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Dimethylheptyl [3-(*N*-hetaryl)propyl]silanes: synthesis, antimicrobial and antiblastic activity

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The alkylation of monoazoles, diazoles, triazoles and tetrazoles with dimethylheptyl(3-iodopropyl)silane using liquid/liquid phase-transfer catalysis affords the corresponding [3-(*N*-azolyl)propyl]silanes in high yield, by which means the nonsymmetric ambident heterocycles 1,2,4-triazole and tetrazole undergo alkylation regiospecifically in position 1 and 2, respectively. Dimethylheptyl[3-(*N*-imidazolyl)propyl]silane demonstrated high fungistatic activity with respect to *S.cerevisiae* and *T.rubrum* in combination with high cytotoxicity.

Keywords: *N*-Alkylation, phase-transfer catalysis, [3-(*N*-azolyl)propyl]dimethylheptylsilanes, [(*N*-azolyl)pyrrolyl, carbazolyl, pyrazolyl, imidazolyl, benzimidazolyl, 1-(1,2,4-triazolyl), 1- and 2-benzotriazolyl, 2-tetrazolyl], antimicrobial activity, cytotoxicity

INTRODUCTION

Cybernetic analysis of structure–antimicrobial activity relationships for a large number of organosilicon amines having the general formula $R^1R^2R^3Si(CH_2)_nNR^4R^5$ has shown that active compounds occur most frequently when the total number of carbon atoms in the alkyl substituents at silicon (R^1,R^2 and R^3) is equal to 9–13, with the nitrogen atom being isolated from the silicon atom by three methylene groups ($n = 3$).[1] On the other hand, there are several patented antimicrobial drugs containing an *N*-heterocyclic moiety such as imidazole 1,2,4-triazole, e.g. Bifonazole® and Clotrimazole® (Bayer), Miconazole®, Econazole® and Isoconazole® (Janssen Pharmaceutica), Fluconazole® (Pfizer).

Bearing this in mind we decided to prepare compounds containing a trialkylsilyl group with a total of nine carbon atoms (namely Me_2HpSi, where $Hp = n\text{-}C_7H_{15}$) and a monoazole, diazole, triazole or tetrazole fragment isolated from silicon by three methylene groups, and to study their antimicrobial properties. Moreover, the antiblastic activity of some of these compounds was studied too.

RESULTS AND DISCUSSION

Synthesis

There are two possible approaches to [3-(*N*-azolyl)-propyl]dimethylheptylsilane synthesis: (1) via the hydrosilylation of *N*-allylazoles with dimethylheptylsilane and (2) via the *N*-alkylation of azoles with dimethyl(3-halopropyl)heptylsilane.

The usefulness of the first route was examined for the case of *N*-allylimidazole hydrosilylation with Me_2HpSiH in the presence of Speier's catalyst ($H_2PtCl_6 \cdot 6H_2O$). The reaction proceeds very slowly in dioxane (10% yield at 100°C for 24 h) and xylene (20% yield at 140°C for 24 h), whereas in diglyme, THF or in the absence of solvent it does not proceed at all. Hence, this route appears inadequate for the preparation of [3-(*N*-azolyl)propyl]silanes.

Among the possible variants of the second synthetic route we have chosen phase-transfer catalysed (PTC) *N*-alkylation of azoles, one of the most simple and convenient methods, whose efficiency has been demonstrated elsewhere.[2] An appreciable advantage of PTC in the alkylation of ambident azoles is the high

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$$CH_2=CHCH_2Cl \xrightarrow[H_2PtCl_6\cdot 6H_2O]{Me_2ClSiH} \underset{\mathbf{1}}{Me_2ClSi(CH_2)_3Cl} \xrightarrow[Et_2O]{HpMgBr} \underset{\mathbf{2}}{Me_2HpSi(CH_2)_3Cl} \xrightarrow[Bu_4N^+I^-]{NaI/H_2O/PhMe} \underset{\mathbf{3}}{Me_2HpSi(CH_2)_3I}$$

N-regioselectivity of this procedure, as compared with the conventional technique, facilitating the isolation and purification of the desirable *N*-substituted heterocyclic derivatives.

