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# STUDIES IN SPIROHETEROCYCLES : PART XXVIII : INVESTIGATION OF THE REACTION OF 3-AROYLMETHYLENEINDOLIN-2-ONES WITH THIOSEMICARBAZIDE AND SYNTHESIS OF SPIRO[3H-INDOLE-3,4'(3'H)-PYRIMIDIN]-2(1H)-ONES

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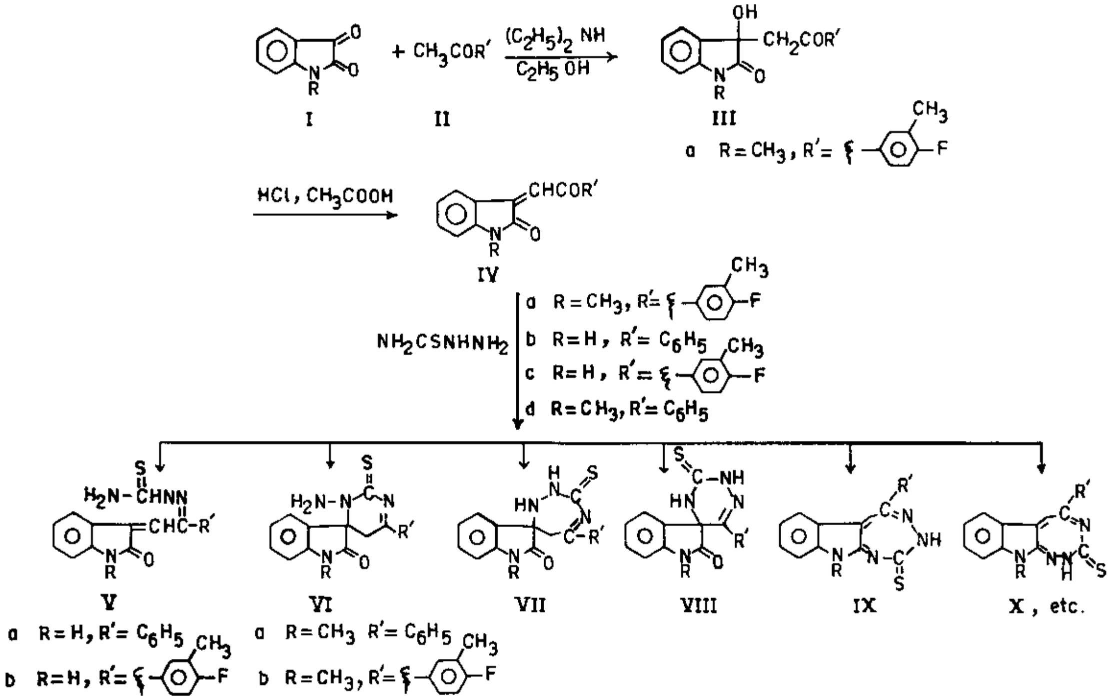
**Abstract** - Simple and N-substituted 3-aroylmethyleneindolin-2-ones (IV) have been obtained by the reaction of indole-2,3-diones with methyl ketones followed by dehydration. The reaction of IV with thiosemicarbazide has been investigated to study the effect of substitution on N atom. Our studies revealed that IV (R=H), on reaction with thiosemicarbazide, afforded exclusively the hydrazone (V) but under exactly similar conditions, N-methyl-3-aroylmethyleneindolin-2-ones (IV; R=$CH_3$) afforded spiro[3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-ones (VI).

Indoline-2,3-dione has been a target of synthetic organic chemists due to its high reactivity.[1] On reaction with acetophenones, it affords 3-hydroxy-3-phenacylindolin-2-ones (III) which on dehydration with HCl and $CH_3COOH$ furnishes 3-aroylmethyleneindolin-2-ones (IV). The latter compounds are highly reactive due to presence of an alkene system flanked by carbonyl groups and besides, the nature of the substituent on the nitrogen atom plays a determining role regarding the product formed.[2,3] The reactions of IV with various compounds having $NH_2$-X-$NH_2$, e.g. hydrazines,[4,5] urea and thiourea,[6] have been recently investigated by us. However, the reaction with thiosemicarbazide has not so far been studied and is the subject of the present report. Theoretically, this reaction offers various possibilities(V-X) depending on the site of the condensation. Our results indicate that IV (R=H) yields, 3-aroyl-2-thiosemicarbazonomethyleneindolinon-2-one(V) but when (R=$CH_3$), instead of V a spiro-[3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-one(VI) is obtained (Scheme I). 1-Methyl-3-(4'-fluoro-3'-methylbenzoyl)methyleneindolin-2-one (IVa) has been prepared by the reaction of N-methylindolin-2,3-dione with methyl 4-fluorophenyl ketone followed by dehydration. The formation of IIIa was confirmed on the basis of ir spectrum where the absorptions at

