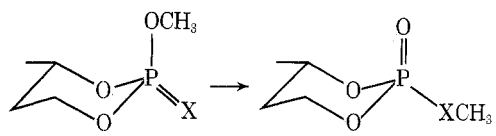
In the light of the above overall explanation it is clear that secondary alkyl esters do not undergo this rearrangement because secondary and tertiary carbon atoms of R in **2** and/or **4** are less available for nucleophilic attack on the sulfur atom. Experimental results are collected in Table I.

Some experiments require further comments.

(a) Phosphoroselenoates (expt 7 and 8) undergo more facile rearrangement than their sulfur analogues owing to more enhanced nucleophilicity of the "soft" selenium atom.

(b) Fifty percent conversion of *cis*-2-methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinane to *trans*-2-methylthio-2-oxo-4-methyl-1,3,2-dioxaphosphorinane ✓ (expt ✓6) ✓is achieved three times faster than that of *trans*- into *cis*-(expt 5). The faster rearrangement of the isomer with an axial sulfur atom may be explained in terms of an enhanced Lewis basicity of axially orientated sulfur relative to one in an equatorial position. This conclusion as applied to axial and equatorial oxygen has been reached by Verkade.[8]



trans, X = S, Se cis

(c) Rearrangement of *O*-allyl dimethylphosphinothionates proceeds much faster than that of other *O*-alkyl derivatives. However, rearrangement of *O*-γ-phenylallyl dimethylphosphinothioate (expt 3) gives exclusively *S*-γ-phenylallyl ester, without any trace of the *S*-α-phenyl isomer. The same product was obtained by thermal rearrangement of $Me_2P(S)OCH_2CH{=}CHC_6H_5$. Its structure was proved by ^1H NMR spectra: δ_{PSCH_2} −3.8 ppm, $^3J_{PSCH_2}$ = 12.3 Hz (2 H). The rearrangement of *O*-allyl-*3,3-d*$_2$ dimethylphosphinothionate (δ_{POCH_2} −4.56 ppm, $^3J_{POCH_2}$ = 10.9 Hz) gave *S*-allyl-*3,3-d*$_2$ dimethylphosphinothiolate [δ_{PSCH_2} −3.56 ppm, $^3J_{PSCH_2}$ = 11.9 Hz (2 H), Me_4Si internal standard]. These findings argue against a cyclic Claisen-type mechanism of rearrangement, postulated by Pudovik and Aladsheva[9] on the basis of their studies on the rearrangements of *O*-crotyl *O,O*-dimethylphosphorothionate. Enhanced reactivity of allyl esters may be explained in terms of known higher electrophilic reactivity of the allyl group toward nucleophiles.

Experimental Section

All melting and boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use. ^1H NMR spectra were recorded at 60 MHz with a JEOL C-60H spectrometer and Perkin-Elmer R12B. ^{31}P NMR spectra were obtained on a JEOL C-60H operating at 24.3 MHz with external H_3PO_4 as the reference. Mass spectra were obtained on an LKB-9000S spectrometer at 70 eV ionizing energy. GLC analyses were performed on a Varian Aerograph 1520. Ir spectra were obtained on a Zeiss-Jena UR-10.

General Procedure. At the temperature given in Table I the thionoester was added to the protic acid with intensive stirring and external cooling. Reactions were followed by means of ^1H and ^{31}P NMR. When the conversion of the substrate to the product reached 95%, excess of trifluoroacetic acid was removed under reduced pressure, the residue was diluted with either benzene or ether, and aqueous sodium carbonate was added for neutralization of the molar amount of acid involved in complex formation.[6] When H_2SO_4 was used, neutralization was done with gaseous ammonia. Following dilution by ether, ammonium sulfate was collected by filtration. The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure, and the product was distilled or crystallized from a suitable solvent. Satisfactory analyses were obtained for all reported compounds.

***O*-γ-Phenylallyl dimethylphosphinothionate** was obtained by reaction of cinnamyl alcohol with an equimolar amount of dimethyl phosphinobromothioate[10] in the presence of triethylamine. Attempts at its distillation caused rearrangement of the syrupy liquid to the thiolo isomer: ^{31}P NMR δ −91.3 ppm (external H_3PO_4); ^1H NMR δ_{POCH_2} −4.7 ppm, $^3J_{POCH_2}$ = 11.4 Hz.

