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Beckmann Rearrangements. An Investigation of Special Cases

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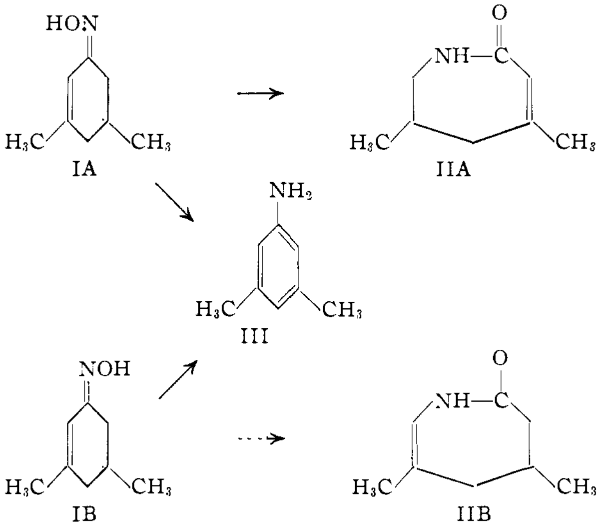
A number of special or abnormal cases of oxime rearrangements have been investigated. In each instance polyphosphoric acid has been found to provide a normal Beckmann reaction, indicating a high degree of effectiveness and specificity of this reagent in the Beckmann rearrangement.

Polyphosphoric acid has been found to be a remarkably effective reagent for the Beckmann rearrangement of ketoximes[1] and aldoximes.[2] In simple cases, where the oximes are relatively stable substances, the reaction is carried out by heating the oxime in polyphosphoric acid at about 130°. The yields in such cases are nearly quantitative, unless there are special difficulties in isolation of the products. In cases where the oxime is less stable or is easily isomerized to a mixture of stereoisomers, the yields are lower, but even in these instances we have observed rearrangements which have not been carried out previously.

This study has been continued with an examination of a number of special or so-called abnormal reactions. In general, these are cases in which a normal Beckmann rearrangement occurs only under extreme conditions, or in which a cleavage or some other kind of reaction occurs in preference to rearrangement. Since all of these reactions represent special cases, each is discussed separately in the following sections.

Wolff Aromatizations.—Oximes of cyclohexenones undergo a dehydration–aromatization under acid conditions to yield the aromatic amine corresponding in carbon skeleton to the original oxime. This reaction, which was apparently first observed by Semmler,[3] is sometimes known as the Wolff aromatization.[4] When employed for preparative purposes, it is usually carried out in acetic acid–acetic anhydride solution in the presence of hydrogen chloride. Under Beckmann conditions, the result is usually partial aromatization and partial destruction of the organic materials.



The reaction of 3,5-dimethyl-2-cyclohexen-1-one oxime with polyphosphoric acid was investigated. This oxime[5] is probably not stereochemically homogeneous, but with polyphosphoric acid at 130° rearrangement occurred to give a neutral amide fraction from which the cyclic amide IIA was isolated in 30% yield. The stereoisomeric oximes are IA and IB, and the corresponding products of rearrangement are the lactams IIA and IIB. The rearrangement product IIB, which would involve migration of an ethylenic carbon atom, was not isolated. The structure assigned to IIA is based upon analysis, upon an infrared absorption spectrum which indicated an amide or lactam structure, and upon an ultraviolet absorption spectrum which indicated α,β-unsaturation for the carbonyl function. The mechanism of the Wolff aromatization is not known, but if the configuration of the oxime is not a factor, both oximes would lead to III.

A modified form of this aromatization was studied by Schroeter[6] in the tetralone series. The oximes or oxime acetates of tetralone-1 and certain chloro, nitro and methoxy substituted tetralones were aromatized with hydrogen chloride in acetic acid–acetic anhydride to the corresponding α-naphthylamines. In a similar series of reactions, 5,8-dimethyltetralone-1 yielded the expected product of a Beckmann rearrangement. While these studies were designed to study aromatizations rather than Beckmann rearrangements, the results indicated that no particular correlation between structure and ease of rearrangement could be drawn, except that in general most tetralones underwent aromatization in preference to rearrangement. In the case of the parent compound, tetralone-1, attempts to obtain a Beckmann rearrangement of the oxime have not been successful, and in consequence the expected product, homodihydrocarbostyril, cannot be obtained in this way. It can, however, be obtained[7] through the Schmidt reaction from tetralone-1, indicating that a rearrangement does occur under some circumstances. The treatment of tetralone-1 oxime with polyphosphoric acid therefore presented a direct test of the effectiveness and specificity of polyphosphoric acid in inducing Beckmann rearrangements; when this experiment was tried at 130° a 91% yield of homodihydrocarbostyril resulted.

