Synthesis and Antifertility Activity of 1,5-Diaryl-3-(3′-indolyl)formazans

Mazaahir KIDWAI,*[,a] Neena NEGI,[a] and S. D. GUPTA[b]

Department of Chemistry, University of Delhi,[a] Delhi-110007, India and Central Drug Research Institute,[b] Lucknow, India. Received January 5, 1994; accepted June 10, 1994

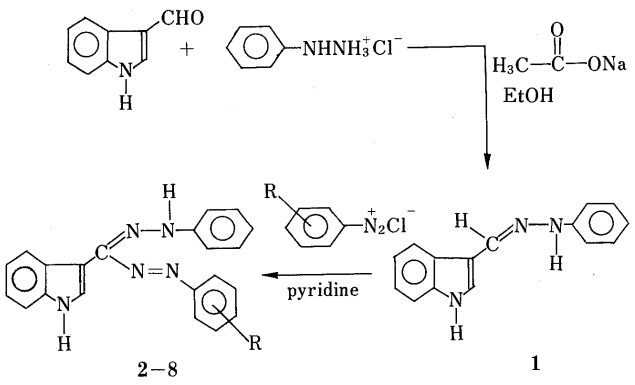
The synthesis and antifertility activity of 1,5-diaryl-3-(3′-indolyl)formazans with a substituted aryl group (2—8) are described.

Keywords formazan; 1,5-diaryl-3-(3′-indolyl) group synthesis; antifertility activity

In view of the association of indoles, particularly their 3-substituted derivatives, with hypotensive,[1] antiparkinsonian,[2] anthelmintic,[3] antibacterial[4] and central nervous system (CNS), central vascular system (CVS)[5] activities, we have synthesized several indoles incorporating the formazan pharmacophores and examined their biological activities.

Chemisty

The 1,5-diaryl-3-(3′-indolyl)formazans **2**—**8** were synthesized by the route shown in Chart 1. The required 3-indolecarbaldehyde phenylhydrazone **1** was prepared by the condensation of phenylhydrazine with 3-indolecarbaldehyde. This hydrazone **1** was subsequently converted into formazans **2**—**8** by reaction with the diazonium chloride of different amines.



	R		R
2	H	5	4-NO_2
3	3-NO_2	6	2-Cl
4	4-Cl	7	4-OCH_3
		8	2-OCH_3

Chart 1

Biological Results

Biological Evaluation Recent studies have been shown that 1-(3-nitrophenyl)-4,4,6-trimethyl-1*H*,4*H*-pyrimidine-2-thiol (3NTPT)[6] and 1,2-*cis*-1-[*p*-(*β*-pyrrolidinoethoxy)-phenyl]-2-phenyl-5-methoxyindane[7] exhibit antifertility activity. The antifertility activity of formazan derivatives is presented in Table I. Four compounds, **3** (in rats), **5**, **6**, and **7** (in hamsters) exhibited antifertility activity in the range of 50—67%. The maximum activity of 67% was observed with compound **6**, followed by compounds **3** and **7** (60% activity) compound **5** was found to possess 50% activity. The results for **7** and **8** indicate that a methoxy group at position 4 (compound **7**) results in better activity (60%) than at position 2 (compound **8**). The R=H compound showed little activity, but R=NO_2 gave encouraging results (compounds **3** and **5**).

Antifertility Screening Mature healthy female rats or hamsters of the Central Drug Research Insitute colony were caged with male rats or hamsters of proven fertility in the ratio of 2:1. Next morning vaginal smears were examined under a microscope for the presence of spermatozoa. The rats or hamsters whose vaginal smears showed the presence of sperm were separated and considered to be at day one of pregnancy. These pregnant

TABLE I. Antifertility Activity of 1,5-Diaryl-3-(3′-indolyl)fromazans (**2**—**8**)

Compd. No.	R	Dose (mg/kg)	Antifertility activity: No. of pregnant animals/animals used		Activity (%)	No. of corpora lutea	No. of total implants	No. of normal implants (mean±S.D.)
			Rats	Hamsters				
2	H	25	9/10	—	10	10.2±1.9	10.0±1.9	9.6±1.3
3	3-NO_2	25	4/10	—	60	10.1±1.0	10.0±1.7	9.7±2.1
Control		—	9/10		10	9.4±1.8	8.9±2.3	8.7±2.3
4	4-Cl	25		4/6	33	8.3±2.0	8.8±2.6	8.8±2.6
5	4-NO_2	25		3/6	50	7.6±1.9	8.7±1.5	8.7±1.5
6	2-Cl	25		2/6	67	7.5±2.7	7.5±3.8	7.5±3.5
7	4-OCH_3	25		4/10	60	7.5±1.5	8.8±1.3	8.5±1.7
8	2-OCH_3	25		6/7	14	8.1±1.5	8.3±1.3	7.7±1.9
Control		—		9/10	10	8.8±1.4	8.5±2.1	8.2±1.9

