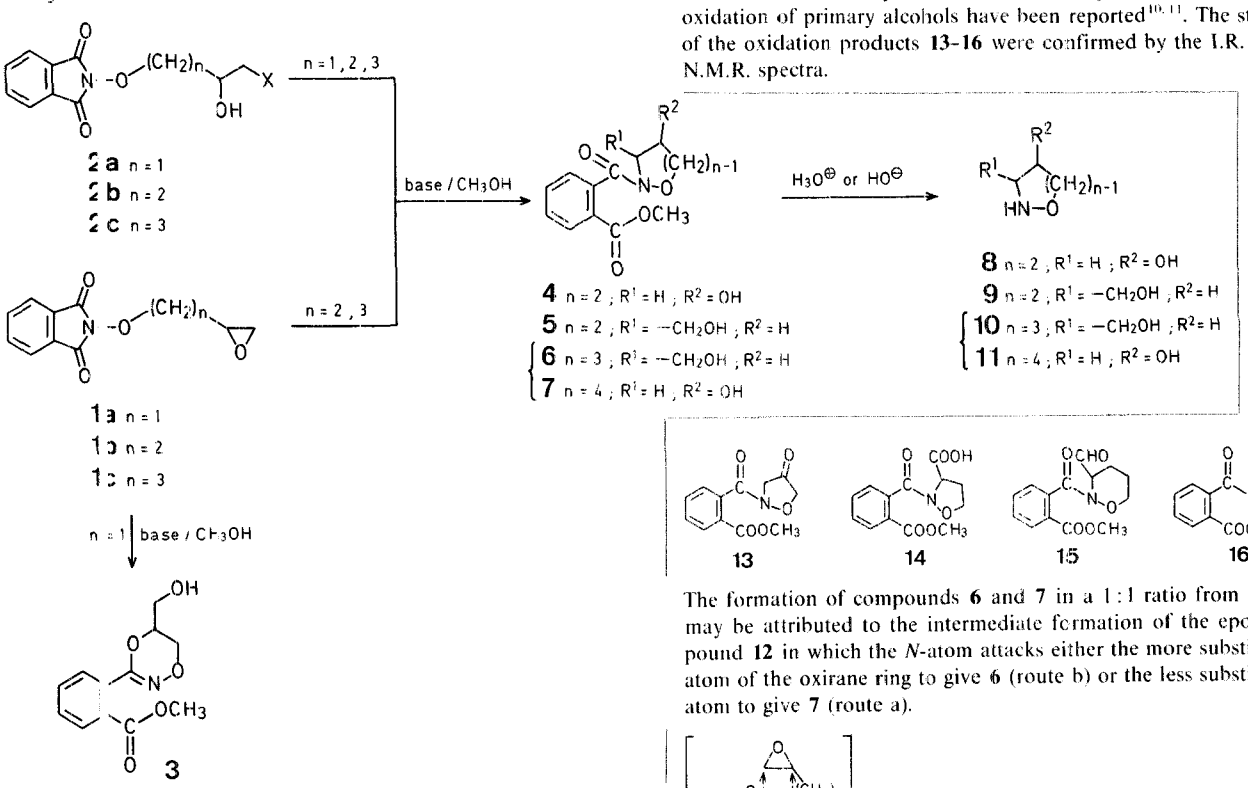
Synthesis of the New Heterocyclic Hydroxy Compounds 4-Hydroxyisoxazolidine, 3-Hydroxymethylisoxazolidine, 3-Hydroxymethylhexahydro-1,2-oxazine, and 4-Hydroxyhexahydro-1,2-oxazepine

Nourdine AMLAIKY, Gérard LECLERC*

Institut de Pharmacologie, U. 206 de l'INSERM, ERA 142 du CNRS, Faculté de Médecine, 11 rue Humann, F-67000 Strasbourg, France

We recently reported[1] an unusual base-catalyzed reaction of *N*-(oxiranylmethoxy)-phthalimide **(1a)** and *N*-(3-halo-2-hydroxypropyloxy)-phthalimide **(2a)** which leads to the formation of 5-hydroxymethyl-3-(2-methoxycarbonylphenyl)-5,6-dihydro-1,4,2-dioxazine **(3)** and 4-hydroxy-2-(2-methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (isoxazolidine **4**), respectively.



