



Research Article

DESIGN, SYNTHESIS AND SPECTRAL CHARACTERIZATION OF 5-[2(3)-DIALKYLAMINO ALKOXY] INDOLE 3-HYDRAZONE 2-ONE AND 5-HYDROXYINDOLE 3-THIOSEMICARBAZONE 2-ONES

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ABSTRACT

In the present work, some new 5-[2(3)-dialkylamino alkoxy] Indole 3-hydrazone 2-one and 5-[2(3)-dialkylamino alkoxy] indole 3-thiosemicarbazone 2-ones were prepared from 5-hydroxy isatin. The structures of the products were characterized by IR, NMR, MASS Spectral studies. Simplicity of the reaction conditions, easy workup procedure and good yields are the key features of this protocol.

Keywords: Synthesis, 5-[2(3)-dialkyl amino alkoxy] Indole 3-hydrazone 2-one, 5-Hydroxyindole, 3-thiosemicarbazone 2-ones.

INTRODUCTION

Isatin is an endogenous compound isolated in 1988 and reported [1] to possess a wide range of central nervous system activities. Surendranath pandya [2] et al. reported the synthesis and anticonvulsant activity of some novel n-methyl/acetyl, 5-(un)-substituted isatin-3-thiosemicbazones. In the last few years, Isatin derivatives have been discovered which show potential hypnotic [3], antibacterial [4-6] and MAO inhibitory [7] activity. We are reporting in the present communication the synthesis and characterization of some new compounds 5-[2(3)-dialkylamino alkoxy] Indole 2-one 3-hydrazones and 5-[2(3)-dialkylamino alkoxy] Indole 2-one, 3-thiosemicbazones.

5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with hydrazine hydrate / thiosemicbazide hydrochloride for half an hour to get 5-Hydroxy isatin hydrazone/5-Hydroxy isatin

thiosemicbazone. 5-Hydroxyisatin hydrazine/ 5-Hydroxy isatin thiosemicbazone condensed with dialkylamino alkyl halide by using Williamson synthesis to prepare the 5-[2(3)-dialkylamino alkoxy] Indole 2-one 3-hydrazone and 5-[2(3)-dialkylamino alkoxy] Indole 2-one, 3-thiosemicbazones. It is evident from the literature survey that Isatin hydrazone derivatives, isatin thiosemicbazone derivatives and dialkylamino alkyl derivatives showing more promising biological activities. Keeping in view of these two molecular moieties viz., 5-hydroxy isatin (Resembles serotonin) and dialkylamino alkyl (Resembles NT), it is our endeavor to bring such important moieties into a single molecular frame as a model for molecular conjunction by appropriate synthetic routes and to screen them for possible biological activity.

Materials and Methods

The compounds were mostly synthesized by conventional methods and described in experimental selection and also by the methods established in our laboratory.

Chemicals

Dialkylaminoalkylhalides, Hydrazinehydrate, Thiosemicarbazide hydro-chloride purchased from Sigma- Aldrich Chemicals Private Limited, Hyderabad, India. p-amino phenol, hydroxylamine hydrochloride, sodium sulfate were purchased from Merck Chemicals Pvt Limited, Hyderabad, India.

Chemistry

Solvents were dried or distilled before use. Melting points were obtained on a Thoshniwall melting point apparatus in open capillary tubes and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel -G plates(Merck).Infrared spectra(IR) were recorded with KBR pellet on a Perkin-Elmer BX series, Infrared spectrophotometer. Mass spectra were recorded by the direct inlet method on Thadmmam-mass-quantam API 400H mass spectrophotometer.¹H NMR spectra were recorded on Brucker spectrospin 400 MHz spectrophotometer in DMSO-d₆. 5-Hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer[8] method. It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitroso-acetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield.

Preparation of 5-Hydroxyindole 3-thiosemicarbazone 2-one (II) and 5-Hydroxyindole 2-hydrazone (IV)

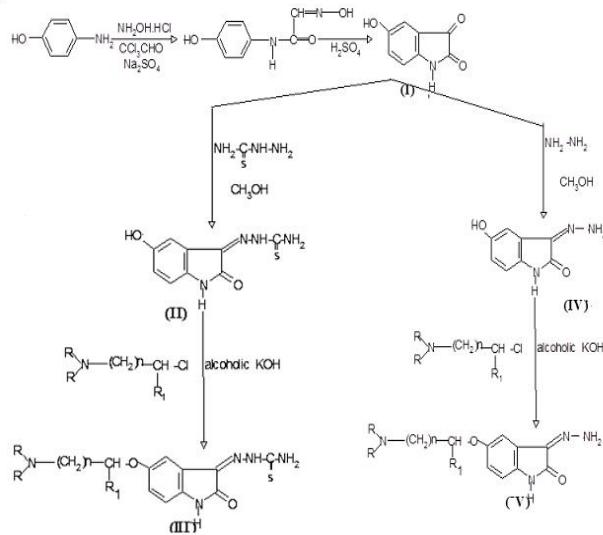
5-Hydroxyisatin was heated under reflux in methanol containing two or three drops of acetic acid with thiosemicarbazide hydrochloride/Hydrazine hydrate for half an hour. The product thus separated was filtered and purified by recrystallization from suitable solvent.(Yield 89%, m.p.270oc(II), Yield 90%, m.p.284 oc (IV))

