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NITROGEN BRIDGEHEAD COMPOUNDS. PART 67[1]. PREPARATION OF NOVEL POLICYCLIC QUATERNARY SALTS

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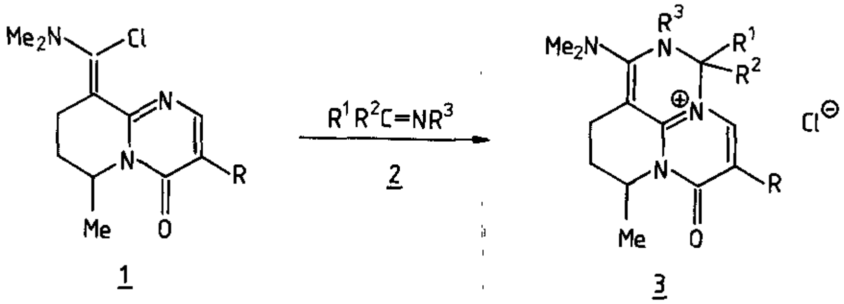
Abstract- The first representatives of new polycyclic ring systems - thiazolo- and oxazolo-[2,3-b] triazaphenalenes, benzoxazolo- and benzothiazolo-[2,3-b] triazaphenalenes and isoquinolo-[1,2-b]triazaphenalenes - are prepared by the cycloaddition of pyrido[1,2-a]pyrimidine derivatives with cyclic azomethines.

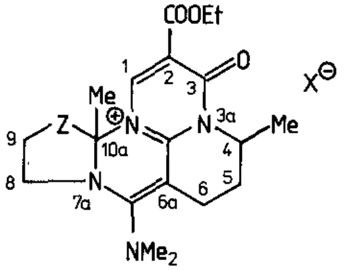
Earlier we have reported[2] that tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (1) containing an α-chloroenamine moiety cyclise with aldimines and ketimines (2) affording 2,6a-diaza-3a-azoniaphenalene ring system (3). The versatile chemical behaviour of this new type of heterocycles has also been published[3,4,5]. From pharmacological considerations,numerous tricycles 3 varying in R^1,R^2,R^3 and R^4 and their derivatives were prepared. The mild and simple conditions required for the cyclisation process tempted us to carry out the ring closure with compounds of more elaborated structure possessing C=N double bond. A great number of cyclic imines have pharmacological activity so it seemed reasonable to make our trial with such type of compounds.

It has turned out that the cyclisation of 1 with various types of cyclic imines proceeds easily in polar solvents and the polycyclic products are stable salts soluble in water.



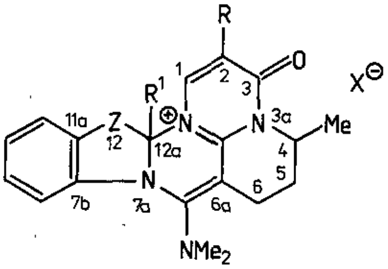
R = COOEt, CN

The reaction of 1 with 2-methyl-thiazoline and -oxazoline, 2-methyl-benzoxazole and -benzothiazole, and 3,4-dihydro-isoquinoline gave the corresponding novel condensed tetra- and penta-cyclic quaternary salts 4-13, respectively.



4 Z = S

5 Z = O

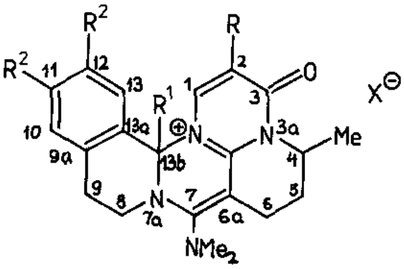


6 R = COOEt, R^1=H, Z=S

7 R = CN, R^1=H, Z=S

8 R = COOEt, R^1=Me, Z=O

The structures of the new ring system 4-13 are unambiguously proved by correct elemental analysis, ir and nmr spectra (Table 1 and 2).



