

form a plane with a maximum deviation of 0.01 Å, while C(13) is 0.62 Å from this plane. The six-membered ring also has a four atom plane (N(3), C(4), C(5), and C(6)) with a maximum deviation of 0.001 Å. N(1) and C(2) are 0.87 Å and 0.57 Å, respectively, from this plane; both are on the same side. The guanidine moiety (N(1), C(2), N(3), and N(10)) is planar with a maximum deviation of 0.003 Å. All of the C—N bonds of both guanidines are the same within experimental error (1.32 (1) Å) except N(9)—C(8) which is 1.36 (1) Å.

Structure 3 is compatible with all of the published chemical and spectral data of saxitoxin if an equilibrium exists between 3 and its keto form. Thus under vigorous drying conditions (110° at 10⁻⁵ mm to constant weight)^{3b} saxitoxin is dehydrated which reconciles the proposed molecular formulas. Presumably the ketone hydrates readily in saxitoxin because of the strongly electron withdrawing guanidinium groups on the α carbon. It is entirely possible that the two forms of saxitoxin seen on countercurrent distribution are the ketone and ketone hydrate which revert to a single form in acid.⁶ We would also attribute the very weak ketone absorption observed in the ir spectrum to a small amount of keto form.⁹ The keto form is also responsible for the reduction (H₂-PtO₂ or NaBH₄) reaction which eliminates the ketone ir absorption.⁹

The two hydroxyl groups of the hydrated form are diastereotopic. Vigorous drying followed by rehydration with H₂¹⁸O incorporates one ¹⁸O which is subsequently lost upon vigorous drying.^{3b} From inspection of molecular models it is clear that the bottom surface of the molecule is more accessible to attack. Thus O(14)H is probably the fragment lost as water to form the ketone and added to generate the ketone hydrate.

The NMR^{3b} spectral assignments are now δ 4.27 (1 H, q, *J* = 11, 9 Hz) and 4.05 (1 H, q, *J* = 11, 5 Hz) to the two H's on C(16), δ 3.87 (1 H, d of q, *J* = 9, 5, 1 Hz) to the lone H on C(6), and δ 4.77 (1 H, d, *J* = 1 Hz) to the bridgehead H on C(5). The dihedral angle of 72° between these last two hydrogens in the crystalline state explains their relatively small coupling. The protons on C(11) are responsible for the resonances at δ 3.85 and 3.57. The δ 2.37 multiplet is attributed to the protons on C(12) when saxitoxin is in the keto form.

Details of the results of X-ray crystallography and spectral analysis will be presented in a subsequent paper.

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Supplementary Material Available. The fractional coordinates (Table I), important bond distances (Table II), important bond angles (Table III), and structure factors (Table IV), will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.50 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-1238.

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- (4) The biological activity is in fact greater than anticipated. Purified saxitoxin has a specific toxicity of 5500 ± 500 mu/mg.⁵ Thus the bis-*p*-bromobenzenesulfonate derivative should have had 2400–2900 mu/mg rather than the observed 4088 mu/mg. Possible explanations for this enhanced activity are (1) preferential crystallization of one of the two forms of saxitoxin⁶ or (2) synergistic effects with the reagent.
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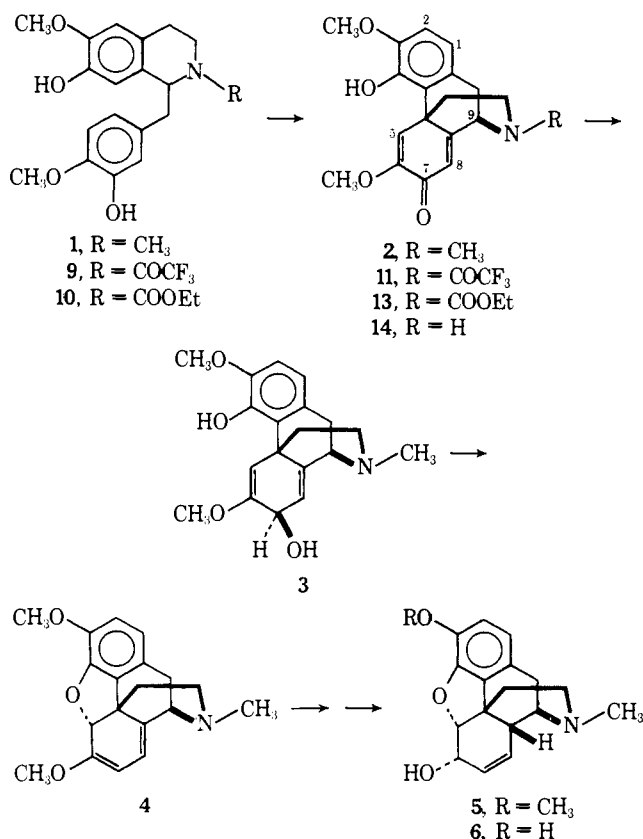
A Biogenetically Patterned Synthesis of the Morphine Alkaloids

Sir:

