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STUDY OF THE ALKYLATION REACTIONS OF ISATIN UNDER LIQUID-SOLID PHASE TRANSFER CATALYSIS CONDITIONS USING LONG CHAIN ALKYL BROMIDES

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Abstract: In this current work we report the alkylation reactions of isatin by long carbon chain alkyl bromides under liquid-solid phase transfer catalysis (PTC) conditions. The structures of 1-alkyl-indoline-2,3-diones obtained were elucidated on the basis of spectral data (^{1}H NMR, ^{13}C NMR, IR and mass spectrometry).

Moreover their structures were confirmed by the single-crystal X-ray diffraction studies.

Keywords: Isatin, long carbon chain alkyl bromides, alkylation, spectral data, X-ray diffraction

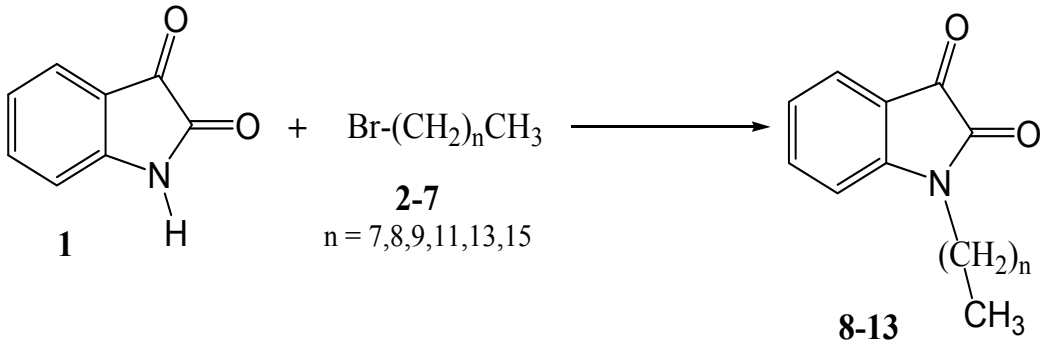
Introduction:

Due to their biological and pharmacological properties, isatin and its derivatives were extensively used as intermediates for the synthesis of a wide variety of organic compounds [1]. Furthermore isatin scaffold constitutes the core of several alkaloids [2] and medicinal drugs [3] as well as dyes [4]. Moreover isatin derivatives present diverse applications including antibacterial [5], antifungal [6], antiviral [7], anti HIV [8], anti-microbacterial [9], anticancer [10], inflammatory [11] and anticonvulsant [12] activities.

In continuation of our previously research works on synthesis, functionalization, and physicochemical properties of isatin and derivatives [13-26], we report in this current work the alkylation reactions of isatin using long carbon chain alkyl bromides as an alkylating reagents.

Results and discussion

In this work we study the alkylation reactions of isatin **1** using as alkylating reagents long carbon chain alkyl bromides **2-7** under liquid-solid phase transfer catalysis (PTC) conditions. The reactions studied were carried out in N,N-diméthylformamide (DMF) in the presence of potassium carbonate as base and tetra n-butyl ammonium bromide (TBAB) as catalyst at room temperature for 48 hours (Scheme 1).



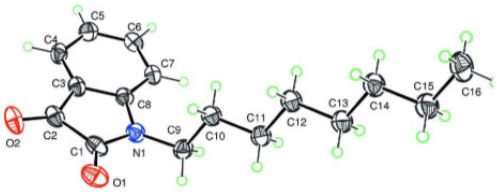
Scheme 1: Synthesis of 1-alkyl indole-2,3-diones **8-13**

The structures of compounds **8-13** were elucidated on the basis of spectral data (^{1}H NMR, ^{13}C NMR, mass spectrometry and confirmed by a single-crystal X-ray diffraction studies.

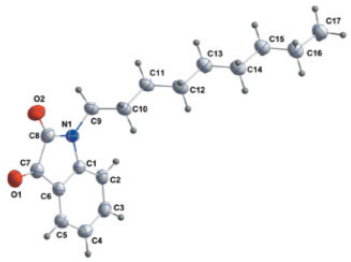
Thus, ^{1}H NMR spectra, taken in DMSO-d6 highlight in particular a triplets at 3,60 - 3,70 ppm due to the methylene groups linked to the nitrogen atom of the indoline moiety.

The ^{13}C NMR spectra of compounds **8-13** show in particular a signals at 58,02 - 58,22 ppm corresponding to the carbon of the methylene groups linked to the nitrogen atom of the indoline nucleus as well as two signals at 154,12 - 154,52 ppm and 183,96 - 184,04 ppm related to the amidic and ketonic carbonyl groups respectively.

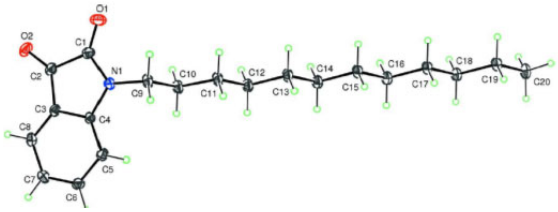
It is wortly to note that the structures of compounds **8-12** were confirmed by single-crystal X-ray diffraction studies [13-17] (figure1).