***O*-Allyl-*3,3-d*$_2$ dimethylphosphinothionate** was prepared by condensation of allyl-*3,3-d*$_2$ alcohol[11] with dimethyl phosphinobromothioate in the presence of triethylamine. Distilled product, bp 35–40 °C (0.05 mmHg), was checked by ^{31}P NMR ($\delta_{^{31}P}$ −93 ppm, external H_3PO_4) and GC–MS.

Registry No.—**1**, 152-18-1; **3**, 57969-73-0; **4**, 57969-74-1; **5**, 1217-91-0; **6**, 23168-88-9; **7**, 23168-89-0; **8**, 33996-02-0; **9**, 33996-01-9; cinnamyl alcohol, 104-54-1; dimethyl phosphinobromothioate, 6839-93-6; allyl-*3,3-d*$_2$ alcohol, 16315-95-0.

References and Notes

(1) H. Teichmann and G. Hilgetag, *Angew. Chem.*, **79**, 1077 (1967).
(2) R. G. Cooks and A. F. Gerrard, *J. Chem. Soc. B*, 1327 (1968).
(3) V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 000 (1968).
(4) G. Mavel, "Progress in NMR Spectroscopy", Vol. 1, J. W. Emsley, I. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1966, Chapter 4, pp 251–373.
(5) Z. Skrowaczewska and P. Mastalerz, *Rocz. Chem.*, **31**, 531 (1957).
(6) W. J. Stec and J. Michalski, *Z. Naturforsch., B*, **25**, 554 (1970).
(7) G. Hilgetag and H. Teichmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 914 (1965).
(8) J. G. Verkade, *Bioinorg. Chem.*, **3**, 165 (1974).
(9) A. N. Pudovik and J. M. Aladsheva, *Zh. Obshch. Khim.*, **30**, 2617 (1960).
(10) Houben-Weyl, "Methoden der Organischen Chemie", Vol. XII, Georg Thieme Verlag, Stuttgart, 1963, p 275.
(11) K. D. Michael, *J. Am. Chem. Soc.*, **89**, 2943 (1967).

The Position of the Phenolic Function in Tiliacorine and Related Alkaloids[1]

Maurice Shamma* and James E. Foy

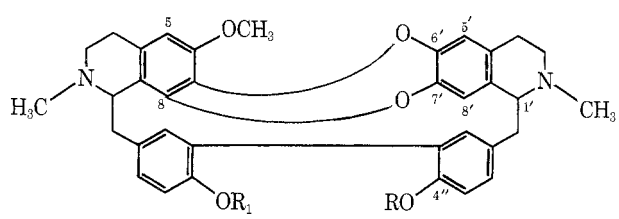
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Tuticorin R. Govindachari and Narayana Viswanathan

CIBA-GEIGY Research Centre, Goregaon East, Bombay, India

Received October 21, 1975

The bisbenzylisoquinoline alkaloid tiliacorine, found in *Tiliacora racemosa* Colebr. [*T. acuminata* (Lam.) Miers], has been assigned structure **1a** or **1b** since the exact position of the phenol in the lower half of the alkaloid was still uncertain.[2] We now wish to present evidence in favor of expression **1a** for tiliacorine.



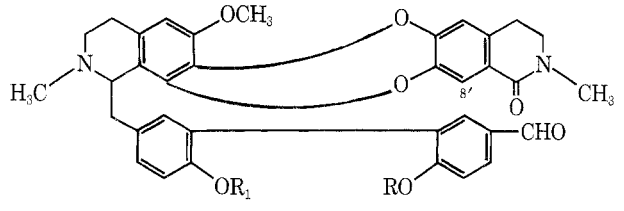
1a, R = H; R_1 = CH_3
b, R = CH_3; R_1 = H
c, R = R_1 = CH_3
d, R = Ac; R_1 = CH_3

Our attention was called to this problem during a study of the selective oxidation of several bisbenzylisoquinolines using potassium permanganate in acetone. That investigation revealed that in every case oxidation occurred at the doubly benzylic bond of the isoquinoline moiety unsubstituted at C-8′ (or C-8) to afford an aldehydo lactam.[3]

Treatment of the known *O*-methyltiliacorine (**1c**)[2] with excess potassium permanganate in refluxing acetone fol-

lowed by preparative TLC gave an 8% yield of the desired aldehydo lactam oxidation product **2c**, ν_{max} ($CHCl_3$) 1630 (lactam) and 1705 cm^{-1} (aromatic aldehyde). Close inspection of the NMR spectrum revealed that the C-8′ proton appeared downfield at δ 7.20, consistent with an aromatic hydrogen peri to a lactam carbonyl.[3] Thus, oxidation had taken place, as expected, at the doubly benzylic bond of the isoquinoline unit unsubstituted at C-8′.

