On Triazoles XLVI [1]. Synthesis of 1,3a,5,6,10c-Pentaazaacephenanthrylenes

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Dedicated to Professor Gyula Schneider on the occasion of his 70th birthday

A novel route to the synthesis of 6,7,8,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazoline derivatives **4** through **5** and **6** was elaborated. During the synthesis of derivatives **6** novel type tetracyclic 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** were formed as by-products. Their structure was proved by spectroscopic methods and by X-ray diffraction spectra. There were also elaborated direct synthetic routes to derivatives **9**. Unexpectedly, the *S*-alkyl groups of derivatives **9** could be easily replaced by different amines, which is contrary to all our previous results. Possible explanations to this enhanced reactivity are given.

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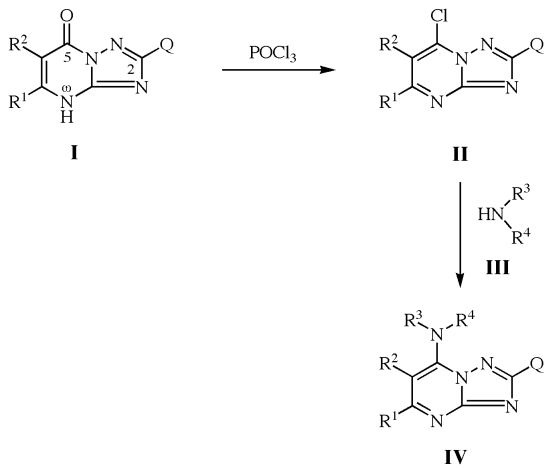
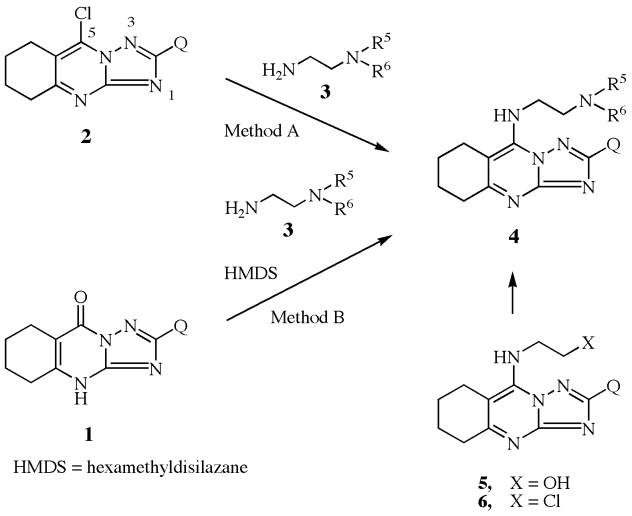
Recently, we have reported on the synthesis and some reactions of type **II** 5-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives prepared from the corresponding type **I** 1,2,4-triazolo[1,5-*a*]pyrimidin-5(ω*H*)-ones [2-3] (Scheme 1). Their reactive chloro atoms could be replaced with different amines (**III**, R^3 = alkyl, R^4 = H, and R^3 = R^4 = alkyl, respectively) leading to type **IV** 5-alkylamino- and 5-dialkylamino-1,2,4-triazolo[1,5-*a*]pyrimidines (R^3 = alkyl, R^4 = H, and R^3 = R^4 = alkyl, respectively) possessing valuable cardiovascular activity [4]. The most active type **IV** derivatives were the 1,2,4-triazolo[5,1-*b*]quinazolines (**4**) having in position 5 a (2-dialkylaminoethyl)amino moiety (Scheme 2) that were prepared from the corresponding 5-chloro-1,2,4-triazolo[5,1-*b*]quinazolines (**2**) and the corresponding 2-dialkylamino-ethylamines [**3**, R^3 = 2-(R^5,R^6)aminoethyl, R^4 = H] (Method A, Scheme 2, Table I). Derivatives **4** could also be prepared directly from the corresponding type **1** 1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-ones and the corresponding 2-dialkylamino-ethylamines [**3**, R^3 = 2-(R^5,R^6)aminoethyl, R^4 = H] using a silylation-amination method analogous to that elaborated by Vorbrüggen and Krolikiewicz [5] (Method B, Scheme 2, Table I).

Scheme 1



Scheme 2



However, as we needed derivatives **4** for biological screening with very different 2-dialkylaminoethyl moieties and only a few of type **3** amines were commercially available, other methods for the synthesis of derivatives **4** were required based on common intermediates. Such intermediates could be the 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**6**, Scheme 2), obtainable from the corresponding 5-(2-hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazolines (**5**, Scheme 2).

A possible synthetic route to the 5-(2-hydroxyethyl)-amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**5**, Q = alkylthio or dialkylamino) is the reaction of the corresponding type **2** 5-chloro-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (Q = alkylthio or dialkylamino) with (2-hydroxyethyl)amine (**7**) (Method C,

Table I

Synthetical Data of 5-(2-Dialkylaminoethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives **4**

Compound	Q	NR^5R^6	Method	Reaction Time (hours) / Temperature (°C)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula (MW) [ms]	Analysis Calcd / Found C	H	N	S	lit. [4] mp (°C)
4/1	Methylthio	Pyrrolidin-1-yl	A	0.5	85	130-132 (EtOAc)	$C_{16}H_{24}N_6S$ 332.47	57.80 / 57.75	7.28 / 7.33	25.28 / 25.19	9.64 / 9.68	130-132
4/2	Methylthio	Piperidin-1-yl	A	1	91	140-141 (2-PrOH)	$C_{17}H_{26}N_6S$ 346.50	58.93 / 59.02	7.56 / 7.66	24.25 / 24.20	9.25 / 9.31	140-141
4/3	Methylthio	Morpholin-4-yl	A B	1 6 / 170	84 92	164-165 (2-PrOH)	$C_{16}H_{24}N_6OS$ 348.47	55.15 / 55.09	6.94 / 7.01	24.12 / 24.07	9.20 / 9.23	164-165
4/4	Ethylthio	Piperidin-1-yl	A	2	81	130.5-132.5 (CH_3CN)	$C_{18}H_{28}N_6S$ 360.53	59.97 / 59.88	7.83 / 7.89	23.31 / 23.27	8.89 / 8.80	
4/5	Ethylthio	Morpholin-4-yl	A	0.5	87	156-158 (CH_3CN)	$C_{17}H_{26}N_6OS$ 362.50	56.33 / 56.40	7.23 / 7.31	23.18 / 23.09	8.85 / 8.81	156-158
4/6	1-Methylethylthio	Dimethylamino	A	0.5	91	130-132 (CH_3CN)	$C_{16}H_{26}N_6S$ 334.49	57.45 / 57.40	7.83 / 7.88	25.12 / 25.24	9.59 / 9.51	
4/7	1-Methylethylthio	*N*-Benzylmethyl-amino	H	0.2 / 150	67 [a]	127-129 (CH_3CN)	$C_{22}H_{30}N_6S$ 410.59 EI: M^+= 410	64.36 / 64.28	7.36 / 7.42	20.47 / 20.51	7.81 / 7.77	
4/8	1-Methylethylthio	Diallylamino	H	1.5 reflux (bp ~110°)	47 [a]	82-84 (*n*-Hexane)	$C_{20}H_{30}N_6S$ 386.57 EI: M^+= 386	62.14 / 62.08	7.82 / 7.89	21.74 / 21.70	8.29 / 8.33	
4/9	1-Methylethylthio	Piperidin-1-yl	B	12 / 160	85	167.5-168.5 (EtOAc)	$C_{19}H_{30}N_6S$ 374.56	60.93 / 60.90	8.07 / 8.05	22.44 / 22.47	8.56 / 8.53	
4/10	1-Methylethylthio	4-Hydroxy-piperidin-1-yl	H	0.2 / 150	71	152-153 (CH_3CN)	$C_{19}H_{30}N_6OS$ 390.55 EI: M^+= 390	58.43 / 58.37	7.74 / 7.70	21.52 / 21.48	8.21 / 8.16	
4/11	1-Methylethylthio	4-Methyl-piperidin-1-yl	H	0.2 / 150	71	135-137 (CH_3CN)	$C_{20}H_{32}N_6S$ 388.58 EI: M^+= 388	61.82 / 61.93	8.30 / 8.44	21.63 / 21.60	8.25 / 8.21	
4/12	1-Methylethylthio	Hexamethyl-eneimin-1-yl	H	0.2 / 150	86	151-153 (CH_3CN)	$C_{20}H_{32}N_6S$ 388.58 EI: M^+= 388	61.82 / 61.77	8.30 / 8.32	21.63 / 21.67	8.25 / 8.18	
4/13	1-Methylethylthio	Morpholin-4-yl	A H	1.5 0.2 / 150	95 83	190-191 (CH_3CN)	$C_{18}H_{28}N_6OS$ 376.53 EI: M^+= 376	57.42 57.44	7.50 7.57	22.32 22.28	8.52 8.49	190-191
4/14	1-Methylethylthio	Thiomorpholin-4-yl	H	16 CH_3CN (Reflux)	51 [a]	194-195 (CH_3CN)	$C_{18}H_{28}N_6S_2$ 392.59	55.07 / 54.99	7.19 / 7.25	21.41 / 21.44	16.33 / 16.29	
4/15	1-Methylethylthio	4-Methylpiperazin-1-yl	H	0.25 / 160	60	147-149 (2-Pr_2O/EtOAc)	$C_{19}H_{31}N_7S$ 389.57	58.58 / 58.51	8.02 / 7.93	25.17 / 25.11	8.23 / 8.27	
4/16	1-Methylethylthio	4-Benzyl-piperazin-1-yl	H	0.2 / 150	84	162-163 (CH_3CN)	$C_{25}H_{35}N_7S$ 465.67 EI: M^+= 465	64.48 / 64.32	7.58 / 7.66	21.06 / 20.97	6.89 / 6.99	
4/17	1-Methylethylthio	4-(2-Hydroxyethyl)-piperazin-1-yl	H	0.5 / 140	81	122-123.5 (EtOAc)	$C_{20}H_{33}N_7OS$ 419.60	57.25 / 57.29	7.93 / 8.11	23.37 / 23.31	7.64 / 7.58	
4/18	1-Methylethylthio	4-(3-Chlorophenyl) piperazin-1-yl	H	0.2 / 150	68 [a]	166-168 (CH_3CN)	$C_{24}H_{32}ClN_7S$ 486.09 EI: M^+= 485	59.30 / 59.37	6.64 / 6.83	20.17 / 20.08	6.60 / 6.67	
4/19	1-Methylethylthio	4-(2-Pyridyl) piperazin-1-yl	H	0.2 / 150	84	166.5-168 (CH_3CN)	$C_{23}H_{32}N_8S$ 452.63 EI: M^+= 452	61.03 / 60.89	7.13 / 7.30	24.76 / 24.78	7.08 / 7.03	
4/20	1-Methylethylthio	4-(2-Pyrimidyl) piperazin-1-yl	H	0.2 / 150	79	176-177 (CH_3CN)	$C_{22}H_{31}N_9S$ 453.62 EI: M^+= 453	58.25 / 58.33	6.89 / 7.02	27.79 / 27.71	7.07 / 7.01	
4/21	2-Methylpropylthio	Morpholin-4-yl	B	14 / 160	84	159-160 (2-Pr_2O/ EtOAc)	$C_{19}H_{30}N_6OS$ 390.55	58.43 / 58.49	7.74 / 7.89	21.52 / 21.46	8.21 / 8.18	
4/22	*n*-Hexylthio	Morpholin-4-yl	A	1.5	69	107-108 (EtOAc)	$C_{21}H_{34}N_6OS$ 418.61	60.26 / 60.20	8.19 / 8.31	20.08 / 20.03	7.66 / 7.68	107-108
4/23	Allylthio	Morpholin-4-yl	A	1	87	129-130 (EtOAc)	$C_{18}H_{26}N_6OS$ 374.51	57.73 / 57.68	7.00 / 7.11	22.44 / 22.37	8.56 / 8.50	129.5-130.5

