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Base Induced Cyclization of Some Quinolines. Formation of Fused Nitrogen Heterocyclic Ring System

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Condensation of 3,5-dinitro-4-chloro-6-methoxy-2-methylquinoline (**1**) with benzylamine, ethanolamine and/or thioglycolic acid afforded the quinoline derivatives **4a–c**. Cyclization of **4a** and **4b** with alkali and condensation of **1** with glycine in sodium carbonate solution furnish 2*H*-imidazo[4,5-c]quinoline derivatives **5a–c**, respectively. Treatment of **5b** with benzaldehyde in presence of zinc chloride gave the styryl derivative **6**. **1** reacted with sodium azide to give the azido derivative **4d**, which upon treatment with phenylhydrazine or sodium borohydride yielded the 4-amino derivative **4e**. Moreover, **1** was treated with phenylhydrazine to give **4f**, which cyclized in 10% sodium hydroxide solution to the corresponding v-triazolo[4,5-c]quinoline 3-oxide derivative **7**. When however **4f** was treated with dilute hydrochloric acid, the corresponding phenylpyrazolo[3,4,5-de]quinoline derivative **8** was obtained.

(Keywords: Cyclization; Heterocyclic compounds; Quinoline derivatives)

Baseninduzierte Cyclisierung einiger Chinoline. Darstellung höherer Stickstoff-Heterocyclen

Kondensation von 3,5-Dinitro-4-chlor-6-methoxy-2-methylchinolin (**1**) mit Benzylamin, Ethanolamin und/oder Thioglycolsäure ergab die Chinolinderivate **4a–c**. Cyclisierung von **4a** und **4b** mit Alkali und Kondensation von **1** mit Glycin in Natriumcarbonatlösung lieferte 2*H*-imidazo[4,5-c]chinolin-Derivate **5a–c**. Behandlung von **5b** mit Benzaldehyd in Gegenwart von Zinkchlorid ergab das Styrylderivat **6**. **1** wurde mit Natriumazid zum Azidoderivat **4d** umgesetzt, das mit Phenylhydrazin oder Natriumborhydrid zum 4-Aminoderivat **4e** weiterreagierte. **1** ergab mit Phenylhydrazin **4f**, das in 10% NaOH-Lösung zum entsprechenden Triazolo[4,5-c]chinolin-Derivat **7** cyclisierte. Aus **4f** wurde mit verdünnter Salzsäure das Phenylpyrazolo[3,4,5-de]chinolin **8** erhalten.

In this work we were interested to prepare 4-hydroxy-6-methoxy-2-methylquinoline derivatives, as they are considered to be important intermediates in the preparation of a wide variety of biologically active

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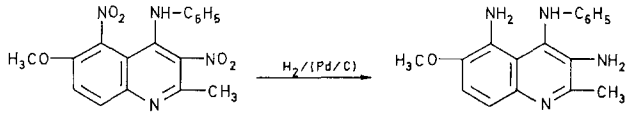
compounds of the quinoline type. Some dinitro derivatives are described, since a variety of preparations containing nitro groups are of therapeutic utility[1].

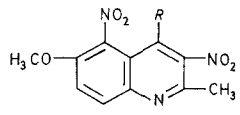
When 3,5-dinitro-4-chloro-6-methoxy-2-methylquinoline (**1**) was reacted with aniline 4-anilino-3,5-dinitro-6-methoxy-2-methylquinoline (**2**) was obtained which on catalytic reduction using Pd/C as catalyst gave 4-anilino-3,5-diamino-6-methoxy-2-methylquinoline (**3**). Attempts to cyclize **2** with paraformaldehyde under different conditions led only to resins.



2 3

Stacy et al.[2,3] have developed a new method for the preparation of 1-hydroxybenzimidazoles by the base catalyzed cyclization of *N*-benzoyl-*o*-nitroaniline. Also 1-benzylamino-2,4-dinitrobenzene[4] on treatment with alkali gave 3-hydroxy-5-nitro-2-phenylbenzimidazole, identical with that prepared by *Russell*[5]. But its cyclization in acetic acid medium failed and gave only starting material.