9 R = COOEt; R^1, R^2=H

10 R = CN; R^1R^2=H

11 R = COOEt, R^1=H, R^2=OMe

12 R = CN; R^1=H, R^2=OMe

13 R = COOEt; R^1=Me, R^2=H

Table 1. Characteristic ^1H Nmr chemical shifts of compounds 4-13

Compound (x^-)	Me-4	H-4	CH_2-5,6	NMe_2-7	H-1	R^1 or H-12a or 13b	COOEt
4 (ClO4)	1.20d	5.02m	1.6-2.6m	3.22s	7.98s	2.32s	1.32t;4.32q
5 (ClO4)	1.19d	4.85m	1.6-3.2m	3.16s	8.20s	1.73s	1.28t;4.24q
6 (ClO4)	1.31d	5.08m	1.5-3.4m	3.27s;3.56s	8.81s	7.15s	1.35t;4.33q
7 (ClO4)	1.23d	4.86m	1.4-3.6m	3.08s;3.52s	8.85s	7.18s	-
8 (ClO4)	1.18d	4.90m	1.6-3.2m	3.32s	8.41s	2.18s	1.28t;4.25q
9 (ClO4)	1.30d	4.96m	1.8-3.4m	3.12s;3.22s	8.05s	6.17s	1.12t;4.03q
10 (Cl)	1.34d	4.94m	1.8-3.4m	3.20s;3.31s	6.79s	6.80s	-
11 (ClO4)	1.30d	4.93m	1.6-3.0m	3.20s;3.30s	6.86s	6.04s	1.16t;4.08q
12 (Cl)	1.31d	4.91m	1.8-3.3m	3.18s;3.28s	6.80s	6.75s	3.99s;3.92s$^+$
13 (ClO4)	1.42d	5.04m	1.6-3.3m	3.17s;3.31s	7.04s	2.17s	1.13t;4.08q

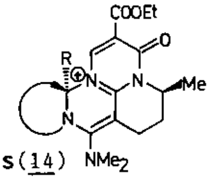
$^+$denotes the signals of MeO group; for 11:3.93s;3.83s

Table 2. Characteristic ^{13}C Nmr chemical shifts of compounds 4-13

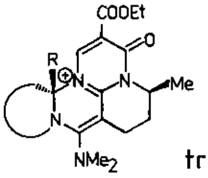
Compound (x^-)	C-1	C-2	C-3	C-4	C-5	C-6	C-6a	C-7	C-10a	C-10c
4 (ClO4)	144.0	106.5	159.0	47.6	25.1	18.8	92.6	148.5	85.2	155.0
5 (ClO4)	142.1	106.7	158.9	47.2	24.9	18.7	83.0	148.1	101.9	154.8
6 (ClO4)	143.6	106.0	155.5	48.1	25.7	19.1	82.5	151.2	87.5$^+$	155.2$^+$
7 (ClO4)	147.3	90.4	155.5	48.3	24.6	18.9	88.0	150.2	82.8$^+$	155.5$^+$
8 (ClO4)	146.3	105.2	154.5	47.7	24.5	18.5	84.7	148.9	108.5$^+$	153.0$^+$
9 (ClO4)	143.5	106.6	161.9	47.4	25.3	19.1	87.1	152.1	71.6*	154.8*
10 (Cl)	144.4	89.8	162.6	46.3	23.8	17.6	86.7	149.9	70.6*	153.9*
11 (ClO4)	143.8	106.7	162.0	42.8	25.4	19.2	86.9	152.2	71.7*	154.9*
12 (Cl)	145.0	89.5	162.3	46.2	23.4	17.3	86.0	149.6	70.8*	153.8*
13 (ClO4)	143.3	106.6	161.4	47.8	25.7	19.3	87.7	149.5	77.3*	154.4*

$^+$denotes the signals of C-12a or C-12c, *denotes the signals of C-13b or C-13d, respectively

In the cyclisation process a second asymmetric centre is formed at the carbon atom attached to R thus diastereoisomers 14 and 15 are to be expected (Fig.1.):



cis(14)



trans(15)

