# On Triazoles XLVII [1]. Synthesis of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes



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To study the influence of planar or bulky cycloalkane rings attached to the 1,3a,5,6,ωc-pentaazaacenaphthylenes to the reactivity of their 4-alkylthio group toward amines - an unexpected reaction observed recently at 1,3a,5,6,10c-pentaazaacephenanthrylenes (**5b**, n = 4) - different size 1,3a,5,6,ωc-pentaazacycloalka[*e*]acenaphthylenes (**5a**, n = 3; **5c**, n = 5; **5d**, n = 6; or **5e**, n = 10) were synthesised and their spectral data compared with that of **5b** (n = 4). Based on the analogy of the chemical shifts of carbon atoms at position 4 with that of **5b**, similar electronic structure and thus a possibility of an analogous nucleophilic attack of amines was proposed and subsequently proved by a preparative method.

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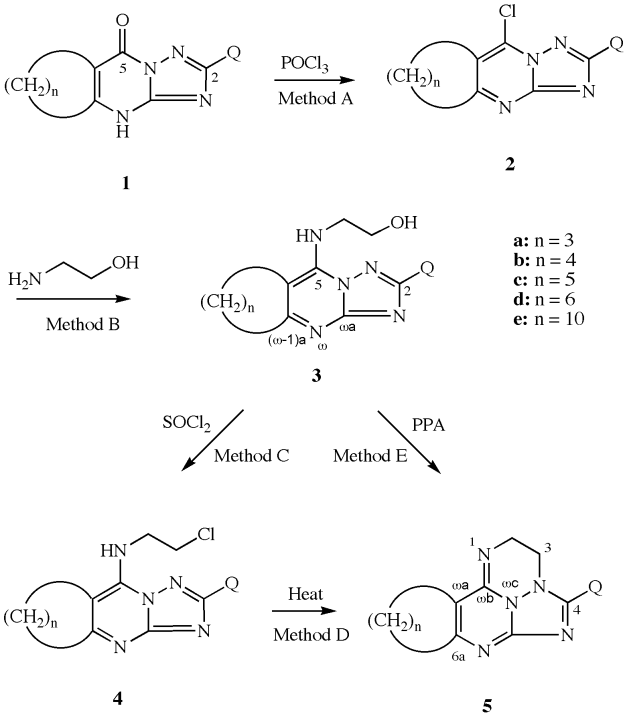
In the previous paper of this series [1] we have reported on the synthesis of different 1,3a,5,6,10c-pentaazaacephenanthrylenes (**5b**, n = 4) observed previously as by-products of the reaction of derivatives **4b** (n = 4) with amines (Scheme 1). Unexpectedly, the 4-alkylthio derivatives **5b** (Q = alkylthio, n = 4) proved to be highly reactive against the nucleophilic attack of amines to yield derivatives **5b** (Q = dialkylamino, n = 4) (Scheme 2). This reaction was contrary to all former results obtained with 3-alkylthio-5-amino-1*H*-1,2,4-triazoles and their condensed-ring derivatives [1]. The reactivity of the 4-alkylthio groups of the 1,3a,5,6,10c-pentaazaacephenanthrylene derivatives **5b** (Q = alkylthio, n = 4) was explained either with the lack of the "*quasi*"-aromatic character of the triazole ring in **5b** (Q = alkylthio, n = 4) or a possibility of increasing contribution of the dipolar mesoionic (zwitter ionic) structures to the ground electronic state in solution, decreasing the stability of the C-4 – S bond.

The question arose whether this newly observed reaction worked only in case of 1,3a,5,6,10c-pentaazaacephenanthrylenes (**5b**, n = 4) having a six-membered cyclohexane ring attached to the 1,3a,5,6,ωc-pentaazaacenaphthylene moiety, or would also proceed with 1,3a,5,6,ωc-pentaazacycloalka[*e*]acenaphthylenes (**5a**, n = 3; **5c**, n = 5; **5d**, n = 6; or **5e**, n = 10), having different size, a more or less coplanar cyclopentane, or bulky cycloheptane, cyclooctane or cyclododecane rings.

The synthesis of the 1,3a,5,6,9c-pentaazacyclopenta[*e*]-acenaphthylenes (**5a**, n = 3), 1,3a,5,6,11c-pentaazacyclohepta[*e*]acenaphthylenes (**5c**, n = 5), 1,3a,5,6,12c-pentaazacycloocta[*e*]acenaphthylenes (**5d**, n = 6), and 1,3a,5,6,16c-pentaazacyclododeca[*e*]acenaphthylenes (**5e**, n = 10), all representing novel ring systems, was performed analogously to that of 1,3a,5,6,10c-pentaazaacephenanthrylenes (**5b**, n = 4) [1] (Scheme 1).

Thus the cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(ω*H*)-ones (**1**, n = 3, 5, 6, 10, Q = alkylthio or dialkylamino) [2,3] were converted by heating with phosphorus oxychloride to the corresponding 5-chloro-derivatives **2** (n = 3, 5, 6, 10, Q = alkylthio or dialkylamino) (Method A)

Scheme 1




(Table I, for their spectral data see Table II) [4,5] that were reacted with 2-aminoethanol to yield derivatives **3** (n = 3, 5, 6, 10, Q = alkylthio or dialkylamino) (Method B) (Table III, for their spectral data see Table IV) (Scheme 1).