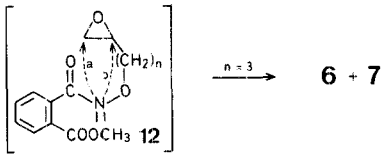
We describe here the synthesis of the *O*—*N* heterocyclic compounds **4**, **5**, **6**, and **7** and their hydrolysis to 4-hydroxytetrahydro-1,2-oxazole (4-hydroxyisoxazolidine, **8**), 3-hydroxymethyltetrahydro-1,2-oxazole (3-hydroxymethylisoxazolidine, **9**), 3-hydroxymethyltetrahydro-1,2-oxazine **(10)**, and 4-hydroxyhexahydro-1,2-oxazepine **(11)**, respectively.

N-(3,4-Epoxybutoxy)-phthalimide **(1b)** and *N*-(4,5-epoxypentyloxy)-phthalimide **(1c)** are prepared by epoxidation of the corresponding *N*-alkenyloxyphthalimides[1] with 3-chloroperbenzoic acid in dichloromethane and the *N*-(bromohydroxyalkoxy)-phthalimides **(2a, b, c)** by cleavage of the corresponding epoxides with hydrogen bromide in chloroform[2]. *N*-(Oxiranylmethoxy)-phthalimide **(1a)** is obtained by reaction of *N*-hydroxyphthalimide with epihalohydrin in dimethylformamide/triethylamine[1].

Treatment of compounds **1a** and **1b** with a base such as *t*-butylamine in methanol leads to the formation of compounds **4** and **5**, respectively, whereas the same treatment of **1c** affords a 1 : 1 mixture of the *O*—*N* heterocycles **6** and **7**. These reactions proceed via attack by methanol on the CO—N group followed either by intramolecular *O*-alkylation with cleavage of the oxirane ring to give the 5,6-dihydro-1,4,2-dioxazine **3**, or by intramolecular *N*-alkylation with cleavage of the oxirane ring to give the saturated *O*—*N* heterocycles **5**, **6**, and **7**. The latter compounds may also be obtained (in the same yields) by treatment of the halohydrins **2b** and **2c** with an equivalent amount of *t*-butylamine in methanol. Compound **4** can only be prepared from halohydrin **2a**.

The structures of compounds **4**, **6**, and **7** were confirmed by chromium(VI) oxidation[3] of these compounds to the corresponding aldehyde or ketones **13**, **15**, and **16**. Compound **5** could not be oxidized to the aldehyde using a wide variety of reagents [dimethyl sulfoxide/acetic anhydride[4], dimethyl sulfoxide/trifluoroacetic anhydride[5], dimethyl sulfoxide/oxalyl chloride[6], dimethyl sulfoxide/dicyclohexylcarbodiimide[7], chromium(VI) oxide/pyridine[3], pyridinium chlorochromate/dichloromethane[8], pyridinium dichromate/dichloromethane[9]] but it could be oxidized to the carboxylic acid **14** using pyridinium dichromate in dimethylformamide[9]. Similar problems concerning the oxidation of primary alcohols have been reported[10,11]. The structures of the oxidation products **13**–**16** were confirmed by the I.R. and ^{1}H-N.M.R. spectra.

The formation of compounds **6** and **7** in a 1 : 1 ratio from **1c** or **2c** may be attributed to the intermediate formation of the epoxy compound **12** in which the *N*-atom attacks either the more substituted C-atom of the oxirane ring to give **6** (route b) or the less substituted C-atom to give **7** (route a).



