Efficient Intramolecular Monophenol Oxidative Coupling

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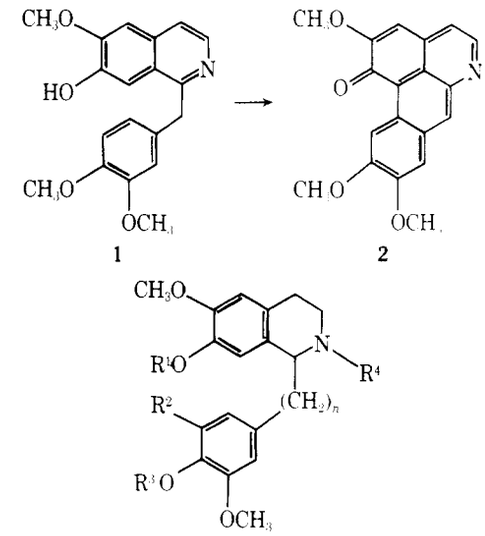
Intramolecular oxidative coupling of monophenolic benzyl- and phenethyltetrahydroisoquinolines using VOF_3–TFA/TFAA as the coupling reagent has resulted in remarkably efficient syntheses of several aporphines, homoaporphines, homoproaporphines, and a homoproerythrinadienone. Treatment of 7-hydroxy-1-benzyltetrahydroisoquinolines **3c, 3f,** and **3h** with VOF_3–TFA/TFAA gave aporphines **4a, 4b,** and **4d** (70–80%). Oxidations of 7-hydroxy-1-phenethyltetrahydroisoquinolines **3i, 3k, 3n,** and **3p** yielded, depending upon the reaction time, homoproaporphines **8a, 8b, 9a,** and **9b** (4–54%) and homoaporphines **7a, 7e, 7f,** and **7g** (54–77%). Oxidation of 6-hydroxy-1-phenethyltetrahydroisoquinoline **11** proceeded smoothly to give homoproerythrinadienone **12** in 98% yield. When the VOF_3–TFA/TFAA oxidation was extended to a monophenolic *N*-benzylphenethylamine (**16**), a dienone (**18**), the precursor of the Amaryllidaceae alkaloid (±)-oxocrinine, was obtained in 88% yield.

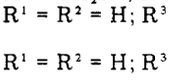
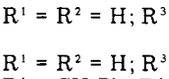
Although diphenolic oxidative coupling reactions play an important role in the biosynthesis of alkaloids,[3] the synthetic utility of intramolecular oxidative coupling of diphenols has been limited by low yields. Recently, attention has been directed toward the utilization of monophenolic substrates in an attempt to develop effective intramolecular coupling methods for use in alkaloid synthesis.[4,5] Schwartz et al. synthesized homomorphinandienones via monophenolic oxidative coupling using thallium tris(trifluoroacetate) in dichloromethane as the reagent.[4a] In 1973, we reported the conversion of the monophenolic benzylisoquinoline (**1**) to the quinonoid oxoaporphine (**2**) using a variety of oxidizing agents.[6] One of the most effective agents was vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) yielding **2** in 59% yield. Since then we have demonstrated that VOF_3 is a useful reagent for intramolecular oxidative coupling of nonphenolic benzyl-[7] and phenethyltetrahydroisoquinolines.[8] We now report the VOF_3-induced intramolecular oxidative coupling of monophenolic tetrahydroisoquinoline derivatives and *N*-benzylphenethylamines resulting in remarkably efficient syntheses of several aporphines, homoaporphines, homoproaporphines, a homoproerythrinadienone, and the Amaryllidaceae alkaloid (±)-oxocrinine precursor (**18**).[9]

(±)-Codamine (**3e**) and (±)-*N*-trifluoroacetylnorcodamine (**3c**), typical monophenolic benzyltetrahydroisoquinoline derivatives, were prepared by the conventional method[8] and subjected to VOF_3–TFA/TFAA oxidation. Treatment of a solution of (±)-*N*-trifluoroacetylnorcodamine (**3c**) in dichloromethane and trifluoroacetic acid:trifluoroacetic anhydride (TFA/TFAA; 20:1 by wt.)[14] at −10 °C with a solution of VOF_3 in ethyl acetate and TFA/TFAA (20:1 by wt) for 10 min, followed by aqueous workup, gave (±)-*N*-trifluoroacetylwilsonirine (**4a,** 70%) along with morphinandienone (**5a,** 8%). The structure of aporphine **4a** was confirmed by transforming it to the naturally occurring aporphine (±)-thalicimidine[11] (**4b**) via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride. The structure of morphinandienone **5a** was confirmed by alkaline hydrolysis to the secondary amine (**5b**), conversion of the secondary amine to the *N*-methyl dienols (**6**) by treatment with formaldehyde–sodium borohydride, and subsequent oxidations of the dienols with manganese dioxide to (±)-*O*-methylflavinantine (**5c**).[12]

Oxidation of codamine (**3e**) by the above procedure gave a complex mixture of products from which only (±)-thalicmidine[11] (**4b,** 38%) was isolable. Interestingly, when codamine (**3e**) was treated with diborane in tetrahydrofuran–dichloromethane, and the resulting protected amine (**3f**) oxidized with VOF_3, thalicmidine (**4b**) was obtained in 80% yield after removal of the blocking group by heating with anhydrous sodium carbonate in methanol under reflux. Morphinandienone **5c** could not be detected by thin layer chromatography in either of the latter experiments. The facile and high yield conversions of the monophenolic benzyltetrahydroisoqunolines **3c** and **3e** to aporphines **4a** and **4b** constitute an efficient route to 1,2,9,10-tetrasubstituted aporphines.



