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Photo induced synthesis of methyl derivative of cryptosanguinolentine

P Pitchai[1], P S Mohan[1]* & R M Gengan[2]

[1]Department of Chemistry, Bharathiar University, Coimbatore 641 046, India

[2]Department of Chemistry, Durban University of Technology, Durban 4001, South Africa

E-mail: ps_mohan_in@yahoo.com

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A simpler method to synthesize methyl derivative of an alkaloid cryprosanguinolentine is described. 4-Hydroxy-2-methylquinoline is iodized using iodine, potassium iodide and aqueous sodium hydroxide and dehydroxyhalogenated with phosphorous oxychloride. The respective anilinoquinoline is prepared and cyclized by UV irradiation. Upon selective methylation 5,6-dimethyl-5*H*-indolo[3,2-*c*]quinoline is produced which is utilized as a DNA intercalating agent.

Keywords: Microwave, photochemical cyclization, cryptosanguinolentine, iodination

In recent years the research group has been concentrated to synthesize biologically important naturally occurring indoloquinoline alkaloids by applying convenient sequences, like Fischer indole synthesis, Bucherer reaction and photo chemical cyclization[1]. It is well known through the literature[2], that these compounds are purely isolated from *Cryptolepis sanquinolenta*, a shrub indigenous to tropical West Africa and the crude soup is biologically used as antibacterial[3] and antimalarial and in the clinical therapy for rheumatism and urinary tract infections[4,5]. The wide spectrum of biological uses of these plants led the isolation of components from their aerial parts and eventually they were identified as indoloquinoline alkaloids called cryptotackiene (also named neocryptolepine), cryptolepine and cryptosanquinolentine (also named isocryptolepine)[2]. The separate injection of these components to different diseases and their positive results augmented the knowledge to present a biosynthesis[6]. Indoloquinoline alkaloids and their methyl derivatives are possessing suitable skeleton for DNA intercalation[7], because these are planar aromatic molecules which can easily intercalate with DNA double helix resulting in dramatic changes in DNA conformation[8] and can inhibit DNA replication, transcription, and/or topoisomerase activities and is considered to be crucial in the medicinal action of some antimytotic drugs[9].

Now a days microwave, a nonionizing radiation, an unconventional energy source, has been used for a variety of applications including organic synthesis[10] where the chemical reactions are accelerated because of selective absorption of microwave energy by polar molecules, nonpolar molecules being inert to the microwave dielectric loss. Avoiding organic solvents during the reactions in organic synthesis lead to a clean, efficient and economical technology (green chemistry)[11]. Applications of microwave technology in well-known cyclization reactions for heterocyclic ring formation and in other important reactions such as nucleophilic substitution, hetero-Diels-Alder reactions and 1,3-dipolar cycloaddition have been well documented in several reviews[12].

In continuation of synthesis of indoloquinoline alkaloids it is interested to develop a new building block that starts from 4-hydroxy-2-methylquinoline **2**. Though large number of cyclization procedures[13] had been reported for the construction of 4-hydroxy-2-methylquinoline **2** system, for the first time the microwave technology is used by reacting β-anilinocrotonate **1**. Here no solvent has been used and the yield is relatively high when compared to reported procedures.

The unconventional, pure electron transfer reaction called photochemical reaction provides mass application in the construction of quinoline, aporphine, and isoquinoline alkaloids[14].

Recent reports on the photochemical approach are described for the synthesis of a variety of pharmacologically significant compounds, namely acridines[15] and indoloquinolines[1]. The method called (term-delete)

heteroatom directed photoarylation[16] had been used and was well reviewed in earlier report[3]. Following the same strategy 6-methyl-11*H*-indolo[3,2-*c*]quinoline **6** is successfully synthesized.

Water, besides being nature's preferred solvent, is useful due to its versatile solvent properties, safety and abundance. In addition to its eco-friendly and economical nature, there has also been a growing realization of the ability of water to facilitate organic transformations[17]. By using the appropriate procedure[18], the important intermediate 4-hydroxy-3-iodo-2-methylquinoline **3** by using water as solvent is synthesized.

Results and Discussion

4-Hydroxy-2-methylquinoline **2** was prepared by cyclization of respective β-anilinocrotonate **1**. β-Anilinocrotonate **2** was heated directly without any solvent for five minutes in 350 watts by a standard domestic microwave oven. The solid formed was collected and was purified. The yield was 80% and was sufficient to proceed towards further steps. The formation of compound **2** was confirmed by its IR spectrum which exhibited characteristic O-H stretching at 3062 and C-H stretching of CH_3 at 2767 cm^{-1} and its ^1H NMR spectrum displayed singlet at δ 2.49 for CH_3 protons, and broad singlet at 11.60 for O-H proton respectively.

