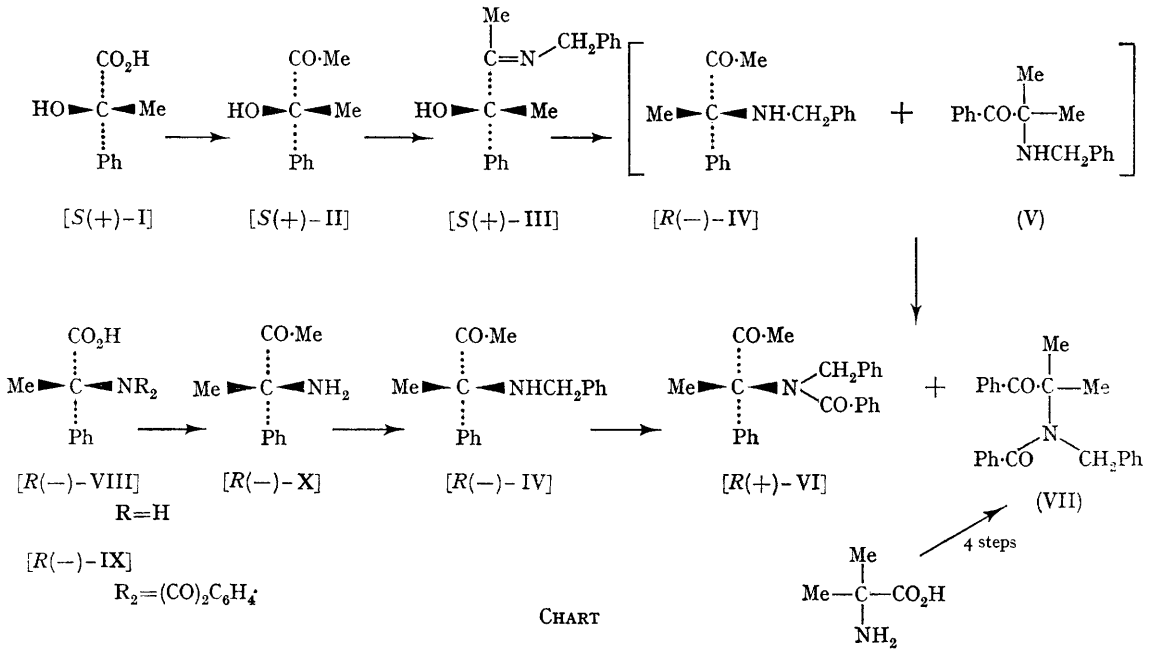
Thermal Rearrangement of Optically Active α-Hydroxy-imines to α-Amino-ketones

By SHUN-ICHI YAMADA,* HATSUHIKO MIZUNO, and SHIRO TERASHIMA
(*Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo, Japan*)

THE thermal rearrangement of α-hydroxy-imines with a tertiary hydroxy-group on the α-carbon atom to give α-amino-ketones is of synthetic and theoretical interest,[1] sometimes being applied to the synthesis of the D-homo-steroidal α-amino-ketones.[2]

The mechanism of this rearrangement has been envisaged as due to its intramolecular concerted manner as seen from both experimental data[1a,b,c,e,f] and kinetic studies,[1d] but no confirmation on this point has been given from a stereochemical point of view.[2] We describe a study on the reaction mechanism, using an optically active open-chain α-hydroxy-imine which contains only one asymmetric centre.

The sequence we employed is shown in the Chart. The material subjected to the rearrangement, [*S*(+)-III], b.p. 161—165°/0·04 m.m., α_D^{33} + 22·7° (*l* 0·1, neat), was prepared in 83% yield by the condensation of benzylamine with *S*(+)-3-hydroxy-3-phenylbutan-2-one [*S*(+)-(II)] in the presence of a trace of toluene-*p*-sulphonic acid in benzene, and

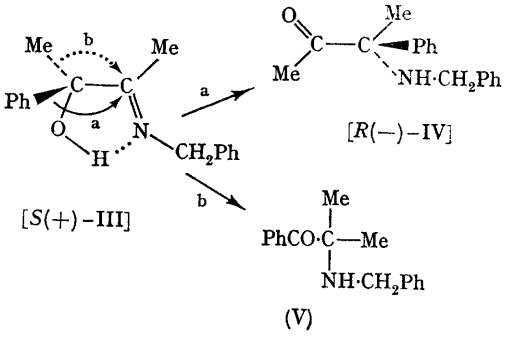


CHART

[S(+)-(II)] was obtained by the reaction of S(+)-atrolactic acid [S(+)-(I)], $[\alpha]_D^{26}$ +34·1° (EtOH), (optical purity 90%[3]) with methyl-lithium.

The thermal rearrangement of [S(+)-(III)] was performed under reflux in decalin for 18 hr. Purification of the reaction products by column chromatography using silica gel gave a mixture of two isomeric α-amino-ketones, (−)-3-benzylamino-3-phenylbutan-2-one [(−)-(IV)], and 2-benzylamino-2-methylpropiophenone (V), in a 38% combined yield. An attempt to separate [(−)-(IV)] and (V) was unsuccessful. The mixture was then benzoylated with benzoyl chloride in pyridine to give (+)-*N*-benzoyl-3-benzylamino-3-phenylbutan-2-one [(+)-(VI)], m.p. 98—109°, $[\alpha]_D^{10}$ +9·19° (EtOH) and *N*-benzoyl-2-benzylamino-2-methylpropiophenone (VII), m.p. 166—180°, which were isolated, respectively, from the reaction mixture with silica gel column chromatography. The [(+)-(VI)] thus obtained was identified by its mixed melting point, i.r. and n.m.r. spectra, and its optical rotatory dispersion curve as compared with the authentic sample [R(+)-(VI)], m.p. 101·5—107°, $[\alpha]_D^{10}$ +9·84° (EtOH), prepared from R(−)-α-methylphenylglycine[4] [R(−)-(VIII)] $[\alpha]_D$ −85·8° (1N-HCl), (95% optical purity) as shown in the Chart. Likewise, (VII) was also identified with an authentic sample, m.p. 188—189°, prepared from 2-amino-2-methylpropionic acid.

Thus, it has been clearly established that the structures of the rearranged ketones are [(−)-(IV)] and (V), one a phenyl migration product and the other a methyl migration product. The absolute configuration of [(−)-(IV)] was shown to be *R* by its correlation with [R(−)-(VIII)].[4]



Since the extent of the retention of optical activity in the rearrangement from [S(+)-(III)] to [R(−)-(IV)] was found to be almost total, as calculated from the optical purity of the starting material [S(+)-(I)] and [R(−)-(VIII)], we conclude that our results are in full agreement with the intramolecular cyclic mechanism suggested by Stevens *et al.*,[1] as

shown below. Methyl group migration may also proceed *via* a similar path. Further studies on this useful rearrangement are now in progress in our laboratory.

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