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Several 4-aryl-1-[3-(2-aryl)indolyl]-3-thiosemicarbazones and 3-aryl-4-oxothiazolin-2-yl-[3-(2-aryl)indolyl]hydrazones were synthesized as possible antifertility agents.

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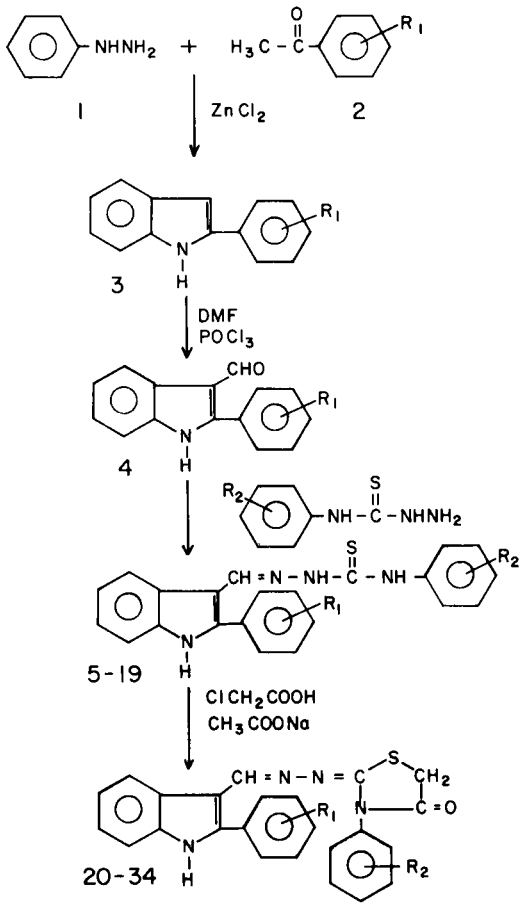
Significant antifertility activity has been reported with 2,3-diphenyl indenes (1-4). Iyer and Gopalachari (5) synthesized some 2,3-diphenyl indoles and found promising antifertility activity with 2-*p*-(β-diethylaminoethoxy)phenyl-3-phenylindole and 2-*p*-(β-*N*-pyrrolidinoethoxy)phenyl-3-phenylindole. Some dithiocarbamoyl hydrazines and 2-substituted-5-nitrothiazoles have also been reported to possess antifertility activity (6,7). Antifertility and anti-inflammatory activities have shown to be possessed by various thiosemicarbazides (8). Furthermore, the ability of 5-hydroxytryptamine to interrupt pregnacy and produce hemorrhage in placenta (9) and the presence of indole nucleus in certain biologically active natural ergot alkaloids prompted us to synthesize some 4-aryl-1-[3-(2-aryl)-indolyl]-3-thiosemicarbazones and 3-aryl-4-oxothiazolin-2-yl-[3-(2-aryl)indolyl]hydrazones by following the methods outlined in Scheme I.




SCHEME I

2-Arylindoles (**3**).

To a mixture of phenylhydrazine **1** (0.2 mole) and suitable acetophenone **2** (0.2 mole), anhydrous zinc chloride (0.2 mole) was added gradually in 5 minutes with constant stirring. A vigorous reaction occurred with the evolution of gaseous products. After completing the reaction, the reaction mixture was poured into 500 ml. of 2*N* hydrochloric acid. The solid mass thus obtained was filtered, washed with water and recrystallized from benzene to yield 2-phenylindole, m.p. 187° (reported m.p. 188-189°) (10); 2-*p*-chlorophenylindole, m.p. 202-203° (reported m.p. 204°) (11); and 2-*m*-aminophenylindole, m.p. 136° (reported m.p. 136°) (12).

2-Arylindole-3-aldehydes (**4**).

Phosphorus oxychloride (0.15 mole) was added slowly with stirring and cooling to dimethylformamide (1.25 mole) and the temperature was maintained between 10 to 15°. To this solution, the appropriate arylindole (0.14 mole) was added in portion with constant cooling and stirring. The temperature of the reaction mixture was kept below 60°. After 45 minutes, the reaction mixture was diluted with 500 ml. of 5% sodium hydroxide. The mixture was then heated on a steam bath for 1 hour. The solid product which separated on cooling was filtered, washed with cold water and recrystallized from acetone to yield 2-phenylindole-3-aldehyde, m.p. 242° (reported m.p. 242°) (13); 2-*p*-chlorophenylindole-3-aldehyde, m.p. 264° (reported m.p. 263°) (14); and 2-*m*-aminophenylindole-3-aldehyde, m.p. 248° (reported m.p. 248°) (15).

