NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS. LVII.*

4-[γ-(TRIALKYLSILYL)PROPYLAMINO]QUINOLINES

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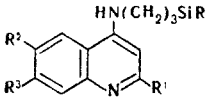
A number of new 4-[γ-(trialkylsilyl)propylamino]quinolines and their hydrochlorides were synthesized by heating 4-chloroquinolines with trialkyl(3-aminopropyl)-silanes in phenol or diglyme. The antimicrobial activity of the products was determined.

A number of 4-aminoquinoline derivatives have high anitmicrobial activity [2-4]. Organosilicon γ-amines also display fungistatic activity [5]. According to patent data [6], 4-[γ-(trimethylsilyl)propylamino]quinolines obtained by heating trimethyl(3-aminopropyl)silane with 4-chloroquinolines in phenol have herbicidal activity. In order to ascertain the relationship between the antimicrobial activity of organosilicon amines of this sort and the character of the substituents bonded to both the silicon atom and the quinoline ring, we synthesized a number of new 4-[γ-(trialkylsilyl)proplamino]quinolines by heating trialkyl(3-aminopropyl)silanes with some substituted 4-chloroquinolines under conditions similar to those described in a patent [6]. The yields of reaction products in most cases did not exceed 30% because of difficulties involved in their isolation and purification. The isolation of the 4-[γ-(trialkylsilyl)propylamino]quinolines is simplified considerably if dry diglyme is used in place of phenol as the solvent and if triethylamine is used as a hydrogen chloride acceptor. Raising the temperature 20°C makes it possible to reduce the reaction time by one-half, and the yield of the target product in this case is increased by 10-15%. Increasing the reaction time has an unfavorable effect on the yield, inasmuch as resinous side products are formed. The addition of anhydrous potassium carbo-

TABLE 1. 4-[γ-(Triaklylsilyl)propylamino]quinolines



Compound	R	R¹	R²	R³	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
							C	H	N	C	H	N	
I	$(C_2H_5)_3$	H	H	Cl	144—145 [a]	$C_{18}H_{27}ClN_2Si$	64,6	8,4	8,9	64,5	8,1	8,4	57
II	$(CH_3)_2i$-C_4H_9	H	H	Cl	114—115 [b]	$C_{18}H_{27}ClN_2Si$	64,7	8,4	9,0	64,5	8,1	8,4	30
III	$CH_3(C_4H_9)_2$	CH_3	H	Cl	137—138 [a]	$C_{22}H_{35}ClN_2Si$	66,8	9,5	7,2	66,9	8,8	7,4	74
IV	$(C_2H_5)_3$	CH_3	CH_3O	H	138—139 [c]	$C_{20}H_{32}N_2OSi$	69,2	9,2	7,7	69,7	9,4	8,1	29
V	$(CH_3)_2i$-C_4H_9	CH_3	CH_3O	H	139—140 [d]	$C_{20}H_{32}N_2OSi$	69,8	9,6	8,3	69,7	9,4	8,1	31

a) From benzene—hexane (1:2); b) from benzene—hexane (1:1); c) from hexane; d) from ethanol—water (2:1).

*See [1] for communication LVI.

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TABLE 2. 4-[γ-(Trialkylsilyl)propylamino]quinoline Hydrochlorides

