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TRANSFORMATION OF 4-NITROALKANE-1,7-DIONES INTO PYRROLIZIDINES

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Abstract: *Depending on the conditions the reduction of 5-nitropentadecane-2,8-dione (**4**) gave as main products the two isomeric pyrrolizidines* **1a** *(xenovenine, $NaBH_3CN/NH_4OAc$; as ^{15}N-**1a** with $NaBH_3CN/^{15}NH_4OAc$) and* **1b** *(H_2-Pd/C), respectively.*

The bicyclic pyrrolizidine (1-azabicyclo[3.3.0]octane) is one of a number of so-called pyrrolizidine alkaloids wide spread throughout the plant and animal kingdom [1]. For example a few 2,8-dialkylated pyrrolizidine bases have been isolated from natural sources, e.g. r-2-heptyl-c-5-hydro-c-8-methyl-1-azabicyclo[3.3.0]octane (**1a**, = xenovenine) from the cryptic thief ant *Solenopsis* (Diplorhoptrum), presumeably *S. xenovenenum* [2]. This compound appears to be part of the ants defensive system.

In continuation of our studies on the transformation reactions of aliphatic and alicyclic nitroketones we have investigated the conversion of aliphatic nitrodiketones of different chain lengths into pyrrolizidine derivatives, indolizidines [3] as well as quinolizidines [4]. When the reduction of aliphatic nitrodiketones is performed under controlled conditions [3] the azabicyclic materials can be synthesized in good yield [3, 5].

In order to synthesize xenovenine (**1a**) and its isomers, the nitrodiketone **4** (5-nitropentadecan-2,8-dione) must first be prepared. The synthesis of **4** by a *Michael* reaction between nitromethane and α,β-unsaturated ketones was found to be more difficult than expected. In contrast to the literature [6], complex mixtures of compounds containing additional C,C-bonds formed by aldol type reactions were observed when the alkyl vinyl ketones reacted with the nitro compounds. The best way to prepare **4** is given in the Scheme.

This includes the stepwise reaction of nitromethane with 0.2 equ of methyl vinyl ketone (benzene, 45°, 2 hrs), catalyzed with tributylphosphine. This gave 5-nitropentan-2-one (**2**) which, after reaction with dec-1-en-3-one (**3**) (under the same reaction conditions as before) yielded compound **4**. The ketone **3** was prepared via a *Grignard* reaction between heptylmagnesium-bromide and acrylaldehyde. Oxidation of the unsaturated alcohol, with a 30 mole excess of MnO_2, afforded the ketone **3**. We then attempted to convert the nitrodiketone **4** into 2-heptyl-5-hydro-8-methyl-1-azabicyclo[3.3.0]-octane by two different methods. Firstly, catalytic hydrogenation in the presence of 10% palladium on carbon gave the expected 5-epi-xenovenine (**1b**) (the expected *syn*-hydrogenation product) in 65% yield. Surprisingly xenovenine (**1a**) itself was also formed in approximately 5% yield. To try and improve the yield of xenovenine, **1b** was oxidized with $Hg(OAc)_2$/AcOH and afterwards reduced with $NaBH_3CN$ [7]. The conversion ratio of **1b** to **1a** is better than 60%. The formation of a small amount of the anti-hydrogenation product **1a** can best be explained in terms of an partial dissociation of the substrate from the catalyst, then its re-absorption, followed by completion of its hydrogenation.

Even more surprising were the results observed when we reduced the nitro-diketone **4** with $NaBH_3CN$, MeOH, NH_4OAc, KOH, and $NaBH_4$. Under these reaction conditions all four isomers were formed but xenovenine (**1a**) was by far the most abundant (nearly 88% of **1a**, against 12% in total of the other three).

In contrast to the catalytic hydrogenation where the nitrogen source for the final products is the nitro group, the nitrogen source for the second reduction is the ammonium ion of NH_4OAc exclusively (shown by ^{15}N labelling and EI-MS analysis [8]). Taking these results into account, the course of the reaction forming the pyrrolizidine from the nitrodiketone **4** must be as follows: Firstly **4** is converted into either the triketone **5** [9], an amino-nitroketone of type **6** [10] or the eight-membered ring compound **7** [12]; then this intermediate cyclizes to give the product **1a**. We favour the ring contraction via compound **7** [14] because of the observed stereoselectivity [12].

