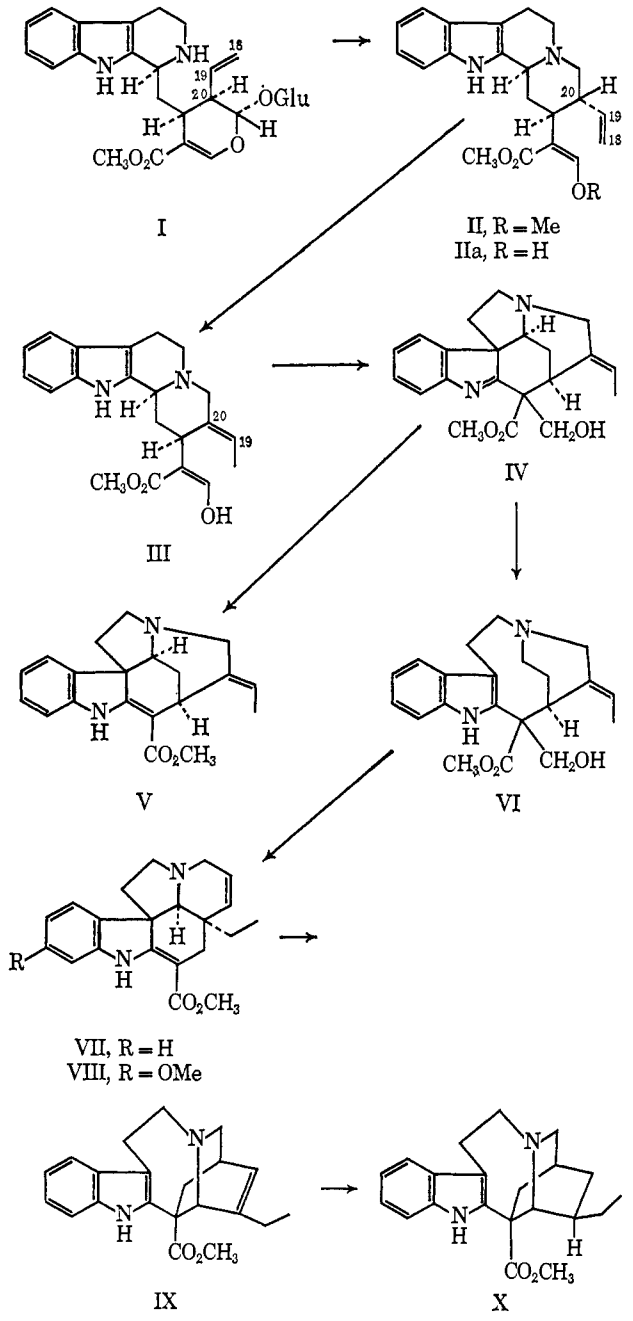
Chart I. Sequential Scheme for Indole Alkaloid Biogenesis



Evidence that geissoschizine (III) is indeed implicated both in *Strychnos* and *Aspidosperma–Iboga* biosynthesis was obtained by feeding Ar-^{2}H-labeled geissoschizine containing 20% d_4 (10 mg) to *V. rosea* seedlings (100 g). The incorporations into derived alkaloids measured from the enrichment of the appropriate (M + 4) mass spectral intensities of akuammicine (V; 1.53%) and coronaridine (X; 0.35%) leave no doubt that, as predicted[1] on the basis of several models and analogies, the intact[5] *Corynanthe* alkaloids serve as intermediates for the *Strychnos* as well as the *Aspidosperma* and *Iboga* series, since tabersonine (VII) has already been shown to be the intermediate for the isomeric catharanthine (IX).

