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A CONVENIENT SYNTHESIS AND REACTIONS OF SPIRO [3H-INDOLE-3,2'-THIAZOLIDINE] -2,4'(1H)-DIONES

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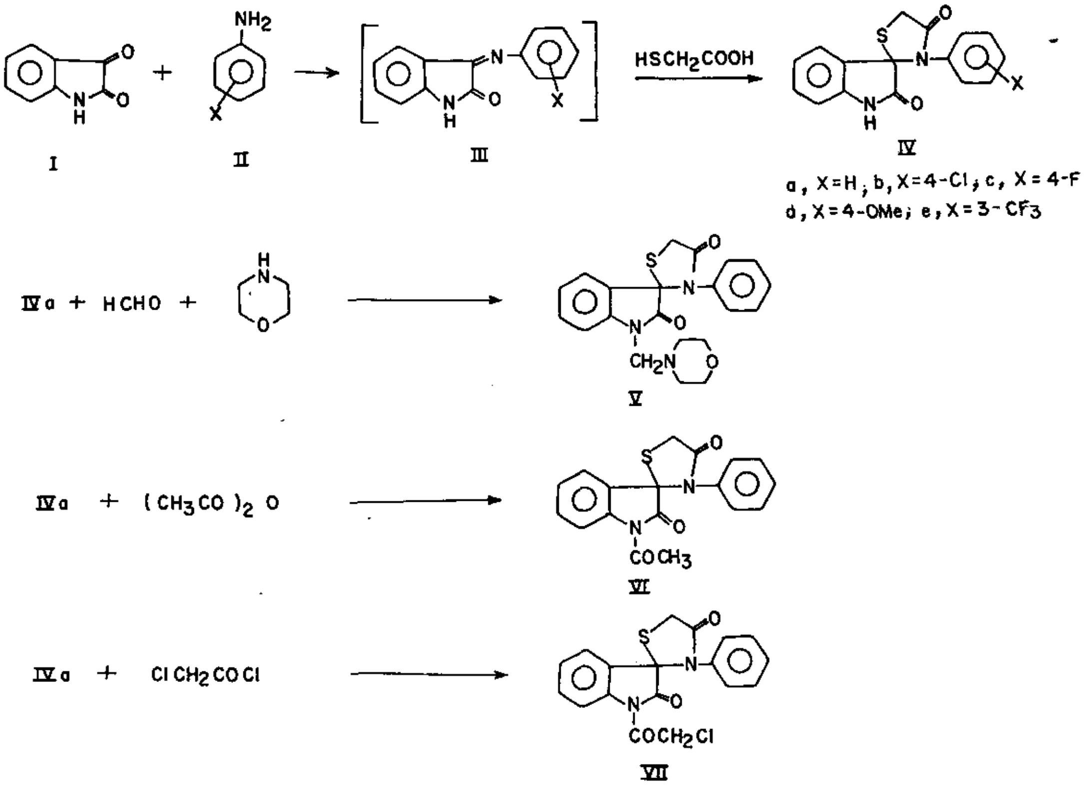
Abstract - Spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones have been obtained by the condensation of indole-2,3-dione, aromatic amine and mercaptoacetic acid without isolating the intermediates i.e., isatin-3-anils. The spiro compounds have further been subjected to Mannich reaction, acetylation and chloracetylation. All the synthesized compounds have been characterized on the basis of elemental analyses and ir and pmr.

A systematic investigation of spiro[3H-indole-3-2'-thiazolidine]-2,4'(1H)-diones appeared to be of interest due to (i) broad spectrum of biological activities[1-5] (ii) presence of different reaction sites ($>C=O$, $>NH$ and $>CH_2$) and (iii) non-availability of spectral data. Further, there are only two references in the literature for the synthesis of such compounds one of which is a patent[6] and the other does not report the yields[7]. The methods involve the preparation of isatin-3-anils by the condensation of isatin and aniline followed by the cyclization of these anils with mercaptoacetic acid in benzene/ethanol. We, therefore, reexamined the synthetic details reported earlier and now report a convenient synthesis of spiro compounds (IV), without isolating the intermediates i.e., isatin-3-anils (III) and also some of their reactions. The condensation of indole-2,3-dione, with aromatic amines in toluene, afforded isatin-3-anils, which, in situ, were cyclized with mercaptoacetic acid to give spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones (IVa-e) in 40-65 % yields. These yields are much better in comparison to those reported by previous workers. The compounds were characterized by ir absorption bands at 1670-1730 cm^{-1} ($>C=O$), 3250-3300 cm^{-1} ($>NH$) and pmr signals at δ 10.5-10.8 (NH), 3.9-4.1 (CH_2) and 6.5-7.5 ppm (aromatic protons).

