INVESTIGATION OF THE REACTION OF 1, 3-DIHYDRO-3- (2-PHENYL-2-OXOETHYLIDENE) -INDOL-2(*H*) -ONES WITH 3 –AMINO – 1 – PHENYL – 2-PYRAZOLIN -5-ONE

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Abstract

Some fluorine containing compounds, 2′, 3′, 3′a, 5′-tetrahydro-5-fluoro- 6′- (4-fluorophenyl) -2′-phenylspiro [indoline-3, 4′-pyrazolo [3,4-b] pyridine] -2, 3′-dione (IIIa), 1, 3-dihydro-3-[2-(3-trifluoromethylphenyl)-2-(1-phenyl-5-oxopyrazol-3-ylimino)ethylidene]indol-2(*H*)-one (IVb), 2-phenyl-5-(3-trifluoromethylphenyl)-11*H*-pyrazolo [3′, 4′; 2, 3]azepino[4, 5-b]indol-1(2*H*)-one (Vb) and 2′, 3′, 3′a, 7′-tetrahydro-4′-(4-fluorophenyl)-2′-phenylspiro[indoline-3, 6′-[6*H*]pyrazolo[3, 4-b]pyridine]-2, 3′-dione (VIc) have been synthesized by the reaction of fluorinated 1, 3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2(*H*)-ones (I) with 3-amino-1-phenyl-2-pyrazolin-5-one (II) in abs, ethanol. All the compounds have been characterized by their elemental analyses and IR, ^{1}H NMR, ^{19}F NMR and mass spectral data.

Key Words

3-aminopyrazolone, 1, 3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-(*H*)-ones.

Introduction

During our study on fluorine containing biologically active indole derivatives[1-3], an interesting reaction was noticed when fluorinated 1, 3-dihydro-3-(2-phenyl-2-oxoethylidene)indol-2-(*H*)-ones (I) were allowed to react with 3-aminopyrazolone (II) leading to react with 3-aminopyrazolone (II) leading to a mixture of products.

Along with indole, a wide spectrum of biological activities are associated with pyrazole nucleus[4-7]. Further, the pyridoindole nucleus, knows as carboline system, is the parent skeleton of several alkaloids[8] and biologically active compounds[9-11]. Fluorinated carbolines are well known for their neuroleptic and antidepressant activities[12]. Recently[13] a new class of antihypertensive agents, bearing the azepino[4, 5-b]indole skeleton, has been synthesized. In view of these findings, we have attempts to incorporate these moieties leading to novel systems by the reaction of 3-aminopyrazolone with 3-(2-oxoethylidene)indole-2-ones (I).

