[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Fragmentation of β-Keto Ether Oximes[1]

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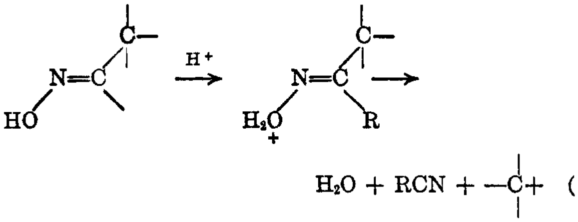
Fragmentation of β-keto ether oximes under Beckmann conditions, into alcohols, nitriles, and carbonyl compounds, has been found to be a general and useful reaction. Aliphatic ethers and cyclic ethers of three, five, and six members undergo the reaction. Applications to the determination of structure of natural products and of the cyclic hydration products of acetylenic diols are discussed.

In addition to the normal rearrangement to amides which most keto-oximes undergo when subjected to the conditions of the Beckmann rearrangement, many oximes take an alternate course of reaction, cleaving into a nitrile and some second fragment.[2] Examination of the structural characteristics of the oximes which display this so-called "second-order" reaction supports the generalization that the reaction is one of a familiar type[3] in which an electron-deficient intermediate ejects, from the β-position, a smaller positive ion (Equation 1); α-substituents which stabilize carbonium ions consequently favor this process. Thus, the fragmentation reaction is given by α-hydroxyoximes,[4,5] α-ketooximes,[4,6] α-oximino acids,[7] α-iminooximes,[8] α-aminooximes,[9] α,α-diaryl oximes,[10] β-keto thio ether oximes,[11] bridged α,α-dialkylketooximes,[12] and α-trisubstituted oximes.[13] A few scattered reports in the literature[14] indicate that an alkoxyl substituent may serve the same function. It is the purpose of this communication to show that the fragmentation of oximes of β-keto ethers, according to Equation 2, offers a valuable method for the identification and specific degradation of this structural class of compounds.



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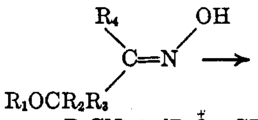

$$R_4CN + [R_1\overset{+}{O}{=}CR_2R_3] \longrightarrow R_1OH + R_2COR_3 \quad (2)$$

This investigation began with a simple β-keto ether; the oxime of benzoin methyl ether cleaved smoothly into benzaldehyde and benzonitrile when treated with *p*-toluenesulfonyl chloride in pyridine or with phosphorus pentachloride (Equation 3). Polyphosphoric acid yielded benzaldehyde and benzamide, the latter formed by hydrolysis of the initially formed nitrile.

It was of interest to determine next whether incorporation of the ether function in an epoxide ring would prevent fragmentation. One of the

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[1] Presented, in part, at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

[2] A. H. Blatt, *Chem. Rev.*, **12,** 215 (1933).

[3] C. A. Grob, *Experientia*, **13,** 126 (1957); *Theoretical Organic Chemistry* (Kekule Symposium), Butterworth Scientific Publications, London, 1959, p. 114.

[4] A. Werner and A. Piguet, *Ber.*, **37,** 4295 (1904); A. Werner and T. Detscheff, *Ber.*, **38,** 69 (1905); R. T. Conley and F. A. Mikulski, *J. Org. Chem.*, **24,** 97 (1959).

[5] A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56,** 1148 (1934); J. S. Buck and W. S. Ide, *J. Am. Chem. Soc.*, **53,** 1912 (1931); J. Schmidt-Thomé, *Ann.*, **603,** 43 (1957); T. Komeno, *Chem. and Pharm. Bull.* (*Japan*), **8,** 680 (1960).

[6] A. H. Ferris, *J. Org. Chem.*, **24,** 580 (1959); **25,** 1813 (1960); G. B. Bachman and D. E. Welton, *J. Org. Chem.*, **12,** 221 (1947); W. Nagata and K. Takeda, *J. Pharm. Soc. Japan*, **72,** 1566 (1952); D. Murakami and N. Tokura, *Bull. Chem. Soc. Japan*, **31,** 1044 (1958); A. I. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).

[7] L. Bouveault and R. Locquin, *Bull. soc. chim. France*, [3], **31,** 1142 (1904); E. E. Blaise and H. Gault, *Bull. soc. chim. France*, [4], **1,** 75 (1907); **9,** 451, 458 (1911); A. Ahmad and I. D. Spenser, *Can. J. Chem.*, **38,** 1625 (1960).

[8] E. C. Taylor, C. W. Jefford, and C. C. Cheng, *J. Am. Chem. Soc.*, **83,** 1261 (1961).

[9] (a) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80,** 126 (1958); (b) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82,** 645 (1960); (c) H. Fischer, C. A. Grob, and E. Renk, *Helv. Chim. Acta*, **42,** 872 (1959); (d) H. Fischer and C. A. Grob, *Tetrahedron Letters*, **26,** 22 (1960).

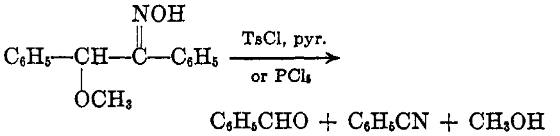
[10] C. C. Price and G. P. Mueller, *J. Am. Chem. Soc.*, **66,** 634 (1934); M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75,** 38 (1953); W. L. Bencze and M. J. Allen, *J. Org. Chem.*, **22,** 352 (1957); S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, **24,** 364 (1959).

[11] J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 4486 (1960).

[12] M. Gates and S. P. Malchick, *J. Am. Chem. Soc.*, **79,** 5546 (1957); H. K. Hall, Jr., *J. Am. Chem. Soc.*, **82,** 1209 (1960).

