Monatshefte für Chemie 132, 753–763 (2001)

Monatshefte für Chemie
Chemical Monthly

On the Synthesis and Reactions of Indole-2-carboxylic Acid Hydrazide

Abd El-Wareth A. O. Sarhan

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

Summary. Indole-2-carboxylic acid hydrazide was prepared and allowed to react with aromatic aldehydes in acidic medium to give the corresponding hydrazone derivatives in good yields. The hydrazones were cyclized to indolo[2,3-*d*]pyridazine derivatives by refluxing with acetyl chloride. The indole carbohydrazide was converted to 2-triazolylindoles which acted as starting materials for several indole derivatives. A number of new indole derivatives were also prepared and structurally confirmed.

Keywords. Indole alkaloids; Synthesis; Hydrazides; Indolopyridazines; Indolyltriazoles.

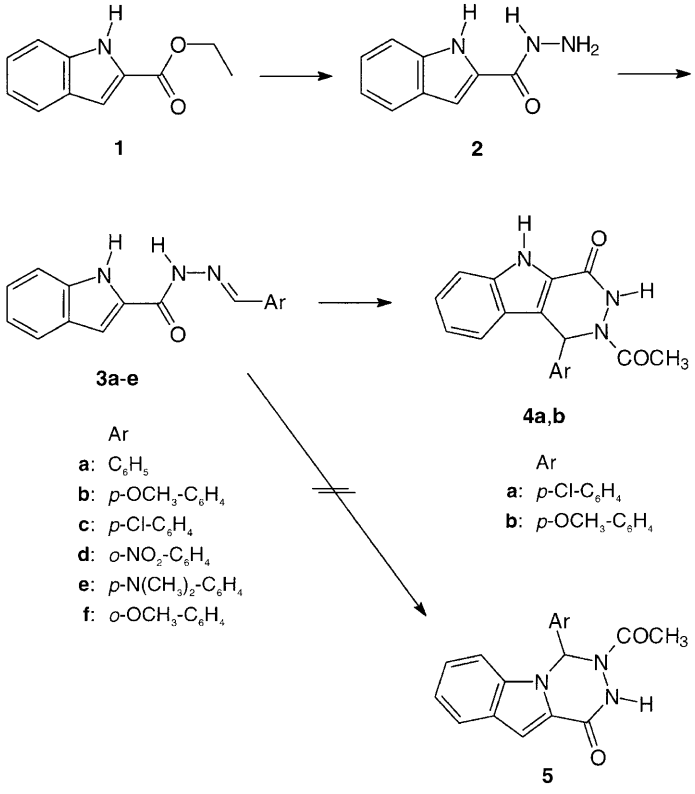
Introduction

Indole has been investigated as a starting material for the synthesis of organic natural products as well as a precursor in alkaloid chemistry. Indole-2-carbohydrazide derivatives have been shown to inhibit monoamine oxidase A activity [1,2]. Some N-methylindole-3-hydrazones have shown antihypertensive activity in spontaneously hypertensive rats [3]. Several 3-substituted indoles proved useful as materials for alkaloids, agrochemicals, pharmaceuticals, and perfumes [4]. Indole acetic acid has been shown to be active against *E. coli* [5]. Several indole-3-carbohydrazide derivatives have been prepared and studied chemically [6, 7]. These findings prompted the synthesis of a number of indole-2-carbohydrazide derived systems of potential biological activity.

Results and Discussions

This work is focused on the synthesis and the chemical behavior of new indole derivatives. Indole-2-carboxylic acid ethyl ester (**1**) was reacted with hydrazine hydrate to give the corresponding indole-2-carboxylic acid hydrazide (**2**) in good yield. The structure of **2** agreed with that reported in the literature [1, 2]. Upon condensation of **2** with aromatic aldehydes, the hydrazone derivatives **3a–f** were obtained in varying yields. Refluxing **3b** and **3c** in acetyl chloride afforded the corresponding indolo[2,3-*d*]pyridazine derivatives **4a**,**b** rather than the indenotriazines **5** (Scheme 1).

The cyclization of **4a** and **4b** was substantiated by spectroscopic data and microanalysis. The IR spectrum of **4b** revealed two NH signals at 3295–3300 cm^{-1}.

