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Studies on Acetylation of Indoles

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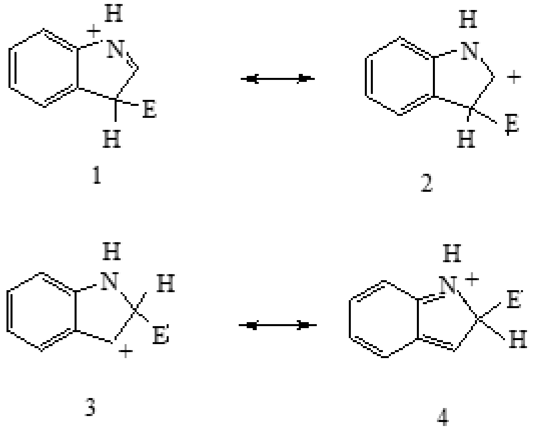
Abstract: Acetylation of indole was carried out by two different methods, and three different products were obtained, *viz* 1-acetyl indole , 3-acetyl indole and 1,3-diacetyl indole. The structures of these products were confirmed by physical and spectral analysis

Keywords: Acetylation , Indole , 1-Acetyl indole , 3-Acetyl indole.

Introduction

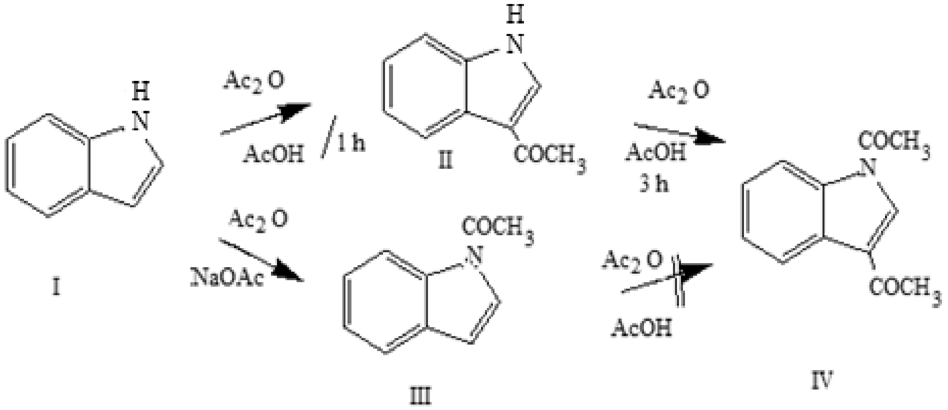
Electrophilic substitution in indoles occurs predominantly in the β-position, and when this is blocked, either at the nitrogen or at the α-position[1].This has been rationalized in terms of the structure of intermediates of reactions. Canonical forms 1 and 2 represent the intermediate of β-substitution and canonical forms 3 and 4 the intermediate for α-substitution[2,3]. It is evident that { 1↔2 } represents a stabler cation for benzene aromaticity is retained in the mesomeric cation { 3↔4 } the positive charged ion can only be delocalized on nitrogen by losing benzene aromaticity. Recent molecular orbital calculations provide theoretical support for the experimental facts[4].

The principal methods have been used for the acetylation of indole are the reaction of indole[5-7]with acetic anhydride at 180-200 °C, which give varying yields of a mixture of mono – and diacetyl – indoles, and of indolyl magnesium halides with acetyl chloride [8-10], and gives low yield of mono acetyl indole. Saxton[11] obtained 1,3-diacetyl indole by the action of acetic anhydride and acetic acid on indole at the boiling point of the mixture . This method is preferred as preparative method, although it gives a dark product which had to be recrystallized several times in order to obtain the pure diacetyl indole. The presence of 10% acetic acid in the reaction mixture is necessary, the yield of clean 1,3-diacetyl indole is about 60 %. β –Acetyl indole can be obtained quantitatively by treating 1,3- diacetyl indole with aqueous alcoholic sodium hydroxide at room temperature . Also it can be obtained directly from indole by adding a small amount of vinyl acetate to acetic anhydride with the omission of acetic acid , and β- acetyl indole is isolated in consistent[12] yield of 66 %. *N*-Acetyl indole was obtained very easily in 60 % yield from the reaction of indole with acetic anhydride in the presence of anhydrous sodium acetate[13], but it is not possible to obtain by hydrolysis of 1,3-diacetyl indole.



Experimental

Melting points were determined on covered slides using a Kofler heating stage, and uncorrected. Ultra-violet (UV) spectra were recorded on a Unicam SP 800 instrument. Nuclear magnetic resonance (NMR) spectra were recorded using a Varian HA 100 MHz instrument, with TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on a A . E . I . MS 9 spectrometer.