3-Iodo-4-hydroxy-2-methylquinoline **3** was prepared from the reaction of 4–hydroxy-2-methylquinoline **2** with the mixtures of iodine, potassium iodide and sodium hydroxide which was reported previously by Renault *et al*[18]. The iodination is confirmed by the ^1H NMR data with the disappearance of singlet at δ 5.90 due to C_3 proton of 4-quinolones. The preformed 3-iodo-4-hydroxy-2-methylquinoline **3** was refluxed with phosphorous oxychloride and here the nucleophilic replacement of hydroxyl group by iodo group has taken place and the product was found to be 4-chloro-3-iodo-2-methylquinoline **4**. It was confirmed by its IR spectrum which showed C-Cl stretching at 758 cm^{-1} and the disappearance of OH peak in the ^1H NMR and as well as appearance of δ110.78 for the corresponding carbon in ^{13}C NMR spectrum.

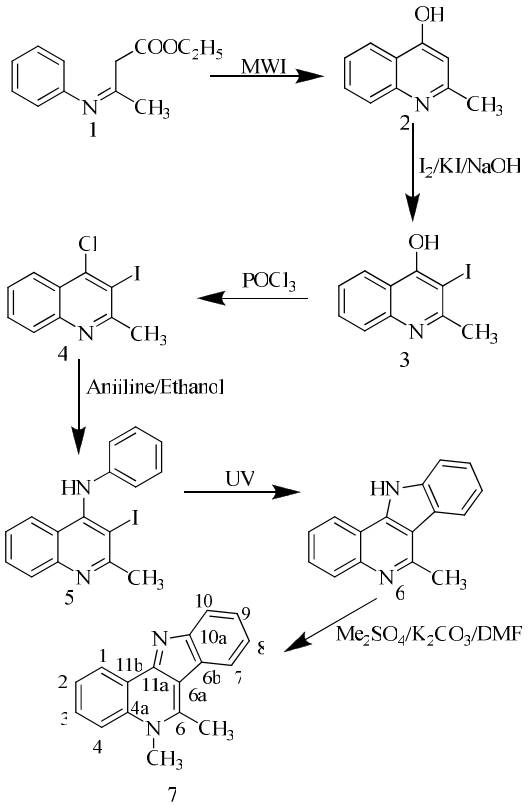
The amination of 4-chloro-3-iodo-2-methylquinoline **4** with aniline was done by stirring the above mixture in ethanol. The pale yellow solid 4-anilino-3-iodo-2-methylquinoline **5** formed was recrystallized with chloroform and the yield was found to be good. The characteristic N-H stretching in IR at 3334 cm^{-1}, a broad singlet at δ 8.56 for N-H proton in ^1H NMR and C_3 signal at δ 51.97 in ^{13}C NMR spectrum confirms the formation of compound **5**.

By using reported procedure, the cyclization of anilinoquinoline was carried out by passing UV irradiation at 365 nm. Here the yield is much higher than that realized by the earlier report[3]. The elimination of iodine due to ring closure was confirmed by the appearance of C_3 signal in ^{13}C NMR spectrum with the value appeared at δ 126.73. The selective methylation has been done in the *N* atom of quinoline and by using dimethylsulphate and potassium carbonate under microwave condition. The final product is the methyl derivative of an alkaloid cryptosanguinelentine **7 (Scheme I)**. The methylation was confirmed by appearance of singlet at δ 3.75 in ^1H NMR.

Experimental Section

General methods

^1H NMR and ^{13}C NMR (400 and 100 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal reference. Melting points were determined and were uncorrected. Chromatographic purification was conducted by column chromatography using 60-120 mesh silica gel. Reagent grade aniline, ethyla-



Scheme I

cetoacetate, phosphorus oxychloride and dimethylformamide were used after usual purification methods. Reaction progress was monitored by TLC. Iodine, potassium iodide, sodium hydroxide, dimethylsulphate and potassium carbonate were purchased and used as received. The immersion type photochemical reactor (400 watts medium pressure mercury lamp, 365 nm) was used for the photochemical cyclization.