Table I (continued)

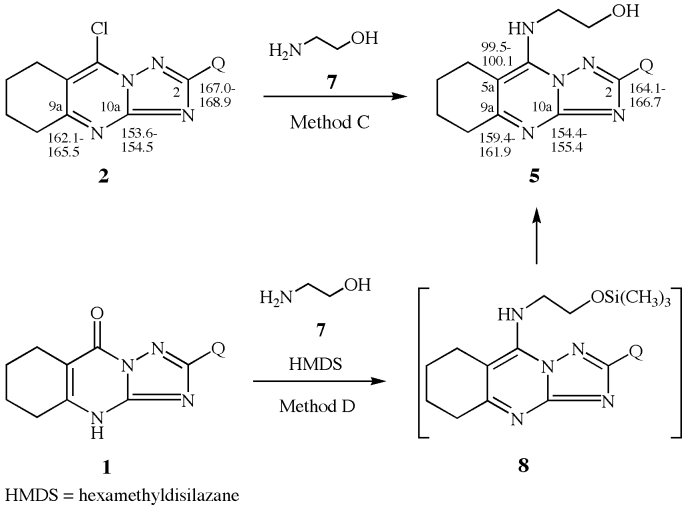
Compound	Q	NR^5R^6	Method	Reaction Time (hours) / Temperature (°C)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula (MW) [ms]	Analysis Calcd / Found C	H	N	S	lit. [4] mp (°C)
4/24	Benzylthio	Morpholin-4-yl	A	1.5	89	139.5-141 (CH_3CN)	$C_{22}H_{28}N_6OS$ 424.57	62.24	6.65	19.79	7.55	139-140
								62.20	6.71	19.83	7.51	
4/25	4-Chlorobenzylthio	Morpholin-4-yl	A	4	76	136-137.5 (CH_3CN)	$C_{22}H_{27}ClN_6OS$ 459.02	57.57	5.93	18.31	6.99	136-137.5
								57.54	5.94	18.27	7.03	
4/26	4-Nitrobenzylthio	Morpholin-4-yl	A	1	82	165-167 (CH_3CN)	$C_{22}H_{27}N_7O_3S$ 469.57	56.27	5.80	20.88	6.83	165-167
								56.31	5.88	20.93	6.80	
4/27	3-Dimethylamino-1-propylamino	Morpholin-4-yl	B	5 / 150	74	174-176 (CH_3CN)	$C_{20}H_{34}N_8O$ 402.55 EI: M^+= 402	59.68	8.51	27.84		
								59.61	8.60	27.78		
4/28	Benzylamino	Morpholin-4-yl	A	1	91	192-194 (MeOH)	$C_{22}H_{29}N_7O$ 407.52	64.84	7.17	24.06		192-194
								64.89	7.31	24.01		
4/29	Dimethylamino	Morpholin-4-yl	A	0.5	88	192-194 (CH_3CN)	$C_{17}H_{27}N_7O$ 345.45 EI: M^+= 345	59.11	7.88	28.38		
								59.17	7.93	28.44		

[a] After dry column flash chromatography on Kieselgel 60 H.

Scheme 3), which proceeded well for all Q substituents used (Table II, for their spectral data see Table IIa).

However, derivatives **5** (Q = alkylthio or dialkylamino) could also be prepared directly from the corresponding 2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-ones (**1**, Q = alkylthio or dialkylamino) and (2-hydroxyethyl)amine (**7**) (Method D, Scheme 3, Table II) by silylation-amination [5] analogously to the case of derivatives **4**. The possible intermediates of these reactions, the corresponding *O*-trimethylsilyl ethers **8**, were not isolated.

Scheme 3



The 5-(2-hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline derivatives (**5**, Q = alkylthio or dialkylamino) were then converted with thionyl chloride to the corresponding 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**6**) (Method E, Scheme 4, Tables II and IIa). The by-products of these reactions were the ring closed novel type tetracyclic 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** (Q = alkylthio or dialkylamino) (Table III).

The structure of derivatives **5** and **6** can easily be deduced by analogy of their pmr and cmr spectra with those of the 5-chloro-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline derivatives **2** (Schemes 3 and 4) reported previously [2-3]. On the other hand the structure of the novel type 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9,** which is consistent with all spectra recorded (Scheme 4, Tables III and IIIa), could be deduced by analogy of their triazole carbon atoms 4 and 5a with those of the corresponding carbon atoms 2 and 10a, respectively, of the 3-substituted-2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazolin-5(3*H*)-ones (**10**) (Scheme 4), reported

Scheme 4

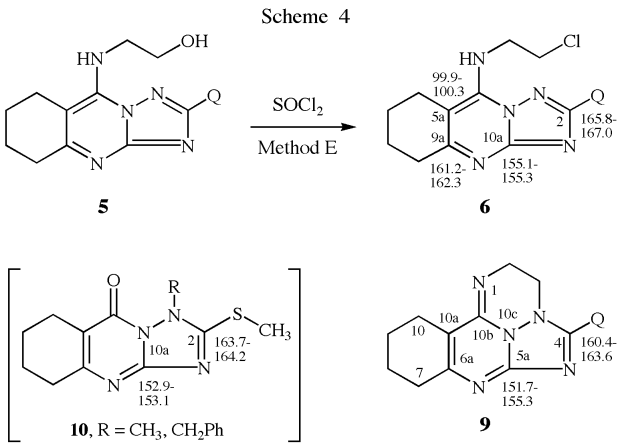


Table Ia

Pmr and cmr Spectroscopical Data of 5-(2-Dialkylaminoethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives **4**

	pmr (deuteriochloroform): δ, ppm							cmr (deuteriochloroform): δ, ppm									
Compound	NH (t)	CH_2-1' CH_2-2'	NR^5R^6	CH_2-6	CH_2-9	CH_2-7, CH_2-8	Q	C-1' C-2'	NR^5R^6	C-2	C-5	C-5a	C-6	C-7 C-8	C-9	C-9a	C-10a	Q
4/1	6.39	4.12 q 2.80 t	2.58 m (4H) 1.84 m (4H)	2.58 m	2.84 t	1.84 m (4H)	2.65 s (3H)	43.3 54.5	53.5 23.6	166.4	145.7	99.6	23.2	22.1 22.5	33.4	162.3	155.4	13.9
4/2	6.55	4.05 q 2.61 m	2.44 m (4H) 1.60 m (4H) 1.5 m (2H)	2.60 m	2.85 t	1.85 m (4H)	2.66 s (3H)	41.2 56.7	53.7 26.1 24.1	166.0	145.6	99.4	23.0	22.0 22.4	33.3	161.9	155.3	13.5
4/3	6.35	4.07 q 2.68 t	2.53 m (4H) 3.75 m (4H)	2.63 t	2.87 t	1.85 m (4H)	2.67 s (3H)	40.5 56.6	52.5 66.6	165.6	145.2	99.2	22.8	21.6 22.0	33.0	161.7	154.8	13.3
4/4	6.50	4.05 q 2.60 m	2.44 m (4H) 1.60 m (4H) 1.5 m (2H)	2.60 m	2.85 t	1.85 m (4H)	3.24 q (2H) 1.45 t (3H) (J = 7.2Hz)	41.2 56.8	53.7 26.1 24.2	165.6	145.7	99.4	23.0	22.1 22.4	33.3	162.0	155.3	25.5 15.2
4/5	6.36	4.07 q 2.68 t	2.53 m (4H) 3.74 m (4H)	2.60 t	2.85 t	1.85 m (4H)	3.24 q (2H) 1.45 t (3H)	41.0 57.1	53.0 66.9	165.6	145.6	99.6	23.0	22.0 22.4	33.4	162.2	155.2	25.2 15.1
4/6	6.27	4.06 q 2.6 m	2.29 s (6H)	2.60 m	2.85 t	1.85 m (4H)	4.00 m (1H) 1.46 d (6H)	42.0 57.9	44.8 (Me)	165.7	145.7	99.5	23.0	22.0 22.4	33.3	162.2	155.4	36.6 23.5
4/7	6.37	4.04 q 2.68 t	2.27 s (3H) 3.57 s (2H) 7.3 m (5H)	2.59 t	2.86 t	1.85 m (4H)	4.02 m (1H) 1.47 d (6H)	41.9 55.4	41.3 (Me) 62.2 (CH_2) 138.3 (Ph-*s*) 128.9, 128.3, 127.2 (*p*)	165.6	145.5	99.3	23.4	22.1 22.5	33.4	162.2	155.1	36.7 23.6
4/8	6.31	4.06 q 2.74 t	3.15 m (4H) 5.83 m (2H) 5.2 m (4H)	2.60 t	2.87 t	1.85 m (4H)	4.00 m (1H) 1.46 d (6H)	41.9 51.7	56.3 134.9 (CH) 118.1 (CH_2=)	165.6	145.6	99.4	23.3	22.1 22.6	33.4	162.2	155.3	36.7 23.6
4/9	6.52	4.07 q 2.58 m	2.44 m (4H) 1.60 m (4H) 1.5 m (2H)	2.60 m	2.85 t	1.85 m (4H)	4.03 m (1H) 1.47 d (6H)	41.1 56.7	53.6 26.0 24.1	165.3	145.6	99.3	22.9	21.9 22.4	33.2	161.9	155.1	36.4 23.4
4/10	6.40	4.08 q 2.65 t	2.80 m (2H) 2.25 m (2H) 1.93 m (2H) 1.62 m (2H) 3.8 m (1H, CH) 2.4 s (1H, OH)	2.59 t	2.86 t	1.85 m (4H)	3.99 m (1H) 1.46 d (6H)	41.5 56.2	50.5 34.6 67.4 (CH)	165.6	145.7	99.6	23.1	22.1 22.5	33.3	162.2	155.3	36.7 23.6
4/11	6.48	4.06 q 2.62 t	2.85 m (2H) 2.06 m (2H) 1.65 m (2H) 1.20 m (2H) 1.4 m (1H,CH) 0.95 d (3H)	2.60 t	2.86t	1.85 m (4H)	4.01 m (1H) 1.47 d (6H)	41.4 56.5	53.2 34.5 30.7 (CH) 21.8 (Me)	165.6	145.8	99.5	23.1	22.2 22.6	33.4	162.1	155.3	36.6 23.6
4/12	6.60	4.03 q 2.77 t	2.67 t (4H) 1.65 m (8H)	2.62 t	2.86 t	1.85 m (4H)	4.01 m (1H) 1.46 d (6H)	42.1 56.6	54.9 28.8 26.8	165.6	145.7	99.3	23.2	22.1 22.6	33.4	162.1	155.3	36.6 23.6
4/13	6.36	4.07 q 2.68 t	2.52 m (4H) 3.72 m (4H)	2.61 t	2.84 t	1.85 m (4H)	3.98 m (1H) 1.47 d (6H)	40.7 56.8	52.8 66.8	165.4	145.4	99.4	23.1	21.9 22.3	33.3	162.1	155.0	36.4 23.4
4/14	6.29	4.05 q 2.7 m	2.7 m (4H) 2.78 m (4H)	2.60 t	2.86 t	1.88 m (4H)	4.00 m (1H) 1.47 d (6H) (J = 6.8 Hz)	40.8 57.0	54.3 28.0	165.5	145.4	99.4	23.2	21.9 22.4	33.3	162.2	155.0	36.5 23.4

