5,6-DIHYDRO-1*H*,4*H*-1,2,5-THIADIAZOLO[4,3,2-*ij*]QUINOLINE-2,2-DIOXIDE: A NEW *N*,*N*'-CYCLIC SULFAMIDE

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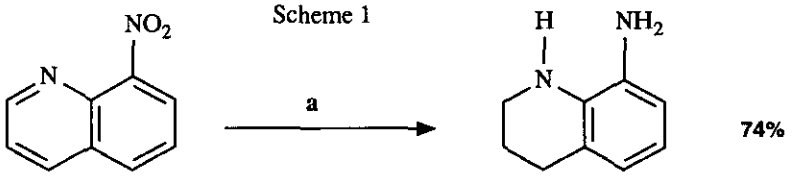
Abstract- The title compound (**1a**) and its potassium salt (**1b**) were prepared in two steps, starting from 8-nitroquinoline.

In the context of our studies on the synthesis of new therapeutical agents, we were interested in a convenient preparation of various heterocyclic systems bearing an *N*,*N*'-cyclic sulfamide moiety. We describe herein an efficient and simple synthesis of such a heterocycle. 5,6-Dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline-2,2-dioxide (**1a**)[1] and the potassium salt (**1b**) are readily prepared in a two-step synthesis from 8-nitroquinoline (**2**) *via* 8-amino-1,2,3,4-tetrahydroquinoline (**3**).[2] The overall yields are 48% and 64% respectively.

To date, two syntheses of **3** have been reported, one by Murahashi[3] who obtained **3** in 81% yield by reduction of 8-nitroquinoline under rhodium catalyzed water-gas shift conditions [cat. $Rh_6(CO)_{16}$, 150°C, water, 2-methoxyethanol, 48 h, pressure of CO: 56 bars] and another by Hazlewood[4] who prepared **3** in *89%* yield by reduction of *8-aminoquinoline by metallic sodium in boiling ethanol.*

The present paper describes an efficient large scale preparation (several tens of grams) of **3** by direct reduction of 8-nitroquinoline (**2**) under mild conditions. Thus, catalytic hydrogenation of **2** (as base form) in acidic medium (glacial acetic acid) in the presence of PtO_2 (pressure of H_2:1.3 bars, 25°C, 24 h, Scheme 1) afforded **3** in 74% yield which was easily purified by a short column chromatography on silica gel. Starting from the hydrochoride salt of **2** the yield is only to 34%. No reduction of **2** (as base form) was observed with $Pd/Ca(CO_3)_2$ in methanolic solution (pressure of H_2: 1.3 bars, 25°C, 24 h).

Scheme 1



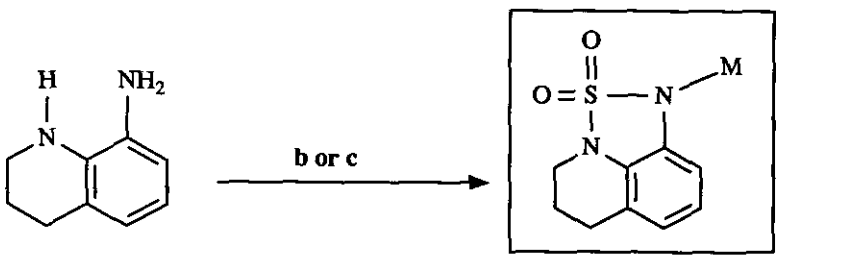
2 **3**

a: PtO_2, pressure of H_2: 1.3 bars, CH_3CO_2H, 25°C, 24 h

Compound (**3**) is air-sensitive and should be used immediately, or stored under inert atmosphere for a maximum of 3-4 days at room temperature[5] and was converted to the desired compound (**1a**) (yield 64.5%) by reaction with sulfamide at 155-160°C in boiling diglyme and purified by flash chromatography.

The potassium salt (**1b**) is obtained directly in 86.5% yield by addition of 8N KOH into the reaction mixture (Scheme 2).

Scheme 2



3

M = H 1a 64.5% method b

M = K 1b 86.5% method c

b: $H_2NSO_2NH_2$, 155-160°C, diglyme, 2 h

c: $H_2NSO_2NH_2$, 155-160°C, diglyme, 2 h then 8N KOH

In conclusion, the synthesis presented here constitutes a convenient preparation of 8-amino-1,2,3,4-tetrahydroquinoline (**3**) and of 5,6-dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline-2,2-dioxide.

ACKNOWLEDGMENT

We were indebted to M[r] M.Vuilhorgne and Coworkers for analysis assistance and to M[rs] R. Kerphirique, M[rs] B. Just, F. Gay, J-C. Szmigel, J. P. Leconte, C. Huon and A. Viroulaud for technical assistance.

EXPERIMENTAL

Commercially available reagents were used as received from suppliers. The progress of the reactions was monitored by tlc on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined using a Reichler-Kofler apparatus and are uncorrected. ^{1}H-Nmr spectra and ^{13}C-nmr spectra were recorded on 300 WP Bruker spectrometers. Ir spectra were recorded on a 983G Perkin-Elmer spectrometer. Ms were obtained on a Finigan 3000 apparatus (electron impact: EI; 70ev). The combustion analyses were performed at Centre de Recherches de Vitry-Alforville (Rhône-Poulenc Rorer). Flash column chromatography was performed on silica gel (Merck Kieselgel, 230-400 mesh).