The condensation of **1** with benzylamine, ethanolamine and/or thioglycolic acid afforded 4-benzylamino-3,5-dinitro-6-methoxy-2-methylquinoline (**4a**), 3,5-dinitro-4-(2′-hydroxyethylamine)-6-methoxy-2-methylquinoline (**4b**) and the acid derivative (**4c**), respectively.



4

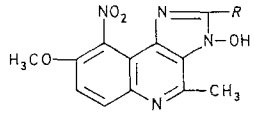
a $R = -NHCH_2C_6H_5$
b $R = -NH(CH_2)_2OH$
c $R = -SCH_2COOH$
d $R = -N_3$
e $R = -NH_2$
f $R = -NHNHC_6H_5$
g $R = -N(C_6H_5)NHCOCH_3$

The IR spectrum of **4b** showed peaks at 3,350 (OH stretching), 3,190 (NH stretching) and 1,280 cm^{-1} ($-CH_2OH$).

Ring closure of **4a** and **4b** was achieved with ethanolic sodium hydroxide solution to give 3-hydroxy-8-methoxy-4-methyl-9-nitro-2-phenyl-2*H*-imidazo[4,5-c]quinoline (**5a**) and 3-hydroxy-8-methoxy-4-methyl-9-nitro-2-hydroxymethyl-2*H*-imidazo[4,5-c]quinoline (**5b**), respectively. Furthermore, when glycine was condensed with **1** in alco-

holic sodium carbonate solution, 3-hydroxy-8-methoxy-4-methyl-9-nitro-2-carboxy-2*H*-imidazo[4,5-c]quinoline (**5c**) was obtained.

Its IR spectrum showed the OH group at 3,250 which may be due to association with the neighbouring carboxylic group, 1,590 (C=N) and 1,030 cm^{-1} (OCH_3). The NMR spectrum ($CDCl_3$) of **5a** showed peaks at τ 7.32 (S, 3H, 4-CH_3), τ 6.01 (S, 3H, 8-OCH_3) and at τ 2.3-3.2 ppm (multiplet, 7H, aromatic protons).



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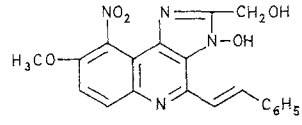


6

a $R = -C_6H_5$
b $R = -CH_2OH$
c $R = -COOH$

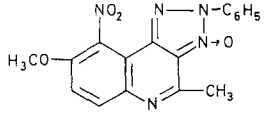
Treatment of **5b** with benzaldehyde in presence of zinc chloride, gave the corresponding styryl derivative **6**. Its IR spectrum showed peaks at 3,290 (OH stretching), 1,260 (CH_2OH), 1,340 (NO_2) and 1,030 cm^{-1} (OCH_3).

When **1** was allowed to react with sodium azide in dimethyl sulphoxide, the 4-azido derivative **4d** was obtained. Its IR spectrum showed a signals at 2,090 (N_3), 1,600 (C=N) and at 1,050 cm^{-1} (OCH_3). Upon treatment of **4d** with phenylhydrazine in absolute alcohol, the azide group was reduced and 4-amino-3,5-dinitro-6-methoxy-2-methylquinoline (**4e**) was obtained. This is not the expected reaction, since it was reported that polynitrophenylazides react with phenylhydrazine in ethanol to give 2-phenylbenzotriazoles[6,7]. The proposed structure **4e** was also established by reduction of **4d** with sodium borohydride. The IR spectrum of **4e** showed two bands due to —NH_2 stretching frequencies shifted from 3,500 to 3,300 cm^{-1}, this shift is attributed to the possibility that a six membered chelate of high stability formed through strong N—H ... O hydrogen bonding[8,9].