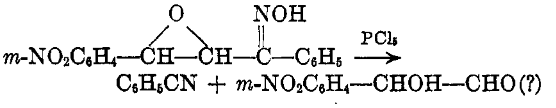
[13] G. H. Whitham, *Proc. Chem. Soc.*, 271 (1959). S. H. Graham and A. J. S. Williams, *J. Chem. Soc.*, 4066 (1959); R. Anliker, M. Müller, M. Perelman, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **42,** 1071 (1959); ref. 9b and other references cited therein.

[14] (a) C. Schöpf, *Ann.*, **452,** 211 (1927); (b) G. F. Hennion and J. L. O'Brien, *J. Am. Chem. Soc.*, **71,** 2933 (1949); (c) T. I. Temnikova, A. K. Petryaeva, and S. S. Skorokhodov, *Zhur. Obshchei Khim.*, **25,** 1575 (1955); *Chem. Abstr.*, **50,** 4891 (1956).



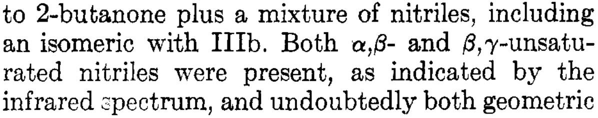
$$C_6H_5-CH(OCH_3)-C(=NOH)-C_6H_5 \xrightarrow[\text{or } PCl_5]{TsCl,\ pyr.} C_6H_5CHO + C_6H_5CN + CH_3OH \quad (3)$$

oximes of α,β-epoxy-β-(m-nitrophenyl)propiophenone was chosen for study. Phosphorus pentachloride cleaved it to benzonitrile and a second unidentified product, which gave a strong positive Fehling's test and thus may be the anticipated α-hydroxyaldehyde (Equation 4).



$$m\text{-}NO_2C_6H_4-\overset{O}{\overbrace{CH-CH}}-C(=NOH)-C_6H_5 \xrightarrow{PCl_5} C_6H_5CN + m\text{-}NO_2C_6H_4-CHOH-CHO(?) \quad (4)$$

The most interesting compounds studied were the oximes of cyclic β-keto ethers. Hennion and O'Brien,[14b] by heating the oxime (Ia) of 2,2,5,5-tetramethyltetrahydrofuran-3-one in aqueous sulfuric acid, obtained acetone, ammonia, and senecioic acid (β,β-dimethylacrylic acid), but regarded the reaction as a normal Beckmann rearrangement followed by hydrolysis of the lactam. Our results indicate that fragmentation is the primary process, as cleavage products were obtained under a variety of nonhydrolytic conditions. Thionyl chloride, phosphorus pentachloride, p-toluenesulfonyl chloride in pyridine, and polyphosphoric acid all cleaved the oxime to acetone and a second fragment whose structure depended on the reagent. The first two reagents gave senecionitrile (IIIa), apparently by dehydration of the intermediate hydroxynitrile IIa. p-Toluenesulfonyl chloride gave a mixture of IIa and IIIa, as evidenced by the infrared spectrum of the reaction mixture, which showed hydroxyl absorption and two distinct nitrile peaks, one conjugated and one unconjugated. Polyphosphoric acid, as anticipated, afforded seneciamide.

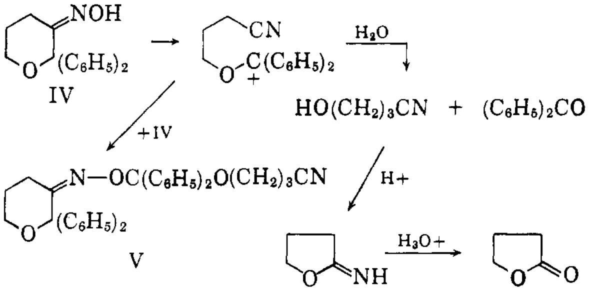


a. $R_1 = R_2 = CH_3$; b. $R_1 = CH_3$, $R_2 = C_2H_5$
c. $R_1R_2 = -(CH_2)_5-$

A homolog of this oxime, 2,5-dimethyl-2,5-diethyltetrahydrofuran-3-one oxime (Ib), gave similar results. Phosphorus pentachloride converted it to 2-butanone plus a mixture of nitriles, including an isomeric with IIIb. Both α,β- and β,γ-unsaturated nitriles were present, as indicated by the infrared spectrum, and undoubtedly both geometric isomers of each were formed. Short treatment of the nitrile mixture with sodium ethoxide gave only the α,β-unsaturated isomer IIIb, which was identical with an authentic sample prepared by condensation of 2-butanone with cyanoacetic acid, decarboxylation, and sodium ethoxide isomerization of the resulting nitrile mixture.

7-Oxadispiro[5.1.5.2]pentadecane-14-one oxime (Ic) was converted in a similar manner by phosphorus pentachloride to cyclohexanone, plus an unidentified product which appeared, from its infrared spectrum, to be IIc.

As an example of a six-membered cyclic ether, the oxime of 2,2-diphenyltetrahydropyran-3-one was investigated. It was readily cleaved by phosphorus pentachloride, and benzophenone was isolated in 95% yield. Benzophenone was again obtained when polyphosphoric acid was the reagent, and it was also possible to identify the other fragment as γ-butyrolactone. It is apparently formed by lactonization, in the strong acid medium, of the expected γ-hydroxybutyronitrile.