8-Amino-1,2,3,4-tetrahydroquinoline (3).

A mixture of 8-nitroquinoline **2** (50 g, 287 mmol) and PtO_2(1.5 g) in glacial acetic acid (600 ml) was stirred under hydrogen pressure (1.3bars) for 24 h (4 moles of hydrogen are absorbed) at room temperature. The solvent was removed under reduced pressure (40°C), and then CH_2Cl_2(1.2 l) and sat. aq. $NaHCO_3$ (500 ml) were added to this crude red oil. This solution was extracted with CH_2Cl_2 (2 x 500 ml). The combined organic layers were washed with H_2O (3 x 250 ml) and dried over $MgSO_4$ in the presence of activated vegetable charcoal. All extractions should be carried out quickly. The solvent was evaporated under reduced pressure at 40°C to give the crude product (43 g) as brown oil, which was immediately dissolved in CH_2Cl_2 (100 ml) and filtered through a short column of silica gel to separate the final product from polar materials. The desired product **(3)** was obtained (31.4 g, 74%) as a brown oil (Rf= 0.60 ethyl acetate). Spectra data of **3** are identical with those described in the literature.[3]

5,6-Dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline-2,2-dioxide (1a).

Compound **(3)** (47 g, 318 mmol) in diglyme (170 ml) was added to a stirred solution of sulfamide (25 g, 364 mmol) dissolved in diglyme (200 ml) at 155-160°C. Stirring and heating were continued for 2 h. The reaction mixture was then cooled to room temperature, hydrolyzed with 350 ml of water, acidified to pH 1 with 1N hydrochloric acid and extracted with ethyl acetate (4 x 500 ml). The combined organic layers were washed successively with water (2 x 300 ml), 0.1N HCl (2 x 300 ml), water (2 x 300 ml), dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford 80 g of a red oil. Flash chromatography on silica gel of this crude product using CH_2Cl_2 as eluent gave pure **1a** as a pale red solid; 43g (64.5%, Rf = 0.83 in ethyl acetate/dichloromethane 1/1): mp 108°C; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 7.60 (s, 1H, NH), 6.8-6.7 (m, 3H, 7,8,9-ArH), 3.75 (t, J=6 Hz, 2H, N-CH_2), 2.80 (t, J= 6 Hz, 2H, $N(CH_2)_2$-$C\underline{H}_2$), 2.10 (m, 2H, NCH_2-$C\underline{H}_2$); ms(EI), m/z (relative intensity) 210 ($M^{+\cdot}$, 50); 145 (100); ir (KBr) 3430, 3220, 2970, 2940, 2885, 2840, 1630, 1605, 1490, 1475, 1460, 1320, 1295, 1155, 1115, 875, 760, 725, 670, 620, 590, 570 cm^{-1}. Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.82; H, 4.89; N, 13.49; S, 15.10.

5,6-Dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline-2,2-dioxide, potassium salt (1b).

The procedure given above for the synthesis of **1a** was modified by the replacement of ethyl acetate as extracting solvent by *tert*-butyl methyl ether (4 x 500 ml). The combined organic layers were washed with water (2 x 100 ml), and activated vegetable charcoal was then added and filtered. Addition of 8N KOH to this ethereal solution precipitates directly **1b**. From 25g (169 mmol) of **2** and 20.3g (211 mmol) of sulfamide, 36.2g (86.5%) of **1b** was obtained as white needles: mp ≥ 200°C; ^{1}H-nmr (DMSO-d^6, 300MHz) δ 6.40 (t, J=7.5 Hz, 1H, 8-ArH), 6.10 (two broad d, J=7.5 and 7.5 Hz, 2H, 7,9-ArH), 3.36 (t, J= 6 Hz, 2H, N-CH_2), 2.55 (m, 2H, $N(CH_2)_2$-$C\underline{H}_2$), 1.90 (m, 2H, NCH_2-$C\underline{H}_2$);

^{13}C-nmr (DMSO-d^6, 75MHz) δ 140.5 (C-9a), 131.5 (C-9b), 118.5 (C-8), 115.5 (C-6a), 113.0 (C-7), 106.0 (C-9), 39.5 (C-4), 23.5 (C-6), 22.0 (C-5); ir (KBr) 3380, 3250, 3050, 2950, 2930, 2880, 2835, 1670, 1620, 1585, 1485, 1460, 1225, 1150, 1125, 900, 750, 725 cm^{-1}. Anal. Calcd for $C_9H_9N_2O_2SK$: C, 43.53; H, 3.68; N, 11.28; O, 12.88; S, 12;91; K, 15,74. Found: C, 42.10; H, 2.00; N, 10.20; S, 11.40.

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5. No degradation was observed (tlc) when an ethyl acetate solution of **3** was exposed to air at room temperature, contrary to methanolic or dichloromethane solutions.

Received, 21st October, 1991