4'-BROMO(and AZIDO)-10,10-DIMETHYLSPIRO[9,10-DIHYDRO-10-SILA-2-AZAANTHRACENE-9,2'-TETRAHYDROFURAN]

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Dehydrobromination of 10,10-dimethyl-9-(2,3-dibromoprop-1-yl)-9,10-dihydro-10-sila-2-aza-9-anthrol with butyllithium follows two routes to give the Z- and E-isomers of furan ring-brominated spiro(dihydrosilaazaanthracene-9,2'-tetrahydrofuran), and the cis- and trans-isomers of 10,10-dimethyl-9-(3-bromoallyl)-9,10-dihydro-10-sila-2-aza-9-anthrol. Analogous compounds have been obtained bearing an azido-group in the tetrahydrofuran ring, and a spiran with a dihydrofuran fragment. The pure isomers have been isolated, and their structures established.

Spiro-compounds of 10-sila-2-azanthracene and its nitrogen-free analog have not been reported. In order to examine the feasibility of synthesizing such compounds, bearing in mind the spatial structure of the silaazaanthracene fragment [1, 2], and to investigate their physiological activity, we undertook the synthesis of the first representative of this type of compound, namely spiro[dihydrosilaazaanthracene-9,2'-tetrahydrofuran]. It has been reported that piperidine- and pyrrolidinespirohexane display antitumor activity [3].

The starting material chosen was 10,10-dimethyl-9-allyl-9,10-dihydro-10-sila-2-aza-9-anthrol (I), obtained from allylmagnesium bromide and the appropriate silaazaanthrone [4]. Bromination of (I) gave a quantitative yield of 10,10-dimethyl-9-(2,3-dibromopropyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (II), dehydrobromination of which with butyllithium in benzene followed two routes, to give (III) and (IV). Intramolecular cyclization gave more than 60% of 4'-bromo-10,10-dimethylspiro-[9,10-dihydro-10-sila-2-azaanthracene-9,2'-tetrahydrofuran] (III). According to its NMR spectrum (400 MHz), this was a mixture of the Z- (IIIa) and E- (IIIb) isomers with respect to the location of the bromine atom relative to the pyridine ring in the dihydrosilaazaanthracene fragment. Chromatographic separation of this mixture gave the pure isomers in a ratio of approximately 5:1. The greater chromatographic mobility of the Z-isomer (R_f 0.62) as compared with the E-isomer (R_f 0.54) was apparently due to transannular interaction of the bromine with the nitrogen of the pyridine fragment of the molecule, which is possible in the Z-isomer.

The mixture of cis- and trans-isomers of 10,10-dimethyl-9-(3-bromoallyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (IV) was obtained in 19% yield.

Treatment of the dibromo-compound (II) with triethylamine in a boiling mixture of benzene and acetone gave 21% of the Z-isomer of the spiro-compound (IIIa). In this case, the extent of reaction of (II) was no greater than 25%. The use of sodamide or potassium nis-(dimethylmetroxysilyl)amide resulted in dehydrobromination of the dibromopropyl radical. In the first case, 22% of the cis-isomer (IVa) was obtained, and in the second case, 13% of the trans-isomer (IVb). The locations of the substituents at the exocyclic doublet bond in the isomers (IVa) and (IVb) were established by their $^3J_{CH=CH}$ values in the PMR spectra (7 Hz for (IVa) and 13.5 Hz for (IVb)](see scheme on following page).