The oxidation of tiliacorine acetate (**1d**) was then performed under identical conditions. Basic hydrolysis of the O-acetylated oxidation product **2b** yielded the phenolic aldehydo lactam **2a** whose uv spectrum, λ_{max} (EtOH) 212,



2a, R = H; R_1 = CH_3
b, R = Ac; R_1 = CH_3
c, R = R_1 = CH_3

282, and 310 sh nm (log ϵ 4.10, 3.44 and 2.94), showed a strong bathochromic shift in base to λ_{max} (EtOH–OH^-) 230, 292, and 340 nm (log ϵ 4.00, 3.27, and 3.21). A bathochromic shift of this magnitude is indicative of a phenolic function para to an aromatic aldehyde,[4] so that tiliacorine must be represented by expression **1a**.

It has already been shown that tiliacorine and tiliacorinine are diastereomeric, so that the latter is also represented by **1a**.[5] Nortiliacorinine A and nortiliacorinine B are *N*-nor bases belonging to the tiliacorinine series.[5] Therefore, the present study also settles the position of the phenolic functions of these alkaloids which must be located at C-4″. The absolute configuration of tiliacorine and its analogues still remains to be established.

It should be noted in conclusion that the two lower rings of tiliacorine type alkaloids are linked through a direct carbon to carbon bond, rather than through the much more common diaryl ether bridge.[6] This unusual structural feature precludes facile chemical interrelationship between tiliacorine bases and other bisbenzylisoquinolines of established structure and stereochemistry.[8]

Experimental Section

NMR spectra were obtained on a Varian A-60A with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were run on an MS-901 spectrometer. All TLC (thin layer chromatography) was on Merck EM F-254 silica gel plates.

General Oxidation Procedure. The bisbenzylisoquinoline, in the present case *O*-methyltiliacorine (**1c**),[2,5] 250 mg, was dissolved in 250 ml of acetone and heated to reflux. Solid $KMnO_4$ (250 mg) was added all at once, and the mixture boiled for an additional 1 h. Filtration of the MnO_2 followed by evaporation of the solvent yielded a gum which was subjected to TLC (10% MeOH–90% $CHCl_3$). Collection of the highest R_f alkaloidal band, detected by short-wave uv light or by the iodoplatinate spray reagent,[7] gave 21 mg (8%) of **2c**, colorless crystals: mp 174–175 °C (MeOH–C_6H_6); λ_{max} (EtOH) 212, 282, and 310 sh nm (log ϵ 4.05, 3.31, and 2.90). The more prominent features of the NMR spectrum were at δ 2.65 (3 H, s, NCH_3), 3.09 (3 H, s, lactam NCH_3), 3.70 (3 H, s, OCH_3), 3.81 (6 H, s, 2 OCH_3), 6.27 (1 H, s, C-5), 7.20 (1 H, s, 8′-H), and 9.80 (1 H, s, -CHO). The mass spectrum showed *m/e* 620 (M^+, $C_{37}H_{36}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 255 ($C_{16}H_{15}O_3$); high resolution M^+ calcd 620.2520, found 620.2466.

The oxidation of tiliacorine acetate (**1d**)[5] was carried out under conditions essentially identical with those described above. The yield of aldehydo lactam **2b** was 8%: ν_{max} ($CHCl_3$) 1630 (lactam), 1705 (aromatic aldehyde), and 1765 cm^{-1} (acetate); λ_{max} (EtOH) 212, 270, and 320 sh nm (log ϵ 4.01, 3.44, and 2.86). The mass spectrum showed peaks at *m/e* 648 (M^+, $C_{38}H_{36}N_2O_8$), 605 ($C_{36}H_{33}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), 283 ($C_{17}H_{15}O_4$), and 240 ($C_{15}H_{12}O_3$); high resolution M^+ calcd 648.2770, found 648.2703.