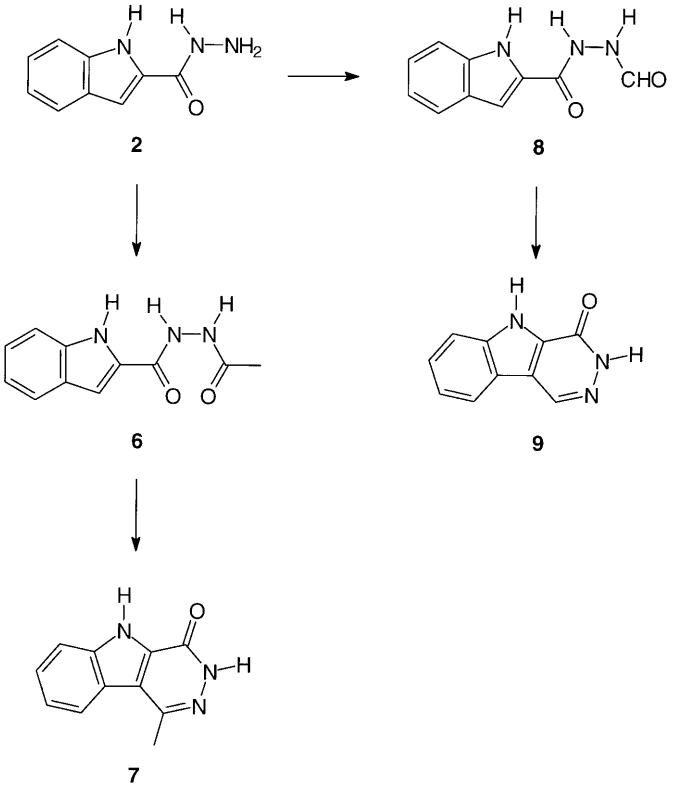


Scheme 1

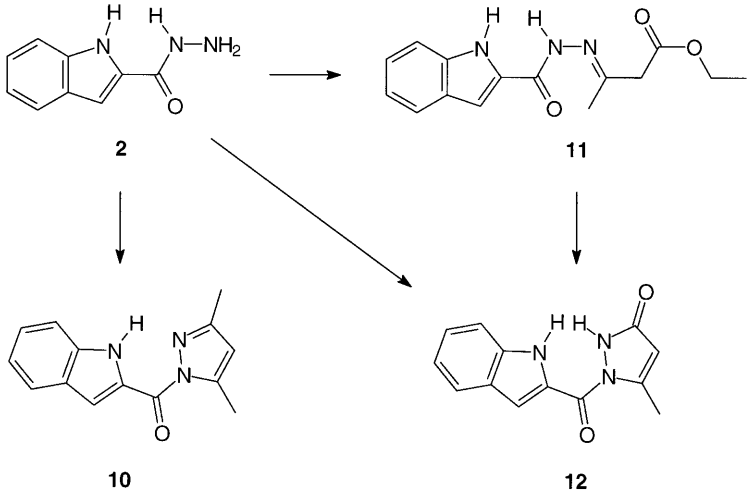
An exchangeable NH proton could be denoted in the ^{1}H NMR spectrum of **4b** which excluded the formation of **5**. The mass spectrum of **4a** provided the expected molecular ion peak. Acetylation of **2** by refluxing in acetic acid afforded 2-acetylhydrazinocarbonylindole (**6**) in high yield. Product **6** could be cyclized directly by refluxing in dioxane containing $POCl_3$ to the indolo[3,2-*b*]pyridazine derivative **7** in low yield. On the other hand, refluxing **2** in formic acid for 5 hours afforded the N-formyl derivative **8** in good yield. The indolo[3,2-*b*]pyridazine derivative **9** has been known for several years as an azacarboline derivative [8]. Here we present a different route for its synthesis. By ring closure of **8** upon heating above its melting point for 10 minutes followed by refluxing in ethanol for further 3 hours, **9** was obtained in 43% yield (Scheme 2).

Upon condensation of **2** with acetylacetone in ethanol containing a catalytic amount of acetic acid, the corresponding derivative **10** was obtained in 64% yield. Reaction of **2** with ethyl acetoacetate without solvent gave the ester derivative **11** in 70% yield. **11** could be cyclized to the pyrazolone derivative **12** by heating above its melting point for 10 minutes followed by refluxing in methanol for further 2 hours. Compound **12** was also obtained independently in 34% yield *via* direct refluxing of **2** with ethyl acetoacetate in ethanol/acetic acid mixture for 5 hours (Scheme 3).

On the other hand, reaction of **2** with KSCN in refluxing ethanol containing catalytic amounts of HCl gave after work up the salt **13** which was converted

