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# UNUSUAL REGIOCHEMISTRY IN A BECKMANN-LIKE REARRANGEMENT OF CAMPHOR. α-CAMPHIDONE VIA METHYLENE MIGRATION.

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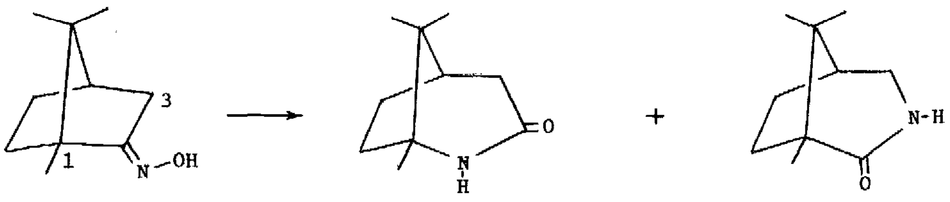
Summary: Reaction of camphor with hydroxylamine-O-sulfonic acid affords the nitrogen insertion product α-camphidone by migration of the methylene group rather than the bridgehead. Since Beckmann rearrangements of trigonal oximes afford bridgehead cleavage products with camphor, an alternative synchronous rearrangement of a tetrahedral intermediate is proposed for this Beckmann-like reaction.

Beckmann rearrangement of camphor anti-oxime **1**[1] can lead in principle to lactam **2** via tertiary bridgehead migration, or to α-camphidone **3** via primary methylene migration. On the basis of generally observed mechanisms for the Beckmann rearrangement, the migratory aptitudes of carbon-1 and carbon-3 of camphor oxime **1** would be expected to depend upon either; (1) the oxime configuration, if there is a stereospecific migration of the carbon anti to the oxime leaving group; or (2) the relative abilities of the designated carbons to support positive charge in the rearrangement transition state, if migration occurs subsequent to loss of the oxime leaving group.[2a] By either criterion the lactam **2**, formed by migration of the more highly substituted and sterically larger carbon-1 of camphor anti-oxime **1**, will be the expected major Beckmann lactam. Formation of mainly α-camphidone **3** during a Beckmann rearrangement would be unusual in that migration of methylene carbon-3 of **1** is required. Although by this analysis α-camphidone **3** is the "abnormal" Beckmann lactam, the term "unusual" Beckmann lactam will be used to avoid confusion with the unfortunate phrase, "abnormal Beckmann reaction," used to describe cleavage processes.[2b]

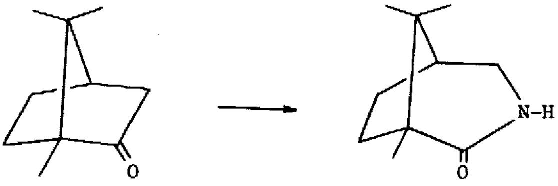
Other than one exception noted below, Beckmann rearrangement catalysts and camphor oxime **1** afford neither the expected lactam **2**, nor the "unusual" α-camphidone **3**, but a variety of cleavage and cleavage/rearrangement products[2c,3] derived from fragmentation at the quaternary bridgehead carbon-1 of oxime **1**. For example, thionyl chloride,[4-6] sulfuric acid,[7,8] hydroiodic acid,[9] polyphosphoric acid,[2c,3] benzenesulfonyl chloride/sodium hydroxide,[10] phosphorus pentoxide,[11] photolysis in methanol,[12] and pyrolysis,[12] failed to afford lactams



1 2 3

2 or 3 from camphor oxime 1. Only upon photoirradiation in methanol acidified with acetic acid[13] was a lactam, tentatively assigned structure 2, reported in unspecified yield, and in this case a novel photochemically derived oxaziridine intermediate was involved.[14]