A convenient alkylating agent was prepared as follows via the hydrosilylation of allyl chloride with dimethylchlorosilane and the subsequent reaction of the resultant chloro(3-chloropropyl)dimethylsilane (**1**) with n-heptylmagnesium bromide. This afforded (3-chloropropyl)dimethylheptylsilane (**2**). Compound **2** itself can be used as an alkylating agent; however, its reactivity is not high enough. This difficulty was overcome by converting **2** into the corresponding (3-iodopropyl)-silane (**3**) by the reaction of **2** with sodium iodide in a two-phase toluene/water system in the presence of catalyst ($Bu_4N^+I^-$) under conditions similar to those described in Ref. 3 for the synthesis of Me_3SiCH_2I from Me_3SiCH_2Cl. (3-Iodopropyl)silane (**3**) was obtained in 85% isolated yield and characterized by ^1H NMR and mass spectroscopy (see the Experimental section).

The reactions of azoles with silane **3** were carried out in a two-phase benzene/60% aq. potassium hydroxide (KOH) system in the presence of tetrabutylammonium hydrosulphate used as phase-transfer catalyst (the molar ratio azole:**3**:$Bu_4N^+HSO_4^-$ was 1:1:0.05) at reflux temperature. The reaction course was monitored by GLC and GLC MS. The results of PTC reactions involving azoles and 3-iodopropylsilane **3** are summarized in Table 1.

As a rule, the alkylation of pyrrole with simple alkyl and benzyl halides under PTC conditions affords exclusively *N*-alkylation products.[4–7] Only when the alkylation was conducted with allyl bromide,[5,7] a small amount of 2-allylpyrrole was formed. The alkylation of pyrrole with silane **3** leads to three isomeric products (total yield 85%) in the ratio 77:20:3 (GLC data) which, according to GLC MS data, appear to be the products of isomeric monoalkylation (*m/z* 265, M^+). It follows from the ^1H NMR spectrum of this mixture that *N*-substituted pyrrole **4** (δ_{CH_2N}3.87 ppm) is the main product. Therefore the other two products are *C*-alkylated derivatives **5** and **6**; their spectra show that the signals of CH_2 protons attached to the ring are shifted upfield (δ 2.66 and 2.57 ppm, respectively). The *C*-alkylated product whose spectrum contains a triplet resonance at 2.66 ppm prevails in the mixture and on the basis of ^1H NMR data for isomeric alkylpyrroles[8] it can be assigned as a C_2-derivative (**5**) (Table 2). This was confirmed by the upfield shift of pyrrole ring proton resonances observed for **5**, which are characteristic for 2-alkylpyrroles[8] (*ca* 0.2 ppm for H_3 and H_4 and *ca* 0.7 ppm for H_5), as compared with the *N*-substituted product **4**. The minor component of the reaction mixture is therefore the 3-propylsilyl-substituted

Table 1 Physicochemical characteristics of dimethylheptyl [3-(*N*-hetaryl)propyl]silanes

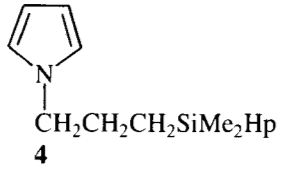
Compound	Yield (%)	B.p. (mm Hg)	Found (%)			Molecular formula	Calculated (%)		
			C	H	N		C	H	N
4,5,6	85[a]	143–145 (4)	71.6	11.2	5.1	$C_{16}H_{31}NSi$	72.5	11.7	5.3
7	95	225–226 (4)	78.2	9.8	3.4	$C_{24}H_{35}NSi$	79.0	9.7	3.8
8	96	147–148 (3)	66.9	11.4	10.5	$C_{15}H_{30}N_2Si$	67.6	11.3	10.5
9	90	170–171 (3)	67.2		10.2	$C_{15}H_{30}N_2Si$	67.6	11.3	10.5
10	90	205–207 (4)	72.5		8.2	$C_{19}H_{32}N_2Si$	72.1	10.1	8.9
11	85	150–151 (2)	62.1		15.5	$C_{14}H_{29}N_3Si$	62.7	10.9	15.7
12,13	70[b]	185–187 (4)	68.2	10.1	13.1	$C_{18}H_{31}N_3Si$	68.2	9.8	13.2
14	80	145–147 (3)	58.6	10.2	20.6	$C_{13}H_{28}N_4Si$	58.1	10.5	20.8

[a] Total yield of *N*- and *C*-alkylated products (**4+5+6**). [b] Total yield of 1- and 2-alkylated products (**12+13**).

