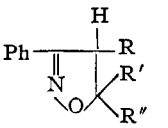
TABLE III

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

(21) A. Janny, *Ber.*, **16**, 174 (1883).

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

The Chemistry of the 2-Isoxazolines: Reductive Cleavages

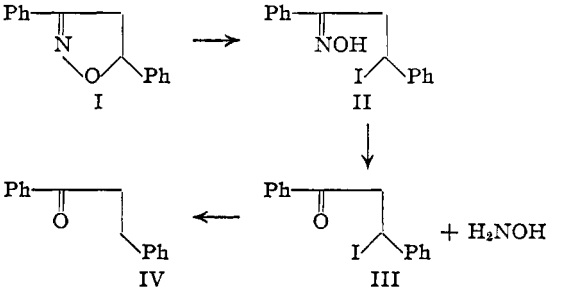
BY G. W. PEROLD AND F. V. K. VON REICHE

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-

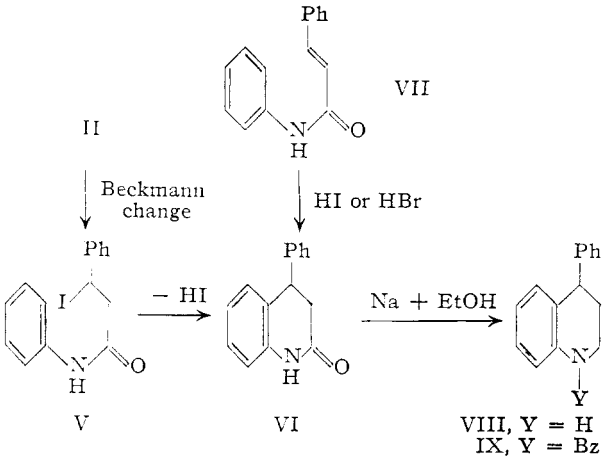
(1) A. Quilico, G. Stagno d'Alcontres and P. Grünanger, *Nature*, **166**, 226 (1950); G. Stagno d'Alcontres and P. Grünanger, *Gazz. chim. ital.*, **80**, 831 (1950).

(2) G. W. Perold, A. P. Steyn and F. V. K. von Reiche, THIS JOURNAL, **79**, 462 (1957).

(3) E. Bamberger and J. Frei, *Ber.*, **35**, 753 (1902).

sient formation of free hydroxylamine.[4] In further agreement with expectation, the neutral portion of the reaction mixture yielded β-phenylpropiophenone as the main product. This reaction has already been usefully employed in the elucidation of the structure of the isoxazoline obtained by the addition of benzonitrile oxide to indene.[5]

A second neutral product, $C_{15}H_{13}ON$, m.p. 180°,



was obtained in low yield. This is the hitherto unknown[5a] 4-phenyl-3,4-dihydrocarbostyril (VI), which is here formulated as the cyclization product of the anilide (V) resulting from the same iodooxime (II) by a Beckmann rearrangement.

The proof for structure VI rests on the occurrence of secondary amide-NH absorption[6] at 3195 cm.$^{-1}$ in conjunction with amide carbonyl absorption[6,7] at 1681 cm.$^{-1}$, the general agreement of the ultraviolet absorption of VI with that of acetanilide as against that of cinnamanilide and the presence of one atom of hydrogen reactive to methylmagnesium iodide. The identical substance was obtained by cyclizing cinnamanilide (VII) in refluxing hydrobromic or hydriodic acid. The reduction of VI with sodium and ethanol furthermore gave 4-phenyl-1,2,3,4-tetrahydroquinoline[8] (VIII), m.p. 72–74°, secondary amine-NH absorption[9] at 3413 cm.$^{-1}$, benzoyl derivative[10] m.p. 145°.

The mechanism proposed for the formation of VI was furthermore supported by the isolation of dihydrocinnamic acid (as its *p*-bromophenacyl ester) together with aniline. These products may clearly result from the reductive hydrolysis of the Beckmann product V shown above as the precursor of 4-phenyl-3,4-dihydrocarbostyril (VI). Benzoic acid, isolated as a further by-product, may well be derived from a cleavage similar to that found[11] for 3,5-diphenylisoxazole under comparable conditions.

