

## The Reaction of 3,5-Dimethylisoxazole with Carbonyl Compounds

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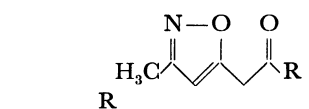
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The reaction product of 3,5-dimethylisoxazole (**1**) with methyl benzoate was found to be 3-methyl-5-(benzoylmethyl)isoxazole in the presence of sodium amide in liquid ammonia. On the other hand, the reaction of **1** with ethyl acetate did not give 3-methyl-5-acetonilysoxazole under similar conditions. The latter reaction product was, however, obtained in a good yield in the presence of lithium amide in liquid ammonia. The reaction of **1** with ketones and aldehydes was proved to give 3-methyl-5-(2-hydroxyalkyl)isoxazoles regiospecifically in the presence of alkali amide. In the above reactions, further alkylation gave 3-methyl-5-(2-alkoxyalkyl)isoxazoles in moderate yields. Compound **1** reacted with acrylaldehyde, crotonaldehyde, and cinnamaldehyde to give 1,2-addition products,<sup>5</sup> 3-methyl-5-(2-hydroxyalkenyl)isoxazoles, exclusively, but methyl cinnamate and cinnamic acid gave only Michael addition products, 4-(3-methyl-5-isoxazolyl)butanoic acid derivatives.

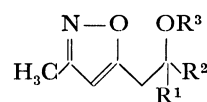
It is well known that some aminoalkylisoxazole derivatives are antipyretic, analgesic, antitussive, anti-inflammatory, and antispasmodic drugs,<sup>1)</sup> that some 3-alkyl-5-(alkoxymethyl)isoxazole derivatives exhibit blood-sugar-reducing activity,<sup>2)</sup> and that some others can also be used as intermediates for the synthesis of terpenes and steroids.<sup>3)</sup> Therefore, we were much interested in synthesizing various kinds of isoxazole derivatives. In the previous papers, we have reported the regiospecific reaction of 3,5-dimethylisoxazole (**1**) with such electrophiles as alkyl halides,<sup>4)</sup> Schiff bases,<sup>5)</sup> benzonitrile,<sup>5)</sup> and ethyl cyanofornate,<sup>6)</sup> affording 5-alkyl-, 5-(2-aminoalkyl)-, 5-(2-amino-2-phenylvinyl)-3-methylisoxazoles, and diethyl (3-methyl-5-isoxazolyl)-malonate respectively. In this paper we wish to report the reaction of **1** with carbonyl compounds in the presence of alkali amide in liquid ammonia.

3,5-Dimethylisoxazole (**1**) was treated with an equimolar amount of methyl benzoate in the presence of an equimolar amount of sodium amide in liquid ammonia. 3-Methyl-5-(benzoylmethyl)isoxazole (**2**) was obtained, it was identified by a direct comparison with an authentic sample.<sup>5)</sup> Under similar conditions, **1** was treated with ethyl acetate. However, 3-methyl-5-acetonilysoxazole (**3**) could not be detected by the GLC analysis of the reaction product. The sole product was identified with ethyl acetoacetate. This result suggested that sodium-hydrogen exchange occurred between the sodium salt (**4**) of **1** and an active methyl of ethyl acetate. From the fact that lithium-hydrogen exchange is much slower than that of sodium-hydrogen,<sup>7)</sup> it is expected that the lithium salt (**5**) of **1** reacts ethyl acetate to give **3**. Actually, a trace of **3** was obtained when **1** was treated with ethyl acetate in the presence of butyllithium in THF. On the other hand, when lithium amide was used in liquid ammonia, **3** was obtained in a 40% yield. No isomers of **3** could be detected by the GLC and NMR analyses of the reaction product. Also, 4-pentanolide with an active methylene, reacted with **1** to give 3-methyl-5-(5-hydroxy-2-oxohexyl)isoxazole (**6**).

