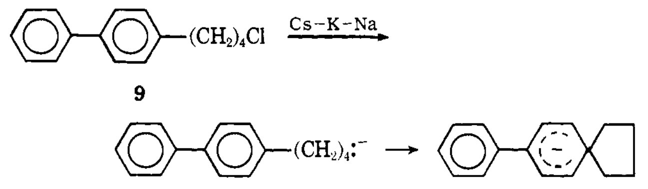
According to Scheme I the spiro anion **4** is an intermediate in the present carbanion rearrangement. In an attempt to detect this intermediate the chloride **1** was allowed to react with excess finely divided Cs–K–Na eutectic[1] in THF at −75° for some 3 min before carbonation. There was obtained, however, only the usual product of rearrangement, 5-*p*-biphenylyl-2,2-diphenylpentanoic acid. This result implies that the spiro anion **4** rearranges readily to **5** even at −75°. Since ready ring opening may be dependent upon the presence of the two phenyl groups which stabilize the final anion **5**, this study has been repeated with the corresponding chloride 4-chloro-1-biphenylylbutane[2] (**9**) in which the activating phenyls have been replaced by hydrogen.

Reaction of **9** with excess Cs–K–Na eutectic at −70° in THF gave a red solution which was carbonated as soon (~4 min) as it started to turn green (radical anion formation). There was isolated a high yield of acid (*ca.* 85%) which consisted of 96% of 8-phenylspiro[4.5]-6,9-decadiene-8-carboxylic acid (**10**), mp 130–131°, and 4% of 2-*p*-biphenylylpentanoic acid (**11**). The analytical and spectral properties of **10** [λ_{max}^{EtOH} 260 nm (ϵ 293); nmr ($CDCl_3$) τ −1.40 (1 H, CO_2H), 2.80 (5 H, s), 4.00 (2 H, d, J = 10 Hz), 4.20 (2 H, d, J = 10 Hz), 8.33 (8 H, br s); mass spectrum, molecular ion *m/e* 254] agree well with the assigned structure. Protonation of the red solution by methanol at −70° gave a neutral product, of which only some 10% was volatile; the latter consisted of about equal amounts of 1-*p*-biphenylylbutane and 8-phenylspiro[4.5]-6,9-decadiene [nmr ($CDCl_3$) τ 2.75 (5 H, s), 4.33 (4 H, d, J = 1 Hz), 6.08 (1 H, t, J = 1 Hz), 8.27 (8 H, br s)]. Reaction of **9** in THF with cesium at 35° or with cesium or potassium at 65° gave a similar mixture of carbanions although the yield of volatile products obtained upon carbonation decreased with increasing temperature. The nmr spectrum at 40° of the red solution from treatment of **9** with Cs–K–Na alloy in THF-d_8 at −70° and addition of mercury to remove excess alkali metal and destroy radical anion [τ 3.1–3.3 (5 H, m), 3.70 (2 H, d, J = 10 Hz), 5.60 (2 H, d, J = 10 Hz), 8.28 (4 H, m), 8.57 (4 H, m)] showed conclusively[8] that the major intermediate was the spiro anion **13**. That the cyclization to **13** occurred *via* the open carbanion **12** was indicated by reaction of **9** with potassium in THF containing *tert*-butyl alcohol, wherein 1-*p*-biphenylylbutane was initially formed but was reduced ultimately to 1-(*p*-cyclohexylphenyl)butane. Since 4-*p*-biphenylyl-1-chlorobutane-*1,1*-d_2 gave 1-(*p*-cyclohexylphenyl)butane-*4,4*-d_2, cyclization did not occur prior to formation of the butane; also reaction of this chloride with sodium in dioxane at 101° gave 1-*p*-biphenylylbutane-*4,4*-d_2.



9

12 13

While species similar to **13** have been long suggested as intermediates or transition states[7b,9] in 1,2 migrations of aryl in polyarylethyllithiums, such carbanions have never previously been isolated from cyclization of ω-arylalkyl anions. A recent study[10] on homoconjugation in pyridylalkyl organometallic compounds indicated on the basis of nmr spectra that the compounds studied existed in the open-chain form, although attack by some electrophilic reagents gave spiro products. Similarly the reaction of the methiodide of 1-chloro-2-methyl-2-(4-pyridyl)propane with lithium in THF gave 1-methyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine.[11]

Acknowledgment. Financial support of this work by the National Science Foundation is gratefully acknowledged.

