SYNTHESIS OF A NOVEL PENTACYCLIC RING SYSTEM FROM THE REACTION OF FLUORINATED ISATIN DERIVATIVES WITH 2-AMINOPHENOL

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Abstract

Derivatives (IVa,b) of novel heterocyclic system indolo [2,3-*e*] dibenzo [*b*,*h*][1,4,7] oxadiazonine have been obtained the condensation of fluorinated isatins (Ia, b) with 2-aminophenol (II) along with some new fluorine containing 2-(2-oxo-2*H*-1,4-benzoxazin-3-yl) anilines (IIIa, b) and isatin-3-(2-hydroxyanil) (V). However, fluorinated 1-acetylisatins (Ic, d) give only IIIc, d.

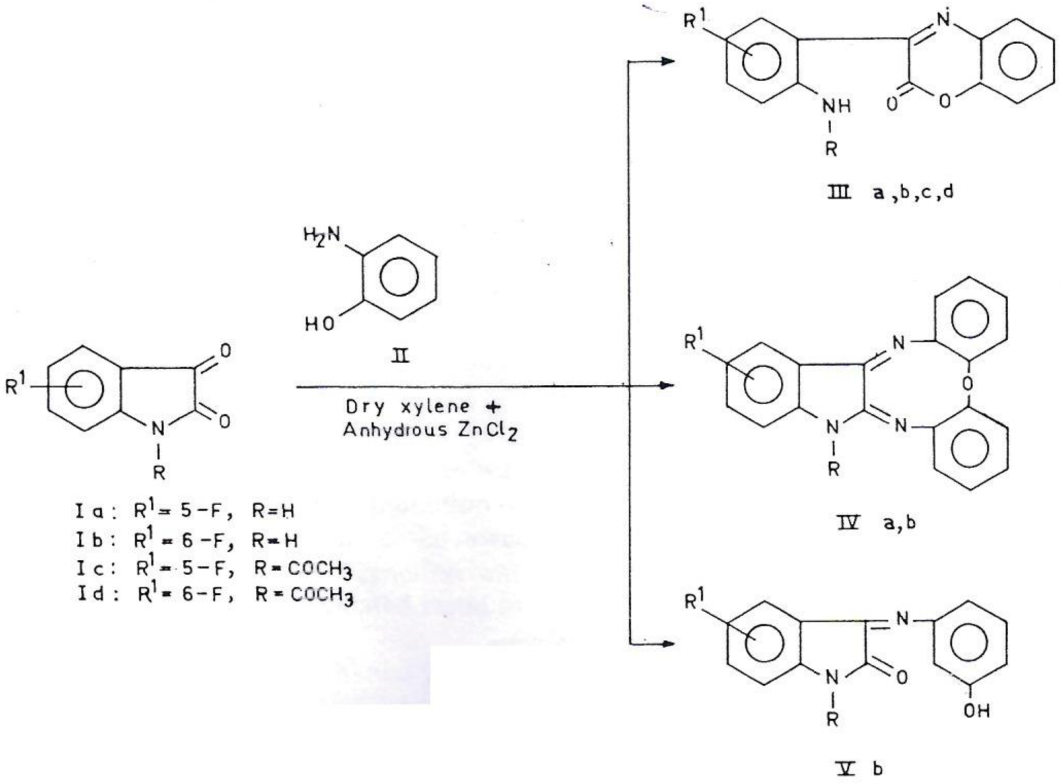
Key words

2-aminothiophenol, 5-jluoroisatin

Introduction

As a part of our study on the synthesis of biologically active indole derivatives[1-7], was have reported earlier[8] the reaction of isatin derivatives with 2-aminophenol and 2-aminothiophenol. The reaction products of ketones and 2-aminophenol have many applications both biological and industrial[9-11]. Fluorine incorporation in heterocycles is known to effect the course of reaction besides influencing the biological activity[12-15]. Prompted by this, we have now investigated the title reaction with fluorinated isatin derivatives and synthesised a novel pentacyclic ring system, indolo[2,3-*e*] dibenzo [*b.h*][1,4,7] oxadiazonine (IV) along with some new fluorine containing 4/5-fluoro-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl) anilmes (IIIa, b), 4/5-fluoro-N-[2-oxo-2*H*-1,4-benzoxazin-3-yl) phenyl] acetamides (IIIc, d) and 6-fluoroisatin-3-(2-hydroxyanil) (V) (Scheme 1).