Reaction Scheme

1,3-Diacetyl indole (IV)

Indole {1} (2 g), acetic acid (2 mL) and acetic anhydride (18 mL) were refluxed for 24 h, the solvent was removed under vacuum and the residue was crystalline at 100 °C. It was recrystallized from ethanol. 1,3-Diacetyl indole (1.9 g, 55 %) was obtained as colorless needles , m.p. 149-151 °C. $R_f = 0.56$ (silica) (Benzene : Ether : MeOH ; 4:1:0.1)

UV λ_{max} (EtOH) 220, 260, 301 nm. ^{1}HNMR (CDCl$_3$, 100 MHz) δ : 2.2 (s, 3H); 2.5 (s , 3H); 7.0-7.6 (m , 4H); 8.7 (s , α-H). MS (7 *ev*) *m/z* (%): 201 (M$^+$, 36); 159 (34); 145 (10); 144(100);117(9)116(12); 89 (16); 43 (24). Analysis calculated for $C_{12}H_{11}NO_2$: C 71.64 ; H 5.47 ; N 6.96 found C 70.98 ; H 5.03 ; N 7.14.

3-Acetyl indole (II)

1,3- Diacetyl indole {IV}(1 g) was suspended in ethanol (5 mL) and sodium hydroxide (10 mL) of 2 N was added. The mixture was stirred and warmed until the diacetyl indole had dissolved, the product after being precipitated by dilution with water, collected and crystallized from ethanol (0.69 g, 87 %) was obtained, m.p. 191-192 °C . $R_f = 0.33$ (the same solvent system).

UV λ_{max} (EtOH) 216, 242, 260 , 296 nm. ^{1}HNMR (CDCl$_3$, 100 MHz) δ : 2.5 (s, 3H) ; 7.0-7.6 (m , 4H) ; 8.1 (s , α-H); 10.1 (s , N-H). MS (70 *ev*) *m/z* (%) : 159 (M$^+$, 50) ; 145 (14) ; 144 (100) ; 116 (30); 89 (21) ; 63 (18). Analysis calculated for $C_{10}H_9NO$: C 75.47 ; H 5.66 ; N 8.80 found C 75.07; H 5.86 ; N 8.35.

N-Acetyl indole (III)

Indole (2 g), acetic anhydride (5 mL) and anhydrous sodium acetate (1 g) were refluxed for 3 h. The solvent was removed in vaccuo, and the residue was extracted with ether (3X15 mL), the ether extracts washed with 2N – H_2SO_4 solution (3 X 10 mL). The aqueous acidic layer was basified with 2N-NaOH solution (40 mL) and re-extracted with ether (3 X 20 mL). The ether was dried over sodium sulphate and evaporated. The N-acetyl indole (1.63 g, 60 %) was collected by distillation a 140-145 / 14 mmHg. R_f =0.82 (the same solvent system).

UV λ_{max} (EtOH) 238 , 288 , 297 nm. ^{1}HNMR (CDCl$_3$, 100MHz) δ : 2.2 (s , 3H) ; 6.5 (d , β-H) ; 7.0-7.5 (m , 4H) ; 7.8 (d , α- H). MS (70 *ev*) *m/z* (%) : 159 (M$^+$, 28) ; 118 (10); 117 (100) ; 90 (25) ; 89 (20) 63 (14) ; 43 (11). Analysis calculated for $C_{10}H_9NO$: C 75.47; H 5.66; N 8.80 found C 75.81; H 5.23 ; N 9.20.

Further acetylation of β-acetyl indole

β-Acetyl indole (0.5g), acetic anhydride (2mL) and acetic acid (1 mL) were refluxed for 2 h. The solvent was removed in vaccuo, the residue crystallized from ethanol to give 1, 3- diacetyl indole (0.6 g), m.p. 150-151° C.

Attempt to acetylate N-acetyl indole

N-Acetyl indole (1 g), acetic anhydride (5 mL) and acetic acid (2 mL) were refluxed for 2 h, after removing the solvent by vaccuo, only the starting material was recovered (0.90 g).

Results and Discussion

On applying the Saxton procedure to acetylate indole by refluxing for 24 h of indole in a mixture of acetic anhydride and acetic acid, the main product obtained was 1, 3-diacetyl indole (~ 60 %). The purpose of the experiment is to find out in which position the indole acetylates forms and the proportion of mono to diacetyl at various stages of the reaction. So we carried out a series of experiments in which the composition of the reaction mixture was followed by TLC and UV spectra. After 5 minutes of indole with acetic anhydride and acetic acid reaction, a faint spot was observed on TLC plate with $R_f = 0.33$ (benzene : ether : methanol , 4 : 1 : 0.1), in addition to that of indole which has $R_f = 0.85$ in the same solvent system. After 10 minutes of reaction, the UV spectrum shows some change, *i.e.* the absorbance increasing at λ = 255 nm and the TLC spot becomes clearer. After 30 minutes, an increase in the absorbance at λ = 239 as well as at 255 nm, a small preparative TLC was made to estimate the proportion of β-acetyl indole which has been known from the mass spectrum *m/z* =159 which corresponds to a mono acetyl indole, but the fragmentation pattern clearly corresponds to β-acetyl indole (~ 12 %) and not the N-acetyl derivative. After 1 h the reaction mixture containing another spot with R_f = 0.56 (same solvent system), this spot is attributed to 1,3-diacetyl indole depending on its mass spectrum *m/z* = 201 and the UV spectrum in which a little decreases in the absorbance was observed.

