Studies in Spiroheterocycles, Part XV. Investigation of the Reaction of 3-(2-Oxocycloalkylidene)-indol-2-ones with Thiourea and Urea Derivatives

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The reaction of 3-(2-oxocycloalkylidene)indol-2-one **1** with thiourea and urea derivatives has been investigated. Reaction of **1** with thiourea and urea in ethanolic potassium hydroxide media leads to the formation of spiro-2-indolinones **2a-f** in 40-50% yield and a novel tetracyclic ring system 4,5-cycloalkyl-1,3-diazepino-[4,5-*b*]indole-2-thione/one **3a-f** in 30-35% yield. 3-(2-Oxocyclopentylidene)indol-2-one afforded 5',6'-cyclopenta-2'-thioxo/oxospiro[3*H*-indole-3,4'(3'*H*)pyrimidin]-2(1*H*)-ones **2a,b** and 3-(2-oxocyclohexylidene)indol-2-one gave 2',4'a,5',6',7',8'-hexahydro-2'-thioxo/oxospiro[3*H*-indole-3,4'(3'*H*)-quinazolin]-2(1*H*)-ones **2c-f**. Under exactly similar conditions, reaction of **1** with fluorinated phenylthiourea/cyclohexylthiourea/phenylurea gave exclusively spiro products **2g-l** in 60-75% yield. The products have been characterized by elemental analyses, ir pmr. ^{19}F nmr and mass spectral studies.

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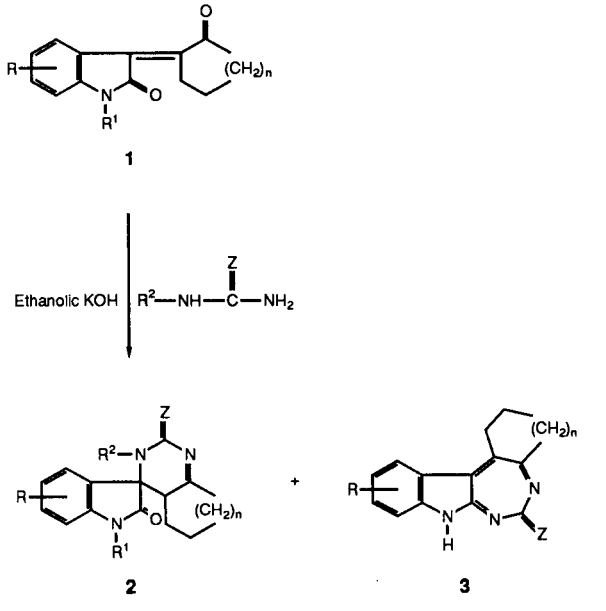
In continuation to our earlier studies on synthesis of indole derivatives [1-3] and spiroindolines [4-7], we have now investigated the reaction of fluorine containing 3-(2-oxocycloalkylidene)indol-2-one with thiourea/urea derivatives for the first time leading to the synthesis of various 3-spiroheterocyclic compounds of the 2-indoline skeleton **2a-l** and novel condensed tetracyclic indole derivatives **3a-f**.

Along with indole derivatives [8], a wide variety of biological activities are also exhibited by pyrimidine and quinazoline systems [9,10] but the chemistry and biological activity of fluorine containing spiro quinazoline/pyrimidine indolines have not been studied so far. Besides, the cycloaddition reactions of 3-(2-oxocycloalkylidene)indol-2-one seem to be quite interesting because in addition to α,β-unsaturated carbonyl system in the side chain, another carbonyl group can also interact. This type of possibility in the reactions of these oxoindolidenes with various amino derivatives [11,12] has not been studied so far although such reactions with various enamines have been studied [13].

In the present study, the reactions of various thiourea/urea derivatives *viz.* phenylthiourea, cyclohexylthiourea, phenylurea, thiourea and urea with fluorine containing 3-(2-oxocyclopentylidene)indol-2-ones and 3-(2-oxocyclohexylidene)indol-2-ones have been investigated in ethanolic potassium hydroxide media for the first time (Scheme 1).