Table Ia (continued)

	pmr (deuteriochloroform): δ, ppm							cmr (deuteriochloroform): δ, ppm									
Compound	NH (t)	CH_2-1' CH_2-2'	NR^5R^6	CH_2-6	CH_2-9	CH_2-7, CH_2-8	Q	C-1' C-2'	NR^5R^6	C-2	C-5	C-5a	C-6	C-7 C-8	C-9	C-9a	C-10a	Q
4/15	6.38	4.05 q 2.68 t	2.58 m (8H) 2.31 s (3H)	2.58 m	2.86 t	1.88 m (4H)	4.01 m (1H) 1.47 d (6H) (J = 6.8Hz)	41.2 56.4	55.2 52.3 45.9 (Me)	165.8	145.7	99.7	23.4	22.2 22.6	33.5	162.4	155.3	36.7 23.6
4/16	6.37	4.05 q 2.66 t	2.5 bs (8H) 3.52 s (2H) 7.3 m (5H)	2.57 t	2.86 t	1.85 m (4H)	4.01 m (1H) 1.47 d (6H)	41.1 56.2	52.4, 53.2 62.9 ($PhCH_2$) 137.9 (Ph-*s*) 129.0, 128.1 127.0 (*p*)	165.6	145.6	99.5	23.2	22.1 22.5	33.4	162.2	155.2	36.6 23.6
4/17	6.33	4.05 q 2.68 t	2.56 m (8+2H) 3.65 t (2H) 2.95 bs (OH)	2.56 m	2.86 t	1.82 m (4H)	4.00 m (1H) 1.47 d (6H) (J = 6.8Hz)	41.1 56.4	52.9, 52.3 57.7 (NCH_2) 59.2 (OCH_2)	165.7	145.7	99.6	23.6	22.1 22.5	33.4	162.3	155.2	36.6 23.6
4/18	6.32	4.12 q 2.73 t	2.67 t (4H) 3.22 t (4H) 6.88 t (1H, J = 2.1 Hz) 7.17 t (1H, J = 8.1 Hz) 6.8 m (2H)	2.59 t	2.86 t	1.85 m (4H)	3.99 m (1H) 1.44 d (6H)	41.1 56.3	52.2, 48.8 152.4 (C-1') 115.7 (C-2') 134.8 (C-3') 119.4 (C-4') 130.0 (C-5') 113.9 (C-6')	165.7	145.6	99.6	23.2	22.1 22.5	33.4	162.3	155.2	36.6 23.6
4/19	6.37	4.13 q 2.73 t	2.64 t (4H) 3.57 t (4H) 8.2 m (1H, CH-3') 7.49 m (1H, CH-5') 6.65 m (2H, CH-4',6')	2.60 t	2.86 t	1.85 m (4H)	3.99 m (1H) 1.44 d (6H)	41.1 56.4	52.2, 45.3 159.3 (C-1') 147.8 (C-3') 113.4 (C-4') 137.4 (C-5') 107.0 (C-6')	165.6	145.6	99.5	23.1	22.0 22.4	33.4	162.2	155.2	36.6 23.5
4/20	6.39	4.13 q 2.73 t	2.59 t (4H) 3.86 t (4H) 8.32 d (2H, J = 4.7 Hz) 6.51 t (1H, J = 4.7 Hz)	2.62 t	2.87 t	1.85 m (4H)	4.00 m (1H) 1.46 d (6H)	41.1 56.5	52.3, 43.7 161.5 (C-1') 157.6 (C-3',5') 110.0 (C-4')	165.7	145.6	99.5	23.2	22.0 22.4	33.4	162.2	155.2	36.6 23.5
4/21	6.34	4.07 q 2.68 t	2.53 m (4H) 3.74 m (4H)	2.62 t	2.85 t	1.8 m (4H)	3.15 d (SCH_2) 2.04 m (1H) 1.05 d (6H)	40.8 56.9	52.9 67.0	166.3	145.5	99.5	23.2	22.0 22.5	33.3	162.2	155.1	39.7 28.7 (CH) 21.7 (Me)
4/22	6.34	4.10 q 2.68 t	2.53 m (4H) 3.74 m (4H)	2.60 t	2.86 t	1.88 m (4H)	3.21 t (SCH_2) 1.80 m (2H) 1.48 m (2H) 1.29 m (4H) 0.88 t (3H)	40.8 57.0	52.8 66.8	165.7	145.4	99.5	23.0	21.9 22.3	33.2	162.0	155.0	31.1 31.1 29.6 28.2 22.2 13.7
4/23	6.40	4.10 q 2.69 t	2.53 m (4H) 3.73 m (4H)	2.60 t	2.83 t	1.84 m (4H)	3.87 d (SCH_2) 5.2 m (2H) 6.05 m (1H)	40.7 56.8	52.8 66.9	164.9	145.5	99.6	23.1	21.9 22.3	33.3	162.2	155.0	33.8 (SCH_2) 117.5 (CH_2=) 133.7 (CH)
4/24	6.36	4.03 q 2.64 t	2.48 m (4H) 3.68 m (4H)	2.57 t	2.80 t	1.8 m (4H)	4.47 s (SCH_2) 7.25 m (3H) 7.40 m (2H)	40.8 56.9	52.8 66.8	165.1	145.5	99.6	23.0	21.9 22.3	33.3	162.1	155.0	35.2 (SCH_2) 137.6 (Ph-s) 126.9 (*p*) 128.1 128.6

Table Ia (continued)

Compound	pmr (deuteriochloroform): δ, ppm						cmr (deuteriochloroform): δ, ppm								
	NH (t)	CH_2-1' CH_2-2'	NR^5R^6	CH_2-6	CH_2-9	CH_2-7, CH_2-8	Q	C-1' C-2'	NR^5R^6	C-2	C-5	C-5a	C-6	C-7 C-8	C-9	C-9a	C-10a	Q
4/25	6.33	4.03 q 2.64 t	2.49 m (4H) 3.69 m (4H)	2.56 t	2.83 t	1.83 m (4H)	4.42 s (SCH_2) 7.21dd (2H) 7.39 dd (2H)	40.8 56.9	52.8 66.8	164.8	145.6	99.7	23.1	21.9 22.3	33.3	162.3	155.0	34.5 (SCH_2) 136.6 (Ph-*s*) 128.2 130.1 132.6 (C-Cl)
4/26	6.36	4.06 q 2.66 t	2.51 m (4H) 3.71 m (4H)	2.59 t	2.86 t	1.86 m (4H)	4.54 s (SCH_2) 7.65 dd (2H) 8.08 dd (2H)	40.9 56.9	52.9 66.8	164.2	145.6	100.0	23.1	21.9 22.3	33.3	162.5	155.0	34.4 (SCH_2) 146.9 (Ph-*s*) 123.2 129.6 146.1 (Ph-*s*)
4/27	6.25	3.98 q 2.66 t	2.52 m (4H) 3.74 m (4H)	2.64 m	2.82 t	1.82 m (4H)	5.14 t (NH) 3.44 q (2H) 1.82 m (2H) 2.39 t (2H) 2.23 s (6H)	41.7 57.7	52.9 66.8	166.0	145.2	99.0	23.3	22.1 22.5	33.1	160.5	154.6	40.7 ($NHCH_2$) 27.3 ($\mathbf{C}CH_2C$) 57.2 (NCH_2) 45.2 (Me)
4/28	6.19	3.97 q 2.62 t	2.48 m (4H) 3.68 m (4H)	2.62 t	2.85 t	1.8 m (4H)	4.90 t (NH) 4.60 d (2H) 7.3 m (5H)	40.8 57.3	53.0 67.1	165.9	145.6	99.5	23.7	22.4 22.8	33.4	161.2	154.9	47.1 (NCH_2) 139.7 (Ph-*s*) 128.5, 127.5, 127.2
4/29	6.30	3.97 q 2.67 t	2.52 m (4H) 3.75 m (4H)	2.65 m	2.82 m	1.82 m (4H)	3.10 s (6H)	40.6 56.9	52.8 67.0	167.3	145.1	99.1	23.6	22.2 22.7	33.2	160.6	154.9	37.6

recently [6]. The structure of the novel type 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** was corroborated by X-ray diffraction spectra of two differently substituted derivatives **9/3** (Q = 1-methylethylthio) and **9/5** (Q = morpholin-4-yl), as well. Their perspective views are shown on Schemes 5 and 6.

Scheme 5

Some selected bond lenghts (Å) and perspective view of **9/3** (Q = 1-methylethylthio). Atomic displacement ellipsoids are drawn at the 50 % probability level.

Scheme 6

Some selected bond lenghts (Å) and perspective view of **9/5** (Q = morpholin-4-yl). Atomic displacement ellipsoids are drawn at the 50 % probability level.

