

with Wasylishen's predictions, based on INDO-MO calculations.<sup>1</sup> These calculations correlate  $^1J(^{15}\text{N}, ^{13}\text{C})$  with  $\text{P}^2\text{s}(\text{n})\text{s}(\text{c})$ , where  $\text{Ps}(\text{n})\text{s}(\text{c})$  is the bond order between the valence-shell s orbitals of nitrogen and carbon. These density matrix elements may then be related to the hybridization of the ring carbon-nitrogen bond.<sup>11,21,22</sup> The excellent agreement provides a strong indication that the s character of these ring bonds is very low ( $\sim 20\%$ ), indicative of  $\sim \text{sp}^4$  hybridization. The exocyclic N-C bonds showed small coupling constants, indicative of a hybridization similar to that of methylamine<sup>1</sup> [ $^1J(^{15}\text{N}, ^{13}\text{C}) = -3.74$  Hz], and, hence, indicative of substantial p character in the N-C bond. [It is noteworthy from the crystallographic data (**1**) that the C-N-C<sub>6</sub>H<sub>11</sub> bond angle of  $114^\circ$  (interorbital angle,  $\sim 112^\circ$ ) and the exocyclic C-N bond length of  $1.47 \text{ \AA}$  are not indicative of high s character.<sup>23</sup>] It is possible, however, that the lone pair at nitrogen maintains high s character, thus permitting greater p character in all bonding orbitals at nitrogen.<sup>6,24,25</sup>

Jennings et al. regarded the direction of the lone pair at nitrogen as an important factor affecting the magnitude of  $^2J(^{15}\text{N}, \text{H})$  and  $^2J(^{15}\text{N}, ^{13}\text{C})$ , as well as other coupling constants.<sup>14</sup> Thus,  $^2J(^{15}\text{N}, \text{H})$  was shown to be greater in magnitude where the lone pair was roughly parallel to the C-H bond in question. It is known from other extensive work<sup>2</sup> that the cyclohexyl group in **1** and **2** prefers the conformation shown in Figure 1. The  $^2J(^{15}\text{N}, \text{H})$  coupling constant is only observed in **2** but indeed in the situation where C-H was syn to the lone pair. In **2**  $^2J(^{15}\text{N}, ^{13}\text{C})$  was observable ( $-3.1$  Hz) only when the C-C bond was syn to the lone pair, but not to COPh, where the C-C bond was anti to the lone pair.<sup>17,26</sup>

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### An Unusually Facile Ring Opening of 5-Alkoxyoxazoles. Application to the Synthesis of Dimethoxy- $\alpha$ -methylidopa

**Summary:** In the presence of *n*-BuLi, 5-alkoxyoxazoles undergo an unusually facile ring-opening reaction leading directly to lithiated isocyanoacetic acid derivatives, which in turn are versatile intermediates for the preparation of a variety of heterocyclic systems and amino acid derivatives.

**Sir:** As a part of our continuing efforts to exploit the latent functionality of heterocyclic systems, we have recently investigated the preparation of a number of highly substituted oxazoles such as **3** shown in Scheme I.<sup>1</sup> Within this context, it initially appeared that a convenient route to these materials would involve the lithiation and subsequent alkylation of the parent alkoxyoxazoles **1**,<sup>2</sup> and we were further encouraged by the fact that a variety of closely related species have been successfully lithiated and trapped with electrophilic agents.<sup>3</sup> Unexpectedly, however, the lithiation of oxazoles **1** took an entirely different course. Thus, for example, oxazole **1a** reacted rapidly with *n*-BuLi (1.05 equiv, THF,  $-78^\circ\text{C}$ , 5 min), but after quenching with D<sub>2</sub>O the only detectable product was ethyl  $\alpha$ -deuterio- $\alpha$ -isocyanoacetate (**5b**).<sup>4</sup> Similarly, reaction with a variety of alkyl iodides and bromides gave the corresponding alkylated derivatives **5c** to **5j** (Table I),<sup>5</sup> and in analogous fashion, alkoxyoxazole **1b** gave the lithio derivative **4** (cf. Scheme I, R = H).