II.—Stühmer and Heinrich[12] reduced 3,5-diphenyl-2-isoxazoline with sodium amalgam or by catalytic hydrogenation to a mixture of the two diastereoisomeric 1,3-diphenyl-3-aminopropanols, which were later[13] characterized as benzoyl and acetyl derivatives.

The use of lithium aluminum hydride in this reduction now readily afforded 1,3-diphenyl-3-aminopropanol[14] (X), m.p. 121–122°. The monobenzoyl derivative XI, m.p. 169–170°, showed only amide carbonyl absorption[6,7] at 1637 cm.$^{-1}$, while the dibenzoyl derivative XII, m.p. 190–191°, showed ester carbonyl absorption[15] at 1718 cm.$^{-1}$ as well as amide carbonyl absorption (as before) at 1642 cm.$^{-1}$. The structures of the two derivatives are therefore as formulated below and are thus in accordance with the values for Stühmer's β-diastereoisomer[13] of 1,3-diphenyl-3-aminopropanol.

$$\text{I} \xrightarrow{\text{LiAlH}_4} \text{PhCH(NH}_2\text{)CH}_2\text{CH(OH)Ph} \quad \text{(X)}$$
$$\downarrow$$
$$\text{PhCH(NHBz)CH}_2\text{CH(OH)Ph} \quad \text{(XI)}$$
$$\downarrow$$
$$\text{PhCH(NHBz)CH}_2\text{CH(OBz)Ph} \quad \text{(XII)}$$

This facile opening of the isoxazoline ring to give an easily characterized amino-alcohol may well be particularly useful in the study of isoxazolines derived from (non-aromatic) olefins.

Experimental

All m.p.s are corrected. Ultraviolet spectra were taken in ethanol solution on the Zeiss Opton M4Q spectrophotometer. Infrared absorptions were obtained in potassium bromide dispersion using the Perkin-Elmer Model 21 instrument.

The Reduction of 3,5-Diphenyl-2-isoxazoline with Hydriodic Acid.—3,5-Diphenyl-2-isoxazoline[2] (513 mg.) and 10 ml. of constant-boiling hydriodic acid were refluxed for 90 min., iodine being liberated from the beginning. After adding 30 ml. of water the solution was extracted with three 20-ml. portions of ether. The combined ether extracts were decolorized by washing with 10% sodium thiosulfate solution, then washed with two 10-ml. portions of saturated sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate and evaporated to yield 396 mg. of sirupy neutral product. This was dissolved in 2 ml. of benzene and 1 ml. of petroleum ether added and colorless crystals of 4-phenyl-3,4-dihydrocarbostyril separated on standing overnight. These were washed with benzene to give 61 mg., m.p. 178–179°, sublimed *in vacuo* and crystallized from ethanol to m.p. 179–180°; λ_{max} 254 mμ, log ε 4.08.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27; 1 act. H, 0.45; mol. wt., 223.3. Found: C, 80.56; H, 5.87; N, 6.12; act. H, 0.42; mol. wt. (ebull. in benzene), 226.

The mother liquor material recovered from the filtrate above (333 mg.) was dissolved in 20 ml. of benzene + petroleum ether (1 + 3), 5 mg. of undissolved gum discarded and the solution adsorbed on 50 g. of alumina. Elution with 200 ml. of the original solvent removed 67 mg. of fore-fraction; 300 ml. of benzene + petroleum ether (1 + 1) then eluted 164 mg. of crystals. Recrystallizing these from petroleum ether gave 117 mg. (24%)[16] of colorless

(4) K. A. Hofmann and F. Kroll, *Ber.*, **57**, 941 (1924).

(5) G. W. Perold and F. V. K. von Reiche, in preparation.

(5a) ADDED IN PROOF.—After this paper had been accepted for publication, a synthesis of 4-phenyl-3,4-dihydrocarbostyril by reduction of 4-phenyl-carbostyril was reported by E. F. M. Stephenson, *J. Chem. Soc.*, 2557 (1956). We are greatly indebted to Dr. Stephenson for supplying us with a sample of her product, m.p. 180.0–180.5°, which could be shown by mixed m. p. and infrared absorption to be in all respects identical with our product.