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[1] E. C. Horning and V. L. Stromberg, THIS JOURNAL, **74**, 2680 (1952).

[2] E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 5151 (1952).

[3] W. Semmler, *Ber.*, **25**, 3352 (1892).

[4] L. Wolff, *Ann.*, **322**, 351 (1902).

[5] E. Knoevenagel, *ibid.*, **281**, 104 (1894).

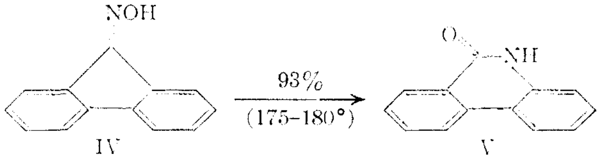
[6] G. Schroeter, *Ber.*, **63**, 1308 (1930).

[7] P. A. S. Smith, THIS JOURNAL, **70**, 320 (1948).

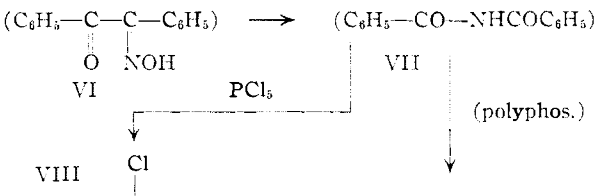
No attempt was made to extend the investigation to substituted tetralones, but it is clear that the reaction conditions with polyphosphoric acid are substantially free from factors which induce aromatization rather than rearrangement.

Phenanthridone Synthesis.—Fluorenone oxime (IV) is a highly stable compound, and its rearrangement to phenanthridone (V) does not occur under the rather mild conditions often employed for Beckmann rearrangements. It can, however, be induced to undergo rearrangement by heating with zinc chloride or phosphorus pentachloride.[8]

With polyphosphoric acid at a temperature of 100–150°, under circumstances where all oximes studied previously were found to undergo rearrangement, fluorenone oxime was unchanged. When the reaction was carried out at 175–180° a smooth reaction occurred and phenanthridone was obtained in 93% yield. The effectiveness of the reagent was maintained, although a higher temperature than usual was necessary.



Rearrangement of α-Benzil Monoxime.—The two stereoisomeric monoximes of benzil, α-benzil monoxime (m.p. 140°) and β-benzil monoxime (m.p. 114°), have been subjected to extensive investigation. Although the nature of the products has varied with the conditions of the reactions, in general each monoxime has been shown under certain circumstances to yield products which could arise from an initial Beckmann rearrangement of the normal kind.[9] For example, the α-oxime on treatment with phosphorus pentachloride in ether yields N-benzoylbenzimido chloride (VIII) as a product[10]; this material on hydrolysis yields ammonia and the expected quantity of benzoic acid (2 moles). This product (VIII) might be expected if the configuration of the α-oxime is that represented by VI, and if a normal Beckmann reaction occurs under these circumstances. On the other hand, the so-called second-order Beckmann rearrangement of a monoxime of a diketone, which may undergo a normal reaction in ether with phosphorus pentachloride, leads to an acid and a nitrile.[11] This reaction occurs on treatment of the oxime with benzenesulfonyl chloride in pyridine or in alkaline solution.

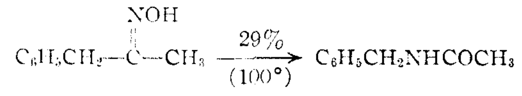


$$(C_6H_5{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{NOH}{|}}{C}{-}C_6H_5) \longrightarrow (C_6H_5{-}CO{-}NHCOC_6H_5)$$

$$C_6H_5CON{=}\overset{\overset{Cl}{|}}{C}{-}C_6H_5 \qquad C_6H_5COOH + C_6H_5CONH_2$$

The formation of a chloro derivative is not possible with polyphosphoric acid, and accordingly the reaction products should include (VII) or its hydrolysis products if a normal Beckmann rearrangement were to occur in this instance; the "second-order" products should be benzoic acid and benzonitrile. An investigation of this case, using polyphosphoric acid at 115°, resulted in the isolation of benzoic acid in quantitative amount (one mole) together with 40% of the theoretical amount of benzamide. Benzonitrile was not detected. From this it must be concluded that α-benzil monoxime undergoes a normal rather than a "second order" Beckmann reaction in polyphosphoric acid, but that cleavage of the initial product occurs as a subsequent reaction.