Derivatives **3** (n = 3, 5, 6, 10, Q = alkylthio or dialkylamino) were either converted with thionyl chloride to derivatives **4** (n = 3, 5, 6, 10, Q = alkylthio or dialkylamino) (Method C) (Table III, for their spectral data see Table IV) that could be ring closed by heating neat or boiling in acetonitrile (Method D), or ring closed directly by heating in polyphosphoric acid (Method E) (Table V, for their spectral data see Table VI) (Scheme 1) to the desired derivatives **5a** (n = 3), **5c** (n = 5), **5d** (n = 6) and **5e** (n = 10), respectively.

Table I

Synthetical and Analytical Data of 5-Chloro-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines

| Compound | n | Q | Reaction | | | Yield (%) | Mp (°C) (Cryst. from) | Molecular Formula (MW) | Analysis Calcd/Found | | | | | MS EI | Lit. mp (°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Method | Time (hours) | Temperature (°C) | | | | C | H | N | S | Cl | | |
| **2/1** | 3 | Methylthio | A1 | 1 | 90 | 91 | 132-133 (ether) | $C_9H_9ClN_4S$ 240.72 | 44.91 45.02 | 3.77 3.92 | 23.28 23.24 | 13.32 13.28 | 14.73 14.85 | 240 | 126-128 [5] |
| **2/2** | 3 | 1-Methylethylthio | A1 | 1 | 90 | 88 | 91-93 ($^iPr_2O$) | $C_{11}H_{13}ClN_4S$ 268.77 | 49.16 49.07 | 4.88 4.92 | 20.85 20.88 | 11.93 11.88 | 13.19 13.08 | | |
| **2/3** | 3 | Dimethylamino | A1 | 1 | 85 | 85 | 134-138 (ether) | $C_{10}H_{12}ClN_5$ 237.69 | 50.53 50.48 | 5.09 5.21 | 29.46 29.55 | | 14.92 15.02 | | |
| **2/4** | 3 | Morpholin-4-yl | A1 | 1 | 80 | 85 | 216-219 (ether) | $C_{12}H_{14}ClN_5O$ 279.72 | 51.53 51.50 | 5.04 5.11 | 25.04 24.98 | | 12.67 12.60 | 279 | 213-215 [5] |
| **2/5** | 5 | Methylthio | A1 | 2 | 90 | 96 | 120-121 (EtOAc) | $C_{11}H_{13}ClN_4S$ 268.77 | 49.16 49.22 | 4.88 4.96 | 20.85 20.78 | 11.93 12.04 | 13.19 13.25 | | 119-120.5 [5] |
| **2/6** | 6 | Methylthio | A2 | 4 | 85 | 85 | 90.5-92 (cyclohexane) | $C_{12}H_{15}ClN_4S$ 282.80 | 50.97 50.88 | 5.35 5.50 | 19.81 19.86 | 11.34 11.28 | 12.54 12.48 | | 90.5-92 [5] |
| **2/7** | 10 | Methylthio | A2 | 6 | 85 | 91 | 128-129 (EtOAc) | $C_{16}H_{23}ClN_4S$ 338.91 | 56.71 56.64 | 6.84 6.92 | 16.53 16.61 | 9.46 9.51 | 10.46 10.55 | | 128-129 [5] |

Table II

Nmr Data of 5-Chloro-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines

| | pmr (deuteriochloroform) | | | | cmr (deuteriochloroform) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $CH_2$-6 | $CH_2$-(ω-1) | Other $CH_2$ | Q | C-2 | C-5 | C-5a | C-(ω-1) | C-(ω-1)a | ωa | Other $CH_2$ | Q |
| **2/1** | 3.09 t | 3.17 t ($CH_2$-8) | 2.27 m ($CH_2$-7) | 2.72 s (3H) | 168.4 | 132.9 | 123.1 | 35.2 (C-8) | 173.0 (C-8a) | 156.8 (C-9a) | 22.9 (C-7) 28.1 (C-6) | 13.9 |
| **2/2** | 3.08 t | 3.15 t ($CH_2$-8) | 2.30 m ($CH_2$-7) | 4.04 m (1H) 1.47 d (6H) | 167.6 | 132.9 | 123.3 | 35.1 (C-8) | 173.1 (C-8a) | 156.5 (C-9a) | 22.9 (C-7) 28.0 (C-6) | 36.9 (CH) 23.3 ($CH_3$) |
| **2/3** | 3.01 t | 3.08 t ($CH_2$-8) | 2.24 m ($CH_2$-7) | 3.16 s (6H) | 167.8 | 131.9 | 120.6 | 35.0 (C-8) | 170.1 (C-8a) | 156.4 (C-9a) | 22.7 (C-7) 28.1 (C-6) | 37.5 |
| **2/4** | 3.03 t (8 Hz) | 3.11 t (8 Hz) | 2.26 m (8 Hz) | 3.65 m ($NCH_2$) 3.81 m ($OCH_2$) | 167.3 | 132.5 | 121.4 | 35.2 (C-8) | 171.0 (C-8a) | 156.3 (C-9a) | 22.9 (C-7) 28.2 (C-6) | 45.7 ($NCH_2$) 66.4 ($OCH_2$) |
| **2/5** | 3.04 m | 3.16 m ($CH_2$-10) | 1.9 m (2H) 1.8 m (4H) | 2.72 s (3H) | 168.3 | 134.5 | 122.8 | 39.6 (C-10) | 169.6 (C-10a) | 154.0 (C-11a) | 25.9, 27.1, 28.4, 31.1 (C-8 !) | 13.7 |
| **2/6** | 3.03 t | 3.10 t ($CH_2$-11) | 1.84 m (4H) 1.42 m (4H) | 2.73 s (3H) | 168.6 | 135.1 | 121.2 | 36.0 (C-11) | 168.5 (C-11a) | 154.5 (C-12a) | 25.6, 25.8, 26.8, 28.8, 30.4 | 13.8 |
| **2/7** | 2.91 m | 2.91 m ($CH_2$-15) | 2.0 m (2H) 1.8 m (2H) 1.5 m (12H) | 2.72 s (3H) | 168.9 | 136.4 | 121.5 | 33.1 (C-15) | 168.0 (C-15a) | 154.2 (C-16a) | 22.3, 23.1, 24.9, 25.8, 26.1, 26.2, 26.7 (2 peaks), 26.8 | 13.8 |