In the case of benzaldehyde, **1** gave 3-methyl-5-(2-hydroxy-2-phenylethyl)isoxazole (**7**) in the presence of sodium amide, its structure was confirmed by dehydration to 3-methyl-5-styrylisoxazole (**8**).<sup>5)</sup> The similar treatment of **1** with *p*-tolualdehyde, *p*-anisal-



- 2** C<sub>6</sub>H<sub>5</sub>  
**3** CH<sub>3</sub>  
**6** CH<sub>2</sub>CH<sub>2</sub>CH(OH)CH<sub>3</sub>

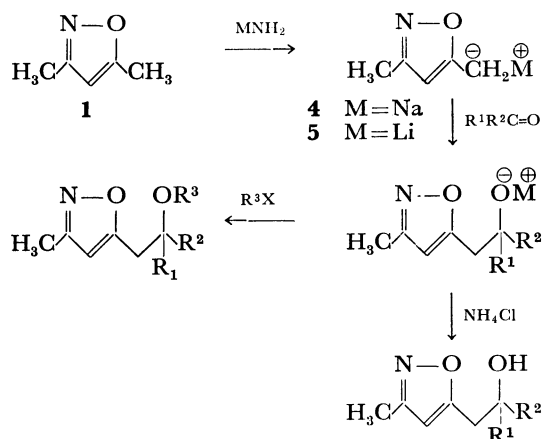


	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
<b>7</b>	C <sub>6</sub> H <sub>5</sub>	H	H
<b>9</b>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	H
<b>10</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	H
<b>11</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H
<b>12</b>	CH <sub>3</sub>	CH <sub>3</sub>	H
<b>13</b>	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	H
<b>14</b>	(CH <sub>2</sub> ) <sub>5</sub>		H
<b>16</b>	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>
<b>17</b>	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>2</sub> CH <sub>3</sub>
<b>18</b>	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>2</sub> CH=CH <sub>2</sub>
<b>19</b>	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
<b>20</b>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>
<b>21</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>
<b>22</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
<b>33</b>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>

Fig. 1.

dehyde, and benzophenone gave the corresponding 2-hydroxy products, **9**, **10**, and **11**<sup>8)</sup> respectively. In the presence of lithium amide, acetone, acetophenone, and cyclohexanone were also treated with **1** to produce the corresponding products, **12**, **13**, and **14**. However aliphatic aldehydes, such as butyraldehyde and acetaldehyde, did not still react with **1** in the presence of sodium or lithium amide in liquid ammonia.

The mechanism of these reactions is speculated to be as is shown in the Scheme, that is, the salt (**4** or **5**) of **1** attacks a carbonyl group, and an oxide anion (**15**) is formed. This intermediate, **15**, is neutralized with ammonium chloride to give a hydroxy derivative. If **15** is treated with alkyl halides before neutralization, alkoxy derivatives are formed. Thus, the addition of methyl iodide to the mixture of **1**, benzaldehyde, and sodium amide gave two products, namely, the expected alkoxy derivative, 3-methyl-5-(2-methoxy-2-phenyl-



ethyl)isoxazole (**16**), and **7**. Also, the alkylation with ethyl bromide, allyl bromide, and benzyl bromide gave the corresponding 2-alkoxy products, **17**, **18**, and **19**. Similarly, compounds **20**, **21**, and **22** were prepared from *p*-tolualdehyde, *p*-anisaldehyde, and benzophenone respectively.

