diphenylanthracene peroxide (0.08 g). The over-all yield of di- and triamide was 92%.

We are investigating mechanistic aspects of the process by which oxygen is transferred from photoperoxide to acceptor, as well as the possibility that other types of cyclic peroxides may provide sources of singlet oxygen.

Acknowledgment. This work was supported in part by Grant GM-13854 from the National Institutes of Health.

(14) National Institutes of Health Postdoctoral Fellow, 1966–1967.

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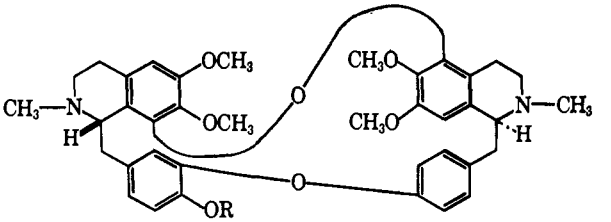
The Isolation and Structural Elucidation of Thalidasine, a Novel Bisbenzylisoquinoline Alkaloid Tumor Inhibitor from *Thalictrum dasycarpum*[1,2]

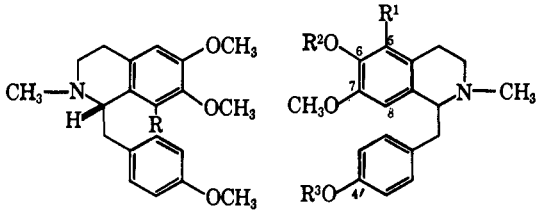
Sir:

The genus *Thalictrum* has served as a uniquely profuse source of new and novel benzylisoquinoline and aporphine alkaloids.[3–6] We report herewith the isolation and elucidation of the structure (Ia) of thalidasine, a new alkaloid tumor inhibitor[7] from *T. dasycarpum*. Thalidasine appears to be the first bisbenzylisoquinoline recognized to contain a diphenyl ether terminus at C-5 and the first unsymmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring.[8] Furthermore, the alkaloid thalfoetidine, from *T. foetida*,[9] is shown to possess structure Ib on the basis of evidence which includes interrelation with thalidasine.

Thalidasine (Ia), $C_{39}H_{44}N_2O_7$, mol wt (mass spectroscopy)[10] 652, is an amorphous solid, mp 105–107°, $[\alpha]^{27}D$ −70° (*c* 0.89, MeOH), λ_{max}^{EtOH} 275 mμ (ε 4560), 282 mμ (ε 4530), and nmr signals (in $CDCl_3$) at τ 7.38, 7.75 (6 H, two NCH_3), 6.09, 6.13, 6.25, 6.50, 6.73 (15 H, five OCH_3), and 2.46–3.70 (9 H, aromatic H). The alkaloid was characterized as the oxalate, mp 160–162°, picrate, mp 175–177°, and methiodide, mp 182–183°. Permanganate oxidation of Ia yielded 2-methoxydiphenyl ether 4′,5-dicarboxylic acid (V), characterized by mixture melting point and infrared comparison with an authentic sample.[11] Sodium in liquid ammonia reduction of Ia afforded, as principal products, L-O-methylarmepavine (IIa), mp 61–62°, $[\alpha]^{26}D$ +99° (*c* 1.10, $CHCl_3$), and a dihydroxydimethoxybenzylisoquinoline (A), $C_{19}H_{33}NO_4$, mp 194–196°, $[\alpha]^{27}D$ +51° (*c* 0.50, MeOH), λ_{max}^{EtOH} 279 mμ (ε 2750), nmr signals at τ 7.48 (3 H, NCH_3), 6.13, 6.45 (6 H, two OCH_3), 4.33 (1 H, C-8 H), 3.92 (2 H, two OH), 3.08, 3.35 (4 H, two doublets, J = 8.5 cps). Methylation of phenol A with diazomethane gave 1-(4-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa), characterized by infrared and nmr comparison with the *dl* compound.[4b] Nmr spectral characteristics and reactivity toward Gibbs reagent[12] led to consideration of 4′,6-diphenol (IIIb) and 4′,5-diphenol (IIIc) structures as most likely for phenol A. However, the infrared spectrum of synthetic [*via* the dibenzyl ether IIId, mp 83–86°, nmr signals at τ 7.49 (3 H, NCH_3), 6.19, 6.55 (6 H, two OCH_3), 4.97, 5.02 (4 H, two OCH_2Ph), 3.02, 3.13 (4 H, two doublets, J = 8.5 cps, disubstituted aromatic

