NEIGHBOURING GROUP INTERACTION IN ORTHO-SUBSTITUTED AMINOPYRIDINES. FORMATION OF 1,2,4-OXADIAZOLYLPYRIDINES AND PYRIDO(2,3-d)PYRIMIDINE 3-OXIDES

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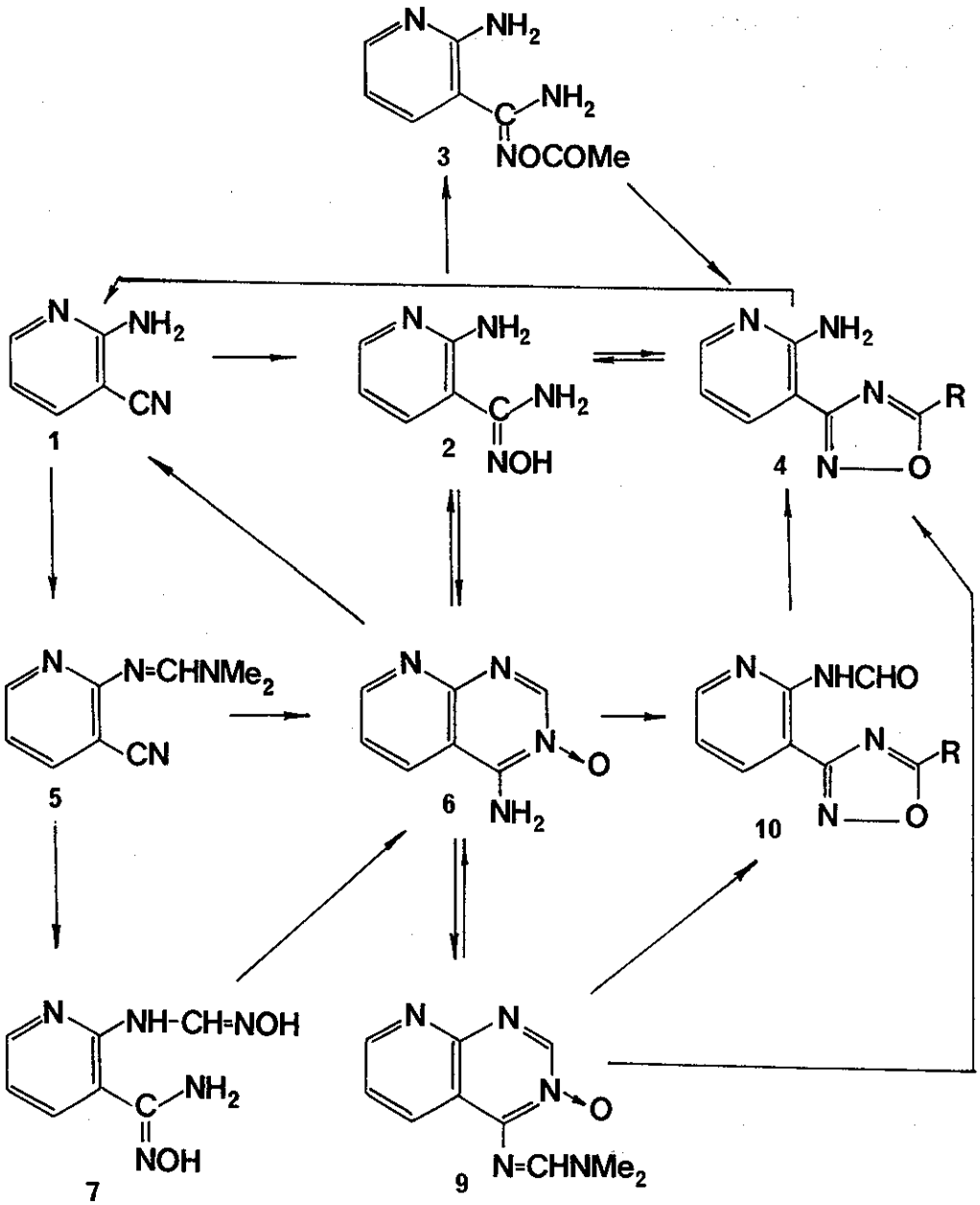
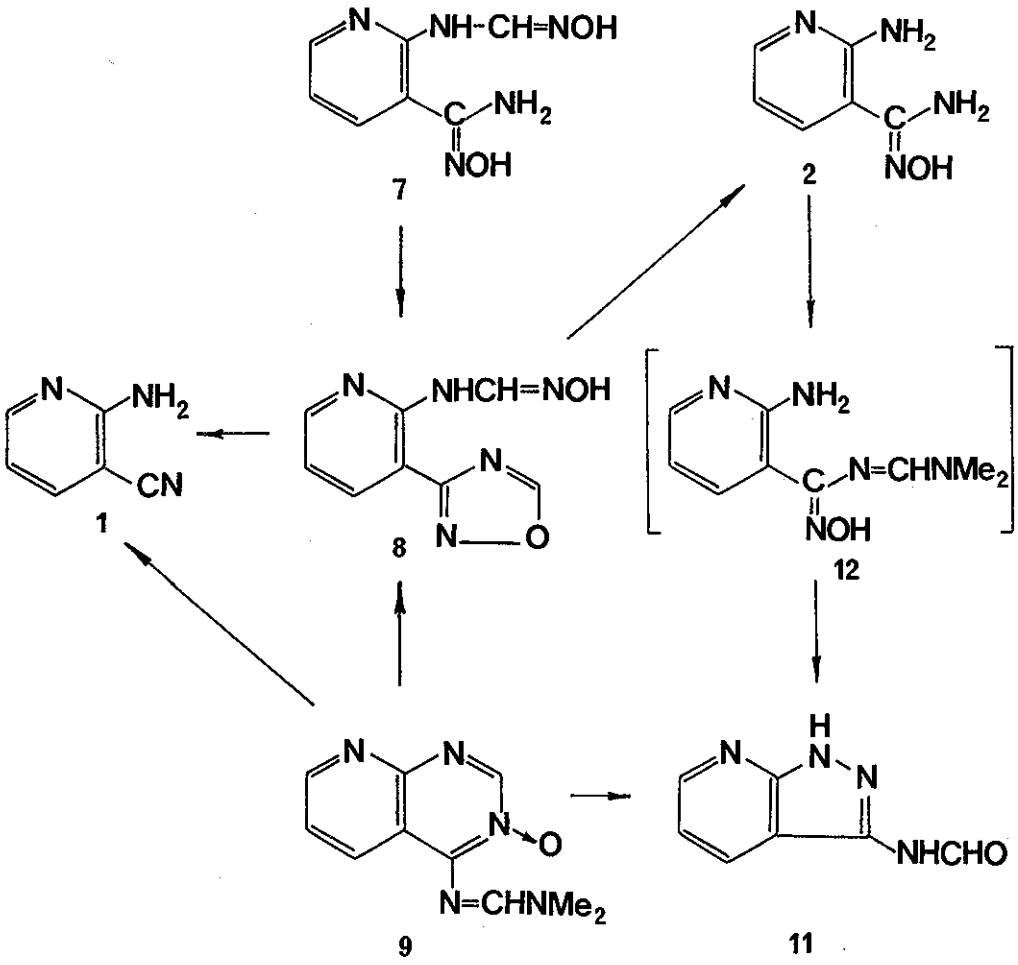
Transformations of 2-amino-3-cyanopyridine with hydroxylamine and various one carbon atom connecting reagents are described. Various paths of interconversion of 4-aminopyrido (2,3-d)pyrimidine 3-oxide and 2-amino-3-(1',2',4'-oxadiazolyl-3')pyridine are described. In some of the transformations also a pyrazolo(3,4-b)pyridine derivative was formed.

