was removed under reduced pressure. The reaction was again worked up under nitrogen. The residue was treated with water and 5% ammonium hydroxide (2 ml) and extracted five times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and evaporated. The brown gummy residue (346 mg) was separated by tlc on silica gel HF preparative plates developed in methanol. The dark bands with R_f *ca.* 0.5 (seen under ultraviolet light) were cut out and extracted with methanol (300 ml) at room temperature with stirring for 1 hr. The silica gel was collected by filtration and treated with warm methanol in the same way for an additional 1 hr. The combined filtrates were evaporated under reduced pressure to leave a light brown, homogeneous gum (0.20 g). Recrystallization from ether–petroleum ether afforded small needles (**16**): mp 89–92°; uv λ_{max}^{MeOH} 276 (ϵ 3830) and 282 mμ (ϵ 3750); nmr τ 6.12, 6.25 (6 H, 2 OCH_3), 4.92, 4.97 (4 H, 2 OCH_2Ph), 3.55 (1 H, C-8 **H**), and 3.88 and 3.08 (4 H, 2 d, J = 8 Hz, aromatic **H**).

Anal. Calcd for $C_{32}H_{33}NO_4$: C, 77.55; H, 6.71; N, 2.83. Found: C, 77.45; H, 6.65; N, 2.75.

***dl*-1-(4′-Benzyloxybenzyl)-5,7-dimethoxy-6-benzyloxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3d).**—A solution of **16** (0.16 g) in methanol (10 ml) was treated with formalin (5 ml). The mixture was stirred for 3.5 hr at room temperature and gradually became clear. The reaction mixture was cooled in ice and an excess of sodium borohydride (0.75 g) was added in portions while the temperature of the reaction mixture was kept below 40°. After the addition was complete, the solution was stirred for 1 hr at room temperature. The organic solvents were removed under reduced pressure and the residue was treated with water and 5% ammonium hydroxide and extracted five times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and evaporated. The residue crystallized upon standing overnight, and was recrystallized from ether–petroleum ether to yield **3d** (106 mg): mp 83–86°; nmr τ 7.49 (3 H, NCH_3), 6.19, 6.55 (6 H, 2 OCH_3), 4.97, 5.02 (4 H, 2 OCH_2Ph), 4.14 (1 H, C-8 **H**), 3.00 and 3.19 (4 H, 2 d, J = 9 Hz, benzylic Ph **H**), and 2.63 (10 H, benzyl ether Ph **H**).

The **oxalate** salt, mp 165–169°, showed λ_{max}^{MeOH} 277 (ϵ 3360) and 283 mμ (ϵ 3310).

Anal. Calcd for $C_{35}H_{37}NO_8$: C, 70.10; H, 6.22; N, 2.34. Found: C, 70.21; H, 6.21; N, 2.40.

***dl*-1-(4′-Hydroxybenzyl)-2-methyl-5,7-dimethoxy-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (3b).**—A solution of **3d** (95 mg) in absolute ethanol (9 ml) was hydrogenated over 30% palladium on charcoal catalyst (50 mg) for 13 hr. The catalyst was removed by filtration and washed with warm ethanol. The filtrate was evaporated to dryness under reduced pressure and the residual yellow green gum (61 mg) was crystallized from dichloromethane–petroleum ether (yield 37 mg). Recrystallization from the same solvents gave **3b** as pale yellow needles: mp 148–151°; uv λ_{max}^{EtOH} 281 mμ (ϵ 3200); nmr τ 7.43 (3 H, NCH_3), 6.15, 6.47 (6 H, 2 OCH_3), 5.18 (2 H, 2 OH), 4.23 (1 H, C-8 **H**), and 3.11 and 3.29 (4 H, 2 d, J = 8.5 Hz, benzylic Ph **H**).

Anal. Calcd for $C_{19}H_{23}NO_4 \cdot {}^1/_3CH_2Cl_2$: C, 66.78; H, 6.86; N, 4.03. Found: C, 67.00; H, 6.81; N, 4.00.

Registry No.—**1a**, 21899-44-5; **1a** picrate, 21927-69-5; **2b**, 21899-45-6; **3b**, 16687-92-6; **3c**, 16623-60-2; **3d**, 21899-48-9; **3d** oxalate, 21899-49-0; **7**, 21882-87-1; **11**, 21882-88-2; **12**, 21882-89-3; **13**, 21882-90-6; **13** oxalate, 21882-91-7; **14**, 21882-92-8; **16**, 21899-61-6.

Tumor Inhibitors. XLIII.[1a] Solapalmitine and Solapalmitenine, Two Novel Alkaloid Tumor Inhibitors from *Solanum tripartitum*

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An alcoholic extract of *Solanum tripartitum* Dunal was found to show significant inhibitory activity when tested *in vitro* against cells derived from human carcinoma of the nasopharynx (KB). Systematic fractionation led to the separation of solapartine, a liquid alkaloid mixture which possessed significant inhibitory activity against the Walker 256 carcinosarcoma in rats. Further fractionation of solapartine resulted in the separation of two growth-inhibitory compounds, solapalmitine and solapalmitenine. A combination of chemical degradations, mass spectrometry, and total synthesis led to assignment of structure **9** for solapalmitine and **11** for solapalmitenine.

In the course of our search for tumor inhibitors of plant origin, an alcoholic extract of *Solanum tripartitum* Dunal[3] (Solanaceae) was found to show significant cytotoxic activity when tested *in vitro* against cells derived from the human carcinoma of the nasopharynx (KB). We report herein the systematic fractionation, isolation, structural elucidation, and synthesis of the two major components, named solapalmitine and solapalmitenine. Solapartine, solapalmitine, and solapalmitenine showed significant inhibitory activity against the Walker 256 intramuscular carcinosarcoma in rats, at 10 mg/kg.[4,5]

The preliminary fractionation of the alcohol extract is summarized in Chart I. Fraction E was chromatographed on basic alumina and the fractions were analyzed by thin layer chromatography. This procedure led to the isolation of solapartine (F), a liquid alkaloid which appeared homogeneous when subjected to analysis by thin layer chromatography and countercurrent distribution. The cytotoxicity data for fractions obtained in a typical experiment are reported in Table I.