The structures of the E- and Z-isomers of the spiro-compound (III) were established by their PMR spectra (Table 1). Typical five-spin systems for the protons of the substituted furan ring were seen in the PMR spectra of both isomers, having almost identical chemical shifts and coupling constants for the corresponding protons. The geminal J_{ab} value for the methylene protons (−8.5 Hz) adjacent to the oxygen heteroatom is typical for the tetrahydrofuran ring [5]. Only the chemical shifts of the 1-H and 8-H protons differ significantly in

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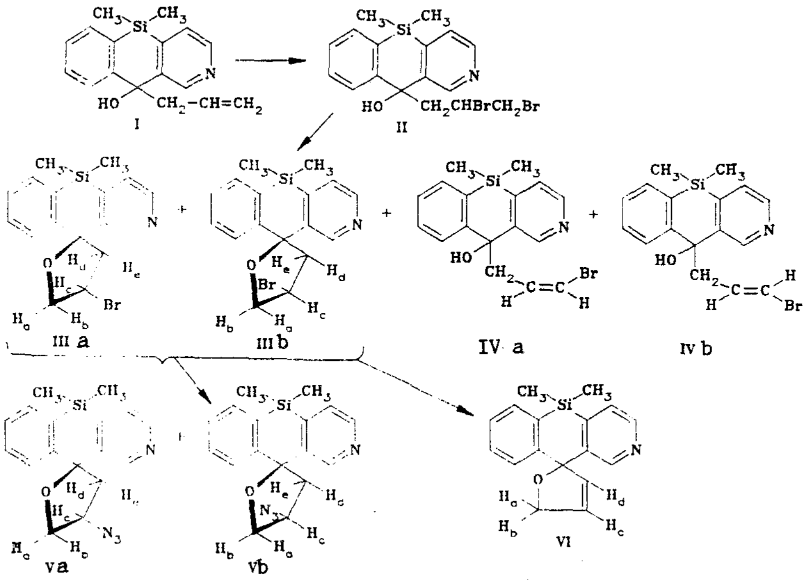

the isomers. On the assumption that Z-orientation of the bromine atom causes a low-field increment in the shift of the corresponding proton, we have assigned the Z-configuration to isomer (IIIa), the signal for the 1-H proton in which lies at lower field, and the E-configuration to (IIIb), for which the signal for the 8-H proton is at lower field. This assignment was subsequently confirmed by the two-dimensional nuclear Oberhauser effect (NOESY) [6] obtained for the Z-isomer (Fig. 1). The presence in this spectrum of a cross-peak for the pair 8-H—H_a, and the absence of a peak for the pair 1-H—H_c, provide direct evidence for the Z-configuration. The stronger cross-peaks for the pairs 8-H—H_a and 1-H—H_b show that protons H_a and H_b occupy the trans- and cis-positions to the bromine atom respectively. Hence, $^3J_{trans(bc)} > {}^3J_{trans(ac)}$ (Table 1).

Reaction of the mixture of Z- and E-isomers of the spiro-compound (III) with sodium azide in DMF results in replacement of the bromine atom by the azido-group to give a mixture of the Z- and E-isomers of 4'-azido-10,10-dimethylspiro[9,10-dihydro-10-sila-2-azaanthracen-9,2'-tetrahydrofuran] (Va, b), which were obtained by chromatography in the pure state, and their structures established by PMR (Table 1). As for isomers (IIIa) and (IIIb), in the Z-isomer (Va) the signal for the 1-H proton occurs at lower field, and that for 8-H at higher field than in the E-isomer (Vb). In their chromatographic mobility, the Z- and E-isomers of (III) and (V) had a similar relationship.

Isomers (Va) and (Vb) were isolated in proportions of approximately 1:1.3. Bearing in mind that the original mixture (III) contained the Z- and E-isomers in a ratio of ~5:1, it may be assumed that nucleophilic replacement of bromine by the azide ion occurs by the S_N1 mechanism, since attack on the intermediate carbonium ion by the azide ion from either side of the tetrahydrofuran moiety is not sterically hindered.