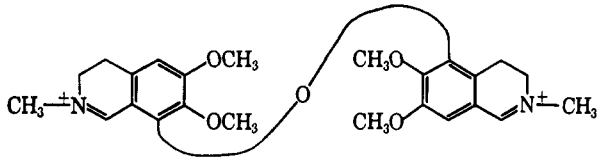


Ia, R = CH_3
b, R = H

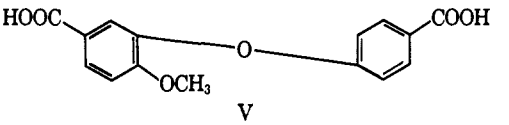


IIa, R = H
b, R = OH

IIIa, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$
b, $R^1 = OCH_3$; $R^2 = R^3 = H$
c, $R^1 = OH$; $R^2 = CH_3$; $R^3 = H$
d, $R^1 = OCH_3$; $R^2 = R^3 = CH_2Ph$
e, $R^1 = H$; $R^2 = CH_3$; $R^3 = H$



IV



V

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(8) Cissampareine was the first symmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring (S. M. Kupchan, S.Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *J. Am. Chem. Soc.*, 88, 4212 (1966)).

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(11) The authors thank Professor M. Tomita cordially for the authentic sample of 2-methoxydiphenyl ether 4′,5-dicarboxylic acid.

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ring), 2.63 (10 H, monosubstituted aromatic ring)] *dl*-IIIb [mp 136–140°, λ_{max}^{EtOH} 281 mμ (ε 3200), nmr signals at τ 7.43 (3 H, NCH_3), 6.15, 6.47 (6 H, two OCH_3), 5.18 (2 H, two OH), 4.23 (1 H, C-8 H), 3.11, 3.29 (4 H, two doublets, J = 8.5 cps)] differed from that of phenol A. Hence phenol A was assumed to have the 4′,5-diphenol structure IIIc, and thalidasine, an unprecedented diphenyl ether terminus at C-5. Evidence for both structures was adduced from the experimental results which follow.

Characterization of the *minor* phenolic products of reduction with sodium in liquid ammonia and mass spectroscopic evidence[10] strongly support assignment of structure Ia for thalidasine. One minor phenolic cleavage product was L-armepavine (IIIe), $[\alpha]^{27}D$ +99° (*c* 0.14, $CHCl_3$), infrared and nmr spectra superimposable with those of authentic sample.[13] A second minor phenolic product was L-1-(4-methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (IIb), $[\alpha]^{27}D$ +32° (*c* 0.40, $CHCl_3$), infrared and nmr spectra superimposable with those of a sample of *dl* compound.[14] The most intense peak in the mass spectrum of thalidasine is a doubly charged ion (IV) of *m/e* 213 ($C_{24}H_{30}N_2O_5$). This type of fragmentation has been shown to be characteristic of alkaloids of the unsymmetrical bisbenzylisoquinoline type.[5b,15] Fragments with compositions $C_{27}H_{29}NO_4$, $C_{15}H_{14}O_2$, $C_{14}H_{11}O_2$, $C_{12}H_{16}NO_3$, and $C_{12}H_{16}NO_2$, are readily explicable on the basis of structure Ia.

Thalfoetidine's chemistry supports the structural features assumed earlier,[9] apart from the termini of the diphenyl ether linkage. Methylation of thalfoetidine with diazomethane yielded O-methylthalfoetidine,[9,16] and direct comparison (infrared, nmr) has established the identity of the methylation product with thalidasine. Hence thalfoetidine possesses structure Ib.

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(16) We thank Dr. N. Mollov cordially for a sample of thalfoetidine.

