Synthesis and Antifungal Activity of some Allylamine Derivatives

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Benzo- and mesitonitrile oxides react with allylamine to yield 5-aminomethyl-2-isoxazolines and open-chain *N*-substituted amidoximes. The allylamine derivatives were evaluated as potential antifungal and antibacterial agents. The *N*-allylbenzamidoxime **2a** was found to be only moderately active against dermatophytes.

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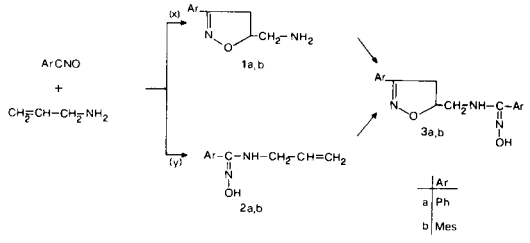
In continuation of our interest in the selectivity in cycloadditions [1], we wish to report the results dealing with the reactions of nitrile oxides with allylamine. As a dipolarophile, allylamine shows a different behaviour with respect to monosubstituted olefins such as 1-propene, 1-hexene, allyl alcohol, allyl acetate, allyl ethyl ether [2]. In the presence of two competitive functional groups in the allylamine molecule, namely, the free amino group and the allylic unsatured bond, different adducts can be obtained.

We considered the allylamine reactions of some interest, since in the literature some allylamine derivatives are reported to possess significant antifungal properties [3].

As expected, the reactions of benzonitrile oxide (PhCNO) and mesitonitrile oxide (MesCNO) with the allylamine, along with the usual 1,3-cycloaddition products, afforded the 1,3-addition products, as illustrated in Scheme 1. The nitrile oxides can react either with the double bond

Scheme 1



of the allylamine in the typical manner [4], giving the 5-substituted-2-isoxazolines **1** (route X), or with the amino group [5], giving the open-chain *N*-substituted amidoximes **2** (route Y). When an excess of benzonitrile oxide (or mesitonitrile oxide) was used, from both monoadducts **1a** and **2a** (or **1b** and **2b**) the same bisadduct **3a** (or respectively **3b**) was obtained, whether by addition to the free amino group in the isoxazoline **1** or by cycloaddition to the double bond still present in the amidoxime **2**. To avoid the formation of bisadducts, which made the separation of the reaction mixtures more complicated, we chose the dipole-dipolarophile ratio about 1:10; under these conditions, the amounts of bisadducts were negligible and only monoadducts **1** and **2** were obtained in fair yields.

The reaction mixtures were analyzed by hplc. In the case of benzonitrile oxide, the quantitative determination gave a 2,1:1 amidoxime:isoxazoline ratio, whereas with the sterically more hindered mesitonitrile oxide the observed ratio was 1:1. These data indicate that the nucleophilic additive activity of the primary amino group is almost similar to the dipolarophilic activity of the unsatured bond, being slightly more consistent in the reactions with benzonitrile oxide. Different results were reported for the propargyl amine-benzonitrile oxide reaction, where the products derived from a 1,3-addition are far the most prevailing than those from the cycloaddition to isoxazole derivatives [6].

The structural resemblance between the products so obtained and some of the reported biologically active allylamine derivatives [3] led us to test the antimycotic and antibacterial properties of our products. The mono- and

Table 1

Antifungal and Antibacterial Activity of Allylamine Derivatives

Compounds	MIC (μg/ml)					
	C.a.	*A.n.*	*T.m.*	*M.c.*	*S.a.*	*E.c.*
1a	>128	>128	>128	>128	>128	>128
1b	>128	>128	>128	>128	>128	>128
2a	>128	>128	128	64	>128	>128
2b	>128	>128	>128	128	>128	>128
3a	>128	>128	>128	>128	>128	>128
3b	>128	>128	>128	>128	>128	>128
Clotrimazole	5	10	1.25	1.25	1.25	>128