On heating the mixture of Z- and E-isomers of the spiro-compound (III) with N-methylpiperazine in DMF, dehydrobromination occurs to give 67% of 10,10-dimethylspiro[9,10-dihydro-10-sila-2-azaanthracene-9,2'-(2',5'-dihydro)-furan] (VI). This reaction does not, however,

TABLE 1. PMR Spectral Parameters of Spiro[dihydrosilaazaanthra-

Compound	Chemical shifts, σ, ppm*†												
	1-H	3-H	4-H	5-H	6-H	7-H	8-H	a	b	c	d	e	Si—CH₃
IIIa	9,13	8,55	7,45	7,62	7,31	7,42	7,69	4,44	4,90	4,33	2,48	2,74	0,51, 0,58
IIIb	8,86	8,54	7,51	7,60	7,32	7,47	7,92	4,59	4,82	4,31	2,48	2,71	0,51, 0,58
Va	9,08	8,54	7,48	7,35 ... 7,70			7,73	4,40	4,60	4,33	2,33	2,45	0,52, 0,59
Va	8,91	8,51	7,46	7,35 ... 7,70			7,90	4,40	4,60	4,33	2,33	2,45	0,52, 0,59
VI	9,08	8,48	7,26	7,43	7,25	7,40	7,76	4,84	4,84	5,67	5,41	—	0,31, 0,39

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*The spectra of (IIIa, b) and (Va, b) were obtained in $CDCl_3$, and
†1-H, 3-H, and 8-H are protons of the dihydrosilaazaanthracene

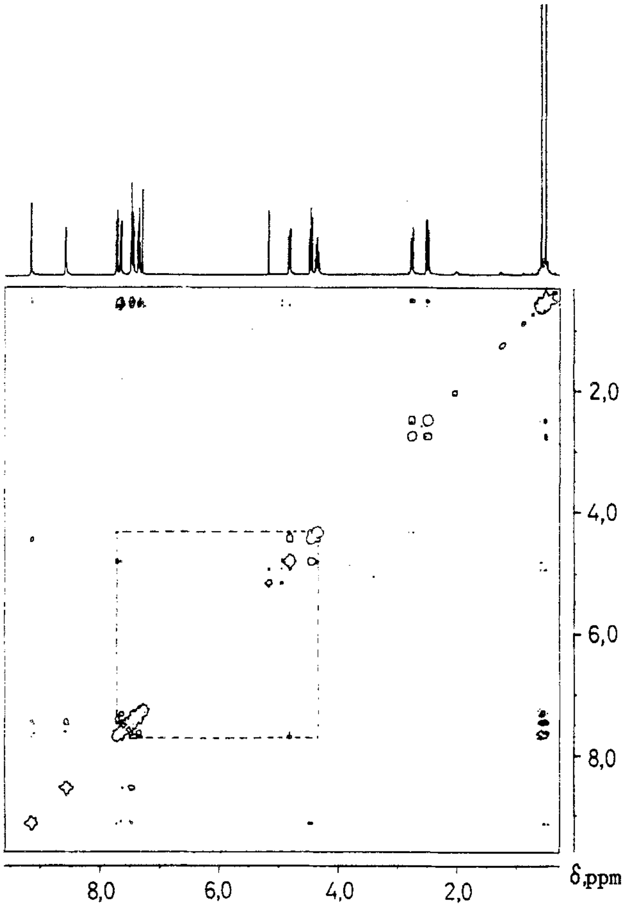

Fig. 1. Two-dimensional NOESY for (IIIa). The broken lines indicate cross-peaks from the proton pair 8-H–H_c.

take place in boiling ethanol. The presence in the PMR spectrum of (VI) of a signal for the methylene group at 4.84 ppm shows that the double bond in the dihydrofuran moiety is located at positions 3',4'.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrophotometer in KBr disks. PMR spectra were recorded on Bruker WP-80 and WM-400 instruments, internal standard TMS. Mass spectra were measured on MX-1303 and CH-8 spectrometers. Column chromatography was carried out using Brockman grade II alumina, and TLC on bound layers of Silufol UV-254.