1 **2**

3a, $R^1 = CH_2Ph$; $R^2 = R^4 = H$; $R^3 = CH_3$; $n = 1$
b, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 1$
c, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 1$
d, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = R^4 = CH_3$; $n = 1$
e, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$; $n = 1$
f, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 =$  ; $n = 1$
g, $R^1 = R^2 = H$; $R^3 = CH_2Ph$; $R^4 = CH_3$; $n = 1$
h, $R^1 = R^2 = H$; $R^3 = CH_2Ph$; $R^4 =$  ; $n = 1$
i, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
j, $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = R^4 = CH_3$; $n = 2$
k, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$; $n = 2$
l, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = H$; $n = 2$
m, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
n, $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = COCF_3$; $n = 2$
o, $R^1 = CH_2Ph$; $R^2 = OCH_3$; $R^3 = R^4 = CH_3$; $n = 2$
p, $R^1 = H$; $R^2 = OCH_3$; $R^3 = R^4 = CH_3$; $n = 2$

In order to test the general applicability of the VOF_3–TFA/TFAA coupling method for the synthesis of 1,2,9,10-tetrasubstituted aporphines, the total synthesis of (±)-bracteoline (**4d**) was undertaken. The monophenolic benzyltetrahydroisoquinoline **3g** required for the synthesis was prepared by the method of Hara et al.[13] Treatment of **3g** with diborane in THF–CH_2Cl_2 gave the desired protected amine **3h.**

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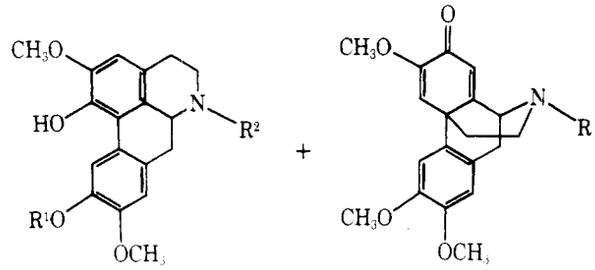
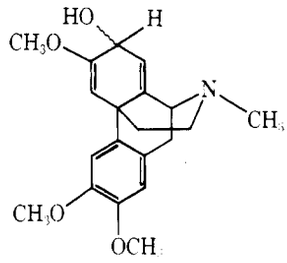
3c, e, f, h →



4a, $R^1 = CH_3$; $R^2 = COCF_3$
b, $R^1 = R^2 = CH_3$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$
d, $R^1 = H$; $R = CH_3$

5a, $R = COCF_3$
b, $R = H$
c, $R = CH_3$



6

Oxidation of **3h** with VOF_3, according to the procedure described earlier, gave (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (**4c**) in 75% yield after removal of the blocking group by heating with sodium carbonate in methanol under reflux. Catalytic debenzylation of **4c** afforded (±)-bracteoline[13] (**4d**) in 78% yield.

To evaluate the potential of the monophenolic oxidative coupling procedure using VOF_3–TFA/TFAA for the synthesis of homoaporphines, and homomorphinandienones, 7-hydroxy-1-phenethyltetrahydroisoquinolines **3i, 3k, 3n,** and **3p** were prepared by the conventional method[8] and subjected to VOF_3 oxidation.

Oxidative coupling of the phenethyltetrahydroisoquinoline **3i** with VOF_3 at −15 °C for 10 min according to the procedure described earlier yielded the homoaporphine **7a**[8] (40%) along with the homoproaporphine **8a** (18%). The structure of the homoproaporphine **8a** was assigned on the basis of the following evidence. Treatment of **8a** with boron trifluoride etherate in dichloromethane at room temperature for 2 h gave homoaporphine **7d,** which on hydrolytic cleavage of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride treatment gave a diphenolic homoaporphine (**7c**), identical with the product obtained from the dienone–phenol rearrangement of **8b.**[21]

Oxidation of phenethyltetrahydroisoquinoline **3k** with VOF_3 at −10 °C for 6 min gave the homoproaporphine **8b**[17,18,21] (42%) in addition to homoaporphine **7e**[19] (14%).

Interestingly, only one isomer of the homoproaporphine, **8a** or **8b,** was obtained in the oxidation of **3i** or **3k** in contrast to the diastereoisomeric mixtures obtained by oxidation of the diphenolic precursor.[8]

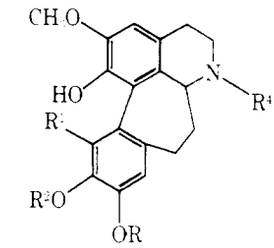
Oxidation of the phenethyltetrahydroisoquinoline **3n** with VOF_3 at −10 °C for 10 min yielded homoaporphine **7f** and homoproaporphine **9a** in 46 and 4% yield, respectively. The structure of homoaporphine **7f** was confirmed by transformation into the naturally occurring homoaporphine (±)-kreysigine (**7g**) via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation with formaldehyde–sodium borohydride. The structure of homoproaporphine **9a** was assigned on the basis of its physical and spectral data (see Experimental Section).

Oxidation of phenethyltetrahydroisoquinoline **3p** with VOF_3 at −10 °C for 10 min gave homoproaporphine **9b**[20] (54%) in addition to (±)-kreysigine[20] (**7g,** 16%).

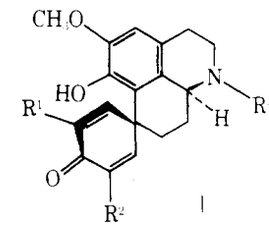
Homoproaporphines **8a, 8b, 9a,** and **9b** underwent smooth dienone–phenol rearrangement upon treatment with boron trifluoride etherate in dichloromethane at room temperature. Thus, homoproaporphine **8a** afforded homoaporphine **7d** in 93% yield. The structure of **7d** was confirmed by transforming it to homoaporphine **7c,** as described above. Homoproaporphine **8b** afforded homoaporphine **7c**[21] in 70% yield. Homoproaporphine **9a** gave homoaporphine **7h** in 87% yield. The structure of homoaporphine **7h** was assigned on the basis of its physical and spectral data (see Experimental Section). Homoproaporphine **9b** afforded homoaporphine (±)-multifloramine (**7i**)[20] in 72% yield.

