was crystallized from *n*-hexane and then recrystallized from *n*-hexane–ethyl acetate to give the heptatriene **5** (50 mg, 50%); mp 166–167 °C. Concentration of the filtrate gave starting **7** (40 mg, 40%), mp 174–175 °C, from *n*-hexane. Both compounds gave satisfactory mixture melting points.

X-Ray Structure of Photoproduct B. Colorless crystals of tricyclophotoproduct **7** were grown from a hexane solution. The crystal selected for structure analysis was a parallelepiped with approximate dimensions 0.30 × 0.23 × 0.23 mm and was mounted on a glass fiber with silicone adhesive. Precession photographs of this crystal led to a space group assignment of $P2_1/c$ with lattice constants of a = 14.813 (2) Å, b = 10.717 (2) Å, c = 16.827 (3) Å, and β = 80.84 (2)°. The observed and calculated densities, assuming four molecules of $C_{37}H_{30}$ per unit cell volume, were 1.18 g/mL.

Data were collected on a Picker FACS 1 diffractometer by using the θ–2θ scan technique with Zr-filtered Mo Kα radiation and a takeoff angle of ~2.5°. Each of the 3774 independent data ($2\theta \leq 45.77°$) was scanned 1.2° in 2θ plus an allowance for spectral dispersion at a rate of 1°/min, and backgrounds were of 20-s duration. Three standards inserted after every 100 reflections remained statistically constant.

The data were reduced to a set of $|F_o|$'s by application of Lorentz and polarization corrections (Lp). Standard deviations were calculated according to

$$\sigma_F = [(C + k^2B)/4|F_o|^2(Lp)^2]^{1/2}$$

where C and B are the counts of scan and backgrounds, respectively, and k is the ratio of scan to background counting time. Some 2897 data with $F_o > 2\sigma_F$ were taken as observed and used in final stages of refinement.

Normalized structure factor amplitudes $|E|$'s were calculated[16] and the largest 400 were used in the reiterative application of the Sayre equation.[17] Carbon atomic positions found from an E map[18] were used in full-matrix isotropic refinement[19,20] followed by block-diagonal anisotropic refinement[21] which produced an R value of 10.7%, where $R = \sum||F_o| - |F_c||/\sum|F_o|$. A Fourier difference synthesis[18] at this stage provided for the 30 H atoms.

In order to reduce the number of varied parameters, theoretical positions of the 20 phenyl hydrogens were calculated at a distance of 0.95 Å from their respective carbons and included as fixed contributors in the subsequent cycles of refinement[21] while the coordinates of the 10 hydrogens in the fused-ring system were varied. This unit-weighted refinement converged with an R value of 6.1% and R_w = 6.1%, where $R_w = \sum[w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$. Empirical weights were then calculated as described previously[22] and used in the final cycles of refinement, which produced R = 5.76% and R_w = 5.91%.

Acknowledgments. We are indebted to N. C. Yang and G. Griffin for helpful discussions and to T. Kinstle for some mass spectral data. L. J. Radonovich acknowledges the University of North Dakota for a Summer Research Professorship and the Computer Center for computer time. N. F. Woolsey acknowledges financial support of the Petroleum Research Foundation, administered by the American Chemical Society, and the University of North Dakota Faculty Research Committee. The National Science Foundation provided financial assistance in purchase of the carbon-13 NMR spectrometer.

Registry No. **1b**, 33593-04-3; **4**, 23934-49-8; **5**, 70456-57-4; **6**, 70456-58-5; **7**, 70456-59-6; **9**, 70456-60-9; **10**, 70456-61-0; **11**, 70456-62-1; tetracyclone, 479-33-4; *trans*-1-phenyl-1-propene, 873-66-5; 1-phenylpropyne, 673-32-5; *cis*-1-phenyl-1-propene, 766-90-5; maleic anhydride, 108-31-6; tetrachloroethylene, 127-18-4.

Supplementary Material Available: Tables of bond distances (Table I) and angles (Table II), atomic coordinates (Table III), and thermal parameters (Table IV) for photoproduct **7** (6 pages). Ordering information is given on any current masthead page.

(16) Program FAME by R. Dewar and A. Stone was used.
(17) Program REL by R. E. Long was used.
(18) Program FORDAP by A. Zalkin was used.
(19) Atomic form factors from D. T. Cromer and J. L. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).
(20) W. R. Busing, K. D. Martin, and H. A. Levy, "OR-FLS, A Fortran Crystallographic Least-Squares Program", Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, TN, 1962.
(21) Program REFINE by J. J. Park was used. The function minimized was $\sum w|F_o| - |F_c|^2$.
(22) L. J. Radonovich, A. Bloom, and J. L. Hoard, *J. Am. Chem. Soc.*, **94**, 2066 (1972).

Synthetic Studies in Unnatural Cyclic Amino Acids

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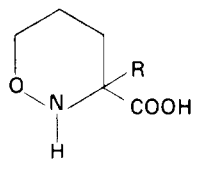
The nitrosation of diethyl (3-chloropropyl)malonate with ethyl nitrite–sodium ethoxide affords ethyl 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (**7**), which was converted into 5,6-dihydro-*N*-methyl-4*H*-1,2-oxazine-3-carboxamide (**10**). Chloroacetylation and acetylation of **10** produce dehydro amides **11** and **12**, respectively. These were converted into derivatives of DL-tetrahydro-2*H*-1,2-oxazine-3-carboxylic acid (**1a**).