Rearrangement of Phenylacetone Oxime.—The fate of phenylacetone oxime under Beckmann conditions was studied extensively by Neber.[12] A normal rearrangement was found to occur under some circumstances, but α-phenyl-α-aminoacetone was also observed as a reaction product. When phenylacetone oxime (IX) was treated with polyphosphoric acid at 100°, a reaction occurred, but the only product which could be isolated was N-benzylacetamide. This was obtained in 29% yield. Apparently a normal reaction occurred in this instance, but the yield was much lower than usual for a normal ketoxime rearrangement.



$$C_6H_5CH_2{-}\overset{\overset{NOH}{\|}}{C}{-}CH_3 \xrightarrow[(100°)]{29\%} C_6H_5CH_2NHCOCH_3$$

IX X

Acknowledgment.—We are indebted to Mrs. Iris Siewers and Miss Alice Bernardi for infrared and ultraviolet absorption spectra. Analyses were carried out by Dr. William Alford and his staff.

Experimental

Rearrangement of 3,5-Dimethyl-2-cyclohexen-1-one Oxime.—The oxime (m.p. 70.5–73.5°) was prepared in the normal way from 3,5-dimethyl-2-cyclohexen-1-one. A 2.0-g. quantity of this oxime,[5] which is usually believed to be a mixture of the two possible stereoisomers, was heated with manual stirring in 60 g. of polyphosphoric acid for five minutes at 130–135°. The mixture was cooled and treated with water, and the resulting solution was subjected to a continuous ether extraction. From the ether extract, after drying and removal of the solvent, there was obtained 1.21 g. of light yellow oil which crystallized on standing (m.p. 51–65°). Two recrystallizations from hexane yielded 0.60 g. (30%) of colorless product, **3,5-dimethyl-7-amino-2-heptenoic acid lactam**, m.p. 71–72.5°. The infrared absorption spectrum was in general agreement with the lactam structure IIA, and the ultraviolet absorption spectrum (in ethanol) showed maximum absorption at 241 mμ indicating α,β-unsaturation with respect to the carbonyl function.

Anal. Calcd. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.07. Found: C, 69.16; H, 9.11; N, 9.96.

Rearrangement of Tetralone-1 Oxime.—A 4.00-g. quantity of tetralone-1 oxime was heated with 120 g. of polyphosphoric acid for ten minutes at 120–130°. The mixture was cooled and treated with 350 ml. of water. The product

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(8) F. J. Moore and E. H. Huntress, This Journal, **49**, 2618 (1927).

(9) N. Sidgwick, "Organic Chemistry of Nitrogen," by T. W. J. Taylor and W. Baker, Oxford University Press, 1942, p. 182.

(10) E. Beckmann and K. Sandel, *Ann.*, **296**, 280 (1897).

(11) A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904); O. Diels and M. Stern, *ibid.*, **40**, 1629 (1907).

(12) P. Neber, K. Hartung and W. Ruopp, *ibid.*, **58**, 1234 (1925); P. Neber and A. Fridolsheim, *Ann.*, **449**, 109 (1926); P. Neber and A. Uber, *ibid.*, **467**, 52 (1928); P. Neber and A. Buigard, *ibid.*, **493**, 281 (1932).

was separated by extraction with chloroform; after washing, drying and evaporation of the chloroform solution there remained 3.64 g. (91%) of slightly discolored crystalline material, m.p. 135.5–138°. Recrystallization from ethanol provided colorless homodihydrocarbostyril, m.p. 142.5–143° (reported[7,13] m.p. 139–141°, 141°). The infrared absorption spectrum was in agreement with the expected structure. The aqueous solution remaining after chloroform extraction was made alkaline with 25% potassium hydroxide solution, and subjected to continuous ether extraction. A small amount (0.1 g.) of red oil was isolated which was not characterized, but which may have contained β-naphthylamine.

Rearrangement of Fluorenone Oxime.—A mixture of 2.00 g. of fluorenone oxime and 60 g. of polyphosphoric acid was heated with manual stirring to 175–180°, and maintained at this temperature for a few minutes. The resulting solution was cooled and treated with 300 ml. of water; the product separated in crystalline form and was removed by filtration. After washing and drying there was obtained 1.85 g. (93%) of phenanthridone, m.p. 286–289°.

Rearrangement of α-Benzil Monoxime.—A solution of 2.00 g. of α-benzil monoxime in 60 g. of polyphosphoric acid was heated with manual stirring to 110–115°, and was then maintained at 90–100° (steam) for 30 minutes. Treatment with 300 ml. of water gave a solution which was extracted well with ether. The ether solution was extracted with 5% sodium hydroxide solution to remove acidic products. The alkaline solution was acidified (hydrochloric acid) to provide 1.08 g. (quantitative yield, based on formation of one mole of benzoic acid) of colorless benzoic acid, m.p. 121–122°, identified by infrared spectrum and mixed melting point with an authentic sample.

A neutral fraction was isolated from the ether solution remaining after alkaline extraction. The ether solution was washed, dried and evaporated to yield 0.42 g. (40%) of colorless solid, m.p. 119–126°. Although the melting range was rather wide, no benzonitrile was detected in this product, and recrystallization from water gave pure benzamide, identified by infrared spectrum and mixed melting point.