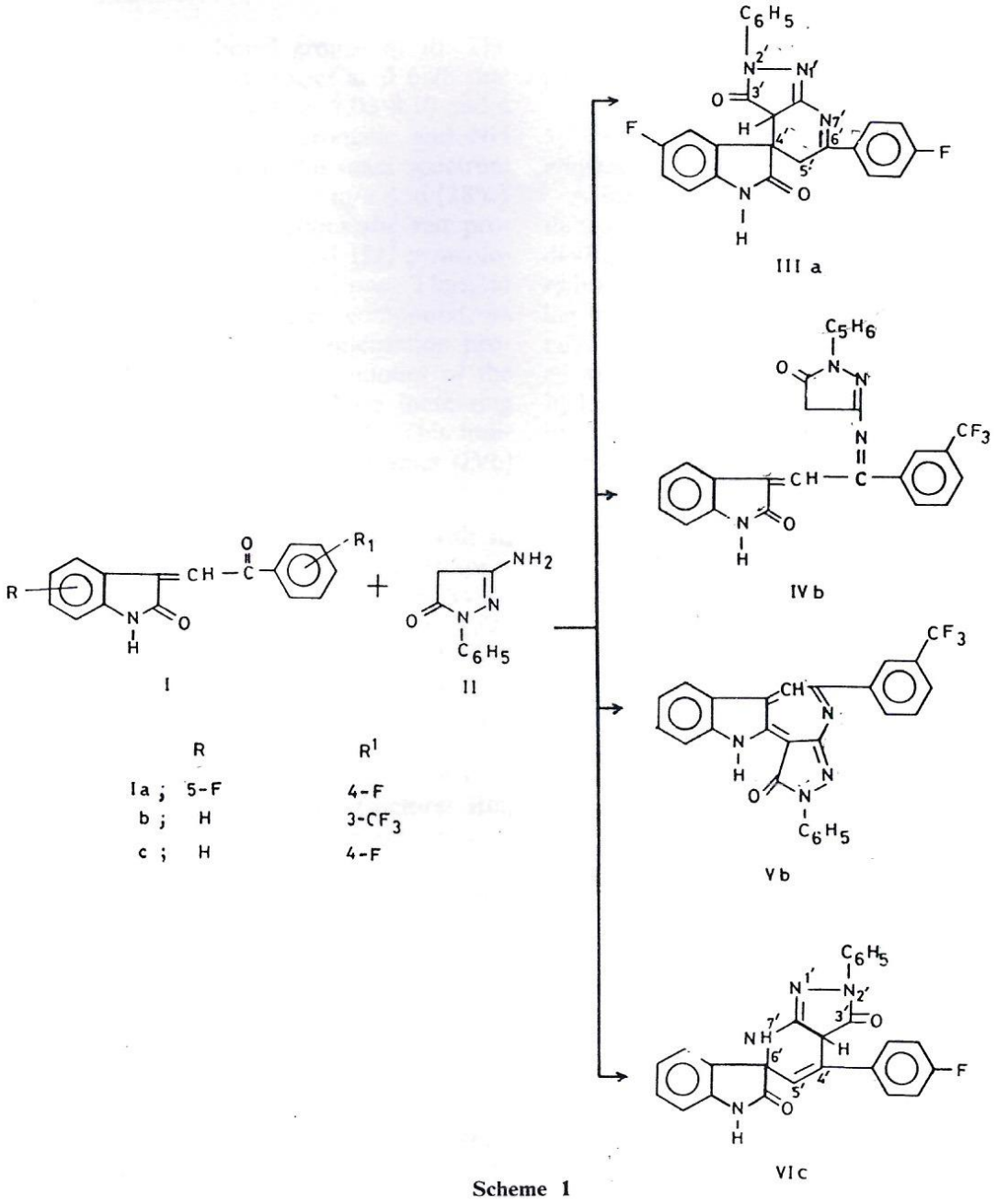
The pyrazolone skeleton reacts with various carbonyl compounds and chalcones leading to a mixture of products[14-16]. Reactions of 3-aminopyrazolone with chalcones have been reported to give pyridopyridine derivatives[17-18]. Its reactions with 3-(2-oxoethylidene)indol-2-ones have not been studied and appeared interesting in view of the fact that the latter can undergo reactions involving either the double bond and lactam carbonyl group or α, β-unsaturated carbonyl group of the side chain or it can undergo condensation involving

both the carbonyl groups[19-20]. We have therefore investigated the title reaction and obtained some interesting results. Besides, we have observed some significant role of the position of fluorine in these reactions leading to the formation of different products (cf. Scheme 1) even though the reaction conditions were similar.

The reaction of 3-(2-oxoethylidene)indol-2-one (Ia) (R=5-F, R′=4-F) with 3-amino-1-phenyl-2-pyrazolin-5-one (II) yielded a light yellow compound after 8hr under reflux. The IR spectrum of this product showed characteristic absorptions at 3420-3200 (NH), 3010-2930 (CH and CH_2), 1720 (CO), 1680 (CO of pyrazolone), 1640 (C=N) and 1590 cm^{-1} (C=N). The PMR spectrum displayed signals at δ 4.01 (dd, CH_2, 2H) and two signals at 5.24 and 5.23 (CH, 1H) due to diastereotropic protons along with the aromatic protons and NH proton at 6.63 – 8.01 (m, 12H) and 9.01 (s, 1H) respectively. On the basis of these spectral studies, it was identified as the spiro compound IIIa. Further support was gathered from its mass spectrum exhibiting the molecular ion peak at m/z 442 along with peaks at m/z 440 (M^+ -2) (2.83%), 351 (M^+ -C_6H_5N) (4.2%), 337 (M^+ -$C_6H_5N_2$) (2.68%), 323 (M^+ -C_7H_5NO) (3.10%), 309 (M^+ -$C_7H_5N_2O$) (5.8%), 297 (M^+ -$C_8H_5N_2O$) (6.3%), 284 (M^+ -$C_9H_6N_2O$) (28%), 256 (M^+ -$C_{11}H_7FN_2$) (28.8%), 163 (M^+ -$C_{16}H_{10}FN_3O$) (20%), 150 (M^+ -$C_{17}H_{11}FN_3O$) (28%), 133 (M^+ -$C_{18}H_{11}F_2N_2O$) (18%), 121 (M^+ -$C_{18}H_{12}FN_3O_2$) (48%) and 91 (M^+ -$C_{19}H_{11}F_2N_3O_2$) (100%).

