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Azirines. II. The Reaction of 2-Phenylazirine with Acylating Agents*[1]

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The reaction of 2-phenylazirine (I) with acid chlorides, anhydrides, an imidoyl chloride, and carboxylic acids were investigated. When I was treated with acid chlorides and anhydrides, the corresponding 2, 5-disubstituted oxazole derivatives were obtained. The reaction of I with phthalic and maleic anhydride, however, gave ring-cleavage products. The reaction of I and *N*-phenylbenzimidoyl chloride gave 1, 2, 5-triphenylimidazole. On the other hand, I and benzoic and thiobenzoic acid gave *N*-benzoylphenacylamine and *N*-benzoyl-α-benzoylthio-β-aminostyrene respectively.

In a preceding paper,1) it was reported that the reaction of 2-phenylazirine with suitably-substituted carbanions gave pyrrole derivatives by ring enlargement. The present paper will deal with the reaction of 2-phenylazirine (I) with cationoid reagents, such as acid chlorides, acid anhydrides, an imidoyl chloride, and benzoic and thiobenzoic acid.

The Reaction of 2-Phenylazirine with Acid Chlorides. When 2-phenylazirine was heated in

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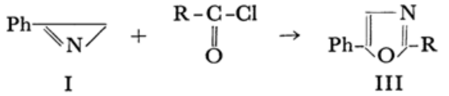
*[1] This work has been partly reported in a preliminary form: S. Sato, H. Kato and M. Ohta, This Bulletin, **40**, 1014 (1967).

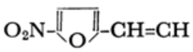
*[2] On leave of absence from the Kyorin Chemical Laboratory.

1) S. Sato, H. Kato and M. Ohta, This Bulletin, **40**, 2936 (1967).

Table 1



I III

R	Mp, °C	Yield, %	Formula	Anal. (Found), %		
				C	H	N
CH_3	55—57[2]	36				
	155—156 (picrate)		$C_{16}H_{12}N_4O_8$	49.55	5.13	14.56
C_6H_5	71—72[3]	32	$C_{15}H_{11}NO$	81.43	5.13	6.42
	172—173 (picrate)		$C_{21}H_{14}N_4O_8$	56.33	2.99	12.43
p-O_2N-C_6H_4	206—207[4]	43	$C_{15}H_{10}N_2O_3$	67.82	3.76	10.80
	199—201 (decomp.)[a]	28	$C_{15}H_{10}N_2O_4$	63.62	3.62	10.25[b]

[a] Yellow-brown crystals, recrystallized from benzene-ethanol.

[b] Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93%.

Table 2. Antimicrobial activity of 2-(5-nitro-2-furfurylidenemethyl)-5-phenyloxazole *in vitro* (Minimum inhibitory concentration mcg/m*l*)

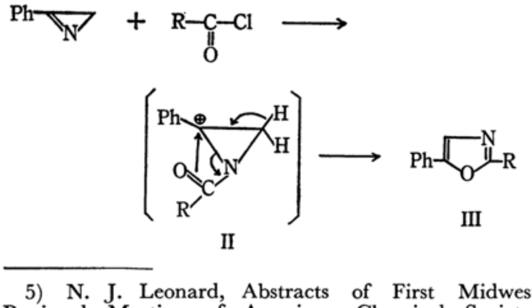
Test organism	
Bacillus subtilis PCI 219	1
Staphylococcus aureus 209 P	>50
Eschricia coli 30	>50
Protus vulgaris OXI9US	>50
Pseudomonas aeruginosa VI	>50
Mycobacterium SP 607	0.5
Mycobacterium phlei	>10
Aspergillus niger	>50
Penicillium chrysogenus 408-701	>10
Trichophyton intergilale	1
Saccharomyces sake	>50
Candida albicans 3147	>50

benzene with acetyl, benzoyl, *p*-nitrobenzoyl, and *β*-(5-nitro-2-furyl)acryl chloride, in the presence of triethylamine, the corresponding 2-substituted 5-phenyloxazoles (III)[2-4] were isolated (see Table 1). 2-(5-Nitro-2-furfurylidenemethyl)-5-phenyloxazole has not yet been described in the literature; the findings of its *in vitro* antimicrobial activities against twelve kinds of organisms are shown in Table 2. The activity against *Mycobacterium* was the strongest, followed by against *Trichophyton interdigilale*.