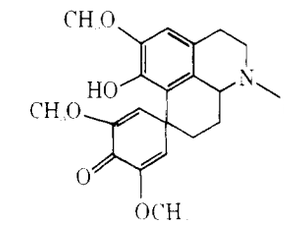
The formation of homoproaporphines **8a, 8b, 9a,** and **9b** and of homoaporphines **7a, 7e, 7f,** and **7g** in the oxidation of **3i, 3k, 3n,** and **3p,** and the demonstrated facile acid-catalyzed rearrangment of homoproaporphines **8a, 8b, 9a,** and **9b** to homoaporphines **7d, 7c, 7h,** and **7i,** suggested that the formation of homoaporphines **7a, 7c, 7f,** and **7g** from **3i, 3k, 3n,** and **3p** may proceed via homoproaporphine-type intermediates (e.g., **10**) and, in part, via direct coupling. Thus, homoaporphines **7a, 7e, 7f,** and **7g** might be obtained in high yields if enough time were allowed for rearrangement of the corresponding homoproaporphine-type intermediates (e.g., **10**) Indeed, the phenethyltetrahydroisoquinolines **3i, 3k,** and **3n** gave homoaporphines **7a** (77%), **7e** (60%), and **7f** (54%), respectively, upon treatment with VOF_3–TFA/TFAA for 30–60 min. The phenethyltetrahydroisoquinoline **3p** failed to give homoaporphine **7g** in high yield even after longer reaction

3i, k, n, p →



7a, $R^1 = H$; $R^2 = R^3 = CH_3$; $R^4 = COCF_3$
b, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$
c, $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$
d, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COCF_3$
e, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$
f, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$; $R^4 = COCF_3$
g, $R^1 = OCH_3$; $R^2 = R^3 = R^4 = CH_3$
h, $R^1 = OCH_3$; $R^2 = H$; $R^3 = CH_3$; $R^4 = COCF_3$
i, $R^1 = OCH_3$; $R^2 = H$; $R^3 = R^4 = CH_3$

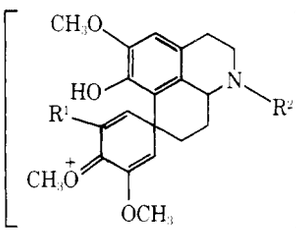




8a, $R^1 = H$; $R^2 = OCH_3$; $R^3 = COCF_3$
b, $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$

9a, $R = COCF_3$
b, $R = CH_3$

3i, k, n, p →



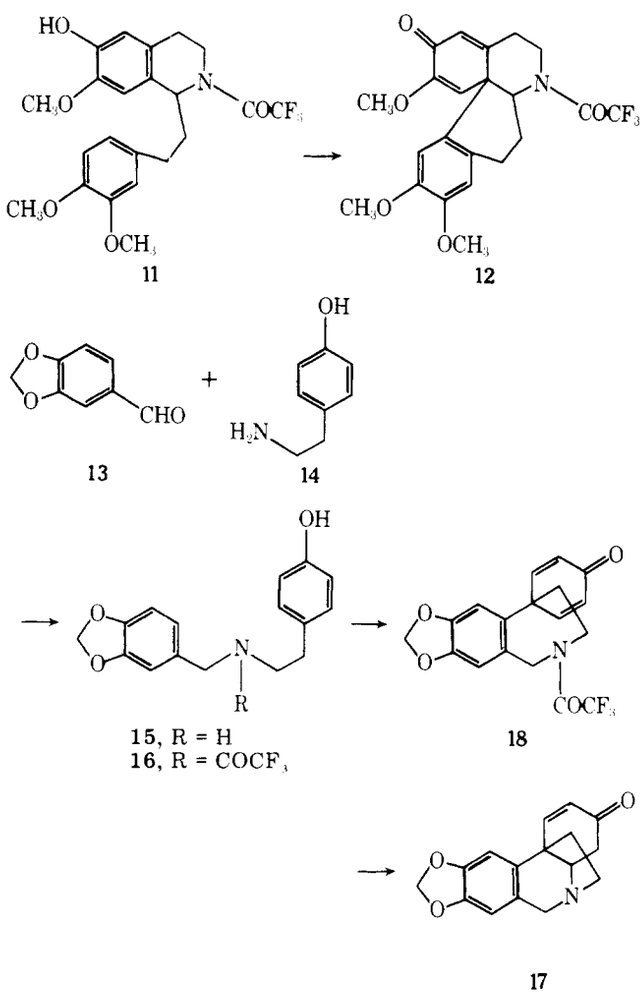
→ 7a, e, f, g

10, R^1 = H or OCH_3; $R^2 = CH_3$ or $COCF_3$

time, probably owing to slow rearrangement of homoproaporphine-type intermediate (**10**).

To evaluate the potential of the monophenol oxidative coupling procedure for the synthesis of homoproerythrinadienones, 6-hydroxyl-1-phenethyltetrahydroisoquinoline **11**, prepared by catalytic debenzylation of 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline,[8] was subjected to VOF_3 oxidation (10 min at −10 °C) and homoproerythrinadienone **12** was obtained in 98% yield. This result contrasts remarkably with those of prior studies of oxidative cyclization of diphenolic precursors using $VOCl_3$ in dichloromethane[22] (35%) and VOF_3–TFA/TFAA[8] (78%).

The remarkable success achieved in the synthesis of various isoquinoline alkaloids using VOF_3–TFA/TFAA as the coupling reagent prompted us to evaluate the potential of this coupling method for the synthesis of dienone **18**, the precursor of the amaryllidaceae alkaloid (±)-oxocrinine (**17**), from monophenolic *N*-benzylphenethylamine **16**. The phenethylamine **15** was prepared by condensation of piperonal (**13**) and tyramine (**14**) to the corresponding imine followed by borohydride reduction.[4a,23] Treatment of the amine **15** with trifluoroacetic anhydride and pyridine yielded the *N*-trifluoroacetylnorbelladine derivative **16**. When a solution of **16** in CH_2Cl_2 and TFA/TFAA was treated with a solution of VOF_3 in EtOAc and TFA/TFAA (at −10 °C for 10 min), the dienone **18** was obtained in 88% yield, as compared to the 19% yield obtained by Schwartz using thallium tris(trifluoroacetate)[4a] as the coupling reagent.



