NITROGEN BRIDGEHEAD COMPOUNDS. PART 53[1]. NEW SYNTHESIS OF 2,3a,6a-TRIAZAPHENALENE-3-THIONES

István Bitter[a1], Béla Pete[a1], Gábor Tóth[a2], István Hermecz[b] and Zoltán Mészáros[b]

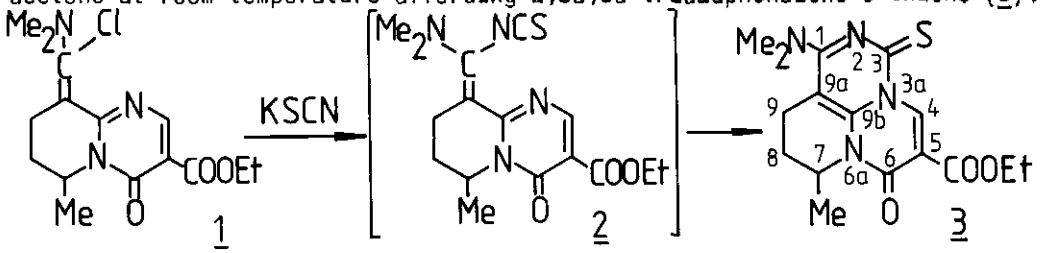
a1. Technical University, Department of Organic Chemistry and Technology, H-1111 Budapest, Hungary

a2. NMR Laboratory of the Institute of General and Analytical Chemistry, H-1111 Budapest, Hungary

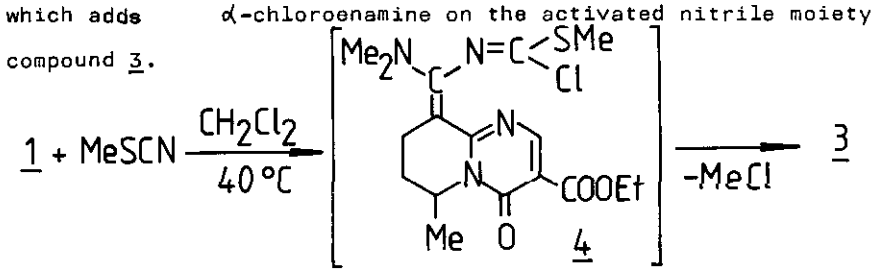
b. CHINOIN Pharmaceutical and Chemical Works, H-1325 Budapest, P.O. Box 110, Hungary

Abstract — Starting from α-chloroenamine 1 and iminochloride 13 a new approach of the neutral 2,3a,6a-triazaphenalene ring has been described.

Recently we have reported the preparation of some representatives of a new heterocyclic quaternary ring system - the 2,3a,6a-triazaphenalenium salts[2]. Since the neutral tricycle could not be achieved by reduction of the quaternary salts we had to find new entries. Similarly to our first synthesis compound 1 proved to be useful for this purpose. It readily reacts with alkali thiocyanate in acetone at room temperature affording 2,3a,6a-triazaphenalene-3-thione (3).