In the reaction of I and benzoyl chloride, a compound with the composition of $C_{15}H_{13}NOCl_2$ was isolated in 20% yield besides 2,5-diphenyloxazole. The infrared spectrum of this compound exhibits bands of a secondary amide group at 3280 and 1620 cm^{-1}; its structure may tentatively be identified as either *N*-benzoyl-2,2-dichloro-2-phenylethylamine or *N*-benzoyl-1,2-dichloro-2-phenylethylamine.

The formation of oxazoles by the reaction of 2-phenylazirine and acid chlorides may be considered to proceed through the initial formation of the intermediates II by means of the attack of an acyl cation on the nitrogen atom of azirine, followed by ring enlargement by the cleavage of the C–N linkage to give oxazole, as is shown in the figure.

One should also, however, consider an alternate path which involves the hydrolysis by moisture of I to phenacylamine, which then reacts with acid chlorides to give the oxazole. This possibility may be rejected, however, because *N*-benzoylphenacylamine was unchanged when it was heated with benzoic acid in benzene. The exclusive formation of the 2,5-disubstituted instead of the 2,4-disubstituted oxazole in these reaction is of interest, because it has been briefly noted in the literature[5] that the acid-catalyzed addition reactions of azirines with active unsaturated compounds gave products that formally arose by the cleavage of the C–N single bond.[*3] The reaction of I and benzoyl chloride in the absence of base also gave only 2,5-diphenyloxazole.



II

III

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[2] S. Gabriel, *Ber.*, **43**, 1284 (1910).

[3] E. Fischer, *ibid.*, **29**, 207 (1896).

[4] J. Lister and R. Robinson, *J. Chem. Soc.*, **1912**, 1312.

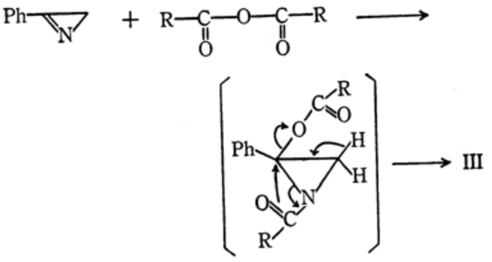
[5] N. J. Leonard, Abstracts of First Midwest Regional Meeting of American Chemical Society, Kansas City, Mo., Nov. 1965, p 40. Cited from; G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966).

[*3] Our attempts to effect such a type of addition in the absence of any catalyst were unsuccessful.

The Reaction of 2-Phenylazirine with Acid Anhydrides. The catalytic reduction of 2-methyl-3-(2, 4-dinitrophenyl)azirine in a mixture of acetic anhydride and pyridine gave 2-acetylamino-1-(2, 4-dinitrophenyl)propene,⁶⁾ This result suggests that azirines are probably not readily attacked by acid anhydrides under these reaction conditions.

When I was refluxed in an excess of acetic anhydride for six hours, 2-methyl-5-phenyloxazole was isolated in 32% yield, but when the same reaction was carried out at 60—70°C and was interrupted after three hours, a compound with the formula $C_{12}H_{13}NO_3$ was isolated. We assigned the structure IV to this compound on the basis of the infrared bands at 1720 cm^{-1} (ester carbonyl) and the lack of absorptions due to an NH group.