Abbreviation: *C.a.*, *Candida albicans* ATCC 753; *A.n.*, *Aspergillus niger* ATCC 17885; *T.m.*, *Trichophyton mentagrophytes* ATCC 8757; *M.c.*, *Microsporum canis* ATCC 11621; *S.a.*, *Staphylococcus aureus* 6538 P; *E.c.*, *Escherichia coli* 078.

bisadducts were evaluated "*in vitro*" for antifungal activity against *Candida albicans, Aspergillus niger, Tricophyton mentagrophytes* and *Microsporum canis*, and for antibacterial properties against *Staphylococcus aureus* and *Escherichia coli.*

Minimum inhibitory concentrations (MICs) were determined by the broth dilution method, following previously established procedures [7]. The results of susceptibility tests are summarized in Table 1. None of the compounds screened showed antifungal or antibacterial activity against the tested microorganisms, as is the case with the reference compound clotrimazole. The only minor exception was the *N*-allylbenzamidoxime **2a**, which exhibits only moderate activity against *Microsporum canis* and *Tricophyton mentagrophytes.*

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed on an Elemental Analyzer Model 1106 C.Erba. The ir spectra were recorded on a Perkin-Elmer 197 spectrophotometer. The pmr spectra were obtained on a Bruker FT 80 spectrometer in the indicated solvent, with TMS as internal standard. Quantitative determinations were performed on an hplc system (Waters M 6000), using a prepacked μBondapak C_{18} 10μm (30 cm x 3.9 mm) column and as mobile phase acetonitrile:PIC B_5 (Waters) 25:75.

N-Allylbenzamidoxime **2a** and 3-Phenyl-5-aminomethyl-2-isoxazoline **1a**.

To a stirred and cooled solution of **2g** (0.012 mole) benzhydroximic acid chloride in 50 ml benzene, 1.1 equivalents of triethylamine were added dropwise. After 10 minutes stirring, the triethylammonium salt was filtered off and 6.8 g (0.12 mole) of freshly distilled allylamine was added to the benzene solution. The reaction mixture was allowed to stand at room temperature for 48 hours, then the solvent was removed under reduced pressure. Flash column chromatography of the residue (silica gel H 60, 230-400 mesh, elution with ethyl acetate:cyclohexane 30:70) gave 1.42 g (63%) of the *N*-allylbenzamidoxime **2a**. Crystallization from 60-80° light petroleum-ethyl acetate yielded **2a** as white crystals mp 91-92°; ir (potassium bromide): ν cm^{-1} 3420 (NH), 3240 (OH), 1635 (C=NO); pmr (deuteriochloroform): δ 7.5 (s, 5H, aromatic), 5.6-6.2 (m, 3H, exchangeable N*H* and O*H*; C*H*=), 5-5.4 (m, 2H, CH_2=), 3.7 (br d, 2H, NCH_2).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.04; H, 6.98; N, 16.13.

By subsequent column elution with methanol, the 3-phenyl-5-aminomethyl-2-isoxazoline **1a** (0.34 g, 15%) was obtained, white needles mp 61-62° from 60-80° light petroleum; ir (potassium bromide): ν cm^{-1} 3365, 3350 (NH_2); pmr (deuteriochloroform): δ 7.2-7.8 (s, 5H, aromatic), 4.75 (m, 1H, isoxazoline H_5), 2.7-3.6 (m, 4H, CH_2N, isoxazoline H_4s), 1.6 (br s, 2H, exchangeable NH_2).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.33; H, 6.72; N, 15.62.

N-(3-Phenyl-5-isoxazolinyl)methylbenzamidoxime **3a**.

