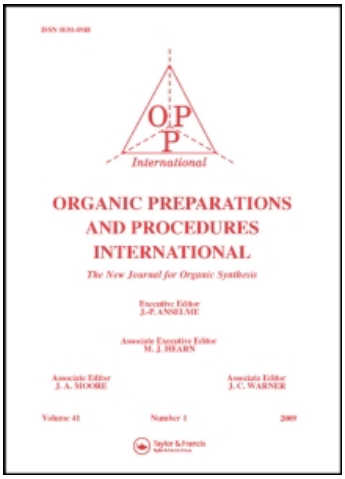

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A CONVENIENT METHOD FOR THE PREPARATION OF *cis*-3,4,8,8a-TETRAHYDRO-6H-[1,3]-DIOXEPINO[5,6-d]OXAZOLES

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A CONVENIENT METHOD FOR THE PREPARATION OF *cis*-3,4,8,8a-TETRAHYDRO-6H-[1,3]-DIOXEPINO[5,6-d]OXAZOLES§

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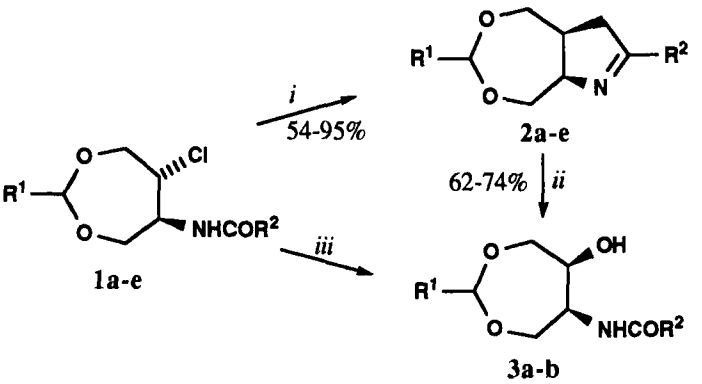
1,3-Dioxepine[1] and 2-oxazoline[2] derivatives find application in several fields, e.g. polymers, biomaterials and corrosion inhibitors. 3,4,8,8a-Tetrahydro-6H-[1,3]-dioxepino[5,6-d]oxazoles **2**, due to the combination of both above structures, may be regarded as the useful intermediates for the same



i) KOH/EtOH, reflux, 60 minutes; *ii*) KOH/H_2O, reflux, 90 minutes; *iii*) Na_2CO_3/H_2O, reflux, 90 minutes[4]

purpose. However, in spite of simplicity of their structure, the dioxepinooxazolines **2** have not hitherto been studied in any great detail.[3] It is well known that dehydrohalogenation of 6-acylamino-5-halogeno-1,3-dioxepanes **1** in boiling aqueous sodium carbonate solution furnishes acylaminodioxepanols **3** in high yields.[4] We now report a simple and convenient method for the preparation of *cis*-dioxepinooxazolines **2** in high to excellent (up to 95%) yields, by refluxing acylaminochloro derivatives **1**[5] in ethanolic potassium hydroxide solution for an hour (Table 1). A short and clean work-up allows the simple separation of **2a-e**.

Structures of the new [1,3]-dioxepino[5,6-d]oxazoles **2** were assigned from their analytical (Table 1) and spectral (Table 2) data and were confirmed by the structures of the corresponding hydroxyamide derivatives **3a** and **3b**, prepared in 83.3 and 72.4% yields, by the base catalyzed hydrolysis of **2a** and **2c** respectively.

