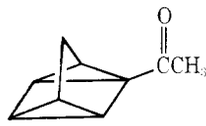
bridge of **9** and the nitrogen bridge of **11**[15] function primarily as slightly electronegative substituents. In connection with substituent effects, the oxidation curve of **19** was of interest. Two half-wave potentials were observed. The lower wave



19

showed $E_{1/2}$ at 1.00 V while the second appeared at $E_{1/2}$ = 1.87 V. Two different oxidative processes are indicated. It is interesting to speculate as to whether these two waves reflect the oxidation of the two different cyclopropyl moieties.[16]

In summary, we have provided a quantitative measure of the ease of oxidation of highly strained polycyclic compounds. The effect of substituents has been evaluated. We are continuing to study both the mechanistic detail and products of these facile oxidations.

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References and Notes

(1) K. B. Wiberg and R. P. Cuila, *J. Am. Chem. Soc.*, **81**, 5261 (1959); W. R. Moore, H. R. Ward, and R. F. Merritt, *ibid.*, **83**, 2019 (1961); K. B. Wiberg, *Rec. Chem. Prog.*, **26**, 143 (1965); and G. W. Klumpp and J. J. Vrielink, *Tetrahedron Lett.*, 539 (1972) provide a few of the many examples of catalytic reduction. For an example of a chemical reduction see W. R. Moore, S. S. Hall, and C. Largman, *ibid.*, 4353 (1969).
(2) A. F. Vellturo and G. W. Griffin, *J. Org. Chem.*, **31**, 2241 (1966); M. Horner and S. Hünig, *J. Am. Chem. Soc.*, **99**, 6120, 6122 (1977).
(3) G. F. Koser and J. N. Faircloth, *J. Org. Chem.*, **41**, 583 (1976).
(4) A. J. Baggaley, R. Brettle, and J. R. Sulton, *J. Chem. Soc., Perkin Trans. 1*, 1055 (1975).
(5) Simple cyclopropane derivatives have been oxidized in a few instances. See T. Shono and Y. Matsumura, *J. Org. Chem.*, **35**, 4157 (1970); T. Shono, Y. Matsumura and Y. Nakagawa, *ibid.*, **36**, 1771 (1971); T. Shono and Y. Matsumura, *Bull. Chem. Soc. Jpn.*, **48**, 2861 (1975); M. Klehr and H. J. Schafer, *Angew. Chem., Int. Ed. Engl.*, **14**, 247 (1975). See also K. B. Wiberg and G. T. Burgmaier, *J. Am. Chem. Soc.*, **94**, 7396 (1972).
(6) T. Shono, A. Ikeda, J. Hayashi, and S. Hakozaki, *J. Am. Chem. Soc.*, **97**, 4261 (1975).
(7) T. Shono, Y. Matsumura, and Y. Nakagawa, *J. Am. Chem. Soc.*, **96**, 3532 (1974).
(8) Simple alkyl-substituted cyclopropanes show half-wave oxidation potentials vs. SCE of 2.0–2.5 V.[5] Unstrained saturated hydrocarbons exhibit half-wave oxidation potentials in excess of 2.5 V.
(9) S. J. Cristol and R. L. Snell, *J. Am. Chem. Soc.*, **80**, 1950 (1958); H. Hogeveen and H. C. Volger, *ibid.*, **89**, 2486 (1967).
(10) P. G. Gassman and T. H. Johnson, *J. Am. Chem. Soc.*, **98**, 861 (1976).
(11) P. v. R. Schleyer, *J. Am. Chem. Soc.*, **80**, 1700 (1958).
(12) P. G. Gassman, T. J. Atkins, and J. T. Lumb, *J. Am. Chem. Soc.*, **94**, 7757 (1972).
(13) A detailed study of the relationship of oxidizability to ionization potential of strained polycyclic hydrocarbons has confirmed this point: P. G. Gassman and R. Yamaguchi, submitted for publication.
(14) L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.*, **92**, 6366 (1970).
(15) The second wave which was observed for both **11** and **12** was attributed to the aryl sulfonamide moiety. Little change occurred in the oxidation in changing from **11** to **12**.
(16) This would require that the two different cyclopropyl rings of **19** have different half-wave oxidation potentials. This should be the case, since two different cation radicals would be generated from the oxidation of the two different rings. Obviously, the two waves which were observed reflect the existence of two close lying high-energy occupied molecular orbitals. The question which requires answering is whether these two high-energy orbitals are associated with the two different cyclopropyl moieties, respectively. We are currently carrying out studies designed to determine the answer to this question.

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A New Synthesis of Amides and Macrocyclic Lactams

Summary: New and general routes to amides and lactams of up to 32 atoms in circumference are described based on boron-containing active esters.