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 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. Benzyl- and phenethyltetrahydroisoquinolines **3a–p** were prepared by a standard method,[8] *i.e.*, condensation of benzyloxyphenethylamines and acids to corresponding amides followed by Bischler-Napieralski cyclization, $NaBH_4$ reduction, N-acetylation or N-methylation, and subsequent debenzylation by hydrogenolysis.

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 wt)] 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 wt)] at −10 °C (ice–salt bath) and the resulting dark blue solution was stirred for various lengths of time (see Table I). 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.

1-(3,4-Dimethoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3a). From 9.8 g (21.6 mmol) of 1-(3,4-dimethoxybenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[10] by $NaBH_4$ reduction in methanol there was obtained 8.84 g (90%) of **3a** as the hydrochloride salt: mp 214.5–215 °C (methanol–ether); NMR ($CDCl_3/CD_3OD$) δ 7.32 (s, 5 H, **Ph**CH_2), 6.77 (m, 4 H, Ar**H**), 6.31 (s, 1 H, Ar**H**), 4.87 (d, 2 H, O**C**H_2, J = 3 Hz), 3.87 (s, 6 H, O**C**H_3), 3.82 (s, 3 H, O**C**H_3).

Anal. Calcd for $C_{26}H_{29}NO_4$·HCl: C, 68.48; H, 6.63; N, 3.07. Found: C, 68.21; H, 6.65; N, 3.12.

1-(3,4-Dimethoxybenzyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3b). From 2.03 g (4.83 mmol) of **3a**, 3 mL of TFAA, and 0.4 mL of pyridine in 25 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and ususal workup, 2.5 g of a white solid. Crystallization from methanol afforded 2.368 g (95%) of **3b:** mp 159.5–160 °C; IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.34 (s, 5 H, **Ph**C**H**$_2$O), 6.50 (m, 5H, Ar**H**), 5.47 (t, 1 H, C**H**, J = 6.0 Hz), 4.96 (s, 2 H, O**C**H_2), 3.86, 3.84, and 3.74 (all s, 9 H, O**C**H_3).

Anal. Calcd for $C_{28}H_{28}O_5NF_3$: C, 65.23; H, 5.47; N, 2.72. Found: C, 65.08; H, 5.49; N, 2.74.

(±)-*N*-Trifluoroacetylnorcodamine (3c). From 1.3 g (2.5 mmol) of **3b** in 50 mL of ethanol containing 200 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 1.012 g (94%) of **3c** as colorless cyrstals: mp 149–150 °C (ether); NMR ($CDCl_3$) δ 6.60 (m, 5 H, Ar**H**), 5.57 (s, 1 H, O**H**), 3.87, 3.84, and 3.75 (all s, 9 H, O**C**H_3); mass spectrum m/e 425 (M^+).

Anal. Calcd for $C_{21}H_{22}O_5NF_3$: C, 59.29; H, 5.21; N, 3.29. Found: C, 59.13; H, 5.26; N, 3.24.

VOF_3 Oxidation of (±)-*N*-Trifluoroacetylnorcodamine (3c). Oxidation of 213 mg (0.5 mmol) of **3c** gave 230 mg of a dark solid. Preparative TLC ($CHCl_3$, four elutions) afforded the following two products: **5a** and **4a.**

5a (16.8 mg; 8%): mp 179.5–181.5 °C (ether); UV λ_{max} (EtOH) (log ε) 236 (4.32), 284 (3.82); IR ($CHCl_3$) 1670 (C=O); 1650 and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.85, 6.63, 6.42, and 6.36 (each s, 4 H, olefinic and aromatic protons), 3.91, 3.87, and 3.82 (each s, 9 H, O**C**H_3); mass spectrum m/e 423 (M^+), 297.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.27; H, 4.76; N, 3.31. Found: C, 59.29; H, 4.80; N, 3.33.

4a (159 mg; 70%): mp 196.5–197 °C ($CHCl_3$–methanol); UV λ_{max} (EtOH) (log ε) 222 (4.56), 282 (4.03), 306 (4.11); IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.12 (s, 1 H, C-11**H**), 6.78 and 6.58 (both s, 2 H, Ar**H**), 6.23 (s, 1 H, O**H**), 3.93 (s, 6 H, O**C**H_3), 3.91 (s, 3 H, O**C**H_3), 3.49 (s, 3 H, C**H**$_3$OH of crystallization); mass spectrum m/e 423 (M^+), 297.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$·CH_3OH: C, 58.01; H, 5.31; N, 3.07. Found: C, 57.80; H, 5.29; N, 3.10.

Conversion of (±)-*N*-Trifluoroacetylwilsonirine (4a) to

Table I. Oxidation of Monophenolic Benzyl- and Phenethyltetrahydroisoquinolines with VOF_3 in CH_2Cl_2–TFA/TFAA

substrate	registry no.	temp, °C	time, min	products	registry no.	yield, %
3c	61659-86-7	−10	10	**4a**	61659-87-8	70
				5a	61659-88-9	8
3f	61659-89-0	−10	10	**4b**	2755-00-2	80
3h	67393-30-0	−10	10	**4c**	60888-76-8	74.5
3i	61659-90-3	−10	10	**7a**	61659-92-5	40
				8a	67393-31-1	18
		−10–30[a]	60	**7a**		77
3k	38726-24-0	−10	6	**8b**	51744-25-3	42
				7e	31735-21-4	14
		−10–30[a]	60	**7e**		60
3n	61659-91-4	−10	10	**7f**	61659-98-1	46
				9a	61659-94-7	4
		−10–30[a]	30	**7f**		54
3p	38726-41-9	−10	10	**9b**	36217-47-7	54
				7g	31735-22-5	16
11	61659-97-0	−10	10	**12**	67393-32-2	98
16	40135-88-4	−10	10	**18**	67393-33-3	88

[a] The reaction mixture was slowly allowed to attain room temperature (30 °C). However, the same results are obtained if the reaction is run at −10 °C.