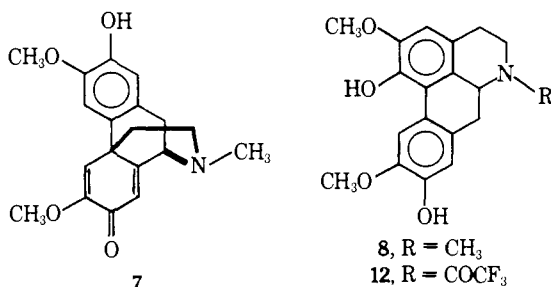
Since the original conception¹ and refinement² of the idea that the morphine alkaloids arise in the plant via oxidative coupling of a phenolic benzyltetrahydroisoquinoline derivative, a great deal of effort has been devoted to elucidating the actual biosynthetic pathway and to applying the biogenetic postulate to a laboratory synthesis of these alkaloids. While the biosynthetic pathway has been thoroughly delineated³ (Scheme I, 1 → 6), the latter goal has proved elusive. The many attempts to effect para-ortho oxidative coupling of (±)-reticuline (1) using K₃Fe(CN)₆,^{3b,4a-d} MnO₂-silica gel,^{4e} AgCO₃-Celite,^{4d} and VOCl₃^{4d,f} have, with one exception, afforded only the para-para coupling product (±)-isosalutaridine (7, yields of 0.3–4%) and/or the ortho-para coupling product (±)-isoboldine (8, yields of 0.4–53%); the exception was Barton and coworkers' ^{3b} detection via isotope dilution techniques of a 0.03% yield of (±)-salutaridine (2) from ferricyanide oxidation of 1. Similarly negative results have also been obtained with *N*-acylnorreticuline derivatives.^{4b,e,5} However, we wish now to report realization of the long-sought laboratory analogy for the in vivo para-ortho coupling of 1 to 2, by thallium tris(trifluoroacetate) (TTFA) coupling⁶ of *N*-acylnorreticuline derivatives 9 and 10.

Treatment of (±)-*N*-norreticuline⁷ with trifluoroacetic anhydride and K₂CO₃ in CH₂Cl₂, followed by stirring in aqueous CH₃OH, afforded the *N*-trifluoroacetyl derivative 9, mp 127–130° (petroleum ether-CHCl₃), mp 148–152° (CH₃OH-CHCl₃). Oxidation of 9 with 1.0 mol equiv of

Scheme I



TTFA⁶ in CH₂Cl₂ for 3 hr at -78° and overnight at -20° gave (\pm)-*N*-trifluoroacetylnorsalutaridine (**11**) in 11% yield: mp $196-201^{\circ}$ dec; ir (CHCl₃) 2.88, 5.95 (sh), 5.98, 6.08, and 6.18 μ ; uv (EtOH) 239 and 282 nm (log ϵ 4.48 and 3.94); NMR, see Table I; molecular ion at *m/e* 409.1150 (calcd 409.1137). Also isolated were the isoboldine analog **12** (7% yield) and starting material **9** (26%); the isosalutaridine (**7**) analog could be detected but was present only in small amount. An attempt to increase the conversion by using 2.0 mol equiv of TTFA resulted in complete disappearance of **11** but with some starting material still present; similarly, diminished yields of **11** were obtained when the reaction was started at 0° or at room temperature.



Oxidation of (\pm)-*N*-ethoxycarbonylnorreticuline^{5a,b} (**10**) with 1.0 mol equiv of TTFA under the same conditions gave the corresponding salutaridine derivative **13** in 23% yield: mp $198-200^{\circ}$ dec; ir (CHCl₃) 2.86, 5.95 (sh), 5.99, 6.10, and 6.19 μ ; NMR, see Table I; molecular ion at *m/e* 385.1516 (calcd 385.1525). Dienones **11** and **13** were interrelated by hydrolysis (K₂CO₃-CH₃OH) of **11** to (\pm)-norsalutaridine (**14**): mp $175-177^{\circ}$ (86% yield); ir (CHCl₃) 2.86, 6.00, 6.10, and 6.19 μ ; NMR in good agreement with that reported⁸ for (\pm)-**2** (see Table I). Acylation of **14** with

Table I. Proton NMR Spectra of Salutaridine Derivatives^a

	11	13 ^b	14	2 ^c
H-1	6.68 d (<i>J</i> = 8.5)	6.63 d (<i>J</i> = 8.5)	6.67 d (<i>J</i> = 8.5)	6.69 d (<i>J</i> = 7)
H-2	6.84 d (<i>J</i> = 8.5)	6.79 d (<i>J</i> = 8.5)	6.76 d (<i>J</i> = 8.5)	6.74 d (<i>J</i> = 7)
H-5	7.54	7.53	7.55	7.55
H-8	6.40	6.34	6.28	6.31
H-9	5.49 m	5.10 m		
O-CH ₃	3.93, 3.77	3.90, 3.75	3.89, 3.76	3.88, 3.74

^a Spectra were taken in CDCl₃ at 270 MHz unless otherwise noted; chemical shifts are reported in ppm downfield from TMS (δ) and coupling constants in Hz. ^b At 90 MHz. ^c Reference 8; in CDCl₃ at 60 MHz.

EtOCOCl-Et₃N in CHCl₃, followed by hydrolysis with NaOH-EtOH, yielded a dienone identical in all respects with **13**.

Reduction of **13** with LiAlH₄ in refluxing THF gave an 82% yield of a 1:1 mixture (by NMR) of the epimeric (\pm)-salutaridinols (**3**, epimers at C-7). Treatment of the mixture with 1 *N* HCl at room temperature for 1 hr afforded^{3a,8} (\pm)-thebaine (**4**), mp $183-186^{\circ}$ (reported,⁸ mp $184-186^{\circ}$), indistinguishable spectrally and chromatographically from authentic thebaine. Since thebaine has been converted to codeinone,⁹ and the latter to codeine¹⁰ (**5**) and thence to morphine¹¹ (**6**), the present work constitutes a formal synthesis of these alkaloids.

The remarkable influence of TTFA as compared with other reagents^{4,5,12} in directing para-ortho coupling in this system is quite likely a coordination phenomenon. We are currently exploring the use of other coordinating agents to obtain the same effect.

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