Reaction of oxime IV with p-toluenesulfonyl chloride in pyridine gave, quite unexpectedly, a crystalline nitrile in nearly quantitative yield, along with a few per cent of benzophenone. Analysis and molecular weight determination of the nitrile showed it to have the formula $C_{34}H_{32}N_2O_3$. The infrared spectrum showed a cyano band at 4.46 μ but no absorption in the hydroxyl or carbonyl regions. The presence of a cyano group was confirmed by alkaline hydrogen peroxide hydrolysis to the corresponding amide. The NMR spectrum showed, in addition to nonequivalent phenyl groups, three different methylene absorption peaks of approximately equal intensity, which were tentatively assigned as follows: a triplet centered about $\tau = 6.41$ and a multiplet peak at 7.85, to the grouping $-O-CH_2-CH_2-$, while another multiplet at $\tau = 7.36$ could be due to a methylene adjacent to an electron-withdrawing group.[15]

A structure which is consistent with all this information is the cyanoketal V, which might be formed by reaction of the intermediate carbonium ion with the hydroxyl of unchanged IV. This supposition was confirmed by mild acid hydrolysis of V, which afforded a mixture of benzophenone and the oxime IV. It is concluded that tosylation of the hindered oxime is slow compared with fragmentation of the oxime tosylate, so that unchanged oxime is always present to attack the carbonium ion.

From these examples, it is clear that the frag-

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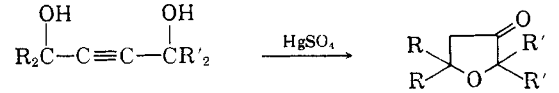
[15] G. V. D. Tiers, *Tables of τ-Values for a Variety of Organic Compounds*, a publication of the Central Research Department, Minnesota Mining and Manufacturing Co., 1958.

mentation reaction provides a useful and specific method of degrading β-keto ethers, by converting the carbon between the ketone and ether functions into a carbonyl group. One interesting problem which becomes easily amenable to study with the aid of this method is the direction of hydration of unsymmetrical acetylenic diols. The three tetrahydrofuranones discussed above were all prepared by the mercuric sulfate–catalyzed hydration-cyclization of readily available acetylenic diols, but this is a reaction whose mechanism is not well understood. In particular, it is difficult to predict with confidence the product of hydration of an unsymmetrical diol such as VI or VII.

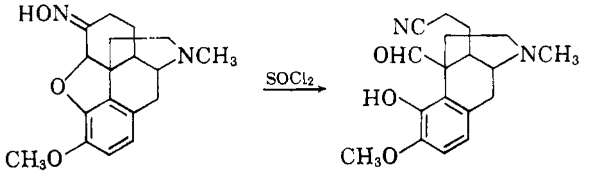


VI. $R = CH_3; R' = H$
VII. $R = CH_3; R_2' = —(CH_2)_5—$
VIII. $R = CH_3; R' = H$
IX. $R = H; R' = CH_3$
X. $R = CH_3; R_2' = —(CH_2)_5—$
XI. $R_2 = —(CH_2)_5—; R' = CH_3$

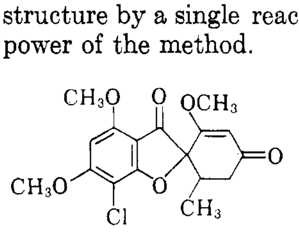
The hydration of 2-methylpent-3-yne-2,5-diol (VI) was studied first. Reaction with aqueous mercuric sulfate yielded a single ketone, whose homogeneity was shown by its narrow boiling range, the presence of a single peak on vapor phase chromatography, and the preparation of a semicarbazone whose melting point rose only two degrees during several recrystallizations. It was possible to show in several ways that the structure of the ketone was VIII and not the alternative IX[16]: (a) It formed a dibenzylidene derivative; (b) it formed an osazone when treated with 2,4-dinitrophenylhydrazine in sulfuric acid[17]; and (c) the oxime was cleaved by phosphorus pentachloride, yielding formaldehyde as the only carbonyl-containing product.

Hydration of a second unsymmetrical acetylenic diol, compound VII, gave a mixture of ketones X and XI, as expected in view of the similarity of the substituents. One of the ketones could be obtained pure by fractional crystallization of the mixture of semicarbazones and regeneration of the ketone from the less soluble semicarbazone by distillation from dilute hydrochloric acid. Infrared analysis showed that this ketone constituted about 43% of the original mixture. Its identification presented a more severe problem than the previous case, for it is difficult to devise a method of distinguishing between X and XI other than the oxime fragmentation. This gave an unambiguous answer, however; the oxime, on treatment with phosphorus pentachloride or polyphosphoric acid, gave only cyclohexanone and no acetone, thus identifying the pure ketone as X.

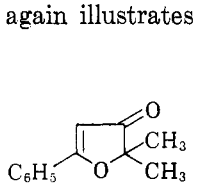
Finally, the application of the fragmentation reaction of β-ketoethers to the determination of structure of natural products may be mentioned. A classic, and apparently the first, example of the reaction is Schöpf's[14a] elegant application of it to dihydrocodeinone oxime, proving the position of attachment of the ethanamine bridge in the morphine alkaloids (Equation 5).



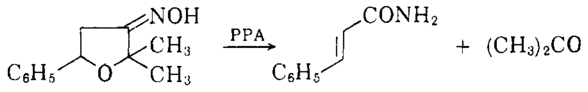
Other natural products containing the requisite β-keto ether moiety are griseofulvin (XII) and bullatenone[18] (XIII), a ketone isolated from the New Zealand shrub Myrtus bullata.[19] Though there is no doubt of the structure of the latter, and a remarkable synthesis has been recorded,[18] it was of interest to apply the fragmentation reaction to its oxime. Through the courtesy of Dr. W. I. Taylor, it was possible to obtain a sample of bullatenone. It readily formed an oxime, but several attempts to bring about fission by p-toluenesulfonyl chloride in pyridine led only to the oxime tosylate. More successful results were attained with the dihydro derivative; it was smoothly converted by phosphorus pentachloride to acetone and cinnamonitrile, and by polyphosphoric acid to acetone and cinnamamide (Equation 6). This unambiguous proof of structure by a single reaction again illustrates the power of the method.



