TRANSFORMATIONS OF HETEROCYCLIC N-OXIDES INTO DERIVATIVES OF α-HETEROARYL SUBSTITUTED α-AMINO ACIDS AND DIPEPTIDES

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Abstract - Heterocyclic N-oxides 1 were converted with oxazolidinone 2 into oxazolinylidene derivatives 3. The opening of the oxazolinone ring produced various derivatives of α-heteroaryl substituted α-amino acids, such as sodium salt 4 and hydrazides 5. Acyl azides 6, obtained by treatment of hydrazides 5 with nitrous acid, were transformed into dipeptides 7. All these compounds exist in tautomeric forms 10 and 14 shown in Schemes.

Heteroaromatic N-oxides undergo a variety of reactions with nucleophiles.[1-4] Of particular interest are reactions with carbon nucleophiles, such as highly activated methylene compounds, [5-7] enamines, indoles, enol ethers, pyridinium salts, Wittig reagents, and others, in the presence of acetic anhydride [4]. Oxazolinones,[8] thiazolinones,[9] and rhodanine [10] have been used for preparation of intermediates which are hydrolyzed into α-aminomethyl and α-mercaptomethyl derivatives of various heterocyclic systems.

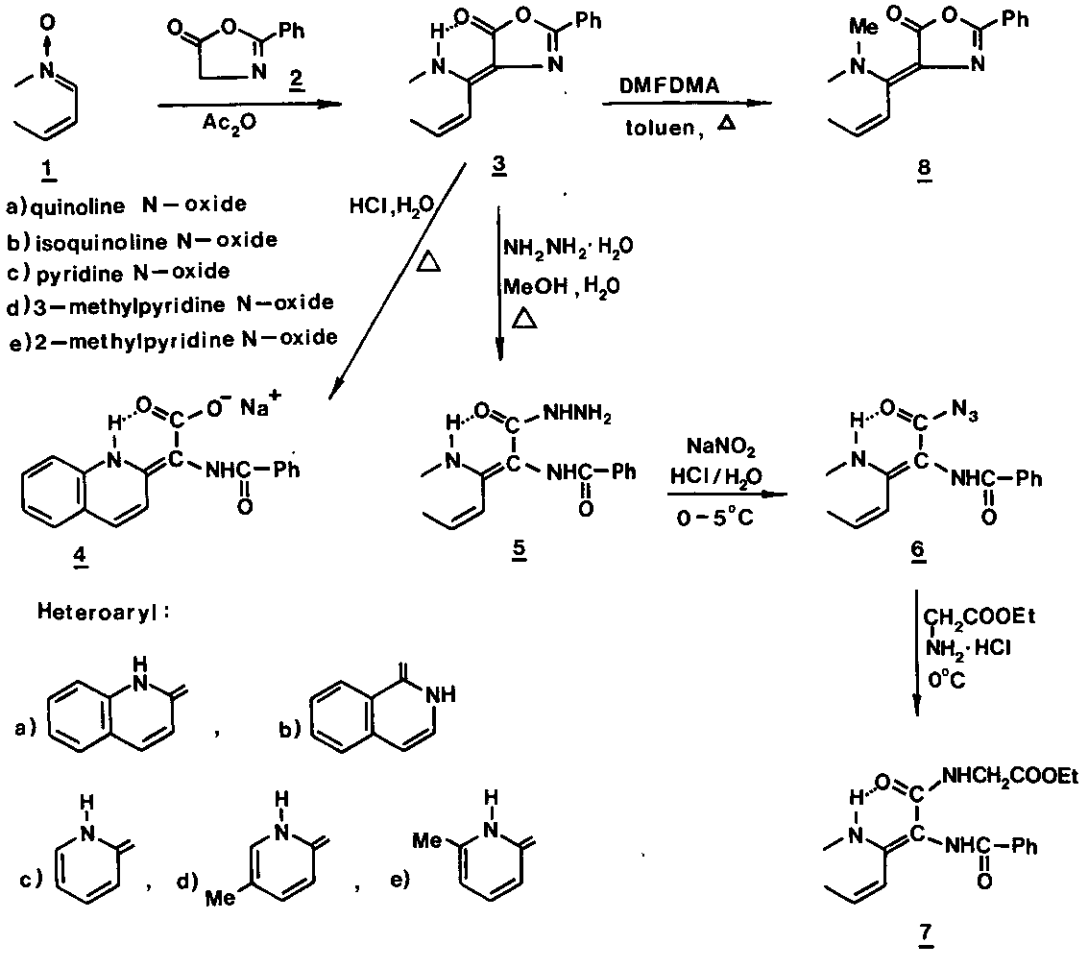
Since some derivatives of amino acids and dipeptides have been introduced as ACE inhibitors and antihypertensive agents, the synthesis of novel amino acids and dipeptides has recently become of considerable interest.[11] In this connection we report in this paper the transformations of heterocyclic N-oxides into derivatives of α-heteroaryl substituted α-amino acids and dipeptides. We used quinoline N-oxide (1a), isoquinoline N-oxide (1b), pyridine N-oxide (1c), 3-methylpyridine N-oxide (1d) and 2-methylpyridine N-oxide (1e) as starting compounds. They were converted with 2-phenyl-2-oxazolin-5-one (2) in the presence of acetic anhydride into oxazolinylidene derivatives of heteroaromatic systems 3a-e. These intermediates undergo a variety of reactions in which oxazoline ring opens to give derivatives of α-heteroaryl substituted α-amino acids. [12] Acid hydrolysis of 3a followed by

