(11) We have examined the $a_{\beta\text{-}H}$ and $a_{\beta\text{-}C}$ values obtained from the contact chemical shifts for many nickel acetylacetonate aniline complexes. The results for alkyl derivatives, unstrained bicyclic molecules, etc. adhere to eq 1 and 2 with reasonable precision. Thus, the conformational analyses of alkyl radicals are apparently reliable.
(12) Fannie and John Hertz Foundation Fellow at the University of Chicago.

Leon M. Stock,* Michael R. Wasielewski[12]
Department of Chemistry, The University of Chicago
Chicago, Illinois 60637
Received, March 17, 1975

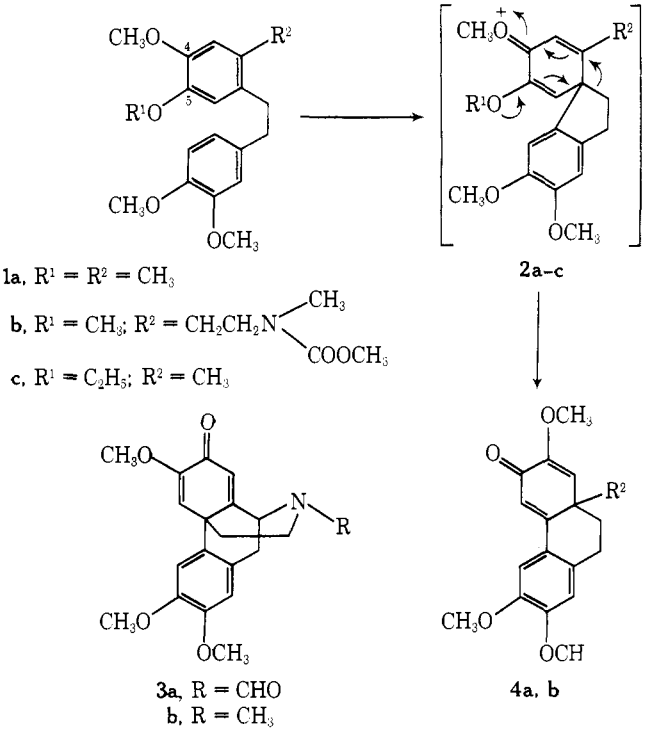
On the Mechanism of Formation of Spirodienone Products of Nonphenol Oxidative Coupling[1,2]

Sir:

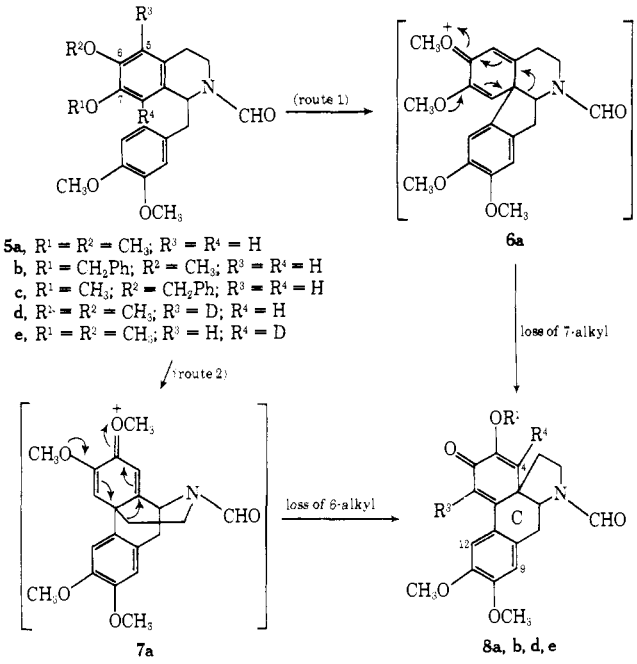
Nonphenol oxidative coupling reactions which yield spirodienone intermediates and products are currently subjects of great interest.[3-7] The first practical syntheses of this type involved electrooxidative coupling of 1-benzylisoquinolines to morphinandienones,[3-5] and the anodic cyclization of an isochroman-3-one derivative was also reported.[6] We have subsequently reported the novel chemical intramolecular coupling of nonphenolic benzylisoquinolines with vanadium oxytrifluoride in trifluoroacetic acid and have demonstrated the usefulness of the reaction for the synthesis of (±)-glaucine and the neospirinedienone **8a**.[7,8] We report herein evidence that the VOF_3–TFA oxidations of *N*-acylnorlaudanosines **5a–e** to neospirinedienones **8a–e** proceed via the intermediacy of morphinandienone intermediates. This finding has important implications for the biosynthesis of dibenzazonine and aporphine alkaloids, and facile biomimetic alkaloid syntheses based on these considerations are reported in the accompanying communication.[9]