Scheme 1



Reaction of thiourea/urea with **1** gave the novel tetracyclic ring system cyclopenta[4,5][1,3]diazepino[7,6-*b*]indole-5-thiones(ones) **3** (n = 1) and the known [14] 1,2,3,4,-6,8-hexahydroindolo[2,3-*d*][1,3]benzodiazepine-6-thiones-(ones) **3** (n = 2) in 30-35% yields in addition to the expected spiro-2-indolinones **2** in 40-45% yield. While a literature survey reveals the formation of only a spiro product by the reaction of 3-(2-oxocyclohexylidene)indol-2-one with thiourea [11] and no attention has been paid to the reaction of urea and thiourea derivatives, it may be pointed out here that although a number of diazepinoindoles [15], are reported yet this particular system with fusion at the 4,5-position is not mentioned in the literature. Further, it was observed that an analogous reaction with fluorinated phenylthiourea/cyclohexylthiourea or phenylurea gave exclusively spiro products **2g-l** in 60-75% yield. Structureal assignment to the products formed is based on elemental analyses and spectral studies (ir, pmr, ^{19}F nmr and mass).

3-(2-Oxocycloalkylidene)indol-2-one derivatives **1** are synthesized by the Knoevengel reaction of indole-2,3-

Table I

Analytical Data of Spiro[3*H*-indole-3,4′(3′*H*)-pyrimidin]-2*H*(1*H*)-ones **2a-b** and Spiro[3*H*-indole-3,4′(3′*H*)-quinazolin]-2(1*H*)one **2c-l**

Compound	R	R¹	R²	Z	n	Yield %	MP °C	Formula	Analysis % Calcd./(Found) C	H	N	S
2a	5-F	H	H	S	1	50	>360	$C_{14}H_{12}FN_3OS$	58.13 (58.19)	4.15 (4.23)	14.15 (14.09)	11.07 (11.00)
2b	5-F	H	H	O	1	45	>360	$C_{14}H_{12}FN_3O_2$	61.53 (61.52)	4.39 (4.40)	15.38 (15.31)	— —
2c	5-F	H	H	S	2	45	>360	$C_{15}H_{14}FN_3OS$	59.40 (59.39)	4.62 (4.61)	13.82 (13.76)	10.36 (10.44)
2d	5-F	H	H	O	2	40	>360	$C_{15}H_{14}FN_3O_2$	62.71 (62.74)	4.87 (4.80)	14.63 (14.53)	— —
2e	4-CF_3	H	H	S	2	50	>360	$C_{16}H_{14}F_3N_3OS$	54.39 (54.31)	3.96 (3.89)	11.89 (11.90)	9.06 (9.13)
2f	4-CF_3	H	H	O	2	48	>360	$C_{16}H_{14}F_3N_3O_2$	56.97 (56.89)	4.15 (4.13)	12.46 (12.39)	— —
2g	H	H	4-FC_6H_4	S	2	68	>360	$C_{21}H_{16}FN_3OS$	66.49 (66.39)	4.74 (4.69)	11.08 (11.12)	8.44 (8.38)
2h	H	CH_3	4-FC_6H_4	S	2	75	>360	$C_{22}H_{20}FN_3OS$	67.17 (67.26)	5.08 (5.12)	10.68 (10.70)	8.14 (8.08)
2i	H	$COCH_3$	4-FC_6H_4	S	2	70	>360	$C_{23}H_{20}FN_3OS$	68.14 (68.22)	4.93 (4.91)	10.37 (10.31)	7.90 (7.82)
2j	5-F	H	4-FC_6H_4	O	2	60	>360	$C_{21}H_{17}F_2N_3O_2$	66.14 (66.12)	4.46 (4.49)	11.02 (11.12)	— —
2k	5-F	H	C_6H_5	O	2	64	>360	$C_{21}H_{18}FN_3O_2$	69.42 (69.40)	4.95 (4.90)	11.57 (11.60)	— —
2l	5-F	H	C_6H_{11}	S	2	60	>360	$C_{21}H_{24}FN_3OS$	65.45 (65.38)	6.23 (6.20)	10.90 (10.85)	8.31 (8.23)