Table II

Synthetical Data of 5-(2-Hydroxyethyl)amino- and 5-(2-Chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**5** and **6**)

Compound	Q	Method	Reaction Time/ Temperature (Hours/ °C)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula (MW) (ms)	Analysis Calcd / Found C	H	N	S	Cl	UV(EtOH) $\lambda_{max}(\varepsilon.10^{-3})$	By-product **9** (%) [a]
5/1 (X = OH)	Methylthio	C	5	97	216-218 (CH_3CN/ EtOH)	$C_{12}H_{17}N_5OS$ 279.37	51.59 / 51.48	6.13 / 6.22	25.07 / 24.99	11.48 / 11.54			
5/2 (X = OH)	Ethylthio	C	2	94	208-211 (CH_3CN/ EtOH)	$C_{13}H_{19}N_5OS$ 293.39	53.22 / 53.26	6.53 / 6.66	23.87 / 23.80	10.93 / 10.88			
5/3 (X = OH)	1-Methyl-ethylthio	C D	2 12 / 155	97 87	204-206 (CH_3CN/ EtOH)	$C_{14}H_{21}N_5OS$ 307.42 EI: M^+= 307	54.70 / 54.67	6.89 / 6.98	22.78 / 22.69	10.43 / 10.47		220 (17.3) 246.5 (34.6) 307 (13.6)	
5/4 (X = OH)	Dimethyl-amino	C	8	99	185-187 (CH_3CN/ EtOH)	$C_{13}H_{20}N_6O$ 276.34	56.50 / 56.55	7.30 / 7.44	30.41 / 30.38				
5/5 (X = OH)	Morpholin-4-yl	C	1	94	235-238 (CH_3CN/ 2-PrOH)	$C_{15}H_{22}N_6O_2$ 318.38	56.59 / 56.64	6.97 / 7.11	26.40 / 26.37				
6/3 (X = Cl)	1-Methyl-ethylthio	E	18	77	146-151 (dec) [b]	$C_{14}H_{20}ClN_5S$ 325.87 EI: M^+= 325	51.60 / 51.66	6.19 / 6.33	21.49 / 21.55	9.84 / 9.85	10.88 / 10.94	218 (18.4) 246.5 (36.0) 307 (13.6)	9
6/5 (X = Cl)	Morpholin-4-yl	E	24	36	170 (dec) [b]	$C_{15}H_{21}ClN_6O$ 336.83	53.49 / 53.55	6.28 / 6.45	24.95 / 25.03		10.53 / 10.48		19

[a] For their synthetical and spectral data see Tables III and IIIa; [b] Triturated with ether after dry column flash chromatography on Kieselgel 60 H.

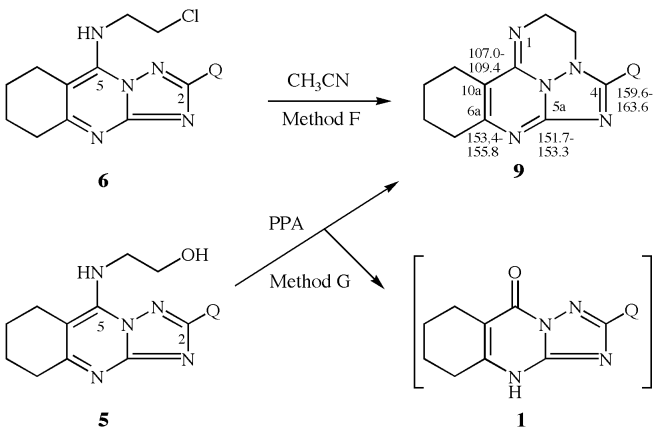
Because the formation of the novel type 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** (Q = alkylthio or dialkylamino) formed during the synthesis of the 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**6**) (Scheme 4) was believed to occur by ring closure of the 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazolines (**6**) once formed, an attempt was made to ring close the 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**6**) (Scheme 7). Carrying out these reactions in boiling acetonitrile (Method F) the 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** (Q = alkylthio or dialkylamino) were obtained with good yield (Table III).

The 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** (Q = alkylthio or dialkylamino) could also be prepared from the corresponding 5-(2-hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazolines (**5**, Q = alkylthio or dialkylamino) by their thermal ring closure performed in polyphosphoric acid (Scheme 7, Method G, Table III). The by-product of these reactions was the corresponding 2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**1**, Q = alkylthio or dialkylamino) formed most probably by the hydrolysis of the starting material **5**.

The 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**6**) reacted easily with secondary amines (**11**, R^5 and R^6 = alkyl) resulting in the required derivatives **4** with good yield (Scheme 8, Method H, Tables I and Ia).

A quite unexpected result was obtained when the 5-(2-chloroethyl)amino-2-(1-methylethylthio)-6,7,8,9-tetra-

Scheme 7



Scheme 8

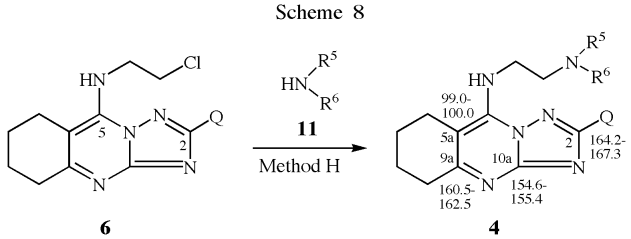


Table IIa

Pmr and cmr Spectral Data of 5-(2-Hydroxyethyl)amino- and 5-(2-Chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**5** and **6**)

		pmr: δ, ppm								cmr : δ, ppm									
Compound	nmr Solvent pmr / cmr	NH	NCH_2	XCH_2	OH	CH_2-6	CH_2-7,8 (4H)	CH_2-9	Q	NCH_2 XCH_2	C-2	C-5	C-5a	C-6	C-7 C-8	C-9	C-9a	C-10a	Q
5/1	a+b /	6.61 t	4.12 q	3.74 t	4.6 bs	2.64 m	1.85 m	2.80 m	2.62 s (3H)	46.6	165.1	146.3	100.1	22.9	22.1	33.1	160.9	155.4	13.3
(X = OH)	b		(5.6Hz)	(5.2Hz)						61.6					21.9				
5/2	b	7.10 t	4.02 q	3.58 q	4.80 t	2.54 m	1.78 m	2.71 m	3.15 q (2H)	46.6	164.4	146.3	100.1	22.9	22.1	33.1	160.9	155.3	25.0
(X = OH)			(6Hz)	(5.4Hz)	(5.4Hz)				1.37 t (3H)	61.6					21.9				15.3
5/3	a+b /	6.49 t	4.11 q	3.75 q	4.76 t	2.64 m	1.85 m	2.81 m	3.93 m (1H)	46.6	164.1	146.3	100.1	22.9	22.1	33.1	160.9	155.2	36.3
(X = OH)	b		(5.6Hz)	(5.2Hz)					1.45 d (6H)	61.6					21.9				23.4
5/4	a	5.83 t	4.10 m	3.92 t	4.6 bs	2.55 m	1.76 m	2.75 m	3.06 s (6H)	46.8	166.7	145.5	99.7	23.4	22.4	32.7	159.7	154.4	37.6
(X = OH)		(6.4Hz)		(5.2Hz)						61.8					21.9				
5/5	b	6.80 t	3.97 q	3.57 q	4.81 t	2.5 m	1.74 m	2.65 m	3.41 m (NCH_2)	46.3	166.3	145.9	99.5	22.9	22.2	33.0	159.4	154.9	45.8
(X = OH)			(6Hz)	(5.5Hz)	(5.3Hz)				3.69 m (OCH_2)	61.7					22.0				65.8
6/3	a	5.97 t	4.40 q	3.80 t	-	2.62 m	1.85 m	2.88 m	3.98 m (1H)	45.9	165.8	145.1	100.3	23.0	22.3	33.3	162.3	155.3	36.5
(X = Cl)			(6Hz)						1.47 d (6H)	44.7					22.0				23.3
6/5	a	5.58 t	4.33 q	3.8 m	-	2.58 m	1.85 m	2.84 m	3.58 m (NCH_2)	45.9	167.0	144.8	99.9	23.0	22.3	33.1	161.2	155.1	45.8
(X = Cl)			(6Hz)						3.8 m (OCH_2)	45.0					22.0				66.4

a: deuteriochloroform, b: DMSO-d_6

Table III

Synthetical and UV Spectroscopic Data of 4-Q-2,3,7,8,9,10-Hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9**

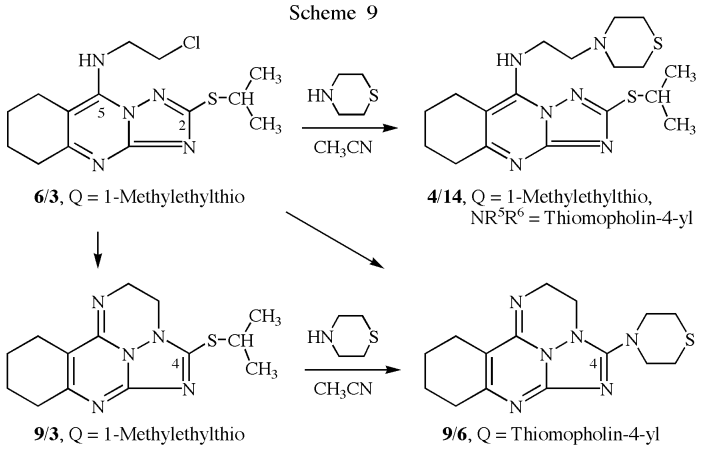
Compound	Q	Method	Reaction Time (hours) / Temperature (°C)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula (MW)	Ms (EI) (M^+)	Analysis Calcd / Found C	H	N	S	UV(EtOH) λ_{max}(ε .10^{-3})	By-product **1** (%)
9/1	Methylthio	G	28 / 140	76	209-211	$C_{12}H_{15}N_5S$		55.15	5.79	26.80	12.27	248 (19.0)	10
					(CH_3CN)	261.35	261	55.20	5.88	26.64	12.18	290 (11.2)	
9/2	Ethylthio	G	9 / 130	88	159-162	$C_{13}H_{17}N_5S$		56.70	6.22	25.43	11.64	250 (18.1)	9
					(CH_3CN)	275.38	275	56.61	6.35	25.40	11.58	291 (10.7)	
9/3	1-Methylethylthio	G	6 / 140	82	153-158	$C_{14}H_{19}N_5S$		58.10	6.62	24.20	11.08	250 (20.4)	[a]
		F	18	84	(ether)	289.41	289	58.02	6.66	24.11	11.02	291 (11.9)	
		E	18 / 25	9 [b]									
9/4	Dimethylamino	G	6 / 130	79	206-209	$C_{13}H_{18}N_6$		60.44	7.02	32.53		246 (23.0)	[a]
					(CH_3CN)	258.33	258	60.52	7.14	32.50		265 (19.5)	
												308 (6.8)	
9/5	Morpholin-4-yl	F	48	75	216-226	$C_{15}H_{20}N_6O$		59.98	6.71	27.98		248 (21.6)	
		E	24 / 25	19 [c]	dec	300.37	300	60.05	6.77	27.89		265 (17.8)	
		G	12 / 140	63	(CH_3CN)							308.5 (6.1)	[a]
		J	4.5 / 110	92									
9/6	Thiomorpholin-	[d]	16	31 [d]	238-244	$C_{15}H_{20}N_6S$		56.94	6.37	26.56	10.13	251 (22.3)	
	4-yl	J	12 [e]	73	dec	316.43	316	56.88	6.45	26.58	10.08	266 (20.2)	
					(THF)							308.5 (6.5)	