Fluorinated isatins are found to be less reactive and require prolonged heating for completion of reaction. Earlier[8], reaction of isatin (R'=H, R=H) yielded two products III and V in 25 and 30% yield respectively after 8 hr of refluxing. In the present investigation, the reaction of 5-fluoroisatin with 2-aminophenol yielded the benzoxazine derivative IIIa (25%) and a novel 7-membered compound IVa (46%) after 20 hr of refluxing. On the other hand



6-fluoroisatin (Ib) yielded a mixture of three products IIIb, IVb and 6-fluoroisatin-3-(2-hydroxyanil) (V).

Fluorinated N-acetylisatins (Ic and Id) behave analogues to their nonfluoro analog and yielded exclusively new fluorine containing compounds IIIc and IIId after 10 hr of refluxing, but the yield of products was lower than in the former case.

The reaction of 5-fluoroisatin with 2-aminophenol yielded two compounds, which were separated by column chromatography. The yellow compound (IIIa) showed IR absorptions at 3420, 3310 (NH_2) and 1620 (CO) cm^{-1}. Its ^{13}NMR spectrum exhibited peaks at δ 159.988 (C=O), 153.017 (C-F), 150.21 (C-3′), 126.091-119.263 (9 aromatic carbon), 117.014 (C-2) and 113.266 (C-6). Further, the mass spectrum did not show the molecular ion peak and instead, the highest peak was observed at m/z 228 (M^+ – CO) (100%) as observed earlier[8]. Other peaks were observed at m/z 227 (M^+ – CHO) (5.62%), 199 (227-$C_2H_2O_2$) (26.2%) and 136 (M^+ – $C_6H_4N_2O$) (15%). On the basis of elemental and spectral studies, compound IIIa was assigned the structure 4-fluoro-2-(2-oxo-2*H*-1, 4-benzoxazin-3-yl) aniline.

The black compound IVa, obtained from ethylacetate-methanol (1:1) fraction, showed complete disappearance of the carbonyl absorptions in the IR spectrum. Characteristics IR absorptions were observed at 3300 (NH), 1590 (C=N) and 1560 (C=N) cm^{-1}. The PMR spectrum exhibited peaks at δ 6.4-7.02 (m, 11H, aromatic protons) and 9.4 (br, 1H indole NH). The mass spectrum showed the molecular ion peak at m/z 329 (M^+) (6.2%) with (M+1) and (M-1) peaks at m/z 330 (4.9) and 328 (27.7%) respectively. Other peaks were observed at m/z 281 (M^+ -H_4N_2O) (39.5%), 254 (M^+ -C_6H_3) (19%), 253 (M^+ -C_6H_4) (100%), 225 (M^+ -$C_6H_4N_2$) (8.6%), 213 (M^+ -$C_8H_4N_2O$) (13.5%), 185 (M^+ -$C_8H_4N_2O$) (21%) and 152 (M^+ -$C_8H_4FN_3O$) (17%). On the basis of elemental analyses and spectral data, it was assigned structure 14-fluoroindolo[2,3-*e*]dibenzo[*b*,*h*][1, 4, 7]oxadiazonine.

Presumably two moles of 2-aminophenol have condensed with isatin yielding first a dianil as was observed in other cases[16] followed by elimination of a water molecular leading to the formation of a novel oxadiazonine ring (IV). This type of reaction was not observed in the case of nonfluorinated isatin as well as with 2-aminophenol.