SCHEME-I



Further, Mannich reaction of 3'-phenyl-spiro-[3H-indole-3,2'-thiazolidine]-2,4'(1H)-dione was investigated. The spiro compound was refluxed with formaldehyde solution (40%) and morpholine in molar ratio using absolute ethanol as the condensation medium for 10 hr. Although there are two reaction sites, one being NH and another the active methylene group of thiazolidine ring but the compound was identified as 1-morpholinomethyl-3'-phenylspiro[3H-indole-3,2'-thiazolindine]-2,4'-dione by the disappearance of NH absorption in ir and pmr spectra. The resonance signal of CH$_2$ protons at δ 3.9 ppm remained as such. The title spiro compound (IVa) was also subjected to acetylation and chloracetylation by refluxing with acetic anhydride and chloroacetyl chloride, respectively. In such cases also, the reaction may occur at both places (NH and CH$_2$), but the compounds obtained have been identified only as N-substituted on the basis of ir and pmr. The physical and spectral properties are given in Table-1.

Experimental Procedure - All melting points are uncorrected. Ir spectra were recorded on Perkin-Elmer (model-557) in KBr pellets and nmr spectra were recorded on Perkin-Elmer (model-R.B.12) at 60 MH_z using TMS as external reference. The purity of all compounds was checked by tlc done on silica gel plates.

3'-Phenyl-spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)dione (IVa) - A mixture of indole-2,3-dione (0.01mole) and an appropriate aromatic amine (0.01 mole) was refluxed in toluene for 2 hr and theoretical amount of water was collected azeotropically. On cooling the mixture, mercaptoacetic acid (0.011 mole) was added and refluxed again for 3 hr under the same conditions. Thereafter, the whole was allowed to cool at room temperature and the supernatent liquid decanted off. The solid obtained, on recrystallization from ethanol, afforded the pure compound.

Compound Nos. IVb-e were also prepared in a similar way.

1-Morpholinomethyl-3'-phenyl-spiro[3H-indole-3,2'-thiazolidine]-2,4'-dione(V) - A mixture of compound IVa (0.01 mole), formaldehyde solution (0.012 mole, 40 %) and morpholine (0.01 mole) was refluxed in absolute ethanol for 10 hr. On cooling, white flakes of the desired compound were obtained. It was filtered and recrystallized from ethanol.

1-Acetyl-3'-phenyl spiro [3H-indole-3,2'-thiazolidine]-2,4'-dione (VI) - Compound IVa (0.01 mole) was refluxed for 6 hr with acetic anhydride (25 ml) and on cooling the mixture, the desired compound was obtained which was purified by recrystallization from ethanol.

1-Chloroacetyl-3'-phenyl-spiro [3H-indole-3,2'-thiazolidine]-2,4'-dione (VII) - A mixture of IVa (0.01 mole) and chloracetyl chloride (25 ml) was refluxed for 6 hr. On cooling, crystals separated out which were purified from ethanol.

All the synthesized compounds, alongwith their yields, physical data and spectral characteristics are recorded in Table-1.

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Table-1 : Physical and Spectral Properties of Spiro Compounds*

Compound No.	Yield %	mp °C	Spectral Data
IVa	53.90	235	Ir ν_{max} cm^{-1} 1670 and 1720 (C=O), 3280(NH); pmr (DMSO) δ 3.9(CH$_2$), 10.5(NH), 6.5-7.4 (aromatic).
IVb	51.17	192	Ir ν_{max} cm^{-1} 1670 and 1725 (C=O), 3300(NH); pmr (DMSO) δ 4.1 (CH$_2$), 10.7 (NH), 6.5-7.4 (aromatic).
IVc	64.70	245	Ir ν_{max} cm^{-1} 1680 and 1730 (C=O), 3250 (NH); pmr (DMSO) δ 4.1 (CH$_2$), 10.8 (NH), 6.5-7.5 (aromatic).
IVd	41.07	210	IR ν_{max} cm^{-1} 1680 and 1725 (C=O), 3260 (NH).
IVe	40.10	200	Ir ν_{max} cm^{-1} 1670 and 1730 (C=O), 3270 (NH); pmr (DMSO) δ 4.0 (CH$_2$), 10.8 (NH), 6.6-7.4 (aromatic).
V	78.9	201	Ir ν_{max} cm^{-1} 1630 and 1720 (C=O); pmr (DMSO) δ 3.4-3.9 (CH$_2$ of morpholine & thiazolidone ring) 4.7 (N-CH$_2$-N), 6.5-6.9 (aromatic).
VI	84.8	231	Ir ν_{max} cm^{-1} 1680, 1720 and 1760 (C=O), pmr (DMSO) δ 2.6 (COCH$_3$), 4.1 (CH$_2$), 6.9-8.0 (aromatic).
VII	86.5	193	Ir ν_{max} cm^{-1} 1690, 1730 and 1760 (C=O), pmr (DMSO) δ 4.1 (CH$_2$), 5.05 (COCH$_2$Cl), 7.0-8.0 (aromatic).

* Satisfactory elemental analyses were obtained in all cases.

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