Fig.1

Among the ^{13}C and ^1H nmr spectra of these compounds, only those of 4 showed the presence of diastereoisomers in 1:1 ratio. (Nmr data of the trans isomer 4 are given in Table 1 and 2). In the case of the other compounds only the thermodynamically more stable diastereoisomer could be isolated - the interconversion to the more stable form may only be slightly hindered as pictured by the compound 8 where the thermodynamically less stable diastereoisomer isomerizes in chloroform at room temperature within 1 h. *In order to establish the configuration at* C-13b we have carried out X-ray investigations with compound 10(Cl^-) crystallized from water[6].

The structure was solved with MULTAN-78[7] using 300 E values (E 1.40), 200 phase relationships and 5 starting reflections. An E-map with the best figure of merit revealed all nonhydrogen atoms of the cation (28 atoms). Unlike the 2,6a-diaza-3a-azoniaphenalenium chloride analogue investigated earlier[2] where the peak of the chlorine atom in the E-map was twice as large as the first peak belonging to the cation, here the sixth peak in order could have been assigned as chlorine atom. This fact putsthe presence of chlorine atom in question. After structure factor calculation with 28 atoms of the cation (R = 0.35), a difference Fourier synthesis revealed four peaks which were assigned as oxygen atoms (solvent water molecules). Isotropic and anisotropic refinement for the 32 atoms converged to R = 0.147, nevertheless, one of the solvent oxygen atoms became non-positive definite. Argentometric titration of the sample gave a value of 7.5 w/w% for the chloride content corresponding to $C_{22}H_{24}ClN_5.3,5H_2O$.

By reassigning O1 to Cl the model could be refined further, the non-positivity of the atom arising from the non-realistic thermal parameters disappeared. Further peak (O5) was found from a subsequent difference Fourier calculation, as its symmetry related peak is 1.5 Å from that, a multiplicity of 0.5 was assigned to that atom. Hydrogen atoms of the cations were entered in calculated positions. The hydrogen atom positions of the water molecule were determined by assuming an O-H...X angle of 180° for the hydrogen bonds. Refinement concluded with R=0.064 and R_w = 0.075 for 2188 reflections. The weghting scheme was $w = 1/[\sigma^2(F_o)+0.01F_o^2]$. PLUTO diagram of 10 cation sorrounded by the hydrogen bonding system is shown in Fig.2. Numeric values represent bond lengths of the cation (max. e.s.d. 0.008 Å) and (O)-H...X hydrogen bond distances (e.s.d. 0.03 Å).

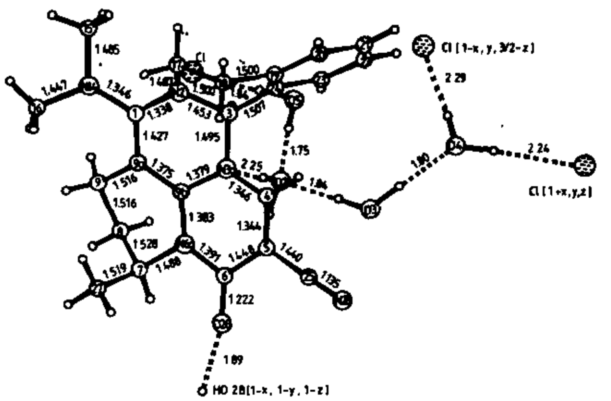


Fig.2. PLUTO diagram of 10 cation surrounded by hydrogen bonds of solvent water molecules and chloride anion

The delocalized bonding system of the cation is very similar to that found at an analogous compound^2 (max. dev. 0.025 Å). The conformation of the ring system is characterized by the endocyclic torsion angles (Fig.3.). Rings A and E are practically planar, B, C and D rings have distorted conformation. B/C, C/D and D/E ring junctions are all cisoid as the signs of the endocyclic torsion angle related to a common bond is in each case the same.