Hydrolysis of compounds **4**, **5**, **6**, and **7** with hydrochloric acid effects cleavage of the carboxamide group to give the sa-

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Table 1. 5,6-Dihydro-1,4,2-dioxazin Derivative **3** and 2-(2-Methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazoles **4** and **5**, -tetrahydro-1,2-oxazine **6**, and -hexahydro-1,2-oxazepine **7**

Educt	Product	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c]	M.S.[d] *m/e* (M^+)	I.R. ($CHCl_3$)[e] ν [cm^{-1}]		
						CO—O	CO—N	OH
1a	**3**	95	95–97° (benzene)	$C_{12}H_{13}NO_5$ (251.2)	251	1715	[1610 (C=N)]	3500
2a	**4**	96	112–113° (benzene)	$C_{12}H_{13}NO_5$ (251.2)	251	1710	1640	3500
1b or **2b**	**5**	96	oil	$C_{13}H_{15}NO_5$ (254.3)	265	1720	1630	3400
1c or **2c**	**6**	45	oil	$C_{14}H_{17}NO_5$ (279.3)	279	1725	1640	3554
	+							
	7	45	133–134° (benzene)	$C_{14}H_{17}NO_5$ (279.3)	279	1720	1635	3448

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.17; H, ±0.16; N, ±0.22.
[d] Recorded at 20 eV with an LKB 2091 spectrometer.
[e] Recorded on a Beckmann IR 33 spectrometer.

Table 2. 4-Hydroxy- and 3-Hydroxymethyltetrahydro-1,2-oxazoles **(8, 9)**, **3**-Hydroxymethyltetrahydro-1,2-oxazine **(10)**, and 4-Hydroxyhexahydro-1,2-oxazepine **(11)**

Educt	Product	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c]	M.S.[d] *m/e*	I.R. ($CHCl_3$)[e] ν [cm^{-1}]
4	 **8**	96	152–153° (isopropanol)	$C_3H_8ClNO_2$[f] (125.5)	89	3400 (OH); 3000 (NH); 1100 (C—O); 950 (N—O)
5	 **9**	95	110–112° (ethyl acetate)	$C_6H_{11}NO_6$[g] (193.1)	103	3400 (OH); 3000 (NH); 1100 (C—O); 950 (N—O)
6	 **10**	95	103–105° (ethyl acetate)	$C_7H_{13}NO_6$[g] (207.1)	117	3400 (OH); 2990 (NH); 1100 (C—O); 948 (N—O)
7	 **11**	94	98–99° (ethyl acetate)	$C_7H_{13}NO_6$[g] (207.1)	117	3440 (OH); 2940 (NH); 1100 (C—O); 950 (N—O)

[a–e] See Table 1.
[f] Hydrochloride salt.
[g] Oxalate salt.

turated 1,2-*O,N* heterocycles **8, 9, 10,** and **11** in nearly quantitative yield, the O—N bond remaining unaffected[12]. The same hydrolytic cleavage can also be carried out under basic conditions (sodium methoxide in methanol)[13], thus rendering possible the preparation of acid-sensitive alcohols of the types **8–11.**

4-Hydroxy-2-(2-methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (4) from 2a; Typical Procedure:

A solution of *N*-(3-bromo-2-hydroxypropyloxy)-phthalimide (**2a**; 0.5 g, 1.6 mmol) and *t*-butylamine (0.13 g, 1.8 mmol) in methanol (4 ml) is stirred at room temperature for 1 h. The solvent is then removed under reduced pressure, the residue is taken up in 10% sodium hydrogen carbonate solution (8 ml), and this solution is extracted with chloroform (3 × 5 ml). The organic extract is dried with magnesium sulfate and evaporated. The residual product is recrystallized from benzene to give pure **4**; yield: 0.5 g (~100%); m.p. 112–113 °C.

The mixture of compounds **6** and **7** which is prepared in an analogous manner is separated by column chromatography on silica gel using ethyl acetate as eluent.