In the reaction of 6-fluoroisatin (Ib) and 2-aminophenol (IIa), a dark yellow compound (Vb) was recovered from benzene-chloroform (4:1) fraction besides the yellow compound from pet. Ether-benzene (9:1) (IIIb) fraction and the black compound (IVb) from ethylacetate-methanol (1:1) fraction. Compounds IIIb and IVb were identified as 5-fluoro-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)aniline and 13-fluoroindolo[2,3-*e*]dibenzo[*b*,*h*][1,4,7]oxadiazonine respectively on the basis of elemental and spectral data. Compound Vb showed characteristic IR absorptions at 3500-3200 (br, OH and NH), 1710 (>>CO) and 1610 cm^{-1}. The PMR spectrum exhibited peaks at δ 6.41-7.09 (m, 7H, aromatic protons), 8.92 (s, 1H, NH) and 10.82 (br, 1H, OH). Further, the mass spectrum showed the molecular ion peak at m/z 256. On the basis of these data the compound was identified as 6-fluoroisatin-3-(2-hydroxyanil) (Vb). This hydroyanil was not obtained in the case of 5-fluoroisatin.

From the reaction of 5/6-fluoro-1-acetylisatin (Ic/Id), only one compound (IIIc,IIId) was obtained after 10 hr of refluxing showing characteristic IR absorptions at 3300-3200 (broad, NH), 1730 (>>CO) and 1690 (CO) cm^{-1}. The PMR exhibited the downfield shift in methyl protons of $NHCOH_3$ (δ2.25) as compared to $NCOCH_3$ protons of N-acetylisatin appearing at δ 2.66 thus supporting the opening of N-C_2 bond of isatin. Other signals were observed at δ 7.28-7.85 (m, 7H, aromatic protons) and 9.77 (s, 1H, NH). Further, the mass spectrum of IIIc showed the molecular ion peak at m/z 298 (44.6%) cm^{-1}. Other characteristic peaks were observed at m/z 270 (M^+ – CO) (7.04%), 255 (M^+ – $COCH_3$) (10.0%), 229 (M^+ - C_3H_3NO) (13.7%) and 228 (M^+ -C_2NO_2) (100%). On the basis of above data compounds IIIc and IIId were identified as 4/5-fluoro-N-[2-(2-oxo-2*H*-1,4-benzoxazine-3-yl]phenyl]-acetamide.

The position of fluorine in various compounds was established by ^{19}F NMR spectra using hexafluorobenzene as external standard. Fluorine attached to the phenyl ring appeared at δ-103 to -106 (IIIa-d) and the single fluorine attached to the indole ring (IVa,b and V) appeared at -113 and -116.

Experimental Procedure

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Hitachi 270-50 spectrophotometer and Fourier IR spectra on a Perkin-Elmer model 1800 spectrophotometer, PMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a JEOL FX 90 Q MHz instrument using TMS as internal standard and ^{13}C NMR spectra in DMSO-d_6 on the same instrument at 22.49 MHz. Mass spectra were recorded on an MS-30 or MS-50 Kratos mass spectrometer at 70 eV. Carbon and hydrogen analyses were carried out on a Coleman ‘C’ and ‘H’ analyzer. Nitrogen analyses were done using Carlo Ebra N-analyzer 1106.

All the reactions were carried out in dry xylene in the presence of anhyd. Zinc chloride and the products formed were separated by column chromatography over silica gel. Fluorinated isatin derivatives (Ia - d) were prepared by literature method[17-19].

Reaction of 5-fluoroisatin (Ia) with 2-aminophenol (II): Formation of 4-fluoro-2-(2-oxo-2H-1, 4-benzoxazin-3-yl) aniline (IIIa) and 14-fluoroindolo-[2, 3-e] dibenzo[b, h][1, 4, 7]oxadiazonine (IVa)

A mixture of 5-fluorisatin (0.01 mol) and 2-aminophenol (0.01 mol) in dry xylene in the presence of anhyd. Zinc chloride (1 g) was refluxed for 20hr. Formation of two compounds was indicated was indicated by TLC. These products were separated by column chromatography. A fluffy yellow compound, obtained from pet. Ether-benzene (9:1) fraction was identified as IIIa, yield 25%, m.p. 96°; IR: 3420, 3310 (NH_2), 1620 (CO), 1560; PMR ($CDCl_3$+DMSO-d_6): δ 6.55-8.09 (m, 7H, ArH); ^{19}FNMR: δ -105.26 (s); MS: m/z 228 (M^+ -CO) (100%) (Found: C, 65.8; H, 3.7; N, 11.0. $C_{14}H_9FN_2O_2$ requires C, 65.6; H, 3.5; N, 10.9%).

