ON THE REACTIVITY OF SOME N-AMINO HETEROCYCLES TOWARDS DIAZOMETHANE

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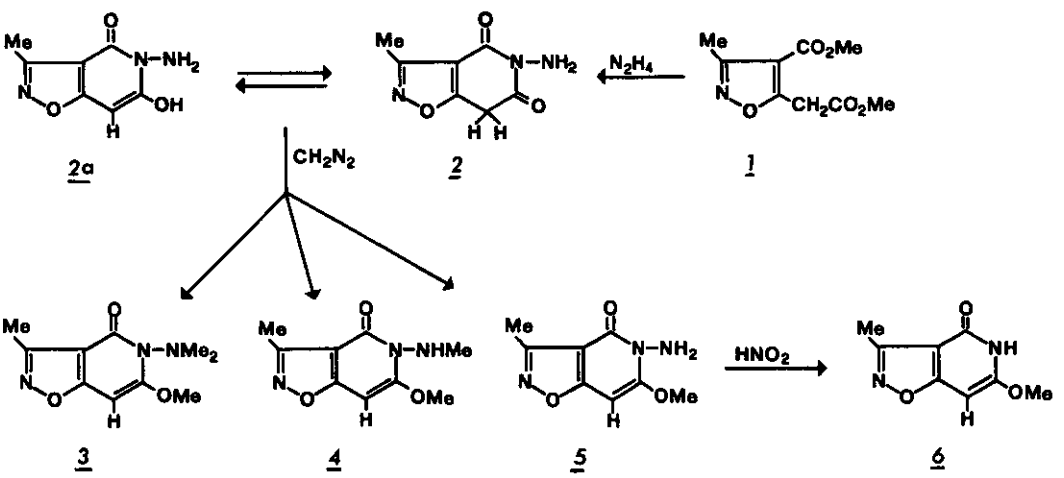
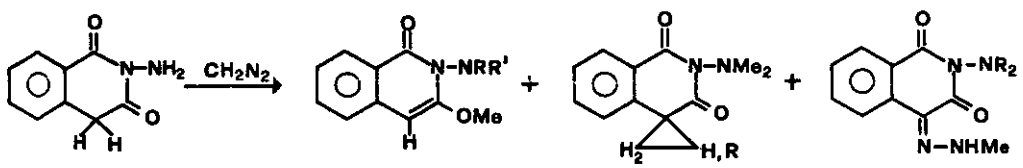
Abstract - The occurrence of hydrogen bonding between the nitrogen atom of the NH_2 group and a neighbouring enolic proton in tautomerizable N-amino heterocycles allows diazomethane methylation on the NH_2 moiety.

It is well known[1] that methylation of the NH_2 group with diazomethane can occur only under particular conditions such as cuprous salts catalysis, amino group protonation or free electron pair coordination by a Lewis acid. Thus amino acids, which exist in zwitterionic forms, afford the corresponding betaines,[2] perchloric, p-toluenesulfonic or fluoboric salts of amines give permethylated ammonium salts and amine-boron trifluoride complexes yield N-methylated amines.[3,4] Investigation of the behaviour of some N-amino heterocycles towards diazomethane led us to establish that also the presence of a tautomeric equilibrium for the ring system can give rise to a methylation on the NH_2 group.

Following our interest in the chemistry of condensed heterocyclic systems,[5] we prepared 5-amino-3-methylisoxazolo[4,5-c]pyridine-4,6-dione (2) by reaction of the diester (1) with hydrazine.



In order to demonstrate the structure of compound (2) by conversion into the known methoxypyridone (6) through (5), we allowed to react the former compound with different amounts of diazomethane. However, the yields of the desired methoxy derivative (5) were always very poor and we isolated from the reaction mixtures 5-dimethylamino-6-methoxy-3-methylisoxazolo[4,5-c]pyridin-4-one (3) as the main product, along with a small amount of the dimethyl derivative (4).
Compound (5) did not react with diazomethane, showing that the NH_2 group methylation occurred before O-methylation. In order to rationalize this type of reactivity, we considered the behaviour towards the same reagent of some N-amino heterocycles structurally correlated to (2). Since the N-aminophthalimide was completely unaffected by diazomethane we concluded that the methylation on the NH_2 group cannot be attributed to the electron withdrawing effects of the two carbonyl groups. However, compound (2) can exist as 6-hydroxy-4-oxo-tautomer (2a) (see Table) and the hydrogen bonding between the OH proton and the NH_2 group can give rise to an effect on the reaction comparable to that of a Lewis acid. Likewise, 2-amino-tetrahydroisoquinoline-1,3-dione (7), whose tautomeric behaviour results very similar to that of (2) (see Table), afforded the derivatives (8a-c) as the main products.