neutralization afforded N-benzoyl-α-heteroaryl-α-amino acid in the form of sodium salt (4). The reaction of 3a-e with hydrazine hydrate produced N-benzoyl-α-heteroaryl-α-amino acid hydrazides 5a-e. Treatment of the hydrazides 5a,b with nitrous acid gave the corresponding acyl azides 6a,b, which were transformed with ethyl glycinate into the corresponding dipeptides 7a,b. All these compounds can be represented in several tautomeric forms. The oxazolidinylidene derivatives 3 can exist in four tautomeric forms 9-12. The structures were assigned on the basis of spectral data and some chemical transformations. Since there is no methine proton present in the nmr spectra of DMSO-d_6 solutions but there is instead a broad singlet, exchangeable with deuterium oxide, which could be assigned only to NH group, the structure 9 is excluded. The ir spectra in KBr exhibit the NH absorption bands at 3100-3180 cm^{-1}, indicating that hydrogen bonded tautomeric form 10 is the most probable. This is further supported by methylation of compounds 3a-c with N,N-dimethylformamide dimethyl acetal (DMFDMA) in which the N-methyl derivatives 8a-c are formed. In the cases of α-heteroaryl substituted α-amino acid derivatives, it is preferable only to suggest that the hydrogen bonded forms 14 are the most probable,because of the absence of a methine proton and the presence of a broad band, exchangeable with deuterium oxide, in nmr spectra, and NH absorption bands at 3080-3150 cm^{-1} in ir spectra.

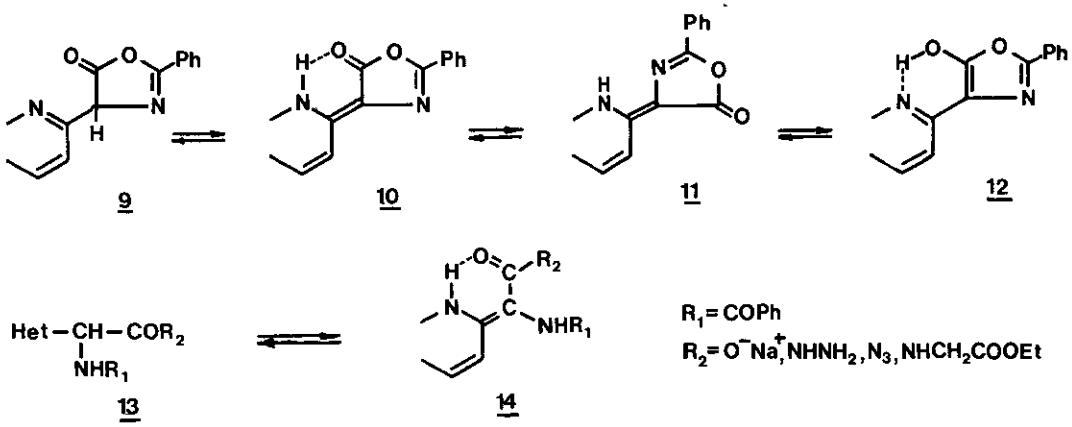
EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^1H nmr spectra were obtained on a JEOL JNM C 60 HL spectrometer with TMS as internal standard, ir spectra on a PERKIN-ELMER instrument 727B, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240 C.