Vast methodology exists in the literature for the synthesis of α-amino acids and their derivatives. However, there is a paucity of information pertaining to the chemistry of unnatural cyclic amino acids, specifically those with a nitrogen–oxygen bond β to the carboxylate function. We were interested in an unambiguous synthesis of DL-tetrahydro-2*H*-1,2-oxazine-3-carboxylic acids (**1a**, R = H; **1b**, R = OCH_3) and their derivatives in connection



1a, R=H
1b, R=OCH_3

with several synthetic goals. Amino acids **1a,b** are of potential utility as biochemical probes as well as synthons

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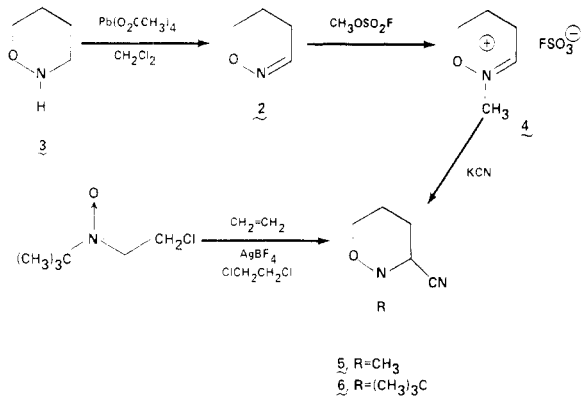
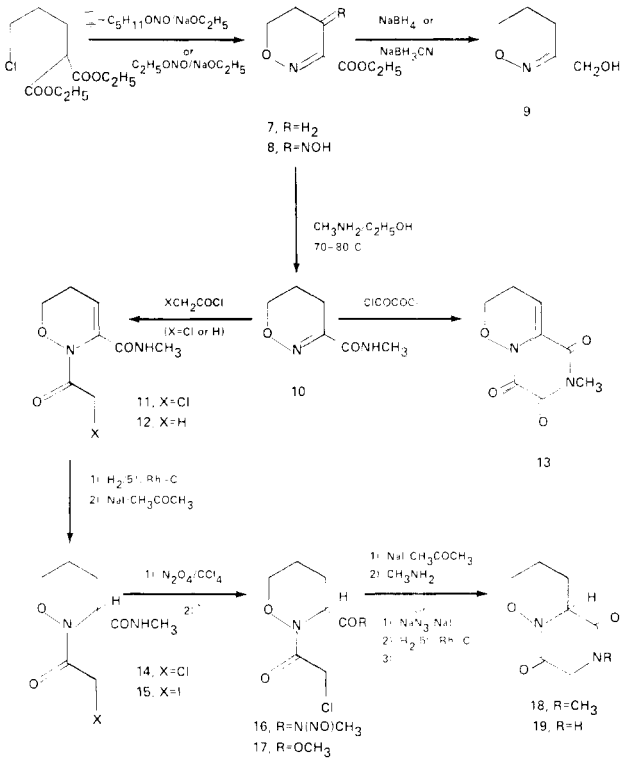
0022-3263/79/1944-2487$01.00/0

Scheme I



Scheme II



of 2-amino-5-hydroxypentanoic acids.

The earlier synthesis of tetrahydro-1,2-oxazines according to King via the double alkylation of *N*-hydroxyurethane with 1,4-dibromoalkanes was unsuitable for the synthesis of **1a,b**.[2] Consequently we chose to functionalize 5,6-dihydro-4*H*-1,2-oxazine (**2**). Attempts at electrophilic addition of cyanide (e.g., liquid hydrogen cyanide or trimethylsilyl cyanide–anhydrous zinc iodide) to oxazine **2** were unsuccessful. Oxazine **2** was obtained in ca. 50% yield from tetrahydro-1,2-oxazine (**3**)[3] by lead tetraacetate oxidation. The corresponding *N*-methyloxazinium salt **4**, obtained by alkylation of **2** with methyl fluorosulfonate, reacted with cyanide readily to afford DL-tetrahydro-2-methyl-1,2-oxazine-3-carbonitrile (**5**). Unfortunately, attempts to remove the *N*-alkyl group from either **5** or **6** were fruitless. Nitrile **6** was obtained via the Eschenmoser chloronitrone method[4] by using the *tert*-butylnitrone from chloroacetaldehyde and ethylene, in ca. 25–28% yield (Scheme I).

Alternatively, we investigated the feasibility of synthesizing ethyl 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (**7**) and its subsequent conversion to derivatives of **1a,b**. Diethyl (3-chloropropyl)malonate on nitrosation (0 °C) with ethyl nitrite–sodium ethoxide afforded ester **7** in 35–65% yield (>95% purity according to ^{1}H NMR integration). *n*-Butyl nitrite or isoamyl nitrite afforded an inseparable mixture of ester **7** and starting malonate concomitant with an alkaline-extractable component **8** which was obtained in yields of <40%. Component **8** was established by ^{1}H NMR, IR, and mass spectroscopy and by elemental analysis to be ethyl 4-oximino-5,6-dihydro-1,2-oxazine-3-carboxylate (Scheme II).

