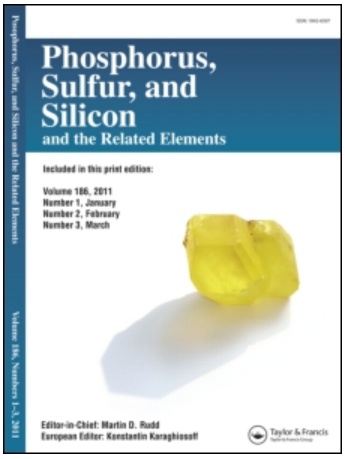

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REACTION OF 3-[1,2,4-TRIAZOL-3-YL IMINO] INDOL-2-ONES WITH THIOACIDS: SYNTHESIS OF SOME NOVEL SULFUR CONTAINING SPIRO INDOLE DERIVATIVES

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A series of novel spiro [3H-indole-3,2'-(1'H)[1,2,4]triazolo[5,1-d][1,3,5]thiadiazepine]-2,5'-(1H,4'H)-diones (II) have been synthesized by the condensation of novel 1,3-dihydro-3-[(1H-[1,2,4]-triazol-3-yl)imino]-2H-indol-2-ones (I) with thioacids, viz. mercaptoacetic and 2-mercaptopropionic acid in dry toluene. I were prepared by the reaction of indole-2,3-diones with 3-amino-1,2,4-triazole in absolute ethanol. All the compounds have been characterized on the basis of elemental and spectral studies and have been screened for their antibacterial activity.

Key words: Sulfur containing spiro indoles, triazolo-thiadiazepine, 3-(triazol-3-yl imino) indol-2-ones, 3-amino-1,2,4-triazole, thioacids.

INTRODUCTION

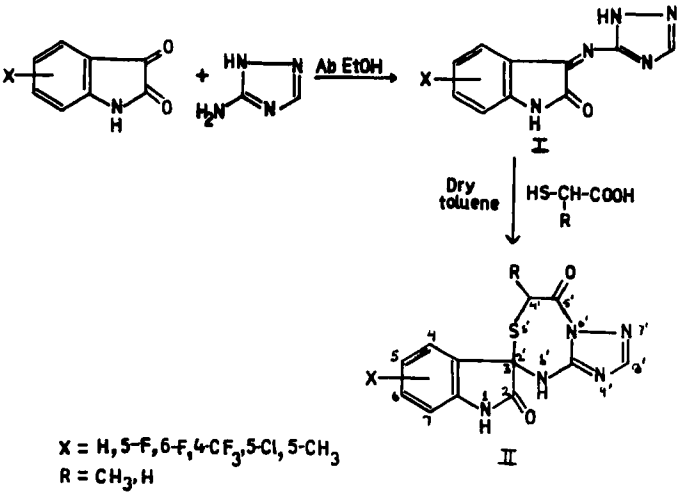
The great importance of the indole nucleus in the field of medicinal chemistry has attracted the attention of chemists for a long time.[1–3]

A perusal of literature revealed that a wide range of pharmacological properties are affiliated with compounds in which an indole ring is joined to sulfur and nitrogen containing heterocycles at the C-3 position through a spiro carbon atom.[4–8] However, most of the references related to these spiro compounds are patents, and yields are not usually mentioned. Some triazolo-indole derivatives are used as potential antifertility agents.[9,10] Prompted by these observations, reaction of 3-[triazol-3-yl imino] indol-2-ones with thio acids was investigated for the first time, and a novel spiro indole triazolo-thiadiazepine system has been synthesized which may lead to the discovery of a new class of drugs.

DISCUSSION

The synthetic approach involved the condensation of appropriate indole-2,3-diones with 3-amino-1,2,4-triazole yielding 1,3-dihydro-3-[(1H-[1,2,4]-triazol-3-yl)imino]-2H-indol-2-ones ($\mathbf{I_{a-f}}$), which reacted with thioacids, viz. mercaptoacetic and 2-mercaptopropionic acid in dry toluene to give spiro [3H-indole-3,2'-(1'H)[1,2,4]triazolo[5,1-d][1,3,5]thiadiazepine]-2,5'-(1H,4'H)-diones ($\mathbf{II_{a-g}}$).