To the stirred and cooled benzene solution of 0.35 g (0.002 mole) *N*-allylbenzamidoxime **2a** and 3-times excess benzhydroximic acid chloride, 1.1 equivalents of triethylamine in 10 ml of benzene was added dropwise. After two days at room temperature, the triethylammonium salt was filtered off and the solvent was removed under reduced pressure. Trituration with ether afforded 0.38 g (65%) of **3a**, which crystallized from 60-80° light petroleum-ethyl acetate in white crystals mp 143-144°; ir (potassium bromide): ν cm^{-1} 3395 (NH), 3220 (OH), 1638 (C=NO); pmr (deuteriochloroform): δ 7.3-7.8 (m, 10H, aromatic), 5.65 (br s, 1H, exchangeable N*H*), 4.5-5.0 (m, 2H, exchangeable O*H*, isoxazoline H_5), 3.35 (br d, 2H, CH_2N), 2.8-3.3 (m, 2H, isoxazoline H_4s).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.37; H, 5.80; N, 14.21.

The same bisadduct can be obtained in a 80% yield by a similar reaction of excess benzonitrile oxide with the 3-phenyl-5-aminomethyl-2-isoxazoline **1a**.

N-Allylmesitylamidoxime **2b** and 3-Mesityl-5-aminomethyl-2-isoxazoline **1b**.

To a solution of 2 g (0.012 mole) of mesitonitrile oxide in 50 ml of benzene, 6.8 g (0.12 mole) of allylamine was added. After one week standing at room temperature, the solvent was removed under reduced pressure. Chromatographic separation of the residue was accomplished as described for the benzonitrile oxide reaction. The amidoxime **2b** (1.29 g, 48%) was crystallized as pearly platelets, mp 123-125° from 60-80° light petroleum-ethyl acetate; ir (potassium bromide): ν cm^{-1} 3415 (NH), 3220 (OH), 1650 (C=NO); pmr (deuterioacetone): δ 8.55 (br s, 1H, exchangeable O*H*), 6.9 (s, 2H, aromatic), 5.5-6.0 (m, 2H, exchangeable N*H*, C*H*=), 4.9-5.3 (m, 2H, CH_2=), 3.4 (br d, 2H, CH_2N), 2.2, 2.3 (3H, 6H, aromatic CH_3).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.61; H, 8.30; N, 12.91.

Elution with methanol gave the 3-mesityl-5-aminomethyl-2-isoxazoline **1b** (1.05 g, 39%) as a pale yellow oil; ir (film): ν cm^{-1} 3380, 3310 (NH_2); pmr (deuteriochloroform): δ 6.9 (s, 2H, aromatic), 4.8 (m, 1H, isoxazoline H_5), 2.8-3.3 (m, 4H, isoxazoline H_4s, CH_2N), 2.2, 2.4 (6H, 3H, aromatic CH_3), 1.9 (s, 2H, exchangeable NH_2).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.39; H, 8.05; N, 13.02.

N-(3-Mesityl-5-isoxazolinyl)methylmesitylamidoxime **3b**.

To the benzene solution of 0.43 g (0.002 mole) *N*-allylmesitylamidoxime **2b**, three-times excess mesitonitrile oxide was added. After one week standing at room temperature, the solvent was removed. Trituration of the residue with ether gave 0.52 g (70%) of the bisadduct **3b**, white crystals from 60-80° light petroleum-ethyl acetate, mp 182-184° dec; ir (potassium bromide): ν cm^{-1} 3405 (NH), 3300 (OH), 1632 (C=NO); pmr (deuterioacetone): δ 8.55 (br s, 1H, exchangeable O*H*), 6.9 (s, 2H, aromatic), 5.9 (m, 1H, exchangeable N*H*), 4.7 (m, 1H, isoxazoline H_5), 2.7-3.5 (m, 4H, isoxazoline H_4s, CH_2N), 2.15, 2.25 (3H, 6H, aromatic CH_3).

Anal. Calcd. for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.90; H, 7.68; N, 10.95.

The same bisadduct **3b** can be similarly obtained in a 68% yield from the 3-mesityl-5-aminomethyl-2-isoxazoline **1b**.

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