As an  $\alpha,\beta$ -unsaturated carbonyl compound, chalcone was treated with **1**. Two 1 : 1 addition products were thus obtained a 1,2-addition product, 1,3-diphenyl-3-hydroxy-4-(3-methyl-5-isoxazolyl)-1-butene (**23**), and a Michael addition product, 4-(3-methyl-5-isoxazolyl)-1,3-diphenyl-1-butanone (**24**). The treatment of methyl vinyl ketone with **1** in the presence of lithium amide also gave two products, **25** and **26**. When **1** was treated with cinnamaldehyde, an 1,2-addition product, 1-(3-methyl-5-isoxazolyl)-4-phenyl-3-buten-2-ol (**27**), was obtained as well as trace amounts of a Michael addition product, 4-(3-methyl-5-isoxazolyl)-3-phenylbutanal (**28**). Similarly, **1** was treated with acrylaldehyde and crotonaldehyde to give the corresponding

1,2-addition products, **29** and **30**. On the other hand, **1** was treated with methyl cinnamate under similar conditions to give a Michael addition product **31**. 1,2-Addition products could not be detected by the IR and NMR spectral analyses of the reaction product. Furthermore, **1** was treated with an equimolar amount of cinnamic acid in the presence of two molar amounts of lithium amide to afford only a Michael addition product, 4-(3-methyl-5-isoxazolyl)-3-phenylbutanoic acid (**32**), in a poor yield. In the presence of sodium amide, the starting materials were recovered.

Additionally, some chemical reactions of these products were examined. Under the nitration condition of **1** on the C-4 position,<sup>9</sup> **16** was nitrated not on the C-4 position, but on the phenyl group, to give two nitro derivatives, **33** and **34**. On the other hand, **16** was iodinated on the C-4 position of the isoxazole ring to give **35**. The hydrogenations of **7**, **16**, and **22** gave the corresponding  $\beta$ -aminoenones, **36**, **37**, and **38** respectively.

### Experimental

All the melting points and boiling points are uncorrected. The IR spectra were recorded on a Hitachi EST-3T spectrometer, and the NMR spectra, on a Hitachi H-60 or a JEOL H-100 spectrometer. The chemical shifts are expressed in ppm, with TMS as the internal standard. The GLC analyses were performed using a Hitachi KGL-2A gas chromatograph on a 1-m column packed with Apiezon grease L.

*General Procedure for the Preparation of 3-Methyl-5-(2-oxoalkyl, 2-hydroxyalkyl, and 2-hydroxyalkenyl)isoxazoles and 4-(3-Methyl-5-isoxazolyl)butanoic Acid Derivatives.* To a Dry Ice cooling suspension of alkali amide (0.01 mol) in liquid ammonia (80 ml), we added, drop by drop, **1** (0.01 mol) in anhydrous ether (15 ml). After stirring for 1.5 h under a nitrogen stream, a carbonyl compound (0.01 mol) was added to the colored solution and stirring was continued for another 2 h (17 h when lithium amide was used) at  $-78^\circ\text{C}$ . To the reaction mixture we then added ammonium chloride (6 g), and the ammonia was removed at room temperature. The residue was decanted with dichloromethane several times. The dichloromethane solution was washed with aqueous sodium chloride and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was purified by silica gel chromatography and distillation or recrystallization. The yields and physical properties of the products are collected in Tables 1 and 3.

*General Procedure for the Preparation of 3-Methyl-5-(2-alkoxyalkyl)isoxazoles.* To a Dry Ice cooling suspension of sodium amide (0.01 mol) in liquid ammonia (80 ml), an anhydrous ether (15 ml) solution of **1** (0.01 mol) was added. After stirring for 1.5 h at  $-78^\circ\text{C}$ , a carbonyl compound (0.01 mol) was added to the colored solution and stirring was continued for another 2 h. An alkyl halide (0.01 mol) in anhydrous ether (15 ml) was then added to the mixture and stirring was continued for 2 h. The following work-up and purification were done in the manner described in *General Procedure for the Preparation of 3-Methyl-5-(2-oxoalkyl, 2-hydroxyalkyl, and 2-hydroxyalkenyl)isoxazoles and 4-(3-Methyl-5-isoxazolyl)butanoic Acid Derivatives*. The yields and the physical properties of the products are collected in Tables 2 and 3.

