[I], with the slope and the least squares fit yielding the K_I value and its estimated uncertainty. In the case of substrates IIIa and Va, the relative rates noted in the discussion were taken from direct comparison of slopes of corresponding segments of the hydrolysis rate curves; the enzymatic rates for these substrates at the concentration level of 1.97×10^{-3} *M* amounted to 85 to 90% of those for the natural substrate acetylcholine at its concentration optimum of 3.3×10^{-3} *M*. These substrates were added to the reaction media in the form of their purified hydrochlorides, and the ensuing neutralizations by the dilute buffer led to *p*H levels of 7.0–7.1 at which the ester hydrolyses were studied.

Preparation of Inhibitors and Substrates. Betaines of Hydroxyproline.—The known betaines of hydroxy-L-proline and allohydroxy-D-proline, betonicine and turicine, respectively, and acetylbetonicine hydrochloride were prepared by action of silver oxide and methyl iodide on the amino acids as described previously.[4] The betaine of allohydroxy-L-proline L-turicine, was similarly prepared and characterized by m.p. 252–254°, $[\alpha]^{20}D$ −39.0° (*c* 1.0 in H_2O); turicine,[4] m.p. 259–260°, $[\alpha]^{25}D$ +37.8°. The methiodide of N-methylpyrrolidine has been described by Willstätter.[12]

N-Carbobenzyloxyhydroxy-L-proline Anilide.—The mixed anhydride procedure with ethyl chlorocarbonate was used to couple aniline with N-carbobenzyloxyhydroxy-L-proline according to the method of Boissonas.[13] The anilide was obtained in 70% yield, m.p. 149–150°, on crystallization of the crude coupling product from ethanol, ethyl acetate and petroleum ether (b.p. 65°). A sample recrystallized a second time had m.p. 150°, $[\alpha]^{20}D$ −49.8° (*c* 1.0 in methanol).

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.17; H, 5.88; N, 8.20.

Hydroxy-L-proline Anilide.—The carbobenzyloxy group was hydrogenolyzed from N-carbobenzyloxyhydroxy-L-proline anilide with 10% palladium-on-charcoal in glacial acetic acid. After evaporation of the solvent *in vacuo*, hydroxy-L-proline anilide was crystallized from ethanol, ethyl acetate and petroleum ether. The analytical sample had m.p. 150–151°, $[\alpha]^{25}D$ −32.8° (*c* 1.0 in methanol).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.89; H, 6.80; N, 13.67.

When the hydrogenolysis was conducted in methanol in the presence of a molar quantity of HCl, hydroxy-L-proline anilide hydrochloride was obtained, m.p. 205–206°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot HCl$: C, 54.43; H, 6.23; N, 11.54. Found: C, 54.15; H, 6.38; N, 11.24.

N-Methyl-hydroxy-L-proline Anilide Methiodide.—Hydroxy-L-proline anilide (0.540 g.) in 10 cc. of methanol was treated at room temperature with silver oxide (0.610 g.) and 1 cc. of methyl iodide. A precipitate of silver iodide rapidly formed and the solution warmed noticeably. After 1 hr. an additional 1 cc. of methyl iodide was added and at the end of 2 hr. the solution was diluted with methanol, filtered and acidified with HI. The residue after evaporation of the solvent *in vacuo* was crystallized from absolute ethanol and ether. In this manner N-methylhydroxy-L-proline anilide methiodide (0.415 g., 44%) was obtained as platelets, m.p. 186–187°, $[\alpha]^{20}D$ +45.2° (*c* 1.0 in water).

Anal. Calcd. for $C_{12}H_{19}N_2O_2I$: C, 43.10; H, 5.29; N, 7.74. Found: C, 43.31; H, 5.18; N, 7.71.

Allohydroxy-D-proline Anilide Hydrochloride.—Aniline and N-carbobenzyloxyallohydroxy-D-proline were coupled by the mixed anhydride procedure as described above for N-carbobenzyloxyhydroxy-L-proline anilide. N-Carbobenzyloxyallohydroxy-D-proline anilide resisted crystallization, but it was convertible to the crystalline allohydroxy-D-proline anilide hydrochloride by hydrogenolysis of the carbobenzyloxy group with 10% palladium-on-charcoal in methanol with a molar equivalent of HCl. Allohydroxy-D-proline anilide hydrochloride crystallized from ethanol and ether as fine needles, m.p. 256–258°, $[\alpha]^{20}D$ +10.2° (*c* 1.0 in water).

