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Studies in spiroheterocycles: Part II†—Synthesis and antibacterial activity of some novel spiro[indole-pyrazolines], spiro[indole-pyrimidines] and spiro[indole-1,5-benzodiazepines] containing 1,8-naphthyridine moiety

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3-Acetyl-2-methyl-1,8-naphthyridine **1** on treatment with different isatins **2** gives the corresponding 3-hydroxy-3-(2-methyl-1,8-naphthyridine-3-carbonylmethyl)-indole-2-ones **3**, which on dehydration afford the substituted 3-(2-methyl-1,8-naphthyridine-3-carbonyl-methylene)-indole-2-ones **4**. Cyclocondensation of **4** with hydrazine hydrate, phenylhydrazine, urea, thiourea and *o*-phenylenediamine afford novel spiro[indole-pyrazolines] **5** and **6**, spiro [indole-pyrimidinones] **7**, spiro[indole-pyrimidinethiones] **8** and spiro[indole-1,5-benzodiazepines] **9** containing 1,8-naphthyridine moiety, respectively. The structures of the compounds **3-9** have been established on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and mass) data. The compounds **4, 6** and **8** have been tested for their antibacterial activity.

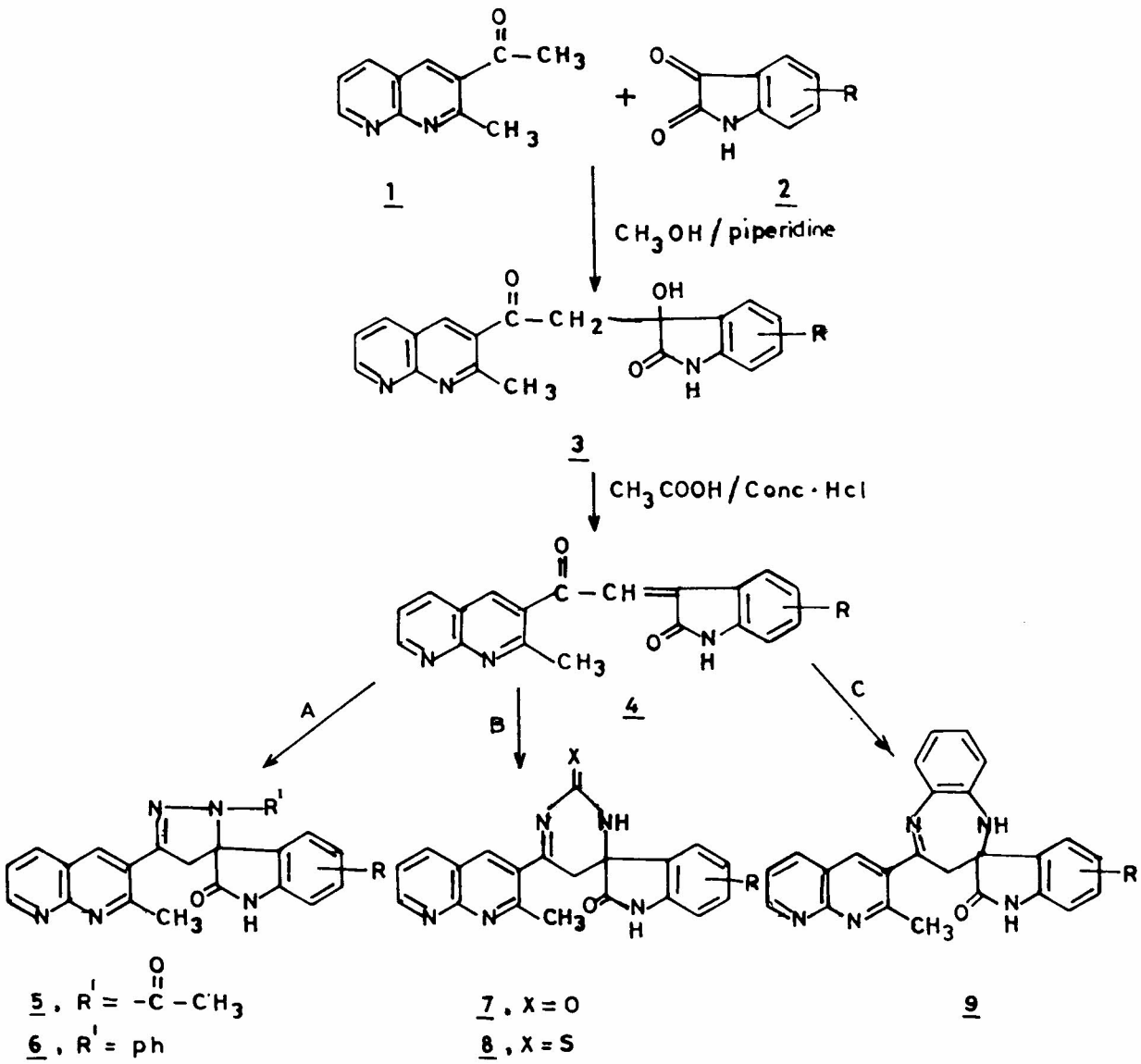
The discovery of nalidixic acid (3-carboxy-1-ethyl-7-methyl-1, 8-naphthyridin-4-one) in the treatment of chronic urinary tract infections has created a great impetus in 1, 8-naphthyridine derivatives as antibacterial agents[1]. Some 1, 8-naphthyridines exhibit marked diuretic[2], antimalarial[3], anti-inflammatory[4] and other pharmacological activities. Further, pyrazolines[5,6], pyrimidines[7,8] and 1,5-benzodiazepines[9,10] have been found to exhibit wide spectrum of biological activities. On the other hand, different indoles are also reported to possess hypoglycemic[11] and antibacterial[12] properties. In view of these facts, and in continuation of our interest in the chemistry of 1, 8-naphthyridines[13-20], we undertook the synthesis of some novel spiroheterocycles, *viz.*, spiro[indole-pyrazolines], spiro[indole-pyrimidinones], spiro [indole-pyrimidinethiones] and spiro [indole-1, 5-benzodiazepines] containing 1, 8-naphthyridine moiety. A few of them are evaluated for their antibacterial activity.