(±)-Thalicmidine (4b). A solution of 30 mg of **4a** in 5 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 6 h. The solution was evaporated to dryness and the residue suspended in water and extracted with ether. The ether solution was washed with brine, dried, and evaporated to give 25 mg of a colorless glass. The glass was dissolved in 1 mL of methanol and treated with 0.1 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, 20 mg of sodium borohydride was added, and the reaction was stirred for 0.5 h. The methanol was evaporated and the residue suspended in water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 25 mg of a light brown gum. Preparative TLC ($CHCl_3$–5% methanol) gave 19.2 mg (80%) of **4b** as colorless crystals: mp 191–193 °C (methanol–ether). The melting point, mixture melting point, UV, IR, TLC, NMR and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **3e**.

Conversion of Morphinandienone 5a to (±)-*O*-Methylflavinantine (5c). A solution of 10.0 mg of **5a** in 1 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 3 h. The reaction mixture was evaporated and the residue suspended in water, and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to give 8 mg of **5b** as a colorless oil. The oil was taken up in 3 mL of methanol and treated with 3 drops of 37% formaldehyde solution. The reaction was stirred at room temperature for 15 min, treated with 20 mg of sodium borohydride, and stirred for an additional 1 h. The reaction mixture was evaporated and the residue suspended in water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to leave 8 mg of an oil (**6**). The oil was taken up in 1 mL of chloroform and stirred with 8 mg of active manganese dioxide at room temperature for 16 h. The oxide was filtered and washed with chloroform. The filtrate and the washings were evaporated to leave 8 mg of a colorless oil. Preparative TLC ($CHCl_3$–5% methanol) afforded 5.2 mg (65% from **5a**) of (±)-*O*-methylflavinantine (**5c**) as colorless needles: mp 161–162 °C (methanol); NMR ($CDCl_3$) δ 6.81, 6.63, 6.36, and 6.33 (each s, 4 H, aromatic and olefinic protons); 3.89, 3.86, and 3.81 (each s, 9 H, OCH_3), 2.47 (s, 3 H, NCH_3). The melting point, mixture melting point, IR, NMR, and mass spectrum were identical with those of authentic sample of (±)-*O*-methylflavinantine.[25]

Preparation of Borane Complex of (±)-Codamine, 3e (3f). A solution of 190 mg (0.55 mmol) of (±)-codamine[10] (**3e**) in 5 mL of chloroform was treated with 0.64 mL of a 1 M solution of diborane in THF (Aldrich) and the reaction was stirred at room temperature for 15 min. The chloroform was evaporated and the residue was chromatographed on a 2 mm preparative silica gel plate using 5% methanol in chloroform. The major band was collected to leave 150 mg of the borane complex as colorless amorphous solid (**3f**): mass spectrum *m/e* 357 (M^+), 341 ($M^+ - BH_3$).

VOF_3 Oxidation of 3f. Oxidation of 111 mg (0.31 mmol) of **3f** gave 120 mg of a light brown glass which was taken up in 15 mL of methanol and heated under reflux with 130 mg of anhydrous sodium carbonate for 2 h. The solution was filtered and evaporated to give a brown residue. Preparative TLC ($CHCl_3$–10% methanol) afforded 90 mg of a light brown gum which was crystallized from methanol–ether to give 85.5 mg (80%) of (±)-thalicmidine (**4b**): mp 191–193 °C dec (lit.[11] mp 190–192 °C). The melting point, mixture melting point, and NMR spectrum were identical with those of an authentic sample of (±)-thalicmidine.[8]

Preparation of a Borane Complex of 3g (3h). A solution of 2.0 g (4.77 mmol) of **3g**[13] in 30 mL of anhydrous chloroform was treated with 12.5 mL of a 1 M solution of diborane in THF according to the procedure given for the preparation of **3f** to give 2.05 g (99%) of **3h** as colorless foam: IR ($CHCl_3$) 2380 cm^{-1} (B–H); mass spectrum *m/e* 433 (M^+, very weak), 419 (100).

VOF_3 Oxidation of 3h. Oxidation of 130.0 mg (0.3 mmol) of **3h** afforded, after removal of the blocking group with anhydrous sodium carbonate in refluxing methanol, 82.5 mg (74.5%) of (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine as the ether solvate (**4c**): mp 73–75 °C (lit.[13] mp 74–76 °C).

(±)-Bracteoline (4d). A solution of 40 mg of **4c** in 10 mL of methanol containing 20 mg of 10% Pd/C was hydrogenated at atmospheric pressure and temperature until uptake of hydrogen ceased. The catalyst was filtered and the filtrate evaporated to a yellow residue which was crystallized from ether–methanol yielding 24.0 mg (78%) of (±)-bracteoline (**4d**): mp 207–210 °C dec (lit.[13] mp 208–210 °C dec).

1-(3,4-Dimethoxyphenethyl)-7-hydroxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3i). From 3.575 g (6.4 mmol) of 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline[8] in 75 mL of ethanol containing 500 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 2.830 g (93%) of **3i** as colorless crystals: mp 138.7–139.6 °C (ether); NMR ($CDCl_3$) δ 6.75 (s, 3 H, Ar**H**), 6.66 and 6.57 (each s, 2 H, Ar**H**), 5.54 (s, 1 H, O**H**), 3.86 (s, 9 H, OCH_3), 3.6–2.24 (m, 8 H, CH_2); mass spectrum *m/e* 439 (M^+), 274 (100).

Anal. Calcd for $C_{22}H_{24}NO_5F_3$: C, 60.13; H, 5.51; N, 3.19. Found: C, 60.26; H, 5.51; N, 3.22.

