull.*, **22**, 1307 (1974).
(32) S. Teitel and A. Brossi, *J. Heterocycl. Chem.*, **5**, 825 (1968).
(33) A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J. Chem. Soc., Perkin Trans. 1*, 1741 (1972).

Utilization of β,γ-Unsaturated Aldehyde Equivalents in the Synthesis of Substituted 2-Halonicotinic Acid Derivatives

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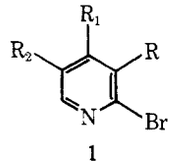
A convenient synthetic method is described for the preparation of 4- and/or 5-substituted 2-halonicotinic acid derivatives. The condensation of alkylidenemalononitriles or alkylidenecyanoacetates with either $HC(OEt)_3$ or DMF acetal yields the equivalent of a β,γ-unsaturated aldehyde which undergoes cyclization with acid to provide polysubstituted pyridines. However, the general utility of the reaction between DMF acetal and alkylidenemalononitriles is severely limited by the formation of dimeric type derivatives, **31–34**. This complication is overcome by the acid-catalyzed reaction of $HC(OEt)_3$ with alkylidenemalononitriles. Conversion of substituted ethyl nicotinates derived from alkylidenecyanoacetates to the corresponding trifluoromethyl derivatives is also described. Reaction of the unsymmetrical olefin 1-methylpropylidenemalononitrile with DMF acetal and with $HC(OEt)_3$ yields, in a regiospecific manner, two different β,γ-unsaturated aldehyde equivalents, which after acid cyclization afford 4-ethyl- and 4,5-dimethyl-2-bromonicotinonitriles, respectively.

An interest in derivatives of 2-halonicotinic acid of the type **1** led to a search for a synthetic method capable of generating such systems. Although several syntheses of the parent, ethyl 2-halonicotinate, and certain substituted derivatives have been described,[1,2] none of these have been extended to provide a versatile method for the introduction of alkyl or aryl groups into the 4 and/or 5 positions.[3]



1

R = CO_2Et, CN, or CF_3
R_1,R_2 = alkyl, aryl, or H

One of the most general of these reported methods involves the Knoevenagel condensation of 1,3-dicarbonyl compounds (**2**) (or their chemical equivalents) with α-cyanoacetamide (**3**). This condensation is accompanied by cyclization, yielding 2-pyridones of the type **4** which are convertible by standard methods[4] to 2-halopyridines (Scheme I). Although a number of 6-substituted and 4,6-disubstituted 2-hydroxynicotinic acid derivatives have been prepared by this procedure, the method

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