Facile Synthesis of Some Novel Spiro[indole-3,4′-dipyrrolopyran] Derivatives

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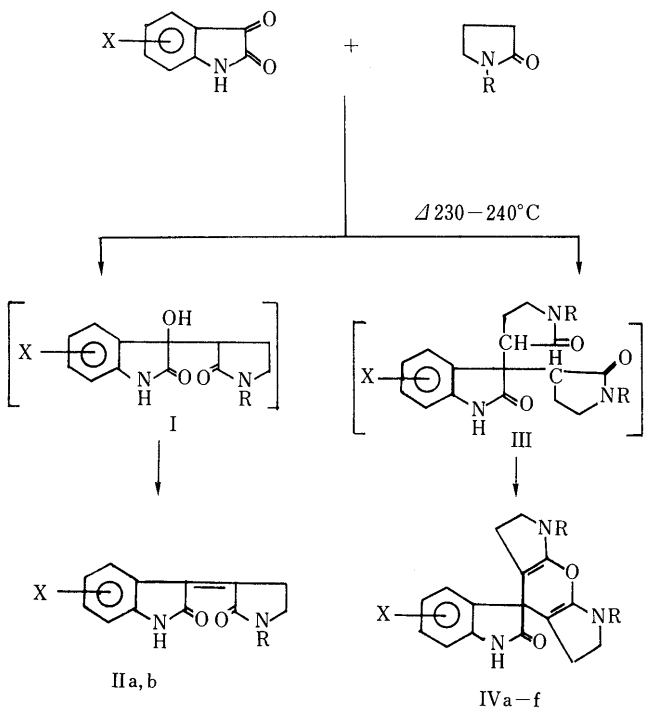
A facile synthesis of novel spiroindole derivatives, spiro[3*H*-indole-3,4′-2′,3′,4′,5′,6′,7′-hexahydro-1*H*-pyrano-[2,3-*b*: 6,5-*b*′]dipyrrole]-2(1*H*)-ones (IV), together with 2,3-dihydro-3-(2,3,4,5-tetrahydro-2-oxo-1*H*-pyrrole-3-ylidene)-1*H*-indol-2-ones (II), was achieved by dry heating of substituted indole-2,3-diones with 2-pyrrolidinone or *N*-methyl-2-pyrrolidinone.

Keywords indole-2,3-dione; 2-pyrrolidinone; spiroindole; 3-(pyrrol-3-ylidene)indole

In pursuing our interest in the synthesis of new heterocycles incorporating spiro indolines[1-5] and indole derivatives[6-9] for pharmacological evaluation, we now wish to report the synthesis of a novel ring system, spiro[3*H*-indole-3,4′-2′,3′,4′,5′,6′,7′-hexahydro-1*H*-pyrano[2,3-*b*: 6,5-*b*′]dipyrrole]-2(1*H*)-one.

The medicinal application of spiro(indole-pyrans) as muscle relaxants and antiinflammatory agents is well known.[10,11] The reaction of 2-pyrrolidinone and *N*-methyl-2-pyrrolidinone with cyclohexanones, benzophenone, aldehydes, cyclohexanedione, α, β-unsaturated aldehydes *etc.* affords a variety of products depending upon reaction conditions.[12-19] Reaction products with cyclohexanones, benzophenones and aldehydes have found application as analgesic, antidiarrhoeal and anti-inflammatory agents.[12-15] The reaction of indole-2,3-dione derivatives with active methylene compounds, also leads to the formation of a variety of products,[20-24] and the reaction with pyrrolidinone appears to be interesting in view of the different reaction sites available in indole-2,3-dione and pyrrolidinone (Chart 1). We examined this reaction in several reaction media, *viz.* weakly acidic (ethanol + acetic acid), more strongly acidic (sulfuric acid + hydrochloric acid) and weakly and strongly basic media (ethanol + diethylamine and ethanol + pyridine) but no significant results were observed. Positive results were only obtained when the reactants in 1 : 2 molar ratio were heated at 230—240 °C, without any solvent or catalyst, producing spiro compounds exclusively in 70—80% yields. An additional compound (II) was also obtained when the reaction was run with the reactants in 1 : 1 molar ratio. In both cases, in addition to the spiro compound, an intractable mixture was obtained which could not be purified or converted into identifiable products. During the present investigation the title reaction led to the formation of II and IV only. It appears that I and III are converted into II and IV, respectively, by dehydration/enolization followed by dehydration during the course of the reaction.

