REARRANGMENT OF SOME QUINOLINE-4-SPIROHETEROCYCLES TO FUSED HETEROCYCLES

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Abstract: 3-Nitro-4-chloro-6 or 7-methoxyquinaldines were reacted with; 1,2-phenylenediamine, 2-aminophenol, ethanolamine and ethylenediamine to give; 6- or 7-substitutedquinolines-4-spiro: 2'-benzimid-azoles **1**, 2'-benzoxazoles **2**, 2'-oxazoles **3** and benzimidazoles **4** respectively. Heating these products **1-4** with sodium carbonate or repeating the reaction in the presence of sodium carbonate produced: quinoxalinoquinolines **5**, benzoxazinoquinolines **6**, morpholinoquinolines **7** and piprazinoquinolines **8**.

Introduction:

Compounds of the 4-aminoquinoline type still play an important role in the treatment of Malaria (1-2). The suggestion that such drugs may be active against other diseases with malarial vector (3) drove us to synthesize other types of derivatives looking for other potential biological activities. Therefore, a new series of quinoline derivatives were prepared (4,5).

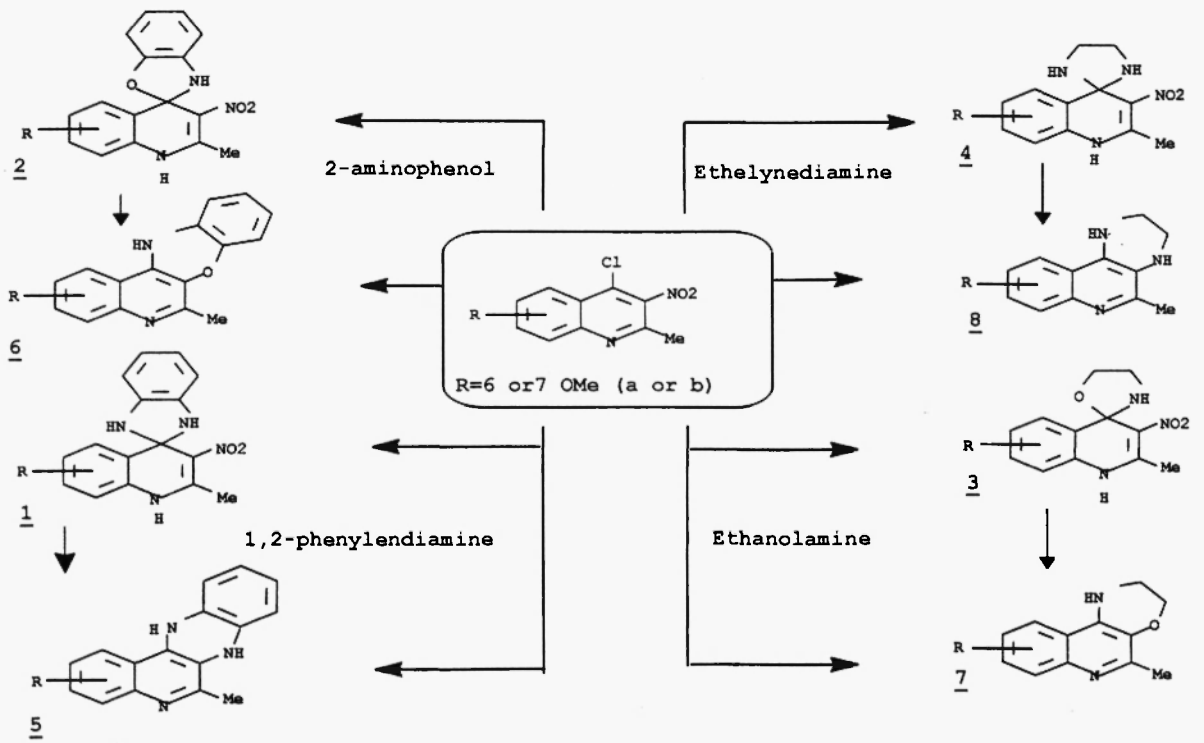
Results and Discussion

In the present work, I would like to introduce a new series of compounds structurally related to the 4-aminoquinoline and bearing either spiroheterocycles namely; benzimidazoles, oxazoles and imidazoles or quinoline [c] fused with quinoxaline, benzoxazine, morpholine and piprazines.