(6) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 176.

(7) Corresponding reference values were obtained as follows: acetanilide, 3300 and 1664; benzanilide, 3333 and 1658; cinnamanilide, 3268 and 1669 cm.$^{-1}$.

(8) W. Koenigs and F. Meimberg, *Ber.*, **28**, 1042 (1895), found m.p. 74°.

(9) Ref. 6, p. 213.

(10) Ref. 8, p. 1043, found m.p. 147°.

(11) J. Wislicenus, *Ann.*, **308**, 248 (1899).

(12) W. Stühmer and W. Heinrich, *Chem. Ber.*, **84**, 224 (1951).

(13) W. Stühmer and H. H. Frey, *Arch. Pharm.*, **286**, 8 (1953).

(14) G. H. Coleman and D. Craig, THIS JOURNAL, **49**, 2595 (1927).

(15) Ref. 6, p. 153.

(16) The yield of pure β-phenylpropiophenone dropped to 19 and 10% on extending the reaction periods to 5 and 7 hours, respectively.

platelets, m.p. 70–71° both alone and in admixture with authentic[17] β-phenylpropiophenone of m.p. 70–71°.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.83; H, 6.61.

The crude acids obtained in another run from 11 g. of 3,5-diphenyl-2-isoxazoline treated as above were recovered from the acidified sodium hydrogen carbonate extracts by ether extraction. The crude product (1.1 g.) on crystallizing from petroleum ether yielded a first crop of 0.17 g. of benzoic acid, m.p. 120–121° both alone and when mixed with pure benzoic acid, followed by further crops of less pure benzoic acid (0.339 g. in all). The non-crystalline acids recovered from the mother liquor (0.545 g.) were dissolved in a slight excess of aqueous alkali and refluxed with 0.5 g. of *p*-bromophenacyl bromide in 15 ml. of ethanol for one hour. On cooling 0.402 g. of crystals separated, which from ethanol gave 0.228 g. of platelets, m.p. 103–104°, and no depression of the m.p. when mixed with the authentic *p*-bromophenacyl ester, m.p. 104°, of hydrocinnamic acid.

Anal. Calcd. for $C_{17}H_{15}O_3Br$: C, 58.80; H, 4.35. Found: C, 58.95; H, 4.31.

Aniline was obtained from the original reaction mixture after refluxing 1 g. of 3,5-diphenyl-2-isoxazoline with 15 ml. of constant boiling hydriodic acid for 2.5 hours. The diluted mixture was extracted with ether and then steam distilled after adding 20 g. of sodium hydroxide. The aniline in the condensate was taken up in benzene and converted to the hydrochloride (34 mg.). Benzoylation in pyridine gave benzanilide, m.p. 161–162°, alone and when mixed with authentic benzanilide.

Anal. Calcd. for $C_{13}H_{11}ON$: C, 79.16; H, 5.62. Found: C, 79.13; H, 5.71.

Cyclization of Cinnamanilide.—Cinnamanilide (100 mg., m.p. 151°) was refluxed for 1 hour with 20 ml. of constant boiling hydriodic acid. The neutral product (70 mg., m.p. 178–179°) from ethanol gave 32 mg. of 4-phenyl-3,4-dihydrocarbostyril, compact prisms, m.p. 179.5° and no depression when mixed with the corresponding product above.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87. Found: C, 80.51; H, 5.86.

The same product was obtained in slightly lower yield when using constant boiling hydrobromic acid as above.

Reduction of 4-Phenyl-3,4-dihydrocarbostyril.—4-Phenyl-3,4-dihydrocarbostyril (156 mg.) in 30 ml. of ethanol was gradually treated under reflux with 4 g. of sodium. After adding water and removing ethanol *in vacuo*, the products were taken up in ether and the base recovered *via* a hydrochloric acid extract as 124 mg. of oil. After two distillations (tube, 110–120° (0.04 mm.)) the product (95 mg.) was filtered in petroleum ether solution through alumina and recovered at 91 mg. of crystals, m.p. 72–74° unchanged on recrystallizing from ethanol of 4-phenyl-1,2,3,4-tetrahydroquinoline.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22. Found: C, 86.03; H, 7.50.