Solapartine was originally formulated as $C_{28}H_{57-59}N_3O$ on the basis of elemental analysis and mass spectrometry [*m/e* 451 ($C_{28}H_{57}N_3O$) and 453 ($C_{28}H_{59}N_3O$)]. The absence of signals in the NH region of the infrared

(1) (a) University of Wisconsin. Part XLII: S. M. Kupchan, T.-H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Org. Chem.*, **34**, 3884 (1969). The investigation at the University of Wisconsin was supported by grants from the National Cancer Institute (CA-04500) and the American Cancer Society (T-275), and a contract with Chemotherapy, National Cancer Institute, National Institutes of Health (PH 43-64-551); (b) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia, Charlottesville, Va. 22901.

(2) University of California. This is Part XXX in the series entitled "High Resolution Mass Spectrometry in Molecular Structure Studies." Part XXIX: S. M. Kupchan, Y. Aynehchi, J. M. Cassady, H. K. Schnoes, and A. L. Burlingame, *J. Org. Chem.*, **34**, 3858 (1969). The investigation at the University of California was supported in part by a grant from the National Aeronautics and Space Administration (NGL 05-003-003).

(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) A preliminary account of this work has been published: S. M. Kupchan, A. P. Davies, S. J. Barboutis, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **89**, 5718 (1967).

(5) Assays were performed under the auspices of the Cancer Chemotherapy National Service Center (CCNSC). The procedures were those described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

CHART I

FRACTIONATION OF TUMOR-INHIBITORY EXTRACT FROM *S. tripartitum* D.

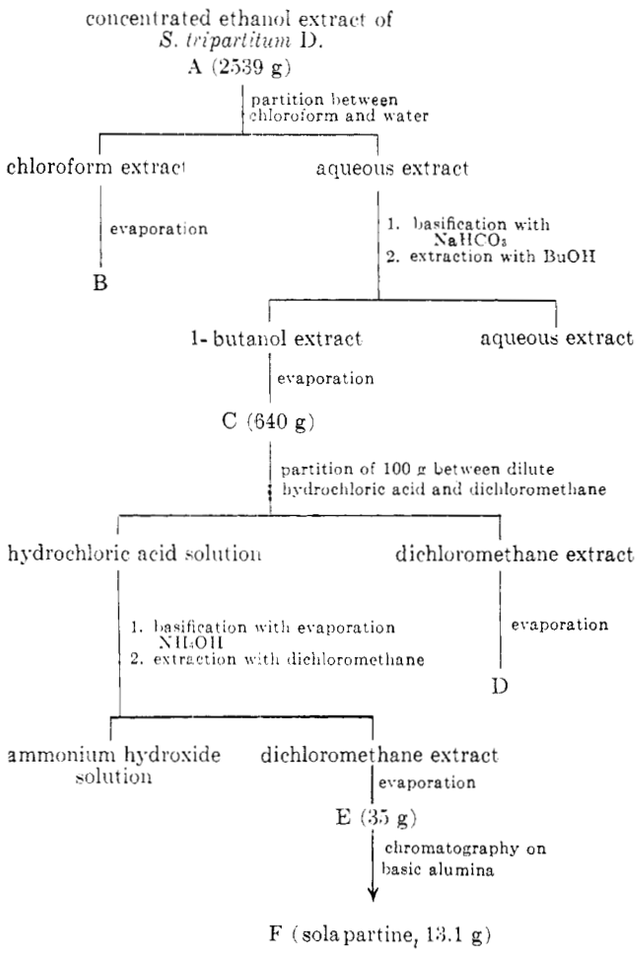


TABLE I

CYTOTOXICITY OF FRACTIONS FROM *S. tripartitum*[a]

Fraction	ED_{50}, μg/ml
A	8.1
B	27
C	2.7
D	100
E	0.64
F	0.21
Solapalmitine (9)	0.22
Solapalmitenine (11)	0.15

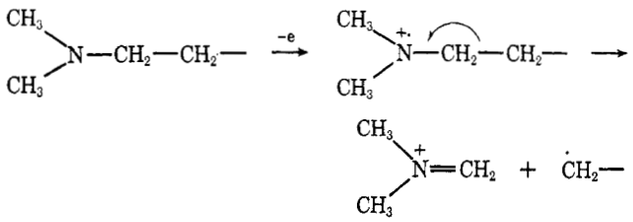
[a] Reference 5.

spectrum and a negative reaction with the carbylamine and Simon tests[6] suggested that primary and secondary amino functions were absent. The nmr spectrum exhibited a strong singlet at τ 7.78, indicative of an N-methyl group. This observation and a positive reaction in the citric acid–acetic anhydride test[7] implied the presence in solapartine of tertiary basic nitrogen atoms. Evidence for this view was forthcoming from mass spectrometry; the base peak at *m/e* 58 in the mass spectrum of solapartine was shown to have the composition C_3H_8N by high-resolution measurement. The fragment was probably formed as a result of cleavage α to a dimethylamino function

(6) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947.

(7) F. Feigl and V. Anger, "Spot Tests in Organic Analysis," 7th English ed, Elsevier Publishing Co., New York, N. Y., 1966.