Compound	R	R¹	R²	R³	mp, °C	Empirical formula	Found, *			Calc., %			Yield, %
							C	H	N	C	H	N	
VI	$(C_2H_5)_3$	H	H	Cl	164—165 a	$C_{18}H_{27}ClN_2Si \cdot HCl$	58,6	7,6	7,3	58,2	7,3	7,6	56
VII	$(C_2H_5)_3$	CH_3	H	Cl	268—269 b	$C_{19}H_{29}ClN_2Si \cdot HCl \cdot H_2O$	56,2	8,2	7,1	56,6	8,0	6,9	73
VIII	$(CH_3)2i\text{-}C_4H_9$	CH_3	H	Cl	236—237 c	$C_{19}H_{29}ClN_2Si \cdot HCl \cdot H_2O$	56,4	8,1	7,0	56,6	8,0	6,9	47
IX	$CH_3(C_4H_9)_2$	CH_3	H	Cl	194—195 c	$C_{22}H_{35}ClN_2Si \cdot HCl \cdot H_2O$	59,7	8,8	6,5	59,4	8,6	6,3	37
X	$(C_2H_5)_3$	H	CH_3O	H	70—71 d	$C_{19}H_{30}N_2OSi \cdot HCl \cdot H_2O$	59,6	8,4	7,3	59,3	8,6	7,3	30
XI	$CH_3(C_4H_9)_2$	H	CH_3O	H	76—77 a	$C_{22}H_{36}N_2OSi \cdot HCl \cdot H_2O$	61,7	9,7	7,1	61,9	9,2	6,6	26
XII	$(C_2H_5)_3$	CH_3	CH_3O	H	98—99 c	$C_{20}H_{32}N_2OSi \cdot HCl \cdot H_2O$	60,1	8,6	7,1	60,2	8,8	7,0	23
XIII	$(CH_3)2i\text{-}C_4H_9$	CH_3	CH_3O	H	81—83 c	$C_{20}H_{32}N_2OSi \cdot HCl \cdot H_2O$	60,2	9,1	7,1	60,2	8,8	7,0	24
XIV	$CH_3(C_4H_9)_2$	CH_3	CH_3O	H	77—79 c	$C_{23}H_{38}N_2OSi \cdot HCl \cdot H_2O$	62,7	9,0	6,6	62,6	9,4	6,3	39

a) From 30% aqueous alcohol; b) from 60% aqueous alcohol; c) from 50% aqueous alcohol; d) from water.

nate does not have a substantial effect on the reaction. Carrying out the reaction in the presence of triethylamine does not always insure the preparation of the free base, inasmuch as the basicities of 4-aminoquinolines [7] are comparable to the basicity of triethylamine, and they are even higher in the case of some 4-aminoquinolines.

A strong band of δ_{Si-C} vibrations of an alkyl group at 1240-1255 cm^{-1}, which is absent in the spectra of the starting quinolines [8], is observed in the IR spectra of 4-[γ-(trialkylsilyl)propylamino]quinolines. The absorption bands of stretching vibrations of an Si—C bond at 700-850 cm^{-1} are difficult to identify, inasmuch as the out-of-plane deformation vibrations of the aromatic ring of quinoline are also found in the same region. A broad absorption band at 3360-3450 cm^{-1} is present in the spectra of hydrochlorides containing crystallization water.

The chemical shifts (δ) of the 3-H protons of the quinoline ring (6.30-6.36 ppm), of the α-CH_2 protons of the propylamino group (3.20-3.26 ppm), and of the NH protons (7.12-7.30 ppm) indicate that the compounds have the 4-aminoquinoline structure with a hydrogen atom attached to the exocyclic nitrogen atom [9]. In the formation of the hydrochlorides, the signals of all of the protons are shifted to weaker fields: NH (9.35-9.58 ppm), 3-H (6.56-6.80 ppm), and α-CH_2 (3.45-3.55 ppm).

The 4-[γ-(trialkylsilyl)propylamino]quinolines have selective antimicrobial activity (Table 3). They do not have an effect on Gram-negative bacteria, moderately suppress the growth of Gram-positive bacteria, and have a considerably stronger effect on pathogenic fungi. Moreover, the triethylsilyl derivative containing a chlorine atom in the 7 position of the quinoline ring is highly active with respect to trichophyton but does not affect Candida and bacteria. The introduction of a methoxy group into the 6 position considerably increases the activity of the compound with respect to these microbes. The quinoline derivatives proved to be more active than the quinaldine derivatives. In the case of 6-methoxy-substituted quinaldine derivatives the dimethylisobutylsilyl derivative displayed greater antimicrobial activity than the corresponding triethyl- and methyldibutylsilyl derivatives.