The implications of the isolation of preakuammicine (IV), the prototype of the *Strychnos* family, will be discussed in a subsequent communication.[3] We note at this time that a prerequisite of the *Corynanthe* → *Strychnos* → *Iboga* change *in vitro* is the presence of the $\Delta^{19,20}$ double bond in geissoschizine. This may be achieved at the vincoside[4,6] (I) or corynantheine aldehyde (IIa) level. Available evidence[1] indicates that at least in young seedlings of *V. rosea* the required isomerization can take place on the intact *Corynanthe* template, IIa → III. Detailed studies of the mechanisms connecting geissoschizine (III) with akuammicine (V), strychnine, and stemmadenine (VI) are in progress. The intermediacy of geissoschizine in *Strychnos*, *Aspidosperma*, and *Iboga* biosynthesis has been independently demonstrated by Battersby and Hall.[6]

Acknowledgment. This work was generously supported by National Institutes of Health Grant CA-11095.

(5) An alternative hypothesis[4] involving formation of IV from I without passing through *Corynanthe* intermediates is rendered less likely by these experiments.

(6) A. R. Battersby and E. S. Hall, *Chem. Commun.*, in press. We thank Professor Battersby for exchange of manuscripts prior to publication.

A. I. Scott, P. C. Cherry, A. A. Qureshi
Sterling Chemistry Laboratory, Yale University
New Haven, Connecticut 06520
Received June 11, 1969

Synthesis of *dl*-Sirenin

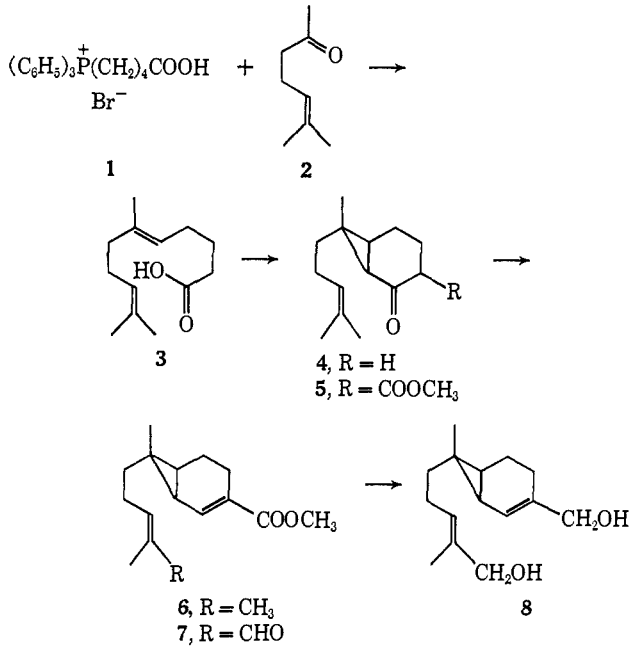
Sir:

The structure of sirenin, the chemotactic hormone produced by female *Allomyces* gametes, has been recently established.[1] We now describe the synthesis of *dl*-sirenin.

Triphenylphosphine and 5-bromovaleric acid, heated 12 hr at 80°, gave the phosphonium salt **1**, mp 205–206°. The salt **1** and 6-methyl-5-hepten-2-one (**2**),[2] dissolved in dimethyl sulfoxide–tetrahydrofuran (1:1), were added to excess sodium hydride in tetrahydrofuran at 0°. After 24 hr the C_{13}-diene acid **3**,[3] bp 147–153° (0.2 mm), containing 13 of the 15 carbon atoms of sirenin, was isolated (75% yield) as a mixture of *cis* and *trans* isomers (*ca.* 1:1, by glpc of the methyl esters prepared using dimethyl sulfate).[4] The corresponding phosphonium salt of the valeric ester cannot be used in the Wittig reaction due to cyclization of the intermediate ylide;[5] however, protection of the carboxyl function as the carboxylate ion allows formation of olefin in the normal manner with retention of carboxyl functionality in the product.