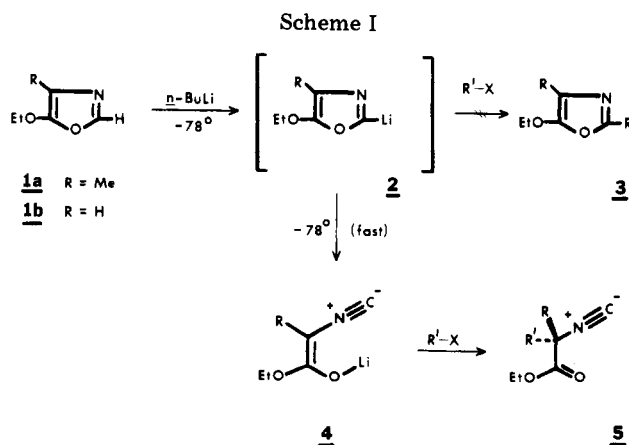
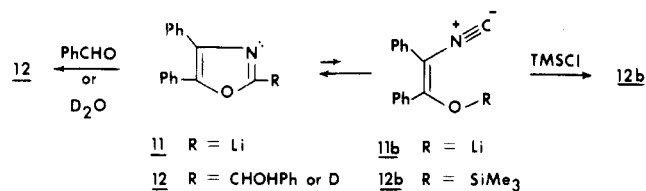


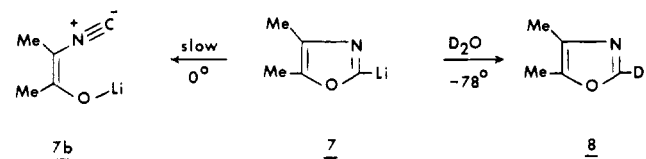
Table I. Alkylation of Alkoxyoxazoles 1

compd no.	R	R'X	yield (isol/GC), %
5a <sup>9</sup>	Me	H <sub>2</sub> O	90/95
5b	Me	D <sub>2</sub> O	90/95
5c	Me	MeI	81/93
5d	Me	EtI	75
5e	Me	<i>n</i> -PrI	74/95
5f <sup>9</sup>	Me	<i>n</i> -BuI	76/99
5g <sup>9</sup>	Me	<i>n</i> -hexyl iodide	59
5h	Me	<i>n</i> -heptyl iodide	74
5i <sup>9</sup>	Me	benzyl bromide	77/86
5j	Me	3,4-dimethoxybenzyl bromide	90
5k <sup>9</sup>	H	H <sub>2</sub> O	68/95

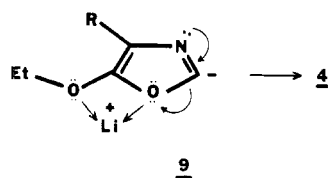
It is of some interest to compare these results with those of Schöllkopf et al., who have previously reported that 2-lithio-4,5-diphenyloxazole (11) exists in mobile equilibrium with the corresponding isocyano derivative 11b (see below).<sup>3d</sup> Thus,



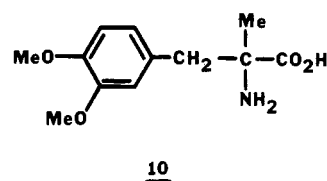
upon quenching with trimethylsilyl chloride the ring-fragmented product 12b was obtained, while trapping with benzaldehyde or D<sub>2</sub>O gave only 12, in which the oxazole ring remained intact.<sup>6</sup> In contrast, however, we find no evidence for the establishment of a similar equilibrium between 2 and 4 in either THF or ether, in the presence or absence of added HMPA. In particular, it seems likely to us that such an equilibrium, if in fact operative, could be readily detected upon quenching with D<sub>2</sub>O (vide supra),<sup>6</sup> since we have obtained a virtually quantitative return of 2-deuterio-4,5-dimethyloxazole (8) from the corresponding lithio species 7 (see below). Rather, the available evidence is suggestive of both an extremely rapid and essentially irreversible conversion of 2 to



4 (by way of comparison, 7 underwent ring opening to the extent of only 9% after 4 h at 0 °C, as adjudged by its trapping with heptyl iodide). Mechanistically, the facility of these ring opening processes may be directly related to the relative stabilities of enolates 4, 7b, and 11b, as suggested by reference 1. One cannot rule out the possibility, however, that a coordinated lithium species such as 9 plays a contributing role in this dichotomy of reaction pathways.<sup>7</sup>