Preparation of 5-[2(3)-dialkyl amino alkoxy] Indole 3-thiosemicarbazone-2-one (III) and 5-[2(3)-dialkyl amino alkoxy] Indole 3-hydrazone-2-one(V)

A mixture of 5-Hydroxyindole3-thiosemicarbazone2-one(II) /5-hydroxy indole 3-hydrazone 2-one(IV) (0.01 moles) and dialkylamino alkylhalide (0.01 moles) placed in 10%

alcoholic potassium hydroxide and this mixture was stirred at room temperature for 6 hours .The alcohol was reduced to half of its volume and cooled. The product separated was filtered, washed with small portions of cold alcohol repeatedly and dried. It was purified by recrystallisation from hydro alcoholic mixtures to get a crystalline solid. Similarly other 5-Hydroxy Isatin derivatives as shown in Scheme -1 were prepared and their melting points were determined in Open capillary tubes using Toshniwall melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC. The physical data of the title compounds were presented in Table-1. The compounds were characterized by spectral data.

Scheme



5-Hydroxy- isatin- 3- thiosemicarbazone derivatives (III)

5-Hydroxy-isatin- 3-hydrazone derivatives (V)

IIIa R=CH₃; R₁=H ;n=1 Va R=CH₃; R₁=H ;n=1

IIIb R=C₂H₅; R₁=H ;n=1 Vb R=C₂H₅; R₁=H ;n=1

IIIc R=CH₃; R₁=H ;n=2 Vc R=CH₃; R₁=H ;n=2

IIId R=CH₃; R₁= CH₃ ;n=1 Vd R=CH₃; R₁= CH₃ ;n=1

IIIe R=CH₃-CH-CH₃; R₁=H ;n=1 Ve R=CH₃-CH-CH₃; R₁=H ;n=1

Table-1: Physical data of 5-[2(3)-dialkyl amino alkoxy] Indole 3-thiosemicarbazone-2-ones(IIIa-IIIe) and 5-[2(3)-dialkyl amino alkoxy] Indole 3-hydrazone-2-ones(Va-Ve)

| S. No | Compound | R | R ₁ | N | X | M.F | % YIELD | M.P | M. Wt |
|-------|----------|-------------------------------|-----------------|---|----------------------|---|---------|------|-------|
| 1 | IIIa | CH ₃ | H | 1 | NNHCSNH ₂ | C ₁₃ H ₁₇ N ₅ O ₂ S | 91% | <320 | 307 |
| 2 | IIIb | C ₂ H ₅ | H | 1 | NNHCSNH ₂ | C ₁₅ H ₂₁ N ₅ O ₂ S | 86% | <320 | 335 |
| 3 | IIIc | CH ₃ | H | 2 | NNHCSNH ₂ | C ₁₄ H ₁₉ N ₅ O ₂ S | 93% | <320 | 353 |
| 4 | IIId | CH ₃ | CH ₃ | 1 | NNHCSNH ₂ | C ₁₄ H ₁₉ N ₅ O ₂ S | 85% | <320 | 353 |
| 5 | IIIE | | H | 1 | NNHCSNH ₂ | C ₁₆ H ₂₄ N ₅ O ₂ S | 81.8% | <320 | 365 |
| 6 | Va | CH ₃ | H | 1 | NNH ₂ | C ₁₂ H ₁₆ N ₄ O ₂ | 92% | <320 | 248 |
| 7 | Vb | C ₂ H ₅ | H | 1 | NNH ₂ | C ₁₄ H ₂₀ N ₄ O ₂ | 83% | <320 | 276 |
| 8 | Vc | CH ₃ | H | 2 | NNH ₂ | C ₁₃ H ₁₈ N ₄ O ₂ | 92% | <320 | 294 |
| 9 | Vd | CH ₃ | CH ₃ | 1 | NNH ₂ | C ₁₃ H ₁₈ N ₄ O ₂ | 86% | <320 | 294 |
| 10 | Ve | | H | 1 | NNH ₂ | C ₁₃ H ₂₆ N ₄ O ₂ | 82% | <320 | 306 |

Spectral data

The compounds have been characterized by the spectral data IR, PMR and Mass.