Scheme I



3400-3300 cm$^{-1}$ due to NH, 3020 cm$^{-1}$ due to OH, and 1680and 1650 cm$^{-1}$ due to carbonyl groups appeared. In the $^{1}$H nmr spectrum it shows singlets at $\delta$10.3 ppm and at $\delta$3.5 ppm due to OH and $CH_2$ respectively. The structure was further confirmed by mass spectrum as the parent ion ($M^{+}$ at m/z 313) corresponded to the molecular weight. The conversion of IIIa to IVa was indicated by the ir spectrum in which the peak due to OH disappeared. In the $^{1}$H nmr spectrum a singlet due to CH appeared at $\delta$6.2 ppm. Further, in the mass spectrum molecular ion ($M^{+}$ at m/z 295) corresponded to the molecular mass. In the product obtained by the reaction of IV with thiosemicarbazide, presence of absorptions due to carbonyl group at 1680 cm$^{-1}$ and NH, $NH_2$ groups at 3300–3190 cm$^{-1}$ in the ir spectrum and broad peaks at $\delta$5.3 ppm due to $NH_2$ and at $\delta$8.7-8.5 ppm due to NH and a singlet at $\delta$ 6.2-6.1 ppm due to CH group in the $^{1}$H nmr spectrum indicated that the compound is hydrazone V and not VI-X. The product obtained by the reaction of IV($R=CH_3$) with thiosemicarbazide showed intense absorption bands in the ir spectrum due to carbonyl group at 1680 cm$^{-1}$ and due to $NH_2$ at 3150 cm$^{-1}$. In the $^{1}$H nmr spectrum, a peak due to $CH_2$ at $\delta$ 2.5 ppm alongwith the multiplet due to aromatic protons at $\delta$ 6.5-7.8 ppm was obtained. These data indicated that the compounds is VI and not V, VII-X.

## EXPERIMENTAL

Melting points were taken in open glass capillaries and are uncorrected. Ir spectra were recorded on Perkin Elmer (Model-577) in KBr pellets ($\nu$max in $cm^{-1}$) and $^1H$ nmr spectra were recorded on Jeol (Model FX-90Q) at 89.55 MHz using TMS as internal reference and $CDCl_3$ as a solvent. Mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer at 70 eV. Purity of all compounds was checked by tlc done on silica gel plates. N-Methylindoline-2,3-dione,[7] 3-hydroxy-3-phenacylindolin-2-ones[8,9] and 3-aroylmethyleneindolin-2-ones[8,9] were prepared by literature methods.

**3-Hydroxy-1-methyl-3-(4'-fluoro-3'-methylbenzoyl)methyleneindolin-2-one IIIa** - A mixture of N-methylindoline-2,3-dione (1.61 g, 0.01 mol), and methyl 4-fluoro-3-methylphenyl ketone (1.52 g, 0.01 mol), diethylamine (2-3 drops) and ethanol (30 ml) was refluxed on a steam bath for 30 min. The reaction mixture was left for 2-3 days at room temperature to give a quantitative (85%) yield of the product which separated as white needles. The compound, thus obtained, was recrystallised from ethanol, mp 175°C, yield 2.66 g (85%) (Anal. Calcd for $C_{18}H_{16}FNO_3$, C, 69.00; H, 5.11; N, 4.47. Found : C, 69.08; H, 5.19; N, 4.51%). $\nu_{max}^{cm^{-1}}$ 3020(OH), 1680, 1650 (both C=O), 1500 ($CH_2$); $^1H$ nmr ($CDCl_3$) : 2.1 (s, 3H, $CH_3$), 3.8 (d, J = 14 Hz, 2H, $CH_2$), 6.5-7.2 (m, 8H, aromatic protons), 10.3 ppm (OH); ms : m/z 313 ($M^+$).

**1-Methyl-3-(4'-fluoro-3'-methylbenzoyl)methyleneindolin-2-one IVa** - A mixture of IIIa (3.13 g, 0.01 mol), conc. HCl (5 ml), and acetic acid (16 ml) was heated on a steam bath for 30 min. Ethanol was then added to the reaction mixture. On cooling, reddish orange needles of IVa crystallised out and were recrystallised from ethanol, mp 106°C, yield 2.65 g (90%). (Anal. Calcd for $C_{18}H_{14}FNO_2$, C, 73.22, H, 4.74; N, 4.74. Found : C, 73.28; H, 4.80; N, 4.80%). $\nu_{max}^{cm^{-1}}$ 1680, 1660 (both C=O); $^1H$ nmr ($CDCl_3$) : 2.2 (s, 3H, $CH_3$), 6.2 (s, 2H, CH), 6.6-7.5 ppm (m, 8H, aromatic protons); ms : m/z 295 ($M^+$).