Attempts to reduce ester **7** afforded several surprises. Catalytic reduction attempts were ineffectual; generally no reaction was attained under any conditions. Reductions with sodium borohydride or sodium cyanoborohydride afforded good yields (≥75%) of the allylic alcohol **9**,[5] but none of the tetrahydro-1,2-oxazine carboxylate.

The inertness of the C=N bond of ester **7** prompted us to investigate the feasibility of direct acylation of the nitrogen atom and trapping of the intermediate 2-acyloxazinium salt with a nucleophilic species. Treatment of ester **7** with chloroacetyl chloride in either methylene chloride or chloroform afforded no adducts. The chloroacetyl amide function was chosen in view of its ease of removal (thiourea[6] or *o*-phenylenediamine[7]) and stability. Auspiciously, similar treatment of 5,6-dihydro-*N*-methyl-4*H*-1,2-oxazine-3-carboxamide (**10**) afforded a mixture of starting amide and 2-chloroacetyl-5,6-dihydro-*N*-methyl-2*H*-1,2-oxazine-3-carboxamide (**11**) (Scheme II). ^{1}H NMR studies showed that the chloroacetylation goes to ca. 60% completion (according to ^{1}H NMR integration) within 24 h in these solvents. When chloroacetylation was performed in anhydrous ether, analytically pure dehydro amide **11** crystallized from the reaction medium as light orange quartzlike crystals in >80% yield! Acetyl chloride, bromoacetyl chloride, and oxalyl chloride afforded similar results, but the ester **7** was resistant to acylation under these conditions. Oxalyl chloride afforded the bicyclic imide **13** in yields of >90%.

Our results are in contrast to those of Ottenheijm[8] and Schmidt,[9] who were successful in pyruvoylating indolenine-2-carboxylic acid and dehydroproline esters and amides. To be sure, these are more basic species than the dihydro-4*H*-1,2-oxazines. The enhanced reactivity of the amide **10** vs. that of the ester **7** is attributed to intramolecular-catalyzed deprotonation by the more basic carboxamide.

(2) (a) H. King, *J. Chem. Soc.*, 432–3 (1942); (b) L. W. Jones, *Am. Chem. J.*, **20**, 1–51 (1898); (c) L. W. Jones, *ibid.*, **38**, 253–7 (1907); (d) C. H. Hecker, *ibid.*, **50**, 444–66 (1913); (e) R. T. Major and E. E. Fleck, *J. Am. Chem. Soc.*, **50**, 1479–81 (1928); (f) F. G. Ridell and D. A. R. Williams, *Tetrahedron*, 1083–6 (1974).

(3) R. O. C. Norman, R. Purchase, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1701–4 (1972).

(4) U. M. Kempe, T. K. DasGupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2187–98 (1972).

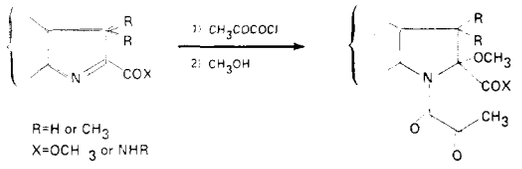
(5) We have observed this phenomenon in other substituted 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylates and 2-isoxazoline-3-carboxylates.

(6) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **74**, 3069–74 (1952).

(7) (a) M. Masaki, T. Kitahara, H. Kurita, and M. Ohta, *J. Am. Chem. Soc.*, **90**, 4508–9 (1968); (b) W. Steglich and H. G. Batz, *Angew. Chem., Int. Ed. Engl.*, **10**, 75–6 (1971).

(8) (a) H. C. J. Ottenheijm, G. P. C. Kerkhoff, J. W. H. A. Bijen, and T. F. Spande, *J. Chem. Soc., Chem. Commun.*, 768–9 (1975); (b) H. C. J. Ottenheijm, J. D. M. Herscheid, G. P. C. Kerkhoff, and T. F. Spande, *J. Org. Chem.*, **41**, 3433–8 (1976).

(9) J. Häusler and U. Schmidt, *Chem. Ber.*, **107**, 2804–15 (1974), and related references therein.



Reduction of the dehydro amide **11** was best accomplished with 5% rhodium-on-carbon in warm methanol (atmospheric pressure reduction apparatus, >95% yield) with no concomitant nitrogen–oxygen or carbon–halogen cleavage. Other catalysts (palladium, platinum, nickel) afforded mixtures of products.

Attempts at hydrolysis of amide **14** to the parent chloroacetylamido acid via aqueous or nonaqueous conditions afforded numerous degradation products. Under the latter conditions neither of the haloacetyl amides **14** or **15** afforded any diketopiperazine **18**. Consequently, transformation of the amide unit to a group more amenable to hydrolysis or displacement reactions was mandatory (e.g., amide → ester). The rarely cited transformation of White was successfully employed.[10] The *N*-methyl amide **14** was converted to the *N*-nitroso amide **16** and subsequently thermolyzed in refluxing dioxane to the methyl ester **17** in >85% yield.

Ester **17** is a stable intermediate that can be hydrolyzed to the acid or employed for peptide synthesis (vide infra). Diketopiperazines **18** and **19** were prepared from ester **17** by standard methodology and found to be thermally stable <110 °C.

