Figure 1. ORTEP drawing of dithiatopazine (I). Bond distances of 1,2-dithietane system (Å): C5a–C12a = 1.571 (6); C12a–S15 = 1.844 (4); S15–S16 = 2.084 (2); S16–C5a = 1.881 (4). Bond angles (deg): C5a–C12a–S15 = 97.4 (3); C12a–S15–S16 = 82.2 (1); S15–S16–C5a = 80.7 (1); S16–C5a–C12a = 96.8 (3). Dihedral angle (deg) between planes C12a–S 15–S16 and C5a–S16–S15 = 11.0 (4).

properties and was confirmed by an X-ray crystallographic analysis (vide infra). Thus, I exhibited the following spectra data: UV-vis (hexane) λ_{max} 213 (ϵ 4074), 426 nm (ϵ 102);[12] IR (CCl_4) ν_{max} 2940, 2840, 1450, 1275, 1160, 1094, 1052, 965 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (m, 1 H, C*H*O closest and syn to S–S bridge), 3.90 (m, 1 H, CH_2O, equatorial), 3.82 (m, 1 H, CH_2O, equatorial), 3.35–3.12 (m, 5 H, C*H*O, CH_2O), 3.00 (m, 1 H, CH_2), 2.54 (m, 1 H, CH_2), 2.34 (m, 1 H, CH_2), 2.15 (m, 1 H, CH_2), 2.03–1.40 (m, 12 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.02, 102.18, 82.69, 80.71, 77.69, 76.17, 67.82, 67.14, 39.04, 34.43, 31.25, 30.86, 29.40, 28.99, 25.80, 25.42; HRMS (CI) calcd for $C_{16}H_{24}O_4S_2$ + H 345.1194, found 345.1233 (M + H).

The chemistry of I is quite intriguing and has already led to a number of novel systems as indicated in Scheme I. Thus, irradiation of I (toluene, Hanovia UV lamp, 1 h) at ambient temperature resulted in extrusion of sulfur and the clean formation of olefin III (90%). Extrusion of sulfur from I and generation of III (95%) was also observed upon thermolysis of I (neat, or in xylene solution, 140 °C). Reduction of I with n-Bu_3SnH–AIBN also produced III in high yield (97%). Treatment of dithiatopazine (I) with PPh_3 (CH_2Cl_2, 25 °C) led smoothly to the fascinating compounds IV (46%) and V[10] (45%) by abstraction of one of the sulfur atoms.[13] The structure of the spiro ketal–thioketone IV was based on its spectral data, particularly its ^{13}C NMR spectrum [125 MHz, benzene-d_6, δ 262.56 (C=S) and 106.32 (O-C-O)], and is smooth conversion to spiro ketal–ketone VI by ozonolysis (85%) (structure VI) and was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Scheme I). The structure of the surprisingly stable episulfide V was assigned on the basis of its spectral data, particularly its ^{13}C NMR spectrum [125 MHz, $CDCl_3$, δ 93.28 (O–C–S) and 86.91 (O–C–S)], and its chemistry. Thus, V suffered loss of sulfur and transformation to olefin III by any one of the following procedures: (i) n-Bu_3SnH–AIBN catalyst, toluene, 110 °C, 93%; (ii) $(EtO)_3P$, toluene, 110 °C, 94%; (iii) xylene, 160 °C, 88%. Furthermore, episulfide V was transformed to the spiro ketal–ketone VI upon exposure to mCPBA–H_2O in CH_2Cl_2 (55%).

In order to confirm the 1,2-dithietane structure of compound I and to determine some of its molecular parameters, an X-ray crystallographic analysis was undertaken. Compound I crystallizes in the orthorhombic space group *Pbca* with a = 9.549 (3) Å, b = 12.024 (3) Å, c = 28.659 (7) Å, v = 3290.7 $Å^3$, and ρ(calcd) = 1.391 g cm^{-3} for z = 8. The structure was solved by direct methods and Fourier techniques and refined by full-matrix least squares to R_1 = 0.049 and R_2 = 0.057 using 1605 unique, observed ($I > 3\sigma$) reflections. Figure 1 shows an ORTEP representation of the molecule and includes a number of bond lengths and bond angles. Of special interest are the rather long S15–S16 [2.084 (2) Å] and C4a–C14a bond [1.571 (6) Å] as well as the remarkably small angles at sulfur [S16–S15–C12a = 82.2 (1)° and S15–S16–C5a = 80.7 (1)°]. The dihedral angle between planes S15–S16–C5a and S16–S15–C12a is notably small, 11.0 (4)°, and suggests considerable repulsive overlap of the lone pairs of electrons on the two sulfurs. Yet, the 1,2-dithietane moiety in this system is phenomenally stable.