**3-Benzoylthiosemicarbazonomethyleneindolin-2-one Va** - 3-Benzoylmethyleneindolin-2-one (IVb) (2.49 g, 0.01 mol), thiosemicarbazide (1.0 g, 0.011 mol), $K_2CO_3$ (3.10 g, 0.015 mol), water (20 ml), and ethanol (80 ml) were heated under reflux for 7 h. The reaction mixture was filtered and cooled; the filtrate on acidification with concentrated hydrochloric acid (5 ml) afforded yellow solid which was purified by column chromatography over silica gel eluting with benzene : ethyl acetate (1:1) and recrystallised from ethanol, mp > 300°C, yield 2.44 g (76%). (Anal. Calcd for $C_{17}H_{14}N_4OS$, C, 63.35; H, 4.34; N, 17.39; S, 10.01. Found: C, 63.40;

H, 4.39; N, 17.41; S, 9.93%). $\nu_{max}^{cm^{-1}}$ 3300-3190 (NH, $NH_2$), 1680 (C=O), 1050 (C=S); $^1H$ nmr ($CDCl_3$) : 8.7-8.5 (brs, 2H, NH), 6.5-7.5 (m, 8H, aromatic protons), 6.1 (s, 1H, CH), 5.4 ppm (s, 2H, $NH_2$); ms : m/z 322 ($M^+$).

**3-(4'-Fluoro-3'-methyl)benzoyl-2-thiosemicarbazonomethyleneindolinon-2-one Vb** - This was prepared as described in Va from IVc and thiosemicarbazide, mp 280°C, yield 80%. (Anal. Calcd for $C_{18}H_{15}FN_4OS$, C, 61.01; H, 4.23; N, 15.79; S, 9.03. Found : C, 61.05; H, 4.26; N, 15.81; S, 9.06%). $\nu_{max}^{cm^{-1}}$ 3350-3150 (NH, $NH_2$), 1680 (C=O), 1050 (C=S); $^1H$ nmr ($CDCl_3$) : 8.8-8.5 (brs, 2H, NH), 6.5-7.8 (m, 7H, aromatic protons), 6.2 (s, 1H, CH), 5.6 (s, 2H, $NH_2$), 2.5 ppm (s, 3H, $CH_3$); ms : m/z 354 ($M^+$).

**3'-Amino-2',5'-dihydro-1-methyl-6'-phenyl-2'-thioxospiro[3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-one VIa** - IVd (2.49 g, 0.01 mol), thiosemicarbazide (1.0 g, 0.011 mol), $K_2CO_3$ (3.10 g, 0.015 mol), water (20 ml), and ethanol (80 ml) were heated under reflux for 7 h. The reaction mixture was cooled, filtered and the filtrate on acidification with conc. hydrochloric acid(5 ml) afforded orange-white solid which was purified by recrystallization from ethanol, mp 360°C (decomp.), yield 2.67 g (80%). (Anal. Calcd for $C_{18}H_{16}N_4OS$, C, 64.28; H, 4.74; N, 16.66; S, 9.53. Found : C, 64.31; H, 4.80; N, 16.71; S, 9.57%). $\nu_{max}^{cm^{-1}}$ 3150 ($NH_2$), 1680(C=O), 1070(C=S); $^1H$ nmr ($CDCl_3$) : 2.5 (s, 2H, $CH_2$), 3.5 (s, 3H, $NCH_3$), 5.2 (s, 2H, $NH_2$), 6.8-7.5 ppm (m, 8H, aromatic protons); ms : m/z 336 ($M^+$).

**3'-Amino-2'5'-dihydro-1-methyl-6'(4-fluoro-3-methylphenyl)-2'-thioxospiro[3H-indole-3,4'(3'H)-pyrimidin]-2(1H)-one VIb** - This was prepared in a similar manner as VIa from IVa and thiosemicarbazide, mp 130°C (decomp.), yield 82%. (Anal. Calcd for $C_{19}H_{17}FN_4OS$, C, 62.22; H, 4.62; N, 15.21; S, 8.79. Found : C, 62.26; H, 4.63; N, 15.27; S, 8.81%). $\nu_{max}^{cm^{-1}}$ 3150($NH_2$) 1685 (C=O), 1060 (C=S); $^1H$ nmr ($CDCl_3$): 2.8 (s, 2H, $CH_2$), 2.2 (s, 3H, $CH_3$), 3.6 (s, 3H, $NCH_3$), 5.1 (s, 2H, $NH_2$), 6.8-7.7 ppm (m, 7H, aromatic protons); ms : m/z 368 ($M^+$).

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