We wish to report the first example of a lactam derived via a non-photochemical Beckmann nitrogen insertion with camphor 4. The unusual Beckmann lactam, α-camphidone[15] 3, has been obtained in 46% isolated yield upon reflux of camphor 4 (620 mg) for 20 hr with hydroxylamine-O-sulfonic acid in formic acid or in 48% isolated yield upon reflux for 8 hr in glacial acetic acid.[17] The formation of α-camphidone 3 by direct nitrogen insertion into camphor 4 has been reported previously only in less than 1% isolated yield using the Schmidt reaction with sodium azide/sulfuric acid/chloroform.[18]



4 3

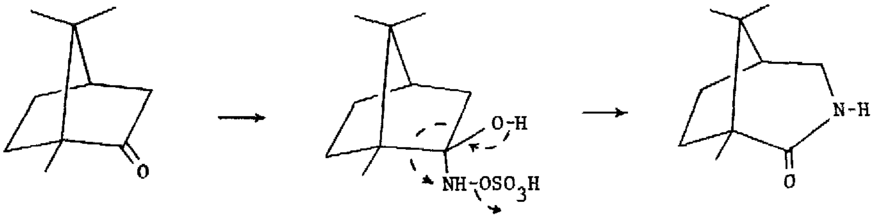
The formation of α-camphidone 3 from camphor 4 is suggested to proceed as in Scheme 1. Addition of hydroxylamine-O-sulfonic acid to camphor 4 affords a tetrahedral intermediate 5, with the stereochemistry of addition remaining unspecified. Synchronous rearrangement of intermediate 5 with loss of sulfuric acid concomitant with methylene migration affords α-camphidone 3.[19] Precedent for such a tetrahedral reactive intermediate is available in the rearrangements of N-alkylnitrones from ketones[19a] and of α-azidohydrins;[19b] preferential methylene migration has been observed from the latter species.[19b]

An alternative mechanism shown in Scheme 2 involves dehydration of the pivotal intermediate 5 to give an oxime-O-sulfonic acid derivative 6, which subsequently rearranges to α-camphidone 3. We reject the Scheme 2 mechanism in this instance, since treatment of oxime 1 with one mol-equivalent of sulfuric acid in formic acid[17a] affords no observable lactam 3 (or lactam 2).

It is to be noted that the O-sulfonic acid leaving group on the hydroxylamine reagent is crucial to the success of the nitrogen insertion with camphor 4. Hydroxylamine hydrochloride in 97% sulfuric acid[20] afforded no observable α-camphidone 3 (or lactam 2) when mixed with camphor 4.

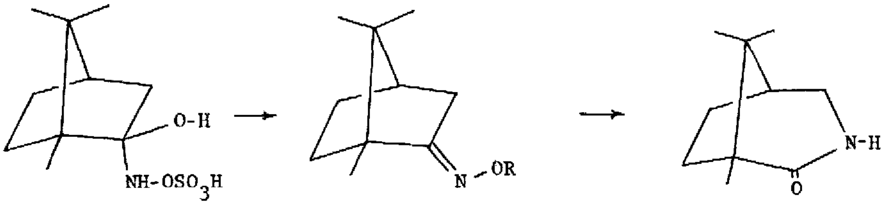
For nitrogen insertion adjacent to methylene in camphor 4, hydroxylamine-O-sulfonic acid/formic or acetic acid is a mild one-pot alternative to the sodium azide/sulfuric acid mediated Schmidt[18] rearrangement to afford α-camphidone 3. From a regiochemical perspective the hydroxyl

Scheme 1. The Tetrahedral Model For Formation Of α-Camphidone 3.



4 5 3

Scheme 2. The Trigonal Model For Formation Of α-Camphidone 3.



5

1 R = H

6 R = $SO_3H$

3

amine-O-sulfonic acid reagent does not provide an alternative in this instance to the Beckmann rearrangement, which affords lactam 2 from camphor oxime 1.[14] Further studies are underway to elucidate those factors influencing the regiochemistry of nitrogen insertion reactions of bridged bicyclic ketones.

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