In an extension of our studies of chemical intramolecular coupling of nonphenolic substrates, oxidation of bibenzyl **1a** with VOF_3 in TFA (Scheme I) gave the dihydrophenanthrone **4a**[10] (76%), and oxidation of **1b**[11,12] gave **4b** (68%;

Scheme I



Scheme II



mp 196–198°; uv λ_{max}^{EtOH} (log ϵ) 240 (4.00), 265 (4.04), 289 (3.97), 352 (4.10) nm; ir λ_{max}^{KBr} 5.92, 6.06, 6.10 μ; NMR (TFA) δ 7.25, 7.09, 6.82, and 6.27 (all s, 4 H, Ar*H* and olefinic *H*), 3.96, 3.93, 3.80, and 3.67 (all s, 12 H, 4-OC*H*$_3$), 2.68 (s, 3 H, N-C*H*$_3$)). When the bibenzyl **1c**[10] was oxidized with VOF_3 in TFA, dihydrophenanthrone **4a** (75%) was obtained, an indication that these chemical coupling reactions proceed through the five-membered ring spiro intermediates **2a–c** followed by rearrangement and loss of the 5-alkyl group to give **4a** and **b**. The proposed intermediates **2a–c** are similar to the proerythrinadienone-type system (e.g., **6a**) and the rearrangement of **2a** to **4a** resembles the demonstrated acid-catalyzed rearrangement of proerythrinadienones to neospirinedienones (e.g., **8**).[13] These facts led us to consider the possibility that the formation of neospirinedienone **8a** by VOF_3–TFA oxidation of *N*-formylnorlaudanosine may occur via route 1 (**5a** → **6a** → **8a**).[7] However, route 2, via a morphinandienone-type intermediate **7a**, could not be precluded. The sequel relates the experimental evidence which demonstrates that route 2, via **7a**, is, indeed, correct.

The consequences for the two plausible routes (Scheme II) from the acylnorlaudanosines (**5a–e**) to the acylneospirinedienones (**8a, b, d, e**) differ in two significant respects: (a) route 1, via the acylproerythrinadienone intermediate, requires loss of the 7-alkyl group, whereas route 2, via the acylmorphinandienone intermediate, requires loss of the 6-alkyl group; (b) route 1 requires that the hydrogen atoms at C-5 and C-8 of the precursor **5a** be attached at C-4 and C-1, respectively, in **8a**, whereas route 2 requires that the attachment be at C-1 and C-4, respectively, in **8a**. When the 7-benzyloxy (**5b**)[14] and 6-benzyloxy (**5c**)[15] analogs of *N*-formylnorlaudanosine (**5a**) were oxidized with VOF_3–TFA, the product from **5c** was **8a** (77% yield, identical with the product obtained from **5a**). In contrast, the structure of the product (**8b**, mp 232–235°, 30% yield) obtained from **5b** showed that the benzyloxy group had been retained, indicative that both oxidations had followed route 2.

Confirmation of the intermediacy of the morphinandienone intermediate **7a** in the route from **5a** to **8a** was achieved by a study of the oxidation of the specifically deuterated analogs **5d** and **5e**.[16-19] The characterization of the

respective formylneospirinedienone products was based on the following assignment of the proton signals in the NMR spectrum (TFA) of **8a**:[20-22] δ 8.66 and 8.24 (s, s, 1 H, C*H*O), 7.28 and 7.22 (s, s, 1 H, C-12 *H*), 7.07 and 6.88 (s, s, 1 H, C-1 *H*), 6.84 and 6.82 (s, s, 1 H, C-9 *H*), 6.34 (s, 1 H, C-4 *H*), 3.99, 3.94, and 3.78 (all s, 9 H, C-11 OCH_3, C-10 OCH_3, C-3 OCH_3). The NMR spectrum of **8d** (the oxidation product of **5d**) lacked the signals attributable to the C-1 proton, and the spectrum of **8e** (the oxidation product of **5e**) lacked the signal attributable to the C-4 proton.

