NOTES

THE SYNTHESIS OF 4-d_2, 5-d_2 AND 4,5-d_4-2-DICYCLOPROPYLMETHYLAMINO-Δ^2-OXAZOLINES

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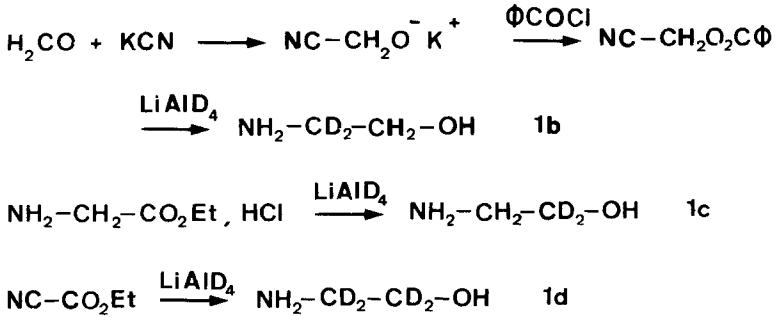
The synthesis of deuterated ethanolamines and deuterated 2-dicyclopropylmethylamine-Δ^2-oxazolines is described.

Key Words : Ethanolamine - 2-dicyclopropylmethylamino-Δ^2-oxazoline S 3341 - Deuterium labelling -

S-3341 (2-dicyclopropylmethylamino-Δ^2-oxazoline 4a) is a potent new antihypertensive compound patented by Servier (France). For the internal standard needed to measure plasma concentration of this drug by mass fragmentography, we chose to synthesize deuterated analogs, which, during analysis, behave like the parent compound, thus rendering drug recovery measurement unnecessary.



Scheme 1

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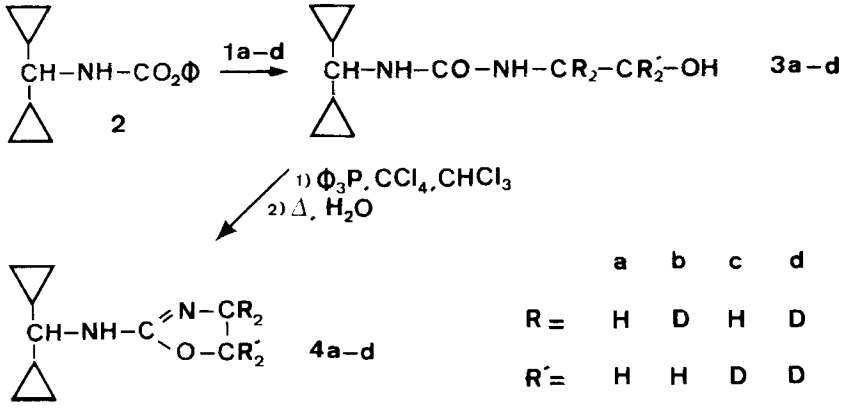
We describe here the synthesis of these standards labelled with deuterium atoms on the carbon 4 and/or 5 of the oxazoline ring, thanks to the use of ethanolamines labelled on the α- and/or β-position relative to the nitrogen. These ethanolamines (1b-1d) are obtained by the action of $LiAlD_4$ on suitable substrates (scheme 1 and 2).



Scheme 2

Isotopic purity, determined by mass fragmentography, is shown in table I. Both dideuterated standards have an M-2 ion (m/e = 180) about 1% of their molecular peak; the M-4 ion of the tetradeuterated derivative is negligible. The dideuterated compounds may also be useful in studying the metabolism of S-3341, for instance, in showing on which carbon atom of the imidazolin ring, oxidation might take place.

m/e	178	179	180	181	182	183	184	185	186
5a	<1%	33%	100%	12%	<1%	-	-	-	-
5b	-	-	1%	33%	100%	12%	1%	-	-
5c	-	-	1%	33%	100%	14%	1%	-	-
5d	-	-	-	<1%	5%	42%	100%	14%	2%

Table 1. Intensity of the ions M-2 to M+2 of 5a-5d

EXPERIMENTAL

Synthesis of 1b (adapted from ref. 1)

50 mM KCN (3.45 g) in 7.5 ml H_2O were mixed at 0°C with 50 mM HCHO (33% solution in water). After 2 hours, 45 mM (∿ 6 g) benzoyl chloride were added slowly (Temp. < 10°C). After overnight mixing, 50 ml of 5% $NaHCO_3$ were added and the aqueous phase was extracted with ether. The ether solution was thoroughly dried.

The solution was then added dropwise to a suspension of 80 mM (3.2 g) $LiAlD_4$ in 80 ml dry ether; after 2 hours, the addition of 3 ml H_2O, 3 ml 15% NaOH and 15 ml H_2O gave a precipitate. After filtration, this precipitate was well washed with water and the ether extracted with water to give an aqueous solution of deuterated ethanolamine used as such.

Synthesis of 1c

60 mM $LiAlD_4$ (2,4 g) were suspended in dry tetrahydrofuran (THF). Small portions of ethylglycinate hydrochloride (60 mM, 8.37 g) were added. After 2 hours, treatment with water and sodium hydroxyde gave a precipitate which was washed with water. This water was added to the THF which was slowly distilled to give an aqueous solution of ethanolamine.

Synthesis of 1d (adapted from ref. 2)

60 mM of $LiAlD_4$ (2.4 g) suspended in dry THF were treated with 50 mM ethylcyanoformate (5 g) in 30 ml THF with vigorous cooling. After 2 hours, the mixture was treated as for 1c.

Synthesis of 3b-d

15 mM (3.47 g) phenyl dicyclopropylmethylcarbamate 2 were added to the aqueous solution of 1b, c or d. After 2 hours reflux, the reaction mixture was cooled and extracted continuously for 10 hours with dichloromethane.

The dichloromethane solution was dried and evaporated, and the residue purified by chromatography on SiO_2, giving ureas 3b-3d with yields of 70%, 70% and 40%.

m.p. of	3a	114-115 (reported by Servier)
	3b	112-114
	3c	114-115
	3d	110-114

Synthesis of 4b-d

7 mM (1.4 g) urea 3b, 3c or 3d were dissolved in 20 ml chloroform containing 20 mM (5.2 g) triphenylphosphine and about 50 mM (7.7 g) tetrachloromethane; after 2 hours reflux, the chloroform was evaporated, the residue dissolved in 30 ml water and refluxed again for 1 hour.

After cooling, the solution was acidified, extracted with ether, alcalinised and the oxazoline was extracted with ether which was then dried and evaporated.

The oxazoline yield ranged from 40 to 50% (after purification by sublimation).

m.p. of	4a	106-7 (reported by Servier)
	4b	107-8
	4c	106-7
	4d	103-6

REFERENCES

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