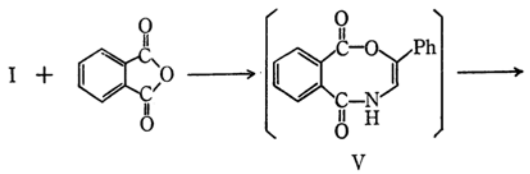
This reaction is considered to proceed through the initial formation of an intermediate (IV) formed by the addition of acetic anhydride to the C=N double bond. The ring enlargement of the intermediate IV, with the elimination of acetic acid, will give the oxazole ring.



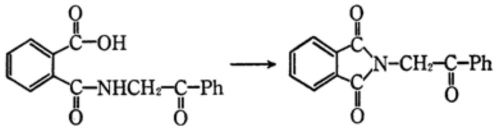
IV

When I was heated with benzoic anhydride in benzene, only 2, 5-diphenyloxazole was isolated.

The reactions of I with phthalic and maleic anhydrides are of interest since, if the reactions were to proceed through an analogous path, it might be possible to obtain fused eight-membered rings, such as V. The product actually isolated by the reaction of I and phthalic anhydride in benzene had the molecular formula of $C_{16}H_{13}NO_4$ and was soluble in aqueous sodium bicarbonate. The infrared absorption bands of this compound, at 3290 (amide NH), 3060 (broad; carboxyl OH), 1720 (carboxyl CO) and 1690 cm^{-1} (amide CO), suggest that its structure is *N*-phenacylphthalmonoamide (VI). This compound was converted by diazomethane into the known *N*-phenacylphthalimide (VII).⁷⁾ The reaction of I and maleic anhydride gave a product with a similar structure: *N*-phenacylmaleinmonoamide. These products probably arose by the hydrolyses of the expected eight-membered products such as V, but the origin of the water is not known.



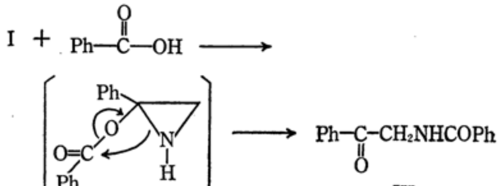
V



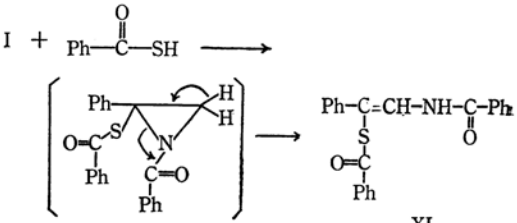
VI VII

The Reaction with an Imidoyl Chloride. It may be reasonable to expect that the formation of oxazoles by the reaction of I and acid chlorides can be extended to the formation of imidazoles by reaction with imidoyl chlorides. That this indeed is true was shown by the reaction of I and *N*-phenylbenzimidoyl chloride, which afforded 1, 2, 5-triphenylimidazole, accompanied by a compound of an unknown structure with the composition of $C_{21}H_{19}N_2OCl$.

The Reaction with Benzoic and Thiobenzoic Acid. When I was heated with benzoic acid in benzene, a compound with the formula $C_{15}H_{13}NO_2$ was isolated. The infrared absorption bands of this compound, at 3360 (NH group), 1690 (amide carbonyl) and 1640 cm^{-1} (benzoyl carbonyl), suggest that its structure is *N*-benzoylphenacylamine.⁸⁾ This reaction is considered to proceed through the initial formation of the intermediate (VIII) by the addition of benzoic acid to the C=N double bond of I. The ring cleavage and the transfer of the benzoyl group to the nitrogen atom will give IX. The reaction with thiobenzoic acid under the same reaction conditions gave a compound with the composition of $C_{22}H_{17}NO_2S$; the



VIII IX



X XI

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6) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

7) S. Gabriel, *Ber.*, **41**, 1132 (1908).