Preparation of β-anilinocrotonate 1

The freshly distilled aniline (0.25 mole) and ethylacetoacetate (0.25 mole) were mixed and 5-10 drops of Conc. HCl was added and the mixture was shaken well. It was left aside for few minutes and the mixture became turbid indicating the liberation of water due to the condensation reaction. At this stage, the mixture was kept inside a vacuum desiccator over Conc. H_2SO_4 and was kept as such for 2-3 days, thereafter, the ethyl-β-anilinocrotonate **1** which formed as a deep yellow oily liquid, was separated, dried over anhydrous sodium sulphate and used for the subsequent cyclization reaction.

Synthesis of 4-hydroxy-2-methylquinoline 2

Ethyl-β-anilinocrotonate **1** (dried, 25 mL) was introduced under microwave heating for 3 min at 360 W. The solid formed was washed with 200 mL ethyl acetate, and then the washing was continued with a mixture of chloroform and petroleum ether (30:10). The pure white powder formed was taken for analysis and further reactions.

Yield: 11 g (80%); m.p. 256°C; IR (KBr, cm^{-1}): 3062, 2767; ^{1}H NMR (DMSO-d_6, δ): 2.49 (s, 3H, C_2-CH_3-H), 5.90 (s, 1H, C_3-H,), 7.26 (t, 1H, C_6-H), 7.49 (d,1H, C_5-H, J = 7.2 Hz), 7.60 (t, 1H, C_7-H, J = 7.6Hz), 8.02 (d,1H,C_8-H, J = 8.0Hz), 11.60 (bs, 1H, OH).

Synthesis of 4-hydroxy-3-iodo-2-methylquinoline 3

A 15% solution of iodine (0.012 mole) in 20% aqueous potassium iodide was added drop-wise to a stirred solution of the 4-hydroxy-2-methylquinoline **2** (1.59 g, 0.01 mole) in 20 mL, 2*N* aqueous sodium hydroxide at 20°C. Stirring was continued (for 1-4 hr) until TLC showed the absence of 4-hydroxy-2-methylquinoline **2**. The mixture was then acidified with acetic acid, the precipitated product was isolated by suction, washed with water, and recrystallized.

Yield: 1.043 g (85%); m.p. 190°C; IR (KBr cm^{-1}): 3257, 2916; ^{1}H NMR (DMSO-d_6, δ): 2.49 (s, 3H, C_2-CH_3-H), 7.37 (t, 1H, C_6-H, J = 7.2 Hz), 7.55 (d, 1H, C_5-H, J = 8.4Hz), 7.69 (t, 1H, C_7-H, J = 8.0 Hz), 8.09 (d, 1H, C_8-H, J = 8.0Hz), 12.20 (s, 1H, OH).

Synthesis of 4-chloro-3-iodo-2-methylquinoline 4

A mixture of 4-hydroxy-3-iodo-2-methylquinoline **3** (1.43 g, 0.005 mole) in 4 mL of phosphorus oxychloride was heated under reflux for 1 hr, and slowly added to ice-water after cooling to RT. The mixture was neutralized with dilute NaOH solution. The precipitate thus obtained was filtered and dried.

Yield: 1.42 g (95%); m.p. 70°C; IR (KBr, cm^{-1}): 1550, 1338, 758; ^{1}H NMR ($CDCl_3$, δ): 3.02 (s, 3H, C_2-CH_3-H), 7.56 (t, 1H, C_6-H, J = 7.2 Hz), 7.74 (t, 1H, C_7-H, J = 8.0Hz), 8.00 (d, 1H, C_5-H, J = 8.0Hz), 8.20 (d, 1H, C_8-H, J = 8.0Hz).

^{13}C NMR ($CDCl_3$, δ): C_2-155.13, C_2-CH_3 -27.34, C_3-110.78, C_4-157.50, C_{4a}-131.77, C_5-120.45, C_6-124.33, C_7-127.62, C_8-129.15, C_{8a}-149.34, C_1'-144.79, C_2'& C_2''-19.42, C_3' and C_3''-115.71, C_4'-120.11.

Synthesis of 4-anilino-3-iodo-2-methylquinoline 5

4-Chloro-3-iodo-2-methylquinoline **4** (1.51 g, 0.005 mole) and 0.93 mL (0.01 mole) of aniline were dissolved in 30 mL of dry ethanol. The initial colour of the reaction mixture was colourless. After 15 minutes the colour was changed into yellow. The reaction was monitored and was confirmed by the formation of new spot in TLC. The reaction-mixture was stirred for further 30 min., dried and recrystalized with chloroform.