Rearrangement of Phenylacetone Oxime.—A mixture of 15.0 g. of phenylacetone oxime and 300 g. of polyphosphoric acid was heated with manual stirring at 90–100° for five minutes. The mixture was treated with 2 l. of water, and the resulting solution was extracted with 1:1 ether–ethyl acetate. The organic solution was washed with saturated sodium chloride solution, dried, and evaporated with heating until the product came to constant weight. There was obtained 14.75 g. of non-basic yellow oil (which did not crystallize) indicating that the amount of basic material formed in the reaction was negligible. The non-basic product was distilled at 0.5 mm. to give the following fractions: (a) to 120°, 1.33 g., (b) 120–123°, 3.05 g., (c) 123–128°, 1.61 g., (d) 128–130°, 1.56 g. Fractions (b) and (c) solidified and were combined to yield 4.66 g. (29%) of colorless solid, m.p. 51–55°. This material was identified as N-benzylacetamide by a mixed melting point determination and by comparison of the infrared spectrum with that of an authentic sample prepared by acetylation of benzylamine. The yield may in fact have been higher than that indicated, since the last fraction (d) may also have contained a small amount of amide. The yield of crystalline material (29%) is smaller than usual for a ketoxime rearrangement.[1]

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(13) J. V. Braun, *Ber.*, **40**, 1843 (1907); Briggs and DeAth, *J. Chem. Soc.*, 45 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF NEW YORK UNIVERSITY]

The Geometry of Sphingosine

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The infrared spectra of sphingosine, sphingosine sulfate, triacetylsphingosine and cerebron all exhibit a pronounced absorption maximum near 10.3 μ. These results provide strong evidence that sphingosine and its cerebroside precursors have the *trans* configuration.

Sphingosine, the common basic constituent of the sphingolipides,[1] has long been the object of structural investigations.[2] A variety of degradative studies,[3] and independent syntheses of dihydrosphingosine,[4] have lent strong support to the presently accepted formulation (I) of sphingosine.

$$\mathrm{CH_3(CH_2)_{12}{-}C^5H{=}C^4H{-}C^3HOH{-}C^2HNH_2{-}C^1H_2OH} \qquad \mathrm{(I)}$$

However the presence of two asymmetric centers and of a double bond in the molecule offers a choice among eight possible stereoisomers, *cis–threo*, *cis–erythro*, *trans–threo*, *trans–erythro*, and the corresponding enantiomers. It has recently been shown[5] that the configuration around carbon atom 2 is D; the number of stereoisomers allowable for the naturally occurring compound has thereby been halved. There still remains the question of the configuration around the "allylic center" of the molecule, which is comprised of carbon atoms 3, 4 and 5.

With regard to the geometry of the double bond, the available literature reports are in conflict. Niemann[6] reported that naturally occurring "α"-sphingosine sulfate was isomerized under acid conditions to a thermodynamically more stable "β-sphingosine sulfate." On the basis of this observation, the *cis* configuration was assigned by him to the "α"-isomer. This result is in contradistinction to the findings of Ono,[7] who obtained *trans*-2-hexadecenal as a product of the lead tetraacetate oxidation of sphingosine; it must be remarked, however, that under these experimental conditions, any *cis*-2-hexadecenal, a possible product of cleavage, if initially formed would be expected to undergo rapid conversion to the *trans* isomer, *via* the enol form.

The present work was designed to yield more

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(1) This term includes the cerebrosides, the sphingomyelins and the gangliosides (H. E. Carter, *et al.*, *J. Biol. Chem.*, **169**, 77 (1947)).

(2) H. Thierfelder and E. Klenk, "Die Chemie der Cerebroside und Phosphatide," J. Springer, Berlin, 1930.

(3) E. Klenk and W. Diebold, *Z. physiol. Chem.*, **198**, 25 (1931); H. E. Carter, F. J. Glick, W. P. Norris and G. E. Phillips, *J. Biol. Chem.*, **170**, 285 (1947); K. Ono, *J. Japan Biochem. Soc.*, **20**, 32 (1948) [*C. A.*, **43**, 6267 (1949)].

(4) G. I. Gregory and T. Malkin, *J. Chem. Soc.*, 2453 (1951); C. A. Grob, E. F. Jenny and H. Utzinger, *Helv. Chim. Acta*, **34**, 2249 (1951).

(5) H. E. Carter and C. G. Humiston, *J. Biol. Chem.*, **191**, 727 (1951).

(6) C. Niemann, THIS JOURNAL, **63**, 1763 (1941).

(7) K. Ono, *J. Japan. Biochem. Soc.*, **19**, 133 (1947) [*C. A.*, **44**, 10752 (1950)].