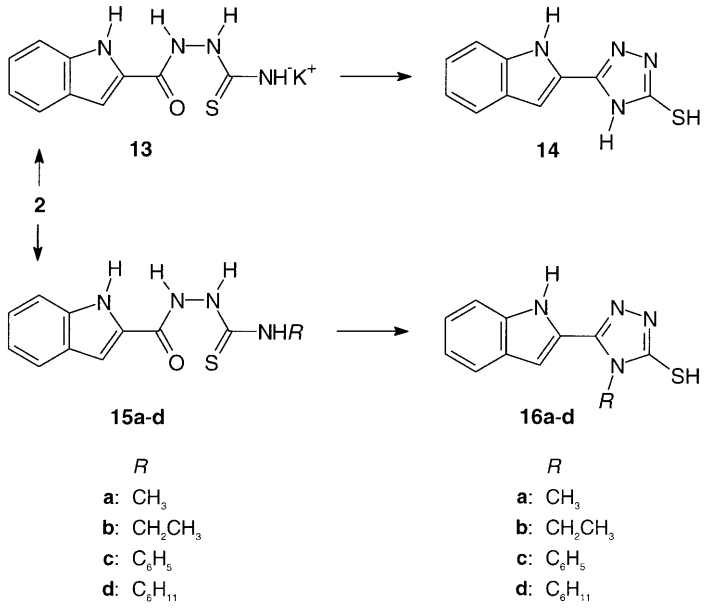


Scheme 2



Scheme 3

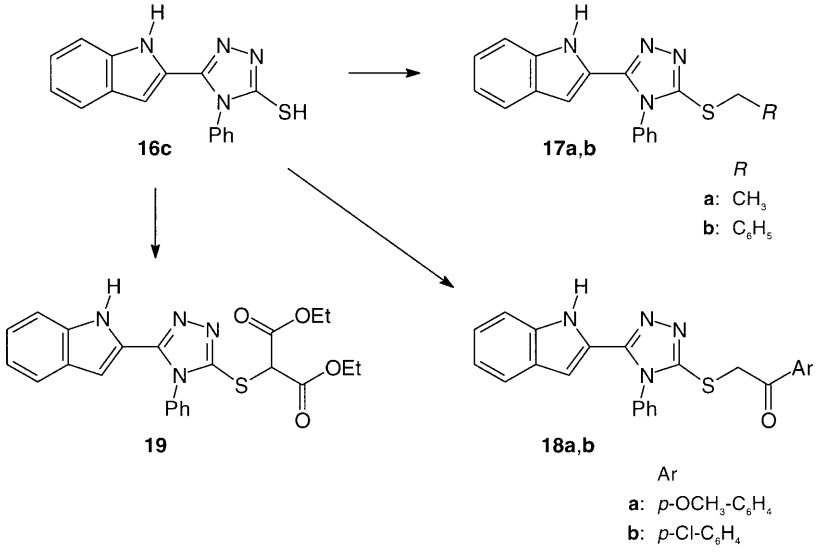
directly to **14** by heating in aqueous KOH followed by acidification with HCl in good yield. When **2** was refluxed with equimolecular amounts of alkyl/aryl-isothiocyanates in ethanol the corresponding thiosemicarbazide derivatives **15a–d** were obtained in high yields. Cyclization of **15a–d** using an aqueous solution of



Scheme 4

KOH followed by neutralization with HCl furnished **16a–d** in excellent yields (Scheme 4).

Alkylation of **16c** using ethyl iodide or benzyl bromide in the presence of KOH gave the S-ethyl and S-benzyl derivatives **17a** and **17b** in good yields. Upon reaction of **16c** with phenacylbromide derivatives in methanol containing KOH or fused sodium acetate, the corresponding thioacetophenone derivatives **18a**,**b** were obtained in good yields. Furthermore, reaction of **16c** with diethyl bromomalonate under the same reaction conditions led to the corresponding thioester **19** (Scheme 5).



Scheme 5

Experimental

Melting points are uncorrected. IR Spectra were measured on a Shimadzu-470 spectrophotometer using KBr discs. Elemental analyses were performed with a Perkin-Elmer elemental analyzer 240-C; the results were in satisfactory agreement with the calculated values. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer operating at 90 MHz; *TMS* was used as an internal standard. Mass spectra were measured on a Shimadzu-GC-MS-QP 1000EX spectrometer using the direct inlet system. Starting materials were commercially available. Solvents were distilled and dried before use.

Indole-2-carboxylic acid hydrazide (**2**; $C_9H_9N_3O$)

A mixture of 1 g 2-ethoxycarbonylindole (**1**; 5.3 mmol) and 2 cm^3 hydrazine hydrate was refluxed in 20 cm^3 ethanol for 4 h. The precipitate formed after cooling was collected by filtration to give 0.73 g (98.5%) of colorless crystals of **2**.

M.p.: 247–248°C [1,2]; IR (KBr): ν = 3300m, 3200m, 3100w, 3080w, 2900w, 1640s, 1615s, 1550m, 780m, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.7 (s, NH_{indole}, exchangeable), 9.85 (bs, NHCO, exchangeable), 7.0–7.8 (m, $4H_{arom} + CH_{indole}$), 4.5 (bs, 2H, NH_2) ppm; MS: *m/z* (%) = 177 [M^{+2}] (16), 176 [M^{+1}] (62), 160 (5), 158 (7), 147 (6), 145 (60), 127 (3), 118 (13), 117 (25), 116 (30), 111 (4), 92 (3), 68 (4), 57 (5), 50 (5).

2-Arylideneaminocarbonylindoles (general procedure)

A mixture of 1 g of **2** (5.7 mmol) and 6.28 mmol of aromatic aldehyde was refluxed in 25 cm^3 ethanol/acetic acid (24:1) for 3 h. The precipitate resulting after cooling was collected by filtration and recrystallized from EtOH to give the 2-arylideneaminocarbonylindoles **3a–f**.

1H-Indole-2-carboxylic acid benzylidene-hydrazide (**3a**; $C_{16}H_{13}N_3O$)

Yield: 74%; m.p.: 194–196°C; IR (KBr): ν = 3400w, 3300w, 3050w, 2900w, 1650m, 1600s, 1565m, 1300s, 740 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 11.2 (s, CONH, exchangeable), 8.3 (s, N=CH), 6.9–7.8 (m, $9H_{arom} + CH_{indole}$) ppm.