8) R. Robinson, *J. Chem. Soc.*, **95**, 2169 (1909).

infrared spectrum of this compound exhibits bonds at 3260 (NH group), 1660 (amide CO) and 1640 cm^{-1} (benzoyl CO). These spectral data suggest that this compound is *N*-benzoyl-α-benzoylthio-β-aminostyrene (XI). This reaction may be explained in terms of the addition of thiobenzoic acid to the C=N double bond and the acylation of the NH group by thiobenzoic acid, followed by ring cleavage to XI.

Experimental

All the melting points were determined on a micro hot stage and have not been corrected. The infrared spectra were taken on KBr tablets.

The Reaction of I with Acid Chlorides. General Procedure. To a solution of 2.3 g (0.02 mol) of I and 2 g of triethylamine in 20 m*l* of benzene, 0.02 mol of an acid chloride was added with cooling and stirring. After the mixture had then been refluxed for 1.5—2.0 hr, the solvent was removed by distillation under reduced pressure. The residual oil was purified by converting it to the picrate, followed by recrystallization from ethanol. A crystalline free base was obtained from the picrate by treat ing itwith 10% ammonium hydroxide.

The Reaction of I and Benzoyl Chloride. a) To a solution of 1.2 g of I and 1 g of triethylamine in 10 m*l* of benzene, a solution of 1.4 g of benzoyl chloride in 10 m*l* of benzene was added. The mixture was then refluxed for two hours, the reaction mixture was washed with aqueous sodium bicarbonate and water, and the solvent was removed by distillation under reduced pressure. The residual oil was partly crystallized on the addition of ether. It was then washed with ether and recrystallized from ethanol to give 0.5 g of colorless leaflets melting at 106—107°C.

Found: C, 61.28; H, 4.54; N, 4.20; Cl, 24.82%. Calcd for $C_{15}H_{13}NOCl_2$: C, 61.22; H, 4.42; N, 4.76; Cl, 24.14%. From the ethereal washings, 1.8 g of 2, 5-diphenyloxazole picrate were isolated. Mp 172—173°C.3)

b) A solution of 2.3 g of I in 10 m*l* of benzene was added to a solution of 3.0 g of benzoyl chloride in 10 m*l* of benzene. After the mixture had then been refluxed for 2.5 hr, it was treated in essentially the same way as had been described above to give 1.8 g of 2, 5-diphenyloxazole picrate as yellow needles melting at 172—173°C. The compound with the composition of $C_{15}H_{13}NOCl_2$, obtained by the same reaction in the presence of triethylamine, was not isolated here.

The Reaction of I with Acetic Anhydride. a) A solution of 2.3 g of I in 10 g of acetic anhydride was gently boiled on an oil bath for six hours. The resultant dark brown solution was poured into water and extracted with benzene; the extract was washed with water and dried over sodium sulfate. The extract was then concentrated, and the residual oil was dissolved in ethanol, after which a solution of picric acid in ethanol was added. The picrate which separated out was collected to give 1.2 g of yellow needles melting at 154—155°C.2)

b) The mixture described above was warmed at 60—70°C for three hours, and then the resultant reddish brown solution was poured into water and extracted with benzene. The extract was then washed with water and dried over sodium sulfate. The concentration of the extract left a paste which partly solidified on the addition of ether. It was washed with ether and recrystallized from ethanol to give 0.6 g of colorless plates melting at 82—83°C.

Found: C, 65.79; H, 5.89; N, 6.57%. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

The Reaction of I with Benzoic Anhydride. A solution of 2.3 g of I in 10 m*l* of benzene was stirred into a solution of 4.5 g of benzoic anhydride in 10 m*l* of benzene at room temperature. The mixture was then refluxed for seven hours and allowed to stand overnight. After the reaction mixture had then been washed with water and dried over sodium sulfate, the solvent was removed by distillation under reduced pressure; the residual oil solidified on cooling, and the solid was dissolved in ethanol and was converted to the picrate to give 2.2 g of yellow needles melting at 172—173°C.

