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# FRAGMENTATION OF α-DISUBSTITUTED KETOXIMES. VIII.

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Recently, it has been demonstrated that α-trisubstituted ketoximes undergo the Beckmann rearrangement (1) in acidic media by a fragmentation-recombination mechanism (2) which, in part, proceeds in a intermolecular fashion (3). It has been tacitly assumed that the configuration of the migrating atom is retained in rearrangements of this type on the basis of the migration of an optically active group, having an α-disubstituted carbon, with almost complete retention of configuration (4). It is possible to postulate that the fragmentation of oximes may well be quite common, dependent only on the availability of the migrating group to stabilize a positive charge as a carbonium ion. If one considers the extreme forms of the intermediate ion (5), it can be seen that collapse of the bridged ion can occur in three directions

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1. For review see: L.G. Donaruma and W.Z. Heldt, Org. Reactions, 11, 1 (1960).
2. R.K. Hill and O.T. Chortyk, J. Am. Chem. Soc., 84, 1064 (1962).
3. R.T. Conley, J. Org. Chem., 28, 278 (1963).
4. J. Kenyon and D.P. Young, J. Chem. Soc., 263 (1941); A. Campbell and J. Kenyon, ibid, 25 (1946).
5. R. Huisgen, J. Witte and I. Ugi, Chem. Ber., 90, 1844 (1957).

(FIG.I), the relative distribution of products depending on the stability charge at either carbon or nitrogen.

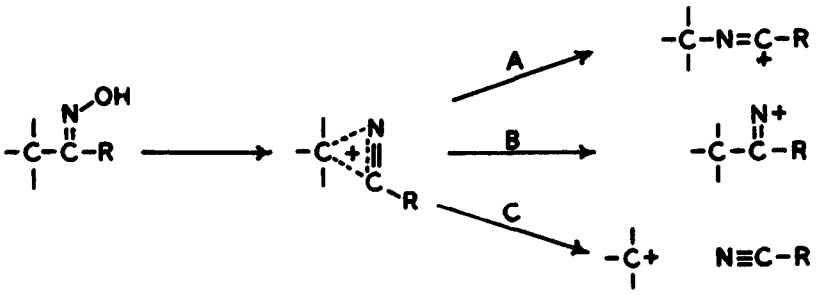


FIG.I

In order to test the fragmentation route (C,FIG. I) as an intermediate stage in the Beckmann rearrangement, we have investigated in detail the products from a number of systems in which the potential fragmenting carbon is fully substituted with alkyl or aryl groups (6). An α-carbon bearing a single hydrogen substituent generally has been considered to rearrange without fragmentation (A, FIG.I). The only reported exceptions to this generality have been the rearrangement of certain bridged bicyclic ketoximes such as norcamphor oxime (7), and oximes having nitrogen, oxygen or sulfur substituents on the α-carbon (8).

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6. R.T. Conley and R.J. Lange, J. Org. Chem., 28, 210 (1963) and references therein.

7. For examples see: R.C. Elderfield and E.T. Losin, J. Org. Chem., 26, 1703 (1961), H.K. Hall, Jr., J. Am. Chem. Soc. 82, 1209 (1960);M. Gates and S.P. Malchick, J. Am. Chem. Soc., 79, 5546 (1957);S. Wawzonek and J.V. Hallum, J. Org. Chem., 24, 364 (1959) and K.W. Bentley and J.P. Ringe, J. Org. Chem. 22, 424 (1957). Other exceptions have been reported, but these cases have been the result of the pyrolytic fragmentation of oximes (cf. M.J. Hatch and D.J. Cram, J. Am. Chem. Soc., 75, 38 (1953) rather than acid or base catalyzed reactions.

8. For review see: R.K. Hill, J. Org. Chem. 27, 29 (1962)

We wish to report the first observed fragmentation at an α-disubstituted carbon center and the possibility of partial recombination of fragments during molecular rearrangements of the carbon-nitrogen type in acidic medium. Heating phenyl cyclohexyl and phenyl cyclopentyl ketoxime, m.p. 158-158.5° and m.p. 130-130.5°, respectively (9,10), in polyphosphoric acid at 130° for 10 minutes yielded, in each case, a mixture of primary and secondary amides. Separation of the amide fraction by column chromatography on alumina yielded benzamide in both cases studied. The secondary amides were only partially separated on the alumina column and therefore the combined secondary amide fraction was hydrolyzed in 30 percent sulfuric acid. The amines were isolated and identified by gas chromatographic techniques. The rearrangement products obtained and identified as described above are summarized in the Table.

To further test the fragmentation-recombination mechanism, phenyl cyclopropyl ketoxime, m.p. 70-75° (11) was rearranged under identical conditions. In this case no fragmentation was expected due to the poor carbonium ion stabilizing character of the cyclopropyl group. Indeed, using a mixture of syn and anti (to phenyl) isomers only phenyl group

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9. M. Mousseron, P. Froger, R. Granger and F. Winternitz, Bull. soc. chim., France, 843 (1947).

