# SOME NEW SYNTHETIC APPROACHES FOR THE PREPARATION OF PTERIDINE-3-OXIDES AND PTERIDINES

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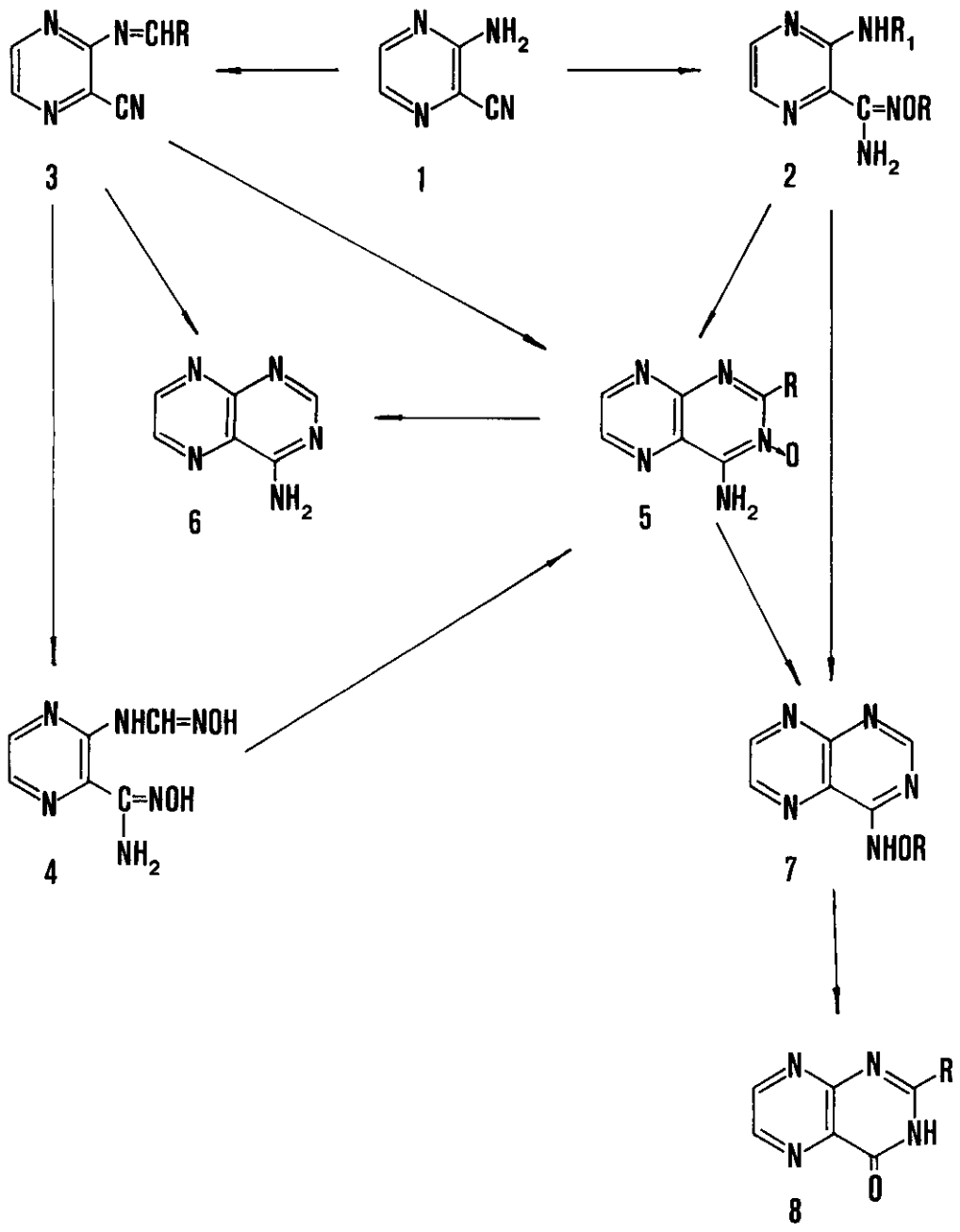
Abstract - Starting from 2-amino-3-cyanopyrazine some new syntheses of 4-substituted pteridines and pteridine-3-oxides have been devised.

The chemistry of o-aminonitriles has been extensively investigated [1] and several useful syntheses have been elaborated in the past for the formation of bi- and polycyclic heterocycles. As a continuation of our investigations to use substituted heterocyclic amidines as synthons for new heterocycles [2-12] we like to report on a new and useful approach for the preparation of various 4-substituted pteridines and their 3-oxides.