2(1H)-(2-Phenyl-5-oxo-4-oxazolinylidene)-quinoline (3a).[13] - To a solution of 1a (1.45 g, 0.01 mole) in acetic anhydride (3 ml) a solution of 2 [14,15] (1.61 g, 0.01 mole) was added dropwise at 0°C. The mixture was left in a refrigerator (12 h) at 0°C. The precipitate was then filtered to give 1.72 g (60 %) of 3a, mp 236-239°C (from methanol), lit.[8] mp 239°C, nmr (DMSO-d_6, 120°C) δ: 7.2-7.5 (m, 2-Ph, H_3, H_4, H_5, H_6, H_7, H_8), 7.6-7.9 (br s, NH).



SCHEME 1



SCHEME 2

The following compounds were prepared according to the same procedure:

1(2H)-(2-Phenyl-5-oxo-4-oxazolinylidene)-isoquinoline (3b). - This compound was prepared from 1b in 21% yield, mp 242-247°C (from ethanol), nmr (DMSO-d_6, 130°C) δ : 6.80 (d, H_3), 7.75 (d, H_4), 7.25-7,90 (m, 2-Ph, H_5, H_6, H_7, H_8), J_{H_3,H_4} = 6.5 Hz. Anal.Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.86; H, 4.27; N, 9.62.

2(1H)-(2-Phenyl-5-oxo-4-oxazolinylidene)-pyridine (3c). - This compound was prepared from 1c in 20% yield, mp 200-204°C (from ethanol), nmr (DMSO-d_6) δ: 6.5-6.85 (m, H_5), 7.2-7.5 (m), 7.6-7.9 (m) (2-Ph, H_3, H_4, H_6). Anal.Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.45; H, 4.04; N, 11.60.

2(1H)-5-Methyl-(2-phenyl-5-oxo-4-oxazolidinylidene)-pyridine (3d). - This compound was prepared from 1d in 12 % yield, mp 216-219°C, nmr (DMSO-d_6, 140°C) δ: 1.86 (s, 5-Me), 7.25-7.50 (m), 7.60-7.90 (m) (2-Ph, H_3, H_4, H_6). Anal.Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.12; H, 4.90; N, 10.71.

2(1H)-6-Methyl-(2-phenyl-5-oxo-4-oxazolidinylidene)-pyridine (3e). - This compound was prepared from 2-methylpyridine 1-oxide (1e) in 16 % yield, mp 148-152°. Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.12; H, 4.82; N,11.06.

2(1H)-Benzoylaminocarboxymethylenquinoline (Sodium Salt) (4). - A mixture of 3a (288 mg, 0.001 mole) and aqueous hydrochloric acid (5 %, 10 ml) was heated under reflux (8 h). The solution was, after cooling, filtered, and the filtrate was neutralized with solid sodium carbonate. The precipitate was separated by filtration and washed with water to give 90 mg (27 %) of 4, mp 128-130°C, nmr (DMSO-d_6) δ: 7.2-7.5 (m) and 7.5-7.8 (m) (PhCO, H_3, H_4, H_5, H_6, H_7, H_8), J_{H_3,H_4} = 7.0 Hz. Anal.Calcd. for $C_{18}H_{13}N_2O_3Na$: C, 65.85; H, 3.99; N, 8.53. Found: C, 65.63; H, 4.29; N, 8.79.