XII



XIII



EXPERIMENTAL

Melting points were taken by capillary and are uncorrected. Infrared spectra were recorded in chloroform or carbon tetrachloride solution on a Perkin-Elmer spectrophotometer, Model 21. NMR spectra were determined on 5% solutions in chloroform at 40 Mc. with a Varian Associates Model

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[16] A compound for which structure IX was suggested has been reported by E. D. Bergmann, H. Davies, and R. Pappo [*J. Org. Chem.*, **17**, 1331 (1952)] and has different physical constants than the ketone obtained in this study.

[17] The product had the empirical formula $C_{18}H_{18}N_8O_9$, which corresponds to the dinitrophenylosazone of the keto diol, $(CH_3)_2C(OH)CH_2COCH_2OH$, a possible acid hydrolysis product of VIII. There is no reasonable way in which an osazone could be formed from IX.

[18] W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.*, 3871 (1958).

[19] C. W. Brandt, W. I. Taylor, and B. R. Thomas, *J. Chem. Soc.*, 3245 (1954).

V4300 B spectrometer, using tetramethylsilane as the internal reference.

General procedures for oxime fragmentations. (a) *With phosphorus pentachloride.* To a solution of the oxime in dry benzene was added slightly more than one molar equivalent of powdered phosphorus pentachloride in small portions, with cooling if necessary. The solution was kept, protected from moisture, at room temperature for 10–12 hr., then washed with water, saturated potassium bicarbonate solution, and saturated salt solution. The organic layer was dried over sodium sulfate, concentrated, and the products identified as described in each specific case.

(b) *With p-toluenesulfonyl chloride.* A solution of the oxime and 1.05–1.10 equivalents of *p*-toluenesulfonyl chloride in dry pyridine was kept at room temperature for the time indicated, then poured onto ice, acidified with dilute hydrochloric acid, and extracted with chloroform. The extracts were washed with water and brine, dried over sodium sulfate, and concentrated.

(c) *With polyphosphoric acid.* The oxime was stirred into twenty-five to thirty times its weight of polyphosphoric acid and stirred at 100–120° for 10 min. The mixture was poured onto ice, nearly neutralized with ammonium hydroxide, and stirred until homogeneous. Ordinarily the solution was extracted with chloroform and the products identified as described.

Benzoin methyl ether oxime. Benzoin was methylated according to the procedure of Wren,[20] and the ether converted to the oxime, m.p. 129–131° as described by Fischer.[21] The oxime is believed to have the configuration shown in Equation 3, as Professor D. S. Trifan has observed that its infrared spectrum in dilute carbon tetrachloride solution shows no evidence of hydrogen bonding of the oxime hydroxyl to the ether oxygen.

(a) *Reaction with phosphorus pentachloride.* The residue from the general procedure described above, beginning with 0.37 g. of the oxime, was refluxed with 1.0 g. of Girard T reagent in 10 ml. of ethanol, 1 ml. of water, and 0.5 ml. of acetic acid for 2 hr. After evaporation of the alcohol, the residue was distributed between ether and water. Treatment of the aqueous solution with Brady's reagent[22] gave benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 237–237.5° after recrystallization from chloroform-ethanol; the melting point was not depressed by admixture with an authentic sample.

Concentration of the dried ether solution left a residue which showed strong nitrile absorption in the infrared. The oil was warmed for 30 min. with 36 ml. of 5% hydrogen peroxide, 5 ml. of 20% potassium hydroxide, and 15 ml. of ethanol. Extraction of the reaction mixture with chloroform, evaporation of the extracts, and recrystallization of the residue from hexane gave benzamide, m.p. and mixed m.p. 127–128°.

(b) *Reaction with polyphosphoric acid.* Extraction of the reaction mixture with chloroform and evaporation of the extracts left an oily residue which showed the characteristic infrared bands of benzaldehyde and benzamide. Treatment of the mixture with Brady's reagent gave benzaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 236.5–237°.

(c) *Reaction with p-toluenesulfonyl chloride.* After standing for 16 hr., the reaction mixture was worked up as described above. The residue showed the characteristic infrared bands of benzaldehyde and benzonitrile, plus some absorption in the N—H region around 3 μ. It was treated with Girard reagent as already described; benzaldehyde was identified in the water-soluble portion by conversion to its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 236.5–237°, while the ether-soluble fraction was shown to be benzonitrile by its infrared spectrum and hydrolysis with alkaline hydrogen peroxide to benzamide.

Fragmentation of 2,2,5,5-tetramethyltetrahydrofuran-3-one oxime. (a) *With phosphorus pentachloride.* A solution of 4.72 g. of the oxime[23] in 60 ml. of benzene was treated with 7.0 g. of phosphorus pentachloride, kept at room temperature for 2 days, and worked up as described above. Distillation of the residue afforded 1.05 g. (43%) of senecionitrile, b.p. 138–148°. The infrared spectrum of the nitrile was identical with that of an authentic sample prepared from isobutyraldehyde cyanohydrin,[24] and which distilled at 140–143°. Hydrolysis of the nitrile, by warming it in 40 g. of polyphosphoric acid at 100–115° for 30 min., gave seneciamide, identified by its infrared spectrum.

The aqueous washings were treated with Brady's reagent, yielding, after recrystallization from ethanol, 0.56 g. of acetone 2,4-dinitrophenylhydrazone, m.p. 124–125°, undepressed by admixture with an authentic sample.

(b) *With thionyl chloride.* To a solution of 4.3 g. of the oxime in 40 ml. of anhydrous ether, cooled in an ice bath, 10 ml. of thionyl chloride was added dropwise. The resulting solution was kept overnight at room temperature, the excess thionyl chloride decomposed with methanol and the mixture distilled. The fraction boiling at 140–146° (1.37 g.) was shown by its infrared spectrum to be senecionitrile, contaminated with traces of a ketonic impurity.