The sodium salt of the mixture of isomers of 6,10-dimethyl-5,9-undecadienoic acid (**3**) was converted to acid chloride (oxalyl chloride in benzene) to which excess ethereal diazomethane was added. Heating the diazo ketone thus formed in refluxing cyclohexane in the presence of cupric sulfate led to cyclization[6] and

(1) W. H. Nutting, H. Rapoport, and L. Machlis, *J. Am. Chem. Soc.*, **90**, 6434 (1968).
(2) Commercially available.
(3) Satisfactory elemental analyses and confirmatory mass spectral data were obtained for all new compounds. Structures assigned are consistent with ir and nmr spectra, the latter being obtained in carbon tetrachloride or deuteriochloroform with internal TMS. Temperatures reported as boiling points are bath temperatures.
(4) F. H. Stodola, *J. Org. Chem.*, **29**, 2490 (1964).
(5) L. D. Bergelson and M. M. Shemyakin, *Angew. Chem.*, **76**, 113 (1964).
(6) Analogous cyclizations of diazo ketones have been reported by, among others, G. Stork and J. Ficini, *J. Am. Chem. Soc.*, **83**, 4678 (1961), and M. M. Fawzi and C. D. Gutsche, *J. Org. Chem.*, **31**, 1390 (1966).



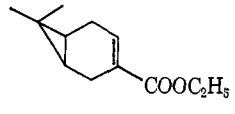
afforded the bicyclic ketone **4** [40% yield from diene acid **3**; bp 95–100° (0.3 mm); ir: 1680 cm^{-1}] as a mixture of isomers. This mixture was easily separated by preparative glpc on 30% QF-1 at 180° into equal amounts of the *exo*-methyl isomer (retention time 27 min 45 sec; nmr: δ 1.13, cyclopropyl CH_3) and the *endo*-methyl isomer (retention time 32 min 8 sec; nmr: δ 1.11, cyclopropyl CH_3), the latter corresponding to the stereochemistry as shown for **4**.

Condensation of bicyclic ketone **4** with dimethyl carbonate (sodium hydride, 90°, 1 hr) gave a quantitative yield of β-keto ester **5** [bp 115–120° (0.2 mm); ir: 1610, 1645 cm^{-1}; nmr: δ 1.03, cyclopropyl CH_3].

Reduction of β-keto ester **5** to an isomeric mixture of β-hydroxy esters was effected by sodium borohydride (2-propanol, 0°, 70% yield), and this mixture (ir: 3500, 1735 cm^{-1}) was dehydrated *via* the xanthate procedure (potassium in xylene followed by carbon disulfide and methyl iodide, then distillation) to the α,β-unsaturated bicyclo[4.1.0] ester **6** [bp 98–108° (0.2 mm); ir: 1695, 1635 cm^{-1}; nmr: δ 0.88, cyclopropyl CH_3; 7.12, cyclic vinyl H; uv: $\lambda_{max}^{C_2H_5OH}$ 252 nm[7]].

Oxidation of unsaturated ester **6** with selenium dioxide in ethanol[8] was highly selective and gave a 55% yield of aldehyde **7** (nmr: δ 0.89, cyclopropyl CH_3; 6.47, acyclic vinyl H; 7.12, cyclic vinyl H; 9.37, CHO). The chemical shift of the aldehyde proton clearly establishes **7** as exclusively the *trans* isomer.[9]

(7) This ultraviolet absorption is identical with what we find for a corresponding α,β-unsaturated ester conjugate with a cyclopropyl group (unpublished work, C. Tang).



(8) V. M. Sathe, K. K. Chakravarti, M. V. Kadival, and S. C. Bhattacharyya, *Indian J. Chem.*, 4, 393 (1966).

(9) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968). Simpler model compounds have similarly given exclusively *trans* aldehydes. In the case of aldehyde **7**, the crude aldehyde was isolated by filtration, evaporation of the filtrate, solution of the residue in ether, washing with bicarbonate, and evaporation of the ether. It was all-*trans* at this point; thus if any *cis* isomer was formed during the oxidation, it was isomerized.