As starting compound 2-amino-3-cyanopyrazine (1) was used. It reacted at room temperature to give the amidoxime (2, R=$R_1$=H) in 85% yield, mp 185-187°C ($H_2O$); m/e 153 ($M^+$) and nmr δ (DMSO-$d_6$) 7.40 and 7.58 (d, $H_5$ and $H_6$), 5.62 and 7.02 (broad s, $NH_2$), 9.64 (s, OH), $J_{5,6}$ = 2.4 Hz. The amidoxime can be O-acylated and the acylation site is shown by further transformations into compound 7 (R = COMe). Thus, with acetic anhydride the O-acetyl compound 2 ($R_1$ = H, R = COMe) was obtained in almost quantitative yield, mp 170-171.5°C (EtOH), m/e 195 ($M^+$), and with benzoyl chloride and in the presence of triethylamine the O-benzoyl derivative 2 ($R_1$ = H, R = COPh) was obtained in 97% yield, mp 216-218°C (EtOH); m/e 257 ($M^+$). Treatment of the amidoxime 2 (R=$R_1$=H) with methyl iodide in the presence of sodium propoxide afforded the O-methyl derivative 2 ($R_1$ = H, R = Me) in 48% yield, mp 108-110°C ($H_2O$); m/e 167 ($M^+$) and nmr δ (DMSO-$d_6$) 7.23 and 7.43 (d, $H_5$ and $H_6$), 3.52 (s, Me), 5.67 and 6.80 (broad s, $NH_2$), $J_{5,6}$ = 2.4 Hz.

On the other hand, compound 1 was transformed with N,N-dimethylformamide dimethyl acetal at room temperature into 3 (R = $NMe_2$) in 89% yield, mp 86-88°C ($CHCl_3$ and petroleum ether); m/e 175 ($M^+$) and nmr δ (DMSO-$d_6$) 8.31 (s, CH), 7.83 and 8.07 (d, $H_5$ and $H_6$), 3.06 (s, Me) 2.97 (s, Me), $J_{5,6}$ = 2.4 Hz. [13] Alternatively, from 1 and triethyl orthoformate after 15 h under reflux the ethoxymethylene derivative 3 (R = OEt) was obtained in 50% yield, mp 119°C (from cyclohexane); m/e 176 ($M^+$) and nmr δ ($CDCl_3$) 8.16 (s, CH), 8.04 (s, $H_5$ and $H_6$), 4.31 (q, $OCH_2Me$), 1.36 (t, $OCH_2CH_3$), $J_{Et}$ = 7.0 Hz. The amidine 3 (R = $NMe_2$) reacted readily with free hydroxylamine at 0° to give compound 4 in 89% yield, mp 230-233°C (conversion into 5, R = H) (EtOH); m/e 196 ($M^+$) and nmr δ(DMSO-$d_6$) 7.77 and 7.86 (d, $H_5$ and $H_6$), 7.60 (d,CH), 7.77 (broad s, $NH_2$), 10.05 (s, OH), 10.59 (d, NH), $J_{5,6}$ = 2.4, $J_{CHNH}$=9.5 Hz.


N=CHR
CN
3
NH2
CN
1
NHR1
C=NOR
NH2
2
6
NH2
R
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NH2
5
NHCH=NOH
C=NOH
NH2
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NH
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8

Several attempts to obtain 4-aminopteridine-3-oxide from the above precursors should be mentioned. The reaction between 2 (R = $R_1$ = H) and triethyl orthoformate afforded the N-oxide 5 (R = H) in 80% yield, mp 275-278°C ($H_2O$); m/e 163 ($M^+$) and nmr δ ($D_2O$, 95°) 8.52 and 8.62 (d, $H_6$ and $H_7$), 8.49 (s, $H_2$), $J_{6,7}$ = 2.0 Hz. Alternatively, the amidine 3 (R = $NMe_2$) when heated in an alcoholic solution of hydroxylamine hydrochloride for 40 min afforded a mixture of several products. The main product, which was filtered from the mixture, obtained after evaporation of the solvent and treatment of the residue with water, was the N-oxide 5 (R = H) (80% yield) and from the filtrate compound 2 (R = $R_1$ = H) could be isolated in 11 % yield. By tlc compound 1 and 2-amino-3-pyrazinecarboxamide could be detected in the filtrate.