Further exploration of the physical, chemical, and biological properties of dithiatopazine (I) and the design, synthesis, and study of other 1,2-dithietane systems are currently being pursued in these laboratories.[14]

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Supplementary Material Available: Spectroscopic and analytical data for compounds II–VI and tables of refined atomic positional and thermal parameters and bond distances and angles for compounds I and VI (7 pages). Ordering information is given on any current masthead page.

(11) TLC analysis of the melt revealed partial decomposition to olefin III, and presumably sulfur.

(12) Slow decomposition to olefin III, and presumably sulfur, was observed during the UV–vis measurements as indicated by decrease of absorbance with time. The reported ϵ values, therefore, must be minima.

(13) Scheme II shows possible mechanistic pathways for these interesting transformations. Thus initial attack by Ph_3P on I may in principle result in two isomeric species VII depending on the regiochemistry of the attack. These stereochemically distinct species may prefer different reaction pathways depending on stereoelectronic effects and may lead to IV (path a) or oxonium species VIII (path b). Oxonium species VIII may then collapse to episulfide V (path c) or rearrange to thioketone IV (path d). Calculations, molecular modeling, and further experiments are expected to provide further mechanistic information.

Scheme II

(14) All new comounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Peptide Synthesis Catalyzed by Lipases in Anhydrous Organic Solvents

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One of the bottlenecks of the rapidly growing field of peptide research is the shortage of general methodologies for facile preparation of a wide range of diverse peptide structures.[1] Enzymatic, namely, protease-catalyzed, synthesis is emerging as a method of choice for the production of short peptides due to its mild reaction conditions, absence of racemization, minimal protection and activation requirements, and inherent regio- and stereoselectivities.[2] However, peptide bond formation catalyzed

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Table I. Peptide Synthesis Catalyzed by Porcine Pancreatic Lipase in Organic Solvents[a]

substrates, amino acid fragment					
carboxy terminal	amino terminal	solvent[b]	product[c]	initial rate,[d] nmol/min (reaction half-time, days)	isolated yield of the product, %
N-Ac-L-Phe-OEtCl	L-Leu-NH_2	toluene	*N*-Ac-L-Phe-L-Leu-NH_2	12.8 (1.4)	83
N-Ac-L-Phe-OEt	L-Leu-NH_2	toluene	*N*-Ac-L-Phe-L-Leu-NH_2[e]	4.2 (4.2)	78
N-Ac-L-Tyr-OEtCl	L-Leu-NH_2	tetrahydrofuran	*N*-Ac-L-Tyr-L-Leu-NH_2[f]	7.5 (2.3)	76
N-Ac-L-Tyr-OEt	L-Leu-NH_2	tetrahydrofuran	*N*-Ac-L-Tyr-L-Leu-NH_2	4.2 (4.2)	67
N-Ac-L-Met-OEtCl	L-Leu-NH_2	toluene	*N*-Ac-L-Met-L-Leu-NH_2[g]	4.3 (4.0)	57
N-Ac-L-Phe-OEtCl	L-Ala-NH_2	toluene	*N*-Ac-L-Phe-L-Ala-NH_2[h]	11.9 (1.5)	82
N-Ac-L-Phe-OEtCl	L-Val-NH_2	toluene	*N*-Ac-L-Phe-L-Val-NH_2[i]	11.8 (1.5)	86
N-Ac-L-Phe-OEtCl	L-Phe-NH_2	toluene	*N*-Ac-(L-Phe)$_2$-NH_2[j]	4.9 (3.5)	48
N-Ac-L-Phe-OEtCl	D-Leu-NH_2	toluene	*N*-Ac-L-Phe-D-Leu-NH_2[k]	9.8 (2.0)	76
N-Ac-L-Phe-OEtCl	L-Ala-OMe	toluene	*N*-Ac-L-Phe-L-Ala-OMe[l]	3.8 (4.5)	*l*
N-Ac-L-Phe-OEtCl	D-Ala-OMe	toluene	*N*-Ac-L-Phe-D-Ala-OMe[l]	3.7 (4.5)	*l*
N-Ac-L-Phe-OEtCl	L-Leu-NHNaph[m]	toluene	*N*-Ac-L-Phe-L-Leu-NHNaph[n]	2.1 (8.3)	51