1H-Indole-2-carboxylic acid (4-methoxy-benzylidene)-hydrazide (**3b**; $C_{17}H_{15}N_3O_2$)

Yield: 67%; m.p.: 220–222°C; IR (KBr): ν = 3300s, 3050w, 1640s, 1600s, 1540s, 1500s, 1255s, 1025s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 9.3 (s, CONH, exchangeable), 8.3 (s, N=CH), 7.0–7.8 (m, $8H_{arom} + CH_{indole}$), 3.85 (s, 3H, OCH_3) ppm; MS: *m/z* (%) = 294 [M^{+1}] (20), 293 [M^+] (84), 276 (4), 263 (4), 235 (7), 177 (4), 160 (48), 150 (40), 144 (100), 134 (8), 117 (7), 116 (26), 89 (39), 77 (7), 63 (6), 51 (4).

1H-Indole-2-carboxylic acid (4-chloro-benzylidene)-hydrazide (**3c**; $C_{16}H_{12}N_3OCl$)

Yield: 58%; m.p.: 251–252°C; IR (KBr): ν = 3300s, 1630s, 1490m, 1540s, 1250s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 9.3 (s, CONH, exchangeable), 8.4 (s, N=CH), 7.0–7.9 (m, $8H_{arom} + CH_{indole}$) ppm; MS: *m/z* (%) = 299 [M^{+2}] (40), 298 [M^{+1}] (37), 297 [M^+] (66), 286 (9), 279 (7), 258 (7), 238 (13), 202 (9), 184 (6), 158 (44), 151 (22), 143 (100), 115 (74), 110 (75), 98 (12), 90 (51), 75 (26), 63 (46), 50 (15), 37 (23).

1H-Indole-2-carboxylic acid (2-nitro-benzylidene)-hydrazide (**3d**; $C_{16}H_{12}N_4O_3$)

Yield: 76%; m.p.: 231–233°C; IR (KBr): ν = 3300s, 3050s, 1660w, 1610s, 1535s, 1510s, 1235s, 730s cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz); 11.8 (s, NH_{indole}, exchangeable), 11.2 (s, CONH, exchangeable), 8.9 (s, N=CH), 7.0–8.3 (m, $8H_{arom} + CH_{indole}$) ppm.

1H-Indole-2-carboxylic acid (4-N-dimethyl-benzylidene)-hydrazide (**3e**; $C_{18}H_{18}N_4O$)

Yield: 72%; m.p.: 218–220°C; IR (KBr): ν = 3400s, 3300s, 3050m, 2900w, 1620s, 1590s, 1590s, 1560s, 1510s, 1250s, 720s cm^{-1}; ^1H NMR (*TFA*, δ, 90 MHz): 8.1 (s, N=CH), 7.0–7.9 (m, $8H_{arom} + CH_{indole}$), 3.2 (s, 6H, $N(CH_3)_2$) ppm.

1H-Indole-2-carboxylic acid (2-methoxy-benzylidene)-hydrazide (**3f**; $C_{17}H_{15}N_3O_2$)

Yield: 67%; m.p.: 243–245°C; IR (KBr): ν = 3325m, 3200m, 3050w, 2960w, 1665s, 1630m, 1520s, 1480s, 1255s, 1050s, 730s cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 7.5 (s, N=CH), 6.3–7.4 (m, $8H_{arom} + CH_{indole}$), 3.5 (s, 3H, OCH_3) ppm.

3-Acetyl-4-aryl-1,2,3,4-tetrahydro-indolo[2,3-d]pyridazin-1-ones (general procedure)

A mixture of 0.1 g of **3b** or **3c** was refluxed in 10 cm^3 acetyl chloride for 3 h. The reaction mixture was cooled, diluted with 50 cm^3 H_2O, and neutralized with Na_2CO_3 solution; the precipitate formed was collected by filtration. The crude product was washed with H_2O (3x) and crystallized from EtOH.

3-Acetyl-4-(4-chloro-phenyl)-1,2,3,4-tetrahydro-indolo[2,3-d]pyridazin-1-one (**4a**; $C_{18}H_{14}N_3O_2Cl$)

Yield: 81%; m.p.: 200–201°C; IR (KBr): ν = 3300s, 3210m, 3050w, 2910w, 1700m, 1660s, 1635s, 1545m, 1485s, 1250s, 1090s, 810s, 740s cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 6.9–7.8 (m, $8H_{arom} + CH_{pyridazine}$), 2.4 (s, 3H, $COCH_3$) ppm; MS: *m/z* (%) = 341 [M^{+2}] (30), 340 [M^{+1}] (24), 339 [M^+] (55), 296 (65), 279 (39), 266 (18), 252 (6), 237 (10), 232 (11), 219 (12), 217 (27), 204 (25), 199 (94), 186 (33), 165 (37), 160 (21), 155 (16), 145 (16), 144 (100), 149 (43), 137 (50), 129 (46), 116 (20), 114 (13), 111 (13), 102 (21), 92 (12), 89 (37), 77 (8), 74 (53), 63 (11), 50 (4), 43 (29).

3-Acetyl-4-(4-methoxy-phenyl)-1,2,3,4-tetrahydro-indolo[2,3-d]pyridazin-1-one (**4b**; $C_{19}H_{17}N_3O_3$)

Yield: 76%; m.p.: 151–153°C; IR (KBr): ν = 3290s, 3200m, 3050s, 2930w, 2820w, 1700s, 1660m, 1600s, 1540m, 1500s, 1245s, 1060s, 830s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 10.1 (s, $NH_{pyridazinone}$, exchangeable), 11.1 (s, NH_{indole}, exchangeable), 6.4–7.4 (m, $8H_{arom} + CH_{pyridazine}$), 3.8 (s, 3H, OCH_3), 2.2 (s, 3H, $COCH_3$) ppm.