The spectral data of derivatives **1a-5a, 1c-5c, 1d-5d** and **1e-5e** were fully analogous to those of the corresponding [1,2,4]triazolo[5,1-*b*]quinazoline (**1b-4b**) and 1,3a,5,6,10c-pentaazaacephenanthrylene (**5b**) derivatives, respectively, the structure of which was proved previously [1], giving evidence for their constitution.

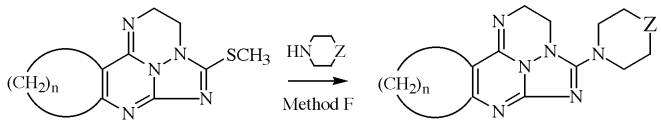
Interestingly the carbon atom 9 of the 1,3a,5,6,11c-pentaaza-7,8,9,10-tetrahydro-11*H*-cyclohepta[*e*]acenaphthylenes **5/6** (n = 5, Q = methylthio) and **5/7** (n = 5, Q = morpholin-4-yl) and that of the corresponding carbon atom 8 of derivatives **2/5** and **3/5** (Q = methylthio, X = chloro or 2-hydroxyethylamino, respectively) (Scheme 3) was also shifted upfield to 32.4 and 32.5 ppm, and 31.1 and 31.3 ppm, respectively, analogously to that of the corresponding carbon atom 8 of the 6,7,8,9,10,11-hexahydrocyclohepta-[*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-one derivatives **1/5** (Q = methylthio, $R^3$ = H) and **6/5** (Q = methylthio, $R^3$ = benzyl), appearing at 32.4 and 31.3 ppm, respectively, attributed previously [3] to the shielding effect of the C=O group.

Table III

Synthetical and Analytical Data of 5-[(2-Hydroxyethyl)amino and 2-Chloroethyl)amino]-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines

| Compound | n | Q | Reaction Time (hours) | Yield (%) | Mp (°C) (Cryst. from) | Molecular Formula (MW) | MS EI | Analysis Calcd/Found C | H | N | S | Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3/1** | 3 | Methylthio | 0.5 | 97 | 191-192 (MeOH) | $C_{11}H_{15}N_5OS$ 265.34 | | 49.79 49.71 | 5.70 5.81 | 26.39 26.33 | 12.08 12.11 | |
| **3/2** | 3 | 1-Methylethylthio | 1 | 98 | 195-196 ($CH_3CN$ / EtOH) | $C_{13}H_{19}N_5OS$ 293.39 | | 53.22 53.30 | 6.53 6.71 | 23.87 23.78 | 10.93 10.97 | |
| **3/3** | 3 | Dimethylamino | 8 | 98 | 216-217 (EtOH) | $C_{12}H_{18}N_6O$ 262.32 | | 54.95 54.87 | 6.92 7.01 | 32.04 32.12 | | |
| **3/4** | 3 | Morpholin-4-yl | 1 | 81 | 225-227 ($CH_3CN$ / EtOH) | $C_{14}H_{20}N_6O_2$ 304.35 | | 55.25 55.30 | 6.62 6.73 | 27.61 27.69 | | |
| **3/5** | 5 | Methylthio | 4 | 93 | 216-217 ($CH_3CN$ / EtOH) | $C_{13}H_{19}N_5OS$ 293.39 | 293 | 53.22 53.17 | 6.53 6.64 | 23.87 23.84 | 10.93 10.88 | |
| **3/6** | 6 | Methylthio | 6 | 95 | 208-209 (EtOH) | $C_{14}H_{21}N_5OS$ 307.42 | 307 | 54.70 54.77 | 6.89 6.98 | 22.78 22.71 | 10.43 10.38 | |
| **3/7** | 10 | Methylthio | 2 | 93 | 202-203.5 (2-PrOH) | $C_{18}H_{29}N_5OS$ 363.53 | | 59.47 59.55 | 8.04 8.11 | 19.26 19.13 | 8.82 8.75 | |
| **4/1** | 3 | Methylthio | 18 | 92 | 174-177 (dec) (ether) | $C_{11}H_{14}ClN_5S$ 283.78 | | 46.56 46.61 | 4.97 5.11 | 24.68 24.66 | 11.30 11.22 | 12.49 12.55 |
| **4/2** | 3 | 1-Methylethylthio | 20 | 86 | 145-147 (dec) (ether) | $C_{13}H_{18}ClN_5S$ 311.84 | | 50.07 50.13 | 5.82 5.96 | 22.46 22.39 | 10.28 10.22 | 11.37 11.42 |
| **4/4** | 3 | Morpholin-4-yl | 19 | 84 | 175-180 (dec) (ether) | $C_{14}H_{19}ClN_6O$ 322.80 | | 52.09 52.01 | 5.93 6.06 | 26.03 25.98 | | 10.98 11.02 |