*Dehydration of 7 to 3-Methyl-5-styrylisoxazole (8).* Compound **7** (0.50 g) was added to concentrated, ice-cooled sulfuric acid (5 ml) at  $0^\circ\text{C}$ . The mixture was stirred for

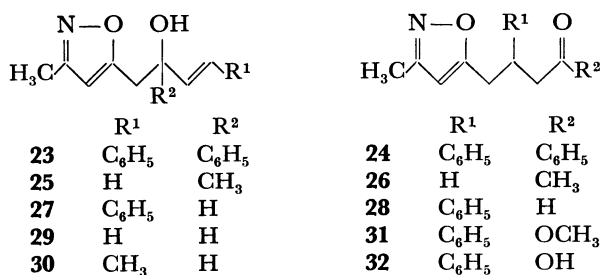


Fig. 2.

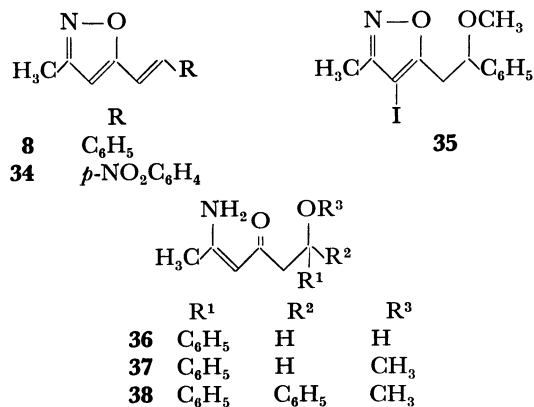


Fig. 3.

TABLE 1. THE YIELDS AND THE PHYSICAL PROPERTIES OF 3-METHYL-5-(2-OXOALKYL, 2-HYDROXYALKYL, AND 2-HYDROXYALKENYL)ISOXAZOLES AND 4-(3-METHYL-5-ISOXAZOLYL)BUTANOIC ACID DERIVATIVES

