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SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL PROPERTIES OF 2-ISOTHIOCYANATO-1-ARYL-3-BUTENES

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Some aliphatic and aliphatic-aromatic isothiocyanates, which occur in plants either in the free state or as glycosides, are reported to be physiologically active and are used in medicine as antibacterial and antifungal agents [1, 4].

Of particular interest as potential antifungal and antibacterial agents are the 2-isothiocyanato-1-aryl-3-butenes; these compounds have been synthesized by the anion-arylation of diene hydrocarbons [3].

It was found that aryldiazonium borotetrafluorides react vigorously with 1,3-butadiene and isoprene in the presence of alkali metal thiocyanates and catalytic amounts of copper salts. The addition of the aryl group took place at position 1, and the thiocyanate group added principally at position 2 of the diene chain. The reaction was carried out in acetone or aqueous acetone at temperatures from −30°C to −15°C.

$$RC_6H_4N_2BF_4 + CH_2{=}CR^1{-}CH{=}CH_2 + MeSCN \rightarrow$$
$$\rightarrow RC_6H_4CH_2\underset{\displaystyle N{=}C{=}S}{\underset{|}{C}}R^1CH{=}CH_2 + N_2 + BF_3 + MeF$$

R=H(I, IV), *n*-CH_3(II, V), *n*-CH_3O(III, VI);
R^1=H(I—III), CH_3(IV—VI); Me=K, Na

Isothiocyantoarylation of dienes also occurred without a catalyst, but gave lower yields of product by 17-24%.

It should also be noted that oxidation of the products of the isothiocyantophenylation of 1,3-butadiene I and isoprene IV gave small quantities of phenylacetic acid and methylbenzylketone, which were isolated by vacuum distillation and identified as the semicarbazones.

This confirms that, in addition to products of 1,2-addition, small amounts of 1,4-addition products were also formed.

The structures of the 2-isothiocyanato-1-aryl-3-butenes were confirmed by IR- and PMR-spectroscopy.

The IR spectra of these compounds contained broad absorption bands with maxima at 2100 cm^{-1}, characteristic of the stretching vibrations of the isothiocyanate group; absorptions at 990 and 930-940 cm^{-1} (CH=) can be attributed to planar and nonplanar conformers. The C=C bond variation gives rise to an absorption band at 1640 cm^{-1} [2].

The PMR spectrum contained signals due to the aromatic ring protons, CH_2 and CH, and to the vinyl group protons at 7.24-6.77, 5.76-4.79, and 4.94-4.78 ppm, respectively. Signals from the two protons of the Ar—CH_2 group occurred at 2.96-2.83 ppm.

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TABLE 1. Constants, Yields, and IR and PMR Spectral Data for 2-Isothiocyanato-1-aryl-3-butenes

Compound	Yield, %	Bp, °C (1 mm mercury)	n_D^{20}	d_4^{20}	Empirical formula	IR-spectrum, ν cm^{-1}	Chemical shifts of protons, δ, ppm
I	63	105—107	1,5766	1,0556	$C_{11}H_{11}NS$	2090	7,24 s (5H, C_6H_5); 5,94 d.d. (J_{H-H} 5 Hz); 5,76 d.d. (J_{H-H} 5 Hz) (1H, CH); 5,04 d (2H, $=CH_2$, J_{H-H} 9 Hz); 4,94 s (1H, CH=); 2,95 d.d. (J_{H-H} 7 Hz); 2,83 d.d. (J_{H-H} 7 Hz) (2H, $-CH_2-$)
II	42	118—120	1,5713	1,0380	$C_{12}H_{13}NS$	2090	7,09 d 2H; 7,00 d (C_6H_4); 5,82 d.d. (J_{H-H} 5 Hz); 5,74 d.d. (J_{H-H} 5 Hz) (1H, CH); 5,06 d (2H, $=CH_2$, J_{H-H} 9 Hz); 4,93 s (1H, CH=); 2,96 d.d. (J_{H-H} 7 Hz); 2,84 d.d. (J_{H-H} 7 Hz) (2H, $-CH_2-$); 2,21 s (3H, CH_3)
III	47	138—140	1,5780	1,1059	$C_{12}H_{13}NOS$	2095	7,10 d 2H, 6,77 d 2H (C_6H_4); 5,84 d.d. (J_{H-H} 5 Hz); 5,75 d.d. (J_{H-H} 5 Hz) (1H, CH); 5,05 d (2H=CH_2, J_{H-H} 9 Hz), 4,94 s (1H, CH); 3,76 s (3H, CH_3O), 2,96 d.d. (J_{H-H} 7 Hz); 2,84 d.d. (J_{H-H} 7 Hz) (2H, $-CH_2-$)
IV	62	118—120	1,5800	1,0610	$C_{12}H_{13}N5$	2070	7,21 s (5H, C_6H_5); 5,03—4,84 m (2H, $CH_2=$); 4,79 s (1H, CH=); 2,92 s, 2,86 s (2H, $-CH_2-$); 1,74 s (3H, CH_3)
V	45	118—120	1,5741	1,0400	$C_{13}H_{15}NS$	2075	7,09 d, 2H, 6,99 d 2H (C_6H_4); 5,00—4,79 m (2H, $=CH_2$); 4,75 s (1H, CH=); 2,89 s, 2,83 s (2H, $-CH_2-$); 2,20 s (3H, $CH_3-C_6H_4$); 1,71 s (3H, CH_3)
VI	47	143—145	1,5684	1,0819	$S_{13}N_{15}NOS$	2080	7,09 d 2H; 6,78 d 2H (C_6H_4); 5,07—4,88 mm (2H, $CH_2=$); 4,81 s (1H, CH=); 3,66 s (3H, CH_3O); 2,93 s, 2,85 s (2H, $-CH_2-$); 1,78 s (3H, CH_3)