Anal. Calcd. for $C_{11}H_{15}N_2O_2Cl$: C, 54.43; H, 6.23; N, 11.54. Found: C, 54.63; H, 6.34; N, 11.43.

N-Methylallohydroxy-D-proline Anilide Hydriodide.—Allohydroxy-D-proline anilide hydrochloride (0.500 g.) was dissolved in 20 cc. of methanol and treated with silver oxide (0.238 g.). After 15 minutes, an additional amount of silver oxide (0.476 g.) and 1 cc. of methyl iodide were added. A further 0.5 cc. of methyl iodide was added after 30 minutes, and at the end of 1 hr., the solution was diluted with methanol, filtered and acidified with HI. Removal of solvent left an oil which on trituration with ethanol and ether yielded 0.228 g. (31%) of crude hydriodide. Several recrystallizations from absolute ethanol afforded an analytical sample of N-methylallohydroxy-D-proline aniline hydriodide m.p. 220–222°. The same compound was obtained when free allohydroxy-D-proline anilide was subjected to the same procedure.

Anal. Calcd. for $C_{12}H_{16}N_2O_2 \cdot HI$: C, 41.39; H, 4.92; N, 8.05; I, 36.45. Found: C, 41.66; H, 4.85; N, 7.93; I, 36.90.

Acetylturicine Hydrochloride.—The conditions used for methylation were those described for acetylbetonicine.[4] The crude crystalline methylation product was converted to its hydrochloride at 0° in ethanol and ethyl acetate with gaseous HCl. Even cautious recrystallization of the product from ethanol and ethyl acetate gave an impure acetylturicine hydrochloride, m.p. 185–187° and $[\alpha]D$ +10.7° (*c* 1.0 in water), whose analysis agreed with that of a mixture containing 75% acetylturicine hydrochloride and 25% turicine hydrochloride.

Anal. Calcd. for $C_9H_{16}NO_4Cl$ (75%) and $C_7H_{14}NO_3Cl$ (25%): C, 44.88; H, 6.90; N, 6.19; CH_3CO, 13.6. Found: C, 44.78; H, 6.95; N, 6.22; CH_3CO, 13.9.

Acknowledgment.—We are indebted to Dr. H. S. Polin for his generous aid in procurement of electric eel tissue extracts.

BETHESDA 14, MD.

(12) R. Willstätter and Heubner, *Ber.*, **40**, 3873 (1907).

(13) Boissonas, *Helv. Chim. Acta*, **34**, 874 (1951).

[CONTRIBUTION FROM THE SCIENTIFIC AND RESEARCH DEPT., SOUTH AFRICAN IRON AND STEEL INDUSTRIAL CORPORATION, LTD.]

The Structures of Isoxazoline Compounds: A Spectral Study

BY G. W. PEROLD, A. P. STEYN AND F. V. K. VON REICHE

RECEIVED JUNE 12, 1956

Ultraviolet absorption characteristics were determined for a series of five isoxazolines, obtained by addition of benzonitrile oxide to various olefins. Correlation with the absorption of model compounds shows that the addition compounds are 2-isoxazolines. The use of infrared absorption in connection with this problem is evaluated.

Isoxazoline compounds are obtained by the interaction of hydroxylamine with β-halogenated ketones[1] as well as with α,β-unsaturated ketones[2] under alkaline conditions. Quilico and his school have in recent years shown[3] that they also are

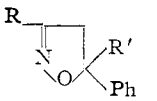
(1) H. Rupe and F. Schneider, *Ber.*, **28**, 965 (1895).

(2) A. H. Blatt, THIS JOURNAL, **53**, 1133 (1931).

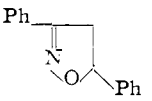
(3) A. Quilico, G. Stango d'Alcontres and P. Grünanager, *Nature*, **166**, 226 (1950); *Gazz. chim. ital.*, **80**, 479 (1950), and further papers from this school.

formed very readily by the addition of benzonitrile oxide to olefins of various types.