1H-Indole-2-carboxylic acid N^1-acetyl-hydrazide (**6**; $C_{11}H_{11}N_3O_2$)

A sample of 0.4 g **2** (2.2 mmol) was refluxed in 10 cm^3 acetic acid for 5 h. The reaction mixture was cooled, and the crystalline product was collected by filtration to give 0.35 g (72%) of **6**.

M.p.: 273–275°C; IR (KBr): ν = 3300s, 3250s, 3050m, 1670s, 1650s, 1540s, 1490s, 1250s, 740s, 700s cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 90 MHz): 11.9 (s, NH_{indole}, exchangeable), 10.3 (s, NHCO, exchangeable), 9.9 (s, NHCO, exchangeable), 7.0–7.9 (m, $4H_{arom} + CH_{indole}$), 2.0 (s, 3H, CH_3) ppm; MS: *m/z* (%) = 217 [M^+] (3), 216 (27), 215 (96), 198 (6), 173 (27), 143 (100), 130 (12), 116 (34), 115 (80), 102 (8), 98 (99), 77 (9), 63 (45), 50 (7).

2,3-Dihydro-4-methyl-indolo[3,2-b]pyridazin-1-one (**7**; $C_{11}H_9N_3O$)

A sample of 0.2 g **6** (0.92 mmol) was refluxed in 10 cm^3 dioxane containing 1.0 cm^3 phosphorus trichloride for 3 h. The reaction mixture was cooled and diluted with ice-cold H_2O, followed by neutralization with NH_4OH. The precipitate formed was collected by filtration and crystallized from aqueous EtOH (50%) to give 43% of **7**.

M.p.: 212–214°C, 211–213°C [10]; IR (KBr): $\nu = 3250$m, 3050w, 2900w, 1650m, 1540s, 1260m, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 6.9–7.5 (m, $4H_{arom}$), 2.0 (s, 3H, CH_3) ppm.

1H-Indole-2-carboxylic acid N^1-formyl-hydrazide (**8**; $C_{10}H_9N_3O_2$)

A sample of 0.21 g **2** (1.2 mmol) was refluxed in 15 cm^3 formic acid for 6 h. The reaction mixture was cooled, and the colourless crystals formed were collected by filtration to give 74% of **8**.

M.p.: 230°C; IR (KBr): $\nu = 3400$s, 3250s, 3100s, 3000m, 2900s, 1665s, 1645s, 1540s, 1420m, 1230s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 10.6 (s, NHCO, exchangeable), 10.3 (s, NHCO, exchangeable), 8.05 (s, 1H, HCO), 7.6–6.8 (m, $4H_{arom} + CH_{indole}$) ppm; MS: *m/z* (%) = 203 [M^+] (100), 185 (1), 175 (3), 160 (2), 145 (7), 144 (66), 116 (3), 90 (1), 89 (10), 63 (1), 39 (1).

2,3-Dihydro-indolo[3,2-b]pyridazin-1-one (**9**; $C_{10}H_7N_3O$)

A sample of 0.1 g **8** (0.5 mmol) was heated to 230°C for 10 min and refluxed in 20 cm^3 EtOH for further 3 h. The reaction mixture was cooled and the precipitate obtained was collected by filtration and crystallized from EtOH to give 43% of **9**.

M.p.: 325–327°C, 326–328°C [9]; IR (KBr): $\nu = 3270$s, 3180m, 3050m, 2900m, 1645s, 1530m, 1440s, 1400s, 1195s, 730s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 12.0 (s, NH_{indole}, exchangeable), 10.7 (s, NH, exchangeable), 9.0 (s, $CH_{pyridazine}$), 8.0–7.1 (m, $4H_{arom}$) ppm.

(3,5-Dimethyl-pyrazol-1-yl)-(1H-indol-2-yl)-methanone (**10**; $C_{14}H_{13}N_3O$)

A mixture of 0.16 g **2** (0.9 mmol), 0.2 g acetylacetone (2.0 mmol), and 1.0 cm^3 acetic acid was refluxed in 10 cm^3 EtOH for 5 h. The precipitate which formed after cooling was collected by filtration and recrystallized from EtOH to give 64% of **10** as colourless crystals.

M.p.: 103–105°C; IR (KBr): $\nu = 3330$s, 3100w, 2960w, 2910w, 1665s, 1585s, 1510s, 1480s, 1430s, 1260s, 1095s, 735s cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 11.2 (s, NH_{indole}, exchangeable), 7.0–7.8 (m, $4H_{arom} + CH_{indole}$), 6.0 (s, $CH_{pyrazole}$), 2.6 (s, 3H, CH_3), 2.3 (s, 3H, CH_3) ppm; MS: *m/z* (%) = 239 [M^+] (14), 238 [M^{-1}] (71), 209 (16), 160 (2), 142 (37), 128 (2), 114 (51), 105 (3), 95 (8), 89 (44), 76 (3), 63 (9), 51 (3), 29 (6).

