Beckmann's Mixture *versus* Beckmann Reaction

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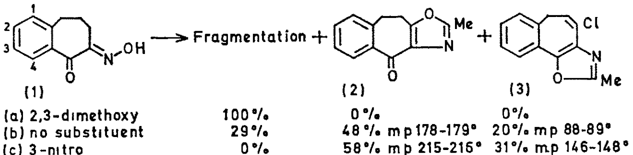
Summary An apparently general, hitherto unobserved reaction pathway for α-oximino-ketones, mechanistically related to the Semmler–Wolff aromatization, is described and put in the framework of "non-Beckmannian reactions"; a novel explanation is suggested for the formation, in Ac_2O–AcOH–HCl, of anomalous Beckmann rearrangement products.

ONE of the original conditions recommended by Beckmann for the rearrangement of ketoximes[1] involved heating in Ac_2O–AcOH–HCl, termed even today as "Beckmann's Mixture."[2a,b] We offer the generalization that the use of this mixture actually favours what one might call "non-Beckmannian" pathways, involving rupture of the N–O but not also of a C–C linkage. A special and well-known case is the Semmler–Wolff aromatization of cyclohexenone-type oximes.[2c] A few other pertinent observations are reported in the literature.[3a–c] Our discovery of such pathways for the important group of α-oximino-ketones suggests the above generalization, and opens new preparative possibilities.



(1)	Fragmentation	(2)	(3)
(a) 2,3-dimethoxy	100%	0%	0%
(b) no substituent	29%	48% mp 178–179°	20% mp 88–89°
(c) 3-nitro	0%	58% mp 215–216°	31% m.p 146–148°
(d) 1-chloro	0%	62% mp 125–126°	35% m.p 50–55°
(e) 3-chloro	0%	60% m.p. 198–199°	30% m p 110–112°

The oximino-benzosuberones (**1**) undergo Beckmann fragmentation to *o*-(3-cyanopropyl)benzoic acids with a number of reagents (PCl_5, polyphosphoric acid, H_2SO_4, *etc.*). In "Beckmann's Mixture," however, the fragmentation is overtaken, depending on the aromatic substituents, by the (rapid and simultaneous) formation of oxazoles (**2**) (**3**).†,‡ This reaction has practical significance.[4]

Similar results were found with open-chain analogues (*e.g.*, oximino-butyrophenones) and from αα′-bisoximinocycloheptanone, products of the "double reaction" (**4**) and (**5**) could be obtained. Intensive past studies on the Beckmann fragmentation of simple systems like αα′-bisoximinocyclohexanone[5] and β-nitroso-α-naphthol[6] failed to uncover their reactions with Ac_2O–AcOH–HCl, now found to lead primarily to 2,6-diacetamido-3,4-dichlorophenol [m.p. 239° (decomp.) 62%] and 2-acetamido-1,4-naphthoquinone (52%), respectively. We found also with *anti*-3-nitrobenzosuberone oxime, that although the Beckmann rearrangement of such systems is known to be fast,[7] in Ac_2O–AcOH–HCl no lactam was formed and the main products were (**6**) (27%) and, rather surprisingly, (**7**) (25%).

Apparently, in Ac_2O–AcOH–HCl, the Beckmann transition state (**8**) (accounting both for rearrangement and fragmentation[8]) is handicapped enough by the poor leaving group AcO^- to permit, quite generally, the alternative transition state (**9**), leading to *ON*-diacetyl intermediates and through them to the "non-Beckmannian" products, to compete successfully. For the Semmler–Wolff reaction, the necessity to postulate[9] such *ON*-diacetyl intermediates

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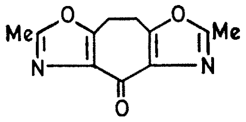
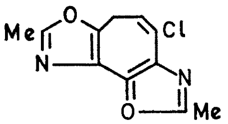
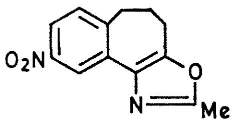
† In our experiments, "Beckmann's Mixture" was prepared by "saturating", at 60—90°, a 2 : 1–3 : 1 mixture of AcOH–Ac_2O with HCl gas, a reflux condenser being used (AcCl). Alternatively (and in some cases, advantageously) AcCl (2—5 moles) was added to a solution of the oxime (monoacetate) in AcOH–Ac_2O.