Benzoylation of 65 mg. of base in pyridine gave 105 mg. of neutral product, m.p. 135°, which from ethanol gave the pure benzoyl derivative, m.p. 145°.

Anal. Calcd. for $C_{22}H_{19}ON$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.13; H, 6.37; N, 4.34.

The Reduction of 3,5-Diphenyl-2-isoxazoline with Lithium Aluminum Hydride.—3,5-Diphenyl-2-isoxazoline (1.920 g.) in 50 ml. of anhydrous ether was added to 0.34 g. of lithium aluminum hydride suspended in ether. After stirring under reflux for 5.5 hours, the cooled mixture was decomposed by adding ice-water and hydrochloric acid. After extraction with ether, the acid solution was made alkaline with sodium hydroxide solution and the crystalline precipitate filtered off (1.208 g., m.p. 114–118°). Crystallization from ethanol gave 1,3-diphenyl-3-aminopropanol, prisms, m.p. 121–122°.

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.25; H, 7.54. Found: C, 79.27; H, 7.59.

The **monobenzoyl derivative** was obtained from 127 mg. of amino-alcohol and 79 mg. (1 mole) of benzoyl chloride in pyridine (1 hour at 96°). The crude product (121 mg., m.p. 120–140°) was recrystallized from benzene and from ethanol to give prisms, m.p. 169–170°.

Anal. Calcd. for $C_{22}H_{21}O_2N$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.92; H, 6.40; N, 4.52.

The **dibenzoyl derivative** was obtained from 235 mg. of amino-alcohol and 491 mg. (3.4 mole) of benzoyl chloride as before as 442 mg. of silky needles, m.p. 175–188°. Crystallization from ethanol raised the m.p. to 190–191°.

Anal. Calcd. for $C_{29}H_{25}O_3N$: C, 79.98; H, 5.79; N, 3.22; mol. wt., 435.5. Found: C, 80.47; H, 5.79; N, 3.25; mol. wt. (ebull. in benzene), 440.

Acknowledgments.—Thanks are recorded to Dr. A. P. Steyn and Miss J. M. Theron of this Department for spectral measurements and microanalyses, 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

(17) R. Adams, J. W. Kern and R. L. Shriner, *Org. Syntheses*, **8**, 36 (1928).

[CONTRIBUTION FROM CIBA RESEARCH LABORATORIES, BASEL, SWITZERLAND]

The Acylation and Alkylation of Imidazolines and Some New Types of Imidazolines[1]

BY ADRIAN MARXER

RECEIVED AUGUST 13, 1956

The acylation of imidazolines I–III results in the formation of diacylalkylidenimidazolidines IV–VI. Intermediates are pseudobasic esters of type VII, proved by the isolation of diacetylacetoxyphenylimidazolidine (IX) from the acetylation of 2-phenylimidazoline. Alkylation usually yields mixtures of quaternary and non-quaternary imidazolines. One exception is described. Reductive methylation gives N-methylimidazolines. By condensation of nitriles with diethylenetriamine, aminoethylimidazolines (XVIII), with triethylenetetramine, bisimidazolines (XIX) joined through the nitrogen atoms by an ethylene bridge are obtained.

Acylation.—Several imidazolines have proved to be of practical importance in the last ten or fifteen years, and for this reason we published some work on the basic chemistry of the imidazoline ring several years ago.[2]

In particular, the acylation of imidazolines attracted our interest, whereby diacylimidazolidines IV–VI, with the double bond shifted exocyclically, resulted from substituted 2-methylimidazolines I–III. The diacetylalkylidenimidazolidines IVa–VIa have been obtained in good yield, but the dibenzoyl derivatives IVb–VIb were more difficult to prepare. We have succeeded, nevertheless, in making the dibenzoyl compound in good yield

(1) Talk given at Dallas, Texas, 129th National A.C.S. Meeting, April, 1956; *cf.* Abstracts of Papers, 25-M.

(2) K. Miescher, A. Marxer and E. Urech, *Helv. Chim. Acta*, **34**, 1 (1951).