The title reaction involves the attack of the carboxyl group of the mercaptoacid at the more basic NH of the triazole ring of I as compared to imino nitrogen atom thus affording a thiadazepine ring system and forming a hitherto unknown heter-



ocyclic system **II**. The structures of the synthesized compounds were further established by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectral studies. Elemental and physical data are given in Tables I and II. The synthesized compounds have been screened for antibacterial activity against gram positive bacteria *Staphylococcus albus* and gram negative bacteria *Escherchia coli*. Tables III and IV include the spectral data of the synthesized compounds whereas results of antibacterial activity are reported in Table V.

IR Spectra

IR spectra displayed the formation of intermediate 3-[triazol-3-yl imino] indol-2-ones ($\mathbf{I_{a-f}}$) by the retention of NHCO absorption at 1710 cm^{-1} and disappearance

TABLE I

Physical and analytical data of 1,3-dihydro-3-[(1H-[1,2,4]-triazol-3-yl)imino]-2H-indol-2-ones(I)

Compound No.	X	M.P (°C)	Yield (%)	Molecular Formula	Nitrogen (%) Found (Calcd)
$\mathbf{I_a}$	H	266	62	$C_{10}N_7N_5O$	32.70 (32.86)
$\mathbf{I_b}$	5F	286	76	$C_{10}H_6FN_5O$	30.47 (30.30)
$\mathbf{I_c}$	6F	272	74	$C_{10}H_6FN_5O$	30.24 (30.30)
$\mathbf{I_d}$	$4CF_3$	280	72	$C_{11}H_6F_3N_5O$	24.79 (24.91)
$\mathbf{I_e}$	$5CH_3$	200*	78	$C_{11}H_9N_5O$	30.74 (30.82)
$\mathbf{I_f}$	5Cl	200*	80	$C_{10}H_6ClN_5O$	28.28 (28.34)

*Decomposes.

TABLE II

Physical and analytical data of spiro[3H-indole-3,2'(1'H)-[1,2,4]triazolo[5,1-d][1,3,5]thiadiazepine]-2,5'(1H,4'H)-diones(II)

Compound No.	X	R	Yield (%)	Molecular Formula	Anals % Found (calcd) N	S
II_a	H	H	62	$C_{12}H_9N_5O_2S$	25.25 (24.39)	11.29 (11.14)
II_b	5F	H	66	$C_{12}N_8FN_5O_2S$	22.79 (22.95)	10.27 (10.49)
II_c	6G	H	60	$C_{12}H_8FN_5O_2S$	22.81 (22.95)	10.34 (10.49)
II_d	$4CF_3$	H	68	$C_{13}H_8F_3N_5O_2S$	19.53 (19.71)	9.17 (9.01)
II_e	$5CH_3$	H	62	$C_{13}H_{11}N_5O_2S$	23.40 (23.25)	10.48 (10.63)
II_f	5Cl	H	68	$C_{12}H_8ClN_5O_2S$	21.68 (21.80)	9.74 (9.96)
II_g	H	CH_3	72	$C_{13}N_{11}N_5O_2S$	23.34 (23.25)	10.25 (10.63)

*Melting point of all compounds exceeded 360°C.

of another CO absorption of isatin moiety and free primary amino frequency of amino triazole at 1680 and 3300–3360 cm^{-1}, respectively. The bands corresponding to C=N and NH absorptions appeared at 1600 and 3150–3250 cm^{-1}, respectively.

IR spectra of spiro [indole-triazolo-thiadiazepines] (II_{a-g}) showed characteristic absorption bands at 3250–3350 (two NH), 2980–2990 (CH_2), 1700–1720 (NHCO), 1665 (C=O of thiadiazepine ring),[11] and 1600 (C=N) cm^{-1}. Shifting of indole NHCO from 1680–1700 in **I** to higher frequency at 1700–1720 cm^{-1} in **II** indicated the disappearance of conjugation of the anil (**I**). Appearance of one more carbonyl absorption at 1665 cm^{-1} indicated the formation of a triazole-fused seven-membered thiadiazepine ring system.[12,13]

^1H NMR and ^{19}F Spectra

In PMR spectra of compounds I_{a-f} characteristic signals were observed at δ10.93 (NH of indole), 8.37 (H—C=N, the methine proton of triazole) and 7.78 (NH of triazole) in addition to the aromatic protons at 6.76–7.87 ppm. All numbers of protons met at expectation in PMR spectra. Presence of the NH proton was confirmed by deuteration.

