SYNTHESIS AND CHARACTERIZATION OF 1-HYDROXY-3-METHYLACRIDIN-9(10H)-ONE AND 3-HYDROXY-1-METHYLACRIDIN-9(10H)-ONE

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Abstract

The syntheses and isolation of 1-hydroxy-3-methylacridin-9(10H)-one and 3-hydroxy-1-methylacridin-9(10H)-one have been achieved by the condensation of methyl anthranilate and 5-methyl resorcinol in heptanol and in the presence of catalytic amount p-toluene sulphonic acid.

1. Introduction

Acridones have gained recent interest because of their broad pharmacological activity. In the field of anti-tumour DNA-binding agents, the class of acridine derivatives (acridones) exhibited significant anti-cancer activities and a number of acridone derivatives (9-acridone) were recently synthesized as potential anti-tumour drugs (Antonini, 2004). A detailed structure-activity relationships (SAR) of some acridone derivatives synthesized via the Ullmann condensation of anthranilic acids with iodobenzenes or 2-chlorobenzoic acids with aniline derivatives were investigated, (Su *et al.*, 1992). The SAR studies showed that 1-hydroxy-9-acridones were more active than their 1-OMe derivatives against cell growth of human leukaemic HL-60 cells in culture.

In this work, the reaction between methyl anthranilate (II) and 5-methyl resorcinol (IIIb) was re-investigated. Earlier work of Smolders *et al.* (1984) on the reaction of (II) with (IIIb) produced a 3:1 mixture of 1-hydroxy-3-methylacridin-9(10H)-one (IVa) and 3-hydroxy-1-methylacridin-9(10H)-one (IVb) by NMR integration without isolating them. The two compounds have now been isolated and characterized by ^{1}H and ^{13}C-NMR, IR and MS. 3-hydroxy-1-methylacridin-9(10H)-one is a precursor for the synthesis of acronycine derivatives (Schneider *et al.*, 1972; Reisch *et al.*, 1983). Acronycine is one of a group of alkaloids first isolated from the Australian shrub ash, Acromychia baueri Schott (Hughes *et al.*, 1984), which has been shown to have broad spectrum antitumour activity against experimental neoplasm (Svoboda *et al.*, 1966) including C-1498 myelogenous leukaemia, a tumour which is singularly non-responsive to other anti-tumour agents (Gout, 1971).

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2. Experimental

Mp's: Kofler hot-stage apparatus. ^{1}H and ^{13}C NMR Spectra: Varian Gemini 200 MHz spectrometer using the TMS as the internal standard. IR spectra: Pye Unicam SP3-200 IR Spectrophotometer. Mass spectroscopic analyses: MAT445 spectrometer. MERC silica gel $60F_{254}$ coated on A1 sheets were used for analytical TLC.

1-Hydroxy-3-methylacridin-9(10H)-one (IVa) and 3-hydroxy-1-methylacridin-9(10H)-one (IVb).

A mixture of 5-methylresorcinol (24.8 g, 0.2 mol), methyl anthranilate (30.2 g, 0.2 mol) and p-toluenesulphonic acid (0.5 g, 0.003 mol) was dissolved in heptanol (100 ml) heated under reflux in a flask fitted with Dean and Stark apparatus until completion of reaction, as monitored by TLC, (46 hrs). The solvent was removed by vacuum distillation to give a yellowish residue, which was dried in air. The residue was dissolved in chloroform, washed three times (3x100 ml) with aqueous Na_2CO_3 solution and the aqueous layer separated. The combined aqueous solution was acidified with aqueous HCl and then extracted with methylene chloride. The methylene chloride phase was washed three times with water (3x25 ml), dried with anhydrous Na_2SO_4, filtered and the solvent removed by vacuum distillation to give dark yellow needles, which was recrystallized from petroleum ether (40-60 ^{0}C)/methylene chloride (v/v) to give pure crystals of 3-hydroxy-1-methylacridin-9(10H)-one **IVb** (3.6 g, 11 %).

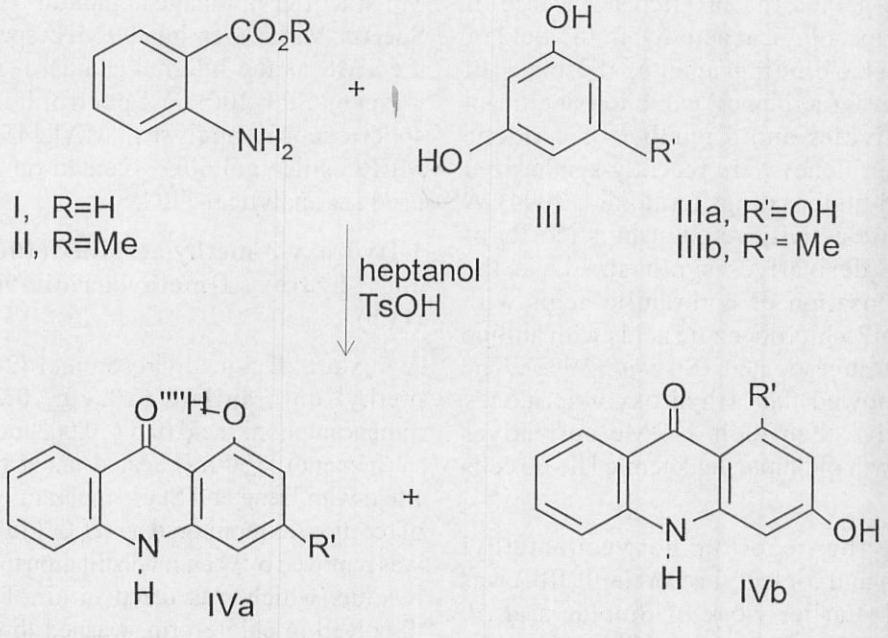
M.p. decomposed >300 ^{0}C, IR (KBr, cm^{-1}) 3595 due to the presence of the phenolic free absorption, 3150 (N-H), 1665 (C=O): MS (70eV): m/z (%) =225 (100, M^{+}), 197 (15, M^{+}-CO); 196 (28, M^{+}-CHOH), 167 (9), 138 (10), 81 (32).