The key intermediate, 3-acetyl-2-methyl-1, 8-naphthyridine **1** required for the preparation of the target compounds, was obtained by the condensation of 2-aminonicotinaldehyde with acetylacetone in boiling methanol containing a catalytic amount of piperidine[21]. The reaction of **1** with different isatins **2** in methanol containing a few drops of piperidine afforded the corresponding 3-hydroxy-3-(2-methyl-1, 8-naphthyridine-3-carbonylmethyl)-indole-2-ones **3**, which on dehydration with gl. acetic acid in the presence of conc. HCl furnished 3-(2-methyl-1, 8-naphthyridine-3-carbonylmethylene)-indole-2-ones **4** in good yields (Scheme I).

Cyclocondensation of **4** with hydrazine hydrate and phenylhydrazine in gl. acetic acid resulted in the formation of 1′-acetyl-3′-(2-methyl-1, 8-naphthyridin-3-yl) spiro[3*H*-indole-3, 5′-pyrazoline]-2(1*H*)-ones **5** and 3′-(2-methyl-1, 8-naphthyridin-3-yl)-1′-phenyl-spiro[3*H*-indole-3, 5′-pyrazoline]-2(1*H*)-ones **6**, respectively. Treatment of **4** with urea in methanol containing a few drops of conc. HCl afforded 4′-(2-methyl-1, 8-naphthlyridin-3-yl)-15dihydrospiro[3 *H*-indole-3, 6′-pyrimidine]-2 2(1*H*)-diones **7**. On the other hand, interaction of **4** with thiourea in methanolic KOH yielded 4′-(2-methyl-1, 8-naphthyridin-3-yl)-2′-thioxo-1′, 5′-dihydrospiro[3*H*-indole-3, 6′-pyrimidine]-2(1*H*)-ones **8**.

Further, compounds **4** were transformed to 4′-(2-methyl-1, 8-naphthyridin-3-yl)-1′, 3′-dihydro-

†For Part I, see ref. 17



Scheme I

spiro-[3*H*-indole-3, 2'-1, 5-benzodiazepine]-2(1*H*)-ones **9** by treating them with *o*-phenylenediamine in gl. acetic acid.

