



compound **3g**, shown in Table 2, are found to be analogous to those of the related carbon atoms in 1,3,5-trisubstituted pyrazoles<sup>6,7,8</sup>; the remaining carbon atoms could be assigned by application of the usual shift parameters<sup>9</sup>.

By reaction of pyrazole **1** ( $R^1 = \text{CH}_3$ ) with benzaldehyde, a mixture of pyrazolooxazines **2f** (*trans*) and **2f'** (*cis*), respectively, in the ratio 30:70 is obtained. The structures **2f** (*trans*) and **2f'** (*cis*) are supported by  $^1\text{H-N.M.R.}$  spectral comparison of the 7-H chemical shifts of these materials (Table 1) with findings concerning the 2-H chemical shifts in tetrahydro-1,3-oxazines<sup>10,11</sup>: an axial proton is shifted to a higher field than an equatorial one.

Use of 4-unsubstituted pyrazoles **1**, as starting material failed to yield the corresponding 3-unsubstituted pyrazolo-oxazines.

### Synthesis of Some 3-Ethoxycarbonyl-2-methyl-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines from 4-Ethoxycarbonyl-5(or 3)-(2-hydroxyalkyl)-3(or 5)-methylpyrazoles

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We have recently reported on the synthesis of 5(or 3)-(2-hydroxyalkyl)-pyrazoles **1**<sup>1</sup>. As a part of our investigations on these substances as a source of fused bicyclic heterocycles, we now describe their conversion to the 4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazine system, a class of compounds hitherto unreported.

Treatment of pyrazoles **1** with carbonyl compounds **2** (cyclohexanone, acetone, benzaldehyde, and paraformaldehyde) affords the 3-ethoxycarbonyl-2-methyl-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines **3**. The first step of this reaction, similar to the known condensation of pyrazoles with carbonyl compounds<sup>2,3,4</sup>, results in the formation of an intermediate 1-(1-hydroxyalkyl)-5-(2-hydroxyalkyl)-pyrazole derivative which undergoes ready cyclodehydration to yield the fused oxazine ring. Synthesis of tetrahydro-1,3-oxazines involving the reaction between  $\beta$ -amino alcohols and carbonyl compounds is known<sup>5</sup>.

The structures of compounds **3** were assigned on the basis of microanalytical and spectral data (U.V., I.R.,  $^1\text{H-}$  and  $^{13}\text{C-N.M.R.}$ , see Table 1).  $^{13}\text{C-N.M.R.}$  chemical shifts for

### 3-Ethoxycarbonyl-2-methyl-7,7-disubstituted-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines **3a-d**; General Procedure:

A solution of **1** (10 mmol) in acetone or cyclohexanone (20 ml), [a catalytic amount of *p*-toluenesulfonic acid (0.01 mmol) is added with acetone] is heated under reflux for 3 h. The carbonyl compound is evaporated under reduced pressure. The residue is dissolved in chloroform, eventually filtered, washed with water, dried, and evaporated in vacuo. Compound **3e** is pure. Compounds **3a** and **3b** are recrystallized from ethanol/water, 1:1 and 2:1, respectively. Compound **3d** is distilled under reduced pressure and crystallizes after a few days.

### 3-Ethoxycarbonyl-2-methyl-7-phenyl-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines **3e, f, f'**:

A solution of **1** (10 mmol), benzaldehyde (11 mmol), a catalytic amount of *p*-toluenesulfonic acid (0.01 mmol) in dioxan (20 ml) is heated under reflux for 3 h. The mixture is then evaporated under reduced pressure, the residue dissolved in chloroform, washed with 10% sodium hydroxide, and water, and then dried. After evaporation of the solvent in vacuo, the residue is purified by chromatography through a column (25 cm  $\times$  17 mm) of silica gel (35 g) using hexane/ethyl acetate (7:3) as eluent. Compound **3e** is obtained in the fraction 100 to 170 ml (yield: 1.67 g). From the mixture **3f/3f'** (30:70), compound **3f** is obtained from the 70 to 100 ml fraction (yield: 0.37 g), a mixture of **3f/3f'** in the ratio 44:56 is obtained from the 100 to 120 ml fraction (yield: 0.56 g), then the compound **3f'** is obtained from the 120 to 170 ml fraction (yield: 0.88 g).

### Preparation of 3-Ethoxycarbonyl-2-methyl-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines (**3g, h**):

A mixture of **1** (10 mmol), paraformaldehyde (11 mmol), and a catalytic amount of *p*-toluenesulfonic acid (0.1 mmol) is placed in a nickel bomb and heated at 120° for 3 h. After cooling, the residue is dissolved in chloroform, dried, and the solvent evaporated in vacuo. Compound **3h** is recrystallized from ethanol/water (1:2). Compound **3g** is purified by chromatography through a