As to the position of the double bond in isoxazolines, Blatt[4] showed that the isoxazolines obtained by addition of free hydroxylamine to dypnone and to benzal-*p*-bromoacetophenone must be the 2-isoxazoline derivatives I and II, respectively. The mode of formation of isoxazolines from benzonitrile oxide by addition to olefins similarly makes likely the formation of 2-isoxazolines. Thus styrene would be expected to yield 3,5-diphenyl-2-isoxazoline (III).[5]

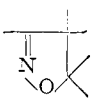


I, R = Ph, R′ = Me
II, R = *p*-Br-phenyl, R′ = H

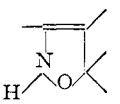


III

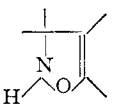
Work in progress in this Laboratory necessitated unequivocal proof for the structure of the isoxazolines obtained by the addition of benzonitrile oxide to various olefins. This seemed the more necessary as models of the three isomeric isoxazoline structures (IV–VI) constructed with Fisher–Taylor–Hirschfelder units show greater ring strain for the 2- (IV) than for the 3- (V) or the 4-isoxazoline (VI).[6]



IV



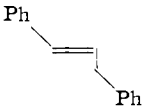
V



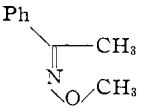
VI

These structures differ both in the nature and the environment of the double bond contained in the ring, so that it should be possible to differentiate between them on the basis of their electronic and molecular absorption characteristics.

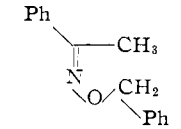
Barnes, Pinkney and Phillips[7] examined the infrared absorption of isoxazolines and attributed strong absorption found at 5.85 μ (1710 cm.$^{-1}$, in dioxane solution) to the C=N grouping. As we could find no specific absorption in this region[8] for a series of five different isoxazolines (below), we studied the spectral absorption characteristics of the isoxazolines in both the ultraviolet and the infrared regions so as to find more definite correlations between absorption and structure. Open chain models of the isoxazolines were constructed for this purpose. These consisted of the styrene type (V and VI) analog, ω-benzylstyrene (VII), as well as the oxime type (IV) analogs of 3,5-diphenyl-2-isoxazoline, *viz.*, acetophenone oxime O-methyl ether (VIII), acetophenone oxime O-benzyl ether (IX), β-phenylpropiophenone oxime (X) and β-phenylpropiophenone oxime O-methyl ether (XI).



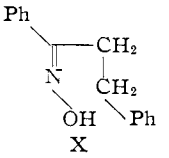
VII



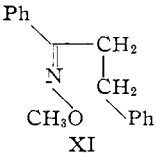
VIII



IX

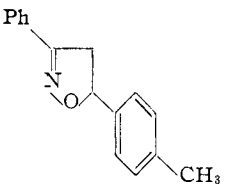


X

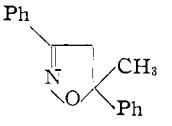


XI

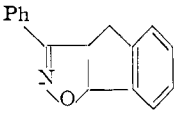
The five isoxazolines studied (III, XII–XV) were all obtained by the addition of benzonitrile oxide to the corresponding olefinic compounds, *viz.*, to styrene, *p*-methylstyrene, α-methylstyrene, indene and dicyclopentadiene.



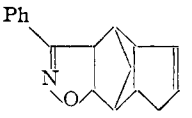
XII



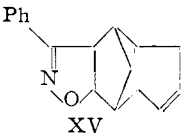
XIII



XIV[9]



or



XV

Ultraviolet Absorption.—ω-Benzylstyrene shows typical styrene absorption (Table I) with well developed, bathochromically displaced benzenoid absorption at 284–293 mμ, log ϵ *ca.* 3, beside the K band at 252 mμ, log ϵ 4.33.

The open chain oxime analogs show normal oxime type absorption, similar in every way to that shown, for instance, by acetophenone oxime,[10] with the K band at 249 ± 4 mμ, log ϵ *ca.* 4.1, smoothly enveloping the benzenoid absorption.[11] The isoxazolines show precisely this type of absorption, except that the K band is here bathochromically displaced[12] to 265 ± 3 mμ, log ϵ *ca.* 4.2. The absorption maxima for the series of compounds are listed in Table I.

Infrared Absorption.—A distinction between 2- and either 3- or 4-isoxazoline structures is represented by the occurrence of a carbon–nitrogen as against a carbon–carbon double bond, conjugated with a benzene nucleus. Clear-cut infrared absorption correlations for the —C=N— grouping which would make possible an unambiguous decision on this point have so far not become available,[13]

(4) A. H. Blatt, THIS JOURNAL, **53**, 1136 (1931).

(5) G. Stagno d'Alcontres and P. Grünanger, *Gazz. chim. ital.*, **80**, 831 (1950).