The structures of **3-9** were confirmed by their elemental analyses and spectral (IR, ^{1}H NMR and mass) data.

Antibacterial activity

Compounds **4**, **6** and **8** were tested for their antibacterial activity *in vitro* against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* and *Bacillus mycoides* using the filter paper disc technique of Vincent and Vincent[22] at 400 and 600

μg/disc concentrations. All the compounds were active against all the bacteria tested at the concentration of 400 μg/disc. Compounds **4a, 6e** and **8c** were most effective, while **4a, 6c** and **8a** were found to have low activity. The remaining compounds showed moderate antibacterial activity. In general, compounds **6** and **8** were more potent than their parent compounds **4.** All the compounds were less active in comparison to streptomycin which was taken as standard drug.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm), and mass spectra on a VG micromass 7070H instrument at 70 eV.

3-Hydroxy-3-(2-methyl-1, 8-naphthyridine-3-carbonylmethyl)-indole-2-one 3a. A mixture of **1** (0.01 mole) and **2** (R=H, 0.01 mole) was dissolved in methanol (50 mL) and piperidine (10 drops) was added. The reaction mixture was left overnight at room temperature, then poured onto crushed ice. The product thus obtained was filtered, washed with water and recrystallized from methanol to give **3a,** m.p. 180-81°, yield 65%; IR (KBr): 3400 (OH), 3250 (NH) and 1723 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ 2.6 (s, 3H, CH_3), 3.2 (s, 2H, CH_2), 3.5 (s, 1H, OH), 10.05 (s,1H, NH), 8.3 (m, 1H, C_4-H), 8.65 (m, 1H, C_5-H), 9.1 (m, 1H, C_7-H) and 6.8-7.6 (m, 5H, C_6-H and 4 Ar-H); MS: m/z 333 (M^+, 8%), 318 (10), 315 (8), 171 (100), 144 (16.4), 143 (91), 119 (94), 102 (59.7), 92 (64), 91 (17.9) and 164 (32.8).

Compounds **3b-g** reported in Table I were similarly prepared.

3-(2-Methyl-1, 8-naphthyridine-3-carbonylmethylene)-indole-2-one 4a. To a solution of **3a** (0.01 mole) in gl. acetic acid (20 mL), conc. HCl (0.5 mL) was slowly added with constant stirring. The reaction mixture was heated on a water-bath for 15 min, allowed to stand at room temperature for 3 hr and poured onto crushed ice. The solid that precipitated out was filtered, washed with water and recrystallized from methanol to afford **4a,** m.p. 238-39°, yield 80%; IR (KBr): 3240 (NH), 1710 (C=O) and 1605 cm^{-1} (C=C); ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 9.8 (s, 1H, NH), 8.2 (m, 1H, C_4-H), 8.7 (m, 1H, C_5-H), 9.2 (m, 1H, C_7-H) and 6.6-7.7 (m, 6H, C_6-H,-CH-C and 4 Ar-H); MS: m /z 315 (M^+; 16.4%), 286 (7.5), 171 (8.9), 144 (100), 143 (17.9), 119 (15), 105 (13.4) and 102 (10).

Compounds **4b-g** reported in Table I were similarly prepared.

1′-Acetyl-3′-(2-methyl-1,8-naphthyridin-3-yl)-spiro[3*H*-indole-3,5′-pyrazoline]-2(1*H*)-one 5a. A mixture of **4a** (0.01 mole) and hydrazine hydrate (0.015 mole) in gl. acetic acid (25 mL) was refluxed for 5 hr, cooled and poured into ice-cold water. The separated solid was filtered, washed with water and recrystallized from methanol to yield **5a,** m.p. 248-49° (d), yield 60%; IR (KBr): 3220 (NH), 1715 (C=O) and 1615 cm^{-1} (C=N); MS: m/z 371 (M^+, 13.4%), 330 (12), 329 (10.4), 315 (55), 198 (50.8), 169 (25), 143 (34), 132 (53.7), 119 (20.9), 105 (82), 104 (100) and 77 (68.7).

Compounds **5b-g** reported in Table I were similarly prepared.

