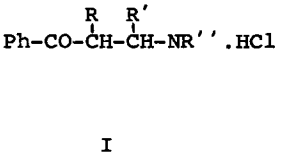
Tetrahedron Letters No. 34, pp. 2993-2996, 1970. Pergamon Press. Printed in Great Britain.

THE FIRST SYNTHESIS OF OPTICALLY ACTIVE Δ^2-ISOXAZOLINES

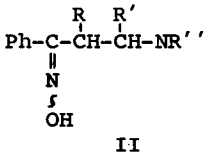
R. J. MacConaill and F. L. Scott,
Chemistry Department, University College,
Cork, Ireland.

(Received in UK 29 May 1970; accepted for publication 18 June 1970)

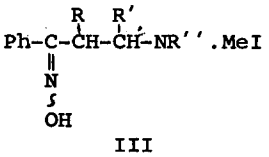
We have established using a variety of methods[1] that the base-induced cyclisation of Mannich base oxime methiodides to yield Δ^2-isoxazolines involves oximate anion as a powerful neighbouring group. The stereochemistry of this process should then involve preservation of overall optical activity at the reaction terminus. We have now used this stereochemical consequence of oxime anchimerism to prepare several optically active Δ^2-isoxazolines - species which have not been previously reported.



I



II



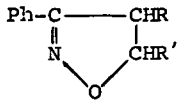
III

a. R = H, R′ = Me, NR′′ = piperidino.
b. R = H, R′ = Me, NR′′ = dimethylamino.
c. R = H, R′ = Ph, NR′′ = dimethylamino.
d. R = Me, R′ = H, NR′′ = dimethylamino.
e. R = Ph, R′ = H, NR′′ = dimethylamino.

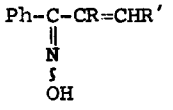
The (-) Mannich base hydrochloride (Ia), m.p. 153-154°, $[\alpha]_{589}^{20}$ -23° (c = 2.8 in water), [lit.,[2] m.p. 147-149°, [α] -18.5° (c = 5 in ethanol)]. was prepared by the method of Andrisano et al.,[2] resolution being achieved via the (-) dibenzoyl tartarate derivative. This salt when subject to our usual oximation procedure[3] gave the Mannich base oxime (IIa)[4], m.p. 171-173° which with methyl iodide gave the (-) methiodide (IIIa), m.p. 200-200.5°, $[\alpha]_{589}^{20}$ -6.6° (c = 3.7 in DMF). Treatment of this methiodide with sodium

ethoxide (1.5 eq.) in ethanol for 3 hr. at 50° gave, after dry column chromatography on alumina (activity III) with methylene chloride, (+)-5-methyl-3-phenyl isoxazoline (IVa) (85%), m.p. 58.5°, $[\alpha]_{589}^{20}$ + 125.5° (c = 1 in $CHCl_3$).

Similarly from the workup of the diastereoisomeric dibenzoyl tartarate the (+) Mannich base hydrochloride (Ia), m.p. 164-165°, $[\alpha]_{589}^{20}$ + 16.0° (c = 5 in water) was obtained and from it on oximation the oxime (IIa), m.p. 175-176°. This gave the (+) methiodide (IIIa), m.p. 193-194°, $[\alpha]_{589}^{20}$ + 5.4° (c = 1.7 in DMF), which when reacted with ethanolic sodium ethoxide gave (-)-5-methyl-3-phenyl isoxazoline (IVa) (88%) m.p. 57.5°, $[\alpha]_{589}^{20}$ -116° (c = 7.0 in $CHCl_3$). In both cases the elimination product anti-1-phenylbutan-2-en-1-one oxime (Va)[5] (5-10%) m.p. 88.5° was obtained from the cyclisation reaction.



IV



V

a. R = H, R′ = Me.
b. R = H, R′ = Ph.
c. R = Me, R′ = H.
d. R = Ph, R′ = H.

These stereochemical transformations were quite sensitive to structural alterations. Thus on changing the Mannich base amino moiety from piperidino [as in (Ia)] to dimethylamino (Ib) neither the (Ib) free base nor the corresponding oxime (IIb) could be successfully resolved using (-) dibenzoyl tartaric acid. However, the racemic oxime methiodide (IIIb) did cyclise in base to give the Δ^2-isoxazoline (IV) in 74% yield. Again when the 3-methyl function in (Ia) was replaced by a 3-phenyl group as in (Ic) attempted resolution of the corresponding free base with (-) dibenzoyl tartaric acid lead to elimination of dimethylamine with formation of benzylideneacetophenone (86%). Again, the racemic methiodide (IIIc) could be cyclised to give a high

yield of 3,5-diphenyl-Δ^2-isoxazoline (IVb)(> 91%).