Scheme 2

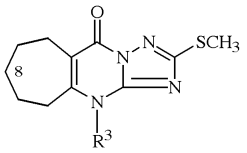



**5**, Q = $SCH_3$ **5**, Q = dialkylamino (Z = O and $CH_2$)

Scheme 3


**5/6**: Q = methylthio
**5/7**: Q = morpholin-4-yl

**2/5**: X = Cl
**3/5**: X = NH-$(CH_2)_2$-OH




**1/5**: $R^3$ = H
**6/5**: $R^3$ = benzyl

As expected (Table VI) the ring size of the cycloalka moiety of derivatives **5a** and **5c-5e** (Q = methylthio) strongly influenced the chemical shift of carbon atoms 6a and ωa. On the other hand, it did not influence the chemical shift of carbon atoms 4 appearing at 161.5, 161.3, 161.4 and 160.8 ppm, respectively, (Table VI), in full analogy with that of derivative **5b** (Q = methylthio) reported to appear at 161.8 ppm previously [1]. This fact predicts analogous chemical surrounding, thus similar electronic structure of carbon atom 4, and consequently the possibility of nucleophilic attack of amines.

Based on the above prediction derivatives **5a** (Q = methylthio) and **5c-5e** (Q = methylthio) were reacted at 100 °C with morpholine and piperidine (Method F, Scheme 2) to yield within a short time (1-2 hours) and in good yield (69–78 %) the expected 4-dialkylamino derivatives **5a** and **5c-5e** (Q = morpholin-4-yl and piperidin-1-yl) (Table V).

As a conclusion it can be stated that different size cycloalkanes, either planar or bulky, attached to the 1,3a,5,6,ωc-pentaazaacenaphthylene do not influence considerably its electronic state. Consequently the 4-alkylthio group of derivatives **5a-5e** (Q = alkylthio) is in all cases activated towards the nucleophilic attack of amines.

## 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. Dry-column flash chromatography was performed according to [7] on Kieselgel 60 H (Merck 107736) and Aluminium oxide 60 G (Merck 101090).

Table IV

Nmr Data of 5-[(2-Hydroxyethyl)amino and 2-Chloroethyl)amino]-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines

| | | pmr | | | | | | | cmr | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Solvent pmr cmr | NH | $NCH_2$ $OCH_2$ ($ClCH_2$) | OH | $CH_2$-6 | other $CH_2$ | $CH_2$-(ω-1) | Q | $NCH_2$ $OCH_2$ ($ClCH_2$) | C-2 | C-5 | C-5a | C-6 | Other $CH_2$ | C-(ω-1) | C-(ω-1)a | ωa | Q |
| **3/1** | b | 7.54 t | 3.64 m (4H) | 4.98 t | 2.84 t | 2.09 qui ($CH_2$-7) | 3.13 t ($CH_2$-8) | 2.65 s (3H) | 44.8 60.4 | 164.3 | 143.4 | 100.5 | 28.0 | 22.3 (C-7) | 33.9 (C-8) | 171.5 (C-8a) | 155.7 (C-9a) | 13.1 |