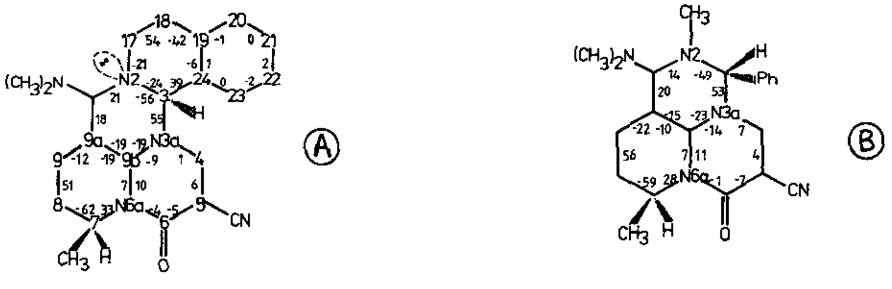


Fig.3. Endocyclic torsion angles: 10 (A), analogous 2,6-diaza-3a-azonia-phenalenium chloride (B)

For comparison the same values for the analogous compound^2 are also given. It is interesting to note that the signs the torsion angles of the common tricyclic system are the same, the attached isoquinoline ring has no significant effect on the shape of this system. Nevertheless the position of the counter ion is completely different due to opposite substitution at C3. Thus the isoquinoline moiety hinders the formation of the C4-H...Cl hydrogen contact observed for the analogous compound.

EXPERIMENTAL

All melting points are uncorrected. The spectra were recorded on a JEOL FX-100 Nmr spectrometer using TMS as an internal standard, a mixture of $CDCl_3$ and $DMSO-d_6$ was used as solvents. The X-ray investigation was performed on an ENRAF-NONIUS CAD 4 diffractometer.

Cyclisation of α-Chloroenamines with 2-Methylthiazoline, 2-Methyloxazoline, Benzothiazole and 2-Methylbenzoxazole (General Procedure)

α-Chloroenamine 1 (0.01 mol) and a cyclic azomethine (0.01 mol) were allowed to react in anhydrous acetonitrile (50 ml) at reflux temperature for about 2 h. After evaporation of the solvent,the residue was washed with ether clarified with charcoal in water. The perchlorate salt precipitated by addition of aqueous $NaClO_4$, was collected by filtration,and crystallized from EtOH.

2-Ethoxycarbonyl-7-dimethylamino-4,5,6,8,9,10a-hexahydro-4,10a-dimethyl-3-oxothiazolo[2,3-b] 2,6a-diaza-3a-azoniaphenalene Perchlorate (4):yield 54 %. Mp 220°C. Anal.Calc. for $C_{19}H_{27}N_4O_3SClO_4$ (490.95): C,46.48; H,5.54; N,11.41 %. Found: C,46.22; H,5.60; N,11.30 %.

2-Ethoxycarbonyl-7-dimethylamino-4,5,6,8,9,10a-hexahydro-4,10a-dimethyl-3-oxooxazol[2,3-b]-2,6a-diaza-3a-azoniaphenalene Perchlorate (5): yield 46 %. Mp 206-208°C. Anal.Calc. for $C_{19}H_{27}N_4O_4ClO_4$ (474.89); C,48.05; H,5.73; N,11.80 %. Found: C,48.22; H,5.78; N,11.56 %.

2-Ethoxycarbonyl-7-dimethylamino-4,5,6,12a-tetrahydro-4-methyl-3-oxobenzothiazolo[2,3-b]-2,6a-diaza-3a-azoniaphenalene Perchlorate (6): yield 68 %. Mp 144-147°C. Anal.Calc. for $C_{22}H_{25}N_4O_3SClO_4$ (524.94): C,50.33; H,4.80; N,10.67 %. Found: C,50.12; H,5.21; N,11.00 %.

2-Cyano-7-dimethylamino-4,5,6,12a-tetrahydro-4-methyl-3-oxobenzothiazolo[2,3-b]-2,6a-diaza-3a-azoniaphenalene Perchlorate(7): yield 74 %. Mp 185°C (decomp.).Anal. Calc. for $C_{20}H_{20}N_5O_3SClO_4$ (477.88): C,50.26; H,4.22; N,14.65 %. Found: C,50.52; H,5.00; N,14.23 %.