Evidence for the postulated facile acid-catalyzed rearrangement of the acylmorphinandienone **7a** to the acylneospirinedienone **8a** was adduced from a study of the chemistry of the *N*-formylmorphinandienone **3a**. Electrooxidative coupling of **5a** in HBF_4[4] yielded **3a** (8%; mp 139–140°; uv λ_{max}^{MeOH} (log ϵ) 238 (4.23), 283 (3.89) nm; ir $\lambda_{max}^{CHCl_3}$ 5.93 (sh), 5.98, 6.07, 6.17 μ; NMR ($CDCl_3$) δ 8.14 and 7.98 (s, s, 1 H, C*H*O), 6.80 (s, 1 H, Ar*H*), 6.55 (s, 1 H, olefinic *H*), 6.32 and 6.30 (s, s, 1 H, C-8 *H*), 6.28 (s, 1 H, olefinic *H*), 3.84, 3.78, and 3.73 (all s, 9 H, 3-OCH_3); mass spectrum *m/e* 355 (M^+)) along with **8a** (2.5%).[23] The structure of **3a** was proven by reduction with $LiAlH_4$ in THF to the oily *N*-methyldienol and oxidation of the dienol with MnO_2 to *O*-methylflavinantine (**3b**, 29%).[24] When **3a** was treated with anhydrous methanolic HCl, rearrangement accompanied ketalization, and the dimethyl ketal[7] of **8a** was obtained (44%). Treatment of **3a** with HBF_4 at room temperature for 30 min gave **8f** ($R^1 = R^3 = R^4 = H$) (74%), and methylation of **8f** with diazomethane gave **8a** (31%).

Morphinandienones have been postulated to be precursors to dibenzazonine alkaloids such as protostephanine, via a pathway involving a neospirine intermediate.[25] Furthermore, biomimetic syntheses[26,27] and the conversion of a labeled morphinandienone precursor to protostephanine in *Stephania japonica*[26] have been reported. The demonstrated sequence **5a** → **7a** → **8a** and our facile conversion of neospirinedienones to dibenzazonine derivatives[7,9] parallel the sequence of skeletal rearrangements proposed for dibenzazonine alkaloid biosynthesis in *Stephania japonica*.