| **3/2** | a+b b | 6.95 t | 3.76 m (4H) | 4.86 t | 2.91 t | 2.17 qui ($CH_2$-7) | 3.18 t ($CH_2$-8) | 3.97 m (1H) 1.44 d (6H) | 44.9 60.8 | 163.5 | 143.9 | 100.8 | 28.5 | 22.8 (C-7) | 34.3 (C-8) | 171.9 (C-8a) | 155.8 (C-9a) | 36.5 (CH) 23.5 ($CH_3$) |
| **3/3** | a+b | 6.76 t | 3.67 m (4H) | 4.98 bs | 2.79 t | 2.08 qui ($CH_2$-7) | 3.10 t ($CH_2$-8) | 3.04 s (6H) | 44.7 60.7 | 166.5 | 143.0 | 99.5 | 28.5 | 22.7 (C-7) | 34.1 (C-8) | 169.6 (C-8a) | 155.4 (C-9a) | 37.4 |
| **3/4** | b | 7.05 t | 3.60 m (4H) | 4.96 t | 2.76 t | 2.03 qui ($CH_2$-7) | 3.08 t ($CH_2$-8) | 3.44 m (4H, $NCH_2$) 3.70 m (4H, $OCH_2$) | 44.8 60.8 | 166.1 | 143.5 | 100.0 | 28.5 | 22.8 (C-7) | 34.2 (C-8) | 170.2 (C-8a) | 155.4 (C-9a) | 45.9 ($NCH_2$) 65.8 ($OCH_2$) |
| **3/5** | b a+c | 6.61 t | 3.88 q (5.4Hz) 3.76 t | 4.8 bs | 2.84 m | 1.85 m (2H) 1.70 m (4H) ($CH_2$-7-9) | 2.98 m ($CH_2$-10) | 2.64 s (3H) | 47.8 61.3 | 166.1 | 145.7 | 106.0 | 25.7, 25.8, 27.4 31.3 (C-8 !) | | 38.5 (C-10) | 169.0 (C-10a) | 153.9 (C-11a) | 13.6 |
| **3/6** | a+b a+c | 6.53 t | 4.08 q (5.3 Hz) 3.78 t | 4.7 bs | 2.87 m | 1.80 qui 1.70 qui 1.49 qui 1.38 qui ($CH_2$-7-10) | 2.91 m ($CH_2$-11) | 2.64 s (3H) | 46.7 61.4 | 165.9 | 145.4 | 102.9 | 23.5, 25.4, 25.9, 28.7, 30.1 (C- 6-10) | | 35.2 (C-11) | 165.85 (C-11a) | 154.9 (C-12a) | 13.2 |
| **3/7** | a+b a+c | 6.93 t | 4.07 q (6 Hz) 3.66 t | 4.7 bs | 2.7 m | 1.82 m (2H) 1.63 m (2H) 1.3-1.56 m (12 H) ($CH_2$-7-14) | 2.7 m ($CH_2$-15) | 2.60 s (3H) | 46.7 61.4 | 166.0 | 146.5 | 103.8 | 22.0, 22.4, 23.1, 24.9, 25.7, 25.9, 26.2, 26.6, 26.8 (C- 6-14) | | 32.2 (C-15) | 165.2 (C-15a) | 155.0 (C-16a) | 13.3 |
| **4/1** | a+b | 7.71t | 3.96 q (6.4 Hz) 3.79 t | | 2.89 t | 2.17 qui ($CH_2$-7) | 3.12 t ($CH_2$-8) | 2.65 s (3H) | 43.5* 44.0* | 164.9 | 143.2 | 100.6 | 28.3 | 22.7 (C-7) | 34.2 (C-8) | 172.0 (C-8a) | 155.9 (C-9a) | 13.4 |
| **4/1** | a+c | | 4.00 m 3.77 t | | 2.97 t | 2.22 qui ($CH_2$-7) | 3.14 t ($CH_2$-8) | 2.66 s (3H) | 43.3* 44.2* | 166.0 | 143.0 | 101.1 | 28.4 | 22.9 (C-7) | 34.1 (C-8) | 173.0 (C-8a) | 155.7 (C-9a) | 13.4 |
| **4/2** | a | 6.42 t | 4.00 m 3.74 t | | 2.99 t | 2.21 qui ($CH_2$-7) | 3.13 t ($CH_2$-8) | 4.0 m (1H) 1.46 d (6H) | 43.5* 44.5* | 165.3 | 142.9 | 101.2 | 28.5 | 23.1 (C-7) | 34.3 (C-8) | 172.5 (C-8a) | 155.5 (C-9a) | 36.9 (CH) 23.5 ($CH_3$) |
| **4/4** | a | 6.32 t | 3.96 q 3.75 t | | 2.92 t | 2.16 qui ($CH_2$-7) | 3.07 t ($CH_2$-8) | 3.58 m (4H, $NCH_2$) 3.77 m (4H, $OCH_2$) | 43.6* 44.3* | 166.5 | 142.4 | 100.0 | 28.6 | 23.1 (C-7) | 34.4 (C-8) | 171.5 (C-8a) | 155.5 (C-9a) | 45.9 ($NCH_2$) 66.4 ($OCH_2$) |