Table 2 ^{1}H NMR spectral data for dimethylheptyl[3-(*N*-hetaryl)propyl]silanes

Compound	Chemical shifts, δ(ppm)[c]
4[a]	0.33(s, 6H, $SiMe_2$), 0.6 (m, 4H, CH_2SiCH_2), 1.07 (dist.t, 3H, $-CH_2CH_3$), 1.36 (bs, 10H, $-(CH_2)_5-$), 1.7 (m, 2H, CH_2CH_2N), 3.87 (t, 2H, J = 7 Hz, NCH_2), 6.16 (m, 2H, H_3 + H_4), 6.68 (m, 2H, H_2 + H_5)
7	0.03 (s, 6H, $SiMe_2$), 0.6 (m, 4H, CH_2SiCH_2), 0.96 (dist.t, 3H, $-CH_2CH_3$), 1.31 (bs, 10H, $-(CH_2)_5-$), 1.9 (m, 2H, NCH_2CH_2), 4.31 (t, 2H, NCH_2, J = 7 Hz), 7.1–7.6 (m, 6H) and 8.1–8.2 (m, 2H) (ring protons)
8	0.03 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.93 (dist.t, 3H, CH_2CH_3), 1.29 (bs, 10H, $-(CH_2)_5-$), 1.9 (m, 2H, NCH_2CH_2-), 4.11 (t, 2H, J = 7 Hz, NCH_2), 6.22 (m, 1H, H_4), 7.36 (m, 1H, H_3), 7.49 (m, 1H, H_5)
9	–0.02 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.89 (dist.t, 3H, CH_2CH_3), 1.27 (bs, 10H, $-(CH_2)_5-$), 1.7 (m, 2H, NCH_2CH_2-), 3.89 (t, 2H, J = 7 Hz, NCH_2), 6.87 (bs, 1H, H_5), 7.03 (bs, 1H, H_4), 7.42 (bs, 1H, H_2)
10	–0.04 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.87 (dist.t, 3H, CH_2CH_3), 1.22 (bs, 10H, $-(CH_2)_5-$), 1.84 (m, 2H, NCH_2CH_2), 4.09 (t, 2H, NCH_2), 7.2 (m, 4H) and 7.8 (m, 1H) (ring protons)
11	–0.02 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.87 (dist.t, 3H, CH_2CH_3), 1.13 (bs, 10H, $-(CH_2)_5-$), 1.84 (m, 2H, NCH_2CH_2), 4.11 (t, 2H, J = 7 Hz, NCH_2), 7.91 (s, 1H) and 8.01 (s, 1H) (ring protons)
12+13[b]	0.0 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.9 (dist.t, 3H, $-CH_2CH_3$), 1.27 (bs, 10H, $-(CH_2)_5-$), 1.9 (m, 2H, NCH_2CH_2), 4.61 (t, 2H, J = 7 Hz, NCH_2 in **13**), 4.69 (t, 2H, J = 7 Hz, NCH_2 in **12**), 7.4 (m, 3H) and 8.0 (m, 1H) (ring protons in **12**), 7.4 (m, 2H) and 7.8 (m, 2H) (ring protons in **13**)
14	–0.02 (s, 6H, $SiMe_2$), 0.5 (m, 4H, CH_2SiCH_2), 0.87 (dist.t, 3H, $-CH_2CH_3$), 1.27 (bs, 10H, $-(CH_2)_5-$), 2.0 (m, 2H, NCH_2CH_2), 4.60 (t, 2H, J = 7 Hz, NCH_2), 8.47 (s, 1H, H_5)

[a] Signals isolated from the spectrum of **4–6** mixture. [b] Spectrum of a mixture. [c] Abbreviations: s, singlet; bs, broad singlet; dist.t, distorted triplet; m, multiplet.