SCHEME I

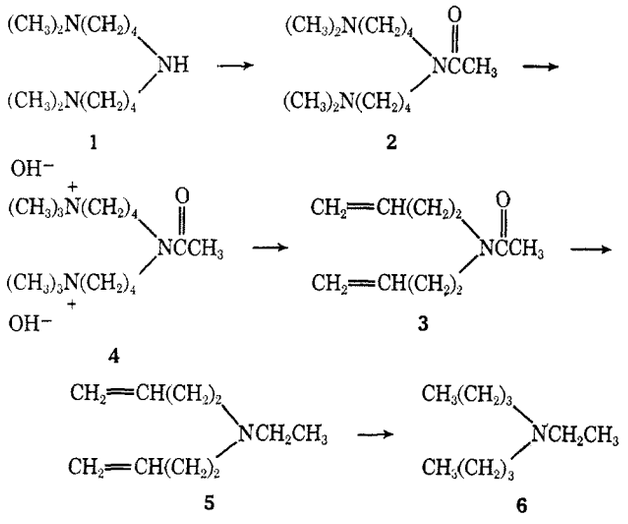


(Scheme I). Other prominent ions were observed at *m/e* 438, 436, 395, 393, 100, 98, and 84. The presence of an amide group (λ_{max} 6.01 μ) and unsaturation (λ_{max} 6.15 and 10.20 μ) was deduced from the infrared spectrum. In addition, the location of the carbonyl stretching absorption and the intensity of the olefinic bands were indicative of an α,β-unsaturated amide. Signals in the nmr spectrum at τ 3.05 (doublet of triplets, J = 15 and 7 Hz, NCOCH=C**H**CH_2–) and 3.82 (doublet, J = 15 Hz, NCOC**H**=$CHCH_2$–) substantiated this conclusion. The nmr spectrum also indicated the presence of additional unsaturation (τ 4.63, multiplet).

Hydrogenation of solapartine over a platinum catalyst gave "hydrosolapartine" [*m/e* 481 ($C_{30}H_{63}N_3O$), 466 ($C_{29}H_{60}N_2O$), 453 ($C_{28}H_{59}N_3O$), 438 ($C_{27}H_{56}N_3O$), 395, 100, 98, 84, and 58] which possessed an isolated tertiary amide group (λ_{max} 6.60 μ), but no unsaturation. Subsequent lithium aluminum hydride reduction afforded "deoxyhydrosolapartine" (*m/e* 467, 439, 353, 228, 100, 98, 84, 71, and 58), a completely saturated, oxygen-free material. Hydrolysis of "hydrosolapartine" with hydrochloric acid gave the amine solamine ($C_{12}H_{29}N_3$) and a fatty acid fraction. Mass spectrometry and gas–liquid partition chromatography (glpc) indicated that the acid fraction was a mixture of palmitic (80%) and stearic acids (20%). This conclusion was confirmed by conversion of the acids to the respective methyl esters; glpc separation yielded products which were characterized by mass spectrometry as methyl palmitate and methyl stearate. These results accounted for the molecular ion peaks at *m/e* 453 (solamine + C_{16} acid) and 481 (solamine + C_{18} acid) in "hydrosolapartine" and revealed that solapartine was not a homogeneous material. Hydrolysis of solapartine gave solamine and a complex mixture of C_{16} and C_{18} acids.

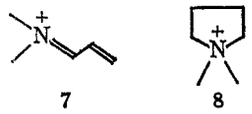
The molecular formula $C_{12}H_{29}N_3$, assigned to solamine (**1**) on the basis of elemental analysis and mass spectrometry [*m/e* 215 (M^+, $C_{12}H_{29}N_3$)], required that solamine be completely saturated and aliphatic. Signals in the NH region (λ_{max} 2.94, 3.03, and 6.01 μ) of the infrared spectrum were attributed to a secondary amine group, the remaining two nitrogen atoms presumably being tertiary. Probably the most useful reaction in structural studies of alkaloids is the Hofmann elimination, and this procedure was used to determine the structure of solamine. N-Acetylsolamine (**2**), prepared from solamine and acetic anhydride, was converted to the dimethiodide, $C_{14}H_{31}N_3O \cdot 2CH_3I$, upon treatment with methyl iodide. Conversion to the dimethohydroxide **4** was effected on a basic ion-exchange resin and the product was heated under reflux in 30% sodium hydroxide solution. The only product that could be isolated was trimethylamine,

indicating that solamine possessed a dimethylamino function; a peak at *m/e* 58 [$(CH_3)_2N^+{=}CH_2$] in the mass spectrum of solamine substantiated this conclusion. Distillation of the dimethohydroxide under reduced pressure gave a neutral methine (**3**, M^+ *m/e* 167) which was reduced with lithium aluminum hydride to a deoxymethine (**5**, M^+ *m/e* 153). The occurrence of the ion *m/e* 112 (M − 41) as the base peak in the mass spectrum of the deoxymethine and the fact that two nitrogen atoms had been eliminated during the Hofmann elimination supported the assignment of structure **3** for the methine. That the deoxymethine had the general structure C_4–N–C_4 was confirmed by hydrogenation. The tetrahydro product (M^+ *m/e* 157) exhibited a mass spectrum identical with that of ethyl di-*n*-butylamine (**6**), while the melting point of its oxalate and picrate salts were undepressed on admixing with the corresponding derivatives of ethyl di-*n*-butylamine. Unambiguous confirmation for the assignment of **1** as the structure of solamine was



obtained by comparing the infrared, nmr, and mass spectra with those of 4,4′-bis(dimethylamino)dibutylamine, prepared from 4-dimethylaminobutyronitrile by hydrogenation.[8]

The peaks at *m/e* 58, 71, 84, and 100 in the mass spectra of solapartine and its reduction products were also present in the spectrum of solamine (Figure 1) and could therefore be attributed to the amine rather than the amide function. The intensities of the ions of *m/e* 84 ($C_5H_{10}N$, **7**) and 100 ($C_6H_{15}N$, **8**) were rather unexpected and were probably due to interaction of the nitrogen functions; in particular the ion **8** was unusual, since it involved C–N bond cleavage.