Finally, in view of the facility of these conversions (the yields of alkylated materials derived from oxazole 1a are comparable or superior to those reported<sup>9</sup> for the alkylation of isocyanide 4a), and in view of their less pungent (and presumably less toxic!) nature, we suggest that oxazoles of type 1 can be considered as convenient, stable sources for the in situ generation of highly reactive isocyanoacetic acid derivatives (oxazole 1a, for example, is available in 90% yield on a 75 g scale from ethyl *N*-formylalaninate<sup>2c</sup>). These latter materials, in turn, have proven to be versatile intermediates for the preparation of a variety of heterocyclic systems,<sup>8</sup> and, not surprisingly, they have found considerable use as well in the synthesis of amino acid derivatives.<sup>9,13a</sup> To illustrate this point we describe below a simple two-step procedure for the conversion of 4-methyl-5-ethoxyoxazole (1a) to dimethoxy- $\alpha$ -methyldopa (10), a compound which has previously been



converted to  $\alpha$ -methyldopa in 81% yield.<sup>10</sup> Thus, 1.27 g (10.0 mmol) of oxazole 1a was dissolved in 10 mL of freshly distilled (LiAlH<sub>4</sub>) THF and the resultant solution was cooled to -78 °C under nitrogen. *n*-BuLi (1.3 M)/hexane (8.04 mL, 10.5 mmol) was then added dropwise with gentle stirring over a period of 10 min, and after stirring an additional 5–10 min a solution of 2.43 g (10.5 mmol) of 3,4-dimethoxybenzyl bromide<sup>11</sup> in 10 mL of THF was added while maintaining a temperature of -78 °C. The reaction was stirred at this temperature for an additional 2 h, then at 0 °C for 1 h, and finally for 1 h at room temperature. The resultant solution was then poured into 50 mL of ice cold 10% KH<sub>2</sub>PO<sub>4</sub>, extracted with ether, dried, and concentrated to give 2.50 g (90%) of chromatographically homogeneous 5j [bp 152–155 °C (0.2 mm); NMR (CDCl<sub>3</sub>)  $\delta$  1.20 (3 H, t, *J* = 7 Hz), 1.57 (3 H, s), 2.87 (1 H, d, *J* = 14 Hz), 3.17 (1 H, d, *J* = 14 Hz), 3.82 (6 H, s), 4.13 (2 H, q, *J* = 7 Hz), and 6.72 (3 H, s)].<sup>12</sup> Without further purification, 0.40 g of this material was added to a mixture of 1 mL of concentrated HCl and 4 mL of MeOH and the resultant solution was heated at 50 °C for a period of 1 h. The solvent and excess HCl were then removed in vacuo and the residue was dissolved in 20 mL of 2 N NaOH and allowed to stand for 5 h at room temperature. After washing with ether, decolorizing, and adjusting to pH 7.8 with concentrated HCl the mixture was cooled overnight and filtered to give 0.31 g (94%) of dimethoxy- $\alpha$ -methyldopa (10), mp 279–281 °C. One crystallization from water gave 0.29 g (88%) of analytically pure material, mp 280–281.5 °C (lit.<sup>13a</sup> mp 279–280; 282–283.5 °C).<sup>13b</sup>

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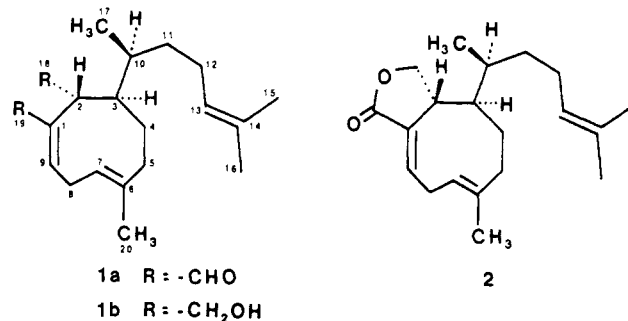
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### Structures of Dictyodial and Dictyolactone, Unusual Marine Diterpenoids

**Summary:** The structures of dictyodial (**1a**), dictyodiol (**1b**), and dictyolactone (**2**) were deduced by spectroscopic means, primarily  $^{13}\text{C}$  NMR and  $^1\text{H}$  NMR spectroscopy, and from single-crystal X-ray diffraction experiments on **1b** and **2**. Dictyolactone (**2**) is produced by oxidation of **1b** with pyridinium chlorochromate, showing that **1a**, **1b**, and **2** have the same absolute configuration.

**Sir:** Marine organisms have attracted considerable recent interest as sources of unusual and potentially useful natural products.<sup>1</sup> Extracts of brown algae of the genus *Dictyota* have been reported to have cytotoxic,<sup>2</sup> antibacterial,<sup>3</sup> and antiviral activities.<sup>4</sup> In this communication we wish to report the structures of two unusual diterpenoids, dictyodial (**1a**) isolated from the brown algae *Dictyota crenulata* and *D. flabellata*, and the closely related dictyolactone (**2**) isolated from the sea hare *Aplysia depilans* (Opisthobranchia). Dictyodial (**1a**) has



been isolated from two taxonomically and geographically distinct *Dictyota* species,<sup>5,6</sup> as a viscous oil,  $[\alpha]_D^{25} -95^\circ$  (*c* 1.2,  $\text{CHCl}_3$ ). The mass spectrum of dictyodial (*m/e* 302) suggested the molecular composition  $\text{C}_{20}\text{H}_{30}\text{O}_2$  and  $^{13}\text{C}$  NMR spectral data (Table I) confirmed this formula.