When the above reaction was carried out with Ib (R=H, R′=3-CF_3), two compounds were obtained after 12hr under reflux. The IR spectrum of the yellow

product showed characteristic absorptions at 3400-3280 (NH), 1710 (CO), 1670 (CO of pyrazolone), 1620 (C=C) and 1590 cm^{-1} (C=N). The PMR spectrum displayed a double doublets for methylene protons at δ 4.43 and a singlet at 6.89 due to the methine proton instead of a singlet at 4.01 and two singlets at 5.24 and 5.23 which were observed in the case of the spiro compound IIIa besides the signals for aromatic and NH protons. Further, the mass spectrum showed the molecular ion peak at m/z 474 (M^+) (5.8%), the base peak at m/z 472 (M^+ -2H) (100%) and other peaks at m/z 353 (M^+ -C_7H_7NO) (6.04%), 339 (M^+ -$C_7H_7N_2O$) (5.6%), 132 (M^+ -$C_{18}H_{11}F_3N_3O$) (13.2%), 119 (M^+ -$C_{19}H_{12}F_3N_3O$) (15.6%), 105 (M^+ -$C_{20}H_{12}F_3N_2O_2$) (12.3%) and 77 (105-N_2) (55%). Although the molecular ion peak also corresponded to the spiro compound IIIa, yet the fragmentation pattern was different. On the basis of these observations, compound IVb was identified as 1, 3-dihydro-3-[2-(3-trifluoromethylphenyl)-2-(1-phenyl-5-oxophyrazol-3-ylimino)ethylidene]indol-(H)-one (IVb).



Scheme 1

The IR spectrum of the red product showed absorptions at 1660 (pyrazolone CO) and 1620 cm^{-1} (C=C) indicating the participation of both the α,β-unsaturated carbonyl groups of Ib. The PMR spectrum displayed a singlet at δ 6.78 due to =CH proton and multiplets at 7.03-8.10 and a broad singlet at 8.99 due to aromatic and NH protons respectively. Further, the mass spectrum showed the molecular ion peak at m/z 456 (28%). On the basis of these observations the red product was identified as 2, 5-diphenyl-11*H*-pyrazolo-[3′, 4′; 2, 3]azepino[4, 5-b]indol-1-(2*H*)-one. Thus, in this reaction, instead of the spiro compound, an imino compound (IVb) and a condensation product (Vb) were obtained and the amount of the imino compound (IVb) decreased on increasing the reaction period as shown by TLC. This indicates the conversion of the imino product (IVb) into Vb.

In the reaction of Ic (R=H, R′=4-F) with II, another red compound was formed. The IR spectrum of this product showed absorptions at 3450-3400 (br, NH), 2990-2856 (CH), 1710 (CO), 1670 (CO of pyrazolone), 1632 (C=N) and 1600 cm^{-1} (C=C). Its PMR spectrum displayed signals at δ 3.82 (s, 1H, CH), 6.69 (s, 1H, =CH), 7.03-8.30 (m, 13H, aromatic protons), 9.57 (s, 1H, NH) and 9.72 (s, 1H, NH). These spectral data are not consistent with any of the structures IIIa, IVb and Vb. Thus, on the basis of above spectral data and considering the earlier proposed structures for the pyrazolopyridine derivatives[16-18], this compound was identified as 2′, 3′,

3′a, 7′-tetrahydro-4′-(4-fluorophenyl) -2′-phenylspiro [indoline-3, 6′[6-*H*] pyrazolo [3, 4-b]pyridine]-2, 3′-dione (VIc). Further support was achieved by the mass spectrum exhibiting the molecular ion peak at m/z 429.

The presence of fluorine and its position were confirmed by ^{19}FNMR. Single fluorine attached to 5-position of the indole ring (IIIa) and 4-position of the phenyl ring (IIIa, IIIc) appeared at δ -115 and -105, respectively. The fluorine atoms of trifluoromethyl group at 3-position of the phenyl ring (IIIb) appeared at δ -132.32.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded in KBr on a Hitachi (270-50) spectrophotometer. PMR and ^{19}FNMR spectra were recorded in TFA and $CDCl_3$ on a Jeol (Fx90Q) instrument at 89.55 MHz and 84.25 MHz respectively using TMS as internal standard for PMR and hexafluorobenzene as external standard for ^{19}FNMR. Mass spectra were recorded on Kratros 30 and 50 mass spectrophotometers at 70 eV. Purity of the compounds was checked by TLC on silica gel plates. 5-Fluoroindole-2, 3-dione and 4-fluoroacetophenone were prepared by literature methods[21-22].