4-Aryl-1-[3-(2-aryl)indolyl]-3-thiosemicarbazones (**5-19**).

Equimolar mixture of **4** (0.1 mole) and the appropriate aryl

## EXPERIMENTAL

All compounds were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in an open capillary tube with an immersion thermometer and are corrected.

Table I

4-Aryl-1-[3(2-aryl)indolyl]-3-thiosemicarbazones

| Compound No. | $R_1$ | $R_2$ | M.p. °C | Yield % | Recrystallizing Solvents | Molecular Formula | Analysis % Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5** | H | 4-$CH_3$ | 228 | 70 | (a) | $C_{23}H_{20}N_4S$ | 71.78 | 5.20 | 14.58 | 71.78 | 5.00 | 14.30 |
| **6** | H | 2-$CH_3$ | 191 | 90 | (a) | $C_{23}H_{20}N_4S$ | 71.78 | 5.20 | 14.58 | 72.33 | 5.19 | 14.10 |
| **7** | H | 3-$CH_3$ | 208 | 85 | (a) | $C_{23}H_{20}N_4S$ | 71.78 | 5.20 | 14.58 | 72.68 | 5.10 | 14.39 |
| **8** | H | H | 213 | 85 | (a) | $C_{22}H_{18}N_4S$ | 71.35 | 4.86 | 15.13 | 71.63 | 5.21 | 15.00 |
| **9** | H | 4-$OCH_3$ | 224 | 75 | (a) | $C_{23}H_{20}N_4OS$ | 69.00 | 4.00 | 14.00 | 69.39 | 4.76 | 14.27 |
| **10** | H | 2-$OCH_3$ | 197 | 78 | (a) | $C_{23}H_{20}N_4OS$ | 69.00 | 5.00 | 14.00 | 69.53 | 4.98 | 14.55 |
| **11** | 3-$NH_2$ | 2-$CH_3$ | 218 | 70 | (b) | $C_{23}H_{21}N_5S$ | 69.15 | 5.26 | 17.54 | 69.39 | 5.65 | 17.11 |
| **12** | 3-$NH_2$ | 3-$CH_3$ | 220 | 80 | (b) | $C_{23}H_{21}N_5S$ | 69.15 | 5.26 | 17.54 | 69.53 | 5.19 | 17.33 |
| **13** | 3-$NH_2$ | 4-$CH_3$ | 234 | 85 | (b) | $C_{23}H_{21}N_5S$ | 69.15 | 5.26 | 17.54 | 69.35 | 5.03 | 17.13 |
| **14** | 4-Cl | 2-$CH_3$ | 206 | 80 | (c) | $C_{23}H_{19}ClN_4S$ | 65.94 | 4.54 | 13.38 | 66.38 | 4.38 | 13.55 |
| **15** | 4-Cl | 3-$CH_3$ | 212 | 85 | (c) | $C_{23}H_{19}ClN_4S$ | 65.94 | 4.54 | 13.38 | 66.52 | 4.21 | 13.12 |
| **16** | 4-Cl | 4-$CH_3$ | 240 | 80 | (c) | $C_{23}H_{19}ClN_4S$ | 65.94 | 4.54 | 13.38 | 66.00 | 4.19 | 13.73 |
| **17** | 4-Cl | H | 226 | 75 | (c) | $C_{22}H_{17}ClN_4S$ | 65.26 | 4.22 | 13.84 | 65.72 | 4.13 | 13.39 |
| **18** | 4-Cl | 2-$OCH_3$ | 235 | 70 | (c) | $C_{23}H_{19}ClN_4OS$ | 63.52 | 4.37 | 12.88 | 63.92 | 4.12 | 13.19 |
| **19** | 4-Cl | 4-$OCH_3$ | 231 | 70 | (c) | $C_{23}H_{19}ClN_4OS$ | 63.52 | 4.37 | 12.88 | 63.62 | 4.27 | 12.97 |

(a) Acetone-ethanol. (b) Ethanol. (c) Acetone.

