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NON-STEREOSPECIFICITY IN THE BECKMANN AND SCHMIDT REACTIONS

by Peter T. Lansbury* and Norman R. Mancuso#
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214

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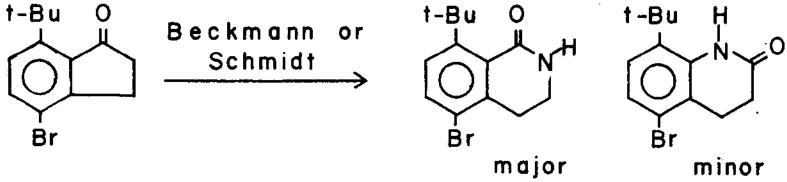
In connection with our work on C-H bond insertion of iminium cations ($>C=N+$) under Beckmann and Schmidt rearrangement conditions (1), we noted that the lactams resulting from rearrangement sometimes consisted mainly of the product of alkyl migration.



Although one might attribute this migrational preference to syn-aryl configurations of the oxime (from isomerization) and/or iminodiazonium ion⁺, inspection of the data below

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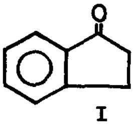
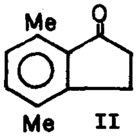
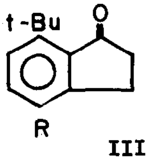
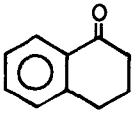
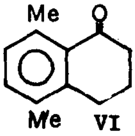
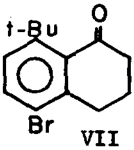
* Alfred P. Sloan Foundation Fellow, 1963-1967.

\# DuPont pre-doctoral Teaching Fellow, 1964-1965.

\+ In the case of phenyl alkyl ketones, Schmidt rearrangements were reported to give increased amounts of alkyl migration, going from methyl to ethyl to isopropyl. In this case increased steric bulk in the alkyl group supposedly results in a greater proportion of syn-aryl iminodiazonium ions (ref. 1) shows that the greatest amount of alkyl migration occurs in those compounds least likely to exist in that configuration, a result incompatible with prior isomerization of oximes. The possibility that the above example constitutes a truly non-stereospecific Beckmann rearrangement in a non-fragmentable ketone instead of *trans* migrations from equilibrated oximes, led us to investigate such ketones more intensely.

We now wish to report data (see Table 1) on the effect of substituents *ortho* to the carbonyl group on migration aptitudes in Beckmann and Schmidt reactions (2), as well as anhydrous diazotization of hydrazones, which strongly suggests that univalent nitrogen intermediates may be involved in the rearrangement mechanism. All reactions were run in polyphosphoric acid (PPA) at elevated temperatures. The oxime rearrangements were carried out at 110-120° for 5-10 minutes and the Schmidt rearrangements and hydrazone diazotizations at 55-60°, with sodium azide or sodium nitrite, respectively, being gradually added to the dissolved ketone-solvent mixture. The lactams were obtained by ether extraction of reaction mixtures quenched in ice water, followed by gas-liquid partition chromatography, using authentic samples of lactams for identification in most cases. All lactams were characterized by infrared and/or n.m.r. spectroscopy and new compounds also were subjected to elemental analysis with satisfactory results. Details will be reported subsequently.

TABLE 1: Migration Aptitudes in Ketone Rearrangements

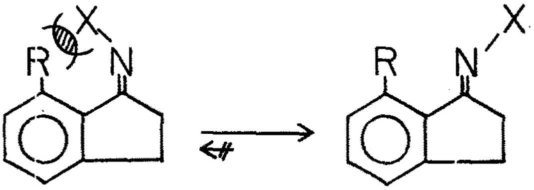
Ketone	Reaction	% Aryl migration[a]	% Alkyl migration[a]	Yield[b]
 I	Schmidt	76	24	60
	Beckmann	90	10	20
	Hydrazone diazotization	91	9	77
 II	Schmidt	37	63	65
	Beckmann	34	66	48
	Hydrazone diazotization	22	78	36
 III, R = Br IV, R = H	Schmidt (III)	15	85	50
	Schmidt (IV)	13	87	25
	Beckmann (III)	19	81	25
 V	Schmidt	87	13	45
	Beckmann	99	1	65
	Hydrazone diazotization	100	--	40
 VI	Schmidt	69	31	62
	Beckmann	99	1	.92
	Diazotization	88	12	93
 VII	Beckmann	100	--	97[c]

[a] Based on lactams only; v.p.c. yield data are considered accurate to better than ± 2%.

[b] Based on starting material.

[c] Product is de-t-butylated lactam.

Models clearly show that syn-aryl oximes and iminodiazonium ions derived from II-IV would be too sterically compressed to exist relative to the anti-isomer.



Thus, the major products from all three reactions arise either predominantly from cis-rearrangements or from non-stereospecific rearrangements of iminium cations, the species previously shown to be responsible for C-H bond insertion (1), a side reaction occurring in these ketones. Although the hypothesis of univalent nitrogen intermediates has been "adequately demolished" (2) for a large number of Beckmann rearrangements, a consideration of ρ-values or reactions of m- and p-substituted acetophenone oximes, where solvents and leaving groups are varied, suggests that a whole spectrum of mechanistic behavior for oxime rearrangements can be expected, the smallest rho reflecting the least contribution by the migrating aryl group in the transition state. A similar argument has been advanced for deducing the quality of the transition state in E2 eliminations of beta-phenylethyl derivatives (3).

Now if iminium ions can be implicated in the indanone reactions, where the migrating group is well "tied back" to begin with, it can be seen that aryl migration becomes

TABLE 2: Substituent Effects in Acetophenone oxime Reactions

Reaction (Ref.)	rho	Remarks
oxime picrates, heated in 1,4-dichlorobutane (4)	-4.1	"phenonium ion-like" transition state; poor ionizing solvent.
oxime in sulfuric acid (5)	-2.0	
oxime in PPA (6)	-0.25	little, if any, aryl participation; good ionizing solvent.

progressively more difficult with increasing bulk of the ortho substituent (more steric compression generated in the transition state). The torsional ring effect (4) also raises the activation energy for aryl migration in all of the indanones studied. Whether the net migration of primary alkyl carbons in I-IV results from fragmentation-recombination or not requires further study.

The results in the tetralone series (V-VII) are compatible with the greatly diminished torsional strain in the transition state for aryl migration in the more flexible tetralone system (4). However, the noticably larger percentages of alkyl shifts in Schmidt reactions, when compared with the Beckmann reactions, suggests that these could result from direct rearrangement of the azidohydrin.*

In conclusion the generalization of trans-stereochemistry in Beckmann and Schmidt reactions must be used with caution in predicting rearrangement products and assigning oxime

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* The absence of torsional strain in this mechanism also helps to explain the noticably higher reported yields of lactams in the Schmidt reaction of 1-indanone (68%) as compared with the Beckmann Rearrangement (2) (10%). Other cases are known where the above two reactions lead to different products from the same ketone (2).

configurations, even when oxime isomerism is unlikely. Conley and coworkers (7) have also observed lack of stereospecificity in Beckmann rearrangements where either oxime isomerization or univalent nitrogen intermediates could be the cause; however an unambiguous choice between the alternatives, as with ketones III and IV, was not possible.

References

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