[a] deuteriochloroform; [b] DMSO-$d_6$; [c] deuteriomethanol.

Table V

Synthetical and Analytical Data of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes

| Compound | n | Q | Method | Starting Material | Reaction | | Yield (%) | Mp (°C) (Cryst. from) | Molecular Formula (MW) | Analysis Calcd/Found | | | | MS EI | UV(EtOH) $\lambda_{max}$(ε .10$^{-3}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time (hours) | Temperature (°C) | | | | C | H | N | S | | |
| **5/1** | 3 | Methylthio | E1 | **3/1** | 14 | 140 | 80 | 197-202 (dec) | $C_{11}H_{13}N_5S$ | 53.42 | 5.30 | 28.32 | 12.96 | | 249 (18.0) |
| | | | [a] | | 27 | 140 | 91 | ($CH_3CN$) | 247.32 | 53.38 | 5.44 | 28.27 | 12.92 | 247 | 284.5 (11.4) |
| | | | | | | | | | | | | | | | 294.5 (11.3) |
| **5/2** | 3 | 1-Methylethylthio | D1 | **4/2** | 66 | reflux | 67 | 153-157 | $C_{13}H_{17}N_5S$ | 56.70 | 6.22 | 25.43 | 11.64 | | 250 (16.8) |
| | | | E2 | **3/2** | 2 | 130 | 77 | (ether) | 275.38 | 56.80 | 6.36 | 25.38 | 11.59 | 275 | 290 (10.4) |
| **5/3** | 3 | Dimethylamino | E1 | **3/3** | 22 | 130 | 90 | 196-199 | $C_{12}H_{16}N_6$ | 59.00 | 6.60 | 34.40 | | | 247.5 (14.1) |
| | | | | | | | | ($CH_3CN$) | 244.30 | 58.91 | 6.73 | 34.28 | | 244 | 265 (12.1) |
| | | | | | | | | | | | | | | | 310 (4.8) |
| **5/4** | 3 | Piperidin-1-yl | F | **5/1** | 1 | 100 | 71 | 175-177 | $C_{15}H_{20}N_6$ | 63.36 | 7.09 | 29.55 | | | 253.5 (22.3) |
| | | | | | | | | (ether) | 284.37 | 63.32 | 7.21 | 29.49 | | 284 | 267 (20.5) |
| | | | | | | | | | | | | | | | 310.5 (6.0) |
| **5/5** | 3 | Morpholin-4-yl | D1 | **4/4** | 110 | reflux | 72 | 230-236 (dec) | $C_{14}H_{18}N_6O$ | 58.73 | 6.34 | 29.35 | | | 245.5 (25.1) |
| | | | | | | | | (EtOAc) | 286.34 | 58.59 | 6.44 | 29.28 | | 286 | 266.5 (23.1) |
| | | | D2 | **4/4** | 0.25 | 180 | 54 | 234-239 (dec) | | | | | | | 307.5 (8.2) |
| | | | E2 | **3/4** | 9 | 130 | 89 | 216-228 (dec) | | | | | | | |
| | | | F | **5/1** | 1 | 100 | 71 | 231-238 (dec) | | | | | | | |
| | | | | | | | | ($CH_3CN$) | | | | | | | |
| **5/6** | 5 | Methylthio | E1 | **3/5** | 8.5 | 140 | 75 | 216-219 (dec) | $C_{13}H_{17}N_5S$ | 56.70 | 6.22 | 25.43 | 11.64 | | 245 (19.9) |
| | | | [a] | | | | | ($CH_3CN$) | 275.38 | 56.66 | 6.17 | 25.38 | 11.60 | 275 | 287.5 (10.1) |
| **5/7** | 5 | Morpholin-4-yl | F | **5/6** | 1.5 | 100 | 70 | 215-222 (dec) | $C_{16}H_{22}N_6O$ | 61.13 | 7.05 | 26.73 | | | 247 (20.6) |
| | | | | | | | | (ether) | 314.39 | 61.08 | 7.15 | 26.70 | | 314 | 263.5 (18.6) |
| | | | | | | | | | | | | | | | 314.5 (6.8) |
| **5/8** | 6 | Methylthio | E1 | **3/6** | 3 | 140 | 72 | 214-217 (dec) | $C_{14}H_{19}N_5S$ | 58.10 | 6.62 | 24.20 | 11.08 | | 245 (19.5) |
| | | | [a] | | | | | ($CH_3CN$) | 289.41 | 58.16 | 6.58 | 24.06 | 11.14 | 289 | 288 (10.4) |
| **5/9** | 6 | Morpholin-4-yl | F | **5/8** | 2 | 100 | 69 | 225-237 (dec) | $C_{17}H_{24}N_6O$ | 62.17 | 7.37 | 25.59 | | | 248 (20.8) |
| | | | | | | | | (ether) | 328.42 | 62.22 | 7.45 | 25.54 | | 328 | 267.5 (18.3) |
| | | | | | | | | | | | | | | | 312 (6.9) |
| **5/10** | 10 | Methylthio | E2 | **3/7** | 4.5 | 130 | 73 | 223.5-226 | $C_{18}H_{27}N_5S$ | 62.57 | 7.88 | 20.27 | 9.28 | | 249 (19.3) |
| | | | [a] | | | | | (ether) | 345.51 | 62.64 | 7.96 | 20.18 | 9.22 | 345 | 296 (10.9) |
| **5/11** | 10 | Morpholin-4-yl | F | **5/10** | 1 | 120 | 78 | 211-212.5 | $C_{21}H_{32}N_6O$ | 65.60 | 8.39 | 21.86 | | | 248 (24.6) |
| | | | | | | | | (ether) | 384.53 | 65.56 | 8.44 | 21.81 | | 384 | 268 (22.5) |
| | | | | | | | | | | | | | | | 307.5 (7.8) |

[a] Type **1** by-product isolated, see Note [6].