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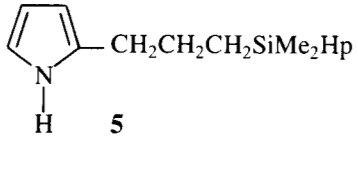

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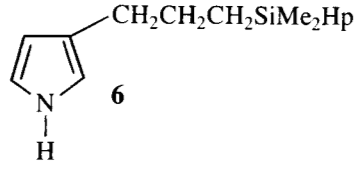

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pyrrole **6**. The formation of *C*-alkylated products during PTC alkylation of pyrrole with silane **3** is also indicated by the presence of a very broad signal at *ca* 7.9 ppm exchangeable with D_2O in the spectrum of mixture **4–6**. This signal can evidently be assigned to the NH protons of isomers **5** and **6**. The mass spectra of the isomeric silylalkylpyrroles **4–6** differ insignificantly (Table 3); their fragmentation under electron impact mainly involves the loss of heptyl radical leading to the (pyrrolyl)$CH_2CH_2CH_2SiMe_2^+$ radical ion with 100% intensity.

PTC alkylation of carbazole with silane **3**, as in the case of alkyl and benzyl halides, proceeds smoothly to afford [3-(*N*-carbazolyl)propyl]silane (**7**) in almost quantitative yield. The structure of **7** was confirmed by elemental analysis, ^{1}H NMR and mass spectroscopy (Tables 1–3).

The *N*-alkylation of unsubstituted diazoles with common alkylation agents under PTC conditions proceeds easily without any complications.[9,10] The

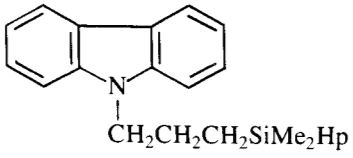

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Table 3 Mass spectral data for dimethylheptyl[3-(*N*-hetaryl)propyl]silanes

Compound	*m/z* (relative abundance, %)[a]
4	265 (M^+, 10), 167 (16), 166 (100), 124 (12), 81 (16), 80 (10), 59 (41)
5	265 (M^+, 19), 250 (10), 167 (16), 166 (100), 158 (10), 157 (64), 80 (23), 59 (21)
6	265 (M^+, 8), 250 (M^+ −Me, 9), 167 (18), 166 (100), 157 (18), 138 (10), 80 (13), 59 (13)
7	365 (M^+, 34), 266 (20), 224 (10), 181 (16), 180 (100), 59 (10)
8	266 (M^+, 0.4), 251 (M^+, −Me, 16), 168 (17), 167 (100), 125 (25), 81 (16), 59 (60), 43 (14), 41 (12)
9	266 (M^+, 2), 251 (M^+, −Me, 7), 168 (18), 167 (100), 59 (57), 43 (10)
10[b]	317 (M^+, +1, 24), 301 (M^+ −Me, 2), 217 (10), 133 (10), 73 (30), 59 (100)
11	252 (M^+ −Me, 12), 169 (15), 168 (100), 126 (17), 59 (32)
12	317 (M^+, 0.6), 302 (M^+ −Me, 8), 219 (19), 218 (100), 148 (14), 59 (66)
13	317 (M^+, 0.4), 302 (M^+ −Me, 15), 219 (12), 218 (62), 191 (12), 190 (42), 176 (11), 157 (11), 148 (10), 87 (12), 77 (22), 74 (11), 73 (17), 59 (100)
14	253 (M^+ −Me, 7), 170 (14), 169 (100), 157 (10), 142 (12), 141 (24), 73 (11), 59 (83), 43 (11)

[a] The peaks of characteristic ions and peaks with ≥ 10% intensity are presented. [b]FAB MS (thioglycerine as matrix, argon as reagent gas).

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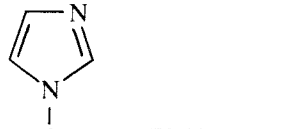

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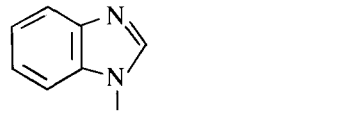

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PTC reactions of pyrazole, imidazole and benzimidazole with 3-iodopropylsilane **3** also proceed readily to afford the corresponding [3-(*N*-hetaryl)propyl]silanes (**8**–**10**) in high yield. The physicochemical characteristics of compounds **8**–**10** and the appropriate spectral parameters confirming their structure are summarized in Tables 1–3.