[a] In all experiments (except for the one depicted in the first line, which is described in the text), 2.5 mmol of both substrates was dissolved in either toluene or tetrahydrofuran, followed by addition of 5 g[8] of porcine pancreatic lipase. The suspension[8] was shaken at 45 °C and 250 rpm for the period of time after which no more formation of the alcohol product (Cl-EtOH or EtOH) was detected by gas chromatography, and then the dipeptide synthesized was isolated following the general outline given in the text. In no case was any peptide formation detected (by GC, HPLC, or TLC) in the absence of the enzyme or in the presence of lipase irreversibly preinactivated by diethyl *p*-nitrophenyl phosphate.[7] [b] Both solvents were of analytical grade and subjected to no additional purification prior to use apart from drying by storing in the presence of 3-Å molecular sieves (Linde). [c] All isolated crystalline products were 100% pure by HPLC and their compositions were confirmed by elemental analysis (see below). [d] The initial rates were measured by gas chromatography following formation of the alcohol. Since the alcohol can also be produced via lipase-catalyzed hydrolysis of the esters (with a small amount of water present in the system), the latter reaction was independently studied following formation of *N*-Ac-L-amino acid by HPLC. In all cases, the rates of enzymatic hydrolysis were found to be less than 5% of those of the aminolysis reaction. [e] Mp 252–254 °C, $[\alpha]^{25}_D$ −19.2° (*c* 0.33, MeOH) (lit.[9] 253–258 °C and −19.8 ± 4.8°, respectively). Anal. Found: C, 63.76; H, 7.92; N, 13.06. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.95; H, 7.84; N, 13.17. [f] Mp 245–247 °C (lit.[9] 249–250 °C), $[\alpha]^{25}_D$ −7.7° (*c* 0.33, MeOH). Anal. Found: C, 60.91; H, 7.62; N, 12.55. Calcd for $C_{17}H_{25}O_4N_3$: C, 60.71; H, 7.44; N, 12.50. [g] Mp 221–223 °C, $[\alpha]^{25}_D$ −36.7° (*c* 0.24, MeOH). Anal. Found: C, 51.66; H, 8.42; N, 13.66; S, 10.72. Calcd for $C_{13}H_{25}N_3O_3S$: C, 51.49; H, 8.25; N, 13.86; S, 10.56. [h] Mp 232–234 °C (lit.[9] 242–243 °C), $[\alpha]^{25}_D$ + 5.4° (*c* 0.33, MeOH). Anal. Found: C, 60.36; H, 6.87; N, 14.97. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.65; H, 6.86; N, 15.16. [i] Mp 274–276 °C (lit.[9] 284 °C), $[\alpha]^{25}_D$ −8.6° (*c* 0.17, MeOH). Anal. Found: C, 62.97; H, 7.65; N, 13.75. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.95; H, 7.54; N, 13.77. [j] Mp 259–261 °C (lit.[9] 266–268 °C), $[\alpha]^{25}_D$ −13.0° (*c* 0.23, MeOH). Anal. Found: C, 67.93; H, 6.61; N, 11.91. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.99; H, 6.52; N, 11.90. [k] Mp 213–215 °C, $[\alpha]^{25}_D$ + 74.4° (*c* 0.10, MeOH) (lit.[9] 215–218 °C and +82.7°, respectively). Anal. Found: C, 63.79; H, 7.98; N, 13.03. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.95; H, 7.84; N, 13.17. [l] Enzymatic peptide synthesis was carried out at the analytical scale only, due to difficulties in preparatively converting the commercial Ala–OMe·HCl into a free base. [m] NHNaph denotes β-naphthylamide. [n] Mp 256–258 °C, $[\alpha]^{25}_D$ − 35.9° (*c* 0.20, MeOH). Anal. Found: C, 72.69; H, 7.02; N, 9.34. Calcd for $C_{27}H_{31}N_3O_3$: C, 72.81; H, 6.97; N, 9.44.

by proteolytic enzymes suffers from some shortcomings including an unfavorable thermodynamic equilibrium, a narrow substrate specificity, and an undesirable proteolysis of the growing polypeptide chain.[2a,e] Although the first drawback has been alleviated by using proteases in biphasic aqueous organic mixtures,[3] reverse micelles,[4] and nonaqueous media,[5] the remaining problems, which stem from the physiological function of proteolytic enzymes, still persist.[2e]

Recently, we have found that lipases (and other groups of enzymes[6]) can act as catalysts in anhydrous organic solvents and under these conditions catalyze processes impossible in water, e.g., the reaction between carboxylic esters and aliphatic amines.[7] This aminolysis, if general, points to the possibility of using *nonproteases* for the formation of peptide bonds which seems appealing, since lipases may not have the same limitations as proteases.

