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BECKMANN FRAGMENTATION VERSUS BECKMANN REARRANGEMENT IN DEHYDRONORCAMPHOR DERIVATIVES

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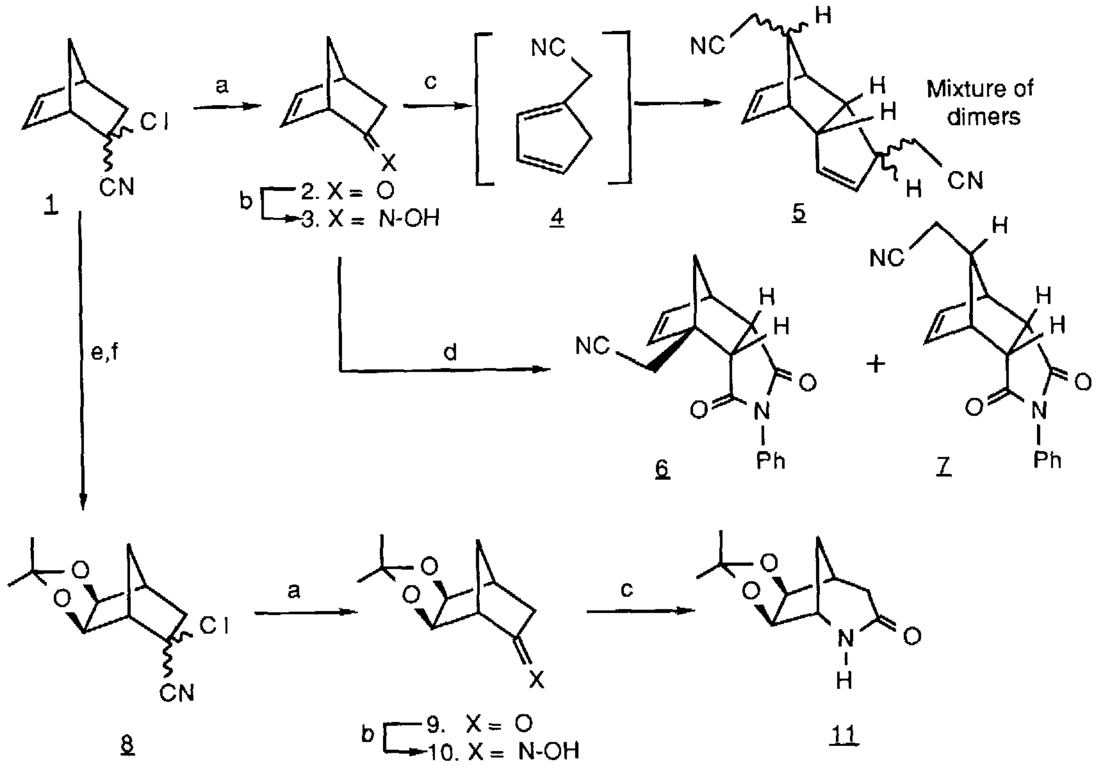
Summary: Attempted Beckmann rearrangement of dehydronorcamphor oxime resulted in Beckmann fragmentation and dimerization of the intermediate cyanomethylcyclopenta-1,3-diene isomers. The dienes can be trapped by N-phenylmaleimide to yield two isomeric crystalline adducts. When the olefin in dehydronorcamphor oxime is effectively blocked, Beckmann rearrangement takes place to provide stereochemically pure bicyclic lactam.

The Beckmann rearrangement of ketoximes has been used extensively in organic synthesis due to the simplicity at which the reaction affects nitrogen insertion into a carbon framework and the fact that the rearrangement is usually stereospecific[1]. However, in [2.2.1]bicyclo-2-heptanone systems[2] the rearrangement is not straightforward and in many cases the fragmentation reaction is the major pathway observed. Various reports on the rearrangement of norcamphor oxime offer both conflicting accounts of fragmentation versus rearrangement and uncertainty as to the actual structures of the isomeric lactams produced[3]. We have been studying the possible Beckmann rearrangement of dehydronorcamphor oxime for the purpose of preparing 2-azabicyclo[3.2.1]oct-6-en-3-one and report here an interesting fragmentation reaction which produced an unstable cyclopentadiene derivative[4].