7 **8**

A detailed examination of the highest mass peaks of solapartine (*m/e* 481, 479, 477, 475, and 473) and its reduced derivatives indicated that a high percentage of the unsaturation corresponding to the resonance at τ 4.63 in the nmr spectrum of solapartine was present in amides with C_{18}-acyl residues. The principal components, however, were the α,β-unsaturated C_{16}-acyl amide (M^+ *m/e* 451) and the corresponding saturated amide (M^+ *m/e* 453). In addition, the ion of *m/e* 451 could correspond to the presence of an unsaturated C_{16}-acyl amide other than the α,β-unsaturated compound. Separation of the two major components from the solapartine mixture was accomplished by the procedure which follows. Treatment of solapartine with peroxyacetic acid (Scheme II) and recovery of unchanged components by alumina chromatography gave a mixture which showed molecular ion peaks at *m/e* 451 and 453, but neither peaks at *m/e* 473–479 nor an nmr signal at τ 4.63. This material was treated with bromine to yield two compounds separable by chromatography on alumina. One compound, solapalmitine (**9**), was assigned the molecular formula $C_{28}H_{59}N_3O$ on the basis of elemental analysis and mass spectrometry [*m/e* 453 (M^+), 438 (M − CH_3), 409, 395, 381, 367, 276, 227, 214, 199, 100, 98, 84, 71, and 58 (base peak)]. A band in the infrared spectrum at λ_{max} 6.06 μ was attributable to an amide group, while a four-proton multiplet at τ 6.67 in the nmr spectrum corresponded to the protons deshielded by this group. N-Methyl, methylene, and C-methyl groups exhibited resonances at τ 7.78, 8.73, and 9.13, respectively. The mass spectrum of solapalmitine was identical (apart from minor signals attributable to the presence of residual solapalmitenine) with that of **9** prepared by acylating solamine with palmitoyl chloride in the presence of triethylamine. The second product from the bromination reaction was a dibromo compound (**10**), assigned the formula $C_{28}H_{57}Br_2N_3O$ by mass spectrometry [*m/e* 531 and 529 (M − HBr), 451 (M − Br_2), 450 (M − HBr − Br)]. An amide absorption at λ_{max} 6.01 μ in the infrared spectrum and the nmr spectal data (τ 4.80–5.30, 2 H, multiplet, NCOCHBrCHBrCH_2−) supported the presence of an α-bromo amide function.

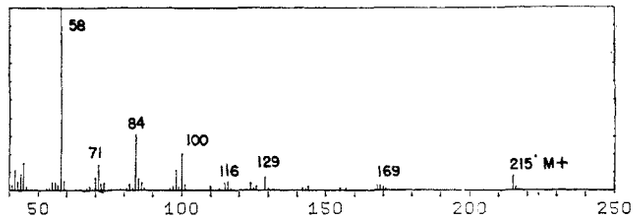
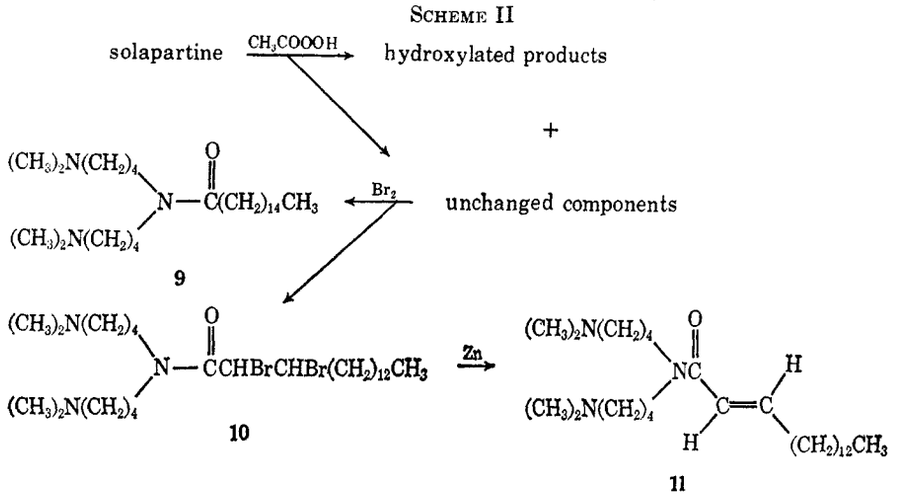


Figure 1.—Mass spectrum of solamine (**1**).

Debromination of the dibromo derivative **10** with zinc in refluxing acetone gave solapalmitenine (**11**), whose mass spectrum exhibited a molecular ion peak at *m/e* 451 ($C_{28}H_{57}N_3O$) and other prominent ions at 436 (M − CH_3), 407, 393, 379, 365, 268, 225, 214, 211, 197, 100, 98, 84, 71, and 58 (base peak). Bands at 6.16 and 10.20 μ in the infrared spectrum indicated the presence of a *trans*-disubstituted double bond. This function was shown to be part of an α,β-unsaturated amide group by the resonances at τ 3.12 (1 H, doublet of triplets, J = 15 and 7 Hz, NCOCH=CHCH_2−) and 3.89 (1 H, doublet, J = 15 Hz, NCOCH=CHCH_2−) in its nmr spectrum. Confirmation for the structure of solapalmitenine was obtained by comparing the infrared, nmr, and mass spectra with those of **11** prepared by the acylation of solamine with *trans*-hexadec-2-enoyl chloride in the presence of triethylamine.

(8) M. Freifelder, *J. Amer. Chem. Soc.*, **82**, 2386 (1960).

SCHEME II



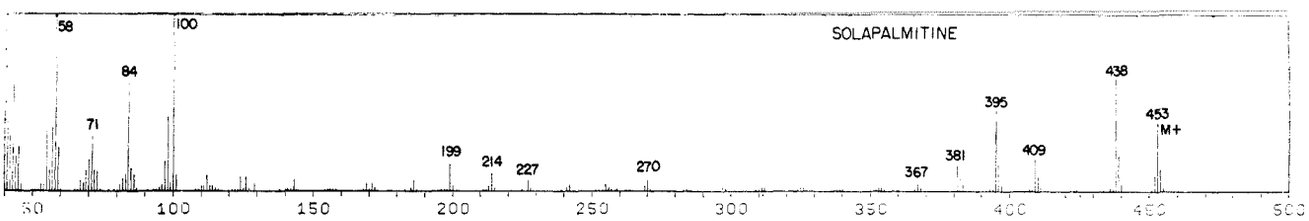


Figure 2.—Mass spectrum of solapalmitine (9).