**Table 1.** 3-Ethoxycarbonyl-2-methyl-4,5-dihydro-7H-pyrazolo[1,5-c]-1,3-oxazines **3**

Product	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield [%]	m.p. or b.p./torr	Molecular Formula <sup>a</sup>	I.R. (CCl <sub>4</sub> ) <sup>b</sup> ν <sub>max</sub> [cm <sup>-1</sup> ]	U.V. <sup>c</sup> λ [nm] (ε)	<sup>1</sup> H-N.M.R. (CDCl <sub>3</sub> ) <sup>d</sup> δ [ppm]
<b>3a</b>	H	—(CH <sub>2</sub> ) <sub>5</sub> —		62	78°	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> (278.3)	1710–1720, 1300, 1215, 1165, 1140, 1100	233 (10800)	1.17–2.35 (m, 13 H); 2.47 (s, 3 H); 3.20 (t, 2 H, <i>J</i> = 6 Hz); 4.11 (t, 2 H, <i>J</i> = 6 Hz); 4.39 (q, 2 H, <i>J</i> = 7 Hz)
<b>3b</b>	CH <sub>3</sub>	—(CH <sub>2</sub> ) <sub>5</sub> —		60	91°	C <sub>16</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> (292.4)	1710–1720, 1315, 1210–1225, 1170, 1155, 1140, 1110, 1095, 1065	233 (11100)	1.10–2.30 (m, 16 H); 2.50 (s, 3 H); 2.60–3.58 (m, 2 H); 4.03–4.65 (m, 3 H)
<b>3c</b>	H	CH <sub>3</sub>	CH <sub>3</sub>	71	55°	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> (238.3)	1710–1720, 1300, 1230, 1150, 1130, 1090	233 (9200)	1.38 (t, 3 H, <i>J</i> = 7 Hz); 1.74 (s, 6 H); 2.53 (s, 3 H); 3.26 (t, 2 H, <i>J</i> = 6 Hz); 4.19 (t, 2 H, <i>J</i> = 6 Hz); 4.44 (q, 2 H, <i>J</i> = 7 Hz)
<b>3d</b>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	75	58°; 120°/0.7	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> (252.3)	1710–1720, 1315, 1210–1230, 1160, 1140, 1110, 1085, 1060	233 (9500)	1.35 (t, 3 H, <i>J</i> = 7 Hz); 1.41 (d, 3 H, <i>J</i> = 6 Hz); 1.68 (s, 3 H); 1.77 (s, 3 H); 2.47 (s, 3 H); 2.57–3.58 (m, 2 H); 3.99–4.65 (m, 3 H)
<b>3e</b>	H	H	C <sub>6</sub> H <sub>5</sub>	58	73°	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> (286.3)	1710–1720, 1285, 1220, 1135, 1090, 1060	231 (12700)	1.38 (t, 3 H, <i>J</i> = 7 Hz); 2.48 (s, 3 H); 3.34 (t, 2 H, <i>J</i> = 6 Hz); 4.00–4.30 (m, 2 H); 4.43 (q, 2 H, <i>J</i> = 7 Hz); 6.61 (s, 1 H); 7.36–7.68 (m, 5 H)
<b>3f</b> ( <i>trans</i> )	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	60	53–54°	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> (300.4)	1715–1725, 1310, 1225, 1150, 1140, 1110, 1090, 1075	231 (12700)	1.28 (d, 3 H, <i>J</i> = 6 Hz); 1.36 (t, 3 H, <i>J</i> = 7 Hz); 2.55 (s, 3 H); 2.63–3.67 (m, 2 H); 3.78–4.65 (m, 3 H); 6.88 (s, 1 H); 7.13–7.68 (m, 5 H)
<b>3f'</b> ( <i>cis</i> )	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H		77–78°	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> (300.4)	1710–1720, 1315, 1295, 1225, 1170, 1140, 1110, 1090, 1075	231 (12200)	1.33 (t, 3 H, <i>J</i> = 7 Hz); 1.43 (d, 3 H, <i>J</i> = 6 Hz); 2.41 (s, 3 H); 2.56–3.63 (m, 2 H); 3.83–4.58 (m, 3 H); 6.38–6.48 (m, 1 H); 7.52 (s, 5 H)
<b>3g</b>	H	H	H	30	101°	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> (210.2)	1710–1725, 1300, 1205, 1160, 1120, 1100, 1080	231 (9400)	1.38 (t, 3 H, <i>J</i> = 7 Hz); 2.51 (s, 3 H); 3.27 (t, 2 H, <i>J</i> = 6 Hz); 4.09–4.29 (m, 2 H); 4.41 (q, 2 H, <i>J</i> = 7 Hz); 5.60 (s, 2 H)
<b>3h</b>	CH <sub>3</sub>	H	H	50	90°	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (224.3)	1710–1725, 1310, 1210–1230, 1165, 1140, 1125, 1105, 1095, 1045	231 (8900)	1.38 (t, 3 H, <i>J</i> = 7 Hz); 1.47 (d, 3 H, <i>J</i> = 6 Hz); 2.50 (s, 3 H); 2.68–3.57 (m, 2 H); 3.82–4.67 (m, 3 H); (2d, 2H, AB system. δ <sub>A</sub> = 5.55, δ <sub>B</sub> = 5.71, <i>J</i> <sub>AB</sub> = 9 Hz)

<sup>a</sup> Microanalyses were in satisfactory agreement with the calculated values (C ± 0.27, H ± 0.19, N ± 0.22).<sup>b</sup> Measured on a Beckmann Acculab 2 spectrometer.<sup>c</sup> Measured on a Beckmann DB spectrometer as ethanol solutions.<sup>d</sup> Measured on a Varian A-60 spectrometer.**Table 2.** <sup>13</sup>C-N.M.R. Data<sup>a</sup> for Product **3g**

C-Atom	C-2	C-3	C-3a	C-4	C-5	C-7	CH <sub>3</sub>	CO—CH <sub>2</sub> —CH <sub>3</sub>
Shift δ [ppm]	151.0	108.6	141.0	24.3	64.0 <sup>b</sup>	78.9	13.9	163.8    59.6 <sup>b</sup> 14.5

<sup>a</sup> Measured on a Varian XL-100-12FT spectrometer in CDCl<sub>3</sub> solution.<sup>b</sup> No attempt was made to assign these resonances to a specific methylene group, these values can be eventually interchanged.

column (25 cm × 17 mm) of silica gel (35 g) using hexane/ethyl acetate (3:7) as eluent. Compound **3g** is obtained from the 70 to 110 ml fraction (yield: 0.65 g).

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