3-((1H-Indole-2-carbonyl)-hydrazono)-butyric acid ethyl ester (**11**; $C_{15}H_{17}N_3O_3$)

A mixture of 0.21 g **2** (1.2 mmol) and 0.2 g ethyl acetoacetate (1.6 mmol) was condensed without solvent at 180–190°C for 10 min. The reaction mixture was cooled and reflux in 25 cm^3 EtOH for 2 h. The precipitate formed after cooling was collected by filtration and recrystallized from EtOH to give 70% **11** as colourless crystals.

M.p.: 100–102°C; IR (KBr): $\nu = 3300$s, 3220w, 3050w, 2990w, 1725m, 1680s, 1635s, 1525s, 1470m, 1240s, 1200s, 1020s, 740s cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 90 MHz): 11.6 (s, NH_{indole}, exchangeable), 10.2 (s, CONH, exchangeable), 7.8–6.9 (m, $4H_{arom} + CH_{indole}$), 4.4–4.1 (q, $J = 7$ Hz, 2H, CH_2CH_3), 3.4 (s, 2H, CH_2), 2.2 (s, 3H, CH_3), 1.5–1.3 (t, $J = 7$ Hz, 3H, CH_2CH_3) ppm.

1-(1H-Indole-2-carbonyl)-5-methyl-1,2-dihydro-pyrazol-3-one (**12**; $C_{13}H_{11}N_3O_2$)

Method A: A mixture of 0.16 g **2** (0.9 mmol), 0.2 g ethyl acetoacetate, and 1.0 cm^3 acetic acid was refluxed in 10 cm^3 EtOH for 5 h. The precipitate formed after cooling was collected by filtration and recrystallized from EtOH to give colorless crystals of **12**.

Yield: 34%; m.p.: 270–271°C; IR (KBr): ν = 3350m, 3300s, 3050w, 1660s, 1640s, 1520s, 1480s, 1420s, 1240s, 1195s, 740s, 700s cm^{-1}; ^{1}H NMR (*TFA*, δ, 90 MHz): 7.9–7.3 (m, $4H_{arom} + CH_{indole}$), 4.4 (d, J = 7 Hz, $CH_{pyrazolone}$), 1.5 (s, 3H, CH_3) ppm; MS: *m/z* (%) = 240 [M^{-1}] (10), 197 (11), 166 (15), 160 (8), 158 (14), 142 (9), 127 (28), 115 (9), 96 (23), 80 (9), 77 (8), 66 (10), 64 (100), 41 (10), 30 (22).

Method B: A sample of 0.1 g **11** (0.35 mmol) was refluxed in EtOH:CH_3COOH = 10:2 for 8 h. The reaction mixture was cooled, and the crystals formed were collected by filtration and crystallized from EtOH to give 67% **12** as colourless crystals.

5-(1H-Indol-2-yl)-4H-[1,2,4]triazole-3-thiol (**14**; $C_{10}H_8N_4S$)

A mixture of 0.5 g **2** (2.8 mmol) and 0.5 g KSCN (5.1 mmol) was refluxed in 25 cm^3 ethanol containing a few drops of conc. HCl for 3 h. The precipitate formed was collected by filtration and dried to give **13** (75%) which was used without further purification. A mixture of 0.4 g **13** (1.3 mmol) and 0.1 g KOH (1.6 mmol) was refluxed in 25 cm^3 H_2O for 3 h. The reaction mixture was cooled and then acidified with HCl to give 30% **14**.

M.p.: 294–296°C; IR (KBr): ν = 3300s, 3200m, 3050w, 2920m, 1640s, 1590s, 1540s, 1490m, 1220m, 1195s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 13.9 (s, $NH_{triazole}$, exchangeable), 13.7 (s, $NH_{triazole}$, exchangeable), 11.9 (s, NH_{indole}, exchangeable), 7.7–6.9 (m, $4H_{arom} + CH_{indole}$) ppm.

1H-Indole-2-carboxylic acid N^1-thiaalkoyl/aroyl-hydrazides (general procedure)

A mixture of 0.5 g **2** (2.8 mmol) and 2.9 mmol alkyl/arylisothiocyanate derivative was refluxed in 25 cm^3 EtOH for 3–5 h. The precipitate formed was collected by filtration and dried to give the corresponding derivatives **15a–d**.

1H-Indole-2-carboxylic acid N^1-thiaacetyl-hydrazide (**15a**; $C_{11}H_{12}N_4OS$)

Yield: 74%; m.p.: 242–243°C; IR (KBr): ν = 3320s, 3200s, 2905m, 1635s, 1545s, 1520s, 1230s, 1200s, 730s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 10.5 (s, NH, exchangeable), 9.3 (s, NH, exchangeable); 6.8–7.5 (m, $4H_{arom} + CH_{indole}$), 2.8 (d, J = 5 Hz, 3H, CH_3) ppm.