Experimental Section

Melting points were determined on a Kofler hot-stage instrument and are uncorrected, as are all boiling points. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. Thin-layer and preparative-layer chromatographic separations were performed on commercially available (Analtech) plates that were used as received. After preparative work compounds were eluted from the absorbents with 0–5% methanol in methylene chloride. Column chromatography was performed with activity I Woelm silica gel. Dry ether was distilled under argon from potassium–benzophenone ketyl. Dry methylene chloride, chloroform, 1,2-dichloroethane, and carbon tetrachloride were distilled under nitrogen from calcium hydride. Dry ethanol and methanol were distilled under argon from magnesium turnings. Routine workup of reaction mixtures is represented by the following format: extraction solvent, washing solutions, drying agents. Solvents were removed under aspirator vacuum on a rotary evaporator.

Infrared spectra were recorded on a Perkin-Elmer Model 137 instrument. Nuclear magnetic resonance (^1H NMR) were obtained on a Varian HFT-80 instrument in the Fourier transform mode. Mass spectra were determined on an AEI MS-9 double-focusing instrument at 70 eV and inlet temperatures of 125–300 °C.

DL-**Tetrahydro-2-methyl-1,2-oxazine-3-carbonitrile (5).** A solution of 8.7 g (100 mmol) of 1,2-tetrahydrooxazine (**3**)[2a] in 75 mL of dry methylene chloride was treated dropwise with a solution of 50.0 g (113 mmol) of recrystallized lead tetraacetate in 150 mL of like solvent. After 30 min, the reaction mixture was quenched with 5 mL of ethylene glycol followed, 10 min later, with water. The crude 5,6-dihydro-4*H*-1,2-oxazine (**2**) was worked up (methylene chloride; water, NaCl; Na_2SO_4), dissolved in 50 mL of dry methylene chloride, and cooled to −40 °C under an argon atmosphere. Methyl fluorosulfonate (Aldrich, "Magic Methyl") (11.4 g, 8.1 mL, 100 mmol) was added over a 30-min period. The solution was warmed to 25 °C over a 1-h period and stirred with 100 mL of saturated potassium cyanide for 15 min. Workup (methylene chloride; water (2×), NaCl; $MgSO_4$) and column chromatography over alumina (Fisher, 85 g, 28 mm × 280 mm) with methylene chloride elution afforded a yellow liquid. Distillation afforded 6.2 g (50%) of colorless nitrile: bp 59–60 °C (2 mmHg); IR (film) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.40 (m, 4 H, 4- and 5-CH_2), 2.76 (s, 3 H, NCH_3), 3.91 (m, 3 H, CH and 6-CH_2).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21. Found: C, 57.16; H, 8.03; N, 22.35.

DL-**Tetrahydro-2-(*tert*-butyl)-1,2-oxazine-3-carbonitrile (6).** A mixture of 819 mg (10 mmol) of *tert*-butylhydroxylamine, 1.00 g (10.1 mmol) of chloroacetaldehyde hydrate, 2.0 g of anhydrous sodium sulfate, and 60 mL of anhydrous ether was stirred under argon at 0 °C for 2 h, filtered, and concentrated in vacuo ($T \leq 25$ °C).

The crude nitrone in 20 mL of dry 1,2-dichloroethane was added via a syringe drive (0.2 mL/min) to a solution of 2.00 g (10.0 mmol) of silver tetrafluoroborate in 30 mL of dry 1,2-dichloroethane saturated with ethylene at 0 °C. During the nitrone addition, ethylene was continuously bubbled through the reaction mixture. After 30 min, the slurry was filtered and the filtrate shaken with saturated potassium cyanide for 15 min and worked up (methylene chloride (2×); water, NaCl; $MgSO_4$). The crude residue was percolated through a column of alumina (Fisher) with methylene chloride elution and distilled in a Kugelrohr apparatus (oven temperature 60 °C, vacuum 0.2 mmHg): 400 mg (24%); IR (film) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (s, 9 H, *tert*-butyl), 1.40–2.10 (m, 4 H, 4- and 5-CH_2), 4.02 (m, 2 H, 6-CH_2), 3.87 (m, 1 H, CH).

Ethyl 5,6-Dihydro-4*H*-1,2-oxazine-3-carboxylate (7). A cold (0 °C) solution of 70.0 g (295 mmol) of diethyl (3-chloropropyl)malonate,[11] 26.3 g (350 mmol) of ethyl nitrite, and 200 mL of dry ethanol, under an argon atmosphere, was treated with freshly prepared ethanolic sodium ethoxide (300 mL, 300 mmol, 1 M) over a 6-h period. After the solution was stirred for an additional 6 h at 0–5 °C and 2 h at 25 °C, the solvent was removed in vacuo ($T \leq 30$ °C) until ca. 100 mL of residue was obtained. After addition of water (250 mL) to the orange residue, the mixture was worked up (methylene chloride (3×); water, NaCl; $MgSO_4$) yielding a light-brown liquid. Vacuum distillation via a short-path distillation apparatus afforded 30.1 g (64%) of faintly yellow colored ester **7**: bp 135–139 °C (5 mmHg) [lit.[12] bp 99–105 °C (2.0 mmHg)]. A colorless analytical sample was prepared by Kugelrohr distillation (oven temperature 100–105 °C, vacuum 0.5 mmHg): IR (film) 1730, 1600, 1290, 1265, 1115, 1025, 965, 930 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3 H, J = 7.1 Hz, CH_3), 1.97 (m, 2 H, 5-CH_2), 2.44 (t, 2 H, J = 6.5 Hz, 4-CH_2), 4.05 (t, 2 H, J = 5.2 Hz, 6-CH_2), 4.30 (q, 2 H, OCH_2CH_3).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.06; N, 8.91. Found: C, 53.70; H, 7.14; N, 8.84.