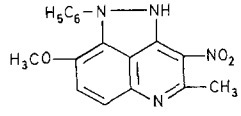
Moreover, **1** was treated with phenylhydrazine in boiling ethanol to give 3,5-dinitro-6-methoxy-4-phenylhydrazino-2-methylquinoline (**4f**). The fact that 4-chloroquinolines condense with aromatic amine[10] easier than aliphatic amines[11] suggested that a compound such as **4g** might be obtainable. However, when **1** was refluxed with *N*-acetyl-*N'*-phenylhydrazine, only the starting material was recovered.

When **4f** was refluxed in 10% sodium hydroxide solution, it gave a product formulated as 8-methoxy-4-methyl-9-nitro-2-phenyl-2*H*-1,2,3-triazolo[4,5-c]quinoline 3-oxide (**7**). Its NMR spectrum (CF_3COOH) showed peaks at τ 7.28 (S, 3H, 4-CH_3), τ 5.92 (S, 3H, 8-OCH_3) and at τ 1.7-2.5 ppm (multiplet, 7H, 7 aromatic protons).

When however **4f** was treated with dilute hydrochloric acid evolution of nitrous fumes occured and 1,2-dihydro-8-methoxy-4-methyl-3-nitro-1-phenylpyrazolo[3,4,5-de]quinoline (**8**) was obtained. The IR spectrum of **8** showed signals at 1,480 and 926 cm^{-1} which have been reported to be characteristic of pyrazoles[12]. Its NMR spectrum ($CDCl_3$) showed peaks at τ 7.20 (S, 3 H, 4-CH_3), τ 5.95 (S, 3 H, 8-OCH_3), and τ 1.70–2.55 ppm (multiplet, 7 H, aromatic protons).



7



8

When cyclization of **4f** was carried out in acetic acid or dimethylformamide, **8** was obtained as the major product. Another product was also formed which analyzed for $C_{17}H_{13}N_5O_4$ (**9**) which was not investigated further. Also attemps to cyclize **4f** under neutral conditions gave only the starting material.

Experimental

Melting points are uncorrected and were determined in a Gallenkamp electric melting point apparatus and Boëtius melting point microscope. The IR spectra were obtained on a "UR 10" Carl-Zeiss Jena Infrared Spectrophotometer using KBr wafers. NMR spectra were performed on deuterochloroform or trifluoroacetic acid solutions with a Varian Associates model "A-60" Spectrometer. The elemental analyses (C, H,N) for **2, 3, 4a–f, 5a–c,** and **6–9** were in good agreement with the proposed structures.

4-Anilino-3,5-dinitro-6-methoxy-2-methylquinoline (**2**)

A mixture of 0.6 g (0.002 mol) of 3,5-dinitro-4-chloro-6-methoxy-2-methylquinoline (**1**), 0.2 g (0.0022 mol) of pure aniline, 0.2 g (0.0024 mol) of fused sodium acetate and 5 ml glacial acetic acid was gently warmed on a steam bath for one hour. The reaction mixture was cooled and poured onto 100 ml water. The precipitate formed was filtered and washed several times with water and then dried; m. p. 195–200 °C. Recrystallization from alcohol gave 0.5 g (71%) of **2** as bright brown needles, m. p. 209–210 °C.

4-Anilino-3,5-diamino-6-methoxy-2-methylquinoline (**3**)

To a solution of 0.35 g (0.001 mol) of **2** in 20 ml absolute alcohol was added 0.01 g of palladized charcoal. Hydrogen gas was passed through the mixture, then shaken at normal pressure for 3 h until the calculated amount of hydrogen was consumed. The catalyst was removed by filtration and the filtrate was distilled. The residue was then recrystallized from aqueous alcohol to give 0.2 g (68%) of **3** as violet crystals, m. p. 132–133 °C.

4-Benzylamino-3,5-dinitro-6-methoxy-2-methylquinoline **4a**

A mixture of 0.6 g (0.002 mol) of **1** and 0.43 g (0.004 mol) of benzylamine was gently refluxed in 20 ml dry benzene for half an hour. The reaction mixture was

filtered from the precipitated benzylamine hydrochloride. The filtrate was then concentrated and poured onto 20 ml of *n*-hexane where an orange precipitate was obtained. It was filtered and dried, m.p. 157–158 °C. Recrystallization from ethanol gave 0.45 g (61%) of **4a** as yellow orange needles, m.p. 158–159 °C. ν_{max} 3,420 (NH stretching), 1,600 (NH bending), 1,080 (OCH_3) and 1,360 cm^{-1} (NO_2).