Recently, we have described neighbouring group interactions in ortho-substituted aminopyridines and formation of pyrido(2,3-d)-pyrimidines via 1,3,4-oxadiazolylpyridines.[1] We now report some interesting interconversions in related systems starting from 2-amino-3-cyanopyridine (1). Treatment of this compound with free hydroxylamine in ethanol afforded the corresponding formamidoxime (2), mp 128-130°. This compound, when acetylated to 3 (mp 147-160° with cyclization into 4) and the acetylated product when heated in water afforded a compound with molecular formula $C_8H_8N_4O$


N
NH2
NH2
C
NOCOMe
3
N
NH2
CN
1
N
NH2
C
NH2
NOH
2
N
NH2
N
R
N
O
4
N
N=CHNMe2
CN
5
N
N
N
O
NH2
6
N
NHCHO
N
R
N
O
10
N
NH-CH=NOH
C
NH2
NOH
7
N
N
N
O
N=CHNMe2
9

and mp 145° which exhibited no carbonyl band in its ir spectrum. For this compound, structure 4 (R = Me) or the 2-methyl derivative of 6 could be envisaged. The compound has the structure of 1,2,4-oxadiazolylpyridine (4, R = Me) (nmr (DMSO-d_6) τ = 7.31 (s, Me), 1.84 (d, H_4 and H_6), 3.20 (broad s, NH_2), 3.29 (dd, H_5), $J_{4,5}$ = = $J_{5,6}$ = 7.0 Hz) as shown by an X-ray structure determination.[2] Compound 4 (R = Me) decomposed in hot dilute alkali into a mixture of the amidoxime (2) and the starting pyridine derivative (1). In this connection it should be mentioned that disubstituted 1,2,4-oxadiazoles are renowned for their remarkable thermal stability as well as stability towards hydrolysis in solution, whereas monosubstituted derivatives are more readily hydrolyzed by ring opening.[3-5]

However, ehen the amidoxime (2) was treated with boiling triethyl orthoformate for 2 hours, a mixture of two compounds with mp 270-275° and 147-148°, respectively, was obtained. Both compounds analyzed for a $C_7H_6N_4O$ molecular formula, a carbonyl absorption band in the ir spectra was absent and in both cases besides three pyridine ring protons, a singlet at τ = 1.20 and 1.o5, respectively, could be observed in the nmr spectra. The minor product (1.3%) with mp 147-148° was identified as 4(R = H) (nmr ($CDCl_3$) τ = 1.20 (s, H_5,), 1.63 (dd, H_4), 3.25 (dd, H_5), 1.74 (dd, H_6), $J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz) and the major product (89%) as compound 6. Compound 4 (R = H) was transformed in boiling water after 8.5 hours into 1. The formation of the N-oxide (6) could be regarded as to arise from a thermal conversion of 4 (R = H). By separate experiment it could be shown that this conversion does not occur, although from related amidoximes, 1,2,4-oxadiazoles we-


NH-CH=NOH
NH2
NOH
7
NH2
NH2
NOH
2
NH2
CN
1
NHCH=NOH
N
O
8
NH2
N=CHNMe2
NOH
12
N
O
N=CHNMe2
9
H
N
N
NHCHO
11

re readily obtained.[6,7] Therefore, the ortho standing group must play here an important role and it is involved more readily in ring closure than the amino group from the amidoxime function.

On the other hand, if compound 1 was treated with N,N-dimethylformamide dimethyl acetal (2 hours at reflux) the corresponding dimethylaminomethyleneamino derivative (5) with mp 66-69° was obtained. This compound when treated with a methanolic solution of hydroxylamine hydrochloride at room temperature, also gave compound 6 (mp 270-275°), the same as reported above for the reaction of 2 and triethyl orthoformate. On the other hand, if for the above transformation a methanolic solution of free hydroxylamine was used, the formamidine (5) was transformed at room temperature into 7, mp 190-205° (with cyclization into 6, mp 270-275°). From compound 7 the pyridopyrimidine derivative (6) (nmr (D_2O, 98°) τ = 1.05 (s, H_2), 1.45 (dd, H_5), 2.30 (dd, H_6), 0.97 (dd, H_7), $J_{5,6}$ = 8.4, $J_{6,7}$ =4.5 and $J_{5,7}$ = 2.0 Hz) could be obtained after treatment with polyphosphoric acid (70°, 2 hours). On the other hand, compound 7 was transformed with triethyl orthoformate into a mixture of the bicyclic compound (6) and a compound with mp 180-190° (dec.), analyzing for $C_8H_7N_5O_2$. The nmr spectrum of this latter product revealed besides the pyridine ring protons, a singlet at τ = 0.21 corresponding to a ring CH-group and a doublet at τ = 1.90, corresponding also to a CH-group which is coupled with a neighbouring NH group with J = 9 Hz. Structure 8 appears to be consistent with this nmr data. Compound 8 was also obtained from 6 which was first transformed into 9, mp 209-210°, and thereafter treated with methanolic hydroxylamine hydrochloride at room temperature to give the product 8 after several minutes.