1-(3,4,5-Trimethoxyphenethyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3l). From 8.1 g (16.2 mmol) of 1-(3,4,5-trimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[19] by $NaBH_4$ reduction in methanol there was obtained 7.4 g (91%) of **3l** as the hydrochloride salt: mp 195.7–196 °C (CH_3OH–ether); NMR ($CDCl_3$) δ 10.37 (mound, 1 H, **H**Cl), 9.73 (mound, 1 H, N**H**), 7.40 (m, 5 H, **Ph**CH_2O), 6.62 (s, 1 H, Ar**H**), 6.55 (s, 3 H, Ar**H**), 5.08 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.82 (s, 9 H, OCH_3), 3.68–2.5 (m, 8 H, CH_2).

Anal. Calcd for $C_{28}H_{34}O_5NCl$: C, 67.25; H, 6.85; N, 2.80. Found: C, 67.13; H, 6.76; N, 2.89.

1-(3,4,5-Trimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3m). From 2.315 g (5 mmol) of **3l**, 2.6 mL of TFAA, and 0.5 mL of pyridine in 40 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and the usual workup, 2.9 g of a yellow oil which was crystallized from methanol yielding 2.69 g (96%) of **3**: mp 127.3–128 °C; IR ($CHCl_3$) 1685 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.37 (m, 5 H, **Ph**CH_2O), 6.62, 6.57 (each s, 2 H, Ar**H**), 6.38 (s, 2 H, Ar**H**), 5.47 (t, 1 H, C-1**H**, J = 7.0 Hz), 5.09 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3),

3.82 (s, 3 H, OCH_3), 3.8–2.05 (m, 8 H, CH_2).

Anal. Calcd for $C_{30}H_{32}O_6NH_3$: C, 64.39; H, 5.76; N, 2.50. Found: C, 64.46; H, 5.78; N, 2.49.

1-(3,4,5-Trimethoxyphenethyl)-7-hydroxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3n). From 2.54 g (4.57 mmol) of **3m** in 75 mL of ethanol containing 500 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 2.082 g (97%) of **3n**: mp 145–146 °C (methanol); NMR ($CDCl_3$) δ 6.67, 6.58 (both s, 2 H, ArH), 6.41 (s, 2 H, ArH), 5.57 (s, 1 H, OH), 3.86 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.5–2.1 (m, 8 H, CH_2).

Anal. Calcd for $C_{23}H_{26}O_6NF_3$: C, 58.84; H, 5.58; N, 2.98. Found: C, 58.82; H, 5.60; N, 2.96.

VOF_3 Oxidation of 3i. Oxidation of 110 mg (0.25 mmol) of **3i** gave 140 mg of a dark brown residue. Preparative TLC ($CHCl_3$–4% methanol) afforded the following two products: **7a** (44 mg; 40%); mp 200–201 °C (transition at 110 °C). The melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those of an authentic sample.[8]

8a (19 mg; 18%): mp 192.5–193.5 °C (ether); NMR ($CDCl_3$) δ 6.92 (dd, 1 H, H_B, J_{AB} = 2.5 Hz, J_{BX} = 10 Hz), 6.60 (s, 1 H, ArH), 6.24 (d, 1 H, H_X, J_{BX} = 10 Hz), 5.82 (d, 1 H, H_A, J_{BA} = 2.5 Hz), 5.64 (s, 1 H, OH), 3.85 (s, 3 H, aromatic OCH_3), 3.67 (s, 3 H, olefinic OCH_3), 3.5–1.7 (m, 8 H, CH_2); UV λ_{max} (EtOH) (log ε) 290 (3.78), 243 (sh); IR ($CHCl_3$) 1690 (C=O), 1665, and 1635 (C=C), 3530 cm^{-1} (OH); mass spectrum *m/e* 423 (M^+), 395, 380.

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.55; H, 4.76; N, 3.30. Found: C, 59.62; H, 4.76; N, 3.38.

Rearrangement of Homoproaporphine 8a with Boron Trifluoride Etherate. A mixture of 30 mg of **8a,** 5 mL of CH_2Cl_2, and 3 drops of boron trifluoride etherate was stirred at room temperature for 2 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water, dried, and evaporated to an oil which was crystallized from ether giving 26 mg (93%) of diphenolic homoaporphine **7d**: mp 167–168 °C; IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.04 (s, 1 H, C-12H), 6.84 (s, 1 H, C-3H), 6.61 (s, 1 H, C-9H), 5.72 (s, 2 H, OH), 3.92, 3.87 (both s, 6 H, OCH_3), 5.08 (t, 1 H, CH, *J* = 7 Hz), 3.3–2.2 (m, 8 H, CH_2); mass spectrum *m/e* 423 (M^+).

Anal. Calcd for $C_{21}H_{20}NO_5F_3$: C, 59.57; H, 4.76; N, 3.31. Found: C, 59.34; H, 4.84; N, 3.25.

Conversion of *N*-Trifluoroacetylhomoaporphine (7d) to *N*-Methylhomoaporphine (7c). A 25-mg sample of **7d** was treated with 1 N methanolic sodium hydroxide and then subjected to reductive methylation according to the procedure described for the conversion of **4a** to **4b,** to give 11 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol) gives, after crystallization from methanol–ether, 5 mg of **7c**: mp 238–240 °C dec (lit.[21] mp 241–242 °C).

VOF_3 Oxidation of Homocodamine (3k). Oxidation of 95 mg (0.266 mmol) of **3k**[15] gave 95 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol; two elutions) afforded the following two products: **7e** and **8b.**

7e (13 mg; 14%): mp 190–192 °C (CH_2Cl_2–ether; lit.[15] mp 195–196 °C).

8b (38 mg; 42%): mp 200–201 °C (benzene–hexane; lit.[26] mp 200–202 °C). The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of an authentic sample.[8]

VOF_3 Oxidation of 3n. Oxidation of 235 mg (0.5 mmol) of **3n** gave 250 mg of a brown residue. Preparative TLC ($CHCl_3$–4% methanol) afforded the following two products: **7f** and **9a.**

7f (107 mg; 46%): mp 161–162 °C (ether); UV λ_{max} (EtOH) (log ε) 258 (4.11), 296 (3.72) nm; IR ($CHCl_3$) 3540 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.65, 6.63 (both s, 2 H, ArH), 6.24 (s, 1 H, OH), 3.91 (s, 9 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.6–2.3 (m, 8 H, CH_2); mass spectrum *m/e* 467 (M^+), 450, 436, 341.