In the present work we demonstrate, for the first time, the application of lipases for preparative synthesis of peptides. In a representative experiment, 18.5 mmol of *N*-acetyl-L-phenylalanine 2-chloroethyl ester and 16.7 mmol of L-leucinamide were dissolved in 330 mL of dry toluene. Then 33 g of porcine pancreatic lipase[8] was added, and the suspension[8] was shaken at 45 °C and 250 rpm for 3 days. The precipitated product along with the enzyme was decanted and washed with toluene, and the product was extracted with warm ethanol. Following solvent evaporation, washings with 5% aqueous $NaHCO_3$ and water, and recrystallization from methanol, 13.8 mmol (4.4 g, 83% isolated yield) of *N*-acetyl-L-phenylalanyl-L-leucinamide was obtained. The structure of the dipeptide was confirmed by elemental analysis, NMR, and mass spectrometry; the dipeptide's mp of 252–254 °C and $[\alpha]^{25}_D$ of −19.2° (*c* 0.33, MeOH) were in agreement with the literature data,[9] and it was pure by TLC and HPLC.

The scope of the proposed synthetic methodology was examined by varying the nature of the side chain at both the carboxy and amino terminal amino acids, the protecting and activating groups, and the solvent. The results obtained, presented in Table I, indicate that porcine pancreatic lipase is a quite flexible catalyst of peptide bond formation in organic solvents. Various amino acid residues can be incorporated into either side of the dipeptide. An activated ester (2-chloroethyl) in the C-terminal fragment is more reactive than a nonactivated one (ethyl).[10] A number of both amide and ester derivatives of the N-terminal amino acid can be used. Significantly, L and D isomers serve equally well as nucleophiles. Millimole quantities of a variety of dipeptides were readily prepared in either toluene or tetrahydrofuran (Table I); the enzyme also catalyzed peptide synthesis in other dry organic solvents including xylenes, acetonitrile, *tert*-butyl alcohol, isopropyl and butyl ethers, styrene, and cyclohexanone. Porcine pancreatic lipase was not a unique nonprotease to form a peptide bond: e.g., mold lipase[11] catalyzes the process depicted in the first line of Table

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(8) The enzyme (EC 3.1.1.3) was purchased from Sigma as a powder with a specific activity of 11 units/mg solid. The seemingly large amount of lipase used in this work is misleading, for the commercial preparation employed is crude (less than 1% purity) in order to keep the cost low (5 cents/g). Enzymes are insoluble in toluene and nearly all other organic solvents. When porcine pancreatic lipase was assayed after the preparative synthesis described in the text, its specific activity was nearly 100% of the original level; hence the enzyme can be reused.

(9) Mp 253–258 °C and $[\alpha]^{25}_D$ −19.8 ± 4.8° (*c* 0.13, MeOH) as reported: Morihara, K.; Oka, T. *Biochem. J.* **1977**, *163*, 531–542.

(10) No appreciable reaction was detected between the free acid *N*-Ac-L-Phe and L-Leu-NH_2.

I with a comparable efficiency under the same conditions.

This study adds a new class of enzymes to proteases[12] as catalysts used in peptide synthesis.[2] The use of organic solvents instead of water as the reaction medium solves the equilibrium and solubility problems, and lipases, in contrast to proteolytic enzymes, have a broad specificity and do not catalyze secondary hydrolysis[2e] of peptides. We are currently applying the lipase strategy[13] to the synthesis of biologically active peptides.

(11) Lipase from *Mucor* sp. was obtained from Amano International Enzyme Co. as a powder with a specific activity of 10 units/mg solid. It was dried under vacuum prior to use to lower the enzymatic ester hydrolysis.

(12) Catalysis of peptide bond formation cannot be attributed to a possible presence of proteases in the lipase samples, for both porcine pancreatic and *Mucor* lipases (100 mg/mL) failed to hydrolyze *N*-Ac-L-Phe-L-Leu-NH_2 (1 mM) in water (pH 7.8, 5% dimethylformamide) (3-day incubation at 45 °C, assay by HPLC).

(13) Lipases as catalysts in organic solvents appear an evermore useful synthetic methodology which has been successful in regioselective acylations of glycols (Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotechnol.* **1985**, *11*, 401–407) and sugars (Therisod, M.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 5638–5640) and for stereoselective conversions of alcohols and acids (Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072–7076. Langrand, G.; Baratti, J.; Buono, G.; Triantaphylides, C. *Tetrahedron Lett.* **1986**, *27*, 29–32. Margolin, A. L.; Crenne, J.-Y.; Klibanov, A. M. *Tetrahedron Lett.* **1987**, *28*, 1607–1610.