Ethyl 4-Oximino-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (8). A cold (0 °C) solution of 11.8 g (50 mmol) of diethyl (3-chloropropyl)malonate, 7.8 g (60 mmol) of freshly distilled isoamyl nitrite, and 100 mL of anhydrous ethanol, under an argon atmosphere, was treated with 50 mmol of freshly prepared 0.5 M ethanolic sodium ethoxide over a 4-h period. The reaction mixture was allowed to equilibrate slowly to 20 °C overnight and worked up (methylene chloride (2×); water, NaCl; $MgSO_4$) to afford an inseparable mixture of starting malonate ester and ester **7**. Acidification of the alkaline aqueous phase and workup (ethyl acetate (3×); water, NaCl; $MgSO_4$) afforded a dark orange semisolid. Chromatographic purification on silica gel with methylene chloride elution afforded a yellowish orange solid. Crystallization from ether–pentane (2×) afforded 3.85 g (40%) of oxime ester **8**: mp 107–108 °C; IR (KBr) 3230, 1730, 1690, 1085, 1035, 1024, 956 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7.0 Hz, CH_3), 2.97 (t, 2 H, J = 6.5 Hz, 5-CH_2), 4.35 (t, 2 H, J = 6.5 Hz, 6-CH_2), 4.39 (q, 2 H, OCH_2CH_3), 10.5 (s, 1 H, NOH).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.35; H, 5.46; N, 15.00.

5,6-Dihydro-4*H*-1,2-oxazine-3-methanol (9). A cold solution of 1.57 g (10 mmol) of ethyl 5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (**7**) in 20 mL of cold ethanol, under argon, was treated with 379 mg (10 mmol) of sodium borohydride and allowed to stand at 25 °C overnight. Excess borohydride was destroyed with

(10) E. H. White, *J. Am. Chem. Soc.*, 77, 6008–10, 6011–4, 6014–22 (1955).

(11) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67–71 (1968).

(12) Use of a short-path distillation apparatus minimizes thermal decomposition of **7**.

3 N hydrochloric acid and the solvent removed in vacuo. The residue was diluted with water (40 mL) and worked up (methylene chloride (3×); water, NaCl; $MgSO_4$) followed by Kugelrohr distillation (oven temperature 100 °C; vacuum 0.5 mmHg) to afford 990 mg (85%) of alcohol **9**: IR (film) 3380, 1060, 1030, 903, 845 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (m, 2 H, 5-CH_2), 2.15 (m, 2 H, 4-CH_2), 2.65 (s, 1 H, OH), 3.97 (t, 2 H, J = 5.5 Hz, 6-CH_2), 4.15 (s, 2 H, CH_2OH).

5,6-Dihydro-*N*-methyl-4*H*-1,2-oxazine-3-carboxamide (10). A solution of ester **7** (6.28 g, 40 mmol) in 50 mL of saturated ethanolic methylamine was sealed in a glass pressure vessel and heated at 70–80 °C for 6 h in an oil bath. The resultant yellow oily residue, after concentration, was percolated through a column of alumina (Fisher, 25 mm × 225 mm). Elution with methylene chloride (250 mL) followed by methanol–methylene chloride (2:98, 500 mL) gave a colorless liquid which crystallized after ca. 1 h. Crystallization from ether–pentane (2×) afforded 4.8 g (85%) of amide **10**: mp 72–72.5 °C; IR (KBr) 3350, 1680, 1540, 1160, 1020, 925 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (m, 2 H, 5-CH_2), 2.45 (t, 2 H, J = 6.5 Hz, 4-CH_2), 2.83 (d, 3 H, J = 7.0 Hz, $NHCH_3$), 4.00 (t, 2 H, J = 5.4 Hz, 6-CH_2), 6.85 (bs, 1 H, NH).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.70; H, 7.09; N, 19.70. Found: C, 50.72; H, 7.13; N, 19.98.

2-Chloroacetyl-5,6-dihydro-*N*-methyl-2*H*-1,2-oxazine-3-carboxamide (11). Chloroacetyl chloride (1.70 g, 15 mmol) was added to a suspension of 1.42 g (10 mmol) of *N*-methylamide **10** in 40 mL of anhydrous ether. After 22 h at 25 °C, the light orange crystals were collected and washed well with anhydrous ether to afford 1.85 g (86%) of dehydro amide **11**, which was homogeneous by TLC (silica gel GF_{254}, methanol–chloroform (5:95)); mp 132–134 °C. Recrystallization from methanol–ether or acetone afforded analytically pure yellow cubic crystals: mp 134–135 °C; IR (KBr) 3350, 1675, 1550, 1175, 1085, 1052, 988, 935, 868, 830, 790, 765, 742 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (m, 2 H, 5-CH_2), 2.86 (d, 3 H, J = 5.2 Hz, $NHCH_3$), 4.27 (t, 2 H, J = 6.2 Hz, 6-CH_2), 4.29 (s, 2 H, CH_2Cl), 5.95 (bs, 1 H, NH), 6.17 (t, 1 H, J = 6.1 Hz, CH=).