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8a) R,R'=H
b) R=H,R'=Me
c) R,R'=Me

9a) R=H
b) R=Me

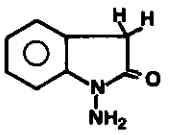
10a) R=H
b) R=Me

Furthermore, according to previous findings on the reactivity with diazomethane of 2-methyl-1,2,3,4-tetrahydroisoquinoline-1,3-dione[6] or 6-hydroxy-2-pyridone,[7] we also isolated the spirocyclopropanes (9a,b) and the methylhydrazones (10a,b); all these compounds, except for (10a), obtained in very low yield, were dimethylated on the NH_2 moiety. The structures of compounds (9a,b) and (10a,b) were assigned on the basis of their spectral data (Experimental section), which were strictly comparable with those of the analogous products previously reported in the literature.[6,7]
A confirmation of our suggestion concerning the activation of the NH_2 group followed from the behaviour towards diazomethane of two five membered N-amino heterocycles such as 1-aminoindolone (11) and 1-amino-5-hydroxypyrazole (12a). Compound (11),[8a] which exists exclusively in the amidic form (see Table) according to the behaviour of 1-substituted indolones,[8b] was completely inert towards diazomethane. On the contrary, the tautomerizable 1-aminopyrazole (12a) gave, in addition to the previously reported[9]

Table – ^{1}H Nmr data of the N-amino heterocycles

(2)	2.55(s,Me), 4.17[a](s,CH_2), 5.03[a](br s,NH_2)
(7)	4.11[a](s,CH_2), 5.21[a](s,NH_2), 7.21-7.91 and 8.10-8.46(m,C_6H_4)
(11)	3.43[b](s,CH_2), 4.30[a](s,NH_2), 6.85-7.54(m,C_6H_4)
(12a)[c]	1.50(d,J 7.8,s with D_2O,Me), 2.06(s,Me), 3.60[a](q,J 7.8,CH), 4.55[a](br,NH_2 and OH/NH), 7.27-7.72(m,C_6H_5)

a) Signal disappears on deuteriation. b) Signal does not disappear on deuteriation, showing the absence of a tautomeric equilibrium. c) This compound exists in deuteriochloroform as 1.6:1 equilibrium mixture of CH and OH/NH tautomers.



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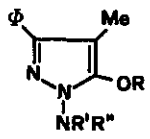
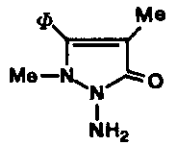


12a) R,R',R"=H
b) R=Me, R',R"=H
c) R, R'=Me, R"=H
d) R,R',R"=Me



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1-amino-5-methoxypyrazole (12b) and 1-amino-2-methylpyrazolin-5-one (13), a small amount of 1-methylamino- and 1-dimethylamino-5-methoxypyrazoles (12c) and (12d).

EXPERIMENTAL SECTION

Ir spectra were recorded on a Perkin Elmer 283 spectrophotometer for KBr disks. ^{1}H Nmr spectra were recorded for solutions in deuteriochloroform with a Perkin Elmer R 600 instrument; chemical shifts (J in Hz) are reported in ppm downfield from internal tetramethylsilane. Uv spectra were measured for solutions in methanol with a Perkin Elmer 124 spectrophotometer. Column chromatography were carried out on Lobar Si 60 (40-63 μm) (Merck). Light petroleum refers to that fraction boiling in the range 40-70°C.

5-Amino-3-methylisoxazolo[4,5-c]pyridine-4,6-dione (2)

A stirred mixture of methyl (4-methoxycarbonyl-3-methylisoxazol-5-yl)acetate (1)[10] (1 g, 0.0047 mol) and hydrazine hydrate (1 g, 0.02 mol) in water (19 ml) was kept at room temperature for 5 h. Acidification of the resulting solution (pH 2) afforded compound (2) (0.4 g, 47%), mp 140-141°C after sublimation at 100°C and 0.01 mm

Hg followed by crystallization from benzene; ir 3355, 3260 (NH_2), 1725, 1675 (CO) cm^{-1}; uv max (log ε): 208 (4.12) and 289 nm (4.01); Anal. Calcd. for $C_7H_7N_3O_3$: C, 46.41; H, 3.89; N, 23.20. Found: C, 46.54; H, 3.87; N, 23.00%.