Compd	Yield <sup>a)</sup> (%)	Mp or Bp (°C) (°C/mmHg)	IR <sup>b)</sup> (cm <sup>-1</sup> )	NMR ( $\delta$ , ppm), $J$ are in Hz			
				3-CH <sub>3</sub> <sup>c)</sup>	4-CH <sup>d)</sup>	5-CH <sub>2</sub>	Others
3	40	105—100/3	1725, 1612	2.24 or 2.28	6.08	3.86 (s)	2.24 or 2.28(s, 3H) <sup>e)</sup>
6	18	142—153/2	3420, 1612	2.18	6.00	3.78 (s)	1.11(d, 3H, $J=6.6$ ), 1.8—2.8 (m, 4H), 3.5—4.5(m, 1H) <sup>f)</sup>
7	22	140—145/2	3400, 1605	2.08	5.67	2.95 (d, $J=6.6$ )	3.6(br. s, 1H), 4.86(t, 1H, $J=6.6$ ), 7.18(s, 5H) <sup>f)</sup>
9	17	130—140/2	3390, 1607	2.08	5.66	2.91 (d, $J=7.2$ )	2.30(s, 3H), 3.7(br. s, 1H), 4.80(t, 1H, $J=7.2$ ), 7.04 (s, 4H) <sup>f)</sup>
10	41	150—165/2	3400, 1611	2.07	5.66	2.91 (d, $J=6.6$ )	3.66(s, 3H), 3.7(br. s, 1H), 4.77(t, 1H, $J=6.6$ ), 6.93(ABq, 4H, $J_{AB}=8.4$ , $\Delta\nu_{AB}=23.8$ ) <sup>f)</sup>
12	18	144—147/20	3400, 1605	2.29	5.98	2.91 (s)	1.30(s, 6H), 2.39(s, 1H, exchanged with D <sub>2</sub> O) <sup>e)</sup>
13	35	50—60/0.001	3410, 1608	2.11	5.57	3.10 (s)	1.52(s, 3H), 3.1(br. s, 1H), 7.1—7.5(m, 5H) <sup>f)</sup>
14	27	55—60/0.001	3400, 1605	2.23	5.87	2.78 (s)	1.1—1.9(m, 10H), 2.5(br. s, 1H) <sup>f)</sup>
23	35	107—108 (CCl <sub>4</sub> )	3390, 1600 <sup>g)</sup>	2.17	5.72	3.41 (s)	2.5(br. s, 1H), 6.57(s, 2H), 7.1—7.6(m, 10H) <sup>f)</sup>
24	11	125.5—126.5 (CCl <sub>4</sub> )	1676, 1608 <sup>g)</sup>	2.18	5.64	3.13 (d, $J=6.6$ )	3.53(d, 2H, $J=6.6$ ), 3.5—4.1 (m, 1H), 7.2—8.0(m, 5H), 7.22(s, 5H) <sup>f)</sup>
25	6	104—111/3	3370, 1609	2.27	5.98	2.97 (s)	1.36(s, 3H), 2.85(s, 1H, ex- changed with D <sub>2</sub> O), 5.07(dd, 1H, $J=2.4$ , 10.2), 5.25(dd, 1H, $J=2.4$ , 17.4), 6.01(dd, 1H, $J=10.2$ , 17.4) <sup>e)</sup>
26	8	173—179/23	1710, 1607	2.16 or 2.26	5.88	1.5—3.0 (m)	2.16 or 2.26(s, 3H), 1.5—3.0 (m, 4H) <sup>f)</sup>
27	38	110—125/0.01	3400, 1607	2.23	5.91	3.00 (d, $J=6.6$ )	2.6(br. s, 1H), 4.4—4.8(m, 1H), 6.14(dd, 1H, $J=6.6$ , 15.5), 6.60(d, 1H, $J=15.5$ ), 7.25(s, 5H) <sup>e)</sup>
28	trace	oil	1723, 1605	2.20	5.65	3.04 (d, $J=7.2$ )	2.80(dd, 2H, $J=1.8$ , 7.2), 3.3— 4.0(m, 1H), 7.0—7.5(m, 5H), 9.63(t, 1H, $J=1.8$ ) <sup>e)</sup>
29	5	150—157/20	3410, 1610	2.27	5.95	2.95 (d, $J=6.6$ )	2.72(s, 1H, exchanged with D <sub>2</sub> O), 4.2—4.7(m, 1H), 5.16 (dd, 1H, $J=1.2$ , 10.2), 5.27 (dd, 1H, $J=1.2$ , 16.8), 5.6— 6.3(m, 1H) <sup>e)</sup>
30	43	170—174/21	3390, 1610	2.27	5.97	2.93 (d, $J=6.6$ )	1.71(d, 3H, $J=4.8$ ), 2.63 (s, 1H, exchanged with D <sub>2</sub> O), 4.3—4.6(m, 1H), 5.5—5.9 (m, 2H) <sup>e)</sup>
31	10	47.5—48.5 (hexane)	1733, 1608 <sup>g)</sup>	2.17	5.62	2.69 or 3.05 (d, $J=7.2$ )	2.69 or 3.05(d, 2H, $J=7.2$ ), 3.3—3.8(m, 1H), 3.53(s, 3H), 7.19(s, 5H) <sup>e)</sup>
32	4	137—140/10 <sup>-6</sup>	3030(broad), 1720, 1609	2.18	5.65	2.70 or 3.06 (d, $J=7.2$ )	2.70 or 3.06(d, 2H, $J=7.2$ ), 3.0—3.8(m, 1H), 7.22(s, 5H), 8.9(br. s, 1H, exchanged with D <sub>2</sub> O) <sup>e)</sup>

a) Isolation yield. b) Neat unless otherwise stated. c) Singlet. d) Singlet. e) In CDCl<sub>3</sub>. f) In CCl<sub>4</sub>. g) KBr.