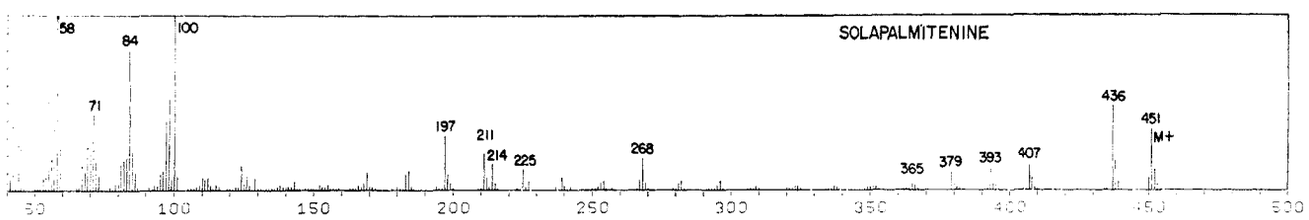


Figure 3.—Mass spectrum of solapalmitenine (11).

The ions at *m/e* 58, 71, 84, and 100 in the mass spectrum of solapalmitine (Figure 2) appear to have had the same origin as those obtained from solamine and appear to have resulted from cleavages involving the basic nitrogen atoms. An intense ion at *m/e* 438 (M − 15) was very unusual, since N-methyl groups do not normally give rise to M − 15 fragments. It was also noted that only the amides gave rise to this peak; the mass spectrum of solamine did not show this peak, but the spectra of the acylated solamines did. Ions at *m/e* 409, 395, 382, and 367 corresponded to M − 44, 58, 71, or 86, respectively, and presumably resulted from the elimination of a dimethylamine function together with zero, one, two, or three carbons, respectively. A β,γ cleavage of the amide chain is presumed to have led to the ion at *m/e* 270. Solapalmitenine exhibited a similar mass spectral fragmentation pattern (Figure 3), with ions corresponding to those of the C_{16}-acyl chain occurring at two mass units lower.

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

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected for stem exposure. Infrared spectra were determined on thin films with a Beckman Model IR-9 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. Mass spectra were determined on a CEC 21-110 mass spectrograph with the high-resolution mass spectra recorded on a photoplate at a resolution of 25,000. Two preliminary mass spectra were recorded on an AEI-MS9 instrument. Thin layer chromatography was conducted on Kieselgel-G (Merck) using the solvent systems benzene–ethyl acetate–diethylamine (7:2:1, TL1) and methanol–acetone–diethylamine (5:4:1, TL2). Dragendorff–Munier and iodoplatinate reagents were used as visualizing sprays, the plates being dried at 110° prior to spraying. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction with bp 60–68°. Evaporations were carried out on a rotary evaporator at water pump pressure and at a temperature of less than 40°.

Extraction and Fractionation of *S. tripartitum*.—Coarsely ground plants (20 kg) were twice extracted continuously with 95% ethanol for 5 and 20 hr, and the ethanol extract was concentrated to a dark gum (A, 2539 g). Fraction A was divided into four portions and each portion was partitioned between water (1.5 l.) and chloroform (1.5 l.). The layers were separated and the aqueous solution was washed with chloroforom (three 600-ml portions). Evaporation of the chloroform layer yielded a brown gum (B). The aqueous solution was basified with sodium bicarbonate (80 g) and partitioned with *n*-butanol (2 l.), the layers were separated, and the aqueous solution was washed with *n*-butanol (four 750-ml portions). Finally, the 1-butanol extract was washed with water (400 ml) and concentrated to give a brown gum (C, 640 g).

Fraction C (100 g) was dissolved in 1 *N* hydrochloric acid (500 ml), and the mixture was filtered and extracted with dichloromethane (three 500-ml portions), which gave fraction D upon evaporation. Basification of the aqueous layer with concen-

trated ammonia solution, followed by extraction with dichloromethane (five 500-ml portions), gave, upon evaporation of the dried ($MgSO_4$) extract, a brown oil (E, 35 g). Fraction E was dissolved in benzene and chromatographed on basic alumina (Woelm, activity III, 1300 g). Elution with benzene–ether (3:7) and ether gave a pale yellow oil (F, 13.1 g), which appeared as a single spot on tlc (TL1 and several other systems). The material was designated as solapartine: ir λ_{max} 6.01 (amide CO), 6.15, and 10.20 μ (-CH=CH-); nmr τ 3.05 (d of t, J = 15 and 7 Hz, NCOCH=CHCH$_2$-), 3.82 (d, J = 15 Hz, NCOCH=CHCH$_2$-), 4.63 (m, vinyl **H**), 6.62 (m, CH_2NCOR), 7.78 (NCH_3), 8.73 (CH_2) and 9.12 (t, CCH_3); mass spectrum m/e 451 ($C_{28}H_{57}N_3O$, by high-resolution mass spectrometry), 453 ($C_{28}H_{59}N_3O$), 438, 436, 395, 393, 100, 98, 84, and 58 [$(CH_3)_2N^+$-CH_2] and small peaks at m/e 473, 475, 477, 479, and 481.

Hydrogenation of Solapartine.—Solapartine (1 g) in 0.2 N hydrochloric acid (40 ml) was stirred in an atmosphere of hydrogen with prereduced platinum oxide (164 mg). After the consumption of hydrogen (67 ml, 1.3 mol equiv) ceased, after 3.5 hr, the catalyst was removed and the solution was basified with concentrated ammonia solution. Extraction with ether followed by drying ($MgSO_4$) and evaporation yielded hydrosolapartine (820 mg) as a yellow oil: ir λ_{max} 6.06 μ; nmr τ 6.66, 7.77, 8.73, and 9.12; mass spectrum 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.

Lithium Aluminum Hydride Reduction of Hydrosolapartine.—A solution of hydrosolapartine (400 mg) in anhydrous ether was treated with an excess of an ethereal solution of lithium aluminum hydride for 15 min at 25°. Water was added slowly to decompose the excess of reagent, the mixture was filtered, and the dry ($MgSO_4$) filtrate was evaporated to give a yellow oil, deoxyhydrosolapartine (350 mg): nmr τ 7.77, 8.72, and 9.12; mass spectrum m/e 467, 439, 353, 228, 100, 98, 84, 71, and 58.