TABLE II. Physical Data for 1,5-Diaryl-3-(3′-indolyl)formazans (**2**—**8**)

Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2	H	65	188—90	$C_{21}H_{17}N_5$	74.33	5.01	20.64	74.28	4.96	20.63
3	3-NO_2	55	92—95	$C_{21}H_{16}N_6O_2$	67.62	4.16	21.87	67.60	4.11	20.86
4	4-Cl	45	126	$C_{21}H_{16}N_5Cl$	67.46	4.28	18.74	67.45	4.26	18.72
5	4-NO_2	60	115	$C_{21}H_{16}N_6O_2$	65.62	4.16	21.87	67.60	4.11	21.86
6	2-Cl	70	80	$C_{21}H_{16}N_5Cl$	67.46	4.28	18.74	67.45	4.26	18.72
7	4-OCH_3	62	95—97	$C_{22}H_{19}N_5O$	71.54	5.14	18.97	71.53	5.13	18.96
8	2-OCH_3	55	110	$C_{22}H_{19}N_5O$	71.54	5.14	18.97	71.53	5.13	18.96

TABLE III. Spectral Data for 1,5-Diaryl-3-(3′-indolyl)formazans (**2**—**8**)

Compd. No.	IR ν_{max}^{Nujol} cm^{-1} NH	N=N	C=N	NO_2	C–Cl	C–O–C	^{1}H-NMR ($CDCl_3$) δ (ppm)	MS *m/z*
2	3180	1590	1650	—	—	—	7.05—7.90 (m, 15H, Ar-H), 8.55 (br, 2H, NH)	339 (M^+), 235, 142, 93, 116, 105, 77
3	3250	1580	1640	1475 1340	—	—	7.12—7.67 (m, 14H, Ar-H), 8.57 (br, 2H, NH)	384 (M^+), 235, 142, 93, 116, 150, 122, 76
4	3200	1595	1640	—	790	—	7.15—7.50 (m, 14H, Ar-H), 8.58 (br, 2H, NH)	373 (M^+), 235, 142, 93, 139, 111
5	3200	1590	1645	1480 1340	—	—	7.10—7.58 (m, 14H, Ar-H), 8.57 (br, 2H, NH)	384 (M^+), 235, 142, 93, 116, 150, 122, 76
6	3230	1575	1645	—	795	—	7.12—7.70 (m, 14H, Ar-H), 8.52 (br, 2H, NH)	373 (M^+), 235, 142, 93, 116, 139, 111
7	3250	1580	1660	—	—	1230	3.92 (s, 3H, $-OCH_3$), 6.95—7.62 (m, 14H, Ar-H)	369 (M^+), 235, 143, 93, 116, 135, 107, 92, 64
8	3240	1595	1650	—	—	1220	3.90 (s, 3H, $-OCH_3$), 6.97—7.70 (m, 14H, Ar-H)	369 (M^+), 235, 143, 93, 116, 135, 107, 92, 64

animals were divided into four groups, a control and three treatment groups. Various doses of compounds were prepared in distilled water and gum acacia and administered orally with the help of a syringe fitted with a feeding needle on days 1—10 of pregnancy. Pregnant rats were laparotomized under anesthesia on the sixteenth day and hamsters on the fourteenth day of pregnancy. Both horns of the uteri and ovaries were examined for implantations and corpora lutea, and the results are summarized in Table I.

Experimental

Melting points were determined on a Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer R-21 spectrometer. The ^{1}H-NMR spectra were recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer using tetramethylsilane (TMS) as an internal standard and mass spectra were recorded on a JMSD 300 instrument fitted with a JMA 2000 data system at 70 eV.

Elemental analyses of **2**—**8** are shown in Table II and spectral data in Table III.

3-Indolecarbaldehyde This was prepared by the reported method.[8]

3-Indolecarbaldehyde Phenylhydrazone (1) A solution of 3-indolecarbaldehyde (1.5 g, 0.01 mol) in ethanol and a solution of phenylhydrazine hydrochloride (2 g, 0.013 mol) and sodium acetate (4 g) in 30 ml of water were mixed and refluxed on a water bath for 15—20 min. The yellow compound that separated out was collected by filtration and recrystallized from ethanol. mp 196—197 °C, yield 1 g (80%). IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1620 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 9.9 (–CH=N).

1,5-Diaryl-3-(3′-indolyl)formazans (2—8) The appropriate amine (0.015 mol) in glacial acetic acid (5 ml) and HCl (40 ml) was diazotized with $NaNO_2$ (1.5 g in 10 ml of water) at 0—5 °C. The resultant diazonium chloride solution was added dropwise with stirring to a solution of **1** (0.01 mol in pyridine) at below 10 °C. The reaction mixture was allowed to stand overnight at room temperature, then it was poured into cold water (250 ml) with continuous stirring. A dark colored solid that separated out was collected by filtration, washed repeatedly with water and recrystallized from ethanol. The other formazan derivatives were prepared similarly.

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