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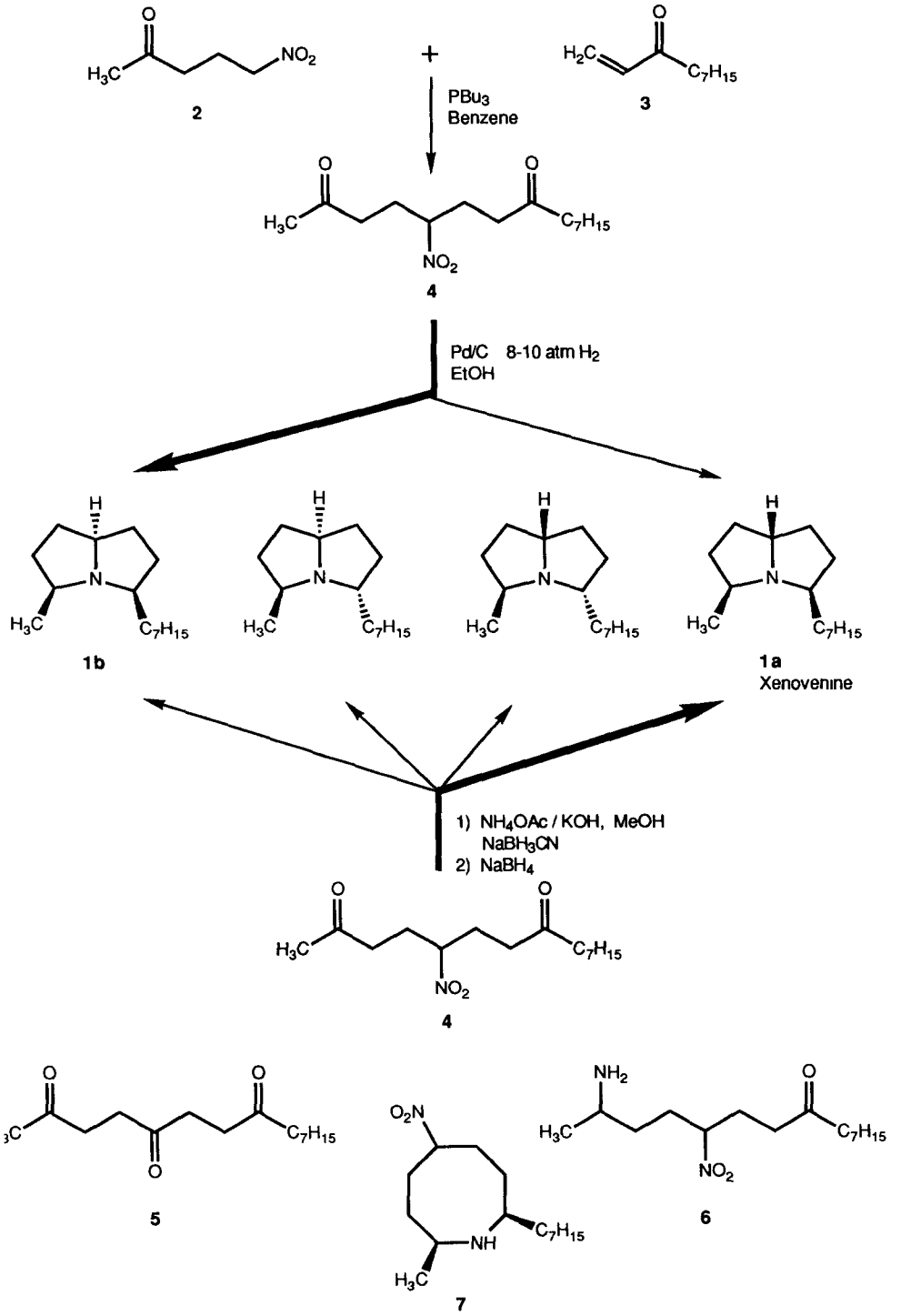
PBu3
Benzene
Pd/C 8-10 atm H2
EtOH
1) NH4OAc / KOH, MeOH
NaBH3CN
2) NaBH4
2
3
4
1b
1a
Xenovenine
5
6
7

References and Notes

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[8] EI-MS of ^{15}N-**1a**: 224 (9, M^+), 223 (6), 209 (14, $[M-CH_3]^+$), 195 (6), 181 (5), 169 (7), 143 (7), 141 (11), 139 (5), 126 (36), 125 (100 $[M-C_7H_{15}]^+$), 111 (12), 98 (15), 85 (26), 81 (22), 69 (19), 55 (26), 41 (35).

[9] Treatment of **5** under the same reaction conditions as for **4** gave a mixture of the pyrrolizidine isomers in approx. the same proportion as in the case of **4** [2].

[10] The intermediate **6** would better explain the loss of the nitro group by neighbouring group participation than anything else, a reaction which was found to influence the stability of nitrolactams on SiO_2 [11].

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[12] The 8-membered **7** can be "bicyclized" by a transannular reaction leading finally to the immonium intermediate from which it is known to give **1a** by $NaBH_3CN$ reduction, and therefore **7** will explain best the ratio of the four isomers. It seems important to note that formation of 2,5-dialkyl-pyrrolidine derivatives from 1,4-diketones gives the *cis/trans* isomers in a nearly 1:1 mixture [13].

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