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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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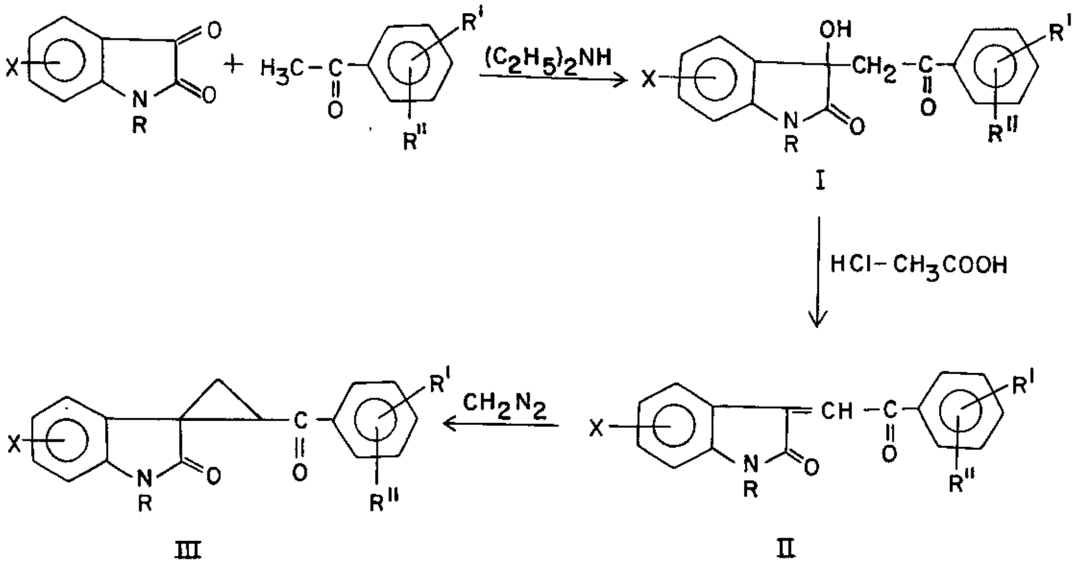
Abstract - Reaction of ethereal diazomethane with fluorinated 3-aroylmethylene-indol-2-ones has been investigated for the first time yielding spiro[cyclopropane-1,3'(3H)indol]-2'(1'H)-ones. The structures of all compounds have been confirmed on the basis of elemental analysis, ir, ^{1}H-nmr and mass 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 $>C=O$ of acyl group. Spectral studies indicate that the cycloaddition occurs at $>C=C<$ bond and since the presence of electron withdrawing carbonyl group at the unsaturated carbon atom makes the α-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



$X = H, 5\text{-}F, 6\text{-}F$

$R = H, COCH_3, CH_2N$ 

$R' = 2\text{-}F, 4\text{-}F;\ R'' = H, 2\text{-}CH_3, 3\text{-}CH_3, 5\text{-}CH_3, 3\text{-}Cl, 3\text{-}F$

The spiro compounds were characterized by correct elemental analysis, ir, ^1H-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 $\geq$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.	Nitrogen % 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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