(c) *With p-toluenesulfonyl chloride.* After 64 hr., the reaction mixture was worked up by the general procedure and the residue distilled. Redistillation of the high-boiling fraction gave a small amount of oil with infrared absorption at 2.8 and 2.9 μ (hydroxyl) and 4.45 and 4.51 μ (unconjugated and conjugated nitrile, respectively).

The aqueous solution from the extraction was treated with Brady's reagent, yielding acetone 2,4-dinitrophenylhydrazone (9%), m.p. and m.p. 123–124°.

(d) *With sulfuric acid.* A solution of 2 g. of the oxime in 20 ml. of concd. sulfuric acid was heated at 100° for several minutes, cooled to room temperature, then poured into ice and water, and extracted with chloroform. The aqueous solution, treated as above, gave acetone 2,4-dinitrophenylhydrazone, m.p. 122.5–123.5°, not depressed by mixing with an authentic sample. Concentration of the chloroform extracts yielded only a few milligrams of starting oxime.

(e) *With polyphosphoric acid.* The aqueous solution was extracted with chloroform (5 × 50 ml.) and the aqueous layer treated with Brady's reagent. The crude product was purified by chromatography over alumina and identified as acetone 2,4-dinitrophenylhydrazone by its infrared spectrum.

The chloroform extracts were washed with water and saturated salt solution, then evaporated to dryness. The residue was recrystallized twice from benzene-hexane, affording colorless needles of seneciamide, m.p. 108.5–109° (lit.[24] m.p. 107–108°), not depressed by admixture with an authentic sample.

Derivatives of 2,5-dimethyl-2,5-diethyltetrahydrofuran-3-one. The *oxime* (Ib) was prepared in good yield by refluxing a solution of the ketone[23] and a slight excess of hydroxylamine hydrochloride in ethanol and pyridine for 4 hr., and distilled at 140–141° (24 mm.).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.72; H, 10.32; N, 7.77.

The *2,4-dinitrophenylhydrazone,* after recrystallization from ethanol, melted at 135–135.8°.

Anal. Calcd. for $C_{16}H_{22}N_4O_5$: C, 54.85; H, 6.33; N, 15.99. Found: C, 54.88; H, 6.49; N, 16.24.

Cleavage of oxime Ib *with phosphorus pentachloride.* The oxime (9.6 g.) was treated by the general procedure described. The combined aqueous washings were treated with a solution of 7.5 g. of 2,4-dinitrophenylhydrazine in 60 ml. of 2:1 sulfuric acid, yielding 7.0 g. (54%) of 2-butanone 2,4-

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(20) H. Wren, *J. Chem. Soc.*, **95**, 1583 (1909).

(21) E. Fischer, *Ber.*, **26**, 2412 (1893).

(22) O. L. Brady, *J. Chem. Soc.*, 756 (1931).

(23) G. Dupont, *Ann. de Chim.*, [8], **30**, 485 (1913).

(24) F. de Laet, *Bull. soc. chim. Belg.*, **38**, 163 (1929).

dinitrophenylhydrazone. Recrystallized from ethanol, it melted at 111.5–112.5°, alone or mixed with a genuine sample.

The remaining benzene solution was distilled, yielding two fractions: (a) 0.54 g., b.p. 145–157°; (b) 1.95 g., b.p. 158–162°. The reported[25] boiling points of the two geometric isomers of β-ethylcrotonitrile (IIIb) are 142–143° and 162–162.5°. Both fractions showed strong infrared absorption at 4.5 μ and 6.1 μ characteristic of α,β-unsaturated nitriles, in addition to slight absorption at 4.45 μ; the latter is probably due to the presence of some of the β,γ-unsaturated isomer.

The nitrile mixture from a second run of the same size was kept at room temperature for 30 min. in a solution of 0.7 g. of sodium in 30 ml. of ethanol. The solution was diluted with water and a few drops of acetic acid and extracted with ether. The extracts were washed with sodium bicarbonate solution, dried and distilled, yielding 1.66 g. of *3-methylpentene-2-nitrile* (IIIb), b.p. 150–160°. The infrared spectrum showed only the conjugated cyano band at 4.51 μ and conjugated olefin at 6.12 μ, and was identical with that of an authentic sample,[26] b.p. 156–160°.

Cleavage of 7-oxadispiro[5.1.5.2]pentadecane-14-one oxime (Ic). The oxime (Ic) was prepared from the ketone[23] with hydroxylamine hydrochloride in ethanol-pyridine. After recrystallization from hexane, it formed glistening needles, m.p. 127–127.5°.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.99; H, 9.72; N, 5.99.

A solution of 0.50 g. of the oxime in 10 ml. of benzene was treated with 0.47 g. of phosphorus pentachloride, worked up as described previously, then treated with Girard's reagent. The aqueous solution of the Girard derivative was treated with Brady's reagent, affording 0.265 g. (45%) of cyclohexanone 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160°, after recrystallization from ethanol.

Concentration of the ethereal solution from the Girard separation left a residue with infrared bands in the hydroxyl (2.9 μ) and nitrile (4.45 and 4.51 μ) regions.

Fragmentation of 2,2-diphenyltetrahydropyran-3-one oxime (IV). (a) *With phosphorus pentachloride.* A solution of 1.04 g. of the oxime[27] in 30 ml. of chloroform was treated according to the general procedure; 0.68 g. (95%) of benzophenone crystallized from the residue on cooling. Recrystallized from hexane, it melted at 49–50°, and did not depress the melting point of an authentic sample.