Characterization of all the products (II and IV) was done on the basis of their spectral data. The IR spectrum of compound (IIa) displayed characteristic absorptions in the region of 3300—3120 (N–H), 2880 (CH_2), 1700, 1680



a : X=H ; R=H
b : X=H ; R=CH_3
c : X=5-Cl ; R=H
d : X=5-Cl ; R=CH_3
e : X=5-CH_3 ; R=H
f : X=5-CH_3 ; R=CH_3

Chart 1

TABLE I. Analytical and Physical Data

Compound[a]	X	R	Yield (%)	Molecular formula	Nitrogen %	
					Found	Calcd
IIa	H	H	10	$C_{12}H_{10}N_2O_2$	13.15	13.08
IId	5-Cl	CH_3	8	$C_{13}H_{11}ClN_2O_2$	10.34	10.68
IVa	H	H	80	$C_{16}H_{15}N_3O_2$	14.60	14.94
IVb	H	CH_3	74	$C_{18}H_{19}N_3O_2$	13.80	13.59
IVc	5-Cl	H	75	$C_{16}H_{14}ClN_3O_2$	13.64	13.33
IVd	5-Cl	CH_3	76	$C_{18}H_{18}ClN_3O_2$	12.15	12.24
IVe	5-CH_3	H	78	$C_{17}H_{17}N_3O_2$	14.60	14.23
IVf	5-CH_3	CH_3	80	$C_{19}H_{21}N_2O_2$	13.15	13.00

a) The melting points of all compounds were above 360 °C.

Table II. IR and ^{1}H-NMR Spectral Data

Compound	IR (cm^{-1})	^{1}H-NMR δ (ppm)					
		CH_2	N-CH_2	N-CH_3	Ar-H	NH	NH
IIa	3300—3120, 2880, 1700, 1680, 1610, 1380, 1280, 1255, 1150, 750	2.72 (t)	3.26 (t)	—	7.16—7.90 (m)	8.02 (s)	8.30 (s)
IId	3300—3150, 2985, 2880, 1710, 1670, 1600, 1375, 1270, 1250, 1140, 740	2.72 (t)	3.24 (t)	4.08 (s)	7.16—8.17 (m)	—	8.30 (s)
IVa	3300—3100, 2880, 1700, 1590, 1430, 1370, 1320, 1260, 1180, 775	2.74 (m)	3.28 (m)	—	7.16—7.57 (m)	7.90 (s)	8.57 (s)
IVb	3400—3200, 2920, 1710, 1600, 1470, 1340, 1310, 1270, 1190, 760	2.74 (m)	3.26 (m)	3.92 (s)	7.14—7.60 (m)	—	8.54 (s)
IVc	3320—3100, 2900, 1710, 1610, 1460, 1360, 1300, 1265, 1180, 750	2.73 (m)	3.28 (m)	—	7.16—7.60 (m)	7.92 (s)	8.57 (s)
IVd	3350—3120, 2900, 1700, 1615, 1450, 1350, 1310, 1275, 1190, 765	2.74 (m)	3.26 (m)	3.90 (s)	7.14—7.62 (m)	—	8.50 (s)
IVe	3350—3120, 2890, 1700, 1590, 1475, 1360, 1320, 1265, 1185, 755	2.73 (m)	3.26 (m)	—	7.14—7.60 (m)	7.90 (s)	8.54 (s)
IVf	3400—3120, 2900, 1700, 1585, 1470, 1350, 1310, 1260, 1180, 760	2.74 (m)	3.26 (m)	3.92 (s)	7.14—7.60 (m)	—	8.53 (s)