9a (9.5 mg; 4%): mp 213–215 °C dec (ether); UV λ_{max} (EtOH) (log ε) 276 (4.09), 235 (sh); IR ($CHCl_3$) 3540 (OH), 1690 (C=O), 1650 and 1615 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.60 (s, 1 H, ArH), 5.87 (d, 2 H, olefinic protons, *J* = 3.5 Hz), 5.62 (s, 1 H, OH), 3.85 (s, 3 H, aromatic OCH_3), 3.68 and 3.60 (both s, 6 H, OCH_3), 3.5–2.2 (m, 8 H, CH_2); mass spectrum *m/e* 453 (M^+), 436, 421.

Anal. Calcd for $C_{22}H_{22}O_6NF_3$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.06; H, 4.98; N, 3.07.

Conversion of *N*-Trifluoroacetylhomoaporphine (7f) to *N*-Methylhomoaporphine (7g). A 50-mg sample of **7f** was treated with 1 N methanolic sodium hydroxide and then subjected to reductive methylation according to the procedure described for the conversion of **4a** to **4b** to give 45 mg of a colorless glass which was crystallized from ether yielding 36 mg of (±)-kreysigine (**7g**): mp 186–187 °C (lit.[20] mp 187–189 °C). The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of (±)-kreysigine obtained by VOF_3 oxidation of **3p.**

VOF_3 Oxidation of 3p. Oxidation of 96 mg (0.25 mmol) of **3p** gave a yellow residue. Preparative TLC ($CHCl_3$–5% methanol) afforded the following two products: **7g** and **9b.**

7g (15 mg; 16%); mp 185–187 °C (ether: lit.[20] mp 187–189 °C).

9b (50.5 mg; 54%); mp 174–176 °C (ether; lit.[20] 176–178 °C).

Rearrangement of 8b with Boron Trifluoride Etherate. A mixture of 20 mg of **8b,** 5 mL of CH_2Cl_2, and 0.4 mL of boron trifluoride etherate was stirred at room temperature for 2 h. After the usual workup and crystallization from methanol–ether there was obtained 14 mg (70%) of homoaporphine **7c:** mp 240–241 °C dec (lit.[21] mp 241–242 °C).

Rearrangement of 9a with Boron Trifluoride Etherate. A mixture of 50 mg of **9a,** 5 mL of CH_2Cl_2, and 1 mL of boron trifluoride etherate was stirred at room temperature for 2 h. After the usual workup and crystallization from ether there was obtained 35.0 mg (87%) of homoaporphine **7h:** mp 208–208.5 °C; UV λ_{max} (EtOH) (log ε) 260 (3.95), 296 (3.77) nm: IR ($CHCl_3$) 3545 (OH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.66 and 6.62 (both s, 2 H, ArH), 3.95, 3.92, and 3.62 (each s, 9 H, OCH_3); mass spectrum *m/e* 453 (M^+), 436, 327.

Anal. Calcd for $C_{22}H_{22}O_6NF_3$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.27; H, 4.98; N, 3.12.

Rearrangement of 9b with Boron Trifluoride Etherate. A mixture of 25 mg of **9b,** 5 mL of CH_2Cl_2, and 0.5 mL of boron trifluoride etherate was stirred at room temperature for 15 h. The usual workup and preparative TLC ($CHCl_3$–12% methanol) afforded 20 mg (80%) of **7i:** mp 189–191 °C (lit.[20] 190–192 °C dec).

1-(3,4-Dimethoxyphenethyl)-6-hydroxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (11). From 500 mg (0.94 mmol) of 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline[8] in 40 mL of ethyl alcohol containing 100 mg of 10% Pd/C there was obtained, after hydrogenolysis at atmospheric pressure and temperature, 363 mg (87%) of **11** as colorless crystals: mp 109–111 °C (ether); NMR ($CDCl_3$) δ 6.76 (s, 3 H, ArH), 6.66, 6.50 (both s, 2 H, ArH), 5.56 (s, 1 H, OH), 3.87 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3).

Anal. Calcd for $C_{22}H_{24}NO_5F_3$: C, 60.13; H, 5.51; N, 3.19. Found: C, 59.97; H, 5.40; N, 3.23.

VOF_3 Oxidation of 11. Oxidation of 110 mg (0.25 mmol) of **11** gave 120 mg of a colorless glass which after chromatography on silica gel ($CHCl_3$) and crystallization from ether afforded 109 mg (98%) of **16** as colorless crystals: mp 125 °C, solidifies and remelts at 160–162 °C. The melting point, mixture melting point, TLC, UV, and NMR were identical with those of an authentic sample.[8]

***N*-(3,4-Methylenedioxybenzyl)-4-hydroxyphenethylamine (15).** A solution of 1.5 g (10 mmol) of piperonal and 1.37 g (10 mmol) of tyramine in 130 mL of methanol was stirred for 2 h. Sodium borohydride (2.5 g) was added portionwise over 45 min and the reaction mixture stirred for an additional hour. The methanol was evaporated and the residue suspended in water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated to a colorless glass which was converted into the hydrochloride salt and crystallized from methanol–ether yielding 2.65 g (89%) of the amine (**15**) as the hydrochloride salt: mp 215–217.2 °C; NMR ($CDCl_3/CD_3OD$) δ 7.09–6.72 (m, 7 H, ArH), 6.01 (s, 2 H, OCH_2O), 4.04 (s, 2 H, $ArCH_2N$).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.90; N, 4.53. Found: C, 62.41; H, 5.95; N, 4.53.