The starting compounds 3-nitro-4-chloro-6 or 7-methoxyquinaldines **9a,b** were prepared according to the described methods (6,7). Reaction of **9** with 2-substituted aromatic amines, (1,2-phenylenediamine, 2-aminophenol) or aliphatic amines (2-aminoethanol, 1,2-diaminoethane) gave: 3-nitro-6 or 7-methoxyquinaldine-4-spiro-2'-[3'H]-benzimidazoles **1a,b**, 3-nitro-6-or 7-methoxy-quinaldine-4-spiro-'2-[3'H]-benzoxazoles **2a,b**, 3-nitro-6-or 7-methoxyquinaldine-4-spiro-2'-[3'H]-4,5-dihydrooxazoles **3a,b** and 3-nitro-6- or 7-methoxyquinaldine-4-spiro-2'-[3'H]-4',5'-dihydroimidazoles **4a,b**.

The unexpected spiro structure was confirmed through: a) studying the analytical and spectroscopic data. IR spectra showed a strong peak corresponding to the nitro group, as it is also shown from the m/z in the mass spectral data. b) hydrolysis of compounds 1-4 by dilute sodium hydroxide solution gave the same product, 3-nitro-4-hydroxy-6 or 7-methoxyquinaldine 10 which is in agreement with the literature reports (8,9) c) similar results were reported on carrying the reactions on the sulphur and oxygen analogues (10,11).

When the same reactions were repeated in the presence of weak inorganic base, sodium carbonate, quinoline(-C-)heterocycles were obtained, i.e 2- or 3-methoxy-6-methyl-7,12-dihydro-quinoxalino(3,2,-c)quinolines **5a,b**, 2- or 3-methoxy-6-methyl-[12 H]-benzoxazino(3,2-c)quinolines **6a,b**. 8 or 9-methoxy-5-methylmorpholino(2,3-c)quinolines **7a,b** and 8 or 9-methoxy-5-methyl-piprazino(2,3-c)quinolines **8a,b**. These results allowed me to suggest that the spiro compounds may be formed first and then transformed or in other words rearranged to the fused products in the presence of sodium carbonate. To confirm this hypothesis, the spiro compounds **1-4** were separately treated with alcoholic sodium carbonate and the products obtained were 4-8, by these results, I could say that the spiro compound is the intermediate step in the formation of **5-8**.



Structure of compounds **5-8** were confirmed by studying their analytical and spectral data, IR showed the disappearance of the NO_2 peak, this also appeared from its mass spectral data. Also, when

compound **5-8** were heated with dilute sodium hydroxide, no reaction had been took place.

Experimental:

Melting points were obtained on a Mel-Temp II melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1430 ratio recording spectrometer.

^{1}H NMR spectra were recorded on a Varian Gemmini (200 Mhz) instrument. All spectra were determined using duteriodimethylsulphoxide as solvent, unless otherwise stated, using tetramethyl-silane as internal standard. Thin-layer chromatography was carried out on 5 X 20 cm coated with silica gel GF 254 type 60, mesh size 50-250.

6- or 7-Methoxy-3-nitro-4-chloroquinaldines 9:

Compounds **9a,b** were prepared according to the literature methods (6-7).

a = 6-methoxy b = 7-methoxy

6- or 7-Methoxy-3-nitroquinaldine-4-spiro-2'-[3'H]benzimidazoles 1a,b:

To a solution of either 9a or b (0.5 g, 0.0020 mole) in dry benzene (20 ml); *o*-phenylenediamine (0.45 g, 0.0042 mole) was added. The mixture was refluxed for two hours on a water bath, on cooling, the precipitate was filtered, then boiled with alcoholic sodium carbonate and filtered, the filterate was concentrated and cooled to give the required products **1a,b**. which crystallized from ethanol.