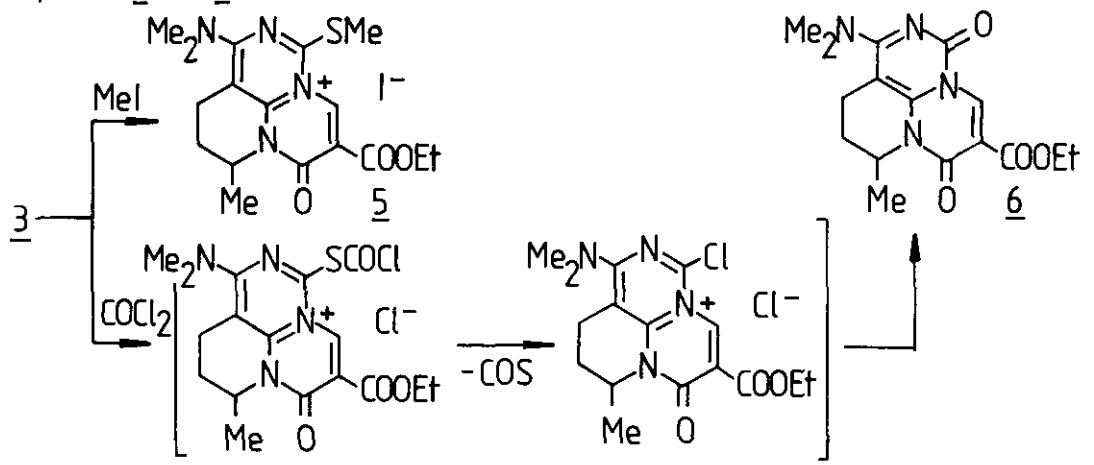


It is not surprising that α-chloroenamine, a hard electrophile, will combine with the hard nucleophilic side of the thiocyanate group and formation of S-substituted compounds was not observed. It is worth noting that methyl thiocyanate which adds α-chloroenamine on the activated nitrile moiety also results in compound 3.

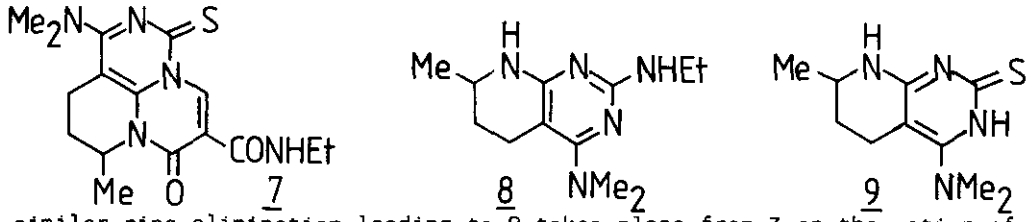


This reaction is regarded to be an unambiguous proof for the structure of 3 and for the reaction pathway suggested. ^{1}H NMR investigation also offers evidence for the ring closure via the isothiocyanate intermediate (2). In compound 3 the signal of the H-4 proton is shifted to over 10 ppm from 8-8.5 ppm[3] owing to the strong deshielding effect of the neighbouring thiocarbonyl group.

The cyclic thiourea moiety of compound 3 could be alkylated and acylated to compounds 5 and 6.

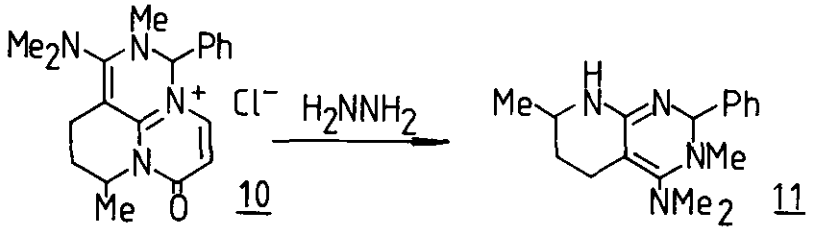


The thiocarbonyl group of 3 proved to be resistant toward amines whilest the isothiuronium salt (5) suffered ring elimination. Compound 3 reacted with ethylamine only on the ester group yielding the amide (7) while 5 gave compound 8 as major product together with some unidentified products.



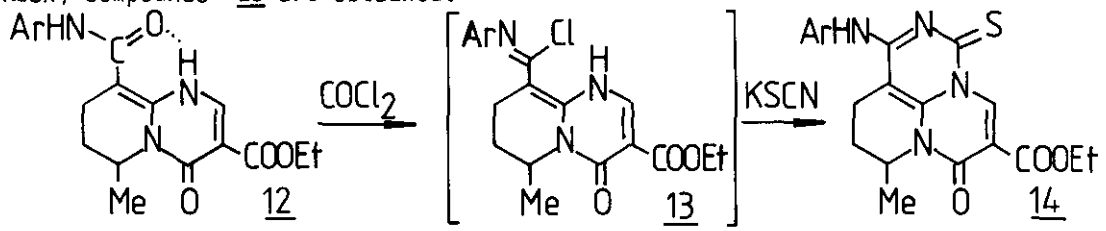
A similar ring elimination leading to 9 takes place from 3 on the action of aqueous NaOH or hydrazine.