3,5-Dinitro-4-(2'-hydroxyethylamino)-6-methoxy-2-methylquinoline **4b**

To a solution of 0.3 g (0.001 mol) of **1** in 10 ml dry benzene was added 0.13 g (0.002 mol) of ethanolamine. The mixture was gently warmed on the water bath for one hour. The benzene layer was separated and concentrated to give 0.2 g (62%) of **4b** as yellow crystals, m.p. 174–176 °C. Recrystallization from ethanol gave m.p. 175–176 °C.

3,5-Dinitro-4-carboxymethylthio-6-methoxy-2-methylquinoline **4c**

A mixture of 0.3 g (0.001 mol) of **1** and 2 g (0.022 mol) of thioglycolic acid was refluxed for one hour. The reaction mixture was cooled, poured onto cold water, filtered and washed several times with water. Recrystallization from aqueous alcohol gave 0.18 g (51%) of **4c** as white crystals, m.p. 192–194 °C. ν_{max} 1,715 (C=O carboxylic), 3,300 (OH stretching), 1,610 (C=N) and 570 cm^{-1} (—C—S—).

3-Hydroxy-8-methoxy-4-methyl-9-nitro-2-phenyl-2H-imidazo[4,5-c]quinoline **5a**

A mixture of 0.37 g (0.001 mol) of **4a** and 10 ml alcoholic sodium hydroxide (5%) was refluxed for 3 h. The reaction mixture after concentration was cooled, and neutralized with dilute hydrochloric acid until *pH* 7. The faint yellow precipitate formed was filtered, washed with water and dried, m.p. 226–230 °C. Recrystallization from ethanol gave 0.2 g (54%) of **5a**, m.p. 232–234 °C as bright yellow needles. ν_{max} 1,600 (C=N) and 1,050 cm^{-1} (OCH_3).

3-Hydroxy-8-methoxy-9-nitro-4-methyl-2-hydroxymethyl-2H-imidazo[4,5-c]quiniline **5b**

A mixture of 0.32 g (0.001 mol) of **4b** and 10 ml of 5% alcoholic sodium hydroxide was refluxed on the water bath for 2 h. The reaction mixture after concentration was cooled, and neutralized with dilute hydrochloric acid to *pH* 7. The faint yellow precipitate formed was filtered and dried, m.p. 290–295 °C. Recrystallization from ethanol gave 0.17 g (56%) of **5b**, m.p. 292–294 °C (decomp.). ν_{max} 3,290 (OH stretching) and 1,260 cm^{-1} (CH_2OH).

3-Hydroxy-8-methoxy-9-nitro-4-methyl-2-carboxy-2H-1,2,3-triazolo[4,5-c]quinoline **5c**

A mixture of 0.3 g (0.001 mol) of **1**, 0.15 g (0.002 mol) glycine and 0.2 g of sodium carbonate in 10 ml ethanol was refluxed with stirring for 3 h. The reaction mixture was cooled, poured onto cold water, neutralized with dilute hydrochloric acid until *pH* 7, then filtered, washed several times with water and dried, m.p. 290–295 °C. Recrystallization from alcohol gave 0.18 g (67%) of **5c** as faint yellow crystals m.p. 298–300 °C (decomp.).

3-Hydroxy-8-methoxy-9-nitro-4-styryl-2-hydroxymethyl-2H-imidazo[4,5-c]quinoline **6**

A mixture of 0.3 g (0.001 mol) of **5b**, 0.1 g (0.001 mol) of benzaldehyde and 0.1 g fused zinc chloride was heated at 160 °C for 2 h. The reaction mixture was

cooled, poured onto cold water, washed several times with water then with alcohol and dried. Recrystallization from dimethylformamide gave 0.15 g (38%) of **6** as yellow needles m. p. over 300 °C.