(6) The need for clarification is underlined by the appearance of a report by P. Grünanger, *Atti accad. nazl. Lincei. Rend., Classe sci. fis. mat. e nat.*, **16**, 726 (1954); *C. A.*, **50**, 305 (1956), on addition of different benzonitrile oxides to styrenes, in which the products are described as 4-isoxazolines.

(7) R. P. Barnes, G. E. Pinkney and G. M. Phillips, THIS JOURNAL, **76**, 276 (1954).

(8) It must be noted that dioxane itself, rendered acetal free according to L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 369, shows a well developed absorption peak at 5.8 μ.

(9) Structure XIV is that to be expected from a normal Markownikoff addition of benzonitrile oxide to indene.

(10) H. Ley and H. Wingchen, *Ber.*, **67**, 507 (1934).

(11) Ref. 10, p. 508.

(12) This shift may be attributed to the closing of the five-membered ring and thus reflects the strained condition of this ring. Similar bathochromic shifts are encountered in the ring ketone series as described by L. Dorfman, *Chem. Revs.*, **53**, 51 (1953).

(13) L. J. Bellamy, "The Infrared Absorption of Complex Molecules," Methuen and Co., Ltd., London, 1954, p. 223.

TABLE I

ULTRAVIOLET ABSORPTION

	$\lambda_{max.}$, mμ	log ε
ω-Benzylstyrene (VII)	252	4.33
	284	3.12
	293	2.92
Acetophenone oxime		
O-methyl ether (VIII)	245	4.18
O-benzyl ether (IX)	253	4.11
β-Phenylpropiophenone oxime (X)	247	3.97
O-methyl ether (XI)	251	4.05
2-Isoxazoline		
3,5-Diphenyl- (III)	263	4.17
3-Phenyl-5-*p*-tolyl- (XII)	262	4.25
3,5-Diphenyl-5-methyl- (XIII)	264	4.24
3-Phenyl-4,5-indano- (XIV)	266	4.09
3-Phenyl-4,5-(dicyclopentadieno)- (XV)	268	4.12

although the summary given by Bellamy[14] leads one to expect specific absorption for this grouping around 1660 cm.$^{-1}$. No such specific absorption could however be observed for the series of isoxazolines mentioned above.

All these compounds and their open-chain analogs, however, with the exception of ω-benzylstyrene, showed well-developed absorption at *ca.* 1570–1580 cm.$^{-1}$. The values for this peak for the compounds studied are set out in Table II, together with the values for the typical "aromatic peak" at *ca.* 1600 cm.$^{-1}$ by way of reference.

TABLE II

INFRARED ABSORPTION IN THE 1560–1610 CM.$^{-1}$ REGION

	State[a]	Cm.$^{-1}$	
Styrene	L	1580ms[a]	1605m[a]
ω-Benzylstyrene (VII)	L	..	1603s[a]
Acetophenone oxime			
O-methyl ether (VIII)	L	1577m	1603m
O-benzyl ether (IX)	L	1580m	1603sh[a]
β-phenylpropiophenone oxime (X)	S	1585m	1608m
O-methyl ether (XI)	L	1572m	1605s
2-Isoxazoline			
3,5-Diphenyl- (III)	S	1570m	1597m
3-Phenyl-5-*p*-tolyl- (XII)	S	1567m	1595m
3,5-Diphenyl-5-methyl- (XIII)	S	1567m	1592m
3-Phenyl-4,5-indano- (XIV)	S	1567m	1595m
3-Phenyl-4,5-(dicyclopentadieno) (XV)	S	1565m	1595m
Benzylidene methyl imine	L	1587m	1605w[a]
Hydrobenzamide	S	1577m	1600m
Benzaldehyde	L	1585m	1597s
Acetophenone	L	1587m	1600ms[a]
Benzaldoxime	L	1582m	1603w

[a] L = neat liquid, S = solid dispersion in potassium bromide; m = medium, s = strong, sh = shoulder, w = weak intensity of absorption. The values are accurate to ±2 cm.$^{-1}$.

The band at 1570–1580 cm.$^{-1}$ is ascribed[15] to an *aromatic* carbon–carbon stretching vibration, enhanced by conjugation with an external center of unsaturation. This is supported by the absorption of both benzylidene methyl imine, PhCH=NCH$_3$, and hydrobenzamide, (PhCH=N)$_2$CHPh, as well as by the observation that acetoxime and acetaldoxime do not show strong absorption in this region.