Methylation of 5-Amino-3-methylisoxazolo [4,5-c] pyridine-4,6-dione (2)

A suspension of N-aminopyridone (2) (0.9 g, 0.005 mol) in ether (20 ml) was treated with ethereal diazomethane (1.26 g, 0.03 mol). After 12 h 5-amino-6-methoxy-3-methylisoxazolo [4,5-c] pyridin-4-one (5) was filtered off and crystallized from water (0.05 g), mp 205-206°C (decomp.); ir 3310-3100 (NH_2) and 1685 (CO) cm^{-1}; uv max (log ε) 213 (4.21), 258 (3.84) and 287.5 nm (4.02); nmr 2.59 (s,Me), 4.04 (s,OMe), 5.27 (exch. s, NH_2) and 5.96 (s, CH); Anal. Calcd. for $C_8H_9N_3O_3$: C,49.23; H, 4.65; N, 21.53. Found: C, 49.12; H, 4.73; N, 21.39%.

Ethereal solution was evaporated in vacuo and the residue chromatographed on column with ether to give the following compounds (in order of mobility): 5-dimethylamino-6-methoxy-3-methylisoxazolo [4,5-c] pyridin-4-one (3) (0.4 g, 36%), mp 147-148°C after crystallization from ligroin; ir 1695 (CO) cm^{-1}; uv max (log ε) 202 (4.18), 256 (3.91) and 287 nm (4.04); nmr 2.54 (s, Me), 3.02 (s, NMe_2), 3.98 (s, OMe) and 5.80 (s, CH); Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.66; H, 5.66; N, 19.09%; 6-methoxy-3-methyl-5-methylaminoisoxazolo [4,5-c] pyridin-4-one (4) (0.05 g, 5%), mp 180-182°C after sublimation at 120°C and 0.01 mm Hg; ir 3260 (NH) and 1690 (CO) cm^{-1}; uv max. (log ε) 211 (4.14), 257 (3.84) and 286 nm (4.02); nmr 2.59 (s, Me), 2.75 (d, J 5.1, s with D_2O, NMe), 4.03 (s, OMe), 5.88 (s, CH) and 5.91 (exch. br, NH); Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C,51.87; H, 5.23; N, 19.90%;5-amino-6-methoxy-3-methylisoxazolo [4,5-c] pyridin-4-one (5) (0.15 g, total yield 20.5%). When this reaction was carried out employing a lower amount of diazomethane, minor yields of the above products were obtained, and some starting material was recovered.

Deamination of N-Aminomethoxypyridone (5)

A stirred solution of compound (5) (0.1 g, 0.0005 mol) in 3M hydrochloric acid (7 ml) was treated with sodium nitrite (0.05 g,0.0007 mol) in water (4 ml). 6-Methoxy-3-methylisoxazolo [4,5-c] pyridin-4-one (6) (0.08 g, 89%) was collected by filtration and identified by comparison with an authentic sample.[10]

Methylation of 2-Amino-1,2,3,4-tetrahydroisoquinoline-1,3-dione (7)

A suspension of compound (7)[11] (1.76 g, 0.01 mol) in ether (50 ml) was treated with diazomethane (2.52 g, 0.06 mol). After 24 h solvent was removed and the residue chromatographed on column by eluting first with ether/light petroleum 1:1 v/v and after with ether to give the following compounds (in order of mobility): spiro [2-methylcyclopropane-1,4'-(2'-dimethylamino-1',2',3',4'-tetrahydroisoquinoline-1',3'-dione)] (9a) (0.098 g, 4%), mp 98-100°C after sublimation at 80°C and