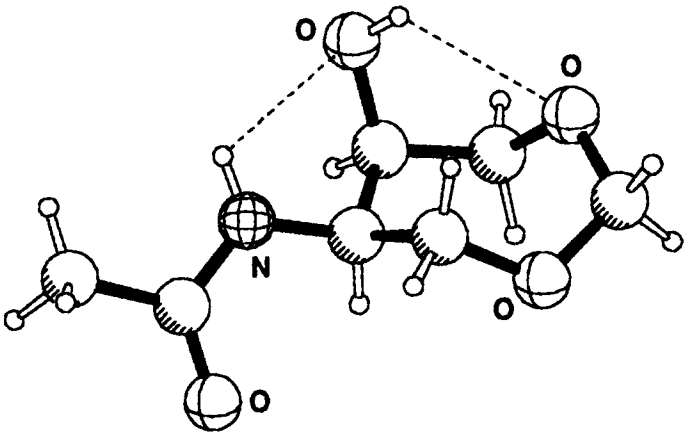


FIGURE 1. PLUTON Drawing of the Crystal Structure of **3a**

It was not possible to prepare a good-quality single crystals for any of the new compounds **2a-e**; however the configuration of the dioxepinooxazolines **2** obtained was elucidated as *cis* by a single crystal X-ray diffraction of hydroxyamide **3a** (Fig. 1)[6] and a well-documented hydrolysis of *cis*-oxazolines to *cis*-amino alcohols without change of configuration.[2]

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on a Büchi aparatus. The IR spectra were recorded as KBr pellets on a Perkin Elmer 257 instrument. The ^{1}H NMR spectra were run on a JOEL FH 90 Q spectrometer (90 MHz) in $CDCl_3$ at 25° using TMS as an internal standard.

***cis*-3,4,8,8a-Tetrahydro-6H-[1,3]-dioxepino[5,6-d]oxazoles (2). General Procedure.**- A solution of *trans*-6-acylamino-5-chloro-1,3-dioxepane **1** (25 mmol) and potassium hydroxide (7.0 g, 125 mmole) in ethanol (60 cm^3) were refluxed for 60 minutes. After cooling, the solid material was removed by filtration and the filtrate was evaporated *in vacuo*. Water (10 ml) was added to the residue and the mixture was extracted with chloroform (2 x 25 ml). The combined extracts were washed with water

(5 ml) and dried over anhydrous sodium sulfate. The chloroform was evaporated *in vacuo* to give crude, TLC pure oxazoline **2**, which was distilled or recrystallized from light petroleum.

TABLE 1. Physical and Analytical Data of [1,3]-Dioxepino[5,6-d]oxazoles **2a-e**

Cmpd	R^1	R^2	Yield (%)	mp (°C)[a] (bp, °C/mm)	Elemental Analysis Calcd.(Found) C	H	N
2a	H	Me	54.2	(77-79/0.30)	53.49 (53.23)	7.06 (7.24)	8.91 (8.69)
2b	H	*n*-Pr	89.8	(83-85/0.35)	58.36 (58.45)	8.16 (8.43)	7.56 (7.61)
2c	*i*-Pr	Me	92.9	68-69	60.28 (60.02)	8.60 (8.51)	7.03 (7.17)
2d	*i*-Pr	*n*-Pr	94.7	58-60	63.41 (63.58)	9.31 (9.37)	6.16 (6.30)
2e	*i*-Pr	CH_2Ph	86.6	95-96	69.79 (70.01)	7.69 (7.61)	5.09 (5.11)

a) Crystallization solvent: light petroleum (bp. 30-60°)

TABLE 2. Spectral Data for the New Oxazolines **2a-e**

Cmpd	^{1}H NMR (δ ppm)	IR (C=N) (cm^{-1})
2a	5.0-3.5 (m, 8H; O-CH_2-O, O-CH_2C-O, O-CH_2C-N, CH-O, CH-N), 1.92 (d, 2H, *J* 1.5 Hz; CH_3)	1680[a]
2b	5.0-3.6 (m, 8H; O-CH_2-O, O-CH_2C-O, O-CH_2C-N, CH-O, CH-N), 2.5-2.0 (m, 2H; N=C-CH_2), 2.0-1.3 (m, 2H; N=CC-CH_2), 1.2-0.8 (m, 3H; CH_3)	1675[a]
2c	5.1-3.2 (m, 7H; O-CHR-O, O-CH_2C-O, O-CH_2C-N, CH-O, CH-N), 2.1-1.3 (m, 1H; -CH<), 2.0 (d, 3H, *J* 1.5 Hz; CH_3), 0.95 (d, 6H, *J* 7.0 Hz; H_3C-C-CH_3)	1670
2d	5.0-3.2 (m, 7H; O-CHR-O, O-CH_2C-O, O-CH_2C-N, CH-O, CH-N), 2.4-1.3 (m, 5H; N=C-CH_2, N=CC-CH_2, -CH<), 1.1-0.8 (m, 9H; N=CCC-CH_3, H_3C-C-CH_3)	1660
2e	7.3 (s, 5H; Ph), 5.0-3.3 (m, 7H; O-CHR-O, O-CH_2C-O, O-CH_2C-N, CH-O, CH-N), 3.6 (s, 2H; N=C-CH_2), 2.0-1.4 (m, 1H; -CH<), 0.9 (d, 6H, *J* 6.0 Hz; H_3C-C-CH_3)	1660