This absorption is, however, not due specifically to a conjugated —C=N— grouping, as the further entries under Table II clearly show. While ω-benzylstyrene shows no absorption at this point, well developed absorption is clearly shown by monomeric styrene, by benzaldehyde, acetophenone and benzaldoxime.

None of the isoxazolines studied shows any absorption in the N–H stretching region around 3300 cm.$^{-1}$, thus excluding the 3- and 4-isoxazoline structures for this series on that account. The absence of expected C=N absorption around 1660 cm.$^{-1}$ is therefore the more striking.

Conclusion.—The infrared absorption spectra of the series of compounds in the 1250–2000 cm.$^{-1}$ region confirm the known presence of aryl-conjugated unsaturation within the ring structures of the isoxazolines, while the absence of absorption around 3300 cm.$^{-1}$ excludes 3- and 4-isoxazoline structures. In the ultraviolet the absorption spectra show that the isoxazolines, as here prepared from benzonitrile oxide and olefins, occur in the apparently more strained form as 2-isoxazolines.

Experimental

Ultraviolet spectra were obtained in ethanol solution using the Zeiss Opton spectrophotometer, model M4Q. Infrared absorptions were obtained in potassium bromide dispersion for solid samples and in the neat state for liquid samples, using the Perkin–Elmer model 21 spectrophotometer.

Isoxazolines.—Benzhydroximic chloride was best prepared according to the general directions of Piloty and Steinbock[16] by passing chlorine gas through the solution of 10.0 ml. of benzaldoxime in 60 ml. of *ca.* 8.3 *N* hydrochloric acid at 0° for 15–20 min. The colorless product was filtered off (m.p. 42–48°, yield up to 76%) and directly used as such.

The preparation of the isoxazolines was carried out without isolating[17] the intermediate benzonitrile oxide. Benzhydroximic chloride (10.7 g.) and 7.2 g. of styrene (1 mole) were dissolved in 50 ml. of ether, cooled to 0° and 45 ml. of 14% aqueous sodium hydroxide solution gradually added. After 15 min. the aqueous layer was drawn off, the ether solution washed with water, then kept overnight and the ether evaporated to yield 12.44 g. (81%) of colorless product, m.p. 73–76°. Crystallization from ethanol gave the pure product, colorless needles, m.p. 76°. Data covering this series of preparations are given in Table III.

Model Compounds. ω-Benzylstyrene.—β-Phenylpropiophenone[18] was reduced with lithium aluminum hydride in ether to yield the carbinol in 86% yield. This (5.23 g.) was heated with its own weight of anhydrous oxalic acid in a bath heated from 130–180° during 30 min. and then held at 180° for 2 hr. After recovering the neutral product (5.13 g.) and chromatographing over 60 g. of alumina, ω-benzylstyrene (5.0 g.) was eluted with petroleum ether and distilled, b.p. 120–130° (bath) (0.06 mm.), yield 4.0 g., n^{20}D 1.6000, lit.[19] $n^{17.5}$D 1.6010.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.84; H, 7.30.

Benzylidene Methyl Imine.—This preparation[20] was here carried out by carefully mixing 20 g. of benzaldehyde with 25 g. of 33% aqueous methylamine solution, and water then removed by azeotropic distillation with benzene. The liquid residue obtained by removal of benzene was stirred

(14) Reference 13, p. 227.

(15) Reference 13, p. 60.

(16) O. Piloty and H. Steinbock, *Ber.*, **35**, 3112 (1902).

(17) A. Quilico, G. Stagno d'Alcontres and P. Grünanger, *Gazz. chim. ital.*, **80**, 487 (1950).

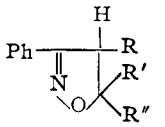
(18) H. A. Weidlich and M. Meyer-Delius, *Ber.*, **74**, 1209 (1941).

(19) J. Boeseken and G. Elsen, *Rec. trav. chim.*, **48**, 364 (1929).

(20) H. Zaunschirm, *Ann.*, **245**, 281 (1888).