Dehydronorcamphor 2[10] was readily converted to the (syn, anti) mixture of corresponding oximes 3 using standard oximation procedures, (see figure). Attempted Beckmann rearrangement using boron trifluoride in sym-tetrachloroethane[5] at 90°C produced a black reaction mixture from which was found the interesting dimer 5 as the only isolable material, (13% yield as a complex mixture of isomers[6]). The dimers must arise through a Beckmann fragmentation reaction followed by dimerization of the intermediate 1-cyanomethylcyclopenta-1,3-diene 4. The Beckmann fragmentation is known to take place when a relatively stable carbocation can result or if the oxime is derived from an aldehyde[7]. In our example there is considerable driving force for



Scheme 1. Reagents; a). KOH, H_2O, DMSO , 85°C. b). H_2NOH-HCl, NaOH, H_2O, EtOH, R.T. c). BF_3-Et_2O, tetrachloroethane, 110°C. d). BF_3-Et_2O, tetrachloroethane, N-phenylmaleimide, 90°C. e). $KMnO_4$, H_2O, EtOH, $MgSO_4$, -50°C. f). acetone, p-TsOH, reflux.

fragmentation since an allylic cation is formed which can lose a proton to generate the cyclopentadiene. In order to substantiate the existence of this intermediate diene, N-phenylmaleimide was added to the reaction mixture (BF_3, tetrachloroethane, 90°C) and consequently, the two crystalline Diels-Alder *endo*- adducts 6 and 7 were isolated, (each in 14 % yield after chromatography[8]). The 1-cyanomethylcyclopenta-1,3-diene is apparently in equilibrium with the isomeric 5-cyanomethyl compound[9] in these reaction conditions and both give rise to the two observed Diels-Alder adducts.

In order to successfully achieve Beckmann rearrangement and produce the desired 2-azabicyclo[3.2.1]octan-3-one system yet maintain functionalization in the 6,7-positions, the olefin of dehydronorcamphor must be effectively masked. We chose to block the alkene as the acetonide protected *cis* -exo diol. Consequently, the known cyanochloride 1[10] was first converted to the protected diol 8 ($KMnO_4$ then acetone, p-TsOH, reflux) then hydrolyzed to the ketone 9, (KOH, DMSO, H_2O, 85°C). Oximation with hydroxylamine produced the (syn, anti) mixture of oximes 10. We were encouraged to discover that the boron trifluoride triggered Beckmann rearrangement at 110°C furnished the 2-aza bicyclic lactam 11 as the only product (61% yield after chromatography). The structure of the lactam was conclusively established as being the 2-aza isomer through ^{1}H-NMR spectroscopic analysis[11]. One can conclude that the Beckmann rearrangement of oximes 10 is possible only because the olefin is effectively blocked as the diol derivative.

Particularly intriguing is the possibility of intramolecular trapping of cyclopentadiene derivatives generated by such a fragmentation process, however, preparative uses will depend upon significant yield improvements. Work toward this goal is currently in progress along with conversions of the 2-aza bicyclic lactam 11 into useful alkaloids.

Acknowledgements

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References and Notes:

1. Donaruma, L.G. and Heldt, W.Z., *Org. React.*, 1960, 11, 1; Gawley, R.E., *Org. React.*, 1988, 35, 1.
2. Krow, G.R., *Tetrahedron*, 1981, 37, 1283.
3. Swiss Patent 270,546, (1951), *Chem. Abstr.*, 1952, 46, 780; Swiss Patent 287,863, (1953), *Chem. Abstr.*, 1955, 49, 2490; Hall, H. K., *J. Am. Chem. Soc.*, 1960, 82, 1209; Elderfield, R.C. and Losin, E.T., *J. Org. Chem.*, 1961, 26, 1703; Fox, B.L. and Reboulet, J.E., *J. Org. Chem.*, 1968, 33, 3639; Fox, B.L. and Rosenberg, *J. Chem. Soc.Chem. Commun.*, 1969, 1115;

