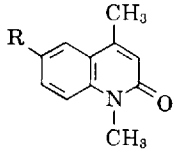
Nitration of 1,4-Dimethyl-2-quinolone and 1,2-Dimethyl-4-quinolone

By I. NABIH and M. NASR

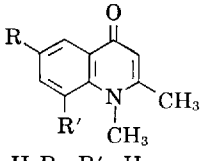
Nitration occurred at position 6 in 1,4-dimethyl-2-quinolone and at 6 and 8 in 1,2-dimethyl-4-quinolone. Structures were confirmed by alternate synthesis.

EXTENSIVE work has been carried out on the nitration of quinolines (1). In the case of quinolones, nitration of 1 - methyl - 2 - quinolone with nitric and sulfuric acids has given 6-nitro-1-methyl-2-quinolone, which on further nitration gave 3,6,8 - trinitro - 1 - methyl - 2 - quinolone (2, 3). 1-Methyl-4-quinolone has been treated with 68% nitric acid to give 3 - nitro - 1 - methyl - 4 - quinolone, and further nitration led to 3,6-dinitro-1-methyl-4-quinolone (4). 1,4-Dimethyl-2-quinolone (I) has been treated with an excess of fuming nitric acid to give a mixture of compounds tentatively assigned the structures of 6-nitro-1,4-dimethyl-2-quinolone (III) and 3,6,8-trinitro-1, 4-dimethyl-2-quinolone (5). The purpose of the present work was to establish structure III, and also to carry out similar studies on the nitration of 1,2-dimethyl-4-quinolone (II) and to establish the structures of the nitration products. Their assignments were mainly dependent upon using compounds of accurate structural assignment as possible starting materials.

Thus, compound III was identified through the preparation of 6-nitro-2-hydroxy-4-methylquinoline (6), which upon treatment with methyl iodide and potassium methoxide gave 6-nitro-1,4-dimethyl-2-quinolone which is identical with III (as shown by mixed melting point).



I, R = H
III, R = NO_2
IV, R = NH_2



II, R = R′ = H
V, R = R′ = NO_2
VI, R = NO_2, R′ = H

NMR spectra were determined for both I and II. The vinyl hydrogen at the 3-position appears in both spectra as a singlet at 3.65 τ and 4.1 τ, respectively, while the aromatic hydrogens in I appeared at 2.8 τ. They split into separate peaks in the spectrum of III at 3.2 τ and 2.3 τ. These correspond to the hydrogen atoms at the 5-position and 7- and 8-positions as shown from their integration values, but the signal arising from the vinyl hydrogen at the 3-position (3.65 τ) remained unchanged, an indication of nonsubstitution at that position.

Reduction of III with stannous chloride and hydrochloric acid led to 6-amino-1,4-dimethyl-2-quinolone (IV).

Nitration of 1,2-dimethyl-4-quinolone (II) in sulfuric–nitric acid medium led to substitution at both the 6- and 8-positions to give V, the structure of which was assigned by alternative synthesis.

6-Nitro-1,2-dimethyl-4-quinolone (VI) was prepared by the action of dimethyl sulfate in an alkaline solution of 6-nitro-2-methyl-4-hydroxyquinoline (7), and further nitration of VI gave 6,8-dinitro-1,2-dimethyl-4-quinolone, which was identical with V. 8-Nitro-2-methyl-4-hydroxyquinoline (8), when subjected to further nitration, led to the 6,8-dinitro derivative, which upon treatment with dimethyl sulfate in an alkaline medium gave V.

EXPERIMENTAL

All melting points are uncorrected and measured on Kofler hot stage.

6 - Nitro - 1,4 - dimethyl - 2 - quinolone (III).—*Method A.*—To a solution of 1,4-dimethyl-2-quinolone (9) (3 Gm., 0.017 mole) in 10 ml. of concentrated sulfuric acid was added 5 ml. of nitric acid (d. 1.42) mixed with 15 ml. of concentrated sulfuric acid, while the temperature was kept at 0°. The reaction mixture was kept for 24 hr. at room temperature, and when poured onto crushed ice, a yellow precipitate formed, m.p. 223–225°. Recrystallization from ethanol gave 3.46 Gm. (90% yield) of III, m.p. 225–227°. [Lit. m.p. 228.5–229° (7).]

Anal.—Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.51; H, 4.75; N, 12.89.

Method B.—To a mixture of 6-nitro-4-methyl-2-hydroxyquinolone (8) (2.04 Gm., 0.01 mole) in 10 ml. of 2 *N* potassium methoxide and 15 ml. of absolute methyl alcohol was added 4 Gm. of methyl iodide. The mixture was heated under reflux for 3 hr., then allowed to cool overnight. The precipitated potassium iodide was separated, the filtrate was diluted with water and made alkaline by addition of sodium hydroxide solution, and a yellow substance precipitated, m.p. 224–225°. Recrystallization from ethanol gave m.p. 225–227° which was undepressed on admixture with an authentic sample, prepared by *Method A*.

Anal.—Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.75; H, 4.52; N, 12.96.

6 - Amino - 1,4 - dimethyl - 2 - quinolone (IV).—To a solution of 6-nitro-1,4-dimethyl-2-quinolone (1.88 Gm., 0.01 mole) in glacial acetic acid (15 ml.), was added a solution of stannous chloride (7.5 Gm.) in concentrated hydrochloric acid (10 ml.). The mixture was refluxed for 3 hr., then kept overnight at room temperature. The precipitated stannic chloride was filtered off, and the filtrate was boiled for 20 min. with 50% aqueous sodium hydroxide (25 ml.). The solid so obtained, m.p. 275–277°, was recrystallized from ethanol, m.p. 279–280°.