***N*-Trifluoroacetyl-*N*-(3,4-methylenedioxybenzyl)-4-hydroxyphenethylamine (16).** The hydrochloride salt of **15** (2.553 g; 8.3 mmol) was converted into the free amine and treated with 5.5 mL of trifluoroacetic anhydride and 0.5 mL of pyridine according to the procedure described for the preparation of **3b** to give 3.21 g of an orange-brown oil. The oil was chromatographed on silica gel eluting with chloroform to give a colorless oil which was crystallized from ether–hexane yielding 2.711 g of **16** as white crystals: mp 118.4–118.9 °C; NMR ($CDCl_3$) δ 7.04–6.55 (m, 7 H, ArH), 5.95 (d, 2H, OCH_2O, *J* = 1.5 Hz), 5.20 (s, 1 H, OH), 4.41 (d, 2 H, $ArCH_2N$, *J* = 25.9 Hz), 3.37 (m, 2 H, $ArCH_2CH_2N$), 2.78 (m, 2 H, $ArCH_2CH_2N$).

Anal. Calcd for $C_{18}H_{16}O_4NF_3$: C, 58.85; H, 4.39; N, 3.81. Found: C, 58.71; H, 4.45; N, 3.75.

VOF_3 Oxidation of 16. Oxidation of 184 mg (0.5 mmol) of **16** gave 202.5 mg of an amorphous solid. Preparative TLC (ether–10% acetone) afforded, after crystallization from ether–hexane–methanol, 160 mg (88%) of **18** as slightly yellow crystals: mp 179.5–181.2 °C (transition at 138.8 °C; lit.[4a] mp 138–142 °C; 181–182 °C); NMR ($CDCl_3$) δ 7.06–6.25 (eight peaks, 6 H, aromatic and olefinic protons), 5.94 (d, 2 H, OCH_2O, *J* = 2.0 Hz), 4.76 (s, 2 H, $ArCH_2N$), 3.93 (m, 2 H, $ArCH_2CH_2$), 2.40 (m, 2 H, NCH_2CH_2).

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Registry No.—**3a**·HCl, 23843-20-1; **3b**, 67393-34-4; **3e**, 5977-85-5; **3g**, 60888-73-5; **3l**, 67393-35-5; **3m**, 67393-36-6; **4d**, 28230-74-2; **5c**, 22169-18-2; **7c**, 59168-20-6; **7d**, 61659-95-8; **7h**, 61659-96-9; **7i**, 16845-28-6; **15**, 56114-14-8; 1-(3,4-dimethoxybenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 41183-10-2; 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline, 61660-08-0; 1-(3,4,5-trimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 67393-37-7; 1-(3,4-dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline, 61660-07-9; piperonal, 120-57-0; tyramine, 51-67-2.

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1,4-Diketones from Skipped Acetylenes

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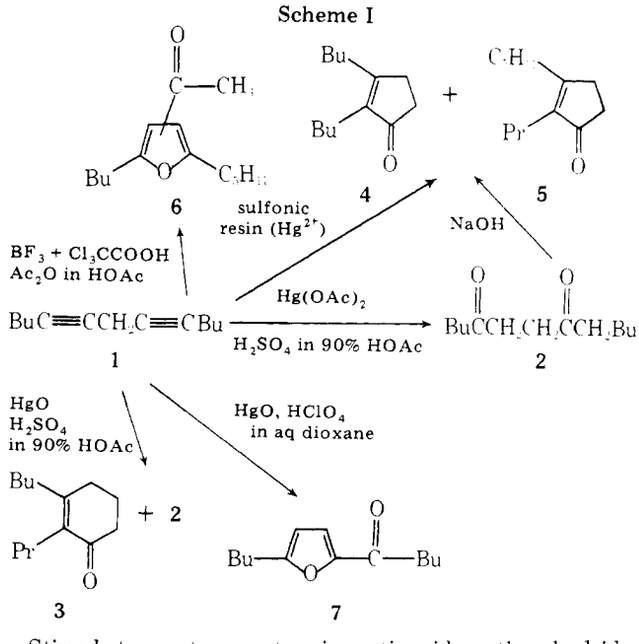
Under various acidic hydrating conditions, 5,8-tridecadiyne gives rise to 5,8-tridecanedione, 2-propyl-3-butyl-2-cyclohexenone, 2-propyl-3-pentyl-2-cyclopentenone, 2,3-dibutyl-2-cyclopentenone, 2-pentanoyl-5-butylfuran, and acetylated 2-butyl-5-pentylfuran. 1,4-Nonadiyne yields 2,5-nonanedione and also can give 5-butylfurfural; 1,4,7-dodecatriyne yields 2,5,8-dodecanetrione. Reaction pathways are proposed that rely on neighboring group effects to direct the course of the several processes.

1,4-Dicarbonyl compounds[1-5] are recognized as useful precursors for preparing five-membered heterocycles as well as cyclopentenones. We wish to report a new general synthesis of this kind of carbonyl compound by the hydration of 1,4- (or skipped) acetylenes, which can be obtained readily by coupling acetylenic Grignard reagents with propargyl bromides. This paper describes the results with 5,8-tridecadiyne (**1**)[6] and 1,4-nonadiyne (**8**),[7] which furnish, respectively, 5,8-tridecanedione (**2**) and 2,4-nonanedione (**9**), as well as other products. Skipped triyne, 1,4,7-dodecatriyne (**12**),[7] also has been investigated, and shown to give 2,5,8-dodecanetrione (**13**).

Results

Hydration[8] of 5,8-tridecadiyne (**1**) in aqueous acetic acid in the presence of mercuric acetate and sulfuric acid produced 5,8-tridecanedione (**2**) in 70% yield. Substitution of mercuric oxide for the mercuric acetate gave the same diketone, although now it was accompanied by small amounts of 2-propyl-3-butyl-2-cyclohexenone (**3**). When a sulfonated resin loaded with mercuric ion[9] was used as a solid catalyst, none of the diketone **2** was obtained; instead the product was a mixture of cyclopentenones **4** and **5** together with a little cyclohexenone **3**. The same cyclopentenones **4** and **5** free of cyclohexenone were obtained more conveniently by cyclizing 5,8-tridecanedione (**2**) with base.[10]

Scheme I



Stirred at room temperature in acetic acid–acetic anhydride containing trichloroacetic acid, mercuric oxide, and boron

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