Hydrolysis of 2b. The acetate **2b** (20 mg) was added to 10 ml of a solution of MeOH previously saturated with K_2CO_3. The mixture was stirred at room temperature for 2 h. Work-up provided 18 mg (90%) of **2a**: mp 185–187 °C (MeOH); ν_{max} ($CHCl_3$) 1630 and 1705 cm^{-1}. The NMR spectrum shows peaks at δ 2.35 (3 H, s, NCH_3), 3.08 (3 H, s, lactam NCH_3), 3.80 (9 H, s, 3 OCH_3), 6.28, 6.64, 6.90, 7.17, 7.67, and 7.85 (6 H, each as s, 6 aromatic H), and 9.86 (1 H, s, -CHO). The mass spectrum had peaks at *m/e* 606 (M^+, $C_{36}H_{34}N_2O_7$), 365 (base, $C_{21}H_{21}N_2O_4$), and 241 ($C_{15}H_{13}O_3$); high resolution M^+ calcd 606.2364, found 606.2295.

Registry No.—**1a**, 27073-72-9; **1c**, 23944-12-9; **1d**, 58220-09-0; **2a**, 58220-10-3; **2b**, 58220-11-4; **2c**, 58220-12-5.

References and Notes

(1) This research was supported by Grant HL-12971 from the National Heart and Lung Institute.
(2) B. Anjaneyulu, K. W. Gopinath, T. R. Govindachari, and B. R. Pai, *J. Sci. Ind. Res., Sect. B*, **21**, 602 (1962); *Chem. Abstr.*, **59**, 1695 (1963).
(3) M. Shamma and J. E. Foy, *Tetrahedron Lett.*, 2249 (1975).
(4) A. I. Scott, "Interpretation of the UV Spectra of Natural Products," Macmillan, New York, N.Y., 1964, p 109.
(5) B. Anjaneyulu, T. R. Govindachari, S. S. Sathe, N. Viswanathan, K. W. Gopinath, and B. R. Pai, *Tetrahedron*, **25**, 3091 (1969).
(6) For a review on the bisbenzylisoquinolines see M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N.Y., (1968, p 115.
(7) E. Stahl, "Thin-Layer Chromatography", Springer-Verlag New York, New York, N.Y., 1969, p 883.
(8) **Note Added in Proof.** A similar conclusion regarding the position of the phenolic function in tiliacorine was reached independently by Professor Norman S. Bhacca of Louisiana State University.

Facile Intramolecular Displacement of Fluoride in Reaction of γ-Fluorobutyronitrile with Phenylmagnesium Bromide

Allen E. Kemppainen, Michael J. Thomas, and Peter J. Wagner*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received November 12, 1975

2-Aryl-1-pyrrolines (5-aryl-3,4-dihydro-2*H*-pyrroles) can be readily synthesized by the addition of aryl Grignard reagents to γ-chloro- or -bromobutyronitrile.[1-4] When cyclization is desired, the magnesium bromide salt of the imine or the free imine is heated. If the ethereal solution of the imine salt is worked up as usual, by acidification and hydrolysis,[5] the γ-halo ketones are obtained in good yields.[1,6] We find that when phenyl Grignard reagent is added to γ-fluorobutyronitrile, the pyrroline is formed even without replacement of solvent and heating.

An ether solution of phenylmagnesium bromide was prepared as usual. Addition of γ-fluoronitrile to this solution produced a more exothermic reaction than normal for aliphatic nitriles. In one run the solution was allowed to reflux during the addition; in another it was kept in an ice bath. The reaction solution was worked up so as to hydrolyze any γ-fluoroimine to the ketone. The only product obtained was identified as 2-phenyl-1-pyrroline.

The very exothermic nature of the Grignard–fluoronitrile reaction and the lack of ketone product suggest that the imine anion readily displaces the fluoride under the mild conditions of the Grignard-to-nitrile addition. Since the chloro- and bromoimine salts do not undergo internal displacement except at high temperature, and since normally Br > Cl ≫ F as leaving groups, we must postulate that the magnesium ion assists the displacement by bonding specifically to the fluorine. The unusual nature of the Grignard reaction is emphasized by the selective displace-