Comp. No.	M.P°C	Yield %	Calcd.for: $C_{17}H_{16}N_4O_3$%			Found		
			C	H	N	C	H	N
1 a	192	77	62.96	4.93	17.28	63.13	5.31	17.51
b	194	62				63.42	5.35	17.46

^{1}H NMR showed the following signals:

a: δ (ppm) 9.8 ppm (s, H, D_2O exch., NH); 9.1 (d, H 8); 8.4 (s, H 5), 8.1 (d, H 7) 7.4-6.5 (m, 4 H, Ar), 4,5 (bs, D_2O exch. 2 H, 2 NH), 4.2 (s, 3 H, OCH_3) and 2.6 (s, 3 H, CH_3).

b: δ (ppm) 9.8 ppm (s, D_2O exch., NH), 9.2 (s, H_8); 8.4 (d, H_5), 8.2 (d, H_6), 7.4-6.5 (m, 4 H, Ar), 4,5 (bs, D_2O exch. 2 H, 2 NH), 4.2 (s, 3 H, OCH_3) and 2.6 (s, 3 H, CH_3).

6- and 7-Methoxy-3-nitroquinaldine-4-spiro-2'-[3'H]benzoxazoles 2a,b:

A mixture of either **9a** or **b** (0.5 g, 0.0020 mole) and 2-aminophenol (0.24 g, 0.0022 mole) in ethanol (20 ml) was refluxed for an hour, the mixture was left to cool, the precipitated hydrochloride was filtered off and recrystallized from ethanol.

The free base was obtained by refluxing the salt with a suspension of sodium carbonate in

ethanol, the excess carbonate was filtered, and the filterate was concentrated and left to cool to give **2a,b**, which crystallized from ethanol.

Comp. No.	M.P °C	Yield %	Calcd.for: $C_{17}H_{15}N_3O_4$ %			Found		
			C	H	N	C	H	N
2 a	235-271(HCl)	87	62.76	4.61	12.92	62.53	4.87	12.82
b	237-273(HCl)	85				63.11	4.83	13.35

^{1}H NMR showed the following signals:

a: δ (ppm) 9.8 ppm (s, D_2O exch., NH), 9.1 (s, D_2O exch., NH), 8.5 (d, H_8), 7.9 (s, H_5), 7.7 (d, H_7), 7.5-6.8 (m, 4 H, Ar), 4.1 (s, 3 H, OCH_3), and 2.7 (s, 3 H, CH_3).

b: δ (ppm) 9.8 ppm (s, D_2O exch. NH), 9.1 (s, D_2O exch., NH), 8.6 (s, H_8), 7.9 (d, H_5), 7.7 (d, H_6), 7.5-6.8 (m, 4 H, Ar), 4.1 (s, 3 H, OCH_3), and 2.7 (s, 3 H, CH_3).

6- or 7-Methoxy-3-nitroquinaldine-4-spiro-2-[3'H](4',5',dihydro)oxazoles 3a,b or imidazoles 4a,b:

A mixture of either **9a** or b (0.5 g, 0.0022 mole), either ethanolamine or ethylenediamine (1.2 g, 0.02 mole) and benzene (20 ml) was refluxed on a water bath for two hours, after cooling, the precipitated hydrochloride was filtered off. The base was prepared as in the previous reaction. The yellow precipitate was separated and recrystallized from ethanol to give **3a,b or 4a,b**.