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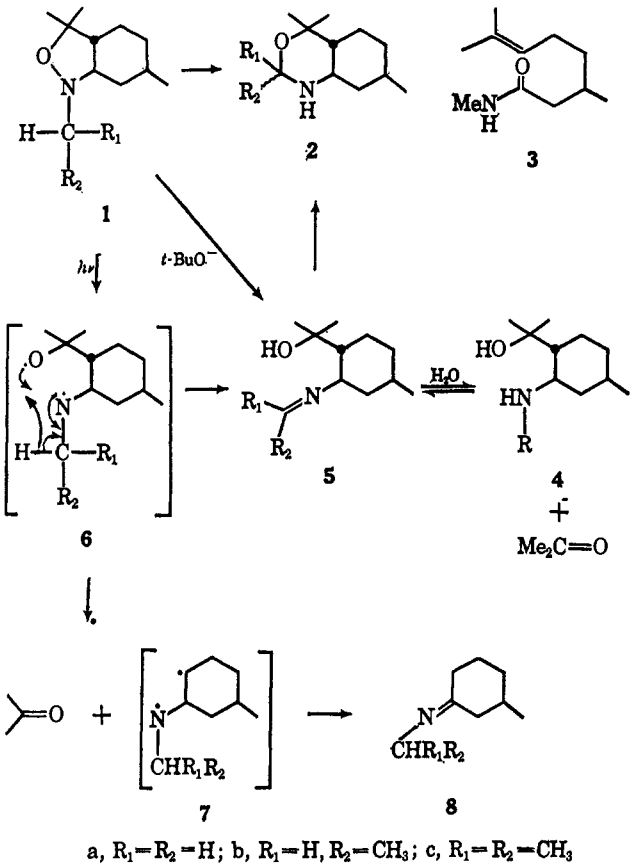
Photochemical and Base-Catalyzed Rearrangements of Isoxazolidines

Sir:

Intra-[1] and intermolecular[2] cycloadditions of nitrones and olefins have provided a new method for the formation of carbon–carbon bonds. Adaptation of this reaction as a synthetic method of broadest possible scope has stimulated investigations of the chemistry of the product isoxazolidine ring system. It is the purpose of this report to disclose our discovery of a rearrangement of N-alkylisoxazolidines to tetrahydro-1,3-oxazines, an isomerization that can be effected both by ultraviolet irradiation and by strong base.

Irradiation of the fused bicyclic isoxazolidine **1a** ($\lambda_{max}^{isooctane}$ 213 mμ (ε 1940)) in hexane solution (0.027 *M*) with 2537-A light[3] afforded a product mixture from which the bicyclic tetrahydro-1,3-oxazine **2a** could be isolated. Minor amounts of the amide **3** were also obtained, and the identity of **3** was established by synthesis from citronellic acid. The photochemical conversion of **1a** to **2a** could be efficiently photosensitized by the use of benzophenone and fluorenone (anthracene, $E_T \sim 42$ kcal/mole, proved to be a poor sensitizer). Under these conditions, the yields of **2a** were 43 and 54%, respectively, and no amide **3** was detected. Similarly, isoxazolidine **1b** was photoisomerized to **2b**.



a, $R_1=R_2=H$; b, $R_1=H, R_2=CH_3$; c, $R_1=R_2=CH_3$

The structures of **2a** and **2b** were supported by their nmr spectra, which for the former showed an AB quartet at 4.25 ppm (2 H, J_{AB} = 10.5 cps), whereas **2b** showed a regular quartet at 4.35 ppm (1 H, J = 5.6 cps). Reduction of each with lithium aluminum hydride produced the known[1] secondary amino alcohols **4**, R = CH_3, and **4**, R = C_2H_5, respectively.

When **1a** and **1b** were heated with 0.5 equiv of potassium *t*-butoxide in DMSO for 5 hr at ~80°, the tetrahydro-1,3-oxazines were again obtained in good yield.

We propose that these reactions are mechanistically similar in that the imino alcohol **5** is a common intermediate. Cyclization of γ-hydroxy imines to tetrahydro-1,3-oxazines is well established.[4] For the photochemical transformation, energy transfer from triplet

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