We next examined a number of 2-substituted Mannich bases. The (+) Mannich base hydrochloride (Id),prepared by literature methods[8], gave by our usual oximation procedure a low yield (13.5%) of the oxime (IId) as a liquid. This formed the methiodide (IIId), m.p. 223-224°, $[\alpha]_{589}^{20}$ +5.15° (c = 9.0 in DMF), which when reacted with sodium ethoxide, (10 eq.) in ethanol for 20 hr. at 50°, gave on chromatographic workup (+)-4-methyl-3-phenyl isoxazoline (IVc) (26%), m.p. 71.5-72°, $[\alpha]_{589}^{20}$ + 100.0° (c = 2.2 in $CHCl_3$) and syn-2-methyl-1-phenylprop-2-en-1-one oxime (Vc) (67%), m.p. 112-113°. In contrast with the 3-phenyl compound when the inactive 2-phenyl methiodide (IIIe) was subject to our cyclisation conditions it formed no isoxazoline, forming only syn-1,2-diphenylprop-2-en-1-one oxime (Vd) (97%), m.p. 133-134°.

The predominance of elimination reactions over cyclisation in the case of the 2-substituted compounds (IIId and e) arose because the oxime group was in an unfavourable (syn to 1-phenyl) configuration for anchimeric cyclisation. Beckmann rearrangements, using PCl_5 in ether, confirmed this. Such rearrangement of the oximes (IIa), (IIb) and (IIc) gave products corresponding to phenyl migration, namely substituted propionanilides in ca. 70% yields, whereas similar reactions with (IIe) gave the product of alkyl migration namely benzamides of the type ($C_6H_5CONHCH_2CH_2NR_2$) 50%, and with (IId) products derived from both phenyl migration (25%) and alkyl migration (25%).

Thus the oximes (IIa), (IIb) and (IIc) have the anti-1-phenyl configuration and the oxime (IIe) the syn-1-phenyl configuration. The oxime (IId) and its methiodide (IIId) appear to be a mixture of syn and anti isomers which we have not been able to separate. While it is most likely that the anti- isomer cyclises exclusively to give the isoxazoline (IVc) and the syn isomer undergoes only elimination to give the syn-vinyl ketoxime (Vc), production of some of the isoxazoline by a syn-anti base catalysed isomerization followed by cyclisation cannot be ruled out. Such an isomerization has been reported by Ginsburg and Wilson[7] who found that certain quaternary β-amino aldoximes undergo a rapid syn-anti isomerization in alkali.

The following sequence involving the production of a small quantity of optically active isoxazoline from a syn-precursor is thus explicable either on the basis of a small amount (< 5%) of anti-isomer being present

or of a small amount of syn-anti isomerism taking place during the cyclisation procedure. Thus the syn Mannich base oxime (IId) prepared by the above method may be resolved with (+)-dibenzoyltartaric acid to give the (-) dibenzoyl tartarate m.p. 147.5-149° (from methanol), $[\alpha]_{589}^{20}$ -51.05° (c = 10.5 in DMF), the free base of the oxime being released with dilute ammonia and the oxime methylated to give a methiodide m.p. 232-232.5° (from ethanol), $[\alpha]_{589}^{20}$ -1.14° (c = 8.3 in DMF). Treatment of this methiodide (with sodium ethoxide in a similar manner to IIId) gave on workup the isoxazoline (IVc) both in small yield (3.0%), m.p. 41.5-43°, and reduced activity $[\alpha]_{589}^{20}$ + 39.2° (c = 2.1 in $CHCl_3$).

Satisfactory microanalytical, i.r., and n.m.r. data for the above compounds have been obtained. Rotations were measured on a Perkin-Elmer 141 polarimeter and we wish to thank Dr. V. Chester of A. I. Guinness and Sons (St. James Gate, Dublin) for the use of this instrument.

References

1. (a) F. L. Scott, J. C. Riordan and A. F. Hegarty, Tetrahedron Letters, 537 (1963); (b) F. L. Scott and R. J. MacConaill, Tetrahedron Letters, 3685 (1967).

2. R. Andrisano, A. S. Angeloni, P. deMaria and M. Tramontini, J. Chem. Soc., (C), 2307 (1967).

3. F. L. Scott, R. J. MacConaill and J. C. Riordan, J. Chem. Soc., (C), 44 (1967).

4. The Mannich base oxime hydrochloride deposited from solution was racemic. The material remaining in solution (19%) was liberated as the free oxime with dilute sodium hydroxide and was optically active.

5. The configurations of this and other vinyl ketoximes mentioned have been deduced by Beckmann rearrangement and by n.m.r. studies. We use the terms syn and anti to describe the position of the oxime -OH relative to the 1-phenyl group in the compounds (II-V).

6. A. Pohland, L. R. Peters and H. R. Sullivan, J. Org. Chem., 28, 2483 (1963).

7. S. Ginsburg and I. B. Wilson, J. Amer. Chem. Soc., 79, 481 (1957).