4-Azido-3,5-dinitro-6-methoxy-2-methylquinoline (**4 d**)

A mixture of 0.3 g (0.001 mol) of **1**, 0.065 g (0.001 mol) of sodium azide and 5 ml of dimethyl sulphoxide was shaken for one hour. The reaction mixture was poured onto cold water, filtered, washed several times with water and dried m. p. 155–160 °C. Recrystallization from alcohol gave 0.2 g (66%) of **4 d** as yellow needles, m. p. 160–162 °C (decomp.).

4-Amino-3,5-dinitro-6-methoxy-2-methylquinoline (**4 e**)

Method A: A mixture of 0.3 g (0.001 mol) of **4 d** and 0.2 g (0.01 mol) phenylhydrazine in 10 ml absolute alcohol was refluxed for 10 h. The reaction mixture was cooled and the precipitate formed filtered off, m. p. 205–210 °C. Recrystallization from ethanol gave 0.15 g (54%) of **4 e** as yellow crystals, m. p. 210–212 °C.

Method B: To a solution of 0.3 g (0.001 mol) of **4 d** in 10 ml of ethanol was added 0.095 g (0.002 mol) sodium borohydride portionwise with continuous stirring for one hour. The precipitate appeared filtered, washed several times with water and dried, m. p. 205–210 °C. Recrystallization from ethanol gave 0.2 g (72%) of **4 e** as yellow crystals, m. p. 210–212 °C. It was found to be identical with that prepared by method A, and showed no depression in the admixed melting point.

3,5-Dinitro-6-methoxy-4-phenylhydrazino-2-methylquinoline (**4 f**)

To a hot solution of 3 g (0.01 mol) of **1** in ethanol (50 ml) was gradually added 2.16 g (0.02 mol) of phenylhydrazine under stirring. After the addition, the mixture cooled and filtered. The product obtained was washed several times with water and then with hot alcohol to give 2 g (54%) of **4 f**. It is sparingly soluble in most organic solvents. An analytical sample was prepared by washing it with alcohol and chloroform to give **4 f** as brownish black crystals, m. p. 193–195 °C (decomp.). ν_{max} 3,240 (NH stretching), 1,580 (NH bending), 1,610 (C=N) and 1,030 cm^{-1} (OCH_3).

8-Methoxy-4-methyl-9-nitro-2-phenyl-2H-1,2,3-triazolo[4,5-c]quinoline 3-oxide (**7**)

To 0.37 g (0.001 mol) of **4 f** was added 10 ml sodium hydroxide solution. The mixture was refluxed for one hour. The reaction mixture was cooled and neutralized with dilute hydrochloric acid. The faint yellow precipitate was filtered and dried, m. p. 255–260 °C. Recrystallization from chloroform gave 0.2 g (57%) of **7** as faint yellow crystals m. p. 262–264 °C. ν_{max} 1,590 (C=N) and 1,030 cm^{-1} (OCH_3).

1,2-Dihydro-8-methoxy-4-methyl-3-nitro-1-phenylpyrazolo[3,4,5-de]quinoline **8**

A mixture of 1.85 g (0.005 mol) of **4 f** and 15 ml of glacial acetic acid, was refluxed for 3 h. Red fumes of decomposed nitrous acid evolved from the condenser, which gave an intense blue colour with potassium iodide and starch. The solution was cooled and then poured onto cold water. The yellowish red precipitate obtained was filtered and washed several times with water then dried, m. p. 150–180 °C. Recrystallization from alcohol gave two substances.

The main yield was easily recrystallized from dilute alcohol gave 0.82 g (50%) of **8** as yellow crystals, m. p. 192–194 °C. ν_{max} 1,580 (C=N) and 1,050 cm^{-1} (OCH_3).

A very low yield of **9** was obtained recrystallized from alcohol, gave 0.4 g as a dark bright red crystals, m. p. 196 °C. This compound is under investigation and more details will published in a separate paper.

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