Table II

3-Aryl-4-oxothiazolin-2-yl-[3(2-aryl)indolyl]hydrazones

| Compound No. | $R_1$ | $R_2$ | M.p. °C | Yield % | Recrystallizing Solvents | Molecular Formula | Analysis % Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **20** | H | 2-$CH_3$ | 247 | 90 | (a) | $C_{25}H_{20}N_4OS$ | 70.75 | 4.71 | 13.20 | 70.93 | 4.37 | 13.40 |
| **21** | H | 3-$CH_3$ | 266 | 90 | (a) | $C_{25}H_{20}N_4OS$ | 70.75 | 4.71 | 13.20 | 71.03 | 4.70 | 13.52 |
| **22** | H | 4-$CH_3$ | 285 | 75 | (a) | $C_{25}H_{20}N_4OS$ | 70.75 | 4.71 | 13.20 | 70.90 | 4.53 | 13.11 |
| **23** | H | -H | 242 | 96 | (b) | $C_{24}H_{18}N_4OS$ | 70.24 | 4.39 | 13.65 | 70.82 | 4.32 | 13.93 |
| **24** | H | 2-$OCH_3$ | 276 | 80 | (b) | $C_{25}H_{20}N_4O_2S$ | 68.18 | 4.54 | 12.72 | 68.32 | 4.62 | 12.43 |
| **25** | H | 4-$OCH_3$ | 222 | 85 | (b) | $C_{25}H_{20}N_4O_2S$ | 68.18 | 4.54 | 12.72 | 68.57 | 4.43 | 12.73 |
| **26** | 3-$NH_2$ | 2-$CH_3$ | 256 | 80 | (c) | $C_{25}H_{21}N_5OS$ | 68.33 | 4.78 | 15.94 | 68.74 | 4.49 | 16.23 |
| **27** | 3-$NH_2$ | 3-$CH_3$ | 199 | 80 | (c) | $C_{25}H_{21}N_5OS$ | 68.63 | 4.78 | 15.94 | 68.63 | 5.04 | 15.49 |
| **28** | 3-$NH_2$ | 4-$CH_3$ | 237 | 82 | (c) | $C_{25}H_{21}N_5OS$ | 68.33 | 4.78 | 15.94 | 68.75 | 5.12 | 16.63 |
| **29** | 4-Cl | 2-$CH_3$ | 277 | 90 | (a) | $C_{25}H_{19}ClN_4OS$ | 65.43 | 4.14 | 12.21 | 65.95 | 4.03 | 11.90 |
| **30** | 4-Cl | 3-$CH_3$ | 300 dec. | 75 | (a) | $C_{25}H_{19}ClN_4OS$ | 65.43 | 4.14 | 12.21 | 65.85 | 4.60 | 11.99 |
| **31** | 4-Cl | 4-$CH_3$ | 295 dec. | 80 | (a) | $C_{25}H_{19}ClN_4OS$ | 65.43 | 4.14 | 12.21 | 65.85 | 4.60 | 12.60 |
| **32** | 4-Cl | H | 302 dec. | 80 | (a) | $C_{24}H_{17}ClN_4OS$ | 64.79 | 3.82 | 12.59 | 65.02 | 4.00 | 12.60 |
| **33** | 4-Cl | 2-$OCH_3$ | 283 | 85 | (b) | $C_{25}H_{19}ClN_4O_2S$ | 63.22 | 4.01 | 11.80 | 63.63 | 4.03 | 11.79 |
| **34** | 4-Cl | 4-$OCH_3$ | 287 | 90 | (b) | $C_{25}H_{19}ClN_4O_2S$ | 63.22 | 4.01 | 11.80 | 63.72 | 4.19 | 11.59 |

(a) Dioxane-petroleum ether. (b) Dimethylformamide-water. (c) Dioxane.

thiosemicarbazides (0.1 mole) in 100 ml. of ethanol containing few drops of glacial acetic acid was refluxed on steam bath for 3-4 hours. The excess of ethanol was removed by distillation under reduced pressure. The crude product which separated out on cooling was filtered, washed with water and recrystallized from suitable solvents. The various compounds recorded in Table I were characterized by their sharp melting points and elemental analyses.

3-Aryl-4-oxothiozlin-2-yl-[3-(2-aryl)indolyl]hydrazones (**20-34**).

To a solution of suitable thiosemicarbazones **5-19** (0.01 mole) in glacial acetic acid was added monochloroacetic acid (0.01 mole) and fused sodium acetate (0.015 mole). The reaction mixture was refluxed on a free flame for 5 hours and poured over crushed ice with continuous shaking. The solid mass thus obtained was filtered, washed with water and recrystallized from suitable solvents. These compounds are recorded in Table II and were characterized by their sharp melting points and elemental analyses.

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