EXPERIMENTAL METHOD

The PMR spectra of 10% solutions of the compounds in d_6-dimethyl sulfoxide (d_6-DMSO) were recorded with a Perkin—Elmer R-12A (60 MHz) spectrometer at 36° with tetramethylsilane as the internal standard. The IR spectra of microlayers of the substances (mineral oil and hexachlorobutadiene suspensions) were recorded with an IKS-14 spectrometer. The antimicrobial activity of the compounds was determined by the method in [10].

4-[γ-(Trialkylsilyl)propylamino]quinolines. A) A mixture of 0.01 mole of 4-chloroquinoline and 0.01 mole of trialkyl(3-aminopropyl)silane in 10 g of phenol was heated at 130° for 2 h, after which it was poured into 100 ml of a 20% solution of sodium hydroxide. The alkaline mixture was extracted with ether, the ether extract was dried with magnesium

TABLE 3. Antimicrobial Activity of 4-[γ-(Trialkylsilyl)propylamino]quinolines and Their Hydrochlorides

Compound	Minimum inhibitory concentration of the substance in μg/ml with respect to test microbes					
	Candida albicans 67/846	Epidermophyton Kaufmann Wolf 41	Trichophyton gypseum 3/4	Staphylococcus aureus haemolyticus 209	Bac. mycoides 537	Escherihia coli 675
I	>50,0	4,2	1,0	> 50	> 50	> 50
II	>50,0	8,3	8,3	> 50	> 50	> 50
V	20,0	10,0	10,0	4,2	4,2	>200
VII	20,0	20,0	13,3	>200	3,1	>200
IX	10,0	20,0	10,0	12,5	>200	>200
X	3,3	10,0	3,3	3,1	2,1	>200
XII	13,3	20,0	13,3	6,2	8,3	>200
XIII	5,0	6,7	5,0	4,2	4,2	>200
XIV	13,3	13,3	3,3	8,3	> 50,0	>200

sulfate, and dry hydrogen chloride was bubbled through the ether solution to precipitate 4-[γ-(trialkylsilyl)propylamino]quinoline hydrochloride.

B) Equimolecular amounts of 4-chloroquinoline and trialkyl(3-aminopropyl)silane were refluxed in dry diglyme at 155-160° for 1 h, after which the solvent was removed by vacuum distillation, and the residue was recrystallized to give 4-[γ-(trialkylsilyl)propylamino]-quinoline hydrochloride. In a number of cases triethylamine hydrochloride precipitated when 1 g of triethylamine was added to the reaction mixture; the hydrochloride was removed by filtration, and the solvent was removed by distillation to give 4-[γ-(trialkylsilyl)-propylamino]quinoline as the free base. Data on the compounds obtained are presented in Tables 1 and 2.

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LITERATURE CITED

1. É. Lukevits, A. Ya. Zile, L. V. Kruzmetra, Yu. I. Khudobin, and M. G. Voronkov, Khim.-Farmats. Zh., No. 1, 14 (1975).
2. W. C. Austin, M. D. Potter, and E. P. Taylor, J. Chem. Soc., 1489 (1958).
3. A. Kreutzberger, Deutsch. Apoth.-Ztg., 112, 1606 (1972).
4. B. M. Gutsulyak, Usp. Khim., 41, 346 (1972).
5. É. Ya. Lukevits, Author's Abstract of Doctoral Dissertation, Riga (1973).
6. W. E. Weesner and J. L. Schaar, US Patent No. 3542786 (1970); Chem. Abstr., 74, 125838 (1971).
7. E. V. Brown and A. C. Plasz, J. Heterocycl. Chem., 7, 335 (1970).
8. A. R. Katritzky (editor), Physical Methods in the Chemistry of Heterocyclic Compounds, Academic Press (1963).
9. J. C. Craig and D. E. Pearson, J. Heterocycl. Chem., 5, 631 (1968).
10. É. Ya. Lukevits, A. Ya. Zile, L. V. Kruzmetra, A. E. Pestunovich, and M. G. Voronkov, Izv. Akad. Nauk Latv. SSR, No. 3, 83 (1974).