1H-Indole-2-carboxylic acid N^1-thiapropionyl-hydrazide (**15b**; $C_{12}H_{14}N_4OS$)

Yield: 89%; m.p.: 219–221°C; IR (KBr): ν = 3350m, 3290s, 3230s, 2990m, 1660s, 1610s, 1530s, 1475s, 1440m, 1260s, 1040s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 11.1 (s, NH_{indole}, exchangeable), 9.7 (s, NH, exchangeable), 9.3 (s, NH, exchangeable), 8.2 (s, NH, exchangeable), 7.9–7.8 (m, $4H_{arom} + CH_{indole}$), 3.4 (dq, J = 0.5 Hz, J = 7 Hz, 2H, $NHCH_2CH_3$), 1.1 (t, J = 7 Hz, 3H, CH_2CH_3) ppm.

1H-Indole-2-carboxylic acid N^1-thiabenzoyl-hydrazide (**15c**; $C_{16}H_{14}N_4OS$)

Yield: 87%; 221–223°C; IR (KBr): ν = 3300s, 3200s, 2900w, 1650s, 1630w, 1590m, 1520s, 1190s, 730s cm^{-1}; ^{1}H NMR (*TFA*, δ, 90 MHz): 7.0–7.6 (m, $9H_{arom} + CH_{indole}$) ppm; MS: *m/z* (%) = 310

[M^+] (21), 309 [M^{-1}] (58), 291 (6), 275 (20), 232 (5), 227 (9), 215 (83), 205 (2), 192 (11), 173 (100), 158 (16), 155 (18), 143 (99), 128 (12), 115 (82), 107 (22), 102 (27), 89 (100), 77 (86), 63 (78), 51 (29), 49 (70), 42 (28), 29 (57).

1H-Indole-2-carboxylic acid N^1-cyclohexanthiocarbonyl-hydrazide (**15d**; $C_{16}H_{20}N_4OS$)

Yield: 94%; m.p.: 225–227°C; IR (KBr): $\nu = 3310$s, 3240m, 3050w, 2915s, 1680s, 1610w, 1520s, 1460s, 1250s, 1180s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 12.05 (s, NH_{indole}, exchangeable), 10.5 (s, NH, exchangeable), 9.3 (s, NH, exchangeable), 6.8–7.9 (m, $4H_{arom} + CH_{indole}$), 4.1 (m, $1H_{cyclohexyl}$), 1.1–2.0 (m, $10H_{cyclohexyl}$) ppm.

5-(1H-Indol-2-yl)-4-alkyl/phenyl-4H-[1,2,4]triazole-3-thiols (general procedure)

A mixture of 0.5 g **15a–d** and 25 cm^3 alcoholic KOH was refluxed for 3 h. The reaction mixture was cooled and acidified with dilute HCl to give the corresponding *s*-triazoles **16a–d**.

5-(1H-Indol-2-yl)-4-methyl-4H-[1,2,4]triazole-3-thiol (**16a**; $C_{11}H_{10}N_4S$)

Yield: 91%; m.p.: 317–319°C; IR (KBr): $\nu = 3310$s, 3100s, 3050s, 2950s, 2800m, 1590s, 1565s, 1510s, 1475s, 1410s, 1230s, 1140s, 1100s, 730s, 700s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 13.3 (s, $NH_{triazole}$, exchangeable), 11.3 (s, NH_{indole}, exchangeable), 6.9–7.7 (m, $4H_{arom} + CH_{indole}$), 3.8 (s, 3H, NCH_3) ppm.

5-(1H-Indol-2-yl)-4-ethyl-4H-[1,2,4]triazole-3-thiol (**16b**; $C_{12}H_{12}N_4S$)

Yield: 94%; m.p.: 279–281°C; IR (KBr): $\nu = 3320$s, 3100s, 2950s, 2925s, 2800m, 1600s, 1590s, 1510s, 1460s, 1280s, 1040s, 720s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 13.1 (s, $NH_{triazole}$, exchangeable), 11.3 (s, NH_{indole}, exchangeable), 7.7 (s, CH_{indole}), 6.9–7.6 (m, $4H_{arom}$), 4.25 (q, $J = 7$ Hz, 2H, NCH_2CH_3), 1.4 (t, $J = 7$ Hz, 3H, NCH_2CH_3) ppm.

5-(1H-Indol-2-yl)-4-phenyl-4H-[1,2,4]triazole-3-thiol (**16c**; $C_{16}H_{12}N_4S$)

Yield: 93%; m.p.: 284–287°C; IR (KBr): $\nu = 3350$s, 3300s, 3100m, 2900s, 2800m, 1590s, 1570s, 1500s, 1460s, 1420s, 1400s, 1230s, 1080s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 14.4 (s, $NH_{triazole}$, exchangeable), 12.1 (s, NH_{indole}, exchangeable), 6.9–7.7 (m, $9H_{arom} + CH_{indole}$) ppm.

5-(1H-Indol-2-yl)-4-cyclohexyl-4H-[1,2,4]triazole-3-thiol (**16d**; $C_{16}H_{18}N_4S$)

Yield: 98%; m.p.: 249–251°C; IR (KBr): $\nu = 3330$s, 3150w, 2950m, 2900w, 2820m, 1600s, 1560m, 1520s, 1240m, 1010s, 740s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 90 MHz): 12.8 (s, $NH_{triazole}$, exchangeable), 11.1 (s, NH_{indole}, exchangeable), 6.9–7.8 (m, $4H_{arom} + CH_{indole}$), 4.7 (m, 1H, NCH), 1.0–2.0 (m, $10H_{cyclohexyl}$) ppm.