3′-(2-Methyl-1, 8-naphthyridin-3-yl)-1′-phenyl-spiro [3*H*-indole-3, 5′-pyrazoline]-2(1*H*)-one 6a. A mixture of **4a** (0.01 mole) and phenylhydrazine (0.015 mole) in gl. acetic acid (30 mL) was heated under reflux for 4 hr. The cold reaction mixture was diluted with water and the solid that separated out was filtered, washed with water and recrystallized from gl. acetic acid to furnish **6a,** m.p. 254-56°, yield 64%; IR (KBr): 3400 (NH), 1710 (C=O) and 1615 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ2.6 (s, 3H, CH_3), 3.1(s, 2H, CH_2), 10.8 (s, 1H, NH), 8.4 (m, 1H, C_4-H of naphthyridine moiety), 8.8 (m, 1H, C_5-H of naphthyridine moiety), 9.05 (m, 1H, C_7-H of naphthyridine moiety) and 6.8-7.7 (m, 10H, C_6-H of naphthyridine moiety and 9 Ar-H); MS: m/z 405 (M^+, 12%), 390 (10.4), 315 (34), 275 (41.8), 262 (9), 236 (68.7), 169 (12), 143 (40.3), 132 (44.8), 119 (16.4), 105 (38.8), 104 (47.8) and 77 (100).

Compounds **6b-g** reported in Table I were similarly prepared.

4′-(2-Methyl-1, 8-naphthyridin-3-yl)-1′, 5′-dihydrospiro[3*H*-indole-3, 6′-pyrimidine]2,2′-(1*H*)-dione 7a. To a mixture urea (0.016 mole)

Table I—Characterization data of compounds 3-9

Compd*	R	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calc.)		
					C	H	N
3a	H	180-81	65	$C_{19}H_{15}N_3O_3$	68.7	4.6	12.7
					(68.5	4.5	12.6)
3b	5-CH_3	176-77	78	$C_{20}H_{17}N_3O_3$	69.4	4.8	12.3
					(69.2	4.9	12.1)
3c	7-CH_3	218-19	73	$C_{20}H_{17}N_3O_3$	69.3	4.8	12.3
					(69.2	4.9	12.1)
3d	5-OCH_3	220-22	76	$C_{20}H_{17}N_3O_4$	66.3	4.9	11.5
					(66.1	4.7	11.6)
3e	5-Cl	252-53	80	$C_{19}H_{14}N_3O_3Cl$	62.3	3.9	11.6
					(62.1	3.8	11.4)
3f	7-Cl	168-69	75	$C_{19}H_{14}N_3O_3Cl$	62.4	3.9	11.5
					(62.1	3.8	11.4)
3g	5-Br	225-27	74	$C_{19}H_{14}N_3O_3Br$	55.5	3.5	10.4
					(55.3	3.4	10.2)
4a	H	238-39	80	$C_{19}H_{13}N_3O_2$	72.5	4.2	13.5
					(72.4	4.1	13.3)
4b	5-CH_3	190-91	86	$C_{20}H_{15}N_3O_2$	72.7	4.7	12.6
					(72.9	4.6	12.8)
4c	7-CH_3	242-43(d)	82	$C_{20}H_{15}N_3O_2$	72.8	4.7	12.7
					(72.9	4.6	12.8)
4d	5-OCH_3	257-59(d)	85	$C_{20}H_{15}N_3O_3$	69.8	4.5	12.4
					(69.6	4.3	12.2)
4e	5-Cl	200-02	90	$C_{19}H_{12}N_3O_2Cl$	65.5	3.5	12.2
					(65.3	3.4	12.0)
4f	7-Cl	228-29	83	$C_{19}H_{12}N_3O_2Cl$	65.4	3.6	12.1
					(65.3	3.4	12.0)
4g	5-Br	236-37	84	$C_{19}H_{12}N_3O_2Br$	57.9	3.2	10.8
					(57.7	3.0	10.7)
5a	H	248-49(d)	60	$C_{21}H_{17}N_5O_2$	67.4	4.8	18.7
					(67.2	4.6	18.9)
5b	5-CH_3	220-21	68	$C_{22}H_{19}N_5O_2$	68.8	4.7	18.4
					(68.6	4.9	18.2)
5c	7-CH_3	160-62	62	$C_{22}H_{19}N_5O_2$	68.9	4.8	18.3
					(68.6	4.9	18.2)
5d	5-OCH_3	286-87(d)	66	$C_{22}H_{19}N_5O_3$	65.6	4.8	17.7
					(65.8	4.7	17.5)
5e	5-Cl	228-29	70	$C_{21}H_{16}N_5O_2Cl$	62.4	4.1	17.4
					(62.2	4.0	17.3)
5f	7-Cl	208-09	64	$C_{21}H_{16}N_5O_2Cl$	62.3	4.2	17.5
					(62.2	4.0	17.3)
5g	5-Br	214-15	65	$C_{21}H_{16}N_5O_2Br$	56.3	3.8	15.7
					(56.0	3.6	15.6)
6a	H	254-56	64	$C_{25}H_{19}N_5O$	74.3	4.9	17.5
					(74.1	4.7	17.3)
6b	5-CH_3	170-71	75	$C_{26}H_{21}N_5O$	74.2	5.1	16.9
					(74.5	5.0	16.7)
6c	7-CH_3	188-89	70	$C_{26}H_{21}N_5O$	74.4	5.2	16.8
					(74.5	5.0	16.7)
6d	5-OCH_3	272-74(d)	76	$C_{26}H_{21}N_5O_2$	71.9	4.9	16.3
					(71.7	4.8	16.1)
6e	5-Cl	218-19	80	$C_{25}H_{18}N_5OCl$	68.4	4.3	15.8
					(68.3	4.1	15.9)
6f	7-Cl	252-53	74	$C_{25}H_{18}N_5OCl$	68.5	4.2	15.7
					(68.3	4.1	15.9)