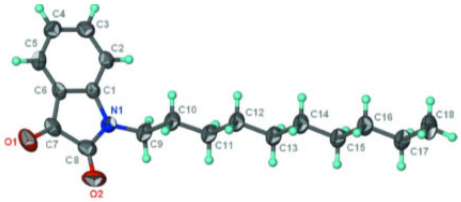
Compound **8**



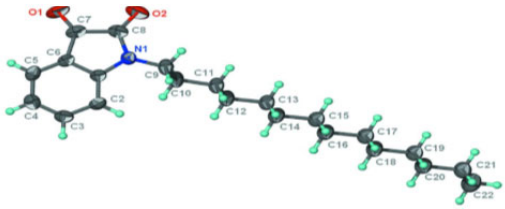
Compound **9**



Compound **10**



Compound **11**



Compound **12**

Figure1: ORTEP of compounds **8-12**

Conclusion

In this current work we report the synthesis of six long carbon chain alkyl isatins **8-13** using liquid-solid phase transfer catalysis conditions. The structures of the compounds obtained have been identified on the basis of spectral data and confirmed for compounds **8-12** by X-ray diffraction technique.

Experimental part

Melting points were determined via the use of open capillaries with an Electrothermal melting point apparatus and are reported uncorrected. The 1H and 13C NMR data were obtained on a Bruker Avance 300 MHz NMR in DMSO-d6 Solution .The chemical shifts are reported in δ (ppm) downfield from tetramethylsilane as an internal standard; coupling constants (J) are in Hz. The following abbreviations are used to describe peak patterns where appropriate: s,singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; dt, double triplet; m, multiplet. The X-ray diffraction were made on a Bruker X8 APEXII kappa CCD area-detector diffractometer.

General procedure:

To a solution of isatin (6.8 mmol) dissolved in DMF (50ml) were added alkyl agent (6.8 mmol), potassium carbonate (7.4 mmol) and a catalytic quantity of tetra-n-butylammonium bromide. The mixture was stirred at room temperate for 48 hours; the reaction was monitored by thin layer chromatography. After filtration of the salts, the solvent was removed under vaccum and the residue taken up in dichloromethane to precipitate the remaining salts. After a second filtration and evaporation of the solvent, the pure products were obtained after recrystallization from ethanol.

1-Octylindoline-2,3-dione : **8** Yield(%) = 80% ; Mp = 50-52 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.63 (t, 2H, NCH_2, ^{3}J = 7,2 Hz) ; 1.18-1.56 (m,12H,CH_2) ; 0.80 (t, 3H, ^{3}J = 6.7Hz) ; 7.18-7.65(m, 4H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.03 (NCH_2) ; 19.63-39.95 (6x CH_2); 117.82, 151.18, Cq: 117.82, 123.64, 138.76 (CH_{Ar}) ; 158.49 (C=O amide) ; 184.04 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$(m/z)=259

1-Nonylindoline-2,3-dione : **9** Yield(%) = 76% ; Mp = 58-60 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.61 (t, 2H, NCH_2, ^{3}J = 7.2 Hz) ; 1.18-1.56 (m,14H,CH_2) ; 0.80 (t, 3H, ^{3}J = 6.7Hz) ; 7.00-7.65(m, 14H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.02 (NCH_2) ; 22.50-40.39 (7x CH_2); 117.83, 151.18, Cq: 117.82, 123.64, 124.95, 138,76 (CH_{Ar}) ; 158.50(C=O amide) ; 184.04 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$ (m/z)=273

1-Decylindoline-2,3-dione : **10** Yield(%) = 80% ; Mp = 68-70 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.63 (t, 2H, NCH_2, ^{3}J = 7,2 Hz) ; 1.21-1.61 (m,16H,CH_2) ; 0.83 (t, 3H, ^{3}J = 6.7Hz) ; 7.08-7.64(m, 4H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.18 (NCH_2) ; 19.67-40.37 (8x CH_2); 117.89, 151.27, Cq: 111.18, 123.59, 124.91, 138.71 (CH_{Ar}) ; 158.48 (C=O amide) ; 184.00 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$ (m/z)=287

1-Dodecylindoline-2,3-dione : **11** Yield(%) = 80% ; Mp = 74-76 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.70 (t, 2H, NCH_2, ^{3}J = 7,2 Hz) ; 1.24-1.87 (m,20H,CH_2) ; 0.87(t, 3H, ^{3}J = 6.7Hz) ; 6.87-7.57(m, 4H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.22 (NCH_2) ; 22.66-40.29 (10x CH_2); 117.80, 151.11, Cq: 110.12, 123.54, 125.41, 138.22 (CH_{Ar}) ; 158.12 (C=O amide) ; 184.64 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$ (m/z)=315

*1-Tetradecylindoline-2,3-dione :**12*** Yield(%) = 80% ; Mp = 76-78 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.70 (t, 2H, NCH_2, ^{3}J = 7,2 Hz) ; 1.26-1.58 (m,24H,CH_2) ; 0.83(t, 3H, ^{3}J = 6.7Hz) ; 7.10-7.63(m, 4H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.20 (NCH_2) ; 22.66-40.37 (12x CH_2); 117.80, 151.27, Cq: 111.17, 123.58, 124.91, 138.70 (CH_{Ar}) ; 158.47 (C=O amide) ; 184.99 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$ (m/z)=343

1-Hexadecylindoline-2,3-dione : **13** Yield(%) = 80% ; Mp = 50-52 °C (ethanol); ***^{1}H*** NMR (DMSO-d6, 300 MHz) δ (ppm) : 3.63 (t, 2H, NCH_2, ^{3}J = 7,2 Hz) ; 1.18-1.56 (m,12H,CH_2) ; 0.80 (t, 3H, ^{3}J = 6.7Hz) ; 7.18-7.65(m, 4H,H_{Ar}); ***^{13}C NMR*** (DMSO-d6): 58.03 (NCH_2) ; 19.63-39.95 (6x CH_2); 117.82, 151.18, Cq: 117.82, 123.64, 138.76 (CH_{Ar}) ; 158.49 (C=O amide) ; 184.04 (C=O ketone); Mass spectrum (IE) : $M^{+\cdot}$ (m/z)=371

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