Table III (continued)

Compound	Q	Method	Reaction Time (hours) / Temperature (°C)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula (MW)	Ms (EI) (M^+)	Analysis Calcd / Found C	H	N	S	UV(EtOH) $\lambda_{max}(\varepsilon .10^{-3})$	By-product **1** (%)
9/7	2-Hydroxy-ethylamino	J	2 / 100 [f,g] 32 [e]	84 69	228-232 (EtOH)	$C_{13}H_{18}N_6O$ 274.33	274	56.92 56.88	6.61 6.73	30.63 30.79		237 (25.8) 261.5 (16.1) 271.5 sh (10.6) 304.5 (8.1)	
9/8	2-Dimethylamino ethylamino	J	2 / 100 [f]	97	217-222 (CH_3CN)	$C_{15}H_{23}N_7$ 301.40	301	59.78 59.75	7.69 7.78	32.53 32.48		237.5 (26.5) 263 (15.8) 307 (6.6)	
9/9	2-(Piperidin-1-yl)-ethylamino	J	1 / 100	96	196-200 dec (CH_3CN)	$C_{18}H_{27}N_7$ 341.46	341	63.32 63.28	7.97 8.11	28.71 28.65		237.5 (25.6) 261 (15.9) 271 sh (10.4) 304.5 (7.9)	
9/10	2-(Morpholin-4-yl)-ethylamino	J	2 / 100	89	220-225 (CH_3CN)	$C_{17}H_{25}N_7O$ 343.44	343	59.46 59.38	7.34 7.41	28.55 28.57		238 (22.7) 262 (13.4) 306 (5.5)	
9/11	3-Dimethylamino-1-propylamino	J	1 /110 [f]	90	193-198 (CH_3CN)	$C_{16}H_{25}N_7$ 315.42	315	60.93 61.00	7.99 8.13	31.08 31.14		238 (24.9) 263 (15.0) 306 (6.6)	
9/12	3-(Morpholin-4-yl)-1-propylamino	J	2 /100	82	175-180 (CH_3CN)	$C_{18}H_{27}N_7O$ 357.46	357	60.48 60.44	7.61 7.66	27.43 27.38		238 (24.4) 262 (14.4) 306.5 (6.0)	
9/13	3-Hydroxy-1-propylamino	J	2 / 100 [f,g]	84	222-227 (CH_3CN)	$C_{14}H_{20}N_6O$ 288.36	288	58.32 58.39	6.99 7.13	29.14 29.09		237.5 (24.8) 261.5 (15.4) 271 sh (10.3) 304.5 (7.7)	
9/14	Benzylamino	J	1 / 100	87	212-216 (CH_3CN)	$C_{18}H_{20}N_6$ 320.40	320	67.48 67.40	6.29 6.31	26.23 26.19		239 (28.5) 263 (15.9) 304.5 (6.3)	
9/15	Piperidin-1-yl	J	1 / 120	97	200-202 (CH_3CN/ EtOAc)	$C_{16}H_{22}N_6$ 298.39	298	64.40 64.51	7.43 7.55	28.16 28.09		252 (23.2) 267 sh (20.5) 309 (6.3)	
9/16	4-Methyl-piperazin-1-yl	J	2 / 120	97	220-228 dec (CH_3CN/ EtOH)	$C_{16}H_{23}N_7$ 313.41	313	61.32 61.44	7.40 7.55	31.28 31.21		247 (22.8) 265 (18.3) 308.5 (6.1)	
9/17	4-(2-Hydroxyethyl)-piperazin-1-yl	J	2 / 120	91	196-198 (CH_3CN/ EtOH)	$C_{17}H_{25}N_7O$ 343.44	343	59.46 59.38	7.34 7.42	28.55 28.70		248 (22.7) 265 (19.4) 308.5 (6.1)	

[a] Detected by tlc but not isolated; [b] Isolated as by-product of **6/3**; [c] Isolated as by-product of **6/5**; [d] Isolated from the reaction mixture of **4/14** prepared by Method H; [e] By refluxing in acetonitrile**;** [f] 8 Mole amine excess; [g] The product was precipitated instead of ether with acetonitrile.

Scheme 9



hydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6/3,** Q = 1-methylethylthio) was reacted with thiomorpholine in acetonitrile (Scheme 9). In this reaction two products were formed in an approximately 5:3 ratio. The main product was the expected 2-(1-methylethylthio)-5-[2-(thiomorpholin-4-yl)ethyl]amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4/14**, Q = 1-methylethylthio, NR^5R^6 = thiomorpholin-4-yl) and the by-product was the unexpected 4-(thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl). Derivative **9/6** (Q = thiomorpholin-4-yl) could have formed either by nucleophilic attack of the thiomorpholine nitrogen atom against the 2-(1-methylethylthio) group of **6/3** (Q = 1-methylethylthio) followed by ring closure or more probably against the 4-(1-methylethylthio) group of the ring closed 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene derivative **9/3** (Q = 1-methylethylthio) (Scheme 9).

Such a nucleophilic attack of the thiomorpholine nitrogen atom against the 2-(1-methylethylthio) group of **6/3** (Q = 1-methylethylthio) is contrary to all our previous results as the alkylthio group of the 5-amino-3-(R-thio)-1,2,4-triazoles, or their condensed ring 2-(R-thio)-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one analogues **1** (Q = alkylthio) could not be replaced by a nucleophilic attack of an amine either in solutions of different polarities, or at high temperature, *e.g.* in boiling benzylamine. This replacement has not proceeded even if the reaction was carried out with the corresponding sulphones [7]. In accordance with the above mentioned observations, the alkylthio groups of the type **1** 1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-ones "survived" also the silylation-amination process, *i.e.* their prolonged boiling with an amine at high temperature (Schemes 2 and 3).

We found also direct preparative proof that the nucleophilic attack mentioned above did not proceed in the reaction of **6/3** (Q = 1-methylethylthio) and thiomorpholine. Thus derivative **2** (Q = 1-methylethylthio) was converted with diethylamine to derivative **12** that was subjected to prolonged amination reaction at high temperature (52 hours, 180-200 °C) with 4-(2-aminoethyl)morpholine **3** (NR^5R^6 = morpholin-4-yl) to yield as a sole product **4/13** (Q = 1-methylethylthio, NR^5R^6 = morpholin-4-yl). Analysis of the reaction mixture with lcms showed that no traces of derivatives **13** and **14** were formed (Scheme 10).

A possible explanation for this unusual behaviour of the 4-(1-methylethylthio) group of 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene derivative **9/3** (Q = 1-methylethylthio) is that the "usual" *quasi*-aromatic character of the triazole ring due to the two conjugated pyridine-like nitrogen atoms in 5-amino-3-(R-thio)-1,2,4-triazoles and their **1, 2, 4, 5** or **6** type condensed ring derivatives is replaced by a pyridine-like and a pyrrole-like nitrogen atom attached to a carbon atom bearing the alkylthio moiety. The isothiourea (or isothiosemicarbazide) arrangement thus present reacts easily with the corresponding secondary amine **16** (Scheme 11). Derivatives **9** (Q = NR^7R^8) thus obtained are stable guanidine (or aminoguanidine) compounds.

An other explanation may also be given for the change in reactivity of the 4-alkylthio group of **9/3** (Q = 1-methylethylthio). Namely, derivatives **9** may also exist in different zwitter ionic forms represented *e.g.* by canonical form **15** (Scheme 11). In this case the positive charge in the neighbourhood of carbon atom C-4 decreases the stability of the C-4 — S bond, consequently enhancing the reactivity of the alkylthio group.

In order to determine the correct structure of type **9** derivatives different spectroscopic methods were applied.

The bond length data of **9/3** (Q = 1-methylethylthio) measured by single crystal X-ray diffraction (Scheme 5) proved that this compound, at least in crystalline form, can be characterised by the neutral canonical form.

On the other hand, in the uv spectra of **9/3** (Q = 1-methylethylthio) taken in different solvents a negative solvatochromic effect was observed. The hypsochromic shift observed for the long wavelength $n \rightarrow \pi^*$ maximum at

Scheme 10

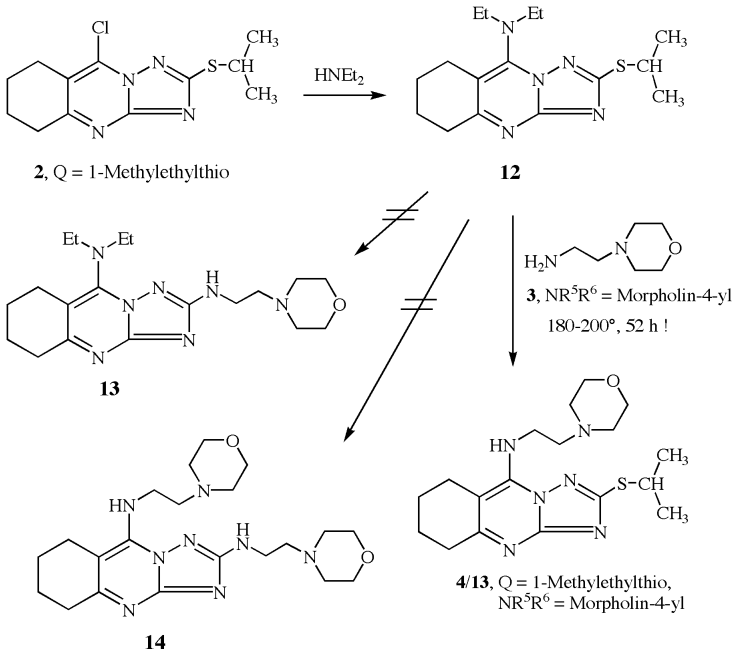


Table IIIa

Pmr and cmr Spectroscopic Data of 4-Q-2,3,7,8,9,10-Hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9**