Table II

Analytical Data of 4,5-Cyclopentyl/cyclohexyl-1,3-diazepino[4,5-*b*]indole-2-thione/one

Compound	R	n	Z	Yield	MP °C	Formula	Analysis % Calcd./(Found) C	H	N	S
3a	5-F	1	S	30	165	$C_{14}H_{10}FN_3S$	61.99 (61.90)	3.69 (3.70)	15.49 (15.35)	11.80 (11.76)
3b	5-F	1	O	35	148	$C_{14}H_{10}FN_3O$	65.88 (65.80)	3.92 (3.85)	16.47 (16.38)	— —
3c	5-F	2	S	30	165	$C_{15}H_{12}FN_3S$	63.15 (63.23)	4.21 (4.28)	14.73 (14.68)	11.22 (11.30)
3d	5-F	2	O	35	196	$C_{15}H_{12}FN_3O$	66.91 (66.95)	4.46 (4.49)	15.61 (15.68)	— —
3e	4-CF_3	2	S	35	186	$C_{16}H_{12}F_3N_3S$	57.31 (57.40)	3.58 (3.62)	12.53 (12.62)	9.55 (9.62)
3f	4-CF_3	2	O	35	135	$C_{16}H_{12}F_3N_3S$	60.18 60.22	3.76 3.70	13.16 13.23	— —

dione and cyclopentanone/cyclohexanone in the presence of diethylamine as catalyst followed by dehydration in the presence of hydrochloric acid-acetic acid [16]. Reaction of **1** with thiourea in ethanolic potassium hydroxide for 24 hours afforded two products and one of them separated as a brownish black substance **2** on keeping the reaction mixture at room temperature. It shows characteristic ir absorptions at 3130-3300 (>NH), 1700 (—NH*CO*), 1590

(>C=N) and 1230 cm^{-1} (>C=S).

Disappearance of the exocyclic C=C at 1620, >C=O absorptions at 1685 cm^{-1} and retention of -NHCO peak at 1700 cm^{-1} indicated the participation of α,β-unsaturated carbonyl system resulting in the formation of spiro heterocycles at position 3 of 2-indolinone [12,13]. The structure assigned to the spiro compound **2** is corroborated by pmr and mass spectra also. The pmr spectra showed a double doublet at δ 4.34 ppm for the methine proton. The protons of the cycloalkyl ring were obtained in the form of three clusters, *viz.*, a triplet at δ 3.38 (2H, -N=C-CH_2), multiplet at 2.34-2.92 (4H in case of the cyclohexyl ring, 2H in cyclopentyl ring) and a multiplet at 1.66 (2H, CH-CH_2-CH_2) ppm. Apart from these, signals for aromatic protons were observed at δ 6.83-7.42 (m, Ar*H*), and two -NH protons appeared at δ 8.96 (1H, NH of indole) and 8.42 (1H, N*H*) ppm. Mass spectra of compound **2a** and **2c** showed molecular ion peaks at m/z 289 and 303 respectively corresponding to their molecular weight. On the basis of these observations, the product formed by 3-(2-oxocyclopentylidene)-indol-2-one is identified as 5',6'-cyclopenta-2-thioxo/oxospiro[3*H*-indole-3,4'-(3'*H*)pyrimidin]-2(1*H*)-one **2a,b** and the product obtained from 3-(2-oxocyclohexylidene)indol-2-one is identified as 2',4'a,5',6',7',8'-hexahydro-2'-thioxo/-oxospiro[3*H*-indole-3,4'(3'*H*)-quinazolin]-2(1*H*)-ones **2c-f**. The filtrate, after the separation of **2**, when kept for 24 hours at room temperature, yielded another pale yellow solid **3** in 30-35% yield. The ir spectra of **3** showed complete disappearance of CO absorption. The pmr spectra also did not display any signal at δ 4.34 ppm for the methine proton and in addition to signals for the cycloalkyl ring and aromatic protons only one NH signal was obseved at δ 8.79 ppm. Further, the mass spectra of **3a** and **3c** showed reasonably intense molecular ion peak at m/z 271 (74.2%) and 285 (42.3%). On the basis of these observations and keeping in view the observations of Tacconi *et al.* [13] these compounds were identified as the novel 1,2,3,7-tetrahydrocyclopenta[4,5][1,3]diazepino[7,6-*b*]indole-5-thiones(ones) **3** (n = 1) and the known [14] 1,2,3,4,6,8-hexahydroindolo[2,3-*d*][1,3]benzodiazepine-6-thiones(ones) **3** (n = 2) involving the condensation at both of the carbonyl groups. An analogous reaction with urea also gave two products identified as **2** and **3** on the basis of spectral studies.