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[8] For the nmr spectra of some related carbanions see R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 205 (1967).

[9] E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Amer. Chem. Soc.*, **83**, 2537 (1961); E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **89**, 2348 (1967).

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[11] J. J. Eisch and C. A. Kovacs, *J. Organometal. Chem.*, **25**, C33 (1970).

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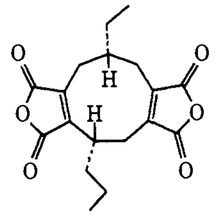
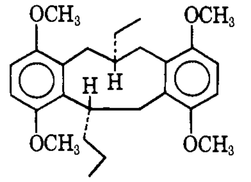
The Total Synthesis of (±)-Byssochlamic Acid

Sir:

The nonadrides[1] form an unusual and fascinating class of mold metabolites which are characterized by the presence *inter alia* of a substituted nine-membered ring fused to two five-membered anhydride systems.[2,3] We now report the first total synthesis of one of these natural products, byssochlamic acid (**1**). As an intermediate target we selected the bishydroquinone dimethyl ether (**2**) in which the aromatic rings serve not only as latent (less reactive) anhydride systems, but also play a decisive role in allowing the establishment of the two cis alkyl substituents.



1



2

Enamine alkylation[4] of 5,8-dimethoxy-2-tetralone,[5] as the pyrrolidine enamine, with propyl iodide (17-hr refluxing in methanol) produced **3** in ~80% yield, mp 53–54° [6] (from pentane at −18°). Elaboration of the ring system now required 2,3-dichloromethyl-1,4-

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[1] *Cf.* J. K. Sutherland, *Fortschr. Chem. Org. Naturst.*, **25**, 131 (1967).

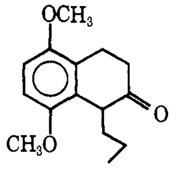
[2] D. H. R. Barton, *et al.*, *J. Chem. Soc.*, 1769, 1772, 1779, 1787 (1965).

[3] I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 5502 (1963).

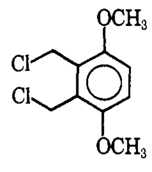
[4] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

[5] T. R. Lewis, W. B. Dickinson, and S. Archer, *ibid.*, **74**, 5321 (1952).

[6] All substances gave analytical and/or spectral data consistent with the postulated structures.



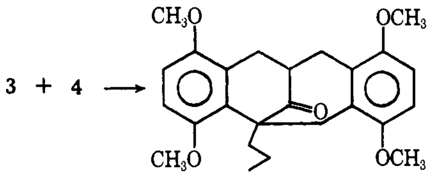
3



4

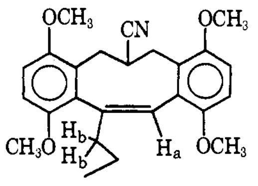
dimethoxybenzene (**4**). This was prepared by lithium aluminum hydride reduction of the diethyl ester derived from 3,6-dimethoxyphthalic anhydride[7] to the diol, mp 143–144°, which then (concentrated hydrochloric acid, 0°) gave **4**, mp 139–140°, after chromatography on silica gel (hexane–benzene).

Cycloalkylation of **3** with **4** was carried out by the slow addition of 5.28 g of **3** in 330 ml of glyme to a heated suspension of 1.83 g of sodium hydride in 250 ml of glyme containing 5.15 g of the dichloride **4**, followed by refluxing for 5 hr. The tetracyclic product **5**, mp 126–128° (from ethanol), was thus obtained in ~80% yield.



5

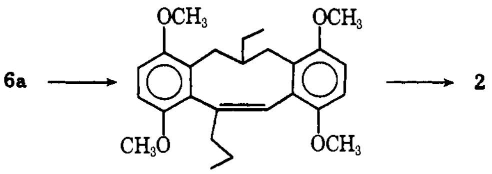
Transformation of **5** to a substituted nine-membered ring could be effected smoothly by formation of the oxime (quantitative, mp 232–233°), followed by fragmentation with phosphorus oxychloride–pyridine at 0° for 22 hr. Two isomeric olefinic nitriles **6a** and **6b** were isolated, in addition to a small amount of lactam, by successive crystallization of the ether extracts. Olefinic nitrile **6a** (46% yield), mp 171–172° (from methanol and a small amount of chloroform, δ 6.51 (H_a, t, J = 1–2 Hz, becoming a singlet on irradiation of H_b at ~2.2–2.6), was less soluble than its isomer **6b**, mp 144–148° (40% yield), and moved more slowly on silica gel (R_f 0.66 and 0.70 in 25% ethyl acetate–hexane for **6a** and **6b**, respectively).