(both C=O) and 1610 (C=C) cm^{-1}. The ^{1}H-NMR spectrum showed a pair of triplets (J=6 Hz each) at δ 2.72 ($C\underline{H}_2$–C=) and 3.26 (N–CH_2) ppm. The presence of conjugated carbonyl absorptions, and the absence of –OH stretchings and ether linkage in the IR spectrum ruled out the possibility of formation of IV, I or III. The geometry of both pyrrolidinone moieties in compound II is probably *cis*.

The IR spectrum of compound (IVa) showed characteristic absorption bands at 3300—3100 (N–H), 2880 (CH_2) and 1700 (C=O) cm^{-1}. The presence of the pyran ether linkage was confirmed by the appearance of a band in the region of 1180 cm^{-1}. The ^{1}H-NMR spectrum displayed a pair of multiplets at δ 2.74 ($C\underline{H}_2$–CH_2, 4H) and at 3.28 ppm (N–$C\underline{H}_2$, 4H) due to the pyrrole rings of the dipyrrolo-pyran system, indicating an identical environment of both pyrrole rings. The presence of only one carbonyl absorption and pyran ether linkage absorption in the IR spectrum indicated the formation of IV. Further, in the mass spectra of IIa and IVa, weak molecular ion peaks were observed at m/z 214 and 281 corresponding to the molecular formulae $C_{12}H_{10}N_2O_2$ and $C_{16}H_{15}N_3O_2$, respectively.

Experimental

Melting points were determined on a Toshiniwal melting point apparatus, (capillary method) without correction. The purity of the synthesized compounds was assured by thin layer chromatography on silica gel in various nonaqueous solvents. IR spectra were recorded in KBr on a Perkin–Elmer 577 grating spectrophotometer (ν max in cm^{-1}), ^{1}H-NMR spectra in $CDCl_3$ and trifluoroacetic acid on a JEOL FX 90Q (89.55 MHz) using tetramethylsilane as an internal standard (chemical shifts in δ ppm) and mass spectra were recorded on Kratz 30 and 50 mass spectrometers at 70 eV.

Reaction of Indole-2,3-dione and 2-Pyrrolidinone Spiro[3*H*-indole-3,4′-2′,3′,4′,5′,6′,7′-hexahydro-1*H*-pyrano[2,3-*b*: 6,5-*b*′]dipyrrole]-2(1*H*)-one (IVa): A mixture of indole-2,3-dione (0.01 mol) and 2-pyrrolidinone (0.02 mol) was heated at 230—240 °C in an oil bath for 5—6 h. The progress of the reaction was checked by TLC. The reaction mass was discoloured and hardened. The crude product was treated with hot acetic acid and filtered. The dark brown-colored compound, obtained from the acetic acid-soluble portion, was identified as IVa, and purified and recrystallized from acetic acid (yield 2.24 g, 80%).

Synthesis of 2,3-Dihydro-3-[2,3,4,5-tetrahydro-2-oxo-1*H*-pyrrole-3-ylidene]-1*H*-indol-2-one (IIa) and (IVa): When the reaction of indole-2,3-dione and 2-pyrrolidinone was run at 1 : 1 molar ratio, a crude product was obtained, which displayed many spots on TLC. Absolute ethanol was added to the crude mixture, and the brown-colored compound obtained from the ethanol-soluble portion was referred to as IIa. The ethanol-insoluble portion on crystallization from glacial acetic acid, gave another compound, identified as the spiro product IVa (yield 2.02 g, 72%), on the basis of mixed melting point determination and spectral comparisons with the same compound prepared by the above method with the reactants in 1 : 2 molar ratio.

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