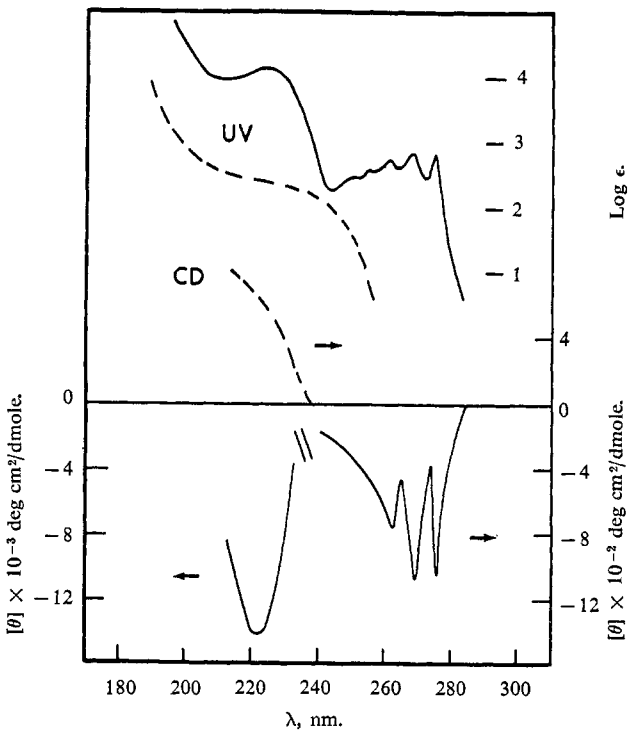

Figure 2. Ultraviolet and CD spectra of (−)-(1*R*,2*R*)-*trans*-1-methyl-2-phenylcyclopropane, (−)-**2** (solid curves), and (−)-(1*R*,2*R*)-*trans*-2-methylcyclopropanecarboxylic acid, (−)-**3** (dashed curves), in methanol solution. See ref 9 for explanation of the ordinate scales.

curve which is shifted in position from either of the component bands.[11]

Accordingly, the isotropic absorption and CD spectra of (−)-**2** were of interest since the carboxyl chromophore has been replaced by a methyl group. In this molecule only the phenyl ring has absorption bands above 210 nm. This point was confirmed by the preparation of *trans*-1-cyclohexyl-2-methylcyclopropane[12] from (−)-**2**. The ultraviolet spectrum of this molecule exhibited only end absorption down to 210 nm. The data for (−)-**2** in methanol solution are presented in Figure 2. It is seen that the 222-nm Cotton effect found in the CD spectrum of (−)-**1** is also present in (−)-**2**. The negative sign of this Cotton effect is characteristic of a phenyl ring attached to a carbon of the *R* configuration of a disubstituted cyclopropane derivative.

Assignment of the 222-nm peak in the isotropic absorption spectrum of (−)-**2** to the ^1L_a transition of the phenyl ring is substantiated by the absence of a corresponding peak in the spectrum of the cyclopropanecarboxylic acid (−)-**3** (Figure 2). Hence, in the CD spectrum of (−)-**2**, the negative Cotton effect at 222 nm is assigned to the optically active ^1L_a transition of the aromatic ring.

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The Isolation, Structural Elucidation, and Synthesis of Solapalmitine and Solapalmitenine, Two Novel Alkaloid Tumor Inhibitors from *Solanum tripartitum*[1,2]

Sir:

In a search for tumor inhibitors from plant sources, alcoholic extracts of *Solanum tripartitum* Dunal[3] showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[4] We report herein the isolation, structural elucidation, and synthesis of *solapalmitine* and *solapalmitenine*, two novel tumor-inhibitory alkaloids from *S. tripartitum*.