TABLE 2. Antibacterial and Antifungal Properties of 2-Isothiocyanato-1-aryl-3-butenes

Compound	Minimum suppressing concentration, μg/ml								
	S. aureues 209	E. coli K-12	P. aeruginosa	B. subtilis	T. rubrum	C. albicans	S. cerevisiae	A. niger	T. mentagrophytes
I	19,6	5000	312	2,4	5000	1250	199,6	156	2,4
II	78	5000	312	2,4	5000	312	9,8	156	2,4
III	312	5000	156	2,4	312	62,5	39	156	2,4
IV	2,4	156	39	2,4	156	1250	39	78	4,8
V	2,4	312	39	2,4	312	2500	4,8	156	4,8
VI	2,4	5000	19,6	2,4	312	312	2,4	78	2,4

Note. All substances were dissolved in dimethylformamide.

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on an IKS-29 apparatus, samples were prepared as thin films. PMR spectra were taken on a Bruker CXP-90 instrument (working frequency 90 MHz), using $CDCl_3$ as solvent. Chemical shifts were measured against the internal standard TMS. The purity of the compounds I-VI was checked by TLC on Silufol UV-254 plates using a 1:1:2 mixture of ether—chloroform—acetone as eluent. Elemental analysis data were in good agreement with calculated values (Table 1).

2-Isothiocyanato-1-phenyl-3-butene (I). Potassium thiocyanate (0.2 mole) was slowly added to a mixture of 1,3-butadiene (0.16 mole), phenyldiazonium borotetrafluoride (0.1 mole), and copper(II) borotetrafluoride (0.005 mole) in acetone (150 ml) (or a mixture of 100 ml of acetone and 50 ml of water) at a temperature between −30°C and −15°C. The addition took 30-40 min. Nitrogen evolution continued for 3 h at the same temperature. The reaction mixture was allowed to stand for 12 h, extracted with ether (250 ml), and the extract washed with water and dried with magnesium sulfate. Evaporation of the solvent, followed by distillation in vacuum, gave 11.9 g (63%) of compound I.

Compounds II-VI were obtained in the same way. The same procedure was used to carry out the reaction without the copper salt.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the synthesized isothiocyanates was studied using the method of double serial dilution in liquid nutrient medium against Gram-positive (S. aureus), Gram-negative (E. coli, P. aeruginosa) and spore forming (B. subtilis) bacteria.

The test compounds exhibited antibacterial activity primarily against spore-forming Gram-positive bacteria. E. coli were found to be stable to the compounds at the concentrations used in the tests.

For the compounds tested, the minimum suppressing concentration was determined by the method of double serial dilution in Saboraud's medium against the yeast fungi C. albicans, dermatophite T. rubrum, and T. mentagrophytes, and also an example of the fungus A. niger.

Compounds I-VI possessed antifungal activity, including activity against fungal microflora. Some pathogenic strains of fungus were more stable to the test compounds.

The data obtained indicate that 2-isothiocyanato-1-aryl-3-butene (Table 2) exhibits both antibacterial and antifungal activity. The introduction of a methyl or methoxy group did not bring about any substantial change in biological properties, confirming that these properties are determined by the overall structure.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF AMINE ANALOGS OF PIRACETAM

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In order to explain the effect of structural factors on nootropic activity, we have synthesized analogs of piracetam (Ia-g) with an amidine group in the side chain in place of the amide group [3, 6].

Compounds Ia, c were obtained by the thermal cyclization of the nitrile of 2-oxopyrrolidine-1-acetic acid (II) with o-phenylenediamine or 3,4-diaminopyridine in the presence of polyphosphoric acid.

Compound Ib was synthesized by the reaction between 4-phenylpyrrolidone-2 and the methyl ester of chloroacetic acid in toluene in the presence of MeONa, followed by fusion of the ethyl 2-oxo-4-phenylpyrrolidine-1-acetate (III) with o-phenylenediamine. Condensation of methyl 2-oxopyrrolidine-1-acetate with 4,5-diamino-1,3-dimethyluracil monohydrate in the presence of a catalytic amount of NH_4Cl gave 4-amino-5-[(2-oxopyrrolidinyl-1)acetamido]-1,3-dimethyluracil monohydrate (IV), which when heated with a dilute solution of NaOH was converted to Ig.

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