Finally, reduction of aldehyde **7** ($LiAlH_4$–$AlCl_3$, 0°, 1 hr) followed by chromatography on alumina (activity 2.5, elution with benzene–chloroform) resulted in an 86% yield of *dl*-sirenin (**8**), identical spectrally (ir, nmr, mass spectra), chromatographically (tlc on SiO_2), and biologically[10] with natural *l*-sirenin. This synthesis also provides a facile approach to various analogs[11] of sirenin which are being prepared for biological evaluation.

(10) The *dl* material is indistinguishable from natural *l*-sirenin by bioassay. Since the assay is not sensitive to a factor of two, these results leave unanswered the question of the biological activity of the *d* isomer; however, they do indicate that the *d* isomer is not inhibitory (personal communication from L. Machlis).

(11) For example, details of the isomeric series in which the cyclopropyl methyl is *exo* will be presented in our full paper.

Jacob J. Plattner, Uday T. Bhalerao, Henry Rapoport
Department of Chemistry, University of California
Berkeley, California 94720
Received June 6, 1969

The Lactone Bond in Thiostrepton. Thiostreptonic Acid, a Degradation Product of the Antibiotic

Sir:

In the ir spectrum of the antibiotic thiostrepton,[1] a sharp carbonyl band of moderate intensity appears at 1750 cm^{-1}. The band is absent in the product obtained on treatment of the antibiotic with dilute sodium hydroxide. Since during this hydrolysis no cleavage of the molecule into two or more parts could be observed, saponification of a lactone bond was suspected. Evidence for this lactone bond was found when a solution of thiostrepton (5 g) was reduced in tetrahydrofuran (200 ml) and methanol (30 ml) with sodium borohydride (2.5 g) at room temperature. After acidification with hydrochloric acid and removal of the solvents, the residue was hydrolyzed with constant boiling hydrochloric acid (250 ml) under reflux in an atmosphere of nitrogen for 22 hr. The solution was evaporated to dryness, the residue was dissolved in water (130 ml), and the filtered solution was extracted with ether and ethyl acetate. The aqueous layer was neutralized and extracted with ether, and the extract was converted to the hydrochloride. Addition of acetone to an ethanolic solution of this salt yielded crystals (390 mg) of compound I; mp 188–190°, $[\alpha]^{24}D$ −95° (*c* 1.2, ethanol); $\lambda_{max}^{H_2O}$ 243 mμ (ϵ 37,000). *Anal.* Calcd for $C_{12}H_{13}NO_3 \cdot HCl$: C, 56.37; H, 5.52; N, 5.48; Cl, 13.9. Found: C, 56.34; H, 5.78, N, 5.62; Cl, 14.7. The uv absorption of the hydrolysate reveals that 1 mole of I was liberated from 1 mole of the antibiotic.

The absorption maximum of I is shifted to 256 mμ in acidic and 258 mμ in alkaline media. Oxidation of I with nitric acid followed by sublimation yielded a mixture of cinchomeronic acid, nicotinic acid, and isonicotinic acid, suggesting that I is related to the quinaldic acids obtained from thiostrepton.[2] The close sim-

(1) J. F. Pagano, M. J. Weinstein, H. A. Stout, and R. Donovick, *Antibiot. Ann.*, **1955–1956**, 554 (1956); J. Vandeputte and J. D. Dutcher, *ibid.*, **1955–1956**, 560 (1956); B. A. Steinberg, W. P. Jambor, and L. O. Suydam, *ibid.*, **1955–1956**, 562 (1956); M. Bodanszky, J. D. Dutcher, and N. J. Williams, *J. Antibiot.* **16**, 76 (1963).

(2) M. Bodanszky, J. Fried, J. T. Sheehan, N. J. Williams, J. Alicino, A. I. Cohen, B. T. Keeler, and C. A. Birkhimer, *J. Am. Chem. Soc.*, **86**, 2478 (1964); *cf.* also C. N. C. Drey, G. W. Kenner, H. D. Law, R. C. Sheppard, M. Bodanszky, J. Fried, and N. J. Williams, *ibid.*, **83**, 3906 (1961).