0.01 mm Hg; ir 1710, 1680 (CO) cm^{-1}; uv max. (log ε) 214 (4.47), 245 (3.99) and 293 nm (3.48); nmr 1.43 (m, Me), 1.58-2.40 (m, cyclopropane protons), 3.00 (s, NMe_2), 6.81 (m, 5'-H), 7.45 (m, 6',7'-H), 8.24 (m, 8'-H); Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.52; H, 6.41; N, 11.24%; a mixture of two components which was resolved by column chromatography with light petroleum/ethyl acetate 1.2:1 v/v, yielding spiro[cyclopropane-1,4'-(2'-dimethylamino-1',2',3',4'-tetrahydroisoquinoline-1',3'-dione)] (9b) (0.115 g, 5%), mp 103-105°C (from hexane); ir 1715, 1675 (CO) cm^{-1}; uv max. (log ε) 213 (4.46), 245 (3.99) and 292 nm (3.43); nmr 1.88 (m, cyclopropane protons), 3.00 (s, NMe_2), 6.79 (m, 5'-H), 7.47 (m, 6',7'-H) and 8.25 (m, 8'-H); Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.17; N, 11.96% and 2-dimethylamino-3-methoxyisoquinolin-1-one (8c) (0.13 g, 6%), mp 67-69°C after sublimation at 50°C and 0.01 mm Hg; ir 1665 (CO) cm^{-1}; uv max. (log ε) 205 (4.38), 229 (4.37), 277 (4.04), 284 sh (4.03) and 343 nm (3.64); nmr 3.07 (s, NMe_2), 3.94 (s, OMe), 5.68 (s, 4-H), 7.24-7.60 (m, 5,6,7-H) and 8.26 (d, J 7.8, 8-H); Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.09; H, 6.55; N, 12.74%; 2-dimethylamino-1,2,3,4-tetrahydroisoquinoline-1,3,4-trione-4-methylhydrazone (10b) (0.22 g, 9%), mp 129-131°C (from ether); ir 3200 (NH), 1680, 1640 (CO) cm^{-1}; uv max. (log ε) 222 (4.36), 257 (4.21) and 373 nm (4.28); nmr 3.05 (s, NMe_2), 3.53 (d, J 4.0, s with D_2O, NMe), 7.22-8.15 (m, C_6H_4) and 12.54 (exch. br s, NH); Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.80; H, 5.59; N, 22.46%; 2-methylamino-3-methoxyisoquinolin-1-one (8b) (0.61 g, 30%), mp 99-101°C after sublimation at 60°C and 0.01 mm Hg; ir 3280 (NH) and 1645 (CO) cm^{-1}; uv max. (log ε) 224 sh (4.39), 228 (4.40), 280 sh (3.93), 286 (3.94) and 342 nm (3.64); nmr 2.80 (s, NMe), 4.01 (s, OMe), 5.60 (exch. br s, NH), 5.80 (s, 4-H), 7.24-7.60 (m, 5,6,7-H) and 8.31 (d, J 7.2, 8-H); Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.59; H, 6.04; N, 13.59%; 2-amino-1,2,3,4-tetrahydroisoquinoline-1,3,4-trione-4-methylhydrazone (10a) (0.09 g, 4%), mp 190-192°C (from benzene); ir 3340, 3190 (NH and NH_2), 1700, 1630 (CO) cm^{-1}; uv max. (log ε) 224 (4.29), 261 (4.14), 310 (3.59) and 376 nm (4.31); nmr 3.55 (d, J 3.6, s with D_2O, NMe), 5.39 (exch. br s, NH_2), 7.27-8.28 (m, C_6H_4) and 12.48 (exch. br, NH); Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.67. Found: C, 55.29; H, 4.74; N, 25.41%; 2-amino-3-methoxyisoquinolin-1-one (8a) (0.55 g, 29%), mp 153-155°C after sublimation at 85°C and 0.01 mm Hg; ir 3320, 3220 (NH_2) and 1640 (CO) cm^{-1}; uv max. (log ε) 223 (4.45), 250 sh (4.02), 287 (3.90) and 341 nm (3.69); nmr 3.97 (s, OMe), 5.43 (exch. br s, NH_2), 5.80 (s, 4-H), 7.26-7.60 (m, 5,6,7-H) and 8.28 (d, J 8.4, 8-H); Anal.Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.27, N, 14.52%.

Methylation of 1-Amino-4-methyl-3-phenylpyrazolin-5-one (12a)

A suspension of compound (12a)[9] (0.5 g, 0.0026 mol) in ether (20 ml) was treated with ethereal diazomethane (0.5 g, 0.012 mol). After 3 h solvent was removed and the residue chromatographed on column eluting first with ether/light petroleum 2:1 v/v and after with ether to give the following compounds (in order of mobility): 1-dimethylamino-5-methoxy-4-methyl-3-phenylpyrazole (12d)[12] (0.013 g, 2%); 5-methoxy-4-methyl-1-methylamino-3-phenylpyrazole (12c)[12] (0.05 g, 9%); 1-amino-5-methoxy-4-methyl-3-phenylpyrazole (12b)[9] (0.25 g, 46.5 %). Further elution of the column with ethanol afforded 1-amino-2,4-dimethyl-3-phenylpyrazolin-5-one (13)[9] (0.15 g, 28%).

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