6a

The isomeric **6b** (m/e 407) could be shown to be the propylidene double bond isomer of **6a** by appropriate nmr decoupling experiments. The relationship was confirmed by showing that **6b** could be slowly isomerized to the more stable **6a** (30% **6b**:70% **6a**, after 24 hr with toluenesulfonic acid in xylene at 125°).

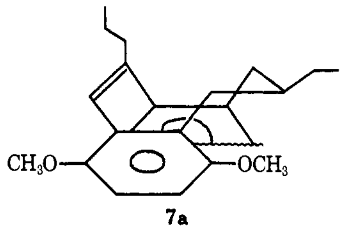
The cyano group of **6a** was transformed into an ethyl substituent by addition (−78°) of an excess of ethereal methyllithium (1.5 hr, room temperature) and reduction of the resulting imine, without isolation, under Wolff–Kishner conditions, thus leading to **7**: mp 115–117° (from methanol); λ_{max}^{EtOH} 288 nm (log ϵ 3.84); 80% yield.



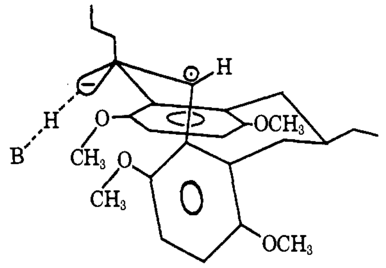
7

The tub shape of **7** (*cf.* **7a**) and the projecting ring methoxyls prevent close approach to the double bond and its catalytic hydrogenation could not be used as a route to **2**.

Although formally a stilbene derivative, compound **7** has a shape which essentially prevents overlap of the olefinic orbitals and the benzene rings (*cf.* **7a**), as is reflected in the low extinction of the uv absorption which is that of the two isolated aromatic rings (*cf.* uv of **2**, below). Addition of an electron to the ethylenic link might, however, permit some rotation around the original double bond, thus allowing stabilization of the radical ion by both rings. Indeed, lithium–ammonia reduction, in the presence of some tetrahydrofuran, led to a single dihydro compound **2** (~80% yield, in addition to ~20% starting material separated by silica gel chromatography). The dihydro compound **2**, mp 106–108°, λ_{max}^{EtOH} 287 nm (log ϵ 3.80), exhibited all the properties of a single substance.[8] We were hopeful that the necessary cis stereochemistry of the two alkyl chains had been produced because the formation of the unwanted trans isomer would have involved moving the propyl group into serious eclipsing interaction with the methoxyls, an interaction which was avoided in the cis transition state **8**.



7a



8

The matter was settled by a single-crystal X-ray structure determination[9] of the product of the lithium–ammonia reduction which indeed proved to be the cis isomer shown in **2**.

The crystals of **2** were triclinic, space group $P\bar{1}$, with: a = 10.122 (5), b = 11.088 (4), and c = 11.905 (4) Å; α = 66.23 (2), β = 73.12 (4), and γ = 83.02

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(7) G. D. Graves and R. Adams, *J. Amer. Chem. Soc.*, **45**, 2439 (1923).

(8) Depending on its rate of crystallization from methanol, **2** could be obtained as needles, mp 103–104°, rhombs, mp 106–108°, or rosettes, mp 109–110°. Differential thermal analysis of these crystals by Dr. J. Jacques of the Collège de France, Paris, to whom we express our thanks, established the polymorphic relationship of these substances which also exhibited identical tlc behavior.

(9) Performed at Hoffmann-LaRoche.