Fractionation of the ethanol extract, guided by assay against KB, revealed that the active principles were concentrated, successively, in the aqueous layer of a chloroform–water partition and in the 1-butanol extract from the basified aqueous solution. Further fractionation involving dilute hydrochloric acid–dichloromethane partition, liberation from the acid solution with ammonium hydroxide, extraction, and chromatography on alumina yielded *solapartine*,[5] an apparently homogeneous liquid alkaloid, λ_{max}[6] 6.01 (amide CO), 6.15 and 10.20 μ (-CH=CH-); nmr τ 3.05 (sextet, J = 15 and 7 cps, NCOCH=C*H*CH$_2$-), 3.82 (doublet, J = 15 cps, NCOC*H*=CHCH$_2$-), 4.63 (multiplet, vinyl H), 6.62 (C*H*$_2$NCOR), 7.78 (NC*H*$_3$), 8.73 (C*H*$_2$), and 9.12 (CC*H*$_3$). The mass spectrum[7] of solapartine exhibited peaks at *m/e* 451 ($C_{28}H_{57}N_3O$, by high-resolution mass spectrometry[7]) and 453 ($C_{28}H_{59}N_3O$), and several small peaks at *m/e* 473, 475, 477, 479, and 481. Other prominent ions occurred at *m/e* 438, 436, 395, 393, 100, 98, 84, and 58 [(CH$_3$)$_2$-

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(2) Supported by grants from the National Cancer Institute (CA-04500), the American Cancer Society (T-275), and the National Aeronautics and Space Administration (NsG 101), and a contract with the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health (PH-43-64-551).

(3) Whole plants were collected in Cochabamba, Bolivia, in April 1964. The authors acknowledge with thanks receipt of the dried plant material from Dr. Alejandro Asbun Lama. Voucher specimens are deposited in the University of Wisconsin Herbarium.

(4) Cytotoxicity and *in vivo* inhibitory activity were assayed under the auspices of the Cancer Chemotherapy National Service Center, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1952).

(5) Solapartine showed significant cytotoxicity (ED_{50}) against KB (human carcinoma of the nasopharynx) cell culture at 0.21 μg/ml. Solapartine, solapalmitine, and solapalmitenine showed significant inhibitory activity against Walker carcinosarcoma 256 in rats at 10 mg/kg.

(6) Infrared spectra were determined as thin films; nmr spectra were determined on solutions in deuteriochloroform.

(7) Both conventional and high-resolution mass spectra were determined on a CEC 21-110 mass spectrograph. Complete high-resolution mass spectra were recorded on a photoplate at a resolution of 25,000.

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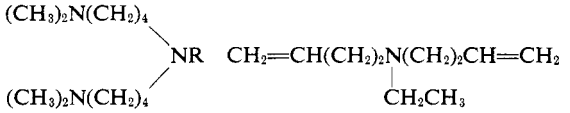
$N^+=CH_2$]. Hydrogenation (consumption, 1.3 molar equiv) furnished hydrosolapartine (λ_{max} 6.06 μ; nmr τ 6.66, 7.77, 8.73, and 9.12), with principal mass spectral peaks at *m/e* 481 ($C_{30}H_{63}N_3O$), 466 ($C_{29}H_{60}N_3O$), 453 ($C_{28}H_{59}N_3O$), and 438 ($C_{27}H_{56}N_3O$), 395, 100, 98, 84, and 58. Subsequent reduction with lithium aluminum hydride gave desoxyhydrosolapartine, nmr τ 7.77, 8.72, 9.12, and principal mass spectral peaks at *m/e* 467, 439, 353, 228, 100, 98, 84, and 58, indicative of the presence of amide and vinyl groupings in solapartine.

Acid hydrolysis of hydrosolapartine gave an amine, *solamine*, $C_{12}H_{29}N_3$ [*m/e* 251 (M^+), 129, 116, 115, 100, 98, 84, 71, and 58 (base peak); λ_{max} 2.94, 3.03, and 6.01 μ (NH); nmr τ 7.77 (NCH_3) and 8.50 (multiplet, CH_2)], and a fatty acid fraction. Mass spectrometry and glpc established that the acid fraction was a mixture of palmitic (80%) and stearic (20%) acids. These results accounted for the molecular ion peaks at *m/e* 453 (solamine + C_{16} acid) and 481 (solamine + C_{18} acid) in hydrosolapartine. Hydrolysis of solapartine gave solamine and a complex mixture of C_{16} and C_{18} acids.