The alkylation of nonsymmetrical triazoles (1,2,4-triazole and 1,2,3-benzotriazole) and tetrazole deserves interest in view of the preparation of their silylalkyl derivatives and the study of regioselectivity of reactions involving these ambident heterocycles. According to GLC and GLC MS data the PTC alkylation of 1,2,4-triazole with iodopropylsilane **3** gives a single product that can be isolated from the reaction mixture in 85% yield (Table 1). The presence of signals of two nonequivalent heterocyclic ring protons with equal integrals clearly indicates the formation of an N_1-alkylated product (**11**), because when the substituent is in position 4 the ring protons are equivalent. Therefore, the alkylation of 1,2,4-triazole occurs regiospecifically. The alkylation of 1,2,4-triazole with β-functionally substituted alkyl halides proceeds similarly,[11] but when benzyl halides are used the mixture of isomers predominantly contains the N_1-substituted 1,2,4-triazole.[12]

The PTC alkylation of ambident 1,2,3-benzotriazole with silane **3** gives a mixture of two products in 35:65 ratio (GLC data), containing, according to GLC MS data, isomeric [3-(*N*-benzotriazolyl)propyl]silanes **12** and **13** (*m/z* 317, M^+; see Table 3). Comparison of spectral parameters of a mixture of **12** and **13** (Table 2) with those known for 1- and 2-alkyl substituted benzotriazoles[13] shows that the prevailing component in the mixture is the N_2-isomer **13**. It should be noted that alkylation with usual alkyl and benzyl halides under PTC conditions also affords, as a rule, a mixture of N_1- and N_2-alkylated products with the predominance of the N_1-isomer.[10,12,14]

The alkylation of tetrazole and some of its derivatives under PTC conditions usually gives a mixture of N_1- and N_2-substituted tetrazoles with the predominance of the latter.[11,15] The PTC reaction of tetrazole with iodopropylsilane **3** proceeds regiospecifically to afford [3-(2-tetrazolyl)propyl]silane (**14**) that can be isolated in 80% yield (Tables 1–3). Assignment of the resulting

$CH_2CH_2CH_2SiMe_2Hp$

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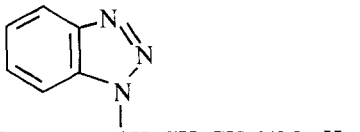
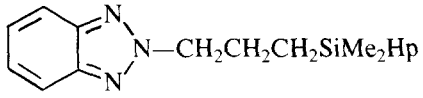


$CH_2CH_2CH_2SiMe_2Hp$

12



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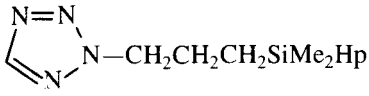

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product to 2-substituted tetrazole was made on the basis of comparison of its ^1H NMR spectrum with the available literature data for N_1 and N_2-substituted tetrazoles.[8,15]

BIOLOGICAL ACTIVITY

Antimicrobial properties

The antimicrobial activity of dimethylheptyl [3-(*N*-hetaryl)propyl]silanes, which can be isolated as a single isomer (**7–9, 11, 14**) was studied in a wide range of pathogenic micro-organisms: fungi which cause dermatomycosis (*Trichophyton rubrum, mentagrophytes*), aspergillosis (*Aspergillus niger*), candidosis (*Candida albicans*), yeast (*Succharomyers cerevisiae*), as well as Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) and sporous (*Bacillus subtilis*) bacteria.