4-Aminopteridine-3-oxide (5, R = H) could be reduced with aqueous solution of titanium trichloride at room temperature into 4-aminopteridine (6) in low yield (11%). The later compound is obtainable in high yield (87%) from the ethoxymethylene derivative 3 (R = OEt) and methanolic ammonia at room temperature after 24 h, mp 309-312°C (EtOH) (Lit. [15] gives mp 305°); m/e 147 ($M^+$) and nmr δ (DMSO-$d_6$) 8.14 (s, $H_2$), 8.36 and 8.63 (d, $H_6$ and $H_7$), 7.50 (broad s, $NH_2$), $J_{6,7}$ = 1.8 Hz. In the same manner the amidine 3 (R = $NMe_2$) afforded at room temperature after 1 week 4-aminopteridine 6 in 58% yield.

4-Aminopteridine-3-oxide could be easily transformed in boling water after 7 h into the 4-hydroxylamino compound 7 (R = H ) in 73% yield, mp over 310°C (from $H_2O$); m/e 163 ($M^+$) and nmr δ (DMSO-$d_6$, 130°) 7.33 (s, $H_2$), 7.96 and 8.10 (d, $H_6$ and $H_7$), $J_{6,7}$ = 2.3 Hz. This transformation proceeds by ring opening at the pyrimidine ring followed by ring closure involving the former 4-amino function. This is substantiated by the presence of a small amount of compounds 1 and 2 (R = $R_1$ = = H) in the filtrate. The hydroxylamino compound 7 (R = H) is acetylated with acetic anhydride to give the O-acetyl derivative (7, R = COMe) which is in turn obtained in 29% yield from the reaction between 2 ($R_1$ = H, R = COMe) and triethyl orthoformate after 6 h under reflux, mp 231-234°C (from $H_2O$); m/e 205 ($M^+$) and nmr δ (DMSO-$d_6$, 50°) 7.52 (s, $H_2$), 8.15 and 8.30 (d, $H_6$ and $H_7$), 2.08 (s, Me), 3.35 (broad s, NH), $J_{6,7}$ = 2.2 Hz. The O-methyl derivative can be prepared in a similar way from 2 ($R_1$ = H, R = Me) in 54% yield, mp 263-266°C (from EtOH); m/e 177 ($M^+$).

The above described reaction paths are suitable also for the synthesis of 2-substituted derivatives as exemplified in the following cases. Acetylation of 1 afforded a mixture of the monoacetyl and diacetyl derivatives in a ratio of about 2:1 and recrystallization from ethyl acetate afforded the pure monoacetyl derivative, mp 147°C, m/e 162 ($M^+$). The diacetyl derivative had mp 70-71°C (from $H_2O$). Each of these compounds reacted with free hydroxylamine at room temperature to give after 80 min the corresponding monoacetylated amidoxime (2, $R_1$ = COMe, R = H) in about 80% yield, mp 159-161°C (from EtOH), m/e 195 ($M^+$). The later compound, when heated either in the presence of glacial acetic acid for 1h under reflux or in the presence of polyphosphoric acid at 70-80°C for 1.5 h, afforded the pteridine 5 (R = Me) in 79% and 40% yield, respectively, mp 278-280°C; m/e 177 ($M^+$)

and nmr δ ($D_2O$, 78°) 8.19 and 8.32 (d, $H_6$ and $H_7$), 2.60 (s, Me), $J_{6,7}$ = 1.8 Hz. However, if compound 1 was acetylated with a mixture of acetic anhydride and glacial acetic acid (1:1) for 3 h, 2-acetylaminopyrazine-3-carboxamide was obtained in 50% yield, mp 219-221°C (from EtOH); m/e 181 ($M^+$) (Lit. [16] gives mp 219°C). At its mp or when heated at 230-235°C the later compound is cyclized into the pteridinone 8 (R = Me) in 52% yield, mp over 200°C (from EtOH and N,N-dimethylformamide) (Lit. [17] gives mp over 200°C); nmr δ (DMSO-$d_6$) 8.66 and 8.75 (d, $H_6$ and $H_7$), 2.39 (s, Me), 3.3 (broad s,NH), $J_{6,7}$ = 2.1 Hz. The analogous desmethyl analog 8 (R = H) could be prepared from the hydroxylamino compound 7 (R = H) by acid hydrolysis (hydrochloric acid, 1:1, 10 min at boiling temperature) in 28% yield, mp over 350°C (Lit. [15] gives mp over 350°C); nmr δ (DMSO-$d_6$, 115°) 8.25 (s, $H_2$), 8.78 and 8.95 (d, $H_6$ and $H_7$), $J_{6,7}$ = 2.2 Hz.

The described reactions represent a new and versatile approach for the preparation of some functionalized pteridines. Satisfactory analyses (C,H,N) were obtained for all compounds.

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