	pmr (deuteriochloroform): δ, ppm					cmr (deuteriochloroform): δ, ppm									
Compound	CH_2-2 CH_2-3	CH_2-7	CH_2-10	CH_2-8,9 (4H)	Q	C-2 C-3	C-4	C-5a	C-6a	C-7	C-8 C-9	C-10	C-10a	C-10b	Q
9/1	3.92 m (4H)	2.64 m	2.46 m	1.77 m	2.79 s (3H)	43.1 41.2	161.8	151.7	155.7	32.5	22.1 22.0	22.6	108.9	144.0	13.8
9/2	3.92 m (4H)	2.65 m	2.47 m	1.78 m	3.40 q (7.5 Hz) (2H) 1.50 t (7.5 Hz) (3H)	43.1 41.2	161.3	151.8	155.8	32.5	22.15 22.05	22.6	108.8	144.1	26.6 14.9
9/3	3.9 m (4H)	2.66 m	2.47 m	1.78 m	4.19 m (1H) 1.53 d (6.8 Hz) (6H)	43.3 41.2	161.0	151.9	155.6	32.6	22.15 22.1	22.7	108.8	144.1	39.2 23.3
9/3 [a]	3.85 t 3.77 t	2.51 m	2.28 m	1.73 m	4.14 m (1H) 1.52 d (6H)	42.8 40.9	159.5	151.2	154.5	32.1	22.0 21.9	22.7	108.6	142.8	38.3 23.2
9/3 [b]	3.36 t 2.82 t	2.80 m	2.72 m	1.64 m	3.96 m (1H) 1.20 d (6H)	43.2 40.6	159.8	152.6	155.2	33.2	22.8 22.7	23.4	109.3	143.4	38.7 23.2
9/3 [c]	4.02 t 3.80 t	2.50 m	2.35 m	1.72 m	4.10 m (1H) 1.51 d (6H)	43.9 42.0	160.9	153.0	155.1	33.2	23.0 22.9	23.6	108.9	143.8	39.4 23.5
9/3 [d]	3.88 t 3.73 t	2.50 m	2.33 m	1.72 m	4.08 m (1H) 1.48 m (6H)	43.7 42.0	160.9	153.2	155.5	33.3	23.05 23.0	23.7	108.9	144.3	39.7 23.6
9/3 [e]	3.95 t 3.69 t	2.46 m	2.29 m	1.67 m	4.02 m (1H) 1.47 d (6H)	42.5 40.9	159.3	151.6	153.7	32.0	21.8 21.8	22.4	107.4	142.4	38.4 22.9
9/3 [f]	4.03 t 3.82 t	2.57 t	2.39 m	1.77 m	4.14 m (1H) 1.54 d (6H)	43.6 42.4	162.6	153.3	156.2	33.0	23.2 23.0	23.6	109.1	145.7	40.3 23.6
9/3 [g]	4.05 t 3.75 t	2.50 m	2.24 m	1.72 m	4.02 m (1H) 1.49 d (6H)	44.07 44.10	163.8	153.9	158.5	34.2	24.5 23.9	24.5	110.7	147.2	42.0 25.3
9/3 [h]	3.99 t 3.95 t	2.65 m	2.46 m	1.90 m 1.85 m	4.29 m (1H) 1.73 d (6H)	43.4 41.3	159.7	151.2	154.4	32.8	22.7 22.6	23.5	109.0	142.5	38.8 23.3
9/4	3.92 t 3.75 t	2.57 m	2.43 m	1.75 m	3.20 s (6H)	45.0 43.6	163.1	153.0	154.5	32.1	22.1 22.1	22.6	108.6	144.9	39.5
9/5	3.92 t 3.70 t	2.58 m	2.43 m	1.75 m	3.62 m (NCH_2) 3.82 m (OCH_2)	44.7 43.9	163.1	152.8	154.6	32.1	22.0 21.95	22.5	109.4	144.8	47.6 65.8
9/5 [g]	3.8 m 3.68 m	2.39 m	2.14 m	1.68 m	3.68 m (NCH_2) 3.9 m (OCH_2)	46.5 45.8	164.8	154.7	157.0	33.8	24.5 23.9	24.5	110.9	147.5	49.8 68.5
9/6	3.90 t 3.67 t	2.56 m	2.41 m	1.75 m	3.85 m (NCH_2) 2.76 m (SCH_2)	44.7 44.0	163.0	152.6	154.2	31.9	22.4 21.8	22.4	109.2	144.5	49.9 26.3

Table IIIa (continued)

	pmr (deuteriochloroform): δ, ppm					cmr (deuteriochloroform): δ, ppm									
Compound	CH_2-2 CH_2-3	CH_2-7	CH_2-10	CH_2-8,9 (4H)	Q	C-2 C-3	C-4	C-5a	C-6a	C-7	C-8 C-9	C-10	C-10a	C-10b	Q
9/7 [e]	3.79 t 3.63 t	2.38 t	2.25 t	1.65 m	3.56 t (2H) 3.38 t (2H) 8.1 bs (1H, NH) 4.9 bs (1H, OH)	43.4 40.7	160.4	152.8*	153.4*	32.0	22.1 22.0	22.7	107.0	143.0	45.0 59.5
9/8	3.84 m (4H)	2.57 m	2.42 m	1.75 m	7.3 bs (NH) 3.54 t ($NHCH_2$) 2.52 t (NCH_2) 2.22 s (6H)	43.8 40.8*	159.6	152.8	155.3	32.4	22.25 22.2	22.8	108.2	144.5	40.0* ($NHCH_2$) 57.4 (NCH_2) 45.1 (Me)
9/9	3.86 t 3.80 t	2.56 m	2.40 m	1.75 m	6.5 bs (NH) 3.56 t ($NHCH_2$) 2.56 m (NCH_2) piperidin-1-yl 2.40 m (4H) 1.55 m (4H) 1.45 m (2H)	43.9 40.8	159.7	152.8	154.7	32.2	22.2 22.1	22.7	108.0	144.4	39.3 ($NHCH_2$) 57.1 (NCH_2) piperidin-1-yl 54.2 25.8 24.1
9/10	3.85 m (4H)	2.60 m	2.46 m	1.75 m	7.5 bs (NH) 3.58 t ($NHCH_2$) 2.60 m (NCH_2) morpholin-4-yl 2.46 m (NCH_2) 3.65 m (OCH_2)	43.8 41.0	160.0	152.9	154.7	32.1	22.15 22.1	22.6	108.1	144.4	39.1 ($NHCH_2$) 56.9 (NCH_2) morpholin-1-yl 53.3 (NCH_2) 66.7 (OCH_2)
9/11	3.87 t 3.70 t	2.56 m	2.43 m	1.75 m	8.7 bs (NH) 3.56 t ($NHCH_2$) 1.75 m (CCH_2C) 2.45 t (NCH_2) 2.24 s (6H)	44.0 40.4	159.8	153.1	155.0	32.4	22.25 22.15	22.8	107.9	144.5	43.8 ($NHCH_2$) 24.8 (CCH_2C) 59.4 (NCH_2) 45.3 (Me)
9/12	3.83 m (4H)	2.55 m	2.45 m	1.76 m	8.5 bs (NH) 3.56 t ($NHCH_2$) 1.79 qi (CCH_2C) 2.55 m (NCH_2) morpholin-4-yl 2.45 m (NCH_2) 3.68 m (OCH_2)	43.9 41.0*	160.0	153.1	154.6	32.1	22.1 22.0	22.6	108.0	144.5	42.6* ($NHCH_2$) 24.5 (CCH_2C) 57.5 (NCH_2) morpholin-4-yl 53.6 (NCH_2) 66.9 (OCH_2)
9/13 [e]	3.76 t 3.63 t	2.37 t	2.25 t	1.64 m	7.95 bs (NH) (1H) 4.55 bs (OH) (1H) 3.48 t (2H) 3.38 t (2H) 1.72 qi (2H)	43.5 40.2	160.4	152.9*	153.3*	32.3	22.2 22.0	22.7	107.1	143.0	39.5 ($NHCH_2$) 58.2 (OCH_2) 32.1 (CCH_2C)
9/14 [f]	3.75 m (4H)	2.52 m	2.37 m	1.75 m	4.59 s ($PhCH_2$) 7.3 m (5H)	44.3 41.7	161.6	154.2	155.8	32.8	23.1 23.1	23.6	108.5	146.1	47.5 139.5 (Ph-*s*) 128.9 128.1 (*p*) 127.5
9/15	3.91 t 3.65 t	2.57 m	2.42 m	1.75 m	3.55 m (4H) 1.70 m (6H)	45.1 44.4	163.6	153.3	154.6	32.2	22.2 22.2	22.7	109.0	145.0	48.7 25.2 23.8
9/16	3.91 t 3.69 t	2.57 m	2.42 m	1.75 m	3.64 m (4H) 2.52 m (4H) 2.34 s (3H)	45.0 44.2	163.2	153.0	154.7	32.2	22.2 22.2	22.7	109.2	144.9	47.5 54.0 46.0 (Me)
9/17	3.93 t 3.67 m	2.55 m	2.43 m	1.75 m	3.67 m (6H) 2.65 m (6+1H)	44.9 44.3	163.2	153.0	155.0	32.3	22.25 22.2	22.7	109.3	145.0	47.7 52.1 57.9 (NCH_2) 59.5 (OCH_2)

[a] Taken in Carbon tetrachloride; [b] taken in Benzene-d_6; [c] taken in Acetone-d_6; [d] taken in CD_3CN; [e] taken in DMSO-d_6; [f] taken in CD_3OD; [g] taken in D_2O; [h] taken in CS_2.

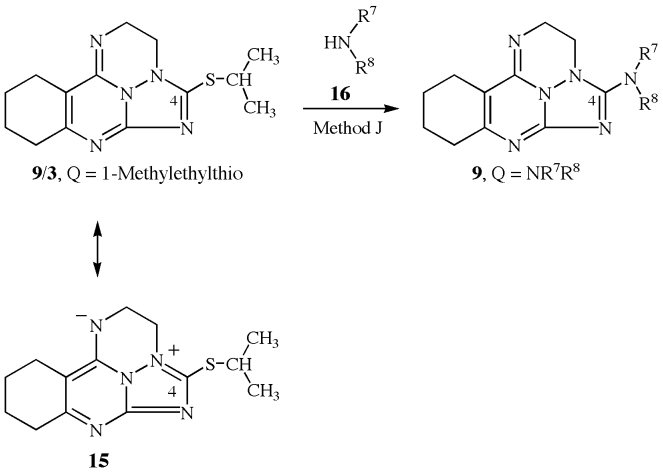
about 340 nm was approximately 10 nm between *n*-hexane and acetonitrile. Consequently in solution the contribution of zwitter ionic forms in the ground state have also been taken in account.