Hydrolysis of Hydrosolapartine.—A solution of hydrosolapartine (2 g) in 8 N hydrochloric acid was heated at 110° in a sealed tube for 48 hr. The product was diluted with water and extracted with ether (four 25-ml portions), and the ether layer was washed with water (5 ml) and dried ($MgSO_4$). Evaporation of the ethereal solution gave a solid fatty acid fraction (910 mg), which was a mixture (glpc) of palmitic acid (80%) and stearic acid (20%). The aqueous layer was basified with concentrated ammonia solution and extracted with ether (four 25-ml portions) and the dry ($MgSO_4$) ether layer was evaporated to give an oil (73 mg), shown by thin layer chromatography (TL1 and TL2) to consist mainly of unchanged hydrosolapartine. Further basification of the aqueous solution with 5 N sodium hydroxide followed by extraction with dichloromethane (five 25-ml portions) gave, on drying ($MgSO_4$) and evaporation, an oil (658 mg). Thin layer chromatography (TL1 and TL2) revealed the product solamine (**1**) to be homogeneous: bp 80–90° (10 mm, bath temperature); ir λ_{max} 2.94, 3.03, and 6.01 μ (NH); nmr τ 7.77 (NCH_3) and 8.50 (m, CH_2).

Anal. Calcd for $C_{12}H_{29}N_3$: C, 66.91; H, 13.57; N, 19.51; mol wt, 215. Found: C, 66.76; H, 13.84; N, 19.36; mol wt, 215 (mass spectrum).

A comparison of the ir, nmr, and mass spectra with those of 4,4′-bis(dimethylamino)dibutylamine revealed them to be identical.

N-Acetylsolamine (2).—A mixture of solamine (111 mg) and acetic anhydride (1 ml) was heated under reflux at 100° in an atmosphere of nitrogen for 2 hr. The excess of reagent was removed by evaporation, and the residue was diluted with water and basified with concentrated ammonia solution. Extraction with ether gave mainly unchanged starting material (6 mg). Basification of the aqueous solution with 5 N sodium hydroxide, followed by extraction with dichloromethane (five 10-ml portions), gave, on evaporation of the dried ($MgSO_4$) organic layer, a gum (120 mg). Trituration with hexane gave N-acetylsolamine as a hexane-soluble oil (117 mg): ir λ_{max} 6.06 μ (amide CO); nmr τ 6.7 [4 H, m, (-CH_2)$_2$NCOCH$_3$], 7.75 (NCH_3), 7.92 (s, $NCOCH_3$), and 8.47 (m, CH_2); mass spectrum m/e 257 (M^+), 242 (M − 15), 213, 199, 186, 100, 98, 84, and 58.

N-Acetylsolamine Dimethiodide.—N-Acetylsolamine (117 mg) in ethanol (2 ml) was treated with methyl iodide (0.5 ml) and left in the absence of light in a nitrogen atmosphere for 2 hr. Evaporation gave N-acetylsolamine dimethiodide (223 mg), which was crystallized from ethanol–acetone–ether as colorless needles, mp 241–243° (softening at 230°).

Anal. Calcd for $C_{14}H_{31}N_3O \cdot 2CH_3I$: C, 34.81; H, 6.76; N, 7.62; I, 46.00. Found: C, 34.44; H, 6.88; N, 7.60; I, 45.60.

N-Acetylsolamine Dimethohydroxide (4).—A solution of N-acetylsolamine dimethiodide (409 mg) in water (50 ml, deionized, CO_2-free) was passed over a basic ion exchange resin (Dowex 1-X4, OH form), the alkaloidal iodide-free aqueous eluent being protected from atmospheric carbon dioxide by a soda lime trap. The eluent (80 ml) was evaporated and the residual dimethohydroxide was dried at 25° (0.05 mm).

Hofmann Elimination. A.—N-Acetylsolamine dimethohydroxide (**4**) in 30% sodium hydroxide solution was heated under reflux (140°) in a current of nitrogen for 4.5 hr. The nitrogen effluent was passed through a cooled solution of methyl iodide in benzene and a white solid settled out as the reaction progressed. A comparison of its melting point and ir spectrum with those of tetramethylammonium iodide revealed them to be identical. Extraction of the basic reaction solution with chloroform gave no material.

B.—Distillation of N-acetylsolamine dimethohydroxide (**4**, 400 mg) at 65–80° (bath temperature, 0.08 mm) gave a colorless distillate. The distillate in ether was dried ($MgSO_4$) and washed with 2 N hydrochloric acid (three 1-ml portions); evaporation of the dried ($MgSO_4$) ethereal solution afforded a neutral methine (46 mg) which appeared as a single spot on tlc (TL1). The methine (**3**) showed ir λ_{max} 3.25, 10.31, 10.93 (CH_2=CH), and 6.06 μ ($NCOCH_3$); nmr τ 3.7–5.2 (6 H, m, vinylic **H**), 5.8–7.1 [4 H, m, (-CH_2)$_2$NCOCH$_3$], and 7.91 (s, $NCOCH_3$); mass spectrum m/e 167 (M^+).

Lithium Aluminum Hydride Reduction of Methine 3.—A mixture of the methine (**3**, 63 mg) and an excess of lithium aluminum hydride in anhydrous ether was heated under reflux for 2 hr. Water was carefully added to the cooled reaction mixture to decompose the excess of reagent, the mixture was filtered, and the precipitate was washed repeatedly with hot dichloromethane. Evaporation of the dried ($MgSO_4$) organic extracts gave a residue rich in deoxymethine **5** as a colorless oil (46 mg): ir λ_{max} 3.25, 5.48 (overtone), 6.11, 10.08, and 10.93 μ (CH_2=CH); nmr τ 3.7–5.2 (5 H, m, vinylic **H**) and 6.3–7.0 (2 H, m); mass spectrum m/e 153 (M^+), 112 (base peak, M-41), 84, 58, and 55. The spectral data indicated that the product was not completely homogeneous.

Hydrogenation of Deoxymethine 5.—Deoxymethine **5** hydrochloride (40 mg) in ethanol (20 ml) was hydrogenated at atmospheric pressure and temperature using Adams catalyst (100 mg) until the uptake of hydrogen (10.4 ml, 2 mol equiv) ceased (0.5 hr). The catalyst was removed by filtration and the solvent was evaporated to give tetrahydrodeoxymethine hydrochloride. Liberation of the free base was effected by treatment of the hydrochloride in water with 5 N sodium hydroxide and extraction with ether (three 5-ml portions). A comparison of the mass spectrum of tetrahydrodeoxymethine with that of ethyl di-*n*-butylamine (**6**) revealed them to be identical.