10,10-Dimethyl-9-allyl-9,10-dihydro-10-sila-2-aza-9-anthrol (I, $C_{17}H_{19}NOSi$). To a

cene-9,2'tetrahydrodihydro) furans]*

Coupling constants, J, HZ												
3—4	5—6	5—7	5—8	6—7	6—8	7—8	*ab*	*ac*	*bc*	*cd*	*ce* (*ad*)	*de* (*bd*)
4.7	7,5	1,5	0,6	7,5	1,2	7,5	−8,5	6,0	7,5	6,5	8,5	−12,5
4,7	7,5	1,5	0,6	7,5	1,2	7,5	−8,5	5,5	8,0	6,0	9,0	−12,5
4.6	7,5	1,5	0,5	7,5	1,1	7,5	−9,0	6,0	6,5	5,0	6,0	−12,5
4,5	7,5	1,5	—	—	—	—	−15	2,3	2,3	6,0	(1,6)	(1,6)

and (VI) in $CDCl_3 + C_6D_6$.
fragment, and a-e are the protons of the tetrahydrofuran fragment.

solution of 6 g (25 mmole) of 10,10-dimethyl-10-sila-2-azaanthrone in 300 ml of dry ether was added over 0.5 h with vigorous stirring a solution of allylmagnesium bromide, obtained from 2.4 g (100 mmole) of magnesium and 12.1 g (100 mmole) of allyl bromide in 100 ml of dry ether. The mixture was boiled for 1 h, cooled, and decomposed with saturated ammonium chloride solution. The reaction products were extracted with ether, and the extract dried over magnesium sulfate. The residue after removal of the ether (7.3 g) was crystallized from heptane, to give 4 g (54%) of the silaazaanthrol (I) as colorless crystals, mp 139-140°C (from heptane). Column chromatography of the mother liquors (eluent, a 1:10 mixture of ethyl acetate and heptane) gave a further 1.3 g of the alcohol (I) (overall yield 72%). IR spectrum: 3170 (bonded OH), 1650 (exocyclic CH=CH), 1255 and 820 cm^{-1} ($Si(CH_3)_2$). PMR spectrum: 8.98 (1H, s, 1-H), 8.28 (1H, d.d, 3-H, J_{34} = 4.2 Hz), 7.92 (1H, d.d, 8-H, J_{87} = 8.0, J_{86} = 0.8 Hz), 7.57 (1H, d.d, 5-H, J_{56} = 7.1, J_{57} = 1.3 Hz), 7.47 (1H, t.d, 7-H, J_{76} = 7.8 Hz), 7.37 (1H, d, 4-H), 7.32 (1H, t.d, 6-H), 5.42 (1H, m, CH= , J_{CH_2} = 7 Hz), 4.94 and 4.82 (2H, m, CH_2=, J_{trans} = 17, J_{cis} = 10 Hz), 3.73 (1H, br.s, OH), 3.08 (2H, d.d, CH_2), 0.45 and 0.50 ppm (6H, s, $SiCH_3$). Found: M^+ 281. Calculated: M 281.

10,10-Dimethyl-9-(2,3-dibromopropyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (II, $C_{17}H_{19}Br_2NOSi$). To a solution of 2.5 g (8.8 mmole) of the silaazaanthrol (I) in 25 ml of chloroform was added a solution of 1.7 g (10 mmole) of bromine in 20 ml of chloroform. The mixture was stirred for 3 h at 20°C, and the residue after removal of the chloroform chromatographed on a column (30 × 2 cm), eluent ether, to give 3.8 g (6.9%) of the alcohol (II) as colorless crystals, mp 123-124°C, R_f 0.19 (ethyl acetate—heptane, 1:1). IR spectrum: 3210 cm^{-1} (bonded OH). PMR spectrum: 9.0 (1H, s, 1-H), 8.25 (1H, d, 3-H, J_{34} = 4.7 Hz), 3.97 (1H, m, CHBr), 3.56 (2H, m, CH_2Br), 2.47 (2H, m, CH_2), 0.46 and 0.51 ppm (6H, s, $SiCH_3$).