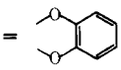
Sir: We wish to report that carboxylic acids react rapidly and smoothly with catecholborane to afford 2-acyloxy-1,3,2-benzodioxaborolanes (**1c**). As one aspect of a general program to prepare clinically interesting maytansinoids and ansamycins,[1] we herein document the use of this mild reaction as the essential carboxyl-activation step for the synthesis of amides and macrocyclic lactams.[2]

Simple acyloxyboranes such as **1a** and **1b** react with amines to furnish amides in moderate yield, but uniformly low conversion.[3] Mechanistic studies by Pelter in 1970 revealed that the leaving groups **2a,b** ejected in this process fragment to liberate 1 equiv of ROH which competitively destroys the active intermediate by attack at the boron atom of **1**.[4]

$$RCO_2BR_1R_2 + R_3NH_2 \longrightarrow RCONHR_3 + HOBR_1R_2$$

1a, R_1, R_2 = alkoxy — **2**

b, R_1, R_2 = 

c, R_1, R_2 = 

We reasoned that acyloxyborane **1c** might circumvent these difficulties, since its leaving group, 2-hydroxy-1,3,2-benzodioxaborolane, ought to resist disproportionation. Moreover, any breakdown of **2c** would form a relatively nonnucleophilic phenol still attached to boron. We further expected the aromatic ring's electron-withdrawing character to enhance the reactivity of the active ester. Modulation of this effect through substitution of polar groups on the arene would enable a high degree of control in designing preparatively useful reagents.

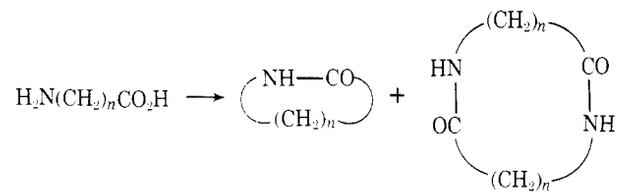
Catecholborane (**3**)[5] is available from Aldrich Chemical Company[6] and converts carboxylic acids (THF, room temperature, 30–60 min) to the corresponding acyloxybenzodioxaborolanes (IR λ_{max} 1740 cm^{-1}) free of anhydride byproduct. At ambient temperatures catecholborane is ideally suited for the C-activation of complex substrates, since it is inert toward alkyl and aryl halides, alkenes, alkynes, amides, anhydrides, disulfides, esters, nitriles, nitro compounds, sulfides, and sulfones.[7] Subsequent addition of an amine to **1c** rapidly forms the amide in greatly improved yield (Table I). Even optically active acids such as *N*-benzoyl-L-leucine can be coupled with no measurable loss (<2%) of enantiomeric

Table I. Formation of Amides from Nonanoic Acid Using Catecholborane

amine	product[a]	% yield[b]
benzylamine	$C_8H_{17}CONHCH_2Ph$	92
pyrrolidine	$C_8H_{17}CON$⟨⟩	85
butylamine	$C_8H_{17}CONHCH_2CH_2CH_2CH_3$	84
morpholine	$C_8H_{17}CON$⟨O⟩	74
benzylmethylamine	$C_8H_{17}CON(CH_3)CH_2Ph$	74
glycine ethyl ester	$C_8H_{17}CONHCH_2CO_2CH_2CH_3$	63

[a] Obtained by inverse addition of the acyloxyborane to the amine (2 equiv) in THF at −78 °C. [b] Product identity was established by comparison with authentic samples. In some cases filtration through a short column of silica gel was necessary to obtain pure product.

Table II. Formation of Lactams from ω-Amino Acids Using Catecholborane



ω-amino acid: n =	lactam: size (% yield)	dimer: size (% yield)[a]	dimer properties
3	5 (>95)		
5	7 (85)		
6	8 (6)	16 (18)	mp 246–249 °C,[b] *m/e* 255 (M^+), 128 (base)
7		18 (10)	mp 273–275 °C,[b] *m/e* 282 (M^+), 142 (base)
11	13 (6)	26 (25)	mp 203–206 °C, *m/e* 394 (M^+, base)
12	14 (9)	28 (22)	mp 152–154 °C, *m/e* 422 (M^+, base)
14	16 (13)	32 (17)	mp 168–171 °C, *m/e* 478 (M^+, base)

[a] All monomers were identified by comparison with authentic samples. Dimers were fully characterized by IR, NMR, and mass spectrometry. [b] This melting point was identical with that of a known sample of dimer (ref 12).

purity.[8] Both 3-methoxy- and 4-nitrocatechol also form the derived boranes in standard fashion and a preliminary survey of their reactivity suggests that the former comprises a somewhat superior coupling reagent.

Our interest in closing rings at the site of an amide bond requires a reagent that is capable of carboxyl activation without interference by a basic amino group. The direct addition of catecholborane to a homogeneous 1:1 mixture of nonanoic acid and benzylamine in THF simulates lactamization conditions and produces the desired nonanoic acid *N*-benzylamide in 85% yield. These "in situ" couplings are general and small amounts of pyridine (2–3 equiv) accelerate them, possibly by transforming the acyloxyborane to a more reactive acylpyridinium salt.