Comp. No.	M.P °C	Yield %	Calcd.for: $C_{13}H_{15}N_3O_4$			Found		
			C	H	N	C	H	N
3a	170	91	56.31	5.41	15.16	56.61	5.54	15.30
b	172	91				56.58	5.62	15.41
			$C_{13}H_{16}N_4O_3$ %					
4a	165	89	56.52	5.79	20.28	56.74	5.84	20.35
b	167	89				56.82	5.64	20.47

^{1}H NMR showed the following signals:

3a: δ (ppm) 9.7 ppm (s, D_2O exch. NH), 8.5 (d, H_8), 7.8 (s, H_5), 7.6 (d, H_7), 5.0 (s, D_2O exch. NH), 4.1 (s, 3 H, OCH_3), 3.6 (t, 2 H, CH_2) 3.5 (t, 2 H, CH_2) and 2.4 (s, 3 H, CH_3).

b: δ (ppm) 9.7 (s, D_2O exch. NH), 8.6 (s, H_8), 7.9 (d, H_5), 7.8 (d, H_6), 5.0 (s, D_2O exch, 2 NH) 4,1 (s, 3 H, OCH_3), 3.6 (t, 2 H, CH_2) 3.5 (t, 2 H, CH_2) and 2.4 (s, 3 H, CH_3).

4a: δ (ppm) 9.7 (s, D_2O exch. 2 NH), 8.5 (d, H_8), 7.8 (s, H_5), 7.6 (d, H_7), 5.0 (s, D_2O exch. NH), 4.1 (s, 3 H, OCH_3), 3.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2) and 2.4 (s, 3 H, CH_3).

b: δ (ppm) 9.7 (s, D_2O exch. NH), 8.5 (s, H_8), 7.9 (d, H_5), 7.8 (d, H_6), 5.0 (s, D_2O exch. NH), 4.1 (s, 3 H, OCH_3), 3.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2) and 2.4 (s, 3 H, CH_3).

Quinoline (3,2- or 2,3-c) heterocycles 5-8:

Method A: A mixture of 3-nitro-4-chloro-6-or 7-methoxyquinaldine **9** (0.5 g, 0.0022 mole), either 1,2-phenylenediamine or 1-aminophenol or ethanolamine or ethylenediamine (0.023 mole), sodium carbonate (0.5 g, 0047 mole) and absolute ethanol (10 ml) was refluxed on a water bath for five hours, after which the mixture was filtered and the precipitate washed with hot alcohol, then, the filterate was collected and concentrated, after cooling the formed precipitate was collected and crystallized from ethanol.

Method B: A mixture of the required spiro compounds **1-4** (0.01 mole), sodium carbonate (1.0 g, 0.01 mole) and absolute ethanol (10 ml) was heated for five hours on a water bath for five hours and the reaction was worked up as above. The products were identical with that of method A, mp. Tlc, IR, NMR.

Compd.No	Formula, *m/z*	Yield	M.p.	Calcd.			Found		
		%	°C	C	H	N	C	H	N
5 , a	$C_{17}H_{15}N_3O$,277	74	156	73.64	5.41	15.16	73.58	5.51	15.45
b		74	159				73.72	5.63	15.53
6 , a	$C_{17}H_{14}N_2O_2$,278	72	145	73.38	5.03	10.07	73.52	5.26	10.34
b		72	148				73.57	5.31	10.22
7 , a	$C_{13}H_{14}N_2O_2$,230	74	223	67.82	6.08	12.17	67.35	6.21	12.41
b		74	227				67.38	6.32	12.37
8 , a	$C_{13}H_{15}N_3O$,229	70	235	68.12	6.55	18.34	68.47	5.26	18.21
b		70	239				67.93	6.81	18.54

^{1}H NMR were the same as that of the spiro compound.

Effect of bases and acids on the spiro compounds 1-4

Refluxing 1,2,3 or 4 with ethanolic sodium hydroxide (5%) for two hours and neutralizing the mixture, a precipitate was formed and characterized as the corresponding 4-hydroxy-derivative **10**. The same products were obtained on refluxing with dil-hydrochloric acid (10%). Tlc, IR and NMR

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