Anal.—Calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.39; N, 14.89. Found: C, 70.08; H, 6.35; N, 14.66.

1,2-Dimethyl-4-quinolone (II).—To a solution of

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2-methyl-4-hydroxyquinoline (15.9 Gm., 0.4 mole) in 150 ml. of aqueous potassium hydroxide (5%), was added dimethyl sulfate (8 ml.). After shaking the mixture for 30 min., potassium hydroxide solution (50 ml.) was added with continuous shaking during an additional 30 min. The reaction mixture was kept for 48 hr. at room temperature. The product was extracted with chloroform, then recrystallized several times from benzene to give 2.59 Gm. (15% yield) of II in the form of light-red needles, m.p. 158–160°. [Lit. m. p. 156–160° (10).]

6,8 - Dinitro - 1,2 - dimethyl - 4 - quinolone (V).—To a solution of 1,2-dimethyl-4-quinolone (0.173 Gm.) in sulfuric acid (5 ml.) was added a mixture of nitric acid (1 ml.) and sulfuric acid (3 ml.) by the same method as described for 1,4-dimethyl-2-quinolone (I). The product obtained, m.p. 258°, when recrystallized from ethanol, gave 0.17 Gm. (65% yield) of V, m.p. 259–261°.

Anal.—Calcd. for $C_{11}H_{12}N_3O_5$: C, 49.62; H, 4.51; N, 15.78. Found: C, 50.02; H, 4.45; N, 15.98.

6 - Nitro - 1,2 - dimethyl - 4 - quinolone (VI).—To a solution of 6-nitro-2-methyl-4-hydroxyquinoline (7) (2.04 Gm.) in 50 ml. of aqueous potassium hydroxide (5%) was added dimethyl sulfate (3.3 Gm.). The mixture was stirred at 70° for 30 min. and kept at room temperature overnight. The formed yellow precipitate, m.p. 215°, was recrystallized from hot benzene to give 1.27 Gm. (40% yield) of VI, m.p. 218–220°.

Anal.—Calcd. for $C_{11}H_{10}N_2O_5$: C, 60.55; H, 4.58; N, 12.88. Found: C, 60.37; H, 4.46; N, 12.75.

6,8 - Dinitro - 1,2 - dimethyl - 4 - quinolone (V).—To a solution of 6-nitro-1,2-dimethyl-4-quinolone (VI) (1.5 Gm.) in concentrated sulfuric acid (10 ml.) at 10° was added a mixture of nitric acid (d. 1.42, 1 ml.) and concentrated sulfuric acid (3 ml.). After standing for 24 hr. at room temperature, the mixture was poured onto crushed ice, the isolated product, m.p. 257°, was recrystallized from ethanol to give 1.13 Gm. (90% yield) of V, m.p. 259–261°. It was identical in melting point with an authentic sample of V, and showed no depression of mixed melting point.

Anal.—Calcd. for $C_{11}H_{12}N_3O_5$: C, 49.62; H, 4.51; N, 15.78. Found: C, 49.78; H, 4.62; N, 15.92.

6,8 - Dinitro - 2 - methyl - 4 - hydroxyquinoline.—A solution of 8-nitro-2-methyl-4-hydroxyquinoline (8) (2.04 Gm., 0.01 mole) in concentrated sulfuric acid (10 ml.) was treated with a mixture of nitric acid and sulfuric acid, as described above. The isolated product, m.p. 258°, was recrystallized from ethanol to give 1.85 Gm. of 6,8-dinitro-2-methyl-4-hydroxyquinoline (75% yield), m.p. 247–249°.

Anal.—Calcd. for $C_{10}H_7N_3O_5$: C, 48.19; H, 2.81; N, 16.86. Found: C, 48.21; H, 3.04; N, 16.85.

When this compound was treated with dimethyl sulfate in an alkaline medium, as for the preparation of 6-nitro-1,2-dimethyl-4-quinolone, the isolated product was identical with V, with no depression of the mixed melting point.

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N-Aminoalkyl-α-aminoacids and Their Corresponding Ethyl Esters

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Fourteen *N*-aminoalkyl-α-aminoacids and their corresponding ethyl esters have been prepared for pharmacological screening. The physicochemical properties and optimal reaction conditions are reported.

DURING RECENT years, α-aminoacid derivatives have been the subject of several studies of biological interest. In particular, Goldin *et al.* (1) have reported that glycine, although free from hypnotic activity, potentiates barbiturate-induced sleep, while Edwards *et al.* (2, 3) have found that the esters of some α-phenylglycines possess good antispasmodic and local anesthetic activity. Furthermore, it has been reported that ethyl esters of *N,N*-disubstituted glycines exert antispasmodic, antihistaminic, and hypotensive activity (4), and that other similar derivatives have been studied in tuberculostatic (5) and herbicidal tests (6).

The present note deals with the preparation of a series of *N*-aminoalkyl-α-aminoacids and their corresponding ethyl esters for submitting to pharmacological screening. In addition, these compounds were useful intermediates for the synthesis of 3-substituted sydnones, as we have recently reported (7).

The esters in question were prepared by alkylation with α-bromo esters of suitable *N*-aminoalkyl-amines. Because of the side reactions resulting from the competitive aminolysis of the ester group (8), the authors studied the synthesis procedure in detail, and found it an advantage to use

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