a) Nujol mulls

***cis*-6-Acetylamino-5-hydroxy-1,3-dioxepanes (3). General Procedure.**- Dioxepinooxazoline **2** (5 mmol) and potassium hydroxide (0.7 g, 12.5 mmol) were refluxed in water (60 ml) for 90 minutes. The water was evaporated *in vacuo* to reduce the volume to 5 ml, and the residue was extracted with chloroform (3 x 20 ml). The combined extracts were washed with water (5 ml), dried over anhydrous

sodium sulfate and evaporated *in vacuo*. The solidified residue of crude hydroxy amide **3** was recrystallized from a mixture of light petroleum-chloroform (3:1).

***cis*-6-Acetylamino-5-hydroxy-1,3-dioxepane (3a).**- Work up by general procedure gives 0.73 g (83.3 %) crude **3a**, mp. 101-103°. After recrystallization, mp. 102-104°:

IR (KBr): 3290-3180 (broad, s, OH, NH); 1625 (vs, C=O); 1540 (vs, amid II) cm^{-1}; ^1H NMR ($CDCl_3$, 25°, TMS): *d* 6.5-6.1 (m, 1H, NH), 4.75 (s, 2H, O-CH_2-O), 4.4-3.3 (m, 7H, O-CH_2-C-O, O-CH_2-C-N, -CH-O, -CH-N, OH), 2.05 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 48.28; H, 7.57; N, 7.99

***cis*-6-Acetylamino-5-hydroxy-2-isopropyl-1,3-dioxepane (3b).**- Work up by general procedure gives 0.81 g (74.2%) crude **3b**, mp. 101-103°. After recrystallization, needles, mp. 103-105°: IR (KBr): 3540-3210 (broad, OH, NH), 1645 (vs, C=O), 1555 (s, Amid II) cm^{-1}; ^1H NMR ($CDCl_3$, 25°, TMS); δ 6.3-6.2 (m, 1H, NH), 4.30 (d, 1H, *J* 7.6 Hz, O-CHR-O), 4.1-3.0 (m, 7H, O-CH_2-C-O, O-CH_2-C-N, -CH-O, -CH-N, OH), 2.0 (s, 3H, $COCH_3$), 2.0-1.5 (m, 1H, -CH<), 0.9 (d, 6H, *J* 6.3 Hz, CH_3-C-CH_3).

Anal. Calcd. for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.29; H, 8.63; N, 6.30

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3. The only [1,3]-dioxepino[5,6-d]oxazole synthesized so far (**2**; R^1 = H, R^2 = NH_2) is covered by a patent [N. L. Yang, A. Anerbach, J. L. Paul and R. Pesce, (Hoechst Celanese Corp.) EP 340926, Nov. 08, 1989; *Chem. Abstr.* **112**, 180033a (1990)] and its preparative method is not well known.

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6. Crystallographic data for **3a**: monoclinic, space group *P* n, *a* = 8.767(1), *b* = 7.117(2), *c* = 7.260(2) Å, β = 110.23(2)°, *V* = 425.0 (2) Å^3, *Z* = 2, D_c = 1.37, D_m = 1.38 g cm^{-3}, μ = 0.71 cm^{-1}, *R* = 0.032, R_w = 0.041; 1014 independent reflections, of which 904 were observed ($I \geq 3\sigma(I)$) were taken on Philips PW1100 diffractometer with MoKα radiation and graphite monochromator. Further details of crystal structure investigation see: M. Vinković, M. Dumić and B. Kamenar, *Acta Cryst. C*, 48 (**1992**).