Yield: 1.29 g (98%); m.p. 180°C; IR (KBr, cm^{-1}): 3334 ; ^{1}H NMR ($CDCl_3$, δ): 3.18 (s, 3H, C_2-CH_3-H), 7.07 (d, 2H, Ph-C_2'&C_2''-H, J = 8.0Hz), 7.22 (t, 2H, C_3'&C_3''-H, J = 8.0 Hz), 7.38 (m, 3H, C_5-H, C_6-H, C_7-H, J = 8.0Hz), 7.54 (d, 1H, C_8-H, J = 8.0Hz), 7.72 (t, 1H, C_4'-H, J = 7.2Hz), 8.56 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, δ): C_2-159.01, C_2-CH_3 -13.05, C_3-51.97, C_4-148.27, C_{4a}-125.16, C_6-124.33, C_7 & C_8-129.76, C_{8a}-147.39, C_1'-131.08, C_2'& C_2''-96.43, C_3'& C_3''-129.46, C_4' & C_5-125.82.

Synthesis of 6-methyl-11*H*-indolo[3,2-*c*]quinoline 6

Irradiation of a solution of **5** (1.96 g, 0.005 mole) in the solvent system of benzene:methanol:sulphuric acid (60:30:1) and iodine (20 mg, 0.1 mmole) was carried out in a immersion type photochemical reactor fitted with 400 watts medium pressure mercury lamp, wavelength of 365 nm and was irradiated for 48 hr. Reaction was monitored by TLC which showed

complete disappearance of **5** and the solvent was removed in vacuo. After treating with thio solution, iodine was removed and the compound was extracted with ethyl acetate. Using column chromatography with silica gel and petroleum ether and ethyl acetate (80:20) as eluants afforded the pure photoproduct **6**.

Yield: 0.90 g (78%); m.p. 210°C; IR (KBr, cm^{-1}): 3307 ; ^{1}H NMR ($CDCl_3$, δ): 2.43 (s, 3H, C_6–CH_3), 7.33-7.88 (m, 7H, Ar-H), 8.07 (d, 1H, C_4-H), 10.51 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, δ): C_1-127.41, C_2-124.69, C_3-126.73, C_4-129.44, C_{4a}-150.17, C_6-154.75, C_6-CH_3-23.14 , C_{6a}-122.57, C_{6b}-126.78, C_7-120.29, C_8-124.43, C_9-119.54, C_{10}-118.64, C_{10a}-135.67, C_{11a} -136.73, C_{11b}-130.11.

Synthesis of 5,6-dimethyl-5*H*-indolo[3,2-*c*]quinoline 7

A mixture of compound **6** with 1.5 mL of dimethylsulphate was taken in 10 mL of dimethylformamide and 500 mg of potassium carbonate added. The whole mixture was introduced for microwave heating for 3 min at 360 W. The completion of the reaction was monitored through TLC. The mixture was poured into 300 mL of crushed ice and extracted with ethyl acetate. The combined organic layers subjected to silica gel column chromatography yielded the product 5,6-dimethyl-5*H*-indolo[3,2-*c*]quinoline **7** in the gradient elution with petroleum ether and ethyl acetate in the ratio 35:65.

Yield: 1.03 g (82%); m.p. 189°C; IR (KBr, cm^{-1}): 1626 ; ^{1}H NMR($CDCl_3$, δ): 2.43 (s, 3H, C_6–CH_3), 3.75 (s, 3H, C_5–CH_3), 7.36-7.92 (m, 7H, Ar-H), 8.26 (d, 1H, C_4-H, *J* 8.2Hz); ^{13}C NMR ($CDCl_3$, δ): C_1-127.41, C_2-124.69, C_3-126.73, C_4-129.44, C_{4a}-150.17, C_6-154.75, C_6-CH_3-23.14 , C_{6a}-122.57, C_{6b}-126.78, C_7-120.29, C_8-124.43, C_9-119.54, C_{10}-118.64, C_{10a}-135.67, C_{11a} -136.73, C_{11b}-130.11.

Conclusion

A convenient five step procedure for synthesizing an indoloquinoline alkaloid is illustrated which implies to be a good intercalating agent. The starting materials can easily produce by an eco-friendly method and is a newer one to increase the yield. The yield of the photochemical cyclization is increased by introducing iodine in the respective position.

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