Intramolecular C–H Bond Insertion Reaction of Optically Active Acyl Azide with Complete Retention of Configuration

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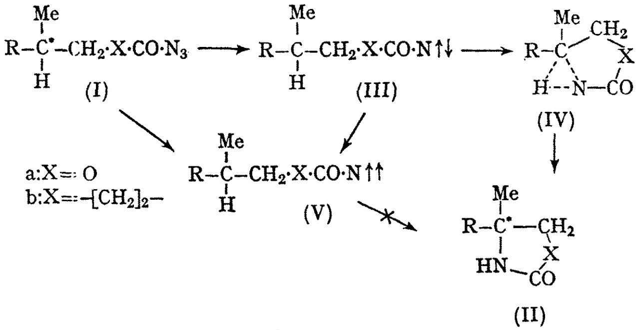
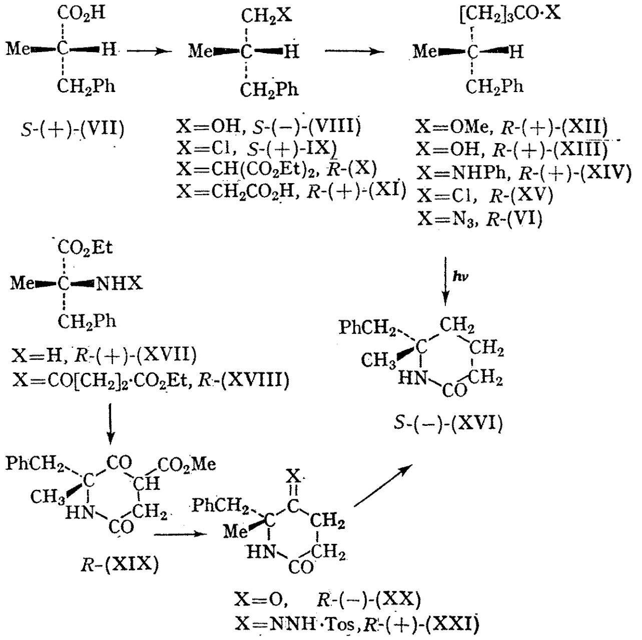
THE thermal and photochemical decomposition of optically active alkyl azidoformates (Ia) were shown[1] to give optically active 2-oxazolidinone (IIa) with nearly 100% retention of configuration *via* a transition state such as (IVa). It seemed likely that the singlet-state alkoxycarbonyl-nitrene (IIIa) produced from (Ia) was involved in this intramolecular insertion reaction and not the triplet-state alkoxycarbonyl-nitrene (Va) which might be formed from (Ia) and/or (IIIa).



SCHEME 1

We decided to study the photochemical decomposition of the optically active acyl azide (Ib), in order to examine the spin state of the acyl-nitrene which could intervene in intramolecular lactam formation from (Ib).[2]

(*R*)-5-Methyl-6-phenylhexanoyl azide, (R)-(VI), was selected for the photochemical reaction, and prepared as illustrated in Scheme 2.



SCHEME 2

Reduction of *S*-(+)-2-methyl-3-phenylpropionic acid [*S*-(+)-VII] α_D^{19} + 2·686° (*l* 0·1, neat), optical purity 100%,[1,3,4] with $LiAlH_4$ followed by the treatment with thionyl chloride gave the *S*-(+)-chloride, *S*-(+)-(IX). The chloride was condensed with diethyl malonate to afford the *R*-diester, *R*-(X), which was saponified and then decarboxylated to give *R*-(+)-4-methyl-5-phenylvaleric acid, *R*-(+)-(XI), m.p. 55—56°, $[\alpha]_D^{19}$ + 18·3° ($CHCl_3$).† The *R*-(+)-(XI) thus obtained, was converted into the *R*-(+)-methyl ester, *R*-(+)-(XII), *via* acid chloride and diazo-ketone as usual. *R*-(+)-5-Methyl-6-phenylhexanoic acid, *R*(+)-(XIII, b.p. 158—160·5° 2 mm., $[\alpha]_D^{18}$ + 13·1° ($CHCl_3$), was obtained by the hydrolysis of *R*-(+)-(XII), and confirmed as the *R*-(+)-anilide, *R*-(+)-(XIV), m.p. 91—92°, $[\alpha]_D^{20}$ + 15·3° ($CHCl_3$).† A mixture of the *R*-acid chloride, *R*-(XV) prepared from *R*-(+)-(XIII) with thionyl chloride, and 10 equiv. of NaN_3 in methylene chloride was stirred for 6 hr. at −15 to 0°, giving a methylene chloride solution of *R*-(VI). This solution was irradiated[1] immediately using a 30 w low-pressure mercury lamp for 18·5 hr. at 5—10°. A brown oil obtained by the evaporation of the reaction solution, was purified with silica gel column chromatography‡ affording (−)-6-benzyl-6-methyl-2-piperidone [(−)-XVI] m.p. 84·5—87·5°, $[\alpha]_D^{17}$ − 70·6° (EtOH)† [isolated yield from *R*-(VI), 4·3%].

Authentic *S*-(−)-(XVI) was synthesized from *R*-(+)-α-methylphenylalanine ethyl ester [*R*-(+)-XVII][1,5] α_D^{27} + 1·166° (*l* 0·1, neat), (optical purity 100%) as shown in Scheme 2. The *R*-diester, *R*-(XVIII), prepared by the acylation of *R*-(+)-(XVII), was submitted to the Dieckmann condensation using sodium methoxide as a base, to give the *R*-keto-ester *R*-(XIX), which was hydrolysed and decarboxylated to afford *R*-(−)-piperidine-2,5-dione, *R*-(−)-(XX).† The *R*-(+)-tosylhydrazone, *R*-(+)-(XXI)† obtained from *R*-(−)-(XX), was reduced with $NaBH_4$ in pyridine, affording *S*-(−)-(XVI)† m.p. 89·5—90°, $[\alpha]_D^{18·5}$ −72·2° (EtOH); (−)-(XVI) obtained by the photochemical decomposition of *R*-(VI) was identified with *S*-(−)-(XVI) by i.r. spectra, g.l.c., o.r.d., and mixed m.p.

Thus, (−)-(XVI) prepared from *R*-(VI) has the *S*-configuration and is 98% optically pure. The intramolecular reaction again proceeds with almost 100% retention of configuration and lactam (IIb) is formed solely from the singlet-state acyl-nitrene (IIIb) through transition state (IVb) in a similar manner to the formation of (IIa) from (Ia).[1]

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† Spectral and analytical data are in agreement with the assigned structure.

‡ Formation of reaction products other than (−)-(XVI), such as *R*-(+)-5-methyl-6-phenylhexyl isocyanate and 5-(1-methyl-2-phenyl)ethyl-2-pyrrolidone, will be discussed in detail in the full report.

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