This reaction is supposed to involve a nucleophilic attack on the C-4 carbon atom followed by N-3a — C-4 bond fission, similarly to the reaction described



previously for the 2,3a,6a-triazaphenalenium quaternary salts[4]. If the salt (10) not containing a reactive group in position 5, was treated with hydrazine a reaction quite similar to that of compound 3 was observed.

We have found another route for the preparation of the title compounds. If 9-(N-arylcarbamoyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (12)[5,6] are treated with phosgene and the resulting iminochlorides are allowed to react with KSCN, compounds 13 are obtained.



a: C_6H_5; b: 4-ClC_6H_4; c: 3-ClC_6H_4; d: 3,4-Cl_2-C_6H_3.

EXPERIMENTAL

All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-100 instrument using $SiMe_4$ as an internal standard, in $CDCl_3$ and DMSO-d_6 solutions.

Ethyl 1-Dimethylamino-7-methyl-6-oxo-3-thioxo-7,8-dihydro-3H,6H,9H-2,3a,6a-triazaphenalene-5-carboxylate (3).

Method A. A stirred suspension of 9-[(dimethylamino)chloromethylene]pyrido[1,2-a]pyrimidine (1) (3.26 g, 10 mmol) and KSCN (0.97 g, 10 mmol) in dry acetone (25 ml) was allowed to react at ambient temperature for 24 h. The yellow product (3) (3.1 g, 89%) was precipitated with water (50 ml), filtered off and washed with ethanol. Mp 204-206 °C (from dioxane).

Method B. A solution of compound 1 (3.26 g, 10 mmol) and MeSCN (2.19 g, 30 mmol) in dichloromethane (40 ml) was refluxed for 4 h. The solvent was evaporated to dryness in vacuo. The residue was recrystallized from dioxane to give 3 (2.50 g, 70%). Mp 204-206 °C.

Anal. Calcd. for $C_{16}H_{20}N_4O_3S$ (348.418): C, 55.15; H, 5.78; N, 16.08. Found: C, 55.25; H, 5.71; N, 16.17%. ^1H NMR ($CDCl_3$): $MeCHCH_2CH_2$ 1.34d, 5.12m, 1.65-2.60m, 2.70-3.30m; OCH_2CH_3 4.39q, 1.41t; NMe_2 3.35s; H-4 10.18s.

1-Dimethylamino-5-ethoxycarbonyl-7-methyl-3-methylthio-6-oxo-7,8-dihydro-6H,9H-2,6a-diaza-3a-azoniaphenalene Iodide (5).

A mixture of triazaphenalene (3) (3.48 g, 10 mmol) and methyl iodide (2.85 g, 20 mmol) in acetone (35 ml) was refluxed for 3 h. The precipitated product was

filtered off, washed with acetone, dried and recrystallized from ethanol to give the quaternary salt (5) (3.82 g, 78%). Mp 190-192 °C (decomp.). Anal. Calcd. for $C_{17}H_{23}N_4O_3SI$ (490.356): C, 41.63; H, 4.72; N, 11.42. Found: C, 41.53; H, 4.68; N 11.46%. ^{1}H NMR ($CDCl_3$): $MeCHCH_2CH_2$ 1.32d, 5.12m, 1.90-2.30m, 2.80-3.30m; OCH_2CH_3 4.37q, 1.40t; MeS 2.85s; NMe_2 3.57s; H-4 8.67s.

Ethyl 1-Dimethylamino-7-methyl-3,6-dioxo-7,8-dihydro-3H,6H,9H-2,3a,6a-triazaphenalene-5-carboxylate (6).

Into a solution of triazaphenalene (3) (3.48 g, 10 mmol) in dichloromethane (20 ml) phosgene was introduced at ambient temperature. After COS evolution ceased the reaction mixture was washed with aqueous 10% Na_2CO_3 solution. The dried (Na_2SO_4) organic solvent was evaporated to dryness in vacuo. The residue was recrystallized from ethanol to give compound 6 (2.66 g, 80%). Mp 185-186 °C. Anal. Calcd. for $C_{16}H_{20}N_4O_4$ (332.352): C, 57.82; H, 6.06; N, 16.85. Found: C, 57.68; H, 6.09; N, 16.89%. ^{1}H NMR ($DMSO-d_6$): $MeCHCH_2CH_2$ 1.37d, 5.12m, 1.72-209m, 2.65-3.10m; NMe_2 3.28s; OCH_2CH_3 4.37q, 1.40t; H-4 9.21s.