Z- and E-Isomers of 4'-Bromo-10,10-dimethylspiro[9,10-dihydro-10-sila-2-azaanthracene-9,2'-tetrahydrofuran] (IIIa, b, $C_{17}H_{18}BrNOSi$) and 10,10-Dimethyl-9-(3-bromoallyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (IV, $C_{17}H_{18}BrNOSi$). A. To a solution of 1 g (2.3 mmole) of the silaazaanthrol (II) in 30 ml of dry benzene was added under argon 1.42 ml (2.3 mmole) of a 1.6 mole/liter solution of butyllithium in hexane. The mixture was heated for 3 h at 45-50°C, filtered, and the residue (0.75 g) after removal of the benzene chromatographed on a column (40 × 1.7 cm). Elution with a mixture of ethyl acetate and heptane (1:20) gave first 0.33 g (40%) of the Z-isomer (IIIa) as colorless crystals, mp 102-103°C (from heptane-ethyl acetate), R_f 0.62 (ethyl acetate—heptane, 1:1), followed by 0.13 g of a mixture of (IIIa) and (IIIb), and 0.06 g (7%) of the E-isomer (IIIb), colorless crystals, mp 130-131°C (from heptane—ethyl acetate), R_f 0.54 (ethyl acetate—heptane, 1:1). Finally, elution with ethyl acetate—heptane (1:1) gave 0.16 g (19%) of mixed isomers of the alcohol (IV), mp 105-107°C (from heptane), R_f 0.35 (ethyl acetate—heptane, 1:1), IR spectrum: 3230 cm^{-1} (bonded OH). Found: M^+ 361. Calculated: M 361.

B. A solution of 0.8 g (1.8 mmole) of the silaazaanthrol (II) and 5 g (49.5 mmole) of triethylamine in 10 ml of dry benzene and 5 ml of dry acetone was boiled for 20 h. The residue after removal of the solvents and excess triethylamine was chromatographed on a column (55 × 1.3 cm), eluent heptane—ethyl acetate (1:10). There was obtained 0.14 g (21%) of the Z-isomer (IIIa), mp 104-105°C. A mixed melting point with the material obtained above gave no depression. Finally, elution with ethyl acetate—hexane (1:2) gave 0.5 g (62%) of the starting (II), mp 121-123°C. A mixed melting point with an authentic sample gave no depression.

10,10-Dimethyl-9-(3-cis-bromoallyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (IVa, $C_{17}H_{18}BrNOSi$). A mixture of 1 g (2.3 mmole) of the silaazaanthrol (II) and 0.98 g (25.1 mmole) of sodamide in 20 ml of dry benzene was boiled for 5 h. The mixture was decomposed with moist benzene, and the residue after removal of the solvent chromatographed on a column (50 × 1.5 cm), eluent light petroleum—ethyl acetate (10:1), to give 0.18 g (22%) of the cis-isomer (IVa) as colorless crystals, mp 163-164°C, R_f 0.33 (ethyl acetate—hexane, 1:1). IR spectrum: 3180 cm^{-1} (bound OH). PMR spectrum: 9.07 (1H, s, 1-H), 8.36 (1H, d, 3-H), 7.96 (1H, d, 8-H), 7.43-7.70 (m, 4H-7H), 5.78 (2H, m, CH=, CBrH=, $J_{CH=CH}$ = 7 Hz), 3.43 (1H, br. s, OH), 0.44 and 0.49 ppm (6H, s, $SiCH_3$).