Table VI

Nmr data of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes

| | pmr (deuteriochloroform) | | | | | cmr (deuteriochloroform) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Compound | $CH_2$-2 $CH_2$-3 | $CH_2$-7 | other $CH_2$ | $CH_2$-ω | Q | C-2 C-3 | C-4 | C-5a | C-6a | C-7 | other C | C-ω | C-ωa | C-ωb | Q |
| **5/1** | 3.96 s (4H) | 2.85 m | 2.11 m ($CH_2$-8) | 2.79 m ($CH_2$-9) | 2.81 s (3H) | 42.9 41.3 | 161.5 | 154.3 | 164.5 | 35.0 | 21.9 (C-8) | 27.0 (C-9) | 111.8 (C-9a) | 142.6 (C-9b) | 13.8 |
| **5/2** | 3.93 s (4H) | 2.85 t | 2.10 m ($CH_2$-8) | 2.77 t ($CH_2$-9) | 4.20 m (1H) 1.54 d (6H) | 43.0 41.2 | 160.7 | 154.4 | 164.7 | 35.1 | 22.0 (C-8) | 27.0 (C-9) | 111.6 (C-9a) | 142.6 (C-9b) | 39.2 (CH) 23.0 ($CH_3$) |
| **5/3** | 3.91 t 3.83 t | 2.76 t | 2.06 m ($CH_2$-8) | 2.72 t ($CH_2$-9) | 3.20 s (6H) | 44.8 43.7 | 162.8 | 155.3 | 163.0 | 34.8 | 21.7 (C-8) | 27.0 (C-9) | 111.4 (C-9a) | 143.2 (C-9b) | 39.5 |
| **5/4** | 3.91 t 3.71 t | 2.78 t | 2.06 m ($CH_2$-8) | 2.73 t ($CH_2$-9) | 3.55 m (4H) 1.70 m (6H) | 45.0 44.5 | 163.5 | 155.6 | 163.4 | 35.0 | 22.0 (C-8) | 27.2 (C-9) | 112.0 (C-9a) | 143.5 (C-9b) | 48.8 25.3 23.8 |
| **5/5** | 3.91 t 3.76 t | 2.78 t | 2.07 qui ($CH_2$-8) | 2.73 t ($CH_2$-9) | 3.62 m (4H) 3.82 m (4H) | 44.7 44.1 | 162.8 | 155.1 | 163.2 | 34.9 | 21.8 (C-8) | 27.1 (C-9) | 112.3 (C-9a) | 143.2 (C-9b) | 47.7 ($NCH_2$) 65.9 ($OCH_2$) |
| **5/6** | 3.92 m (4H) | 2.80 m | 1.83 qui ($CH_2$-9) 1.65 qui ($CH_2$-8) 1.57 qui ($CH_2$-10) | 2.73 m ($CH_2$-11) | 2.80 s (3H) | 43.1 40.8 | 161.3 | 151.5 | 162.2 | 38.8 | 32.4 (C-9) 26.8 (C-10) 25.8 (C-8) | 23.6 (C-11) | 113.6 (C-11a) | 144.3 (C-11b) | 13.8 |
| **5/7** [a] | 3.91 t 3.71 t | 2.73 m | 1.82 qui ($CH_2$-9) 1.63 qui ($CH_2$-8) 1.55 qui ($CH_2$-10) | 2.69 m ($CH_2$-11) | 3.63 m (4H) 3.81 m (4H) | 44.7 43.5 | 162.8 | 152.5 | 161.0 | 38.5 | 32.5 (C-9) 26.9 (C-10) 25.7 (C-8) | 23.6 (C-11) | 114.2 (C-11a) | 144.9 (C-11b) | 47.7 ($NCH_2$) 65.8 ($OCH_2$) |
| **5/8** | 3.92 m (4H) | 2.72 m | 1.78 qui (2H) 1.66 qui (2H) 1.45 m (4H) ($CH_2$- 8-11) | 2.72 m ($CH_2$-12) | 2.80 s (3H) | 43.1 40.9 | 161.4 | 152.0 | 158.8 | 34.5 | 29.7, 29.2, 26.6, 26.0 (C- 8-11) | 23.7 (C-12) | 111.6 (C-12a) | 143.6 (C-12b) | 13.8 |
| **5/9** [a] | 3.91 t 3.70 t | 2.66 m | 1.76 qui (2H) 1.64 qui (2H) 1.45 m (4H) ($CH_2$- 8-11) | 2.66 m ($CH_2$-12) | 3.62 m (4H) ($NCH_2$) 3.82 m (4H) ($OCH_2$) | 44.8 43.7 | 162.9 | 153.1 | 157.6 | 34.2 | 29.6, 29.3, 26.6, 26.1 (C- 8-11) | 23.8 (C-12) | 112.1 (C-12a) | 144.3 (C-12b) | 47.7 ($NCH_2$) 65.9 ($OCH_2$) |
| **5/10** | 3.98 s (4H) | 2.68 t | 1.88 m (2H) 1.73 m (2H) 1.3-1.6 m (12 H) ($CH_2$- 8-15) | 2.64 t ($CH_2$-16) | 2.82 s (3H) | 42.3 41.2 | 160.8 | 151.7 | 162.3 | 31.8 | 26.2 (two peaks), 26.0 (two peaks), 25.5, 24.1, 23.3, 23.1 (C- 8-15) | 22.1 (C-16 ) | 111.8 (C-16a) | 144.4 (C-16b) | 13.9 |
| **5/11** | 3.92 t 3.67 t | 2.57 t | 1.85 m (2H) 1.70 m (2H) 1.3-1.6 m (12 H) ($CH_2$- 8-15) | 2.54 t ($CH_2$-16) | 3.61 m (4H) ($NCH_2$) 3.81 m (4H)) ($OCH_2$) | 44.9 43.8 | 163.4 | 153.1 | 157.8 | 31.3 | 26.3, 26.05, 26.0, 25.9, 25.4, 24.1, 23.3, 23.1 (C- 8-15) | 22.1 (C-16 ) | 112.7 (C-16a) | 145.1 (C-16b) | 47.8 ($NCH_2$) 65.9 ($OCH_2$) |

[a] Assignment corroborated by 2D-nmr.

General Method for the Synthesis of 5-Chloro-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine Derivatives **2**.

Method A.

To a suspension of 0.03 mole of the corresponding cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(ω*H*)-one (**1**) and 23.0 g (0.15 mole, 14.0 ml) of phosphorus oxychloride 0.79 g (0.01 mole, 0.8 ml) of pyridine was added. The mixture was stirred at the temperature and for time given in Table I. The brown solution obtained was decomposed by pouring it into 200 g of crushed ice and stirred for 1 hour.

Method A1.

The crystals that precipitated were collected by filtration and washed free of acids with cold water and 5 % aqueous sodium hydrogen carbonate solution. The air-dried product was dry-column flash chromatographed on Kieselgel 60 H (eluents: different mixtures of *n*-hexane and chloroform of continuously increasing polarity) to yield after evaporation of the appropriate fractions *in vacuo* the corresponding 5-chloro-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine derivative **2**, that was recrystallised from an appropriate solvent (Table I, for the spectral data see Table II).

Method A2.

The oily product separated was taken in chloroform, the chloroform solution was washed with cold water and 5 % aqueous sodium hydrogen carbonate solution until the washings were neutral. After drying over anhydrous sodium sulphate and evaporating the solvent the residue was purified as in A1.

General Method for the Synthesis of 5-(2-Hydroxyethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine Derivatives **3**.

Method B.