Tetrahydrodeoxymethine hydrochloride in water was treated with a saturated aqueous solution of picric acid and the solution was left at room temperature for 1 hr. The yellow needles that formed were centrifuged off, washed with water, and dried [25° (0.05 mm)]. The melting point, 85–87°, was undepressed on admixture with ethyl di-*n*-butylamine picrate.

To an ethereal solution of tetrahydrodeoxymethine was added a saturated solution of oxalic acid dihydrate in ether to complete precipitation. The solid was washed repeatedly with ether and the residue was crystallized from ethyl acetate as rosettes, mp 92–95°, undepressed by admixture with ethyl di-*n*-butylamine oxalate.

Anal. Calcd for $C_{12}H_{25}NO_4$: C, 58.27; H, 10.19; N, 5.66. Found: C, 58.07; H, 10.08; N, 5.61.

Ethyl Di-*n*-butylamine.—Treatment of di-*n*-butylamine (2.1 g) with acetic anhydride (10 ml) by the method used for preparing N-acetylsolamine yielded N-acetyl di-*n*-butylamine as a clear oil (2.46 g). Reduction of N-acetyl di-*n*-butylamine (1.6 g) with lithium aluminum hydride in refluxing ether gave, after the usual work-up, a solution of ethyl di-*n*-butylamine. Treatment with oxalic acid and crystallization of the precipitate from ethyl acetate gave colorless rosettes, mp 94–98°.

Anal. Calcd for $C_{12}H_{25}NO_4$: C, 58.27; H, 10.19; N, 5.66. Found: C, 58.31; H, 10.08; N, 5.65.

Ethyl di-*n*-butylamine hydrochloride was treated with a saturated aqueous solution of picric acid and the solid obtained was crystallized from water to yield yellow needles, mp 85–87°.

Anal. Calcd for $C_{16}H_{26}N_4O_7$: C, 49.73; H, 6.78; N, 14.50. Found: C, 49.70; H, 6.81; N, 14.54.

Peroxyacetic Acid Treatment of Solapartine.—A solution of

solapartine (2.15 g) in peroxyacetic acid (30 ml, 40% w/v) was kept at 40° in the absence of light and in a nitrogen atmosphere for 6 hr. The excess of peroxyacetic acid was destroyed with platinum, the solution was filtered, and the filtrate was acidified strongly with concentrated hydrochloric acid (50 ml). Zinc dust (20 g) was added in portions with constant stirring over 2.5 hr and the solution was stirred for an additional 15 hr. The mixture was filtered and basified with concentrated ammonia solution, and the solution was adjusted to pH 10 by the addition of 5 *N* sodium hydroxide solution. Extraction with ether (five 40-ml portions) gave, after drying ($MgSO_4$) and evaporation of the solvent, a product (1.75 g) shown by tlc (TL1) to be essentially single-spot unchanged material. Chromatography of this product on basic alumina (Woelm, activity III, 50 g) gave, on elution with ether, single-spot material (TL1, TL2) (1.28 g), designated as product G: ir λ_{max} 6.02 (α,β-unsaturated amide CO), 6.06 (amide CO), 6.15, and 10.2 μ (-CH=CH-); nmr τ 3.1 (sextet, J = 15 and 7 Hz, NCOCH=C**H**CH_2-), 3.83 (d, J = 15 Hz, NCOC**H**=CHCH_2-), 6.66 [4 H, m, (-C**H**$_2$)$_2$NCOR], 7.78, 8.72, and 9.12; mass spectrum *m/e* 451 and 453 (no peaks at *m/e* 473–479).

Bromine Treatment of Product G.—A solution of product G (451 mg) and bromine (0.17 ml, 3 mol equiv) in dry, ethanol-free chloroform (5 ml) was left in the dark at 25° for 7 hr, and then heated at 50° under reflux for 13.5 hr. The orange-colored product was evaporated to dryness and the residue was dissolved in chloroform and diluted with a half-volume of water. A solution of sodium sulfite was added dropwise with shaking until the orange color was completely discharged. Basification with concentrated ammonia solution and extraction with chloroform gave, after drying ($MgSO_4$) and evaporation, a yellow oil (506 mg). The product was dissolved in benzene and chromatographed on neutral alumina (Woelm, activity II, 20 g). Elution with ether–benzene (6:4) gave two oils which were both homogeneous on tlc (TL1, TL2). Fraction 1 (**10**, 65 mg) showed ir λ_{max} 6.01 μ (α-bromo amide CO); nmr τ 4.8–5.3 (2 H, m, NCOC**H**Br**CH**Br-CH_2-), 6.6 [4 H, m, (-C**H**$_2$)$_2$NCOR], 7.53 (NC**H**$_3$), 7.67 (NC**H**$_3$), 8.72, and 9.12 (3 H, t, CC**H**$_3$); mass spectrum *m/e* 531 and 529 (M − HBr), 451 (M − Br_2), and 450 (M − HBr − Br, in accord with the formula $C_{28}H_{57}Br_2N_3O$). Fraction 2, solapalmitine (**9**, 65 mg), bp 150° (bath temperature, 0.05 mm), exhibited ir λ_{max} 6.06 μ (amide CO); nmr τ 6.67 [4 H m, (-C**H**$_2$)$_2$NCOR], 7.78, 8.73, and 9.13; mass spectrum *m/e* 453 (M^+, $C_{28}H_{59}N_3O$), 438 (M − CH_3), 409, 395, 381, 367, 270, 227, 214, 199, 100, 98, 84, 71, and 58 (base peak). The ir, nmr, and mass spectra were identical with those of synthetic solapalmitine.

Anal. Calcd for $C_{28}H_{59}N_3O$: C, 74.09; H, 13.10; N, 9.26. Found: C, 74.12; H, 13.12; N, 9.31.