4-Aminopyrido(2,3-d)pyrimidine 3-oxide (6) was decomposed in hot hydrochloric acid (1:1) into the amidoxime (2), whereas with dilute aqueous sodium hydroxide (2 hours at reflux) a mixture of amidoxime (2) as the main product and the cyano compound (1) was obtained. Furthermore, the bicyclic compound (6) was treated with acetic anhydride at room temperature and the mixture was warmed up to obtain a solution. Upon evaporation of the solvent in vacuo, compound 10 (R = Me) was obtained (mp 140-142°; nmr (DMSO-d_6) τ= 0.45 (d, CHO), 1.52 (dd, H_4), 2.60 (dd, H_5), 1.41 (dd, H_6), -0.15 (broad d, NH), 7.24 (s, Me), $J_{4,5}$ = 8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0, J_{CHNH} = 10 Hz). Upon heating with an aqueous bicarbonate solution compound 10 was transformed into compound 4 (R = Me), mp 145°, obtained also as described above from 3. This conversion is similar to that of adenine 1-oxide where the O-acetyl derivative is formed first and subsequently also the pyrimidine part of the bicyclic compound is opened.[8]

A similar susceptibility for ring opening could be observed with N,N-dimethylaminomethylene derivative (9). In an ethanolic ammonia solution at room temperature the compound was transformed into a mixture of the bicycle (6) and the pyridine derivative (1). In aqueous solution, however, after 20 hours at room temperature compound 9 was decomposed hydrolytically into three different products. One of them, with mp 156-159° (10, R = H) results by pyrimidine ring opening and oxadiazole ring formation. The other product, obtained in almost the same amount, was identified as 1 whereas a small amount (1,2%) of 3-formylaminopyrazolo(3,4-b)pyridine (11), mp. 230-232°, could be also identified. Its formation is somewhat surprising and it could be established by separate expe-

riments that it is not formed under the same reaction conditions either from compound 10 (R = H), 4 (R = H) or 6. It can be therefore anticipated that it may be formed via an intermediate like 12. This is substantiated by the observation that upon heating the amidoxime (2) in the presence of N,N-dimethylformamide dimethyl acetal in toluene under reflux for 1 hour, a mixture of 11 and 4 (R = H) was obtained in a ratio of about 2:1. Compound 11 was identified also by deformylation into authentic 3-aminopyrazolo(3,4-b)pyridine[9] (nmr (DMSO-d_6) τ = 1.87 (dd, H_4), 3.07 (dd, H_5), 1.64 (dd, H_6), 4.5 (broad s, NH_2), -2.0 (broad s, NH), $J_{4,5}$= =8.0, $J_{5,6}$ = 5.0, $J_{4,6}$ = 2.0 Hz).

On the other hand, hydrolysis of compound 9 in aqueous hydrochloric acid (1:1) at room temperature resulted in the formation of only 4 (R = H). A similar transformation of quinazoline with hydroxylamine-O-sulfonic acid and subsequent treatment of the adduct with hot aqueous potassium hydroxide has been reported to give a variety of products, among them also indazole.[10]

The above observations of pyrazolo(3,4-b)pyridine formation prompted us to investigate if this ring system might be formed also from 8. It could be established that both, alkaline or acidic hydrolysis, afforded only a mixture of 2 and 1, resulting from oxadiazole ring opening and complete hydrolysis.

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