The proportion of β-acetyl to 1,3-diacetyl at this time was 3:1 respectively , while at the end of 24 h reflux the main product was 1,3-diacetyl indole (~ 60 %) and 5 % of β-acetyl indole. Prolonged reflux of a mixture of 1,3-diacetyl indole in acetic acid led to no observable change, which demonstrated that the β-acetylation of indole by 1,3-diacetyl indole is not a possible route. It is also found that *N*-acetyl indole is not β-acetylated in refluxing Ac_2O-AcOH ; this rules it out as an intermediate on the way to 1,3-diacetyl indole. Finally , β-acetyl indole was found to be smoothly *N*-acetylated in acetic anhydride / acetic acid, thus confirming the view that indole is first acetylated β and then in a subsequent reaction β-acetyl indole is converted into 1,3-diacetyl indole.

Conclusions

From this study, it is observed that 3-acetyl indole is the precursor of 1,3-diacetyl indole.

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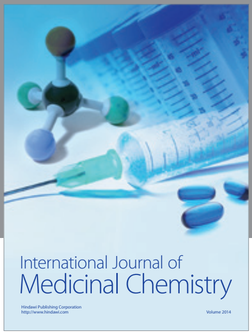
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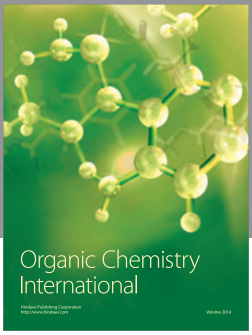
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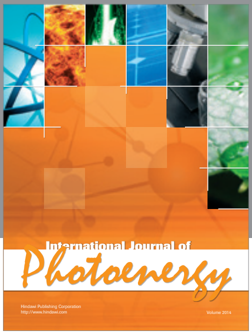
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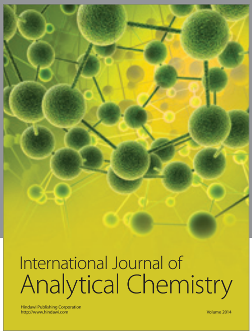
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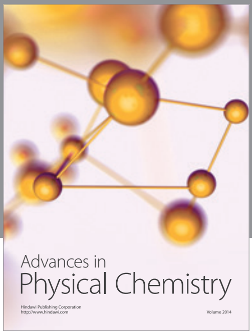
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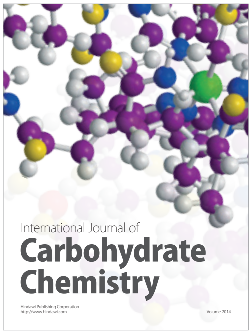
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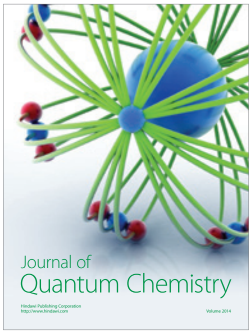
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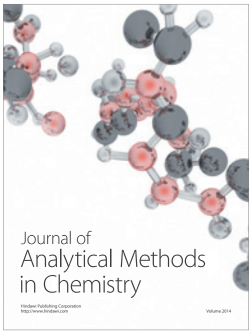
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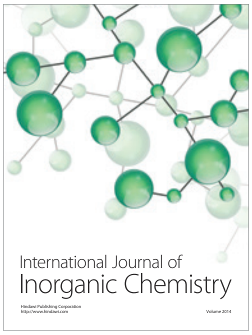
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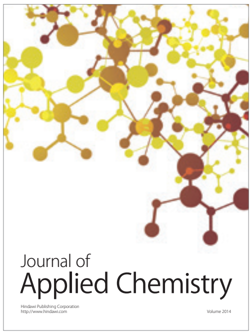
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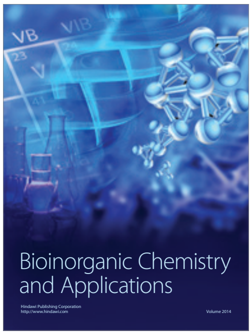
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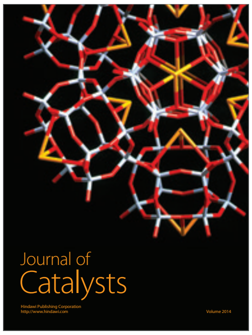
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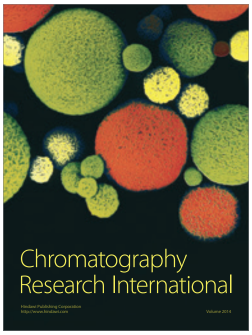
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