To a suspension of 0.024 mole of the appropriate 5-chloro derivative (**2**) in a mixture of 25 ml of 2-propanol and 25 ml of chloroform 3.24 g (0.053 mole, 3.2 ml) of 2-aminoethanol was added and refluxed for time given in Table III. The reaction mixture was evaporated *in vacuo* to dryness, the crystalline residue was suspended in 50 ml of water, collected by filtration and washed with water and a small amount of acetonitrile to yield the corresponding 5-(2-hydroxyethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine derivative **3,** pure enough for further reactions. An analytical sample was recrystallised from an appropriate solvent (Table III, for the spectral data see Table IV).

General Method for the Synthesis of 5-(2-Chloroethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines (**4**).

Method C.

To a suspension of 0.02 mole of the corresponding 5-(2-hydroxyethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine derivative **3** in 60 ml of dichloromethane 4.76 g (0.04 mole, 2.9 ml) of thionyl chloride was added with stirring. A slightly exothermic reaction took place and the yellow solution obtained began to crystallise in 30 minutes. The thick suspension was stirred overnight at room temperature (the time is given in Table III). The crystals (probably **4**.HCl) were collected by filtration and washed with dichloromethane. The product was suspended in 50 ml of chloroform and to the mixture 4.05 g (0.04 mole, 5.6 ml) of triethylamine was added. The solution obtained was washed with water (2 x 20 ml), dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue was purified by dry-column flash chromatography on Kieselgel 60 H (eluents: dichloromethane and a 50:1 mixture of dichloromethane and methanol). The appropriate fractions were collected, evaporated *in vacuo* to dryness, the residue was triturated with ether and collected by filtration to yield 5-(2-chloroethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidines (**4**) (Table III, for their spectral data see Table IV).

General Method for the Synthesis of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes (**5**) by Ring Closure of the Corresponding 5-(2-Chloroethyl)amino-2-Q-cycloalka[*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidines (**4**).

Method D1.

A suspension of 0.015 mole of the appropriate 5-(2-chloroethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4**) in 30 ml of acetonitrile was refluxed for the time given in Table V. The solution obtained was evaporated *in vacuo* to dryness, the residue was suspended in 50 ml of chloroform, 1.67 g (0.0165 mole, 2.3 ml) of triethylamine was added to it and the solution obtained was washed with 3 x 15 ml of water. The chloroform layer was dried over anhydrous sodium sulphate, evaporated to dryness and the residue was purified by dry-column flash chromatography on Aluminium oxide 60 G (eluents: different mixtures of *n*-hexane and chloroform of continuously increasing polarity). The appropriate fractions were collected, evaporated *in vacuo* to dryness and the residue collected by filtration from a suitable solvent (Table V, for the spectral data see Table VI).

Method D2.

5-(2-Chloroethyl)amino-6,7-dihydro-8*H*-2-(morpholin-4-yl)-cyclopenta[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4/4**) (0.81 g, 0.0025 mole) was heated with stirring under argon atmosphere at 180 °C for 15 minutes. After cooling the product was dissolved in methanol, to the solution 0.135 g (0.0025 mole) of sodium methoxide was added, the mixture was evaporated *in vacuo* to dryness and the residue was subjected to dry-column flash chromatography (see Method D1).

General Method for the Synthesis of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes (**5**) by Ring Closure of the Corresponding 5-(2-Hydroxyethyl)amino-2-Q-cycloalka[*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine Derivatives **3** in Polyphosphoric Acid.

Method E.

To 0.015 mole of the corresponding 5-(2-hydroxyethyl)amino-2-Q-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**3**) a six-fold amount (g/g) of polyphosphoric acid (Fluka) was added and the mixture “stirred” at an oil bath temperature and for time given in Table V. During the reaction the starting material was slowly dissolved and a honey-like mixture was obtained. This was cautiously dissolved in 3 x 50 ml of water keeping the inner temperature below 50 °C. The brown solution obtained [6] was neutralised with powdered sodium hydrogen carbonate added in small portions under vigorous stirring (heavy foaming). The pH of the solution was then adjusted with concentrated aqueous ammonia solution to 9-10.

Method E1.

The product that crystallised was immediately collected by filtration and washed with ice-cold water. After drying it was purified by dry-column flash chromatography on Aluminium oxide

60 G (eluent: dichloromethane). The appropriate fractions were collected, evaporated *in vacuo* to dryness, the residue was triturated with a suitable solvent and collected by filtration (Table V).

Method E2.

In case the product did not crystallise the solution was immediately extracted with chloroform, the combined chloroform layers were dried, evaporated *in vacuo* to dryness and purified as in E1.

Nucleophilic Displacement of the 4-Methylthio Group of 1,3a,5,6,ωc-Pentaazacycloalka[*e*]acenaphthylenes (**5**, Q = methylthio) with Dialkylamines.

Method F.

A mixture of 0.005 mole of the corresponding 4-methylthio-1,3a,5,6,ωc-pentaazacycloalka[*e*]acenaphthylenes (**5**, Q = methylthio) and 0.05 mole of the corresponding dialkylamine was stirred at a temperature and for time given in Table V. After cooling 10 ml of ether was added to the solution, the crystals precipitated were collected by filtration and washed with ether. The crude product (**5**, Q = dialkylamino) was subjected to dry-column flash chromatography on Aluminium oxide 60 G (eluents: dichloromethane, followed by a 50:1 mixture of dichloromethane and methanol). The appropriate fractions were evaporated *in vacuo* to dryness, the residue was triturated with ether and collected by filtration (Table V, for their spectral data see Table VI).

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[6] If the brown solution obtained crystallised the crystals were 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-cycloalka[*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(ω*H*)-one (**1**) by-product. Its amount does not exceed 5 %.

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