Anal. Calcd for $C_8H_{11}ClN_2O_3$: C, 43.93; H, 5.07; N, 12.80. Found: C, 43.83; H, 5.04; N, 12.80.

2-Acetyl-5,6-dihydro-*N*-methyl-2*H*-1,2-oxazine-3-carboxamide (12). A suspension of 142 mg (1.0 mmol) of *N*-methylamide **10** in 10 mL of anhydrous ether was treated with 310 mg (4.0 mmol) of acetyl chloride. The resultant colorless solution was kept at 25 °C for 18 h (crystals appeared after 6–7 h) and the crystalline product was collected and washed well with ether. Storage in a vacuum desiccator (0.5 mmHg) over potassium hydroxide pellets followed by drying in an Abderhalden apparatus (ca. 50 °C (1.0 mmHg)) afforded 140 mg (76%) of dehydro amide **12**, homogeneous by TLC: mp 139–141 °C; IR (KBr) 3320, 1675, 1665, 1535, 1175, 978, 933, 904, 870, 827 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (s, 3 H, CH_3CO), 2.45 (m, 2 H, 5-CH_2), 2.85 (d, 3 H, J = 5.0 Hz, $NHCH_3$), 4.18 (t, 2 H, J = 6.1 Hz, 6-CH_2), 6.00 (bs, 1 H, NH), 6.22 (t, 1 H, J = 3.9 Hz, CH=).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.20. Found: C, 52.11; H, 6.71; N, 15.52.

Bicyclic Imide (13). A suspension of 284 mg (2.0 mmol) of *N*-methylamide **10** in 15 mL of anhydrous ether was treated with excess oxalyl chloride. A voluminous amount of gas was evolved, concomitant with precipitate formation. After 6 h, the ivory-colored precipitate was collected, washed well with ether, and dried in an Abderhalden apparatus (ca. 50 °C (1.0 mmHg)) to afford 376 mg (96%) of analytically pure imide **13**: mp 208–210 °C; IR (KBr) 1670–1650, 1640, 1425, 1385, 1320 cm^{-1}; NMR (CD_3SOCD_3) δ 2.59 (m, 2 H, 5-CH_2), 3.09 (s, 3 H, NCH_3), 4.25 (t, 2 H, J = 6.1 Hz, 6-CH_2), 6.50 (t, 1 H, J = 4.1 Hz, CH=).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.99; H, 4.11; N, 14.28. Found: C, 48.63; H, 4.24; N, 14.43.

DL-2-Chloroacetyltetrahydro-*N*-methyl-2*H*-1,2-oxazine-3-carboxamide (14). The dehydro amide **11** (4.58 g, 20.9 mmol) was hydrogenated (atmospheric hydrogenation apparatus) over 600 mg of 5% rhodium-on-carbon catalyst in 150 mL of warm methanol (ca. 30–35 °C). After 8 h (followed by hydrogen consumption graph), the reaction mixture was filtered through a Celite pad, and the filtrates were concentrated under reduced pressure. The crude material was chromatographed on silica gel (220 g, 45 mm × 260 mm) with gradient elution (0–2.5% methanol in methylene chloride, total of 2.5 L) to afford 4.40 g (95%) of TLC homogeneous crystalline chloroacetyl amide **14**; mp 90–92 °C; IR (KBr) 3320, 1722, 1665, 1550, 1425, 1410, 1165, 1015 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.60 (m, 4 H, 4- and 5-CH_2), 2.82 (d, 3 H, J = 7.0 Hz, $NHCH_3$), 4.00 (m, 2 H, 6-CH_2), 4.25 (s, 2 H, CH_2Cl), 5.06 (m, 1 H, CH).

Anal. Calcd for $C_8H_{13}ClN_2O_3$: C, 43.53; H, 5.94; N, 12.69. Found: C, 43.63; H, 6.06; N, 12.92.

DL-2-Iodoacetyltetrahydro-*N*-methyl-2*H*-1,2-oxazine-3-carboxamide (15). A mixture of 2.20 g (10.0 mmol) of the chloroacetyl amide **14**, 1.80 g (12 mmol) of sodium iodide, and 50 mL of distilled acetone was stirred under argon for 12 h at 26 °C. The resultant residue, after concentration in vacuo, was diluted with 75 mL of water and worked up (methylene chloride (3×); water, 5% $NaHSO_3$, NaCl; $MgSO_4$) to afford a yellow oily residue. Chromatography over silica gel (80–85 g, 28 mm × 280 mm) with methanol–methylene chloride (5:95) afforded 2.82 g (90%) of crystalline ivory-colored product **15**: mp 99–100 °C; IR (KBr) 3350, 1670, 1640, 1530, 1228, 1165 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.60 (m, 4 H, 4- and 5-CH_2), 2.84 (d, 3 H, J = 5.0 Hz, $NHCH_3$), 3.88 (s, 2 H, CH_2I), 4.10 (m, 2 H, 6-CH_2), 5.06 (m, 1 H, CH).

Anal. Calcd for $C_8H_{13}IN_2O_3$: C, 30.79; H, 4.20; N, 8.97. Found: C, 31.02; H, 4.26; N, 9.02.