The black compound obtained from ethyl acetate-methanol (1:1) fraction was identified as IVa, yield 46%, m.p. > 360; IR: 3300 (NH), 1600, 1590; PMR (DMOS-*d*6): δ 6.40-7.02 (m, 11H, ArH), 9.40 (br, 1H, NH); ^{19}FNMR: δ -116.64 (s); MS: m/z 330 (M^+ +1) (4.9%), 329 (M^+) (6.2) (Found: C, 72.8;H, 3.8; N, 12.7. $C_{20}H_{12}FN_3O$ requires C, 72.9; H, 3.6; N, 12.8%).

Reaction of 6-fluoroisatin (Ib) with 2-aminophenol (II): formation of 5-fluoro-2-(2-oxo-2H-1, 4-benzosazin-3-yl) aniline (IIIa) and 13-fluoroindolo-[2, 3-e]dibenzo[b, h][1, 4, 7]oxadiazonine(IVb) and 6-fluoroisatin-3-(2-hydroxyanil) (V)

A mixture of Ib (0.01 mol) and II (0.01mol) was refluxed for 22hr. The supernatant liquid on column chromatography furnished three compounds. The pet. ether - benzene (9:1) eluate gave a fluffy yellow compound identified as IIIb, yield 15%, m.p. 103°; IR: 3420, 3340 (NH_2), 1620 (CO), 1550; PMR($CDCl_3$+DMSO-d_6): δ 6.43 - 8.13 (m, 7H, Arh); ^{19}FNMR: δ -103.86 (s) (Found: C, 65.6; H, 3.4; N, 10.8. $C_{14}H_9FN_2O_2$ requires c, 65.6; H, 3.5; N, 10.9%). The dark yellow compound recovered from benzene-chloroform (4:1) fraction was identified as V, yield 10%, m.p. 178°; IR: 3500-3200 (br, OH and NH), 1710 (CO), 1610; PMR(DMSO-d_6): δ 6.41 – 7.04 (m, 7H, ArH), 8.92 (s, 1H, NH), 10.82 (br, 1H, OH); ^{19}FNMR: δ -113.64(s) (Found: C, 65.5; H, 3.7; N, 10.8. $C_{14}H_9FN_2O_2$ requires C, 65.6; H, 3.5; N, 10.9%).

The ethyl acetate-methanol (1:1) fraction gave a black compound identified as IVb, yield 40%, m.p. > 360; IR: 3320 (NH), 1600, 1590; PMR(DMSO-d_6): δ 6.32 – 7.14 (m, 11H, ArH), 9.60 (br, 1H, NH); ^{19}FNMR: δ - 113.32(s) (Found: C,73.1; H, 3.5; N, 13.0. $C_{20}H_{12}FN_3O$ requires C, 72.9; H, 3.6; N, 12.8%).

Reaction of 1-acetyl-5-fluoroisatin (Ic)/1-acetyl-6-fluoroisatin (Id) with 2-aminophenol(II): Formation of 4/5-fluoro-N-[2-(2-oxo-2H-1,4-benzoxazin-3-yl)phenyl]acetamide (IIIc/IIId)

A mixture of Ic/Id (0.01 mol) and 2-aminophenol (0.01 mol) was refluxed for 10hr. The supernatant liquid on concentration gave a yellow crystalline compound which was recrystallized from benzene. It was identified as IIIc/ IIId.

IIIc: yield 40%, m.p. 170°; IR: 3320 (br, NH), 1730 (CO), 1690 (CO), 1600; PMR ($CDCl_3$ + DMSO-d_6): δ 2.24 (s, 3H, $COCH_3$), 7.30-7.80 (m, 7H, ArH), 9.82 (s, 1H, NH); ^{19}FNMR: δ -105.48 (Found: C, 64.6; H, 3.6; N, 9.3. $C16H_{11}FN_2O_3$ requires C, 64.4; H, 3.7; N, 9.4%).

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