The Reaction of I with Phthalic Anhydride. A mixture of 2.3 g of I, 3 g of phthalic anhydride, and 20 m*l* of benzene was heated at 60—70°C for six hours and then, allowed to stand overnight. The crystal which separated out were collected, washed with ether, and recrystallized from benzene-ethanol to give 0.5 g of colorless needles melting at 163—164°C.

Found: C, 67.80; H, 4.61; N, 4.97%. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.95%.

The Reaction of VI with Diazomethane. An ether solution of diazomethane was added to Compound VI until the yellow color of diazomethane persisted. After one hour stirring, the solution was washed with aqueous sodium bicarbonate and dried over sodium sulfate. After the ether had been removed by distillation, the crystals which separated out were collected and recrystallized from methanol to give colorless prisms melting at 167—168°C. The melting point of this substance was undepressed on admixture with an anthentic specimen of *N*-phenacylphthalimide.7) (Found: C, 72.44; H, 4.18; N, 5.41%.)

The Reaction of I with Maleic Anhydride. A mixture of 2.3 g of I, 2 g of maleic anhydride and 20 m*l* of benzene was heated at 60—70°C for two hours; when it was then treated by essentially the same method as has been described above, it gave 1.2 g of pale yellow prisms melting at 161—162°C.

Found: C, 61.99; H, 4.72; N, 5.88%. Calcd for for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01%. IR: 3290, 3060, 1720 and 1690 cm^{-1}.

The Reaction of I with Imidoyl Chloride. A solution of 4.5 g of *N*-phenylbenzimidoyl chloride in 10 m*l* of toluene was stirred into a solution of I in 10 m*l* of toluene. The mixture was then refluxed in an oil bath for two hours, and then crystals which separated out on cooling were collected, washed with benzene, and recrystallized from methanol to give 0.5 g of pale brown crystals melting at 245°C.

Found: N, 9.68%. Calcd for $C_{21}H_{16}N_2$: N, 9.45%. Picrate, mp 234—235°C.

Found: C, 61.53; H, 3.31; N, 13.21%. Calcd for $C_{27}H_{19}N_5O_7$: C, 61.71; H, 3.31; N, 13.33%.

The concentration of the toluene mother liquor gave a dark brown paste which solidified on the addition of ether. It was washed with ether and recrystallized from acetoneethanol to give 0.6 g of white crystals melting at 195—197°C. It was positive to Beilstein's halogen test.

Found: C, 72.89; H, 5.32; N, 8.01%. Calcd for $C_{21}H_{19}N_2OCl$: C, 71.98; H, 5.45; N, 7.99%.

The Reaction of I with Benzoic Acid. A solution of 4.8 g (0.04 mol) of benzoic acid in 10 m*l* of benzene was stirred into a solution of 2.3 g (0.02 mol) of I in 10 m*l* of benzene. The mixture was then refluxed for two hours, the solvent was removed by distillation under reduced pressure, and the residual paste was washed with aqueous sodium bicarbonate and solidified by treatment with ether. The recrystallization of the solid from methanol afforded 1.5 g of *N*-benzoylphenacylamine as pale yellow needles melting at 123—124°C. Reported mp 123°C.[8] (Found: C, 75.20; H, 5.67; N, 6.18%.)

The Reaction of I with Thiobenzoic Acid. To a solution of 2.3 g of I in 10 m*l* of benzene, a solution of 5.5 g (0.04 mol) of thiobenzoic acid in 10 m*l* of benzene was added with cooling and stirring; the mixture was then refluxed for three hours. A vigorous evolution of hydrogen sulfide was observed. After cooling, the yellow crystals which separated out were collected. Recrystallization from methanol gave 0.9 g of XI as pale yellow needles melting at 173—174°C.

Found: C, 73.29; H, 5.10; N, 3.98%. Calcd for $C_{22}H_{17}NO_2S$: C, 73.53; H, 4.77; N, 3.90%.