DL-2-Chloroacetyltetrahydro-*N*-methyl-*N*-nitroso-2*H*-1,2-oxazine-3-carboxamide (16). Anhydrous sodium acetate (250 mg, 3.0 mmol) was cautiously added to 3 mL of 1 M nitrogen dioxide (3.0 mmol) in carbon tetrachloride at −60 °C. The dark yellowish green slurry was warmed to 0 °C in an ice bath and 221 mg (1.0 mmol) of amide **14** in 5 mL of methylene chloride was added. After 30 min at 0 °C, TLC analysis (silica gel GF_{254}, methanol–methylene chloride (5:95)) showed only traces of starting amide **14** and a less polar, yellow component. The reaction was quenched with water (25 mL) and worked up (methylene chloride (2×); water, NaCl; Na_2SO_4) to afford a lemon yellow oil: IR (film) 1680, 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.50 (m, 4 H, 4- and 5-CH_2), 3.12 (s, 3 H, NCH_3), 4.15 (m, 2 H, 6-CH_2), 4.29 (AB quartet, 2 H, CH_2Cl), 6.05 (t, 1 H, J = 6.0 Hz, CH).

Methyl DL-2-Chloroacetyltetrahydro-2*H*-1,2-oxazine-3-carboxylate (17). The crude nitroso amide **16** (vide supra) in 25 mL of heptane–dioxane (1:1) was refluxed until the yellow coloration had disappeared (ca. 1 h) and concentrated in vacuo. TLC analysis (silica gel GF_{254}, methylene chloride) showed a mobile component (A) and an origin component (B). Preparative-thick-layer chromatography (2.0 mm) on silica gel (1 × 200 mm × 200 mm, methylene chloride) afforded the ester **17** (A, 150 mg), as a light yellow oil, and starting amide **14** (B, 40 mg): IR (film) 1748, 1675, 1440, 1220–1250 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.50 (m, 4 H, 4- and 5-CH_2), 3.75 (s, 3 H, OCH_3), 4.08 (m, 2 H, 6-CH_2), 4.24 (AB quartet, 2 H, CH_2Cl), 5.16 (m, 1 H, CH).

Anal. Calcd for $C_8H_{12}ClNO_4$: C, 43.34; H, 5.46; N, 6.32. Found: C, 43.47; H, 5.50; N, 6.28.

Diketopiperazine 18. The chloroacetyl ester **17** (378 mg, 1.7 mmol) was converted to the corresponding iodo ester with sodium iodide and acetone. A solution of the crude iodo ester, 250 mg (2.5 mmol) of triethylamine, and 15 mL of saturated ethanolic methylamine was refluxed for 3 h and concentrated in vacuo. The residue was diluted with water and worked up (methylene chloride (3×); NaCl; Na_2SO_4) to afford an oily residue. Chromatographic purification on silica gel plates (2 × 2 mm × 200 mm × 200 mm; methanol–methylene chloride (5:95)) gave 139 mg (44%) of diketopiperazine **18**: mp 115–116 °C; IR (KBr) 1695, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.65 (m, 4 H, $CHCH_2CH_2$), 2.95 (s, 3 H, NCH_3), 3.85–4.25 (m, 3 H, OCH_2 and CH), 3.96 (AB quartet, 2 H, NCH_2).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.20. Found: C, 51.78; H, 6.62; N, 15.02.

Diketopiperazine 19. A mixture of 30 mL of ethanol–water (1:1), 1.07 g (4.9 mmol) of chloroacetyl ester **17**, 3.0 g (20.0 mmol) of sodium iodide, and 1.4 g (20.0 mmol) of sodium azide was stirred overnight at 25 °C and concentrated to a small volume. The residue was diluted with water and worked up (methylene chloride (3×); water; Na_2SO_4) affording 985 mg (88%) of light yellow *methyl* DL-*2-azidoacetyltetrahydro-2H-1,2-oxazine-3-carboxylate*: IR (film) 2120, 1750, 1680, 1440 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.50 (m, 4 H, 4- and 5-CH_2), 3.78 (s, 3 H, OCH_3), 4.02 (m, 2 H, 6-CH_2), 4.07 (bs, 2 H, CH_2N_3), 5.18 (m, 1 H, CH).

The above azido ester was hydrogenated over 150 mg of 5% rhodium-on-carbon catalyst in 25 mL of methanol. The catalyst was filtered and the filtrate concentrated. The residue was crystallized from acetone affording 475 mg (65%) of diketopiperazine **19**: IR (KBr) 3230, 1665, 1650, 1425, 1335, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.55 (m, 4 H, $CHCH_2CH_2$), 3.95–4.25 (m, 3 H, OCH_2 and CH), 4.06 (bs, 2 H, CH_2NH), 6.25 (bs, 1 H, NH).

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.93; N, 16.46. Found: C, 49.27; H, 6.06; N, 16.59.