The pmr spectrum of **9/3** (Q = 1-methylethylthio) taken in hexadeuteriobenzene (known to solvate preferably the electron deficient centre of the molecule) is also in agreement with the above idea, as the signals of the solute

protons CH_2-2, CH_2-3 and the isopropylthio moiety being in closeness to the most positive nitrogen atom 3a were shifted upfield compared with those taken in other inert solvents, *e.g.* carbon tetrachloride (Table IIIa). The aromatic solvent-induced shift (ASIS) [11] was most pronounced in case of C-3 methylene protons: δ_{CCl4} = 3.77 ppm and δ_{C6D6} = 2.82 ppm (Δ = 0.95 ppm), while ASIS of the protons more distant from the positive centre of the molecule was in the range of 0.1 – 0.5 ppm.

In the cmr spectrum of **9/3** (Q = 1-methylethylthio) taken in carbon tetrachloride and D_2O the signal of the C-4 atom appeared at 159.5 and 163.8 ppm, respectively, in accordance with the increasing contribution of the dipolar mesomeric structures to the ground electronic state. This fact can also explain the relative ease of replacement of the 4-alkylthio group of derivatives **9** (Q = SR) with primary or secondary amines, leading to derivatives **9** (Q = NR^7R^8) (Scheme 11).

Scheme 11



The bond length data of derivative **9/5** (Q = morpholin-4-yl) measured by single crystal X-ray diffraction (Scheme 6) are similar to those of **9/3** (Q = 1-methylethylthio), that is, in crystalline form, this molecule can be also described by the neutral canonical form. It is worth mentioning that the length of the C-4 - N(morpholine) bond is between the length of a single and a double C(sp^2)-N bond (being of approximately 1.40 and 1.32 Å, respectively,[10]) indicating that the lone electron pair of the N atom of the morpholine ring is partially conjugated with the π-electron system of the molecule.

In the uv spectra of **9/5** (Q = morpholin-4-yl), taken in different solvents, a negative solvatochromic effect was again observed. The long wavelength n→π* absorption maxima λ_{max} (nm) were registered at 324 (1,4-dioxane), 323 (THF), 318 (acetonitrile), 308.5 (ethanol), 306.5 (methanol), 302 (water). The blue shift of only 6 nm between the aprotic solvents 1,4-dioxane and acetonitrile, compared with a shift of 22 nm between 1,4-dioxane and water could be interpreted as a result of the superior solvation of ground state in protic solvents [11].

Having recognised the lability of the 4-alkylthio groups of the 2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9** (Q = 1-methylethylthio, ethylthio, and methylthio, respectively), they were reacted with different primary or secondary amines (**16**), like thiomorpholine, morpholine, 1-methyl-piperazine, 1-(2-hydroxyethyl)piperazine, piperidine, benzylamine, (2-hydroxyethyl)amine, and 3-hydroxy-1-propylamine, respectively, to obtain in each case the expected 4-alkylamino- and dialkylamino-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene derivatives [**9**, Q = thiomorpholin-4-yl, morpholin-4-yl, 4-methyl-piperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, piperidin-1-yl, benzylamino, (2-hydroxyethyl)amino, and (3-hydroxy-1-propyl)amino, respectively] in good yield (Scheme 11, Method J, Table III), pointing out the rather general validity of this reaction.

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 882 spectrophotometer. The ultraviolet spectra were obtained using a Varian Cary 1E UV-VIS instrument. The pmr and the cmr measurements were performed on Bruker WM-250 and Varian Unity Inova 400 (400 MHz) instruments. To confirm the assignments in some cases standard Varian HSQC and HMBC 2D-nmr programs were used. The ms spectra were recorded on a Kratos MS25RFA and a VG Trio 1000 instrument using direct inlet probe in EI mode as well as on a VG Quattro instrument (ES). Dry column flash chromatography was performed according to [12] on Kieselgel 60 H (Merck 107736) and Aluminium oxide 60 G (Merck 101090).

General Methods for the Synthesis of 5-(2-Dialkylaminoethyl)-amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives **4**.

Method A.

To a suspension of 0.01 mole of the appropriate 5-chloro-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline derivative **2** in 10 ml of 2-propanol 1.11g (0.011 mole, 1.6 ml) of triethylamine and 0.011 mole of the appropriate (2-R^5,R^6-aminoethyl)amine (**3**) was added and the reaction mixture refluxed for the time given in Table I. The yellow solution obtained was evaporated *in vacuo* to dryness, the residue was triturated with water, filtered and washed with water and a small amount of 2-propanol. The product obtained was recrystallised from an appropriate solvent (Table I).

Method B

To a suspension of 0.04 mole of the appropriate 2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline-5(10*H*)-one derivative **1** in 16.14 g (0.1 mole, 21 ml) of hexamethyldisilazane

(Fluka) 0.1 mole of the appropriate (2-R^5,R^6-aminoethyl)amine (**3**) and 0.76 g (0.004 mole) of *p*-toluenesulfonic acid monohydrate was added and stirred vigorously at the temperature and for time given in Table I (at approximately 70 °C strong liberation of ammonia occured), during which the volatile by-products distilled off. After cooling to approximately 90 °C the reaction mixture started to crystallise. At this temperature 20 ml of 2-propanol was added with stirring to the reaction mixture. After cooling the product was isolated by filtration, washed with 2-propanol and recrystallised from an appropriate solvent (Table I).

General Methods for the Synthesis of 5-(2-Hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives **5**.

Method C.

To a suspension of 0.055 mole of the appropriate 5-chloro-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline **2** in 50 ml of 2-propanol 7.02 g (0.115 mole, 7.0 ml) of (2-hydroxyethyl)-amine (**7**) was added in one portion with stirring. In a few minutes the reaction mixture began to boil and crystallised. The mixture was refluxed for 30 minutes, allowed to cool and evaporated *in vacuo* to dryness. The residue was triturated with 50 ml of water, filtered, washed thoroughly with water and recrystallised from an appropriate solvent (Table II).

Method D

To a suspension of 0.017 mole of the appropriate 2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline-5(10*H*)-one derivative **1** in 16.8 g (0.104 mole, 21.7 ml) of hexamethyldisilazane (Fluka) 3.18 g (0.052 mole, 3.15 ml) of (2-hydroxyethyl)amine (**7**) and 0.19 g (0.001 mole) of *p*-toluenesulfonic acid monohydrate was added and reacted at the temperature and for the time given in Table II. The reaction mixture was evaporated *in vacuo* to dryness, and the residue was desilylated by refluxing with 30 ml of methanol. The mixture obtained was cooled, the product was isolated by filtration, washed with methanol and recrystallised from a solvent given in Table II.

General Method for the Synthesis of 5-(2-Chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives **6** and their Condensed Ring 4-Q-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene By-products **9**.

Method E.

To a suspension of 0.1 mole of the corresponding 5-(2-hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline derivative **5** in 300 ml of dichloromethane 23.8 g (0.2 mole, 14.6 ml) of thionyl chloride was added with stirring. A slightly exotermic reaction took place and a yellow solution was obtained that began to crystallise in 30 minutes. The thick suspension was stirred overnight at room temperature (time given in Table II). The crystals (probably **6**.HCl) were collected by filtration, washed with dichloromethane, then suspended in 300 ml of dichloromethane and 100 ml of water. While stirring 42 g (0.5 mole) of solid sodium hydrogen carbonate was added in small portions (CO_2 was evolved; the foaming could be diminished by addition of a few drops of ether to the mixture). The two phases obtained were separated, the aqueous phase was extracted with dichloromethane, and the combined organic layers were washed with water and dried over anhydrous sodium sulphate. After evaporation of the solvent *in vacuo* the residue was purified by dry column flash chromatography on Kieselgel 60 H (eluents: either benzene, different mixtures of benzene and chloroform, then chloroform, or a 1:1 mixture of *n*-hexane and dichloromethane, followed by dichloromethane and a 50:1 mixture of dichloromethane and methanol). The appropriate fractions were collected, evaporated *in vacuo* to dryness, and the residue was triturated with ether and filtered to yield derivatives **6** (Table II).

Continuing the chromatography with a 50:1 mixture of chloroform and triethylamine and evaporating the appropriate fractions to dryness the corresponding raw 4-Q-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene derivatives **9** were obtained that were purified by dry column flash chromatography on aluminium oxide 60 G (eluents: benzene and 4:1 to 1:1 mixtures of benzene and chloroform) and recrystallised from an appropriate solvent (Table III).

General Method for the Direct Synthesis of 4-Q-2,3,7,8,9,10-Hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes **9**.

Method F.

A mixture of 0.015 mole of the appropriate 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazoline (**6**) and 35 ml of acetonitrile was refluxed with stirring for the time given in Table III. The solution obtained was evaporated to dryness *in vacuo*, the residue (**9**.HCl) was suspended in 50 ml of chloroform, to which 1.67 g (0.0165 mole, 2.3 ml) of triethylamine was added. The yellow solution obtained was extracted with 2 x 15 ml of water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue was triturated with ether, filtered and either recrystallised from an appropriate solvent or purified by dry column flash chromatography on aluminium oxide 60 G (eluents: benzene and 4:1 to 1:1 mixtures of benzene and chloroform) (Table III).

General Method for the Synthesis of 4-Q-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene Derivatives **9** and their 2-Q-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one By-products **1** from 5-(2-Hydroxyethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**5**).

Method G.

A mixture of 0.2 mole of the appropriate 5-(2-hydroxyethyl)-amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**5**) and 300 g of polyphosphoric acid was "stirred" at 130-140 °C (oil bath) for the time given in Table III. During the reaction the starting material was slowly dissolved and a honey-like reaction mixture was obtained. This was cautiously dissolved in 5 x 100 ml of water keeping the inner temperature below 50 °C. The brown solution obtained crystallised upon cooling. The crystal precipitate was collected by filtration and chromatographed on a Kieselgel 60 H column (eluents: chloroform and 50:1 to 19:1 mixtures of chloroform and methanol) to yield the corresponding 2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**1**) by-product (Table III).

To the brown aqueous acidic mother liquor 375 g (4.5 mole) of powdered sodium hydrogen carbonate was added with vigorous stirring in small portions. The carbon dioxide evolution caused a heavy foaming that could be ceased by addition of a few drops of ether to the mixture. To the solution obtained (pH ≈ 7) 60 ml of concentrated aqueous ammonium hydroxide was added, then the solution (pH ≈ 8) was extracted with 4 x 200 ml portions of chloroform. The combined chloroform layers were washed with water,

dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was recrystallised from an appropriate solvent (Table III, for the spectral data see Table IIIa).

General Method for the Synthesis of 5-(2-Dialkylaminoethyl)-amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolines (**4**) from 5-(2-Chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline Derivatives (**6**).

Method H.