Sharp doublets at  $\delta$  9.33 and 10.20 in the  $^1\text{H}$  NMR spectrum (Table I) showed that two aldehydic protons were present. One had to occur as a disubstituted  $\alpha,\beta$ -unsaturated enal group [ $\lambda_{\text{max}}$  (EtOH) 232 nm ( $\epsilon$  7300)] and a doublet of doublets at  $\delta$  6.95 showed that the enal olefinic proton was on the  $\beta$  carbon, oriented cis to the carbonyl, and adjacent to a methylene. Double resonance experiments proved that both aldehydic hydrogens were coupled to a methine proton at  $\delta$  3.04, suggesting part structure **3**. Additional double resonance experiments allowed this structure to be expanded to **4** in which the methylene in **3** was further attached to an olefinic methine of a trisubstituted double bond. This olefinic proton,

Table I. Nuclear Magnetic Resonance Data for Dictyodial

carbon-13 chemical shift <sup>a</sup>	assignment <sup>b</sup>	proton chemical shift
203.5 (d)	18	10.20 (d, $J_{2,18} = 3$ Hz)
194.2 (d)	19	9.33 (d, $J_{2,19} = 1$ Hz <sup>c</sup> )
157.4 (d)	9	6.95 (dd, $J_{9,8\beta} = 3.5$ , $J_{9,8\alpha} = 8.5$ Hz)
148.5 (s)	1	
137.9 (s)	6	
130.9 (s)	14	
124.4 (d)	13	5.06 (tm, $J_{13,12} = 7$ , $J_{13,16} = J_{13,15} = 1.5$ Hz)
122.3 (d)	7	5.35 (ddm, $J_{7,8\beta} = 11$ , $J_{7,8\alpha} = 3.5$ , $J_{7,20} = 1.5$ Hz)
56.5 (dd)	8	3.27 (ddd, $J_{8\alpha,8\beta} = -16$ , $J_{8\beta,7} = 11$ , $J_{8\beta,9} = 3.5$ Hz)
		2.98 (br ddd, $J_{8\alpha,8\beta} = -16$ , $J_{8\alpha,9} = 8.5$ , $J_{8\alpha,7} = 3.5$ Hz)
48.5 (d)	3	1.7
40.7 (t)	5	2.25 (br d, $J_{5\alpha,5\beta} = -11.5$ , $J_{5\alpha,4\alpha} \sim J_{5\alpha,4\beta} \sim 3$ Hz)
		1.98 (td, $J_{5\alpha,5\beta} = -11.5$ , $J_{5\beta,4\alpha} = 11.5$ , $J_{5\beta,4\beta} = 6$ Hz)
37.6 (t)	11	1.21 (dq, $J_{11,11'} = -13.5$ , $J_{11,12} = J_{10,11} = 7$ )
		1.15 (dq, $J_{11,11'} = -13.5$ , $J_{11,12} = J_{10,11} = 7$ )
32.7 (d)	10	2.43 (sextet, $J_{10,11} = J_{10,17} = 7$ Hz)
29.1 (t)	4	1.68 <sup>f</sup>
28.7 (d)	2	3.04 (dd, $J_{2,19} = 1$ , $J_{2,18} = 3$ Hz)
25.7 (t)	12	1.88 (quartet, $J_{12,13} = J_{12,11} = 7$ Hz)
25.4 (q)	16	1.57 (br m)
17.4 (q)	15	1.66 (br m)
17.1 (q)	20	1.77 (br m)
17.0 (q)	17	0.89 (d, $J = 7$ Hz)

<sup>a</sup> Relative to  $\text{CDCl}_3$  (76.9 ppm) as an internal standard [value given in Levy and Nelson, "Carbon-13 NMR for Organic Chemists", p 23]. <sup>b</sup> Based on proton single frequency off-resonance decoupling experiments at 90 MHz (carbon-13) and proton spin-spin decoupling experiments at 100 and 360 MHz (proton). <sup>c</sup> W coupling. <sup>d</sup> Triplet of septets. <sup>e</sup>  $J_{3,10} \sim 0.5$  Hz. <sup>f</sup> Obscured by methyl resonances. <sup>g</sup>  $J_{2,3} = 0$  Hz.