TABLE 2. THE YIELDS AND THE PHYSICAL PROPERTIES OF 3-METHYL-5-(2-ALKOXYALKYL)ISOXAZOLES

Compd	Yield <sup>a)</sup> (%)	Mp or Bp (°C) (°C/mmHg)	IR <sup>b)</sup> (cm <sup>-1</sup> )	NMR ( $\delta$ , ppm), $J$ are in Hz.			
				3-CH <sub>3</sub> <sup>d)</sup>	4-CH <sup>d)</sup>	5-CH <sub>2</sub>	Others
16	14	150—160/4	1603	2.23	5.78	2.9—3.2 (m)	3.20(s, 3H), 4.47(dd, 1H, $J=6.0, 7.8$ ), 7.28(s, 5H) <sup>e)</sup>
17	10	117—129/3	1605	2.16	5.60	2.6—3.3 (m)	1.12(t, 3H, $J=7.2$ ), 3.29(q, 2H, $J=7.2$ ), 4.47(dd, 1H, $J=$ 6.0, 7.8), 7.17(s, 5H)
18	16	130—139/2	1608	2.18	5.63	2.6—3.4 (m)	3.6—3.9(m, 2H), 4.55(dd, 1H, $J=6.0, 7.8$ ), 4.9—5.3 (m, 2H), 5.4—6.1(m, 1H), 7.20(s, 5H)
19	23	195—199/4	1608	2.18	5.58	2.6—3.4 (m)	4.29(ABq, 2H, $J_{AB}=12.0$ , $\Delta\nu_{AB}=12.6$ ), 4.58(dd, 1H, $J=$ 6.0, 7.8), 7.12(s, 5H), 7.22 (s, 5H)
20	28	137—146/4	1610	2.18 or 2.32	5.62	2.6—3.4 (m)	2.18 or 2.32(s, 3H), 3.13 (s, 3H), 4.34(dd, 1H, $J=6.0$ , 7.8), 7.07(s, 4H)
21	13	52 (hexane)	1612 <sup>f)</sup>	2.18	5.66	2.6—3.4	3.13(s, 3H), 3.73(s, 3H), 4.34(dd, 1H, $J=6.0, 7.8$ ), 6.93(ABq, 4H, $J_{AB}=8.4$ , $\Delta\nu_{AB}=20.5$ )
22	13	98—99 (hexane)	1603 <sup>f)</sup>	2.06	5.06	3.68 (s)	3.12(s, 3H), 7.0—7.3(m, 10H)

a) Isolation yield. b) Neat unless otherwise stated. c) In CCl<sub>4</sub> unless otherwise stated. d) Singlet. e) In CDCl<sub>3</sub>. f) KBr.

TABLE 3. THE ELEMENTAL ANALYSES OF 3-METHYL-5-(2-OXOALKYL, 2-HYDROXYALKYL, 2-ALKOXYALKYL, AND 2-HYDROXYALKENYL)ISOXAZOLES AND 4-(3-METHYL-5-ISOXAZOLYL)BUTANOIC ACID DERIVATIVES

