Existence of a Novel Mechanism in the Thermal Rearrangement of Isocyanide to Cyanide

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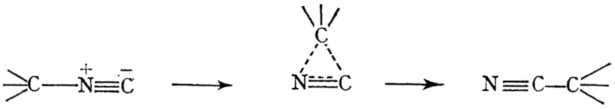
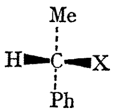
THE thermal rearrangement[1] of isocyanide (I) to cyanide (II) has been considered a typical unimolecular reaction, proceeding through a transition state such as (III) with retention of configuration at the asymmetric carbon involved. We have studied this thermal reaction using optically active isocyanides [S(−)-(VI) and *R*(+)-(XI)] with very simple structures, and find that the reaction of *R*(+)-(XI) proceeds by means of a radical mechanism and that racemization occurs.



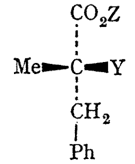
(I) (III) (II)

Optically pure isocyanides [*S*(−)-(VI)], α_D^{14} −3·576° (l 0·1, neat), and [*R*(+)-(XI)], α_D^{24} + 1·069° (l 0·1, neat) were prepared from optically pure *S*(−)-α-phenethylamine [*S*(−)-(IV)],[2] α_D^{13} −3·995° (l 0·1, neat), and *R*(+)-α-methylphenylalanine ethyl ester [*R*(+)-(IX)],[3] α_D^{20} + 1·226°

(l 0·1, neat), respectively, *via* the *N*-formyl derivatives [*S*(−)-(V) and *R*(+)-(X)].



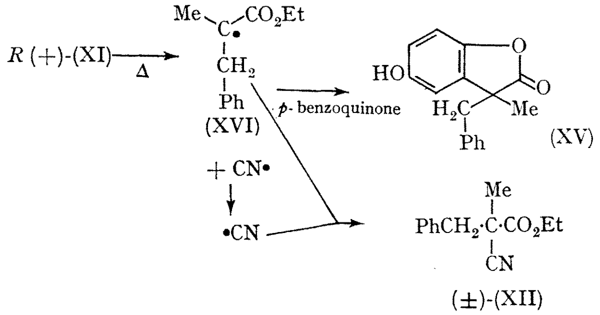
S(−)-(IV) : $X = NH_2$
S(−)-(V) : $X = NHCHO$
S(−)-(VI) : $X = \overset{+}{N}{\equiv}\overset{-}{C}$
S(−)-(VII) : $X = CN$
S(+)-(VIII) : $X = CO_2H$



R(+)-(IX) : $Y = NH_2$, $Z = Et$
R(+)-(X) : $Y = NHCHO$, $Z = Et$
R(+)-(XI) : $Y = \overset{+}{N}{\equiv}\overset{-}{C}$, $Z = Et$
S(+)-(XII) : $Y = CN$, $Z = Et$
S(+)-(XIII) : $Y = CN$, $Z = H$
R(−)-(XIV) : $Y = NHCOMe$, $Z = Me$

Heating *S*(−)-(VI) in diphenyl ether at 200° for 6 hr. gave *S*(−)-α-phenylpropionitrile [*S*(−)-(VII)], α_D^{8} −0·812° (l 0·1, neat) (59%) with 57% retention of configuration after complete disappearance of the starting material. That *S*(−)-(VII) could be obtained with such a retention of configuration was confirmed by the hydrolysis of *S*(−)-(VII) to *S*(+)-hydratropic acid [*S*(+)-(VIII)], $[\alpha]_D^{12}$ +44·5° (benzene).† When the diphenyl ether solution of *S*(−)-(VI) was heated for an additional 18 hr. at the same temperature, the *S*(−)-(VII) (63% yield) showed only 1·4% retention of optical activity. These results clearly show that *S*(−)-(VII) racemized spontaneously under the reaction conditions. Moreover, since racemization of the starting material seems to be inevitable in the reaction medium used,[1c] it seems that the thermal rearrangement of *S*(−)-(VI) proceeds through a cyclic transition state (III) as already reported.

Next, rearrangements of *R*(+)-(XI) were carried out under various conditions. Heating *R*(+)-(XI) in diphenyl ether for 3 hr. afforded *S*(+)-ethyl 2-cyano-2-methyl-3-phenylpropionate [*S*(+)-(XII)], α_D^{18} + 0·155° (l 0·1, neat) (77%). The degree of configuration retention was found to be 9% by comparison with optically pure *S*(+)-(XII), α_D^{24} +1·739° (l 0·1, neat), prepared from *S*(+)-2-cyano-2-methyl-3-phenylpropionic acid [*S*(+)-(XIII)],[4] $[\alpha]_D^{22}$ +24·8° (chloroform), by treatment with diazoethane. However, heating *R*(+)-(XI) at 225—230° for 45 min. or at 205° for 22 hr. without solvent, under nitrogen, gave almost completely racemized nitrile (+)-(XII) in 90 and 77% yield, the degrees of configuration retention being 2 and 0·3%, respectively. When the thermal rearrangement was studied at 225—230° for 1·5 hr. using Nujol as solvent, *S*(+)-(XII) (90% yield) also showed almost complete racemization.



On the other hand, when a diphenyl ether solution of *S*(+)-(XII), α_D^{25} +1·613° (l 0·1, neat), was heated under reflux for 2·5 hr., no racemization was observed in the recovered starting material. Moreover, when the rearrangement of *R*(+)-(XI) was interrupted at about 50% conversion after heating at 210° for 15 min. without solvent, and the un-rearranged *R*(+)-(XI) was isolated as *R*(−)-methyl 2-acetamido-2-methyl-3-phenylpropionate [*R*(−)-(XIV)],‡ m.p. 81—82°, $[\alpha]_D^{16}$ −67·9° (chloroform) by hydrolysis with aqueous hydrochloric acid, followed by acetylation[5] and esterification, the cyanide (XII) was obtained with almost complete racemization (retention of configuration: 0·7%), and *R*(+)-(XI) was recovered with no racemization.

From the fact that this thermal reaction proceeds rapidly even in a nonpolar solvent such as Nujol, and affords cyanide (XII) in a high yield, we assumed a radical mechanism for the rearrangement of *R*(+)-(XI), different from the mechanism for the rearrangement of *S*(−)-(VI). In order to confirm the existence of this new mechanism, the thermal rearrangement of *R*(+)-(XI) in diphenyl ether was carried out in the presence of *p*-benzoquinone as a radical scavenger. Purification of the reaction products by column chromatography (silica gel) gave a lactone (XV), m.p. 166·5—167°, in 5% yield based on *R*(+)-(XI); its structure was confirmed by spectral data and elemental analysis. Formation of (XV) seems to be a clear demonstration of the presence of the radical (XVI) in the reaction medium.

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† The optical rotation of *S*(+)-(VIII), $[\alpha]_D$ + 92·5° (benzene), assumed to be 100% optically pure, and extent of racemization of *S*(+)-(VIII) under the hydrolysis conditions (13·8%) were corrected. (*cf.* C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 1939, 916.)

‡ The optical rotation of *R*(−)-(XIV) and $[\alpha]_D^{23.5}$ − 60·1° (chloroform); assumed to be 100% optically pure. [K. K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. and Pharm. Bull.* (*Japan*), in the press].

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