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A New Type of Pericyclic Chemiluminescence

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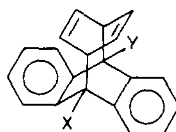
Chemiluminescence and its related bioluminescence involve the generation of light-emitting excited-state molecules by chemical means. The phenomenon and mechanism of chemiluminescence have been subjects of interest to many scientists.[1] In connection with our interest in the chemistry of energy-rich dimers of aromatic hydrocarbons, we have synthesized a number of para,para′ dimers of benzene and substituted anthracenes bearing substituents at the bridgehead positions (**1b–d**).[2] Thermolyses of some of these compounds are chemiluminescent.



1a, X=Y=H
b, X=COOH, Y=H
c, X=Y=COOH
d, X=CH_3, Y=H
e, X=CN, Y=H

The formation of excited-state molecules in a chemical reaction is governed by both an energy factor and a probability factor. In the former factor, the energy available from the chemical reaction, the sum of free energy and free energy of activation of the reaction,

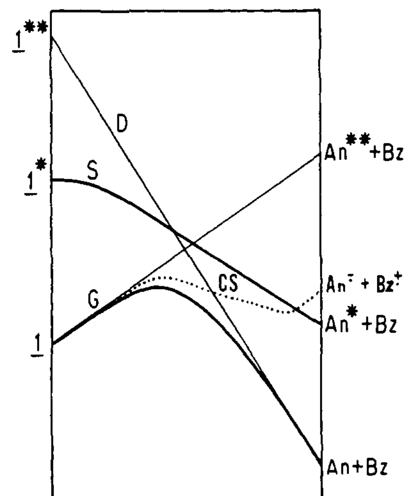
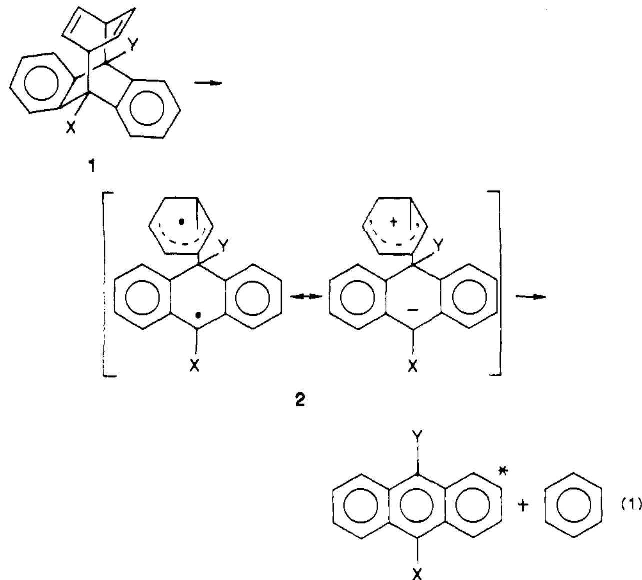


Figure 1. Schematic diagram of the reaction coordinate of thermolysis of **1**.

must exceed the excitation energy of the luminescent product. In the latter factor, there must be a pathway for the product in gaining access to the excited state. We had synthesized the parent dimer **1a** and found that its thermolysis to benzene and anthracene was not chemiluminescent, in spite of the fact that the available energy exceeds the excited energy of anthracene.[2] Since the thermolysis of **1** is symmetry-forbidden as a concerted process, the reaction may proceed via a biradical or biradical-like intermediate **2**. If **1** contains an appropriate substituent at the bridgehead position, such as an electronegative substituent W at the 9-position of the anthryl moiety, the substituent may introduce a polar character into **2** (eq 1). The partial anionic character



in the anthryl moiety may proceed further along a reaction pathway which may ultimately lead to the formation of a radical ion pair of benzene radical cation and anthracene radical anion. This pathway may become endoergic as these ions separate to overcome the electrostatic attraction between them (dotted line CS, or charge-transfer surface, in Figure 1). In the meantime, excited anthracene can be formed efficiently from excited **1** in a symmetry-allowed and highly exoergic process, line S, or singlet excited surface.[2] Conceivably, the crossing of these two surfaces may lead to the formation of excited anthracene from the initial polar dissociation of **1**; i.e., introduction of an electron-withdrawing group at the bridgehead of **1** may enhance the probability of chemiluminescence in the thermolysis of these compounds.

Our initial goal was to synthesize the cyano derivative **1e**, but our attempts in its synthesis have not been successful. However,

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