(Contd.)

Table I—Characterization data of compounds **3-9**—*Contd.*

Compd*	R	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calc.)		
					C	H	N
6g	5-Br	248-49	78	$C_{25}H_{18}N_5OBr$	62.2	3.8	14.7
					(62.0	3.7	14.5)
7a	H	272-73	55	$C_{20}H_{15}N_5O_2$	67.3	4.3	19.8
					(67.2	4.2	19.6)
7b	5-CH_3	292-94(d)	68	$C_{21}H_{17}N_5O_2$	67.6	4.7	18.8
					(67.9	4.6	18.9)
7c	7-CH_3	280-81(d)	62	$C_{21}H_{17}N_5O_2$	67.7	4.8	18.7
					(67.9	4.6	18.9)
7d	5-OCH_3	267-68	67	$C_{21}H_{17}N_5O_3$	65.3	4.5	18.2
					(65.1	4.4	18.1)
7e	5-Cl	254-55	70	$C_{20}H_{14}N_5O_2Cl$	61.5	3.7	17.8
					(61.4	3.6	17.9)
7f	7-Cl	274-75	65	$C_{20}H_{14}N_5O_2Cl$	61.6	3.7	17.7
					(61.4	3.6	17.9)
7g	5-Br	285-87(d)	64	$C_{20}H_{14}N_5O_2Br$	55.3	3.4	16.3
					(55.0	3.2	16.1)
8a	H	260-61	58	$C_{20}H_{15}N_5OS$	64.5	4.2	18.9
					(64.3	4.0	18.8)
8b	5-CH_3	270-71(d)	72	$C_{21}H_{17}N_5OS$	65.2	4.6	18.3
					(65.1	4.4	18.1)
8c	7-CH_3	202-03	66	$C_{21}H_{17}N_5OS$	65.3	4.5	18.2
					(65.1	4.4	18.1)
8d	5-OCH_3	256-57	68	$C_{21}H_{17}N_5O_2S$	62.3	4.3	17.6
					(62.5	4.2	17.4)
8e	5-Cl	272-74(d)	75	$C_{20}H_{14}N_5OSCl$	59.3	3.5	17.0
					(59.0	3.4	17.2)
8f	7-Cl	260-61	70	$C_{20}H_{14}N_5OSCl$	59.2	3.6	17.1
					(59.0	3.4	17.2)
8g	5-Br	242-43	72	$C_{20}H_{14}N_5OSBr$	53.4	3.2	15.7
					(53.1	3.1	15.5)
9a	H	278-80	62	$C_{25}H_{19}N_5O$	74.2	4.8	17.5
					(74.1	4.7	17.3)
9b	5-CH_3	230-31	75	$C_{26}H_{21}N_5O$	74.4	5.1	16.8
					(74.5	5.0	16.7)
9c	7-CH_3	248-49	70	$C_{26}H_{21}N_5O$	74.3	5.2	16.9
					(74.5	5.0	16.7)
9d	5-OCH_3	262-63	74	$C_{26}H_{21}N_5O_2$	71.9	4.7	16.2
					(71.7	4.8	16.1)
9e	5-Cl	234-35	78	$C_{25}H_{18}N_5OCl$	68.5	4.2	15.8
					(68.3	4.1	15.9)
9f	7-Cl	272-74(d)	68	$C_{25}H_{18}N_5OCl$	68.4	4.2	15.8
					(68.3	4.1	15.9)
9g	5-Br	258-59	72	$C_{25}H_{18}N_5OBr$	62.3	3.9	14.7
					(62.0	3.7	14.5)