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Registry No. 2, 38636-09-8; **3**, 36652-42-3; **4**, 70235-93-7; **5**, 70235-94-8; **6**, 70235-95-9; **7**, 70235-96-0; **8**, 70235-97-1; **9**, 70235-98-2; **10**, 70235-99-3; **11**, 70236-00-9; **12**, 70236-01-0; **13**, 70236-02-1; **14**, 70236-03-2; **15**, 70236-04-3; **16**, 70236-05-4; **17**, 70236-06-5; **18**, 70236-07-6; **19**, 70236-08-7; *tert*-butylhydroxylamine, 16649-50-6; chloroacetaldehyde, 107-20-0; *N*-(2-chloroethylidene)-*tert*-butylamine *N*-oxide, 37898-43-4; diethyl(3-chloropropyl)malonate, 18719-43-2; ethyl nitrite, 109-95-5; isoamyl nitrite, 110-46-3; chloroacetyl chloride, 79-04-9; acetyl chloride, 75-36-5; oxalyl chloride, 79-37-8; methyl DL-2-iodoacetyltetrahydro-2*H*-1,2-oxazine-3-carboxylate, 70236-09-8; methyl DL-2-azidoacetyltetrahydro-2*H*-1,2-oxazine-3-carboxylate, 70236-10-1; methylamine, 74-89-5.

3,4:3′,4′-Bibenzo[*b*]thiophene

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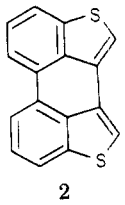
The title compound, isoelectronic with perylene, was prepared in a two-step synthesis. It forms an iodine complex with very similar properties to the known perylene–iodine solids, including electrical conductivity.

One of the first donor–acceptor complexes which exhibited relatively high room-temperature electrical conductivity was a perylene–iodine complex prepared by Akamatu et al., nearly a quarter century ago.[2] Yet it was not until this year that a good single-crystal measurement on the high conductivity of a perylene–iodine complex was performed successfully.[3]

The unusual properties of perylene have been of interest to chemists for some time. Considering its small number of carbon atoms, it exhibits an unusually low ionization potential (IP 7.72 eV) and also an unusually high electron affinity (EA 0.956 eV)![4]

Given these exceptional properties, we decided to determine if replacement of two of the carbon–carbon bonds of perylene by a polarizable element containing a lone pair of electrons (e.g., S, Se, Te) would depress the IP even more and perhaps lead to more stable charge-transfer salts with iodine than those produced by perylene with the same acceptor.[5]

Thus, as a first target we considered the title compound (**1**). Although isomers **2**–**4** would be equally (if not more)



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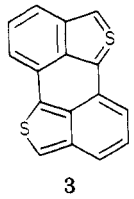

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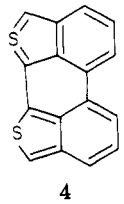

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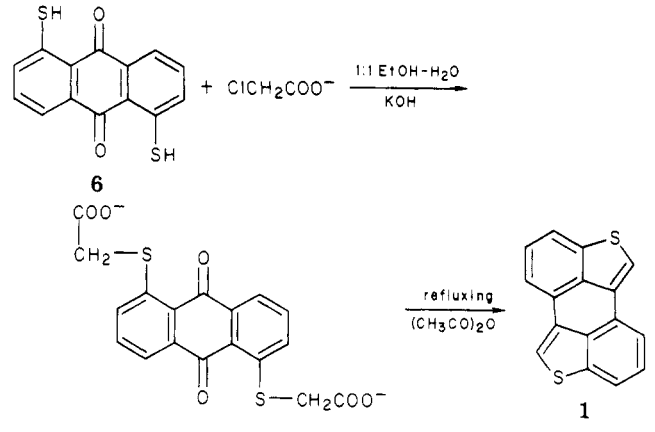
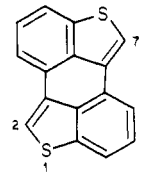
interesting heterocyclic analogues of perylene, from a preparative point of view, **1** (BBT) was the simplest to synthesize. We also anticipated that **3** and **4** might actually be unstable at room temperature since they are homologues of isobenzothiophene, a notably unstable compound.[6]

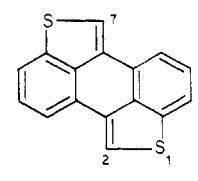
Scheme I



Isomers **1** and **2** can be envisioned as either bibenzothiophenes or derivatives of *p*- and *o*-dibenzoxylylenes, respectively. If one considers the former point of view, compound **1** should exhibit the properties of a perturbed benzo[*b*]thiophene. On the other hand, if one adopts the latter view, positions 2 and 7 should be extremely reactive compared to the reactivity of the same positions in benzo[*b*]thiophene.



1a



1b

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(2) H. Akamatu, Y. Matsunaga, and H. Kuroda, *Bull. Chem. Soc. Jpn.*, **29**, 213 (1956).

(3) M. M. Labes (private communication, July 1978) has discovered that perylene–tetrakis(diiodine) is metallic in its conductivity between 340 and 235 K. Many groups have attempted single-crystal measurements of the conductivity; see, for example, J. Kommandeur and F. R. Hall, *J. Chem. Phys.*, **34**, 129 (1961).

(4) V. D. Parker, *J. Am. Chem. Soc.*, **98**, 98 (1976).

(5) The perylene–iodine complexes are quite unstable at room temperature and atmospheric pressure and tend to lose iodine readily (J. Kommandeur, see ref 3 above).

(6) M. P. Cava, N. M. Pollack, O. A. Mamer, and M. J. Mitchell, *J. Org. Chem.*, **36**, 3932 (1971).

0022-3263/79/1944-2491$01.00/0