IR spectrum (KBr) of compound (I) exhibited absorption bands (cm⁻¹) 3421.47 (OH), 1630.08 (C = O), 1548(Ar,C=C), 1282(C-O-C), 883.85-579.8 (Ar). 1H NMR (300 MHz, DMSO-d6): 13.3 (s,1H, OH), 10.36(s,1H,-CONH), 6.65-7.29 (m, 3 H, Ar-H). Mass spectrum of compound III showed molecular ion(M+) base peak at m/z (164.1).

Compound (IIIa) showed characteristic IR peaks at 3368.41(NH₂), 3282.52(CONH), 1708(C=O), 1576(Ar C=C), 1263(C-O), 1085(C=S), 1576(C=N), 883.85 (Ar C-C). 1H NMR (300 MHz,DMSO-d6): 11.36(s, 1H,CONH),7.29(s,2H,NH₂), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H), 3.2(t,2H, O-CH₂), 2.9(t,2H, N-CH₂),1.36(s, 6H,N-(CH₃)₂). Mass spectrum of compound IIIa showed molecular ion (M+) base peak at m/z 307. The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion. Compound (IIIb) showed characteristic IR peaks at 3368.41(NH₂), 3282.52(CONH), 1165.96 (C=S), 1570.21 (Ar ,C=C), 1243(C-O-C), 845.51(Ar).

1H NMR (300 MHz, DMSO-d6): 10.25(s, 1H,-CONH), 7.03-7.45 (m,3 H,Ar-H), 2.99 (t,2H,O-CH₂), 2.72 (t,2H,N-CH₂) 7.47-7.56(d,2H, NH₂),1.24 (m,6H,N-C-CH₃,1.12(t,N-CH₂).

Mass spectrum of compound IIIb showed molecular ion (M+) base peak at m/z 335. The mass spectrum shows its base peak at m/z 214 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion.

Compound (IIIc) showed characteristic IR peaks at 3368.41(NH₂), 3282.52(CONH),1165.96(C=S), 1579.72 (Ar,C=C), 1266(C-O-C), 805.91(Ar). 1H NMR (300 MHz, DMSO-d6):10.46(s,1H,-CONH),7.21-7.49(m,3 H,Ar-H), 7.51-7.56(d,2H, NH₂),2.84 (t,2H,O-CH₂), 2.51 (m,2H, CH₂),2.48 (t,2H,N-CH₂), 1.25 (S,6H,N-(CH₃)₂). Mass spectrum of compound IIIc showed molecular ion (M+) peak at m/z 353 (100%). The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from the molecule ion.

Compound (IIId) showed characteristic IR peaks at 3368.41(NH₂), 3282.52(CONH),1165.96(C=S), 1546.86 (Ar,C=C),1245(C-O-C),812.71(Ar). 1H NMR (300MHz, DMSO-d6):10.51(s,1H,-CONH),7.12 7.42 (m,3H,Ar-H), 7.51-

7.56(d,2H,NH2),2.76 (m,H,O-CH) , 2.45(d,3H,R1=CH3), 2.31(d,1H,N-CH),1.44 (s,6H,N-(CH3)2). Mass spectrum of compound IIId showed molecular ion (M^+) base peak at m/z 353(100%).The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thiosemicarbazone from molecule ion.

Compound (IIIe) showed characteristic IR peaks at 3368.41(NH2), 3282.52(CONH), 1165.96(C=S), 1576.34 (Ar,C=C),1228(C-O-C),814.53(Ar). 1H NMR (300 MHz, DMSO-d6):10.26(s, 1H,-CONH), 7.34-7.51(m,3 H,Ar-H), 7.51-7.56(d,2H,NH2),2.96 (t,2H,O-CH2) ,2.82 (t,2H,N-CH2), 1.35 (t, 2H,N-CH) ,1.21 (d,12H,C -(CH3)2). Mass spectrum of compound IIIe showed molecular ion (M^+) peak at m/z 365 (100%). The mass spectrum shows its base peak at m/z 93 (100%) may be due to the fragmentation of the thoseemicarbazone from the molecule ion.