2(1H)-Benzoylaminocarbazoylmethylenequinoline (5a). - A mixture of 3a (288 mg, 0.001 mole), hydrazine hydrate (80%, 0.55 ml), methanol (2 ml) and water (0.6 ml) was heated under reflux until solution became clear (approx. 45 min). Water (5 ml) was added and the mixture was left at room temperature (2-3 h) to deposit precipitate, which was filtered to give 261 mg (82 %) of 5a, mp 188-190°C (from a mixture of ethanol and water, 1:1), nmr ($CDCl_3$) δ: 5.85 (d, H_3), 7.2-8.0 (m, PhCO, H_4, H_5, H_6, H_7, H_8), 8.5 (br s, NH_2, NH), J_{H_3,H_4} = 6.0 Hz. Anal.Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.55; H, 4.97; N, 17.57.

The following compounds were prepared according to the same procedure:

1(2H)-Benzoylaminocarbazoylmethyleneisoquinoline (5b). - This compound was prepared from 3b in 88 % yield, mp 193-197°C (from ethanol), nmr (DMSO-d_6) δ: 6.50 (d, H_3), 7.2-7.5 (m), 7.5-8.0 (m) (PhCO, H_5, H_6, H_7, H_8), 7.5 (br s, NH_2, NH), 8.9 (d, H_4), J_{H_3,H_4} = 7.5 Hz. Anal.Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.13; H, 5.30; N, 17.19.

2(1H)-Benzoylaminocarbazoylmethylenepyridine (5c). - This compound was prepared from 3c in 73 % yield, mp 95-97°C (washed with water), nmr (DMSO-d_6) δ: 7.1-7.5 (m) (PhCO, H_4, H_5), 8.25-8.60 (m, H_6), 4.25 (br s), 5.5 (br s), 9.4 (br s) (NH_2, NH, NH). Anal.Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.45; H, 5.22; N, 20.78.

2(1H)-Benzoylaminocarbazoylmethylene-5-methylpyridine (5d). - This compound was prepared from 3d in 53 % yield, mp 198-201°C, nmr ($CDCl_3$) δ: 2.3 (s, 5-Me), 7.1-7.5 (m), 7.6-7.9 (m), 8.1-8.35 (m) (PhCO, H_3, H_4, H_6), 4.3 (br s), 5.7 (br s), 8.8 (br s), (NH_2, NH, NH). Anal.Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.26; H, 5.68; N, 19.37.

2(1H)-Benzoylaminocarbazoylmethylene-6-methylpyridine (5e). - This compound was prepared from 3e in 87 % yield, mp 162-164°C, nmr ($CDCl_3$) δ: 2.45 (s, 6-Me), 6.8-7.4 (m), 7.6-7.9 (m) (PhCO, H_3, H_4, H_5), 5.6 (br s), 8.1 (br s), 8.5 (br s) (NH_2, NH, NH). Analc.Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.30; H, 5.74; N, 19.71.

2(1H)-Azidocarbonylbenzoylaminomethylenequinoline (6a). - To a mixture of 5a (640 mg, 0.002 mole), water (20 ml) and conc. hydrochloric acid (1 ml), a solution of sodium nitrite (207 mg, 0.003 mole) in water (4 ml) was added dropwise at 0°C. The mixture was stirred at 0-5°C (1 h). The precipitate was filtered and washed with cold water to give 540 mg (82 %) of 6a, mp 100-102°C (decomp.), ir (KBr) ν: 2140 cm^{-1} (N_3), nmr ($CDCl_3$) δ: 7.1-7.5 (m), 7.5-8.0 (m) (PhCO, H_3, H_4, H_5, H_6, H_7, H_8). The compound was unstable and decomposed on attempted crystallization. It was used without purification in further experiment.

The following compounds were prepared according to the same procedure:

1(2H)-Azidocarbonylbenzoylaminomethyleneisoquinoline (6b). - This compound was prepared from 5b in 87 % yield, mp 107-110°C (decomp.), ir (KBr) ν: 2150 cm^{-1}, nmr ($CDCl_3$) δ: 7.2-7.5 (m), 7.6-7.9 (m) (PhCO, H_3, H_4, H_5, H_6, H_7, H_8), 8.4 (br s, NH). The compound decomposes at room temperature. It was used without purification in further experiments.