In compounds II_{a-g}, the disappearance of NH peak of triazole ring and appearance of a signal at δ13.32–14.30 ppm due to NH of thiadiazepine ring confirmed the formation of spiro product **II**. Other characteristic signals observed in PMR were singlets at δ4.24 (CH_2—CO), 8.31 (H—C=N of triazole), 10.92 (NH of indole) and a multiplet at 6.71–7.37 ppm due to aromatic protons. The single flourine attached to the indole ring at position 5 and 6 in the compounds II_b and II_c appeared at δ – 115.20 and – 112.023 ppm.

The ^{19}F signal for the CF_3 group is seen as a singlet at δ – 62.82 ppm.

TABLE III

Spectral data of 1,3-dihydro-3[(1H-[1,2,4]-triazol-3-yl)imino]-2H-indol-2-ones(I)

Compound No.	IR (cm^{-1})	^{1}H NMR (δ ppm) —CH$_3$	Ar—H	N—H	N=C—H	NH (indole)
I_a	3250–3050, 2910, 1710, 1610, 1450, 1330, 1250, 1070, 790, 730, 600	—	6.63–7.70 (m)	7.42 (s)	8.37 (s)	11.05 (br,s)
I_b	3200–3080, 2900, 1700, 1600, 1450, 1320, 1240, 750	—	6.60–7.80 (m)	7.60 (s)	8.30 (s)	11.00 (br,s)
I_c	3270–3050, 2920, 1710, 1605, 1470, 1330, 1250, 760	—	6.63–7.87 (m)	7.47 (s)	8.27 (s)	10.90 (br,s)
I_d	3230–3100, 2910, 1705, 1590, 1460, 1060, 750	—	6.70–7.82 (m)	7.58 (s)	8.34 (s)	11.07 (br,s)
I_e	3310–3050, 2900, 1690, 15980, 1455, 1320, 1250, 790	2.23 (s)	6.60–7.83 (m)	7.70 (s)	8.30 (s)	11.02 (br,s)
I_f	3270–3100, 2910, 1680, 1610, 1450, 1330, 1240, 770	—	6.56–7.60 (m)	7.62 (s)	8.28 (s)	10.94 (br,s)

TABLE IV

Spectral data of spiro[3H-indole-3,2′(1′H)-[1,2,4]triazolo[5,1-d][1,3,5]thiadiazepine]-2,5′(1H,4′H)-diones(**II**)

Compound No.	IR (cm $^{-1}$)	^{1}H NMR (δ ppm) —CH$_3$	S—CH2—C/—CH	Ar—H	N=CH	NH (indole)	NH
II$_a$	3250–3150, 1700, 1665, 1600, 1550, 1490, 1340, 1250, 1220, 1000, 950, 900, 750, 640	—	4.08 (s)	6.60–7.37 (m)	8.37 (s)	10.92 (br,s)	13.40 (s)
II$_b$	3240–3210, 1710, 1670, 1600, 1540, 1350, 1250, 1000, 750, 650	—	4.00 (s)	6.42–7.42 (m)	8.38 (s)	10.80 (br,s)	13.38 (s)
II$_c$	3320–3080, 1700, 1665, 1590, 1490, 1350, 1250, 1000, 760, 640	—	4.02 (s)	6.53–7.46 (m)	8.28 (s)	10.90 (br,s)	13.97 (s)
II$_d$	3350–3040, 1705, 1670, 1610, 1500, 1340, 1260, 1220, 1000, 750	—	3.92 (s)	6.60–7.77 (m)	8.37 (s)	10.64 (br,s)	14.09 (s)
II$_e$	3330–3050, 1700, 1660, 1620, 1510, 1350, 1250, 1020, 760, 610	2.25 (s)	4.12 (s)	6.44–7.36 (m)	8.38 (s)	10.70 (br,s)	13.32 (s)
II$_f$	3350–3070, 1710, 1670, 1600, 1480, 1340, 1250, 1230, 990, 750	—	3.97 (s)	6.67–7.60 (m)	8.30 (s)	10.72 (br,s)	14.29 (s)
II$_g$	3350–3160, 1700, 1665, 1590, 1490, 1420, 1335, 1240, 980, 850, 760	1.84 (s)	3.20 (s)	5.58–7.40 (m)	8.29 (s)	10.84 (br,s)	14.30 (s)