References and Notes

(1) Presented at a Meeting of the Heterocyclic Chemistry Group, The Chemical Society, London, Jan 6, 1975.
(2) This investigation was supported by a grant from the National Cancer Institute (CA-12059).
(3) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **93**, 5941 (1971); **95**, 2651 (1973).
(4) E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
(5) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974).
(6) M. Sainsbury and R. F. Shinazi, *J. Chem. Soc., Chem. Commun.*, 718 (1972).
(7) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973).
(8) It is proposed that "neospirinedienone" be used for the dienones of type **8**, and that "neospirine" be used for the parent ring system. The new terms are preferable to those used earlier ("neoproerythrinadienone" and "neoproerythrine", ref 7) insofar as they do not imply a proven biosynthetic role for the compounds.
(9) S. M. Kupchan and C.-K. Kim, *J. Am. Chem. Soc.*, following paper in this issue.
(10) While this work was in progress, it was reported that anodic cyclization–rearrangement of methoxybibenzyls gave dihydrophenanthrones analogous to the products of VOF_3–TFA oxidation: J. R. Falck, L. L. Miller, and F. R. Stermitz, *J. Am. Chem. Soc.*, **96**, 2981 (1974).
(11) Bibenzyl **1b**, mp 85–87°, was prepared by catalytic hydrogenation over Pd/C of 3′,4,4′,5-tetramethoxy-2-(*N*-methyl-*N*-carbomethoxyethylamino)stilbene, mp 146–147°. The stilbene was prepared by treatment of (±)-laudanosine in chloroform with methyl chloroformate under reflux for 15 min.
(12) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic compounds.
(13) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takabashi, and K. Fukumoto, *J. Chem. Soc. C*, 3315 (1971); T. Kametani, K. Takabashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **20**, 1793 (1972).
(14) 1-(3′,4′-Dimethoxybenzyl)-2-formyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (**5b**) was prepared by $NaBH_4$ reduction in methanol of the 3,4-dihydroisoquinoline derivative (M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967)), and formylation with formic acid. The olly product, chracterized spectrally, was oxidized directly.
(15) 1-(3′,4′-Dimethoxybenzyl)-2-formyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**5c**, mp 127–128°) was prepared by treatment of the 3,4-dihydroisoquinoline derivative (M. Tomita, J. Kunitomo, and S. Kikuchi, *Yakugaku Zasshi*, **81**, 108 (1961)) with formic acid–formamide.
(16) The deuterated analogs **5d** and **5e** were prepared from 2-bromo-[17] and 5-bromohomoveratrylamine[18] by reduction with deuterium and Pd/C, followed by condensation with homoveratric acid, cyclization, and formylation.[19]
(17) K. Bessho, *Chem. Pharm. Bull.*, **11**, 1491 (1963).
(18) K. Bessho, *Chem. Pharm. Bull.*, **11**, 1500 (1963).
(19) I. Baxter, L. T. Allen, and G. A. Swan, *J. Chem. Soc.*, 3645 (1965).
(20) The two sets of signals may be attributable to the presence of essentially equal populations of two conformers in solution at room temperature. The conformers are postulated to reflect the two minimum energy conformations corresponding to the inversion of the saturated six-membered C-ring and resulting, in part, from the hindered rotation around the amide bond.[21] This was confirmed by a high temperature NMR study of **8a** in DMSO-d_6. The downfield signals at δ 7.28 and 7.22 were assigned to the C-12 protons in the twisted biphenyl systems. The upfield signal at δ 6.34 was assigned to the C-4 proton.[22] Of the two remaining sets of signals, those at δ 7.07 and 6.88 were assigned to the C-1 proton on the basis that any conformational change would be expected to affect the environment of the C-1 proton more than that of the C-9 proton. The methoxyl protons were assigned by comparison with the NMR spectra of the three monobenzylacylneospirinedienones.
(21) Cf. D. R. Dalton, K. C. Ramey, H. C. Gisler, Jr., L. J. Lendvay, and A. Abraham, *J. Am. Chem. Soc.*, **91**, 6367 (1969).
(22) Neglecting ring strain and other effects, calculations of the approximate chemical shifts of C-1 and C-4 protons in **8a**, using the method of Pascal, Meire, and Simon, gave δ 6.41 for C-1 and δ 5.59 for C-4 protons (L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", Vol. 5, Pergamon Press, Oxford, 1969, pp 184–185). These values are in reasonable agreement with the chemical shifts found for the C-1 (δ 6.51) and the C-4 (δ 5.86, 5.82) protons in $CDCl_3$.
(23) The synthesis of **3a** from **5a** appears to be the first reported electrochemical oxidation of an *N*-acylnorlaudanosine derivative.
(24) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1398 (1968); *J. Chem. Soc. C*, 520 (1969).
(25) D. H. R. Barton, *Pure Appl. Chem.*, **9**, 35 (1964).
(26) A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, *Chem. Commun.*, 1214 (1968).
(27) B. Franck and V. Teetz, *Angew. Chem., Int. Ed. Engl.*, **10**, 411 (1971).
(28) NIH Postdoctoral Fellow, 1973–1974.

S. Morris Kupchan,* Venkataraman Kameswaran[28]
J. Thomas Lynn, David K. Williams, Andris J. Liepa
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901

Received June 3, 1975

Facile Biomimetic Syntheses of Dibenzazonine and Aporphine Alkaloids[1,2]

Sir:

Morphinandienones have recently been recognized as the primary products of chemical[3,4] as well as anodic[5,6] coupling of nonphenol benzylisoquinoline precursors. The ease of acid-catalyzed rearrangement of these spirodienones[4] led us to explore their potential as in vitro alkaloid precursors. We report herein several facile and efficient syntheses of dibenzazonine and aporphine alkaloids via morphinandienone intermediates. In addition, the possible implications of these reactions for alkaloid biosynthesis are discussed.

Electrooxidative coupling of (±)-laudanosine (**5a**)[5] in HBF_4[6] yielded (±)-*O*-methylflavinantine (**1**) in 94% yield. Treatment of **1** with boron trifluoride–etherate at room temperature for 26 hr, followed by hydrogenation over Pt in methanol gave erybidine (**3**),[7] in 85% yield (Scheme I). By analogy with the demonstrated favored rearrangement of morphinandienones to neospirinedienones under the influence of strongly acidic catalysts,[4] the conversion of **1** to **3** is presumed to proceed via the intermediacy of **2** and **4**. The high-yield synthesis of **3** represents the most efficient re-