(b) *With polyphosphoric acid.* The infrared spectrum of the chloroform extracts of the reaction mixture showed carbonyl absorption at 5.63 μ and 6.02 μ and was an almost exact composite of the spectra of benzophenone and γ-butyrolactone. Treated with Brady's reagent, the mixture yielded the 2,4-dinitrophenylhydrazone of benzophenone (27%), m.p. 237.5–238°, after recrystallization from chloroform-ethanol; the melting point was not depressed by mixing with an authentic sample.

(c) *With p-toluenesulfonyl chloride.* A solution of 21.1 g. of oxime IV and 16.0 g. of *p*-toluenesulfonyl chloride in 250 ml. of pyridine was kept at room temperature for 110 hr., then worked up as described previously. The residue was concentrated to a small volume and diluted with ethanol. After keeping in the refrigerator, the colorless crystals were collected and washed with a little ethanol, yielding 19.7 g. (95.4%) of V, m.p. 171.5–172.5°.

Anal. Calcd. for $C_{34}H_{32}N_2O_3$: C, 79.05; H, 6.24; N, 5.42; mol. wt., 516.6. Found: C, 78.90, 79.17; H, 6.32, 6.21; N, 5.48, 5.63; mol. wt. (Rast), 450.

The filtrate was evaporated to dryness and treated with Brady's reagent, yielding 1.3 g. of benzophenone 2,4-dinitrophenylhydrazone; after recrystallization from chloroform-ethanol, it melted at 237–238°, alone or mixed with an authentic sample.

Alkaline hydrogen peroxide hydrolysis of V. A warm solution of 200 mg. of V in 50 ml. of ethanol was treated with 10 ml. of 2*N* sodium hydroxide and 3.0 ml. of 6% hydrogen peroxide, then warmed to 60–70° for 20 min. Another 2.0 ml. of the peroxide solution was added, the mixture heated to boiling for 5 min., then kept at room temperature for 4 hr. The mixture was neutralized with dilute hydrochloric acid, boiled to drive off the alcohol and diluted with water. After cooling, the precipitate was collected and recrystallized from benzene-hexane, yielding 70 mg. of colorless crystals of the amide corresponding to V, m.p. 203–204.5°.

Anal. Calcd. for $C_{34}H_{34}N_2O_4$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.64; H, 6.70; N, 5.07.

Acid hydrolysis of V. A solution of 1.02 g. of the nitrile V in 65 ml. of ethanol and 10 ml. of water was treated with 3 drops of concd. sulfuric acid and refluxed for 165 min. Addition of 155 ml. of water caused the formation of a precipitate (0.47 g.), which was collected and recrystallized from ethanol, affording 2,2-diphenyltetrahydropyran-3-one oxime (IV), m.p. 204–205°, not depressed by admixture with the authentic oxime. The filtrate from the separation of the solid was extracted with chloroform; the extracts were dried and concentrated to yield 0.38 g. of an oily residue. It was converted to the 2,4-dinitrophenylhydrazone and recrystallized from chloroform-ethanol, giving the derivative of benzophenone, m.p. and mixed m.p. 237.5–238°.

Hydration of 2-methyl-3-pentyn-2,5-diol (VI). A mixture of the diol[28] (95 g.) and mercuric sulfate (20 g.) was treated with 500 ml. of hot water, causing an exothermic reaction. The mixture was distilled until no more organic liquid appeared in the distillate, and the distillate, about 300 ml., was saturated with salt and extracted with ether. Distillation of the dried extracts gave 54.2 g. of 2,2-dimethyltetrahydrofuran-4-one (VIII), b.p. 145–148°. Vapor phase chromatography over a silicone column at 104° showed one peak comprising at least 99% of the sample.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.06; H, 9.00.

The *semicarbazone*, formed from 4.36 g. of the ketone, weighed 4.21 g. and melted at 177.5–178.5°. Recrystallization from ethanol gave 3.86 g. of tiny prisms, m.p. 178–179.5°.

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 49.10; H, 7.65. Found: C, 49.13; H, 7.61.

The *oxime* was prepared by refluxing a solution of 10.3 g. of the ketone and 10.5 g. of hydroxylamine hydrochloride in 25 ml. of pyridine and 50 ml. of ethanol for 5 hr., then distilling the ethanol. The residue was diluted with water, acidified with dilute hydrochloric acid and extracted with ether; after drying over magnesium sulfate, the ether was distilled. The water-soluble oxime, 5.97 g., distilled at 120–130° (18 mm.). The center cut was redistilled for analysis, b.p. 105° (bath temperature) at 2 mm.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.67; H, 8.60; N, 11.10.

The *dibenzylidene derivative* of the ketone was prepared by the procedure of Alexander *et al.*,[29] and gave yellow prisms, m.p. 103–105°, after recrystallization from hexane.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.92; H, 6.34.

Treatment of the ketone with Brady's reagent and re-

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(25) P. Bruylants, *Bull. sci. acad. roy. Belg.*, [5], **17**, 1008 (1931); *Chem. Abstr.*, **26**, 1576 (1932).

(26) A. Kandiah and R. P. Linstead, *J. Chem. Soc.*, 2139 (1929).

(27) K. R. Huffman and D. S. Tarbell, *J. Am. Chem. Soc.*, **80**, 6341 (1958).

(28) This diol, as were most of the acetylenic diols used in this study, was a generous gift of the Air Reduction Co., Murray Hill, N. J., for which grateful acknowledgment is made, especially to Mr. M. W. Leeds.

(29) K. Alexander, L. S. Hafner, G. H. Smith, Jr., and L. E. Schniepp, *J. Am. Chem. Soc.*, **72**, 5506 (1950).

crystallization of the crude product from dimethylformamide ethanol gave an *osazone* as an orange powder, m.p. 261°.

Anal. Calcd. for $C_{18}H_{18}N_8O_9$: C, 44.08; H, 3.70; N, 22.85. Found: C, 43.91; H, 3.81; N, 23.18.