4. The only related fragmentation to our knowledge was the report of a trimethylsilyl assisted fragmentation which produced an acyclic diene. Nishiyama, H., Sakuta, K., Osaka, N. and Itoh, K., Tetrahedron Lett., 1983, 24, 4021 Idem, Tetrahedron, 1988, 44, 2413.
5. Conley, R.T. and Ghosh, S., in "Mechanisms of Molecular Migrations", Thyagurajan, B.S., Ed., Volume 4, pp 230-233, John Wiley and Sons, New York, 1971.
6. Reaction conditions are not optimized. All compounds gave satisfactory ^{1}H-NMR spectra, Infrared spectra and elemental analyses.
   Dimers 5 (complex mixture of isomers); ^{1}H-NMR (360 MHz, $CDCl_3$, ∂, overall features only due to complexity) 1.8 m, 2.4 m, 2.8 m, 3.1 m, 5.1 m, 5.8 m, 6.5 m. Found; % C 78.99, % H 6.99, % N 13.92 ; $C_{14}H_{14}N_2$ requires % C 79.97, %H 6.71, % N 13.32.
7. Grob, C.A., Fischer, H.P. and Raudenbusch, W., Helv. Chim. Acta., 1964, 47, 1003. Fischer, H.P., Tetrahedron Lett., 1968, 285.
8. Adduct 6 ; ^{1}H-NMR (360 MHz, $CDCl_3$, ∂) 1.74(d, 1H, J= 8.7Hz), 1.84(dd, 1H, J= 1.35, 8.7Hz), 3.06 (d, 1H, J= 17.3Hz), 3.12(d, 1H, J= 17.3 Hz), 3.26(d, 1H, J= 7.65Hz, exo-H), 3.47 (m, 1H), 3.52 (dd, 1H, J= 4.7, 7.64 Hz, exo-H), 6.04(d, 1H, J= 5.7Hz), 6.35(dd, 1H, J= 2.9, 5.6Hz), 7.12 (dd, 2H, J= 1.43, 8.76Hz), 7.40 (m, 3H), relative to TMS ; Found; % C 73.36, % H 4.86, %N 10.08 ; $C_{17}H_{14}N_2O_2$ requires % C 73.37, % H 5.07 , % N 10.07. MP 135-138 ° C
   Adduct 7; ^{1}H-NMR (360 MHz, $CDCl_3$, ∂) 2.34 (s, 3H), 3.42 (bd, 4H, J= 9.5Hz), 6.17(s, 2H), 7.12(dd, 2H, J= 1.36, 8.75Hz), 7.40(m, 3H), relative to TMS ; Found; % C 73.16, % H 4.95, %N 10.15 ; $C_{17}H_{14}N_2O_2$ requires % C 73.37, % H 5.07, %N 10.07. MP 162-164 ° C
9. For similar equilibrations of methylcyclopentadiene see; McLean, S. and Haynes, P., Tetrahedron, 1965, 21, 2329.
   An astute referee has suggested that fragmentation of 3 forms 5-cyanomethyl-cyclopenta-1,3-diene first, which is trapped in competition with isomerization to 4. This would certainly account for the unexpected 1:1 ratio of adducts 6 and 7.
10. Dworan, E. and Buchbauer, G., Chem. Ber., 1981, 114, 2357.
11. Lactam 11; ^{1}H-NMR (360 MHz, $CDCl_3$, ∂) 1.28 (s, 3H), 1.42 (s, 3H), 1.66 (d, 1H, J=12.2 Hz), 2.12 (d, 1H, J=12.3Hz), 2.26 (d, 1H, J=18.4Hz, endo-C4-H), 2.40 (bt, 1H, J=5.2Hz C5-H), 2.57 (dd, 1H, J=5.7, 18.3Hz, exo-C4-H), 3.56 (bs, 1H, C1-H), 4.50 (ddd, 2H, J=1.3, 5.45, 18.9Hz), 7.23 (bs, 1H, NH) relative to TMS ; Found; % C 60.89, % H 7.73, % N 7.00 ; $C_{10}H_{15}NO_3$ requires % C 60.90, % H 7.67, % N 7.10 ; IR (Nujul), 3260, 2900, 1670, 1615, 1450, 1370, 1345, 1295, 1265, 1210, 1160, 1050, 1020 cm^{-1}. MP 164-165 ° C, (colorless needles from ethylacetate-hexane).

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