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 (H_2–PtO_2 or $NaBH_4$) reaction which eliminates the ketone ir absorption.[9]

The two hydroxyl groups of the hydrated form are diastereotopic. Vigorous drying followed by rehydration with $H_2{}^{18}O$ incorporates one ^{18}O 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.

Acknowledgments. This work was supported in part by the Food Research Institute, University of Wisconsin—Madison, by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation, and U.S. Public Health Grant R01-FD-00605-02.

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.

References and Notes

(1) Taken from talks presented by E. Schantz and J. Clardy at the First International Conference on Toxic Dinoflagellate Blooms, Boston, Mass., on Nov 5, 1974.
(2) V. E. Ghazarossian, E. J. Schantz, H. K. Schnoes, and F. M. Strong, *Biochem. Biophys. Res. Commun.*, **59**, 1219 (1974), and references therein.
(3) (a) F. E. Russell, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **26**, 1206 (1967), attributed to H. Rapoport, M. S. Brown, R. Oesterlin, and W. Schuett, Abstracts, the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964, p 3N; (b) J. L. Wong, R. Oesterlin, and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 7344 (1971).
(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 saxitoxin[6] or (2) synergistic effects with the reagent.
(5) E. J. Schantz et al., *J. Am. Chem. Soc.*, **79**, 5230 (1957).
(6) E. J. Schantz et al., *J. Am. Chem. Soc.*, **79**, 5235 (1957).
(7) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University—Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(8) W. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(9) E. J. Schantz et al., *Can. J. Chem.*, **39**, 2117 (1961).
(10) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977 and Fellow of the Alfred P. Sloan Foundation 1973–1975.

E. J. Schantz, V. E. Ghazarossian
H. K. Schnoes, F. M. Strong
Department of Biochemistry and Food Research Institute
University of Wisconsin
Madison, Wisconsin 53706

J. P. Springer, John O. Pezzanite, Jon Clardy*[10]
Ames Laboratory-USAEC and Department of Chemistry
Iowa State University
Ames, Iowa 50010

Received November 16, 1974

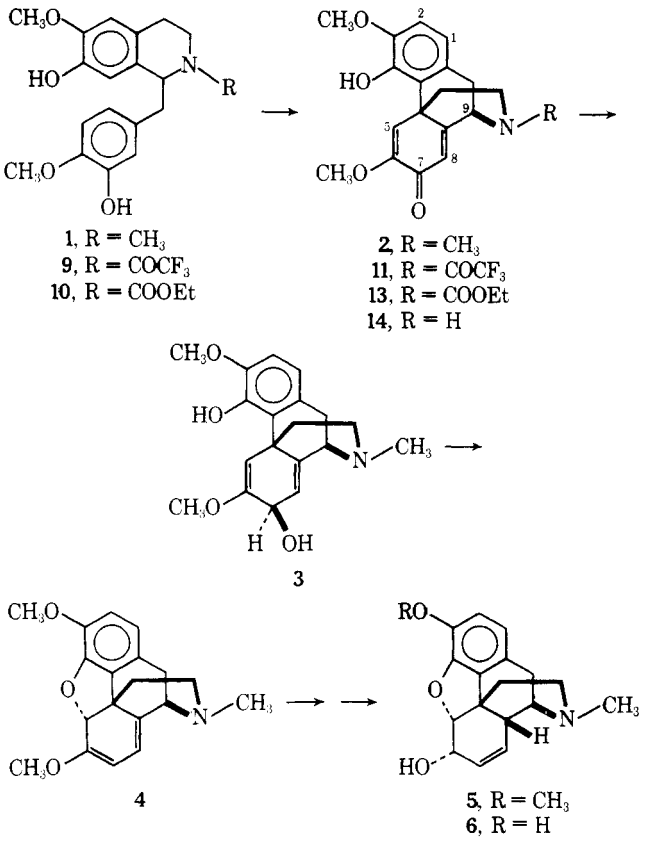
A Biogenetically Patterned Synthesis of the Morphine Alkaloids

Sir:

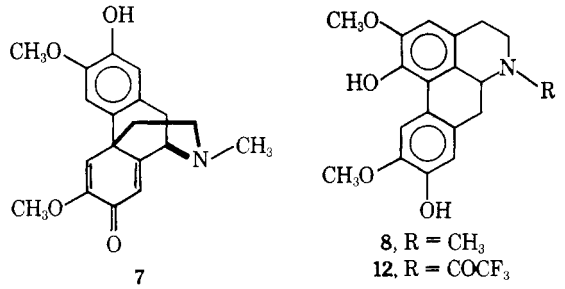
Since the original conception[1] and refinement[2] of the idea that the morphine alkaloids arise in the plant via oxidative coupling of a phenolic benzyltetrahydroisoquinoline derivative, a great deal of effort has been devoted to elucidating the actual biosynthetic pathway and to applying the biogenetic postulate to a laboratory synthesis of these alkaloids. While the biosynthetic pathway has been thoroughly delineated[3] (Scheme I, **1** → **6**), the latter goal has proved elusive. The many attempts to effect para-ortho oxidative coupling of (±)-reticuline (**1**) using $K_3Fe(CN)_6$,[3b,4a-d] MnO_2–silica gel,[4e] $AgCO_3$–Celite,[4d] and $VOCl_3$[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 tristrifluoroacetate (TTFA) coupling[6] of *N*-acylnorreticuline derivatives **9** and **10**.