Fragmentation of 2,2-dimethyltetrahydrofuran-4-one oxime. To a solution of 1.29 g. of the oxime in 25 ml. of benzene was added 2.2 g. of phosphorus pentachloride in small portions. After standing for 10 hr. at room temperature, the dark red solution was washed with four 30-ml. portions of water. The aqueous washings were washed with chloroform, stirred with decolorizing carbon, and filtered. The filtrate gave an instant strong purple color when treated with chromotropic acid and concentrated sulfuric acid. Estimation of the formaldehyde in the filtrate by the method of Bricker and Vail[30] showed that 43% of the theoretical was present.

A portion of the filtrate, when treated with Brady's reagent, gave only the 2,4-dinitrophenylhydrazine derivative of formaldehyde, m.p. 162.5–163.5°, undepressed by admixture with an authentic sample, m.p. 164–165°. Acetone 2,4-dinitrophenylhydrazone was not detected.

1-(1-Hydroxycyclohexyl)-3-methylbut-1-yn-3-ol (VII). To an ethereal solution of the Grignard reagent prepared from 50 g. of magnesium and 300 g. of 1-bromobutane was added 75 g. of 3-methylbut-1-yn-3-ol, with cooling in ice. The mixture was refluxed for 0.5 hr., stirred at room temperature for 1.5 hr., then cooled in ice and an ethereal solution of 87.5 g. of cyclohexanone added slowly. After keeping overnight, the mixture was treated with saturated ammonium chloride solution and enough hydrochloric acid to dissolve the solids. The layers were separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed with water and potassium bicarbonate solution, dried over sodium sulfate, and concentrated. The solid residue was recrystallized from benzene-hexane, yielding 125 g. of the diol, m.p. 98–99.2° (lit.[31] m.p. 94–95°), with a lemon-like odor.

Hydration of diol VII. A mixture of 20 g. of VII, 5.5 g. of mercuric sulfate, and 400 ml. of water was slowly distilled until no more organic liquid appeared in the distillate. The distillate was extracted with ether, and the extracts dried and concentrated. The residue distilled at 108–114° (20 mm.), affording 19.2 g. of a mixture of ketones X and XI.

The mixture of semicarbazones, prepared in the usual way, melted at 153–184°. Four recrystallizations from 50% aqueous ethanol gave the pure semicarbazone of 2,2-dimethyl-1-oxaspiro[4.5]decan-4-one (X), with a constant m.p. of 222–223.5°.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.85; N, 17.56. Found: C, 60.40; H, 8.91; N, 17.88.

The pure ketone (X) was regenerated from 9.0 g. of the semicarbazone by slowly distilling a mixture of it with 20 ml. of concd. hydrochloric acid and 300 ml. of water, replacing the water as necessary, and collecting 400 ml. of distillate. The ketone was obtained by extraction with ether, and distilled at 129–131° (57 mm.); the yield was 6.35 g.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.76; H, 9.85.

Quantitative comparison of infrared spectra of the pure ketone X and the mixture of X and XI, especially at 8.21 μ and 9.07 μ, established that X constituted 43 ± 2% of the mixture.

The *oxime* of X was obtained by refluxing a solution of 2.32 g. of the ketone and an equal weight of hydroxylamine hydrochloride in 10 ml. of pyridine and 15 ml. of ethanol for 5 hr. Recrystallization of the crude solid from dilute ethanol gave 1.79 g. of needles, m.p. 99–100°.

Anal. Calcd. for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.14; H, 9.86; N, 7.29.

Fragmentation of oxime of X. (a) *In polyphosphoric acid.* The reaction mixture was treated with an aqueous sulfuric acid solution of 0.33 g. of 2,4-dinitrophenylhydrazine, kept for 1 hr., then poured into water, and extracted with chloroform. The extracts were concentrated, then chromatographed over alumina in ether. The center fractions were recrystallized from dilute ethanol, giving *cyclohexanone 2,4-dinitrophenylhydrazone,* whose infrared spectrum was superimposable on that of an authentic specimen.

(b) *With phosphorus pentachloride.* The residue from the general procedure was taken up in ether and extracted with 10 ml. of saturated sodium bisulfite solution. These extracts were treated directly with Brady's reagent, yielding cyclohexanone 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 159–160° after recrystallization from ethanol.

Cleavage of α,β-epoxy-β-(m-nitrophenyl)propiophenone oxime. A warm solution of the "β" oxime[32] in chloroform was treated with phosphorus pentachloride and worked up as described above. The residue showed infrared absorption due to hydroxyl (2.9 μ), aromatic nitrile (4.5 μ) and carbonyl (5.76 μ, 5.97 μ), and gave a strong positive test with Fehling's solution. Vapor phase chromatography on a silicone column at 173° showed two peaks, the second having the same retention time as benzonitrile.

Bullatenone oxime. The oxime was prepared by refluxing the ketone with hydroxylamine hydrochloride in pyridine-ethanol for 3–4 hr. Recrystallization from hexane gave tiny colorless prisms, m.p. 144–145°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.63; H, 6.59; N, 6.94.

The *oxime p-toluenesulfonate* was prepared by keeping 200 mg. of the oxime with an equal weight of *p*-toluenesulfonyl chloride in 3.0 ml. of pyridine overnight at room temperature. The green solution was distributed between chloroform and dilute hydrochloric acid, and the chloroform solution washed several times with water, then dried and concentrated. The residue crystallized on trituration with ether and was twice recrystallized from hexane; m.p. 129.5–130°.

Anal. Calcd. for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.35; N, 3.92. Found: C, 63.83; H, 5.33; N, 3.95.