^{1}H NMR ($CDCl_3$): δ H (ppm) 2.82 (3H, s, C 1-CH_3), 3.76 (1H, s, C3-OH), 7.02 (1H, s, C4-H), 7.28 (1H, s, C2-H), 7.71(1H, t, J=7.8, 7.81 Hz, C6-H), 7.86 (1H, d=8.69Hz, C5-H), 8.12 (1H, J=7.27, 7.27Hz, C7-H) and 8.58 (1H, d, J=8.32Hz, C8-H). ^{13}C NMR ($CDCl_3$): δ_c (ppm) 22.5 (CH_3), 105.8 (C-8a), 106.7 (C-2), 110.99 (C-9a), 115.9 (C-4), 118.1 (C-5), 123.7 (C-7), 126.8 (C-8), 138.9 (C-6), 141.7 (C-10a), 155.8 (C-4a), 162.2 (C-1), 163.9 (C-3) and 172.4 (C-9).

Molecular formular: $C_{14}H_{11}NO_2$
Calculated: C 74.65; H 4.92; N 6.22
Found: C 74.57; H 4.78; N 6.26

The methylene chloride phase was washed with water (3x25 ml), dried with anhydrous Na_2SO_4, filtered and the solvent removed by vacuum distillation. The residue obtained was then recrystallised from petroleum ether (40-60°C) / methylene chloride to give yellow needles of 1-hydoxy-3-methylacridin-9(10H)-one **IVa** (17.5g, 52%).

M.p. 314-315 °C. IR (KBr, cm^{-1}) 3250 which was due to O-H (stretch) phenolic hydrogen bonding, 3150, 1660 (C=O), 750. MS (70eV); m/z (%)= 225 (100, M^+), 196 (M^+-COH), 167 (9), 154 (7), 138 (10), 97 (13), 81 (32). ^{1}H NMR ($CDCl_3$), δ_H (ppm) 2.59 (3H, s, C3-CH_3), 6.93 (1H, s, C4-H) 7.28 (1H, s, C2-H), 7.69 (1H, t, J=7.81Hz, C6-H), 7.88 (1H, d, J=8.65Hz, C5-H), 8.12 (1H, t, J=7.27, 7.27Hz, C7-H), 8.56 (1H, d, J=8.44Hz, C8-H). ^{13}C NMR ($CDCl_3$): δ_c (ppm), 22.9 (CH_3),105.7 (C-8a), 106.9 (C-2), 111.2 (C-9a), 116.3 (C-4), 118.5 (C-5), 123.9



Scheme 1: Synthetic route to IVa and IVb

(C-7), 127.3 (C-8), 139.3 (C-6), 142.2 (C-19a), 156.2 (C-4a), 162.6 (C-3) and 172.7 (C-9).

Molecular formular: $C_{14}H_{11}NO_2$ (225)
Calculated: C 74.68, H 4.89, N 6.22
Found: C 74.56, H 4.79, N 6.24

3. Results and Discussion

Anthranilic acid (I) and methyl anthranilate (II) will react with resorcinol derivatives (III) in the presence of heptanol and p-toluene sulphonic acid to give substituted 9-acridones (IVa) and (IVb) (Smolders, *et al.* 1984).

There is a disadvantage in using anthranilic acid because the final reaction mixture is usually contaminated by diphenylamine derivative. In addition, when phloroglucinol (IIIa) was used, Beck *et al.* (1968) found that the crude reaction product, 1,3-dihydroxy-9-acridone, contain about 5% of contaminant.

When methyl anthranilate (II) was heated with 1 mole equivalent of 5-methyl resorcinol (IIIb) in heptanol, in the presence of p-toluenesulphonic acid, a mixture of 1-hydroxy-3-methylacridin-9(10H)-one (52%) and 3-hydroxy-1-methylacridin-9(10H)-one (11%) was obtained. The prepondence of the 1-hydroxy isomer can be explained by the formation

of hydrogen bonding between the hydroxyl group in the 1-position and carbonyl group in the 9-position. Steric effect between the methyl group in the 1-position and the carbonyl group in the 9-position could also reduced the formation of the 3-hydroxy isomer. The structures were assigned by their IR, NMR, MS spectra and elemental analysis.

In the IR spectrum of the 1-hydroxy isomer, there was an absorption at 3250 cm^{-1} which was due to O-H (stretch) phenolic hydrogen bonding while the 3-hydroxy isomer showed the presence of the phenolic free absorption at 3595 cm^{-1}. The absorption at 3150 cm^{-1} in the IR spectra of both isomers was due to the presence of free N-H group while the characteristic stretching frequency of the carbonyl group in the 1-hydroxy isomer was lowered (1660 cm^{-1}) due to hydrogen bonding. The compounds showed comparable fragmentation pattern and base peak from the mass spectrum of each isomer represent the molecular ion of the compound. In the ^{1}H NMR of the compounds, the N-H and OH signals were observed as broad signals. It required additional correlation NMR experiments for precise assignment.

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