TABLE V
Antibacterial activity of compounds I & II

Compound No	E. Coli	S. Albus	Standard Strain for Comparison (NCTC 6571)
I_a	R	10 mm (P.S)	8 mm (P.S)
I_b	10 mm (P.S)	8 mm (P.S)	10 mm (P.S)
I_c	10 mm (P.S)	12 mm (P.S)	10 mm (P.S)
I_d	8 mm (P.S)	10 mm (P.S)	12 mm (P.S)
II_a	14 mm (S)	12 mm (P.S)	12 mm (P.S)
II_b	12 mm (P.S)	10 mm (P.S)	10 mm (P.S)
II_c	R	R	8 mm (P.S)
II_d	14 mm (S)	16 mm (S)	14 mm (S)
II_e	12 mm (P.S)	14 mm (S)	10 mm (P.S)
II_f	10 mm (P.S)	12 mm (P.S)	10 mm (P.S)
II_g	12 mm (P.S)	12 mm (P.S)	8 mm (P.S)

R = Resistant Range < 8 mm per disc.
P.S = Partial sensitive range 8 mm to 12 mm per disc.
S = Sensitive range > 12 mm per disc.

^{13}C NMR

Conversion of I into a spiro system II is further confirmed by ^{13}C NMR. The spectrum of $\mathbf{II_a}$ showed two characteristic signals at δ176.58 and 171.95 ppm which are attributed to the carbonyl groups of the thiadiazepine ring and cyclic amide group, respectively. The spiro carbon was distinctly observed at δ110.95 and the methylene carbon at 69.01 ppm, respectively. Signals of other carbon atoms were observed in the expected region.

Mass Spectra

The mass spectrum of the compound $\mathbf{II_b}$ has shown molecular ion peak M^+ at 305, (43%), corresponding to its molecular mass and $M^+ + 1$ peak at 306, (9.8%). The peak at M/Z 169 (100%) forms the base peak in the spectrum.

EXPERIMENTAL

Melting points, determined on a Toshniwal melting point apparatus, (capillary method) are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 grating spectrometer (ν_{max} in cm^{-1}), PMR spectra in $CDCl_3$ and DMSO-d_6 on a Jeol FX 90 Q (89.55 MHz) using TMS as internal reference (^{19}F NMR on the same instrument) and mass spectra were recorded on Kratz 30 and 50 mass spectrometer at 70 eV.

i) Various substituted 2,3 dihydro indole-2,3-diones were prepared by literature methods.[14-16]

ii) 3-Amino-1,2,4-triazole (make aldrich) is available in the market.

iii) 1,3-Dihydro-3-[(1H-[1,2,4]-triazol-3-yl)imino]-2H-indol-2-ones ($\mathbf{I_{a-f}}$).

An equimolar mixture of appropriate indole-2,3-dione and 3-amino-1,2,4-triazole was refluxed in ab. ethanol (25 ml) for 4–6 hrs. On cooling the orange flakes that separated were filtered, dried and recrystallized from ethanol to give compounds ($\mathbf{I_{a-f}}$).

iv) Spiro[3H-indole-3,2'-(1'H)[1,2,4]triazolo[5,1-d][1,3,5]thiadiazepine]-2,5'(1H,4'H)-diones ($\mathbf{II_{a-g}}$). Equimolar quantities of I and mercaptoacetic/2-mercaptopropionic acid in dry toluene (50 ml) were refluxed for 4 hours using a Dean-Stark apparatus and the water formed was removed azeotropically.

On cooling, white solid was obtained which was recrystallized from ethanol to give title compounds II_{a-g}.

Antibacterial Activity

Synthesized compounds in ethanolic solutions were screened against gram positive bacteria *Staphylococcus albus* and gram negative bacteria *Escherchia coli* following the Kirby Bauer method.[17] The Oxford strain of *staphylococcus albus* (NCTC 6571) was always kept as control for both the tests. The area of inhibition of growth of bacteria produced by diffusion of compounds from disc to the surrounding medium was measured. All experiments were in five replicates. The results obtained are given in Table V.

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