(d) = decompose

*All the compounds were crystallized from methanol except **6a-g** and **9a-g** which were recrystallized from acetic acid.

and methanol (20 mL) was added enough conc. HCl to clear the solution, and then added **4a** (0.01 mole). The reaction mixture was refluxed on a water-bath for 5 hr, concentrated, cooled and treated with ammonia solution. The resultant soild was filtered, washed with water and recrystallized from methanol to give **7a**, m.p. 272-73°, yield 55%; IR (KBr): 3416 (NH), 1716 (C=O) and 1622 cm^{-1} (C=N); MS: m/z 357 (M^+, 9.5%), 300 (40), 267 (43.6), 197 (21.8), 169 (8.5), 143 (27), 132 (23.6), 119 (25), 117 (100), 105 (48), 104 (25) and 91 (63.6).

Compounds **7b-g** reported in Table I were similarly prepared.

4′-(2-Methyl-1,8-naphthyridin-3-yl)-2′-thioxo-1′,5′-dihydrospiro [3*H*-indole-3,6′-pyrimidine]-2 (1*H*)-one 8a. A mixture of **4a** (0.01mole), thiourea (0.01 mole), KOH (0.1 g), water (2 mL) and methanol (30 mL) was refluxed for 4 hr. The precipitate obtained after dilution with water was filtered, washed with water and recrystallized from methanol to afford **8a,** m.p. 260-61°, yield 58%; IR (KBr): 3410 (NH), 1710 (C=O) and 1185 cm^{-1} (C=S); ^1H NMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 3.0 (s, 2H, CH_2), 11.05 (s, 1H, indole NH), 8.2 (m, 1H, C_4-H of naphthyridine moiety), 9.0 (m, 1H, C_7-H of naphthyridine moiety) and 6.7-7.8 (m, 6H, C_6-H of naphthyridine moiety, NH of pyrimidine ring and 4 Ar-H); MS : m/z 373 (M^+, 18%), 256 (26.9), 169 (12), 160 (37.3), 143 (21), 132 (44.8), 119 (19.4), 105 (40), 104 (64), 91 (15) and 64 (100).

Compounds **8b-g** reported in Table I were similarly prepared.

4′-(2-Methyl-1, 8-naphthyridin-3-yl)-1′, 3′-dihydrospiro[3*H*-indole-3, 2′-1, 5-benzodiazepine]-2 (1*H*)-one 9a. A mixture of **4a** (0.01mole) and *o*-phenylenediamine (0.01 mole) in gl. acetic acid (30 mL) was refluxed for 6 hr, cooled and poured onto crushed ice with vigorous stirring. The precipitate thus obtained was filtered, washed with water and recrystallized from gl. acetic acid to furnish **9a**, m.p. 278-80°, yield 62%; IR (KBr): 3250 (NH), 1715 (C=O) and 1610 cm^{-1} (C=N); MS : m/z 405 (M^+, 15%), 300 (7.8), 271 (15.6), 247 (70), 220 (14), 219 (100), 143 (12.5), 119 (32), 117 (68.8),105 (42) 104 (28) and 91 (73.4).

Compounds **9b-g** reported in Table I were similarly prepared.

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