The results in Table 4 suggest that the organosilicon derivatives of azoles possess certain antifungal activity. However, their activity is not as high as one could have expected in connection with the presence of two active sites (a dimethylheptyl radical at the silicon atom and an azole fragment in the molecule). Nonetheless, [3-(imidazolyl)propyl]silane **9** demonstrated substantial fungistatic activity against *S. cerevisiae* and *T. rubrum* (Table 4). The minimum inhibiting concentrations of compound **9** against these strains amount to 1.96 and 6.25 μg/ml, respectively. Thus, silane **9** suppressed the growth of dermatophytes in the same concentration as such known antifungal agents as nystatin, griseofulvin, amphotericin and thiabendazole.[16]

Cytotoxic and antitumour properties

The cytotoxic activity of the compounds synthesized was tested *in vitro* using a melanoma B 16 mouse cell culture. The results are summarized in Table 5. Compounds **8, 11** and **14** demonstrate moderate cytotoxicity in the concentration range 10–32 μg/ml. The only compound possessing a high antifungal and cytotoxic activity was dimethylheptyl[3-(*N*-imidazolyl)propyl]silane (**9**). None of these compounds was active against leukaemia P 388 cells at the maximum tolerated doses of 100–1000 mg kg^{-1} (Table 5).

Table 4 Minimum inhibiting concentrations of dimethylheptyl[3-(*N*-hetaryl)propyl]silanes (μg cm^{-3} (μg/ml))

Compound	*S. cerevisiae*	*T. rubrum*	*T. mentagrophytes*	*A. niger*	*C. albicans*	*B. subtilis*	*P. aeruginosa*	*E. coli* K–12	*S. aureus* 209
7	>500	>500	>500	>500	>500	>500	250	250	500
8	>500	>500	>500	>500	>500	>500	500	500	500
9	1.96	6.25	250	31.2	62.5	62.5	250	500	250
11	500	250	500	250	125	250	500	500	500
14	500	250	500	250	125	125	250	250	250

Table 5 Cytotoxic and antitumour activity of dimethylheptyl[3-(*N*-hetaryl)propyl]silanes

Compound	EC_{50} (μg/ml)	Antitumour activity on P 388 cells	
		Daily dose (mg kg^{-1})	Percentage of T/C
7	>32	100,320,1000	100,100,56
8	32	100,320,1000	100,111,111
9	1.0	100,320,1000	100,78,22
11	10	100,320,1000	100,100,67
14	10	100,320,1000	100,100,56

EXPERIMENTAL

General methods

^{1}H NMR spectra were registered on a Bruker WH-90/DS specrometer using $CDCl_3$ as solvent and tetramethylsilane (Me_4Si) as internal standard. Chromatomass spectra were obtained on a Kratos MS-25 GC MS apparatus (70 eV). GLC analysis was carried out on a Chrom-5 instrument equipped with a flame-ionization detector, the column (1.2 m × 3 mm) used was packed with 5% OV-17/Chromosorb W-HP (80–100 mesh), analysis temperature was 170–250 °C depending on reaction mixture composition. Helium was used as carrier gas (50 cm^3 min^{-1}).

Materials

(3-Chloropropyl)dimethylsilane (**1**) was prepared by the hydrosilylation of allyl chloride with chlorodimethylsilane (Fluka) in the presence of $H_2PtCl_6 \cdot 6H_2O$; b.p. 83 °C/30 mm Hg (Ref. 17, 179 °C/750 mm Hg).

(3-Chloropropyl)dimethylheptylsilane (**2**) was obtained by reacting **1** with heptylmagnesium bromide after the conventional procedure; b.p. 100 °C/1 mm Hg, n_D^{20} 1.4482; ^{1}H NMR, δ(ppm): 0.04 (s, 6H, $SiMe_2$), 0.64 (m, 4H, CH_2SiCH_2), 0.95 (distorted t, 3H, $CH_2C\underline{H}_3$), 1.33 (bs, 10H, $CH_3(C\underline{H}_2)_5CH_2$), 1.80 (m, 2H, $C\underline{H}_2CH_2Cl$), 3.55 (t, 2H, CH_2Cl).

The commercial reagents used included pyrrole (Koch–Light Lab.), carbazole, pyrazole, imidazole, benzimidazole, 1,2,4-triazole, 1,2,3-benzotriazole, tetrazole, tetrabutylammonium iodide, tetrabutylammonium hydrosulphate (Fluka).