Most parent ω-amino acids are but sparingly soluble in nonaqueous solvents, nevertheless we can prepare their lactams by the acyloxyborane technique under heterogeneous conditions. For example, when 6-aminocaproic acid (1.85 mmol) is suspended in pyridine (30 mL) at 80 °C and treated with catecholborane (2.78 mmol), the solid slowly dissolves and caprolactam is formed in 85% yield. γ-Aminobutyric acid similarly affords 2-pyrrolidinone (>95%). Table II summarizes our experience with a series of homologous substrates. Substantial proportions of medium-ring monomers are not formed, although the cyclization becomes more favorable in the case of 14- and 16-membered lactams. In each of these experiments, controls clearly establish that no ring closure whatsoever occurs if the borane is omitted.[9]

Our results contrast with similar studies on the formation of macrocyclic lactones[10] and may reflect more stringent geometric demands imposed on the ring and on the ring-forming process by the planar amide bond. However the heterogeneous conditions we describe are of unknown (but probably high) dilution and make an accurate assessment of rate data impossible. Recently we have discovered the combination of soluble ω-amino acid tetra-*n*-butylammonium salts with *B*-chlorocatecholborane in pyridine also produces lactams and that under such homogeneous circumstances, dimer formation does not occur at up to 0.05 M concentrations. Thus, for example, the 6-, 12-, and 15-carbon ω-amino acid salts furnish only the corresponding monomeric lactams in yields of 65, 15, and 17%, respectively. This result suggests either that two independent cyclization mechanisms are operating or that the observed dimers arise from complex surface effects. In future work we hope to explore these possibilities.

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References and Notes

(1) (a) S. M. Kupchan, et al., *J. Am. Chem. Soc.*, **94**, 1354 (1972); **96**, 3706 (1974); (b) See K. L. Rinehart, *Acc. Chem. Res.*, **5**, 57 (1972).
(2) For a recent review of lactam syntheses see F. Millich and K. V. Seshadri in "High Polymers", K. C. Frisch, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 3.
(3) A. Pelter, T. E. Levitt, and P. Nelson, *Tetrahedron*, **26**, 1539 (1970).
(4) A. Pelter and T. E. Levitt, *Tetrahedron*, **26**, 1545 (1970).
(5) H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **97**, 5249 (1975).
(6) Occasional batches of catecholborane have required redistillation to obtain proper results; this operation is now part of our standard procedure in handling the reagent.
(7) For a review see C. F. Lane and G. W. Kabalka, *Tetrahedron*, **32**, 981 (1976).
(8) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963). The coupling of *N*-benzoyl-L-leucine with ethyl glycinate under standard conditions using catecholborane produced *N*-benzoyl-L-leucylglycine ethyl ester (30%) having $[\alpha]^{24}_D$ −32.7° (*c* 3.1); lit. $[\alpha]^{20}_D$ −34° (*c* 3.1).
(9) No more than 2% of 2-pyrrolidinone is spontaneously formed when γ-aminobutyric acid is heated 16 h in pyridine.
(10) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
(11) The following is a typical experimental procedure. To a flame-dried 50-mL pear-shaped flask fitted with magnetic stirrer, serum cap, and N_2 inlet was added catecholborane (1.0 M in THF, 6.0 mL), then nonanoic acid (0.87 mL, 5.0 mmol) in THF (4 mL). The clear solution was stirred 1 h at room temperature, then taken up in a 10-mL syringe and added dropwise (motor-driven syringe pump, 0.2 mL/min) to a rapidly stirred solution of benzylamine (1.09 mL, 10.0 mmol) in THF (4 mL) at −78 °C. Upon completion of addition the reaction mixture was warmed slowly to room temperature and stirred overnight. The bulk of THF was removed using a rotary evaporator to produce a white solid which was immediately dissolved in 5% NaOH (15 mL) and ether (15 mL). The aqueous phase was extracted three more times with ether and the combined organic layers were washed with water (5 mL), 5% NaOH (20 mL), 5% HCl (30 ml), and brine (30 mL). Drying and concentration afforded 1.12 g (92%) of white powder, mp 66–67 °C, identical with an authentic sample of *N*-benzylnonanoic amide and pure by NMR, IR, and TLC.
(12) M. Rothe, *Angew. Chem.*, **74**, 725 (1962).
(13) Fellow of the Alfred P. Sloan Foundation, 1978–1980.

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S-Oxides of Tetrathiafulvalenes

Summary: The first tetrathiafulvalene *S*-oxides have been synthesized. These include the mono *S*-oxides of tetrathiafulvalene, dibenzotetrathiafulvalene, and tetrakis(carbomethoxy)tetrathiafulvalene. The polarographic properties of these novel sulfoxides are described.

Sir: Tetrathiafulvalene (**1**, TTF) and its derivatives have been the subject of intensive chemical and physical study in recent years, due to the fact that many compounds of this group can form crystalline, electrically conducting charge-transfer salts.[1,2] This property is dependent upon the relative ease with which the TTF system can be oxidized by a variety of means to give the radical cation (**4**) or the dictation (**5**).[3,4] This type of one-electron or two-electron oxidation is, indeed, the only known transformation of the basic TTF system with the exception of the recently described[5] lithium–hydrogen interchange reaction of TTF. We now report the first synthesis of a new type of TTF oxidation product, namely a tetrathiafulvalene *S*-oxide.