# STUDIES IN SPIROHETEROCYCLES: PART X:REACTIONS OF DIAZOMETHANE WITH 3-AROYLMETHYLENE-INDOL-2-ONES AND SYNTHESIS OF SOME NOVEL FLUORINE CONTAINING SPIRO[CYCLOPROPANE-1,3'(3H)INDOL]-2'(1'H)-ONES

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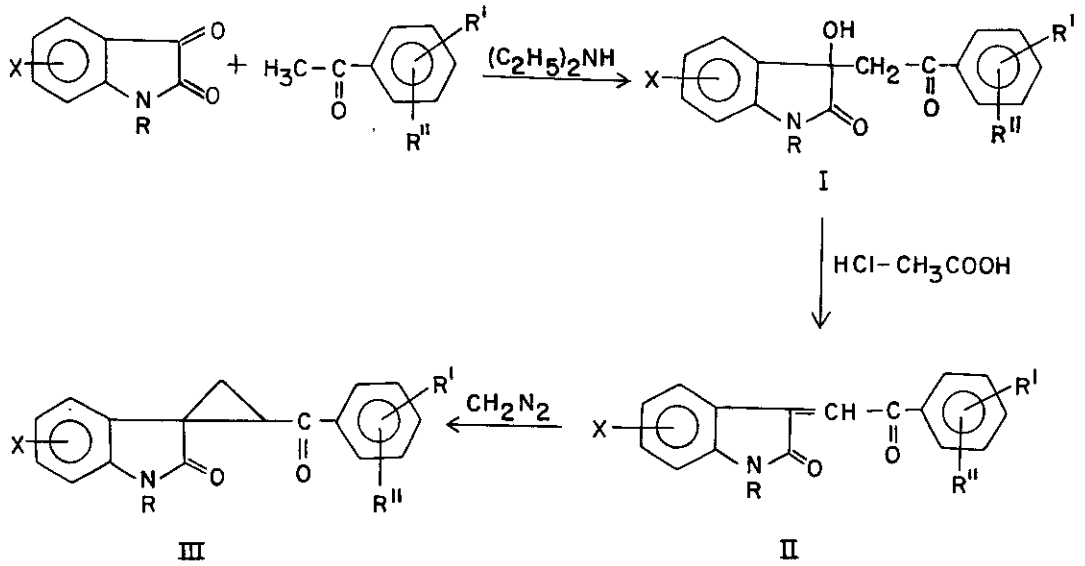
Abstract - Reaction of ethereal diazomethane with fluorinated 3-aroylmethylene-indol-2-ones has been investigated for the first time yielding spiro[cyclopropane-1,3'(3H)indol]-2'(1'H)-ones. The structures of all compounds have been confirmed on the basis of elemental analysis, ir, $^1$H-nmr and mass fragmentation pattern.

The wide spectrum of biological activities associated with indole[1] and the unique structure of isatin makes it an attractive target for synthesizing new spiro systems possessing biological activity. Keeping this in view, we have carried out the reaction of 3-aroylmethylene-indol-2-ones with ethereal diazomethane. A literature survey reports that on addition of diazomethane to 3-alkenyl substituted oxindoles having an acid[2] or ester[3] grouping at the unsaturated carbon atom at C-3, spiropyrrolizines[2,3] are formed. However, when diphenyl diazomethane is added, spirocyclopropanes[3] are obtained. This particular reaction has now been reinvestigated with an acyl group on unsaturated carbon atom at C-3 since this reaction has not been investigated so far and besides, this has an extra reactive site viz $\rangle$C=O of acyl group. Spectral studies indicate that the cycloaddition occurs at $\rangle$C=C$\langle$ bond and since the presence of electron withdrawing carbonyl group at the unsaturated carbon atom makes the $\alpha$-carbon a strong nucleophilic centre, it results in the loss of nitrogen and leads to the formation of spiro[cyclopropane-1,3'(3H)indol]-2'(1'H)-ones instead of spiro[3H-indole-3,3'-pyrazolin]-2-ones as reported earlier. In this investigation,

ethereal diazomethane was treated with 3-aroylmethylene-indol-2-ones(II) at room temperature when spiro[cyclopropane-1,3'(3H)indol]-2'(1'H)-ones(III) were obtained in 60-70% yields. The high yields of the products indicated that cycloaddition reaction occurred only at one unsaturated centre. 3-Aroylmethylene-indol-2-ones(II) were earlier obtained by the dehydration of 3-hydroxy-3-phenacylindol-2-one(I) with HCl-$CH_3COOH$; the latter being prepared by the reaction of indole-2,3-dione with substituted acetophenone in the presence of diethylamine as catalyst (Scheme)

Scheme




X = H, 5-F, 6-F

R = H, $COCH_3$, $CH_2N$⟨⟩

R' = 2-F, 4-F; R"=H, 2-$CH_3$, 3-$CH_3$, 5-$CH_3$, 3-Cl, 3-F

The spiro compounds were characterized by correct elemental analysis, ir, $^1$H-nmr, $^{19}$F-nmr and mass spectra. The ir spectrum showed characteristic absorption bands at 3030-3280 $cm^{-1}$ due to N-H stretching and 1710 $cm^{-1}$ and 1670 $cm^{-1}$ due to two carbonyl groups. This indicates that none of the >C=O groups of 3-aroylmethylene-indol-2-one are involved in this reaction and the cycloaddition

occurs at >C=C< bond. The $^1$H-nmr signals due to >$CH_2$ group appear as two double doublets at δ 2.11 and δ 2.52 ppm indicating a difference in the chemical environment of the two protons. Apart from this, a triplet centred at δ 3.6 ppm due to >CH proton, a singlet at δ 7.7 ppm due to NH proton and a multiplet from δ 6.96 to 7.85 ppm for aromatic protons were also observed. The mass spectrum further supported the formation of 2-(4-fluorobenzoyl)-spiro [cyclopropane-1,3'(3H)indol]-2'(1'H)-one (IIIa) as the parent peak at 281($M^+$) corresponded to the molecular weight. The presence and position of fluorine was confirmed by $^{19}$F-nmr, when fluorine attached to indole ring was observed at -113 to -117 ppm; fluorine attached at 4-position of benzoyl ring at -119 to -120 ppm (IIIa-d,g,h) and at 2-position at -105 to -106 ppm (III e,f).

## EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on Perkin-Elmer (Model-577) in KBr pellets. $^1$H- and $^{19}$F-nmr were recorded on Jeol (Model-FX 90 Q) at 89.5 MHz using TMS as external reference for $^1$H-nmr. $^{19}$F- spectra were taken in $CDCl_3$ at 84.25 MHz using hexafluorobenzene as external reference. Purity of all compounds were checked by tlc on silica gel plates. 5-/6-Fluoroindole-2,3-dione was prepared by literature method[4-6].

3-Hydroxy-3-(4-fluorophenacyl)-indol-2-one (Ia)- Equimolar amount of indole-2,3-dione (0.01 M) and 4-fluoroacetophenone (0.01 M) were refluxed in absolute ethanol (30 ml) in presence of 2-3 drops of diethylamine as catalyst for 30-60 min and then kept at room temperature for 4 days. After filtration and recrystallization with ethanol, the obtained compound (Ia) was checked on tlc as a single spot, yield 1.3 g (65%), mp 165°C. $\nu_{max}^{cm^{-1}}$ : 3200-3380 (N-H and O-H), 1700, 1670 $cm^{-1}$ (both >C=O); $^1$H-nmr ($CDCl_3$): δ 4.2 (broad OH), 5.1 (s,$CH_2$), 6.8 to 8.1 (m, aromatic protons) and 7.8 ppm (s,NH).

3-(4-Fluorobenzoyl)methylene-indol-2-one (IIa) - A mixture of 3-hydroxy-3-(4-fluorophenacyl)-indol-2-one (Ia) (0.01M), conc. HCl (0.5 ml) and glacial acetic acid (10 ml) were heated at 95°C for 15-30 min. After the addition of ethanol (10 ml), the solid compound was filtered and recrystallized from ethanol, yield 2.2 g (80%), mp 187°C. $\nu_{max}^{cm^{-1}}$: 3250 (broad, N-H), 1720, 1690 $cm^{-1}$

Table - I

Physical and Analytical Properties of Spiro [cyclopropane-1,3'(3H)indol]-2'(1'H)-ones(III)*

| S.No. | X | R | R' | R" | Mp (°C) | Yield % | Molecular formula | Nitrogen % Calc. | Found. |
|---|---|---|---|---|---|---|---|---|---|
| a. | H | H | 4-F | H | 197 | 65 | $C_{17}H_{12}FNO_2$ | 4.98 | 4.79 |
| b. | 6-F | H | 4-F | 3-Cl | 148 | 63 | $C_{17}H_{10}F_2ClNO_2$ | 4.19 | 4.17 |
| c. | 5-F | H | 4-F | 3-$CH_3$ | 225 | 68 | $C_{18}H_{13}F_2NO_2$ | 4.47 | 4.45 |
| d. | 5-F | H | 4-F | 2-$CH_3$ | 196 | 68 | $C_{18}H_{13}F_2NO_2$ | 4.47 | 4.42 |
| e. | 5-F | H | 2-F | 5-$CH_3$ | 213 | 60 | $C_{18}H_{13}F_2NO_2$ | 4.47 | 4.44 |
| f. | 5-F | H | 2-F | 3-F | 197 | 64 | $C_{17}H_{10}F_3NO_2$ | 4.41 | 4.40 |
| g. | 5-F | $COCH_3$ | 4-F | H | 158 | 63 | $C_{19}H_{13}F_2NO_3$ | 4.10 | 4.08 |
| h. | 5-F | $CH_2N$⬡ | 4-F | 2-$CH_3$ | 181 | 68 | $C_{24}H_{24}F_2N_2O_2$ | 6.82 | 6.80 |

* The substituents and S.No. are the same for compounds I and II also.

(both >C=O), $^1$H-nmr ($CDCl_3$): δ 5.3 (s,CH), 6.7 to 8.3 (m, aromatic protons), 7.8 ppm (s,NH).

2-(4-Fluorobenzoyl)-spiro [cyclopropane-1,3' (3H) indol]-2'(1'H)-one (IIIa) - Ethereal solution of diazomethane was added in two portions to a suspension of 3-(4-fluorobenzoyl)methylene-indol-2-one(IIa) (2 g) in ether. The reaction mixture was then stirred at room temperature for 3 h. The excess ether was distilled off giving a sticky compound, which was purified by column chromatography on silica gel. Elution was carried out using solvents of increasing polarity, the white compound from benzene - ethyl acetate (4:1) fraction was collected and recrystallized from benzene - ethyl acetate mixture, yield 1.3 g (65%), mp 197°C (Found:C, 72.38; H,4.22; N,4.78. $C_{17}H_{12}FNO_2$ requires C, 72.59; H, 4.27; N, 4.98%). $\nu_{max}^{cm^{-1}}$ : 3280-3030 (broad, N-H), 1700, 1670 $cm^{-1}$ (both >C=O); $^1$H-nmr ($CDCl_3$); δ 2.11, 2.52 (dd, $CH_2$), 3.6 (t,CH), 6.96 to 7.85 (m, aromatic protons) and 7.7 ppm (s,NH). MS m/z 281 ($M^+$). All other compounds given in table-I (IIIb-h) were prepared in a similar manner.

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