Compound	Molecular formula	Found (%)			Calculated (%)		
		C	H	N	C	H	N
3	C <sub>7</sub> H <sub>9</sub> NO <sub>2</sub>	60.19	6.47	9.87	60.42	6.52	10.07
6	C <sub>10</sub> H <sub>15</sub> NO <sub>3</sub>	60.12	7.79	7.36	60.89	7.67	7.10
7	C <sub>12</sub> H <sub>13</sub> NO <sub>2</sub>	70.69	6.44	7.05	70.91	6.45	6.89
9	C <sub>13</sub> H <sub>15</sub> NO <sub>2</sub>	71.71	6.79	6.43	71.86	6.96	6.45
10	C <sub>13</sub> H <sub>15</sub> NO <sub>3</sub>	66.78	6.41	5.79	66.93	6.48	6.01
12	C <sub>8</sub> H <sub>13</sub> NO <sub>2</sub>	62.00	8.60	9.03	61.91	8.44	9.03
13	C <sub>13</sub> H <sub>15</sub> NO <sub>2</sub>	71.70	6.94	6.28	71.68	6.96	6.45
14	C <sub>11</sub> H <sub>17</sub> NO <sub>2</sub>	67.55	8.85	7.27	67.66	8.78	7.17
16	C <sub>13</sub> H <sub>15</sub> NO <sub>2</sub>	71.88	7.06	6.37	71.86	6.96	6.45
17	C <sub>14</sub> H <sub>17</sub> NO <sub>2</sub>	72.57	7.42	6.22	72.70	7.41	6.06
18	C <sub>15</sub> H <sub>17</sub> NO <sub>2</sub>	73.88	6.90	5.71	74.05	7.04	5.76
19	C <sub>19</sub> H <sub>19</sub> NO <sub>2</sub>	77.48	6.48	4.90	77.79	6.53	4.77
20	C <sub>14</sub> H <sub>17</sub> NO <sub>2</sub>	72.51	7.35	5.97	72.70	7.41	6.06
21	C <sub>14</sub> H <sub>17</sub> NO <sub>3</sub>	68.14	7.01	5.59	67.99	6.93	5.66
22	C <sub>19</sub> H <sub>19</sub> NO <sub>2</sub>	78.13	6.53	4.64	77.79	6.53	4.77
23	C <sub>20</sub> H <sub>19</sub> NO <sub>2</sub>	78.71	6.34	4.55	78.76	6.27	4.59
24	C <sub>20</sub> H <sub>19</sub> NO <sub>2</sub>	78.43	6.37	4.68	78.66	6.27	4.59
25	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub>	63.63	8.00	8.56	64.65	7.84	8.38
26	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub>	64.02	7.90	8.33	64.65	7.84	8.38
27	C <sub>14</sub> H <sub>15</sub> NO <sub>2</sub>	73.22	6.61	5.91	73.34	6.59	6.11
29	C <sub>8</sub> H <sub>12</sub> NO <sub>2</sub>	62.55	7.52	9.01	62.72	7.24	9.14
30	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub>	64.46	7.94	8.48	64.65	7.84	8.38
31	C <sub>15</sub> H <sub>17</sub> NO <sub>3</sub>	69.43	6.66	5.43	69.48	6.61	5.40
32	C <sub>14</sub> H <sub>15</sub> NO <sub>3</sub>	68.16	6.30	6.03	68.55	6.16	5.71

15 min and then poured onto crushed ice. Extractive work-up with ether and subsequent purification by recrystallization from hexane afforded **8** (24% yield), whose mp and spectral data were identical with those of an authentic sample.<sup>9)</sup>

**Nitration of 16.** Compound **16** (0.34 g) was treated with concentrated sulfuric acid (1.84 g) and nitric acid ( $d=1.38$ , 0.22 g) in a manner similar to that in the literature.<sup>9)</sup> Work-up and column chromatography (silical gel, chloroform) afforded **33** and **34**.

**3-Methyl-5-[(2-methoxy-2-(p-nitrophenyl)ethyl)]isoxazole (33).** Yield, 10%, mp 93.5–95.0 °C (carbon tetrachloride). IR (KBr): 1611, 1516, 1349, 1104, 1009, 839  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):  $\delta$  2.25 (s, 3H), 3.0–3.2 (m, 2H), 3.27 (s, 3H), 4.63 (t, 1H,  $J=7.2$  Hz), 5.80 (s, 1H), 7.82 (ABq, 4H,  $J_{AB}=9.0$  Hz,  $\Delta\nu_{AB}=44.7$  Hz). Found: C, 59.74; H, 5.57; N, 10.67%. Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$ : C, 59.53; H, 5.38; N, 10.68%.

**3-Methyl-5-(p-nitrostyryl)isoxazole (34).** Yield, 42%, mp 175–177 °C (carbon tetrachloride). IR (KBr): 1593, 1510, 1336, 1008, 833  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):  $\delta$  2.35 (s, 3H), 6.20 (s, 1H), 7.19 (ABq, 2H,  $J_{AB}=16.8$  Hz,  $\Delta\nu_{AB}=18.0$  Hz), 7.91 (ABq, 4H,  $J_{AB}=9.0$  Hz,  $\Delta\nu_{AB}=35.5$  Hz). Found: C, 62.84; H, 4.38; N, 12.09%. Calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3$ : C, 62.60; H, 4.38; N, 12.17%.