The suspension of 0.008 mole of the appropriate 5-(2-chloroethyl)amino-2-Q-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazoline derivative **6** in 0.05 mole of the appropriate R^5,R^6-amine (**11**) was heated at a temperature and for time given in Table I. To the still hot yellow solution obtained, 40 ml of water was added and stirred for 1 hour at room temperature. The crystals that precipitated were collected by filtration, washed with water and a small amount of ether, and purified by dry column flash chromatography (Kieselgel 60 H, eluents: dichloromethane, then dichloromethane containing 2-5 % of methanol). The product obtained was recrystallised from a solvent given in Table I.

2-(1-Methylethylthio)-5-[2-(thiomorpholin-4-yl)ethyl]amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4/14**, Q = 1-methylethylthio, NR^5R^6 = thiomorpholin-4-yl) and 4-(Thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl) from 5-(2-Chloroethyl)amino-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6/3**, Q = 1-methylethylthio)

To a suspension of 3.26 g (0.01 mole) of 5-(2-chloroethyl)-amino-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6/3**, Q = 1-methylethylthio) in 10 ml of acetonitrile 2.27 g (0.022 mole, 2.2 ml) of thiomorpholine was added and the reaction mixture refluxed with stirring for 16 hours. To the still hot solution 60 ml of water was added and the crystals that precipitated were collected by filtration and washed with water and a small amount of ether. The product thus obtained was purified by dry column flash chromatography on Kieselgel 60 H (eluents: benzene and 4:1 to 1:1 mixtures of benzene and chloroform) to yield 2.0 g (51 %) of 2-(1-methylethylthio)-5-[2-(thiomorpholin-4-yl)ethyl]amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4/14**, Q = 1-methylethylthio, NR^5R^6 = thiomorpholin-4-yl), mp 194-195 °C (Table I, for its spectral data see Table Ia).

The pH of the aqueous acetonitrile containing mother liquor of the crude **4/14** (Q = 1-methylethylthio, NR^5R^6 = thiomorpholin-4-yl) was adjusted with concentrated aqueous ammonium hydroxide solution to 10, and the solution thus obtained was extracted with 3 x 20 ml of chloroform. The combined chloroform layers were dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue was triturated with ether, filtered and the crystals were dry column flash chromatographed on Kieselgel 60 H (eluents: chloroform and 50:1 to 19:1 mixtures of chloroform and methanol) to obtain after evaporation the solvents *in vacuo* 1.0 g (31 %) of product, that was recrystallised from 75 ml of acetonitrile to yield 0.82 g of pure 4-(thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl), mp 236-240 °C dec (Table III, for its spectral data see Table IIIa).

4-(Thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl) from 4-(1-Methylethylthio)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/3**, Q = 1-methylethylthio) in Acetonitrile.

To a suspension of 0.145 g (0.0005 mole) of 4-(1-methylethylthio)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/3**, Q = 1-methylethylthio) in 1 ml of acetonitrile 0.083 g (0.0008 mole) of thiomorpholine was added and refluxed for 12 hours. After cooling the crystals that precipitated were collected by filtration (0.060 g, 38 %), the mother liquor was evaporated *in vacuo* to dryness, the residue triturated with ether and filtered to yield a further crop (0.055 g, 35 %) of crystals. The combined crystalline products were purified by dry column flash chromatography on a small aluminium oxide 60 G column (0.2 g) (eluents: benzene and 4:1 to 1:1 mixtures of benzene and chloroform) to yield after recrystallisation from tetrahydrofurane 0.052 g of pure 4-(thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl), mp 238-244 °C dec (Tables III and IIIa). The product is identical (ir) with that of 4-(thiomorpholin-4-yl)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9/6**, Q = thiomorpholin-4-yl) obtained in the previous experiment.

5-Diethylamino-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**12**).

To a suspension of 5.66 g (0.02 mole) of 5-chloro-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**2**, Q = 1-methylethylthio) in 30 ml of 2-propanol 7.31 g (0.1 mole, 10.3 ml) of diethylamine was added with stirring. The mixture was reacted at 60 °C (oil bath) for 30 minutes, and evaporated *in vacuo* to dryness. The oily residue was taken in 60 ml of dichloromethane, washed with 2 x 15 ml of water, dried over anhydrous sodium sulphate, filtered and the dichloromethane solution was dry column flash chromatographed (30 g Kieselgel 60 H, eluent 6 x 80 ml of dichloromethane). After evaporation of the appropriate fractions *in vacuo* the residue was allowed to stand over *n*-hexane. The crystals that precipitated were isolated by filtration to yield 3.64 g (57 %) of 5-diethylamino-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**12**), mp 51.5-53.5 °C; ms (EI): 319 (M^+); pmr (deuteriochloroform): δ, ppm 1.10 (t, 6H, NCH_2CH_3), 1.48 [d, 6H, $CH(CH_3)_2$], 1.82 (m, 2H, CH_2-7), 1.90 (m, 2H, CH_2-8), 2.69 (m, 2H, CH_2-6), 3.00 (m, 2H, CH_2-9), 3.52 (q, 4H, NCH_2), 4.02 (m, 1H, CH); cmr (deuteriochloroform): δ, ppm 13.8 (NCH_2CH_3), 22.1 (C-7), 22.5 (C-8), 23.3 ($CHCH_3$), 25.1 (C-6), 33.1 (C-9), 36.5 (CH), 45.0 (NCH_2), 112.6 (C-5a), 147.6 (C-5), 155.4 (C-10a), 164.3 (C-9a), 165.7 (C-2).

Anal. Calcd. for $C_{16}H_{25}N_5S$ (MW 319.48): C, 60.15; H, 7.89; N, 21.92; S, 10.04. Found: C, 60.22; H, 8.02; N, 22.03; S, 9.98.

2-(1-Methylethylthio)-5-[2-(morpholin-4-yl)ethyl]amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4/13**, Q = 1-methylethylthio, NR^5R^6 = morpholin-4-yl).

A mixture of 1.60 g (0.005 mole) of 5-diethylamino-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazoline (**12**) and 10.03 g (0.077 mole, 10 ml) of 4-(2-aminoethyl)morpholine (**3**, NR^5R^6 = morpholin-4-yl) was stirred on an oil bath of 180-200 °C for 52 hours. The cold reaction mixture was diluted with 30 ml of water and allowed to crystallise overnight. After filtration the crystals obtained (1.43 g) were dry column flash chromatographed on 10 g of Kieselgel 60 H (eluents: dichloromethane and a 50:1 mixture of dichloromethane and

methanol) to yield after evaporation of the appropriate fractions 1.32 g (70 %) of 2-(1-methylethylthio)-5-[2-(morpholin-4-yl)ethyl]amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4/13**, Q = 1-methylethylthio, NR^5R^6 = morpholin-4-yl), mp 187.5-189 °C (CH_3CN). (Table I, for its spectral data see Table Ia).

The product is identical (ir, pmr) with that of obtained by Method A from 5-chloro-2-(1-methylethylthio)-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**2**, Q = 1-methylethylthio) and 4-(2-aminoethyl)morpholine (**3**, NR^5R^6 = morpholin-4-yl).

General Method for the Synthesis of 4-(R^7,R^8-Amino)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes (**9**, Q = NR^7R^8) from 4-Alkylthio-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylenes (**9**, Q = 1-methylethylthio, ethylthio and methylthio) and the Appropriate R^7,R^8-amine (**16**).

Method J.

A suspension of 5.79 g (0.02 mole) of 4-(1-methylethylthio)-, or 5.51 g (0.02 mole) of 4-ethylthio-, or 5.23 g (0.02 mole) of 4-methylthio-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene (**9**, Q = 1-methylethylthio, ethylthio or methylthio, respectively) and 0.1 mole of the appropriate R^7,R^8-amine (**16**) was stirred for a time and at temperature given in Table III. After cooling 40 ml of ether was added to the solution initiating the crystallisation of the product. The mixture was stirred at room temperature for 15 minutes, filtered and the crystals washed with ether to yield the raw 4-(R^7,R^8-amino)-2,3,7,8,9,10-hexahydro-1,3a,5,6,10c-pentaazaacephenanthrylene derivative **9** that after recrystallisation from an appropriate solvent gave the pure product (Tables III and IIIa).

Crystal Structure Determination of **9/3** [8].

Crystal data for compound **9/3** is as follows**:** $C_{14}H_{19}N_5S$, Fwt.: 289.40, orthorhombic, space group *Pbca*, a = 7.518(1)Å, b = 19.131(2)Å, c = 20.464(2)Å, V = 2943.3(6) Å^3, T = 293(2) K, Z = 8, $F(000)$ = 1232, D_X = 1.306 Mg/m^3, μ = 1.931 mm^{-1}, crystal size 0.60 x 0.19 x 0.14 mm. Intensities of 1977 reflections (1912 were unique, 1420 >2$\sigma(I)$) were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu-$K\alpha$ radiation, λ = 1.54184 Å at room temperature in the range $4.32 \leq \theta \leq 57.82°$ using $\omega/2\theta$ scans. An empirical psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.9089 and 0.9910). The structure was solved by direct methods and refined by anisotropic least-squares on F^2 for all non-hydrogen atoms. $R1$ = 0.0484 and $wR2$ = 0.1331 for 1420 [I>2$\sigma(I)$] and $R1$ = 0.0653 and $wR2$ = 0.1426 for all (1912) intensity data, (number of parameters = 184, goodness-of-fit = 0.998). The maximum and minimum residual electron density in the final difference map was 0.231 and -0.292 e.Å^{-3}.

Crystal Structure Determination of **9/5** [9].

Crystal data for compound **9/5** is as follows: $C_{15}H_{20}N_6O$, Fwt.: 300.37, monoclinic, space group $P2_1/c$, a = 8.265(1)Å, b = 14.121(2)Å, c = 12.829(2)Å, β = 103.18(1)°, V = 1457.8(4) Å^3, T = 293(2) K, Z = 4, $F(000)$ = 640, D_X = 1.369 Mg/m^3, μ = 0.092 mm^{-1}, crystal size 0.50 x 0.32 x 0.20 mm.

Intensities of 6874 reflections (6355 unique, 3197 > 2$\sigma(I)$) were collected on an Enraf-Nonius CAD4 diffractometer (graphite monochromator; Mo-$K\alpha$ radiation, λ = 0.710730 Å) at room temperature in the range $2.53 \leq \theta \leq 34.98°$ using $\omega/2\theta$ scans.

A psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.9848 and 0.9904). The structure was solved by direct methods and refined by anisotropic least-squares on F^2 for all non-hydrogen atoms. $R1$ = 0.0524 and $wR2$ = 0.1386 for 3197 [I>2$\sigma(I)$] and $R1$ = 0.1145 and $wR2$ = 0.1546 for all (6355) intensity data, (number of parameters = 196, goodness-of-fit = 0.912). The maximum and minimum residual electron density in the final difference map was 0.328 and -0.217 e.Å^{-3}.

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