TABLE III

3-Ph-2-ISOXAZOLINES



		Formula	Yield, %	M.p., °C. (pure)	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	R = H, R′ = H, R″ = Ph	$C_{15}H_{13}ON$	81	76	80.70	80.68	5.87	6.01
XII	R = H, R′ = H, R″ = *p*-tolyl	$C_{16}H_{15}ON$	96	94	80.98	81.12	6.37	6.46
XIII	R = H, R′ = CH_3, R″ = Ph	$C_{16}H_{15}ON$	60	76	80.98	81.10	6.37	6.38
XIV	RR′ = 2,1-indano, R″ = H	$C_{16}H_{13}ON$	66	134	81.66	81.88	5.57	5.57
XV	RR′ = dicyclopentadieno, R″ = H	$C_{17}H_{17}ON$	40	110–111	81.24	81.28	6.82	6.70

TABLE IV

OXIME O-ETHERS, PhRC=NOR′

R	R	Formula	Yield, %	B.p. (bath) °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	$C_9H_{11}ON$	33	132–135	46	72.45	72.55	7.43	7.27
CH_3	$C_6H_5CH_2$	$C_{15}H_{15}ON$	72	115–119	0.1	79.97	79.79	6.71	6.59
$C_6H_5CH_2CH_2$	CH_3	$C_{16}H_{17}ON$	20	110	0.1	80.30	80.53	7.16	7.24

for 90 min. at room temperature with a large excess of hydroxylamine hydrochloride and sodium hydroxide in aqueous suspension and the benzaldehyde-free product recovered by benzene extraction in 61% yield, b.p. 99–103° (bath) (42 mm.), $n^{17}D$ 1.5522.

Anal. Calcd. for C_8H_9N: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.78; H, 7.64; N, 11.83.

Oxime O-Ethers.—These were prepared according to general directions[21] from the corresponding oxime, halide and slight excess of sodium hydroxide in alcoholic solution. The data are summarized in Table IV.

Acknowledgments.—Thanks are recorded to Miss J. M. Theron and to Mr. W. F. Ross of this Department for micro-analyses and preparative assistance, respectively. Dr. T. J. W. Jorden, the Manager of this Department, is sincerely thanked for his interest and for permission to publish this paper.

PRETORIA, SOUTH AFRICA

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[CONTRIBUTION FROM THE SCIENTIFIC AND RESEARCH DEPT., SOUTH AFRICAN IRON AND STEEL INDUSTRIAL CORPORATION, LTD.]

The Chemistry of the 2-Isoxazolines: Reductive Cleavages

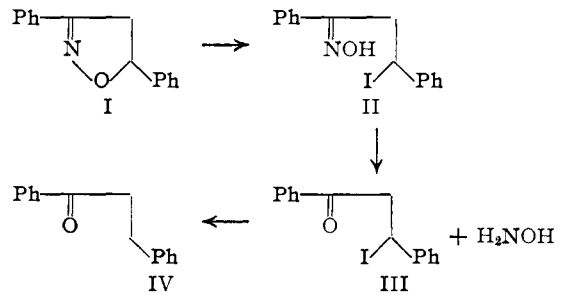
BY G. W. PEROLD AND F. V. K. VON REICHE

RECEIVED JULY 23, 1956

Refluxing constant-boiling hydriodic acid cleaves the isoxazoline ring of 3,5-diphenyl-2-isoxazoline, the main product, β-phenylpropiophenone, being accompanied by dihydrocinnamic acid, aniline and 4-phenyl-3,4-dihydrocarbostyril. This last product is obtained as well by cyclizing cinnamanilide. The changes involved are discussed. Reduction of 3,5-diphenyl-2-isoxazoline with lithium aluminum hydride produces 1,3-diphenyl-3-aminopropanol.

The addition of benzonitrile oxide[1] to styrene produces 3,5-diphenyl-2-isoxazoline.[2] In applying this reaction to other olefinic compounds, it is of some importance to have available a reaction sequence which will permit the derivation of both the structure of the addition compound and the identity of the (unknown) olefin from which it was in the first place obtained. For this study, 3,5-diphenyl-2-isoxazoline (I) was selected as a readily available and typical model substance. It was degraded *via* two separate routes to open-chain derivatives which prove useful for such applications.

I.—The first approach was based on the proof for the 2-isoxazoline structure[2] for the adduct of benzonitrile oxide to styrene. This structure I is that of a cyclic oxime ether. As Bamberger[3] had shown that aldoxime ethers are split to alkyl halides under the conditions of the Zeisel alkoxyl determination, 3,5-diphenyl-2-isoxazoline (I) should under these conditions give as a first product the iodo-oxime (II), which would probably simultaneously be hydrolyzed to chalkone hydroiodide (III) and reduced to give β-phenylpropiophenone (IV).



On carrying out this reaction, free iodine was almost immediately liberated, indicating the tran-

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