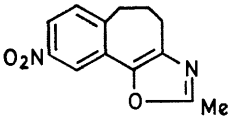
‡ Complete elementary analyses, i.r., u.v., n.m.r., and mass spectra were accumulated on all new compounds discussed. The structures were deduced by considering these data as well as data obtained on analogues and subsequent transformation products. In some cases [*e.g.*, (**7**)] independent synthesis was also carried out. Yields in figures are not necessarily optimal. Mother-liquors were scanned with an LKB Type 9000 g.l.c.–mass spectrometer unit to detect, or exclude, additional reaction products. Some minor products, although characterized, will be reported in a future detailed publication.

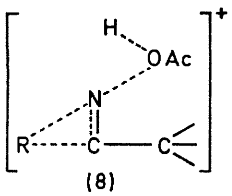
was questioned[3c] and the intermediacy of an *N*-protonated oxime monoacetate was advocated.[3c] Proof for the existence of (**9**) can now be derived from our finding that the monoacetate of (**1b**) gave only fragmentation [and no (**2b**)] when treated with Ac_2O–AcOH–H_2SO_4, *i.e.*, with a reagent which as a protonator is obviously similar to Beckmann's Mixture but which may differ in its acetylating capabilities.


(4) m.p. 230° (decomp.)


(5) m.p. 142°


(6) m.p. 157–159


(7) m.p. 159–160°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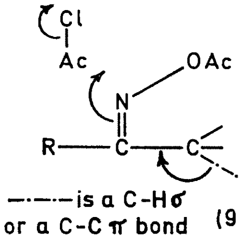
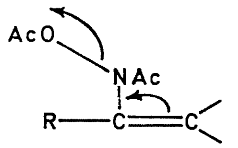
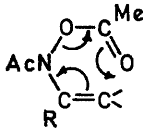
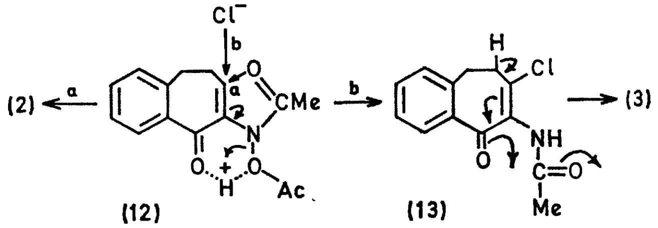


(9)

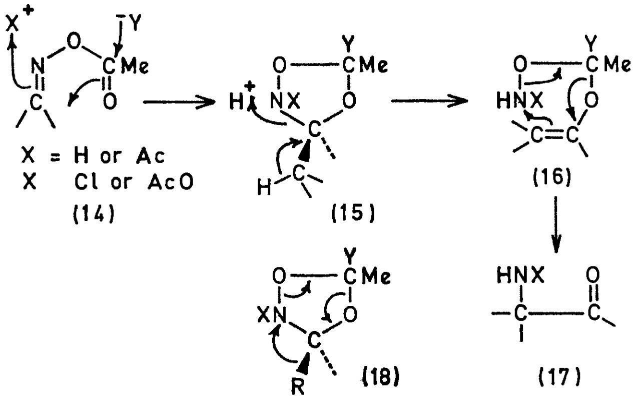

(10)


(11)

We are studying the mode of the N–O fission step. In previous suggestions for the mechanism of the Semmler–Wolff reaction, [2c,9] it was invariably depicted as an ionic procedure (**10**) and such a mechanism could account for our observed products as well [*e.g.* (**12**) *etc.*]. It is reasonable to assume[10] however, that in all these reactions involving (**9**) the N–O linkage is severed in the sigmatropic (N → C acetate transfer) process (**11**) and only the subsequent steps such as the loss of the transferred AcO^-, capture of nucleophiles, proton transfer or loss, (also Wagner–Meerwein rearrangement[9,11]) are ionic.



As to the formation of (**7**), to explain the "interswitch" of functionalities, one must postulate [*i.e.*, in a sequence (**14**—**17**)] the spiro intermediate (**15**). The existence of such intermediates may then explain yet another peculiarity of Beckmann's Mixture: why, if it does convert a ketoxime into an amide (lactam) is the latter often the anomalous, *anti*-Meisenheimer isomer?[12] We suggest the (probably not synchronous) procedure shown at (**18**) instead of the usual (and in some cases[12b] rather untenable) assumption of oxime isomerization preceding a "normal" Beckmann rearrangement.



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