2-Ethoxycarbonyl-7-dimethylamino-4,5,6,12a-tetrahydro-4,12a-dimethyl-3-oxobenzoxazolo[2,3-b]-2,6a-diaza-3a-azoniaphenalene Perchlorate (8): yield 74 %. Mp 190°C. Anal.Calc. for $C_{23}H_{27}N_4O_4ClO_4$ (522.89): C,52.83; H,5.20; N,10.71 %. Found: C,52.02; H,5.30; N,10.11 %.

Cyclisation of α-Chloroenamines with 3,4-Dihydroisoquinolines. (General Procedure)
A solution of isoquinoline (0.01 mol) and the α-chloroenamine 1 (0.01 mol) in anhydrous acetonitrile (50 ml) was refluxed for about 30 min. The products obtained by evaporation of the solvent was washed with ether and crystallized from EtOH. If the chlorides could not be recrystallized perchlorate salts were precipitated from aqueous solutions.

2-Ethoxycarbonyl-7-dimethylamino-4,5,6,8,9,13b-hexahydro-4-methyl-3-oxoisoquinolo-[1,2-b]-2,6a-diaza-3a-azoniaphenalene-Perchlorate-(9): yield: 80 %. Mp 230°C.
Anal.Calc. for $C_{24}H_{29}N_4O_3ClO_4$ (520.95): C,55.33; H,5.61; N,10.75 % .
Found: C,55.12; H,5.78; N,10.23 %.
2-Cyano-7-dimethylamino-4,5,6,8,9,13b-hexahydro-4-methyl-3-oxoisoquinolo[1,2-b]-2,6a-diaza-3a-azoniaphenalene-Chloride-(10): yield 83 %. Mp 129°C.
Anal.Calc. for $C_{22}H_{24}N_5OCl$ (409.90): C,64.46; H,5.90; N,17.08 %. Found: C,64.22; H,6.09; N,17.00 %.
2-Ethoxycarbonyl-7-dimethylamino-4,5,6,8,9,13b-hexahydro-11,12-dimethoxy-4-methyl-3-oxoisoquinolo-[1,2-b]2,6a-diaza-3a-azoniaphenalene-Perchlorate-(11):
yield: 78 %. Mp 244°C Anal.Calc. for $C_{26}H_{33}N_4O_5ClO_4$ (581.01): C,53.74; H,5.72; N,9.64 %. Found: C,53.32; H,5.78; N,10.00 %.
2-Cyano-7-dimethylamino-4,5,6,8,9,13b-hexahydro-11,12-dimethoxy-4-methyl-3-oxoisoquinolo-[1,2-b]-2,6a-diaza-3a-azoniaphenalene-Chloride-(12): yield 72 %.
Mp 125-30°C.Anal.Calc. for $C_{24}H_{28}N_5O_3Cl$ (469.95): C,61.33; H,6.00; N,14.90 %.
Found: C,61.11; H,5.88; N,14.45 %.
2-Ethoxycarbonyl-7-dimethylamino-4,5,6,8,9,13b-hexahydro-4,13b-dimethyl-3-oxoisoquinolo[1,2-b]-2,6a-diaza-3a-azoniaphenalene-Perchlorate-(13): yield 54 %. Mp 205°C.
Anal.Calc. for $C_{25}H_{31}N_4O_3ClO_4$ (534.98): C,56.12; H,5.84; N,10.47 %. Found: C,56.45; H,5.98; N,10.82 %.

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6. X-ray analysis data of 10: a=10.370(1) Å, b=16.723(2) Å, c=26.980(3) Å; Space group Pbcn (No. 60, from systematic absences), Z=8, Radiation Mo-K_α λ = =0.7107 Å, 2188 reflections $(I>3\sigma(I))$, R index 0.064. Calculations were performed on a PDP 11/34 (64 K) minicomputer using EN. SDP program package.

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