Debromination of Dibromosolapalmitenine (10).—A mixture of dibromosolapalmitenine (**10**, 65 mg) and zinc dust (300 mg) in acetone was heated under reflux for 2 hr. The solution was filtered, the filtrate was evaporated, and the product was chromatographed on basic alumina (Woelm, activity III, 2 g). Elution with ether–benzene (1:1) gave solapalmitenine (**11**, 11 mg), homogeneous by tlc (TL1): ir λ_{max} 6.02 (α,β-unsaturated amide CO), 6.16 and 10.20 μ (-CH=CH-); nmr τ 3.12 (1 H, d of t, J = 15 and 7 Hz, NCOCH=C**H**CH_2-), 3.89 (1 H, d, J = 15 Hz, NCOC**H**=CHCH_2-) 6.68, 7.77, 8.74, and 9.14; mass spectrum *m/e* 451 (M^+, $C_{28}H_{57}N_3O$), 436 (M − CH_3), 407, 393, 379, 365, 268, 225, 214, 211, 197, 100, 98, 84, 71, and 58 (base peak). The ir, nmr, and mass spectra were identical with those of synthetic solapalmitenine (**11**).

***trans*-Hexadec-2-enoic acid** was prepared from myristaldehyde and malonic acid by the method of Shapiro, *et al.*,[9] mp 47–48° (lit.[9] mp 48–49°).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.66; H, 12.05.

***trans*-Hexadec-2-enoyl chloride** was prepared from *trans*-hexadec-2-enoic acid by the method of Shapiro, *et al.*,[9] bp 140–145° (0.05 mm) [lit.[9] bp 145–148° (0.05 mm)].

4,4′-Bis(dimethylamino)dibutylamine (1).—4-Dimethylaminobutyronitrile (5 g) and a rhodium-on-alumina catalyst (5%, 500 mg) in methanol (200 ml) were stirred in an atmosphere of hydrogen. Periodically (1-hr intervals), the hydrogenation apparatus was evacuated (to remove the ammonia formed) and then refilled with hydrogen; the consumption of hydrogen ceased after 15 hr (1.8 l., 1.8 mol equiv). The catalyst was removed by filtration and the solvent was evaporated to yield an oil (4.4 g), shown by tlc to be a mixture of two components. The product was chromatographed on basic alumina (Woelm, activity III, 170 g), and, upon elution with benzene–ether (1:1), pure 4,4′-bis(dimethylamino)dibutylamine (**1**, 2.6 g) was obtained: ir λ_{max} 2.94, 3.03, and 6.01 μ (NH); nmr τ 7.77 (NC**H**$_3$) and 8.50 (m, C**H**$_2$); mass spectrum *m/e* 215 (M^+), 129, 116, 115, 100, 98, 84, 71, and 58 (base peak).

Anal. Calcd for $C_{12}H_{29}N_3$: C, 66.91; H, 13.57; N, 19.51. Found: C, 66.92; H, 13.66; N, 19.44.

Solapalmitenine (11).—To a cooled (0°) ethereal solution of 4,4′-bis(dimethylamino)dibutylamine (845 mg, 1 mol equiv) and trimethylamine (4 g, 10 mol equiv) was added with stirring, over 0.5 hr, a solution of *trans*-hexadec-2-enoyl chloride (1.15 g, 1 mol equiv) in ether. The mixture was stirred for 1 hr at 25° and the precipitate was removed by filtration; evaporation of the solvent gave an oil (1.72 g). The product in benzene was applied to a basic alumina column (Woelm, activity III, 68 g) and subjected to gradient elution. Elution with ether–benzene (1:3) to ether–benzene (1:1) gave chromatographically pure solapalmitenine (TL1) (**11**, 781 mg): bp 153° (bath temperature, 0.08 mm); ir λ_{max} 6.02 (α,β-unsaturated amide CO), 6.16, and 10.20 μ (-CH=CH-); nmr τ 3.12 (1 H, d of t, J = 15 and 7 Hz, NCOCH=C**H**CH_2O), 3.89 (1 H, d, J = 15 Hz, NCOC**H**=C**H**CH_2-), 6.68 [4 H, (-C**H**$_2$)$_2$NCOR], 7.77 (NC**H**$_3$), 8.74 (C**H**$_2$), and 9.14 (3 H, t, CC**H**$_3$); mass spectrum *m/e* 451 (M^+), 436 (M − CH_3), 407, 393, 379, 365, 268, 225, 214, 197, 100, 98, 84, 71, and 58 (base peak).

Anal. Calcd for $C_{28}H_{57}N_3O$: C, 74.43; H, 12.72; N, 9.52. Found: C, 74.16; H, 12.79; N, 9.36.

Solapalmitine (9).—From palmitoyl chloride (2.2 g, 2 mol equiv), trimethylamine (1.5 g, 4 mol equiv), and 4,4′-bis(dimethylamino)dibutylamine (**1**, 850 mg, 1 mol equiv) by an analogous procedure was obtained pure solapalmitine (**9**): bp 150° (bath temperature, 0.05 mm); ir λ_{max} 6.06 μ (amide CO); nmr τ 6.67 [4 H, m, (-C**H**$_2$)$_2$NCOR], 7.78 (NC**H**$_3$), 8.73 (C**H**$_2$), and 9.13 (3 H, t, CC**H**$_3$); mass spectrum *m/e* 453 (M^+), 438 (M − CH_3), 409, 395, 381, 367, 270, 227, 214, 199, 100, 98, 84, 71, and 58 (base peak).

Anal. Calcd for $C_{28}H_{59}N_3O$: C, 74.09; H, 13.10; N, 9.26. Found: C, 74.24; H, 13.19; N, 9.20.

Registry No.—**1**, 17232-87-0; **2**, 21882-94-0; **3**, 21882-95-1; **4**, 21882-96-2; **5**, 21882-97-3; **9**, 17232-85-8; **10**, 17232-88-1; **11**, 17232-86-9; N-acetylsolamine dimethiodide, 21899-66-1; ethyl di-*n*-butylamine oxalate, 21899-67-2; ethyl di-*n*-butylamine picrate, 21899-68-3.

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