Compound (Va) showed characteristic IR peaks at 3450.13(NH2), 146.46(CONH), 1708(C=O), 1268 (C-O-C), 1085(C=S), 1528(C=N). 1H NMR (300 MHz, DMSO-d6): 11.36(s,1H,CONH),7.29(s,2H,NH2), 7.03(s,1H,Ar-H), 7.20(d,1H,Ar-H), 7.94(d,1H,Ar-H) 3.2(t,2H, O-CH2), 2.9(t,2H, N-CH2),1.36(s, 6H,N-(CH3)2). Mass spectrum of compound Va showed molecular ion (M^+) base peak at m/z 248 (100%).It also shows peak at m/z (71) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (Vb) showed characteristic IR peaks at 3450.13(NH2), 146.46(CONH),1685.96(C=O),1600.96(C=N)1570.21(Ar,C =C),1243 (C-O-C),845.51(Ar). 1H NMR(300MHz, DMSO-d6):10.25(s,1H,-CONH),7.03-7.45 (m,3H,Ar-H),2.99(t,2H,O-CH2),2.72(t,2H,N-CH2)7.47-7.56(d,2H, NH2), 1.24(s,10H,N-(C2H5)2).

Mass spectrum of compound Vb showed molecular ion (M^+) peak at m/z 276(100%).It also shows peak at m/z(99) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (Vc) showed characteristic IR peaks at 3450.13(NH2), 146.46(CONH), 1698.96 (C=O), 1600.96 (C=N), 1579.72 (Ar, C=C), 1266(C-O-C),805.91(Ar). 1H NMR(300 MHz,DMSO-d6):10.46(s,1H,-CONH), 7.21-7.49(m,3 H,Ar-H), 7.51-7.56(d,2H, NH2), 2.76(m,H,O-CH), 2.45(d,3H, R1=CH3),2.31 (d,1H,N-CH),1.44(s,6H,N-(CH3)2).

Mass spectrum of compound Vc showed molecular ion (M^+) base peak at m/z 294 (100%). It also shows peak at m/z (113) may be due to the fragmentation of the alkyl chain from the molecule ion. Compound (Vd) showed characteristic IR peaks at 3450.13(NH2), 146.46(CONH),1698.96 (C=O),1600.96 (C=N)1546.86(Ar,C=C),1245(C-O-C), 812.71(Ar). 1H NMR (300 MHz, DMSO-d6):10.51(s,1H,-CONH),7.12-7.42(m,3H,Ar-H),7.51-7.56 (d,2H, NH2), 2.76 (m, 2H,O-CH2), 2.45(t,3H,R1=CH3), 2.31 (m,1H,N-CH), 1.44 (s,6H,N-(CH3)2).Mass spectrum of compound Vd showed molecular ion (M^+) base peak at m/z 294 (100%). It also shows peak at m/z (113) may be due to the fragmentation of the alkyl chain from the molecule ion. Compound (Ve) showed characteristic IR peaks at 3450.13(NH2), 146.46(CONH), 1696.96 (C=O), 1600.96 (C=N), 1576.34(Ar,C=C),1228 (C-O-C),814.53(Ar). 1H NMR(300MHz, DMSO-d6):10.26(s,1H,-CONH),7.34-7.51(m,3H,Ar-H),7.51-7.56(d,2H, NH2), 2.96(t,2H,O-CH2),2.82(t,2H,N-CH2), 1.35 (m,2H,N-CH),1.21(d,12H,C-(CH3)2). Mass spectrum of compound Ve showed molecular ion (M^+) base peak at m/z 306(100%).It also shows peak at m/z (129) may be due to the fragmentation of the alkyl chain from the molecule ion.

RESULTS AND DISCUSSION

On the basis of activity of isatin and its derivatives, we envisaged the synthesis of new 5-hydroxy isatin derivatives bearing a dialkylaminoalkoxy group at 5th position and Schiff's bases like hydrazones and thiosemicarbazones of 5-Hydroxy isatins. This is the novel technique for the synthesis of 5-Hydroxy isatin derivatives by using Williamson synthesis for the efficient alkylation method.

To determine the versatility of 5-Hydroxy isatins, 5-[2(3)-dialkyl amino alkoxy] Indole 2, 3 dione derivatives, prepared from 0.01 mole 5 hydroxy isatin Schiff's basis with 0.01 mole dialkyl amino alkyl halides in ethanol by stirring for six hours. The reaction occur smoothly without formation of any side products. We observed that as the alkyl chain increases the yield of the products increases.

CONCLUSION

In conclusion, we have described an efficient protocol for the preparation of 5-hydroxyisatin derivatives by simple conventional method. In this method new series of ten 5-[2(3)-

dialkyl amino alkoxy] Indole 2, 3 dione derivatives were synthesized by reacting 5-hydroxyindole 2,3 dione schiff bases with 2-N,N di alkylamino alkyl halides.All the compounds were characterized by IR, NMR, MASS Spectral studies. The advantages of this system are greater efficiency, low cost, versatility, gram-level preparative scale and simple workup procedure. Application of this strategy to the preparation of 5-Hydroxy Isatin derivatives toward investigation for biological activity is currently being pursued.

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