Dipeptide Derivative 7a. - To a solution of 6a (331 mg, 0.001 mole) in ethanol (5 ml), a solution of ethyl glycinate hydrochloride (350 mg) in ethanol (5 ml) was added and the mixture was left in a refrigerator (6 days) at 0°C. The reaction was followed by TLC (DC-Alufolien Kieselgel 60 F_{254}, 0.2 mm, E.Merck, and a mixture of chloroform and methanol, 5:1, as solvent). The precipitate was then filtered and washed with water to give 97 mg (25 %) of 7a, mp 163-167°C, nmr (DMSO-d_6) δ: 1.05 (t, CH_2Me), 3.90 (q, CH_2Me), 3.75 (d, CH_2NH), 7.25-7.60 (m), 7.6-8.0 (m), (PhCO, H_3, H_4, H_5, H_6, H_7, H_8), 5.9 (br s), 8.3 (br s), 8.9 (br s) (NH, NH, NH), J_{CH_2Me} = 6.5 Hz, J_{CH_2NH} = 5.0 Hz. Anal.Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.08; H, 5.67; N, 10.40.

Dipeptide Derivative 7b. - To a solution of 6b (560 mg, 0.0017 mole) in ethanol (5 ml), a solution of ethyl glycinate hydrochloride (420 mg) in ethanol (6 ml) was added and the mixture was left in a refrigerator (4 days) at 0°C. The reaction was followed by TLC (DC-Alufolien Kieselgel 60 F_{154}, 0.2 mm, E.Merck, and a mixture of chloroform and methanol, 5:1, as solvent). The precipitate was filtered and washed with water to give 250 mg (43 %) of 7b, mp 169-174°C, nmr (DMSO-d_6) δ: 1.05 (t, CH_2Me), 3.75 (d, CH_2NH), 3.90 (q, CH_2Me), 6.5 (d, H_3), 7.2-7.4 (m), 7.5-7.9 (m) (PhCO, H_4, H_5, H_6, H_7, H_8), 8.3 (br s), 8.8 (br s) (NH, NH, NH), J_{CH_2Me} = 6.5 Hz, J_{CH_2NH} = 5.0 Hz, J_{H_3,H_4} = 7.5 Hz. Anal.Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.69; H, 5.42; N, 10.70.

1-Methyl-2(1H)-(2-phenyl-5-oxo-4-oxazolinylidene)-quinoline (8a). - A mixture of 3a (288 mg, 0.001 mole) and DMFDMA (0.2 ml) in toluene (3 ml) was heated under reflux (2 h). The unreacted material, which precipitated after cooling, was separated by filtration. The filtrate was evaporated in vacuo and the dried residue was recrystallized from methanol to give 115 mg (37 %) of 8a, mp 184-187°C, nmr (DMSO-d_6) δ: 3.3 (s, N-Me), 7.25-8.0 (m, 2-Ph, H_3, H_4, H_5, H_6, H_7, H_8). Anal.Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.24; H, 4.61; N, 9.22.

The following compounds were prepared according to the same procedure:

2-Methyl-1(2H)-(2-phenyl-5-oxo-4-oxazolidinylidene)-isoquinoline (8b). - This compound was prepared from 3b in 55 % yield, mp 141-143°C (from methanol), nmr ($CDCl_3$) δ : 3.97 (s, N-Me), 6.85 (d, H_3), 7.1-7.5 (m, 2-Ph, H_4, H_5, H_6, H_7), 7.7-8.0 (m, H_8), J_{H_3,H_4} = 6.5 Hz. Anal.Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.39; H, 4.73; N, 9.20.

1-Methyl-2(1H)-(2-phenyl-5-oxo-4-oxazolinylidene)-pyridine (8c). - This compound was prepared from 3c in 84 % yield, mp 218-220°C, nmr ($CDCl_3$) δ: 4.20 (s, N-Me),

6.3 (m, H_3), 7.0-7.3 (m), 7.6-7.85 (m) (2-Ph, H_4,H_5), 8.5 (m, H_6). Anal.Calcd. for $C_{15}H_{12}N_2O_4$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.27; H, 4.81; N, 11.02.

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13. A modified procedure for the preparation of this compound in comparison to that described in lit.[8] was used.
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