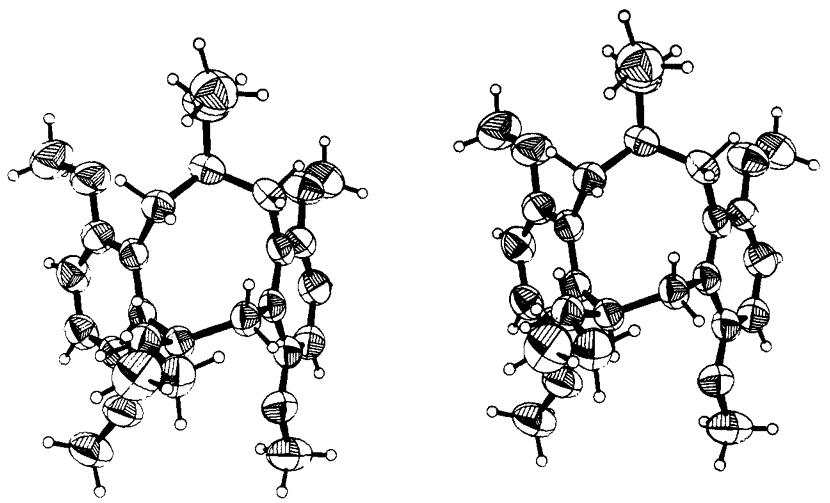

Figure 1. Stereodrawing of **2**. The thermal ellipsoids are scaled at the 50% probability level. The disordered methyl of the ethyl side chain is shown only in one of its conformations.

(3)°; $d_{\mathrm{obsd}} = 1.10$; $d_{\mathrm{calcd}} = 1.16$ g cm^{-3}; $Z = 2$. A total of 4393 reflections (1027 unobservedly weak) was measured on a Hilger-Watts model Y290 full circle diffractometer with Cu Kα radiation ($2\theta < 140°$).

The structure was solved by the symbolic addition method.[10] Hydrogen atoms were located from a difference Fourier calculated after refinement of the heavier atoms. The full structure was refined by block diagonal least squares (ten blocks) with isotropic temperature factors for the hydrogen atoms and anisotropic thermal parameters for all other atoms. The final R is 5.4%.

In the crystal the terminal methyl of the ethyl side chain is disordered. Accordingly, atomic multipliers of 0.5 were assigned to the disordered atoms. The conformation of **2** in the solid state is shown in Figure 1. Both phenyl rings are planar to within ±0.02 Å. The angle between the normals to the two phenyl rings is 120°. The methoxyl carbon and oxygen atoms lie approximately in the plane of their respective phenyl rings. The dihedral angles between the planes of the methoxyls (C_{Me}–O–C_{ϕ}) and their respective phenyl planes range from 4 to 8°.

With the establishment of the correct stereochemistry and molecular framework of **2** there remained only to convert the two substituted benzene rings to the maleic anhydride systems of byssochlamic acid. This was accomplished by cleavage of the tetramethyl ether with boron tribromide in methylene chloride[11] to the unstable bishydroquinone which, without purification, was submitted to oxidation, first with potassium permanganate in aqueous glyme at 0° for 1.5 hr and, finally, with lead tetraacetate in acetic acid containing some water, at 55° for 30 min. The crystalline product (~13% overall from **2**) obtained after preparative tlc on silica gel[12] and trituration, first with 95% ethanol, and then with pentane, had mp 127–129°. Its structure as (±)-byssochlamic acid (**1**) was established by its elemental analysis, and by comparison with the natural substance[13] which showed identical tlc behavior in three different solvent systems, as well as identity of the ir, uv, nmr, and mass spectra (m/e 332.1263).[14]

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for the support of this work.

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[11] J. F. W. McOmie and M. L. Watts, *Chem. Ind. (London)*, 1658 (1963).

[12] Developed twice with 4% acetic acid–benzene. The synthetic byssochlamic acid was recovered by stirring the corresponding band with 5% aqueous NaOH, followed by acidification and ether extraction.

[13] We thank Professor D. H. R. Barton (Imperial College, London) and J. E. Baldwin (King's College, London) for making natural byssochlamic acid available to us.

[14] Final atomic and anisotropic thermal parameters for **2** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-72-4735. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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A Novel Synthesis of Purine β-D-Nucleosides *via* Purine 8,5′-*S*-Anhydronucleosides

Sir:

We have developed a simple and superior procedure for the synthesis of purine 8,5′-*S*-anhydronucleosides which are found to be of considerable utility as chemical precursors for the preparation of purine β-D-nucleosides.[1] This novel synthetic procedure requires the easily accessible adenine derivatives of type III which bear a D-pentofuranos-5-yl group at position 8 as a key intermediate.

Reaction of adenine-8-thiol (I)[2] (sodium salt) with 5-iodo-5-deoxy-1,2-*O*-isopropylidene-β-D-xylofuranose (IIa),[3] methyl 5-iodo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (IIb),[4] and methyl 5-tosyloxy-5-deoxy-

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