10. I. Elphimoff-Felkin and B. Tchonbar, Compt. rend., 237, 726 (1953).

11. Repeated fractional crystallizations of this isomeric oxime mixture gave a sample of anti-phenyl cyclopropyl ketoxime, m.p. 92-93°C. For the purposes of this study the isomeric mixture was investigated in detail. It should be noted that the pure oxime behaves in a fashion analogous to that reported for the isomeric mixture. For the anti isomer: T.R. Marshall and N.H. Perkin, J. Chem. Soc., 59, 853 (1891) reported m.p. 90-92°; J.B. Conant, N.B. Segur and W.R. Kirner, J. Am. Soc., 46, 1882 (1924) report m.p. 90-94°; and, M. Petrus and M.R. Jacquier, Bull. soc. chim., France, 1275 (1961) report m.p. 95-96°.

migration would be expected, since if oxime isomerization occurs through electron deficient nitrogen ($\geq C=N^+$) in this medium (B, FIG.I) it would be competitive with rearrangement. On isolation of the crude reaction products only a single amide product, N-phenyl cyclopropylcarboxamide, could be detected by gas chromatographic analysis of the crude amide and the amine portion of the hydrolysis products.

It should be noted that the isolation of a mixture of secondary amides in the case of phenyl cyclohexyl and phenyl cyclopentyl ketoxime as well as the single secondary amide from the isomeric oxime mixture of phenyl cyclopropyl ketoxime indicates an appreciable amount of oxime isomerization must

TABLE I

Beckmann Rearrangement Products

| Ketoxime | Amide | Yield[d] |
|---|---|---|
| Phenyl Cyclohexyl[a,c] | N-Cyclohexylbenzamide | 62 |
| | N-Phenylcyclohexylcarboxamide | 21 |
| | Benzamide | 9 |
| Phenyl Cyclopentyl[a,c] | N-Cyclopentylbenzamide | 57 |
| | N-Phenylcyclopentylcarboxamide | 29 |
| | Benzamide | 6 |
| Phenyl Cyclopropyl[b,c] | N-Phenylcyclopropylcarboxamide | 96 |

a) The ketones were prepared by the method described by C. H. Tilford and M.G. Van Campen, J. Am. Chem. Soc., 76, 2431 (1954).

b) Commercial material.

c) All oximations were carried out by the pyridine-ethanol procedure described by W.E. Bachmann and M.X. Barton, J. Org. Chem., 3, 307 (1938).

d) Yields were obtained from the column chromatographic isolation procedures and gas chromatographic analysis as described in the text.

have taken place in the polyphosphoric acid medium (12,13). The fact that no cyclohexylcarboxamide was formed is not suprising since it would not be expected that fragmentation to a phenyl cation would take place.

These observations clearly indicate that fragmentation occurs in the rearrangement of α-disubstituted ketoximes as well as in numerous cases already reported of α-trisubstituted ketoxime cleavage.

In addition, if benzonitrile, the expected initial fragmentation product, and cyclohexene are heated under identical experimental conditions as those used to effect oxime rearrangement, N-cyclohexylbenzamide can be isolated in good yield (62%). In addition to the secondary amide, 21% of the hydration product, benzamide, can be obtained by chromatographic procedures. It must be concluded from these data that recombination of the fragmentation products could also have occurred in these rearrangements.

From this study, it is shown that the existing postulates concerned with group migration from carbon to nitrogen in an intramolecular fashion describes only a portion of the mechanistic behavior of α-disubstituted ketoximes in acidic medium. It may well be that these postulates accurately describe only the limited cases involving the transferral of α-methylene groups in detail and represents a mechanistic extreme for these rearrangements. Group transfer in a large number of ketoxime rearrangements most likely proceeds, in part or wholly, by the fragmentation-recombination mechanism depending upon the groups attached to the α-carbon. Therefore, the true mechanistic picture of these processes is more complex than presently believed.

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12. This data differs markedly from the observations reported by N.H.P. Smith, J. Chem. Soc., 4209 (1961) in which the syn and anti forms of 2-bromo-5-nitroacetophenone oxime rearranged without stereochemical interconversion.

13. For a plausibe alternate explanation see: R.T. Conley and L.J. Frainier, J. Org. Chem., 27, 2844 (1962)

In the case of α-disubstituted ketoximes, the migration may, at least in small part, proceed via this mechanism. The migrating group can be essentially free from both the migration origin (the oxime carbon) and the migration terminus (the oxime nitrogen) during the intermediate stages of rearrangement. A detailed description of structure versus mechanism of rearrangement is presently being elucidated and we hope to report our complete findings in the very near future.

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