Dimethylheptyl(3-iodopropyl)silane (3)

To a solution of (3-chloropropyl)dimethylsilane (**2**) (2.4 g, 10 mmol) and tetrabutylammonium iodide (1.48 g, 4 mmol) in toluene (2.4 cm^3) was added a solutioin of sodium iodide (3 g, 20 mmol) in water (3.4 cm^3). The resulting mixture was stirred under reflux for 15 h, fresh portions of NaI (3 g of each) were added twice at 5 h intervals. After reaction completion (GLC control) the mixture was filtered, the precipitate was washed with diethyl ether, the combined organic layer was separated and dried over $MgSO_4$, ether and toluene were distilled off under reduced pressure, the residue was distilled *in vacuo* to give 2.8 g (yield 85%) of silane **3**. Found C,44.35; H,8.15; calc. for $C_{12}H_{27}ISi$: C,44.17; H,8.28; δ ^{1}H NMR (ppm): 0.04 (s, 6H, $SiMe_2$), 0.60 (m, 4H, CH_2SiCH_2), 0.93 (t, 3H, $CH_2C\underline{H}_3$), 1.31 (s, 10H, $CH_3(C\underline{H}_2)_5CH_2$), 1.86 (m, 2H, $C\underline{H}_2CH_2I$), 3.22 (t, 2H, CH_2I).

Alkylation of azoles with dimethylheptyl (3-iodopropyl)silane (3) (general procedure)

To a solution of silane **3** (10 mmol) and $Bu_4N^+HSO_4^-$ (0.5 mmol) in benzene (40 cm^3) was added azole (10 mmol) and an aqueous solution of KOH (40 mmol/1.6 cm^3). The resulting two-phase mixture was stirred for 10–12 h at reflux temperature (GLC control) and then cooled to room temperature. The organic layer was separated, washed with water and dried over $MgSO_4$. After benzene was evaporated the residue was distilled *in vacuo* to give the end products (see Tables 1–3).

Antimicrobial activity

Antimicrobial activity was assayed by the two-fold serial dilution method (pH 7.2–7.4) as described elsewhere.[18,19] The following pathogenic microorganisms were used in the assays: fungi (*T.rubrum*, *T.mentagrophytes*, *C.albicans*, *A.niger*), yeast (*S.cerevisiae*), Gram-positive (*S.aureus*), Gram-negative (*E.coli*, *P.aeruginosa*) and sporous (*B.subtilis*) cocci.

Cytotoxic activity

The cytotoxic activity of synthesized compounds was evaluated using melanoma B 16 cell culture. The B 16

cells were maintained as a monolayer in Iscove's modification of Dulbecco's medium supplemented with 10% foetal calf serum at 37°C in a humidified atmosphere of 10% carbon dioxide in air.

The cells were detached with trypsin-EDTA treatment and 10^4 viable cells contained in 0.3 cm^3 of growth medium were seeded into 96-well flat-bottomed microtest plates (Linbro). On the next day, after cell adherence and growth initiation, the compounds were added in 0.32, 3.2 and 32 μg/ml concentrations providing continuous exposure. On the fifth day, the medium was decanted and the cell monolayer was solubilized with 0.5 mol dm^{-3} NaOH at 55°C. The cell lysate was brought to pH 7 with 0.1 mol dm^{-3} phosphate buffer containing 2 mol dm^{-3} NaCl and Hoechst dye No. 33342 (0.01 μg per well). The fluorescence of the DNA–Hoechst dye complex was measured using 360 nm excitation and 460 nm emission filters. The results of fluorimetric assays were expressed as cell number per well. EC_{50} is the concentration of drugs in $\mu g\ cm^{-3}$ inhibiting cell growth by 50% after four days of exposure. Cytotoxicity calculations and the ranking of data (0.5 log) were performed on an Apple IIe computer. The functional criteria for moderate and high cytotoxicity were equal to 32 and 3.2 μg/ml, respectively.

Antitumour activity

The antitumour activity of synthesized compounds was investigated using leukaemia P 388 cells implanted intraperitoneally (i.p.) into C57BL/6 × DBA/2 mice.

The compounds were administered i.p. at a daily dose of 100, 320 and 1000 mg kg^{-1} on the second and ninth days following inoculation of 10^6 leukaemic cells. Antitumour and toxic effects were evaluated on the basis of the mean life span of mice as end points and expressed as test/control (T/C) (percentage).

The statistical criteria for antitumour activity and toxicity amounted to 120 and 80% T/C, respectively.

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