Dihydrobullatenone (*2,2-dimethyl-5-phenyltetrahydrofuran-3-one*) was prepared as described by Nazarov[33]; it distilled at 113–114° (5 mm.) (lit. b.p. 120–121° at 7 mm.) and gave a semicarbazone melting at 149–150° (lit. m.p. 149°).

The *oxime* was prepared in the usual way from the ketone in pyridine-ethanol and recrystallized twice from hexane; m.p. 62–64°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.44; H, 7.62; N, 6.57.

Fragmentation of dihydrobullatenone oxime. (a) *In polyphosphoric acid.* The oxime (2.0 g.) was treated with polyphosphoric acid as described above. The chloroform extracts were twice washed with water, then with saturated salt solution, filtered, and concentrated. The residue was triturated with ether, affording 0.42 g. of light tan *cinnamamide.* Two recrystallizations from benzene gave colorless crystals, m.p. 145.5–146.5° (reported m.p. 147°). The infrared spectrum showed the characteristic amide absorption at 5.95 μ and 2.93 μ.

The combined aqueous washings and filtrates were stirred with charcoal, filtered, and treated with Brady's reagent. Recrystallization of the crude product from aqueous ethanol gave acetone 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 122–123°.

(b) *With phosphorus pentachloride.* A solution of 1.38 g. of the oxime in 20 ml. of benzene was treated with 1.5 g. of phosphorus pentachloride in small portions and kept for 10 hr. at room temperature. The solution was washed with six 25-ml. portions of water, then with saturated salt solution,

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(30) C. E. Bricker and W. A. Vail, *Anal. Chem.*, **22,** 720 (1950).

(31) A. T. Babayan, *J. Gen. Chem.* (*U.S.S.R.*), **10,** 480 (1940); *Chem. Abstr.*, **34,** 7851 (1940).

(32) S. Bodforss, *Ber.*, **51,** 192 (1918). The oxime used here was found to melt at 151.5–152.5°, while Bodforss reports m.p. 145°.

(33) I. N. Nazarov, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 107 (1946); *Chem. Abstr.*, **42,** 7737 (1948).

filtered, and concentrated to yield 0.60 g. of a pale green oil. The infrared spectrum showed strong hydroxyl absorption and a nonconjugated nitrile band at 4.45 μ. The liquid was distilled at atmospheric pressure, and the distillate purified by chromatography in ether over alumina. Its infrared spectrum was then identical with that of authentic cinnamonitrile.

The aqueous washings were treated with Brady's reagent, and afforded 1.02 g. of *acetone 2,4-dinitrophenylhydrazone*, m.p. and mixed m.p. 125–126°.

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PRINCETON, N. J.

[CONTRIBUTION NO. 1640 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Studies on 1,5-Diphenyl-2,3-pyrrolidinedione and Related Compounds[1,2]

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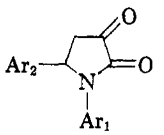
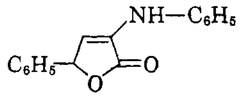
Details are given of structural studies on the Schiff and Gigli compound. This work, previously reported in preliminary form,[1] is in agreement with the most recent findings of Meyer and Vaughan.[8] A synthesis of 1,5-diphenyl-2,3-pyrrolidinedione and its reaction with ozone are described.

In seeking model α-keto-γ-lactams for other studies, we had occasion to reinvestigate the compounds, generally considered to be 1,5-diaryl-2,3-pyrrolidinediones I,[4] obtained in the condensation of pyruvic acid with aromatic aldehydes and aryl amines. The prototype of such products, A, $C_{16}H_{13}NO_2$, m.p. 161° was first prepared by Schiff and Gigli[5] from pyruvic acid and benzalaniline, and, until very recently, was formulated as Ia.



I

Ia. $Ar_1 = Ar_2 = C_6H_5$



II

Although structure Ia accommodates the behavior of A in many respects, there are certain properties of this material which appeared exceptional on the basis of the pyrrolidinedione formulation. In particular, the infrared spectrum, exhibiting bands at 5.68 and 6.01 μ, the ready displacement of aniline from A by amines,[6] and the thermal decarboxylation to cinnamylideneaniline[7] cannot be reconciled easily with structure Ia or with its enolic tautomer. On the other hand, as was outlined earlier[1] (and as has been shown independently by Meyer and Vaughan[8]), the alternative enamino lactone II[9] readily accommodates these and other known properties of A. Our studies on this problem[1] are now presented in detail.

Authentic 1,5-diphenyl-2,3-pyrrolidinedione. We sought to distinguish between the two possible structures for A by first synthesizing authentic 1,5-diphenyl-2,3-pyrrolidinedione by an unambiguous route. The starting material for this preparation was 4-carbethoxy-1,5-diphenyl-2,3-pyrrolidinedione (III), reported in the early literature[10] and recently synthesized independently by Southwick.[11] The properties[5,10–12] of this and related 4-carbalkoxy-2,3-pyrrolidinediones are in complete accord with the assigned structures.

It was expected that hydrolysis of the ester, followed by decarboxylation, would provide a simple route to Ia. However, repeated attempts to effect this hydrolytic cleavage using both acidic and basic reagents were unsuccessful. The drastic conditions required for reaction brought about

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[1] A preliminary account of this work has appeared previously: H. H. Wasserman and R. C. Koch, *Chem. & Ind. (London)*, 428 (1957).

[2] From the doctoral dissertation of R. C. Koch, Yale University, 1957.

[3] Chas. Pfizer and Co. Inc., Groton, Conn. Celanese Corp. Fellow, 1955–56.

[4] For leading reference, *cf.* R. C. Elderfield, *Heterocyclic Compounds*, Vol. IV, John Wiley and Sons, Inc., New York, 1952, pp. 25–29; W. R. Vaughan, *J. Org. Chem.*, **20,** 1613 (1955).

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