4-Hydroxytetrahydro-1,2-oxazole Hydrochloride (8):

4-Hydroxy-2-(2-methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (**4**; 2.5 g, 10 mmol) is heated in refluxing 4-normal hydrochloric acid (20 ml) for 4 h. The mixture is then allowed to cool and is evaporated to dryness under reduced pressure. The residue is taken up in water (3 ml), phthalic acid is filtered off, and the filtrate is evaporated. The residue is stirred with ether (5 ml), the insoluble hydrochloride **8** isolated by suction, and recrystallized from isopropanol; yield: 1.2 g (~100%); m.p. 152–153 °C.

4-Oxo-2-(2-Methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (13); Typical Procedure for Oxidation of Compounds 4, 6, and 7:

Chromium trioxide, 1.2 g (12 mmol) is added to a magnetically stirred solution of pyridine (1.9 ml, 24 mmol) in dichloromethane (30 ml). The flask is stoppered with a drying tube and the solution is stirred for 15 min at room temperature. At the end of this period, a solution of 4-hydroxy-2-(2-methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (**4**; 0.5 g, 2 mmol) in a small volume of dichloromethane is added in one portion. After stirring for 15 min at room temperature, the solution is decanted from the residue, which is washed with ether (10 ml). Evaporation of the solvent at reduced pressure affords the crude kentone **13**

Table 3. Oxidation Products **13–16** obtained from Compounds **4–7**

Educt	Product	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c]	I.R. ($CHCl_3$)[c] ν [cm^{-1}]			^{1}H-N.M.R. ($CDCl_3$/TMS)[b] δ [ppm]
					CO—O	C=O	CO—N	
4	**13**	50	126–127° (CCl_4)	$C_{12}H_{11}NO_5$ (249.2)	1775	1715	1665	3.85 (s, 3H, CH_3); 4.15 (s, 4H, N—CH_2, O—CH_2)
5	**14**	36	oil	$C_{13}H_{13}NO_5$ (279.2)	1730	[1730 (COOH)]	1650	2.3–3.2 (m, 4H, CH_2CH_2); 3.85 (s, 3H, CH_3); 3.7–5.3 (m, 1H, CH)
6	**15**[i]	60	oil	$C_{14}H_{15}NO_5$ (277.2)	1735	1695	1690	2.0–2.9 (m, 4H, CH_2CH_2); 3.7–4.3 (m, 5H, CH_3, CH_2); 5.6 (d, J = 6 Hz); 7.1 (m, OH); 9.55 (s)
7	**16**	80	148–149° (benzene)	$C_{14}H_{15}NO_5$ (277.2)	1730	1670	1670	1.7–2.1 (m, 2H, CH_2); 2.8–3 (m, 2H, CH_2); 3.6–3.9 (m, 2H, OCH_2); 3.9 (s, 3H, CH_3); 4.4–4.7 (m, 2H, NCH_2)

[a,b,c,c] See Table 1.

[b] Recorded at 60 MHz using a Perkin-Elmer R 24 B spectrometer.

[i] In $CDCl_3$ solution, aldehyde **15** exists as a 1:3 mixture of aldehyde and enol.

which is purified by colum chromatography on silica gel using chloroform/ethyl acetate (9:1) as eluent; yield: 0.25 g (50%).

Oxidation of Hydroxy Compound 5 to 2-(2-Methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole-3-carboxylic Acid (14)[9]:

3-Hydroxymethyl-2-(2-methoxycarbonylbenzoyl)-tetrahydro-1,2-oxazole (**5**; 0.5 g, 1.9 mmol) is added to pyridinium dichromate (2.83 g, 7.5 mmol) in dimethylformamide (5 ml) and stirred for 9 h at room temperature. At the end of this time, water (30 ml) is added and the reaction mixture is extracted with chloroform (3 × 5 ml). The organic phase is extracted with 1 normal potassium carbonate (10 ml). The aqueous solution is then acidified with 1 normal hydrochloric acid (25 ml) and extracted with chloroform (3 × 5 ml). The organic extract is dried with magnesium sulfate and evaporated. The product is isolated by column chromatography on silica gel using ethyl acetate/acetic acid (99:1) as eluent; yield: 0.19 g (36%); oil.

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* Address for correspondence.

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