N-Ethyl-1-dimethylamino-7-methyl-6-oxo-3-thioxo-7,8-dihydro-3H,6H,9H-2,3a,6a-triazaphenalene-5-carboxamide (7).

A solution of triazaphenalene (3) (3.48 g, 10 mmol) and ethylamine (1.35 g, 30 mmol) in ethanol (30 ml) was allowed to react at ambient temperature for 3 h. The precipitated crystals were filtered off, washed with ethanol, dried and recrystallized from ethanol to give the carboxamide (7) (2.36 g, 65%). Mp 240-242 °C. Anal. Calcd. for $C_{16}H_{21}N_5O_3S$ (363.434): C, 52.87; H, 5.82; N, 19.27. Found: C, 52.61; H, 5.69; N, 19.11%. ^{1}H NMR ($CDCl_3$): $MeCHCH_2CH_2$ 1.33d, 5.05m, 1.50-2.15m, 2.40-3.05m; NMe_2 3.25s; $HNCH_2CH_3$ 8.72t, 3.42m, 1.20t; H-4 10.34s. ^{13}C NMR ($CDCl_3$): C-1 159.7; C-3 171.1; C-4 149.5; C-5 109.3; CONH 160.1; C-6 160.9; C-9a 88.3; C-9b 158.4 ppm.

2-Ethylamino-4-dimethylamino-7-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine (8).

A mixture of the quaternary salt (5) (4.90 g, 10 mmol) and ethylamine (2.25 g, 50 mmol) in ethanol (30 ml) was allowed to react at ambient temperature for 24 h. The solvent was evaporated to dryness in vacuo. The residue was treated with water. The filtered crystals were recrystallized from ethyl acetate to give the pyridopyrimidine (8) (0.89 g, 38%). Mp 172-174 °C. Anal. Calcd. for $C_{12}H_{21}N_5$ (235.328): C, 61.24; H, 8.99; N, 29.76. Found: C, 61.20; H, 8.89; N, 29.82%. ^{1}H NMR ($CDCl_3$): $MeCH(CH_2)_2$ 1.28d, 3.55m, 1.50-3.10m; NCH_2CH_3 3.35m, 1.19t;

NMe_2 3.02s.

4-Dimethylamino-7-methyl-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidine-2(3H)-thione (9).

Method A. A solution of triazaphenalene (3) (3.48 g, 10 mmol) in ethanol (20 ml) and aqueous 20% NaOH solution (5 ml) was allowed to react at ambient temperature for 24 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was dissolved in water. The aqueous solution was acidified with acetic acid. The precipitated crystals were filtered off, washed with water, dried and recrystallized from ethanol to give pyridopyrimidinethione (9) (1.12 g, 50%). Mp 204-205 °C.

Method B. A solution of triazaphenalene (3) (3.48 g, 10 mmol) and hydrazine hydrate (2 ml) in ethanol (20 ml) was allowed to react at ambient temperature for 24 h. The precipitated product was filtered off, washed with ethanol, dried and recrystallized from ethanol to give pyridopyrimidinethione (9) (1.57 g, 70%). Mp 205-206 °C. Anal. Calcd. for $C_{10}H_{16}N_3S$ (224.326): C, 53.54; H, 7.18; N, 24.98. Found: C, 53.50; H, 7.00; N, 24.85%. ^1H NMR ($CDCl_3$): $MeCHCH_2CH_2$ 1.26d, 3.60m, 1.40-1.65m, 1.85-2.64m; NMe_2 3.05s; NH 7.35 broad.

1-Dimethylamino-2,7-dimethyl-6-oxo-3-phenyl-2,7,8,9-tetrahydro-3H,6H-2,6a-diaza-3a-azoniaphenalene Chloride (10).

