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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3-MERCAPTOINDOLE DERIVATIVES

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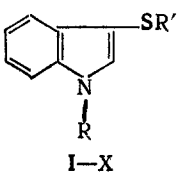
UDC 615.218:547.752

Derivatives of 3-mercaptoindoles (I) [4] are being studied for possible use as various medicinal preparations, including antimicrobial agents [5, 6]. The present work is a study of the antimicrobial properties of previously described alkyl and vinyl derivatives I-II-IX [2, 3] and a recently synthesized trisulfide derivative (X).

The latter was produced by the β-addition of EtSH to both vinyl groups of VI through the action of a radical initiator:



I—X

I: $R = R' = H$; II: $R = H$, $R' = Et$; III: $R = Et$, $R' = H$;
IV: $R = R' = Et$; V: $R = H$, $R' = Br$; VI: $R = R' = CH{=}CH_2$;
VII: $R = H$, $R' = CH{=}CH_2$; VIII: $R = Et$, $R' = CH{=}CH_2$;
IX: $R = CH{=}CH_2$, $R' = Et$; X: $R = R' = (CH_2)_2SEt$.

Trisulfide X is an oily liquid which can be purified by column chromatography.

The thiolation of compound VI in a thermostatic cell of an infrared spectrometer demonstrated that the addition of mercaptan first takes place in the vinyl group on the nitrogen atom. This conclusion was made on the basis of the intensity change in the absorption band of the vinyl groups in various heteroatoms, i.e., 1590 ($SCH{=}CH_2$) and 1640 cm^{-1} ($NCH{=}CH_2$).

The infrared spectrum of compound X is completely devoid of absorption bands that characterize vinyl group fluctuations, but do exhibit bands at 1380 and 2870-2970 cm^{-1} that are associated with the stretching vibrations of the methyl and methylene groups. Two triplets of methyl groups (δ 1.09, 1.13 ppm) are observed in the PMR spectrum of this compound. The protons of the methylene group bonded to the nitrogen atom are represented by a triplet (δ 4.20 ppm). The methylene protons bonded to the sulfur atom resonate in the stronger field (δ 2.33-2.76 ppm).

EXPERIMENTAL (CHEMICAL)

The infrared spectrum was recorded on a UR-20 (GDR) apparatus in a microlayer. The PMR spectrum was recorded on a BS-4878 spectrometer in $CHCl_3$. HMDS was the internal standard. Product purity was controlled by TLC on Al_2O_3. Solvents were ether and $CHCl_3$. Spots were detected on the chromatogram in iodine vapor.

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0091-150X/86/2001-0035$12.50

TABLE 1. Antimicrobial Properties of 3-Mercaptoindole Derivatives (II-X)

Compound	Minimum bacteriostatic concentration, μg/ml				
	Staph. aureus	E. coli	Ps. aeruginosa	Dermatophytes	Candida albicans fungi
I	3,15	>200	>200	100	>200
II	100	>200	>200	...	...
III	>200	>200	>200	...	...
IV	100	>200	>200	...	...
V	125	>200	>200	...	...
VI	25	>200	>200	12	>200
VII	50	100	>200	6	50
VIII	>200	>200	>200	50	>200
IX	>200	>200	>200	25	>200
X	>200	>200	>200	>200	>200

1-(2'-Ethylthio)etio-3-(2'-ethylthio)ethylthioindole (X). A mixture of 2 g (10 mmoles) of VI, 1.8 g (30 moles) of EtSH, and 0.02 g (1%) of azoisobutyric acid dinitrile was kept in a sealed ampule for 24 h at 80°C. The excess mercaptan was distilled off and the residue was dissolved in $CHCl_3$ and then purified on a column with Al_2O_3 (eluant $CHCl_3$). Compound X was then separated. Yield 2.3 g (72%), n_D^{20} 1.6092, d_4^{20} 1.1321. Found, %: C 59.52, H 7.17, S 29.41. $C_{16}H_{23}NS_3$. Calculated, %: C 59.02, H 7.12, S 29.54.

EXPERIMENTAL (BIOLOGICAL)

The primary microbiological screening of mercaptoindole I and its derivatives II-X consisted of assaying the test substances' minimal bacteriostatic doses in a liquid culture and their mycostatic doses in solid culture media. The bacterial test cultures employed were *Staph. aureus* strain 209P, *E. coli* strain 675, and *Ps. aeruginosa* strain 2789. The fungal test cultures used were anthropophilic and zoophilic dermatophytes belonging to the species *Trichophyton rubrum, Trichophyton introdigitalis, Trichophyton mentagraphytes,* and *microsporum lanosum,* as well as the yeastlike *Candida albicans* fungi.

As can be seen from Table 1, compound I is highly active against *Staphylococcus*. The introduction of ethyl radicals to various positions of the heteroring reduces the activity of compound I, although that activity is retained in butylthioindole IV. In comparing the test results for the unsaturated mercaptoindoles, one should note that the introduction of a thiovinyl group to position 3 of the ring (compounds VI-VIII) is accompanied by a high degree of antifungal activity against dermatophytes which cause dermatomycoses in humans and animals. In addition, the antibacterial properties are also retained. The activity of compound X against the tested microorganisms is markedly reduced by the introduction of a thioethyl group to divinylthioindole VI.

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