Structural elucidation of solamine was accomplished *via* conversion of N-acetylsolamine (*m/e* 257 (M^+), 242 (M − 15), 213, 199, 186, 100, 98, 84, 58; λ_{max} 6.06 μ) successively to its dimethiodide and dimethohydroxide, respectively. Heating under reduced pressure gave a neutral methine (*m/e* 167 (M^+), 126, 84) and trimethylamine. Reduction of the methine with lithium aluminum hydride produced a desoxymethine [*m/e* 153 (M^+), 112 (base peak, M − 41), 84, 58, and 55], characterized as IV. Unambiguous confirmation was provided by hydrogenation of IV to its tetrahydro product [*m/e* 157 (M^+), 114, 86, and 58] and direct comparison (mass spectroscopy and mixture melting point of picrate, 85–87°, and oxalate, 92–97°) with synthetic ethyldi-*n*-butylamine. The conclusion that solamine possesses structure I was confirmed by direct comparison (infrared, nmr, mass spectra) with a sample prepared by hydrogenation of 4-dimethylaminobutyronitrile.[8]



I, R = H
II, R = $CO(CH_2)_{14}CH_3$
III, R = *trans*-$COCH{=}CH(CH_2)_{12}CH_3$
IV

A detailed examination of the highest mass peaks for solapartine and its reduced derivatives indicated that the unsaturation corresponding to the nmr signal at τ 4.63 was present in amides with C_{18}-acyl residues. The principal components in the solapartine mixture, however, were the α,β-unsaturated C_{16}-acyl amide (mol wt 451) and the corresponding saturated C_{16}-acyl amide (mol wt 453). Separation of these two major components from the solapartine mixture was accomplished by the procedure which follows. Treatment of solapartine with peroxyacetic acid and recovery of unchanged starting material by alumina chromatography gave a mixture which showed molecular ion peaks at *m/e* 451 and 453, but no peaks at *m/e* 473–479 or at τ 4.63 in the nmr spectrum. This material was treated with bromine to yield two compounds, separable by alumina chromatography. Solapalmitine, $C_{28}H_{59}N_3O$, *m/e* 453 (M^+), 438 (M − Me), 409, 395, 381, 367, 270, 227, 214, 199, 100, 98, 84, 71, 58 (base peak), showed λ_{max} 6.06 μ (amide CO); nmr τ 6.67 (4 H, CH_2NCOR), 7.78, 8.73, 9.13. The mass spectrum of solapalmitine was identical (apart from very minor signals attributable to residual solapalmitenine) with that of II prepared by acylation of solamine with palmitoyl chloride and triethylamine. The second product was a dibromo compound, $C_{28}H_{57}Br_2N_3O$, *m/e* 531, 529 (M − HBr), 451 (M − Br_2), 450 (M − HBr − Br); λ_{max} 6.01 μ (amide CO); nmr τ 4.80–5.30 (2 H, multiplet, $-CHBrCHBr-$), 6.60 (4 H, multiplet, CH_2NCOR), 7.53 (NCH_3), 7.67 (NCH_3), 8.72, and 9.12. Debromination with zinc in acetone gave solapalmitenine, $C_{28}H_{57}N_3O$, *m/e* 451 (M^+), 436 (M − Me), 407, 393, 379, 365, 268, 225, 214, 211, 197, 100, 98, 84, 71, and 58 (base peak); λ_{max} 6.02 (amide CO), 6.16, and 10.20 μ ($-CH{=}CH-$); nmr τ 3.12 (1 H, sextet, J = 15 and 7 cps, $NCOCH{=}CHCH_2-$), 3.89 (1 H, doublet, J = 15 cps, $NCOCH{=}CH-$), 6.68, 7.77, 8.74, and 9.14. The infrared, nmr, and mass spectra of solapalmitenine were identical with those of III prepared by acylation of solamine with *trans*-hexadec-2-enoyl chloride[9] in the presence of triethylamine.

Further synthetic investigations are in progress which are aimed at determination of the structural requirements for activity among these novel tumor inhibitors.

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Reduction of *gem*-Halofluorocyclopropanes with Tri-*n*-butyltin Hydride

Sir:

The geometry of the cyclopropyl radical has long been a subject of investigations, and a number of unsuccessful attempts at intercepting the nonplanar radical have been reported.[1-3] Here we wish to report on the stereospecificity observed in the reductions of some *gem*-halofluorocyclopropanes with tri-*n*-butyltin hydride, which strongly suggests a pyramidal structure for the fluorocyclopropyl radical.

The *gem*-halofluorocyclopropanes employed in the present work were 7-chloro-7-fluoronorcarane (Ia and Ib),[4] 6-chloro-6-fluorobicyclo[3.1.0]hexane (IIIa

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