10,10-Dimethyl-9-(3-trans-bromoallyl)-9,10-dihydro-10-sila-2-aza-9-anthrol (IVb, $C_{17}H_{18}BrNOSi$). To 2.14 g of a 26% solution of KOH in methanol (10 mmole) was added 4.01 g (12.6 mmole) of hexamethylcyclotrisilazane. After the mixture had heated up and solidified, it was heated for 2 h at 100-110°C. All operations were carried out with protection from atmospheric moisture. The resulting potassium bis(dimethylmethoxysilyl)amide was dissolved in 20 ml of dry tetrahydrofuran, and a solution of 1 g (2.3 mmole) of the silaazaanthrol (II) in 20 ml of dry tetrahydrofuran added. After 16 h, 6 ml of methanol was added, and the mixture heated for 2 h on the water bath. It was then poured into 100 ml of water, and acidified with 18% hydrochloric acid. Neutral products were extracted with ether. The residual salts of organic bases were neutralized with sodium carbonate solution, and extracted with ether. The ether extracts were dried over magnesium sulfate, and the residue (0.3 g) after removal of the ether chromatographed on a column (40 × 1.8 cm), eluent ethyl acetate—hexane (1:20) to give 0.1 g (13%) of the trans-isomer (IVb) as colorless crystals, mp 74-75°C (from heptane—ethyl acetate), R_f 0.38 (ethyl acetate—hexane, 1:1). IR spectrum: 3200 cm^{-1} (bonded OH). PMR spectrum: 8.80 (1H, s, 1-H), 8.48 (1H, d, 3-H), 7.80 (1H, d, 8-H), 7.30-7.65 (m, 4H-7-H), 6.02 (1H, d, CHBr, $J_{CH=CH}$ 13.5 Hz), 5.88 (1H, m, CH=), 2.95 (2H, d, CH_2, J_{CH_2CH} 6.5 Hz), 1.70 (1H, br. s, OH), 0.45 and 0.48 ppm (6H, s, $SiCH_3$). Found: M^+ 360. Calculated: M 360.

Z- and E-Isomers of 4'-Azido-10,10-dimethylspiro[9,10-dihydro-10-sila-2-azaanthracene-9,2'-tetrahydrofuran] (Va, b, $C_{17}H_{18}N_4OSi$). A solution of 1 g (2.78 mmole) of the mixed isomers of the spiro-compound (III) and 0.2 g (3.1 mmole) of sodium azide in 20 ml of DMF was heated at 130-135°C for 12 h. Water (30 ml) was then added, and the reaction products extracted with ether. The extracts were dried over magnesium sulfate, and the residue (1.65 g) after removal of the ether chromatographed on a column (45 × 2 cm) with silica gel L 100/250, eluent hexane—ethyl acetate (3:1). First eluted was 0.3 g (34%) of the Z-isomer (Va) as colorless crystals, mp 89-90°C (from heptane), R_f 0.52 (ethyl acetate—hexane, 1:1). Found: M^+ 322. Calculated, M 322. Next, 0.02 g of a mixture of (Va) and (Vb) was eluted, and finally 0.4 g (45%) of the E-isomer (Vb), colorless crystals, mp 94-95°C (from heptane—ethyl acetate), R_f 0.25 (ethyl acetate—hexane, 1:1). Found: M^+ 322. Calculated: M 322.

10,10-Dimethylspiro[9,10-dihydro-10-sila-2-azaanthracene-9,2'-(2',5'-dihydro)furan] (VI, $C_{17}H_{17}NOSi$). A mixture of 0.21 g (2.14 mmole) of N-methylpiperazine, 0.77 g (2.14 mmole) of the mixed isomers (III), and 0.15 g (11 mmole) of potassium carbonate in 20 ml of DMF was heated at 120-130°C for 10 h. The mixture was worked up as in the preceding preparation. Chromatography on a column (50 × 2.5 cm) of silica gel (eluent ethyl acetate—hexane, 1:3) afforded 0.4 g (67%) of the spiro-compound (VI), colorless crystals, mp 116-117°C (from hexane—ethyl acetate), R_f 0.3 (ethyl acetate—hexane, 1:1). Found: M^+ 279. Calculated: M 279.

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