The compound 10 was prepared from 9-[(dimethylamino)chloromethylene]-6-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one[6] and N-benzylidenemethylamine as described earlier[2]. Yield 63%. Mp 240 °C (acetonitrile). Anal. Calcd. for $C_{20}H_{25}N_4OCl$ (372.885): C, 64.41; H, 6.76; N, 15.02. Found: C, 64.23; H, 6.69; N, 15.09%.

4-Dimethylamino-3,7-dimethyl-2-phenyl-2,3,5,6,7,8-hexahydropyrido[2,3-d]pyrimidine (11).

A mixture of compound 10 (3.73 g, 10 mmol) and hydrazine hydrate (10 ml) was allowed to react at ambient temperature for 24 h. The precipitated crystals were filtered off, washed (ethanol), dried and recrystallized from ethanol to give compound 11 (1.28 g, 45%). Mp 153 °C. Anal. Calcd. for $C_{17}H_{24}N_4$ (284.394): C, 71.79; H, 8.51; N, 19.70. Found: C, 71.43; H, 8.41; N, 19.73%. ^1H NMR ($CDCl_3$): $MeCH(CH_2)_2$ 1.31d, 3.40m, 1.70-2.60m; NMe_2 2.93s; NMe 2.88s, NCHN 5.42s; Ph 7.30m.

Ethyl 1-Arylamino-7-methyl-6-oxo-3-thioxo-7,8-dihydro-3H,6H,9H-2,3a,6a-triazaphenalene-5-carboxylates (14). (General procedure).

Into a solution of compound 12[5,6] (10 mmol) in dichloromethane (50 ml) phosgene

was introduced at ambient temperature. Instead of phosgene dichloromethylenedimethyliminium chloride (1.78 g, 11 mmol) can also be used. The solvent was evaporated to dryness in vacuo. The residue was dissolved in acetone (30 ml). KSCN (1.35 g, 15 mmol) was added to the solution which was allowed to react at ambient temperature for 24 h. The precipitated product was filtered off, washed with acetone, dried and recrystallized from i-PrOH - DMF to give compound 13.

Compound 13a: Yield 38%. Mp 242-244 °C. Anal. Calcd. for $C_{20}H_{20}N_4O_3S$ (396.458): C, 60.58; H, 5.08; N, 14.13. Found: C, 60.62; H, 5.07; N, 14.10%. ^{1}H NMR (DMSO-d_6): $MeCH(CH_2)_2$ 1.20d, 4.90m, 1.70-3.30m; OCH_2CH_3 4.30q, 1.24t; Ph 7.15--7.70m; NH 9.14s; H-4 10.26s.

Compound 13b: Yield 42%. Mp 248-250 °C. Anal. Calcd. for $C_{20}H_{19}ClN_4O_3S$ (430.907): C, 55.74; H, 4.44; N, 13.00. Found: C, 55.80; H, 4.28; N, 13.10%. ^{1}H NMR (DMSO-d_6): $MeCHCH_2CH_2$ 1.20d, 5.00m, 1.75-2.20m, 2.50-2.80m; OCH_2CH_3 4.29q, 1.31t; Ar 7.47d, 7.72d; NH 9.24s; H-4 10.24s.

Compound 13c: Yield 30%. Mp 239-241 °C. Anal. Calcd. for $C_{20}H_{19}ClN_4O_3S$ (430.907): C, 55.74; H, 4.44; N, 13.00. Found: C, 55.76; H, 4.32; N, 12.91%. ^{1}H NMR (DMSO-d_6): $MeCHCH_2CH_2$ 1.20t, 4.96m, 1.70-2.15m, 2.40-2.80m; OCH_2CH_3 4.25q, 1.23t; Ar 7.05-7.90m; NH 9.22s, H-4 10.25s.

Compound 13d: Yield 48%. Mp 254-256 °C. Anal. Calcd. for $C_{20}H_{18}Cl_2N_4O_3S$ (465.356): C, 51.61; H, 3.89; N, 12.04. Found: C, 51.58; H, 3.75; N 12.12%. ^{1}H NMR ($CDCl_3$): $MeCHCH_2CH_2$ 1.29d, 5.21m, 1.80-2.25m, 2.50-2.70m; OCH_2CH_3 4.41q, 1.41t; Ar 7.2-7.65m, H-4 10.31s.

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