**Iodination of 16 to 3-Methyl-4-iodo-5-(2-methoxy-2-phenylethyl)isoxazole (35).** A mixture of **16** (0.22 g), iodine (0.12 g), and nitric acid ( $d=1.38$ , 2 drops) was stirred at 80 °C for 30 min. The resulting mixture was extracted with ether. The ether solution was washed with aqueous sodium thiosulfate and water. Work-up and column chromatography (silica gel, benzene) gave **35**. Yield, 70%, bp 156–161 °C/2 mmHg. IR (neat): 1605, 1501, 1407, 1101, 1060, 748  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):  $\delta$  2.20 (s, 3H), 2.7–3.5 (m, 2H), 3.17 (s, 3H), 4.56 (dd, 1H,  $J=6.0, 7.2$  Hz), 7.27 (s, 5H). Found: C, 45.69; H, 4.23; N, 4.25%. Calcd for  $\text{C}_{13}\text{H}_{14}\text{INO}_2$ : C, 45.50; H, 4.12; N, 4.08%.

**Catalytic Hydrogenation of Isoxazoles 7, 16, and 22.** The catalytic hydrogenation of an isoxazole (1 mmol) in ethanol (15 ml) was carried out over platinum oxide (15 mg) at room temperature, then it was filtered to remove the catalyst. The filtrate was concentrated and purified by recrystallization or distillation.

**5-Amino-1-hydroxy-1-phenyl-4-hexen-3-one (36).** Yield, 70%, mp 124–126 °C (benzene-ethyl acetate). IR (KBr): 3300, 3180, 1600, 1528, 1410, 1053  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):

$\delta$  1.89 (s, 3H), 2.63 (d, 2H,  $J=6.6$  Hz), 4.8 (br. s, 1H), 4.97 (s, 1H), 5.08 (t, 1H,  $J=6.6$  Hz), 5.5 (br. s, 1H), 7.1–7.5 (m, 5H), 9.7 (br. s, 1H). Found: C, 70.31; H, 7.28; N, 6.85%. Calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}_2$ : C, 70.22; H, 7.37; N, 6.82%.

**5-Amino-1-methoxy-1-phenyl-4-hexen-3-one (37).** Yield, 90%, bp 155–160 °C/2 mmHg. IR (neat): 3350, 3170, 1619, 1527, 1142, 1097  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):  $\delta$  1.90 (s, 3H), 2.3–3.1 (m, 2H), 3.21 (s, 3H), 4.69 (dd, 1H,  $J=4.8, 8.4$  Hz), 5.00 (s, 1H), 5.3 (br. s, 1H), 7.30 (s, 5H), 9.7 (br. s, 1H). Found: C, 71.26; H, 7.86; N, 6.14%. Calcd for  $\text{C}_{13}\text{H}_{17}\text{NO}_2$ : C, 71.20; H, 7.82; N, 6.39%.

**5-Amino-1,1-diphenyl-1-methoxy-4-hexen-3-one (38).** Yield, 60%, mp 133–134 °C (hexane-benzene). IR (KBr): 3300, 3170, 1600, 1525, 1070, 740  $\text{cm}^{-1}$ , NMR ( $\text{CDCl}_3$ ):  $\delta$  1.63 (s, 3H), 3.20 (s, 3H), 3.29 (s, 2H), 4.35 (s, 1H), 4.9 (br. s, 1H), 7.1–7.5 (m, 10H), 9.6 (br. s, 1H). Found: C, 77.75; H, 7.26; N, 4.74%. Calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_2$ : C, 77.26; H, 7.17; N, 4.74%.

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