When the same reaction was repeated with fluorinated phenylthiourea/cyclohexylthiourea and phenylurea only one compound separated after 24 hours and was identified as the corresponding spiro products **2g-l**. Even on keeping the filtrate for a long time, no other compound was obtained.

Lastly, the acetylation and alkylation reactions of spiro compound **2g** have also been studied. Acetylation by acetic anhydride resulted in the formation of *N*-acetyl derivatives at the indole nitrogen as indicated by spectral studies. An attempted alkylation with methyl iodide failed. *N*-Methylspiro compound **2h** was alternatively synthesized by starting with 1-methylindole-2,3-dione.

The presence and position of fluorine in all compounds have been confirmed on the basis on ^{19}F nmr. Single fluorine at the 5-position and a CF_3 group at the 4-position of the indole ring appeared at δ 115 and 60.7 ppm respectively. Fluorine attached to the phenyl ring appeared at δ 105.29 ppm.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using Perkin-Elmer 557 spectrophotometer. The ^{1}H and ^{19}F nmr spectra were recorded in TFA and DMSO-d_6 respectively on Jeol (model FX 90 Q) spectrometer at 90 MHz using TMS as an external reference. Hexafluorobenzene (at δ −162.9 ppm) is used as external reference for ^{19}F nmr. The mass spectra were recorded on MS-30 and MS-50 Kratos mass spectrometers operating at an ionisation potential of 70 eV.

3-(2-Oxocycloalkylidene)indol-2-one **1**.

These compounds were synthesized by our earlier method [16].

Reaction of 3-(2-oxocycloalkylidene)indol-2-one with Thiourea/urea to Synthesize Spiro-2-indolinones **2a-f** and 4,5-cyclopentyl/cyclohexyl-1,3-diazepino[4,5-*b*]indole-2-thione/ones **3a-f**.

A mixture of **1** (0.01 mole) and thiourea/urea (0.01 mole) in 30-40 ml ethanolic (1 g) was refluxed for 24 hours. The mixture was allwoed to stand overnight. The brownish black solid separated, was filtered, dried and recrystallized from hot ethanol. This was identified as spiro products **2a-f**. The analytical data of all the compounds prepared are recorded in Table I.

When the filtrate was allowed to stand further for 24 hours, a light yellow solid was obtained, which was filtered and recrystallized from ethyl acetate. This was identified as the condensed system **3a-f**. Analytical data for all compounds **3a-f** are recorded in Table II.

An analogous reaction of **1** with fluorinated phenylthiourea/-cyclohexylthiourea/phenylurea resulted in the formation of only one compound, which is separated on keeping the solution for 24 hours, recrystallized from hot ethanol and was identified as the corresponding spiro products **2g-l**. Keeping the filtrate for several days did not give any product as obtained in the previous case. The analytical data of all the compounds are listed in Table I.

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