1, 3-Dihydro-3-[2-(2-trifluoromethylphenyl)-2-oxoethtylidene] indol-2(H)-one (Ib)

A mixture of indole-2, 3-dione (0.01 mol), 3-trifluoromethylphenylacetophenne (0.01 mol) and diethylamine (0.3 ml) in 30 ml abs. ethanol was refluxed for 45 min on a steam-bath. After standing for 24hr at room temperature, a white crystalline solid was obtained which was filtered, dried and recrystallized from ethanol to give 1, 3-dihydro-3-hydroxy-3-[2-(3-trifluoromethylphenyl)-2′-oxoethyl]indol-2-(*H*)-one. A solutions of this compound in gl. acetic acid (16 ml) and conc. HCl (5 ml) was further heated for 20 min on a steam bath. A red crystalline solid was obtained, which was recrystallized from ethanol to give Ib, m.p. 192°, yield 80%; IR (KBr); 3210 (NH), 1730 (CO)[19], 1695 (CO), 1620 cm^{-1} (C=C); PMR(TFA+$CDCl_3$): δ 9.01 (s, 1H, NH), 8.02 – 6.62 (m, 8H, aromatic protons), 7.4 (s, 1H, =CH) (Found: C, 64.3; H, 3, 1: N, 4.4. $C_{17}H_{10}F_3NO_2$ requires C, 64.4; H, 3.2; N, 4.4%).

Compounds Ia and Ic have been synthesized earlier[23].

2′, 3′, 3′a, 5′-Tetrahydro-5-fluoro-6′-(4-fluorophenyl)-2′-phenylspiro[indoline-3, 4′-pyrazolo-[3, 4-b]pyridine]-2, 3′-dione (IIIa)

A mixture of 1, 3-dihydro-5-fluoro-3-[2-(4-fluorophenyl)-2-oxoethylidene]indol-2(*H*)-one (Ia) (0.01 mol) and 3-aminopyrazolone (II; 0.01 mol) in abs. ethanol was refluxed for 8hr. The reaction mixture was concentrated and the precipitated solid, obtained after cooling the reaction mixture, was filtered, dried and recrystallized from ethanol to give IIIa, m.p. 175°, yield 70%; PMR(TFA+$CDCl_3$): δ 4.01 (dd,2H,CH_2) 5.24 (s, 1H, CH), 5.23 (s, 1H, OH), 6.63 – 8.01 (m, 12H, Ar-H), 9.01 (s, 1H, NH) (Found: C, 67, 67.8; H, 3.6; N, 12.6. $C_{25}H_{16}F_2N_4O_2$ requires C, 67.9; H, 3.6; N, 12.7%).

1, 3-Dihydro-3-[2-(3-trifluoromethylphenyl)-2-(1-phenyl-3-oxopyrazol-3-ylimino) ethylidene]-indol-2(H)-one (IVb) and 2-phenyl-5-(3-trifluoromethylphenyl)-11H-pyrazolo[3′, 4′: 2, 3]azepino-[4, 5-b]indol-1(2H)-one (Vb)

A mixture of Ib (0.01 mol) and II (0.01 mol) was refluxed for 12hr and kept at room temperature for 12hr when a yellow solid appeared which was filtered, dried and recrystallized with ethanol to give IVb.

The filtrate yielded a red compound which was recrystallized from methanol and identified as Vb.

Compound IVb: m.p. 309°, yield 26%; PMR (TFA+$CDCl_3$): δ 8.99 (s, 1H, NH), 7.92-6.42 (m, 13H, Ar-H), 4.43 (dd, 2H, CH_2), 6.89 (s, 1H, =CH) (Found: C, 65.8; H, 3.5; N, 11.8. $C_{26}H_{17}F_3N_4O_2$ requires C, 65.8; H, 3.6; N, 11.8%).

Compound Vb: m.p. 322° (at 190° it becomes yellow), yield 36%; IR(KBr): 3480 (NH), 2520-2840 (CH), 1660 (CO of pyrazolone), 1610 (C=C), 1590 (C=N): PMR(TFA+$CDCl_3$): δ 8.59 (s, 1H, NH), 7.03-8.10 (m, 13H, Ar-H), 6.78 (s, 1H, =CH) (Found: C, 68.5; H, 3.3; N, 12.3. $C_{26}H_{15}F_3N_4O$ requires C, 68.4; H, 3.3; N, 12.3%).

2′, 3′, 3′a, 7′-Tetrahydro-4′-(4-fluorophenyl)-2′-phenylspiro[indoline-3, 6-[6H] pyrazolo[3, 4-b]-pyridine]-2, 3′-dione (VIc)

An equimolar mixture of 1, 3-dihydro-3-[2-(4-fluorophenyl)-2-oxoethylidene]indol-2(*H*)-one (Ic; 0.01 mol) and II (0.01 mol) in abs. ethanol (30 ml) was refluxed for 10hr. On concentrating the reaction mixture, a red compound was obtained which was recrystallized from ethanol to give VIc, m.p. 340°, yield 65% (Found: C, 70.7; H, 4,1; N, 13.2. $C_{25}H_{17}FN_4O_2$ requires C, 79.8; H, 4.0; N, 13.2%).

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