Treatment of (±)-*N*-norreticuline[7] with trifluoroacetic anhydride and K_2CO_3 in CH_2Cl_2, followed by stirring in aqueous CH_3OH, afforded the *N*-trifluoroacetyl derivative **9**, mp 127–130° (petroleum ether–$CHCl_3$), mp 148–152° (CH_3OH–$CHCl_3$). Oxidation of **9** with 1.0 mol equiv of

Scheme I



TTFA[6] in CH_2Cl_2 for 3 hr at −78° and overnight at −20° gave (±)-*N*-trifluoroacetylnorsalutaridine (**11**) in 11% yield: mp 196–201° dec; ir ($CHCl_3$) 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 (±)-*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° dec; ir ($CHCl_3$) 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 (K_2CO_3–CH_3OH) of **11** to (±)-norsalutaridine (**14**): mp 175–177° (86% yield); ir ($CHCl_3$) 2.86, 6.00, 6.10, and 6.19 μ; NMR in good agreement with that reported[8] for (±)-**2** (see Table I). Acylation of **14** with EtOCOCl–Et_3N in $CHCl_3$, followed by hydrolysis with NaOH–EtOH, yielded a dienone identical in all respects with **13**.

Table I. Proton NMR Spectra of Salutaridine Derivatives[a]

	11	13[b]	14	2[c]
H-1	6.68 d (J = 8.5)	6.63 d (J = 8.5)	6.67 d (J = 8.5)	6.69 d (J = 7)
H-2	6.84 d (J = 8.5)	6.79 d (J = 8.5)	6.76 d (J = 8.5)	6.74 d (J = 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	393, 3.77	3.90, 3.75	3.89, 3.76	3.88, 3.74

[a] Spectra were taken in $CDCl_3$ 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 $CDCl_3$ at 60 MHz.

Reduction of **13** with $LiAlH_4$ in refluxing THF gave an 82% yield of a 1:1 mixture (by NMR) of the epimeric (±)-salutaridinols (**3**, epimers at C-7). Treatment of the mixture with 1 *N* HCl at room temperature for 1 hr afforded[3a,8] (±)-thebaine (**4**), mp 183–186° (reported,[8] mp 184–186°), indistinguishable spectrally and chromatographically from authentic thebaine. Since thebaine has been converted to codeinone,[9] and the latter to codeine[10] (**5**) and thence to morphine[11] (**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.

Acknowledgments. We thank Mr. Richard Rosanske for determination of the NMR spectra and Professor H. M. Walborsky for stimulating discussions. This work was supported by Public Health Service Grants CA-10136 and GM-21182.

References and Notes

(1) J. M. Gulland and R. Robinson, *Mem. Proc. Manchester Lit. Philos. Soc.*, **69**, 79 (1925).
(2) D. H. R. Barton and T. Cohen, *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag*, 117 (1957).
(3) (a) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 2423 (1965); (b) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc. C*, 128 (1967); (c) H. I. Parker, G. Blaschke, and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 1276 (1972).
(4) (a) W. W.-C. Chan and P. Maitland, *J. Chem. Soc. C*, 753 (1966); (b) A. H. Jackson and J. A. Martin, *ibid.*, 2061 (1966); (c) T. Kametani, K. Fukumoto, A. Kozuka, H. Yagi, and M. Koizumi, *ibid.*, 2034 (1969); (d) T. Kametani, A. Kozuka, and K. Fukumoto, *ibid.*, 1021 (1971); (e) B. Franck, G. Dunkelmann, and H. J. Lubs, *Angew. Chem., Int. Ed. Engl.*, **6**, 1075 (1967); (f) M. A. Schwartz, *Synth. Commun.*, **3**, 33 (1973).
(5) (a) M. P. Cava and K. T. Buck, *Tetrahedron*, **25**, 2795 (1969); (b) T. Kametani, T. Sugahara, and K. Fukumoto, *ibid.*, **25**, 3667 (1969); (c) J. M. Bobbitt, *Heterocycles*, **1**, 181 (1973).
(6) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973).
(7) D. H. R. Barton, C. J. Potter, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 346 (1974).
(8) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc. C*, 2030 (1969).
(9) L. Knorr and H. Hörlein, *Ber.*, **39**, 1409 (1906); H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).
(10) M. Gates, *J. Am. Chem. Soc.*, **75**, 4340 (1953).
(11) H. Rapoport, C. H. Lovell, and B. M. Tolbert, *J. Am. Chem. Soc.*, **73**, 5900 (1951).
(12) As another example, oxidation of **9** with $VOCl_3$–CH_2Cl_2 at −78° gave the isoboldine analog **12** (46% yield) as the only isolable product.

Martin A. Schwartz,* Ismail S. Mami
Department of Chemistry, The Florida State University
Tallahassee, Florida 32306
Received November 27, 1974