2-(5-Ethyl/benzylsulfanyl-4-phenyl-4H-[1,2,4]triazol-3-yl)-1H-indoles (general procedure)

A mixture of 0.12 g **16c** (0.4 mmol) and ethyl iodide (5.0 mmol) or benzyl bromide (4.0 mmol) in 10 cm^3 EtOH was treated with aqueous KOH at room temperature for 20 min. The precipitate formed was collected by filtration and crystallized from EtOH to give colourless crystals of **17a–b**.

2-(5-Ethylsulfanyl-4-phenyl-4H-[1,2,4]triazol-3-yl)-1H-indole (**17a**; $C_{18}H_{16}N_4S$)

Yield: 95%; m.p.: 229–230°C; IR (KBr): $\nu = 3205$s, 3050m, 2950w, 1590s, 1570s, 1490s, 1250m, 1120s, 785s, 730s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 11.4 (s, NH_{indole}, exchangeable), 6.8–7.7 (m, $9H_{arom}$), 5.6 (s, CH_{indole}), 3.4–3.1 (q, $J = 7$ Hz, 2H, SCH_2CH_3), 1.3–1.5 (t, $J = 7$ Hz, 3H, SCH_2CH_3) ppm; MS: *m/z* (%) = 319 [M^{-1}] (100), 304 (4), 291 (55), 287 (16), 259 (2), 232 (6), 218 (14), 210 (13), 182 (10), 164 (2), 156 (4), 149 (18), 141 (29), 129 (4), 116 (16), 105 (30), 102 (5), 77 (38), 51 (8).

2-(5-Benzylsulfanyl-4-phenyl-4H-[1,2,4]triazol-3-yl)-1H-indole (**17b**; $C_{23}H_{18}N_4S$)

Yield: 81%; m.p.: 218–221°C; IR (KBr): $\nu = 3200$w, 3030w, 2900w, 1610m, 1595w, 1520m, 1485m, 1310s, 1020m, 730s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 6.6–7.4 (m, $14H_{arom}$), 5.5 (s, CH_{indole}), 4.1 (s, 2H, SCH_2) ppm.

2-(5-(1H-Indol-2-yl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-1-aryl-ethanone (general procedure)

A mixture of 0.12 g of **16c** (0.4 mmol) and the corresponding phenacyl bromide derivative (0.42 mmol) in 10 cm^3 EtOH was refluxed for 3 h in the presence of 0.2 g of anhydrous CH_3COONa. The precipitate formed was collected by filtration and washed with H_2O (3x). The crude product was recrystallized fom EtOH to give colorless crystals of **18a**,**b**.

2-(5-(1H-Indol-2-yl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-1-(4-methoxy-phenyl)-ethanone (**18a**; $C_{25}H_{20}N_4O_2S$)

Yield: 88%; m.p.: 258–261°C; IR (KBr) $\nu = 3245$s, 3050m, 2950w, 2900w, 2870w, 1680s, 1595s, 1570s, 1490s, 1250s, 1170s, 820s, 795s, 725s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 6.8–7.8 (m, $13H_{arom}$), 5.5 (s, CH_{indole}), 4.7 (s, 2H, SCH_2), 3.8 (s, 3H, OCH_3) ppm.

2-(5-(1H-Indol-2-yl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-1-(4-chloro-phenyl)-ethanone (**18b**; $C_{24}H_{17}N_4OSCl$)

Yield: 67%; m.p.: 238–241°C; IR (KBr): $\nu = 3240$s, 3050m, 2960w, 2910w, 2870w, 1685s, 1590s, 1570s, 1495s, 1250s, 1160s, 820s, 795s, 730s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 11.8 (s, NH_{indole}, exchangeable), 6.7–7.7 (m, $13H_{arom}$), 5.5 (s, CH_{indole}), 4.75 (s, 2H, SCH_2) ppm.

2-(5-(1H-Indol-2-yl)-4-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-malonic acid diethyl ester (**19**; $C_{23}H_{22}N_4O_4S$)

A mixture of 0.12 g **16c** (0.4 mmol) and bromodiethyl malonate (0.4 mol) in 10 cm^3 EtOH was refluxed in the presence of 0.2 g anhydrous CH_3COONa for 3 h. The precipitate formed was collected by filtration and washed with H_2O (3x). The crude product was recrystallized from EtOH to give colorless crystals.

Yield: 81%; m.p.: 181–183°C; IR (KBr): $\nu = 3240$s, 3050m, 2970w, 2800w, 1740s, 1630s, 1600s, 1580s, 1490s, 1300s, 1260s, 1170s, 795s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, δ, 90 MHz): 11.4 (s, NH_{indole}, exchangeable), 6.9–7.7 (m, $4H_{arom}$), 5.75 (s, 1H, SCH), 5.45 (s, CH_{indole}), 4.1–4.3 (q, $J = 7$ Hz, 4H, $2CH_2$), 1.2–1.4 (t, $J = 7$ Hz, 6H, $2CH_3$) ppm.

Acknowledgment

We are grateful thank to Prof. *H. Falk*, Chemistry Department, University of Linz, A-4040 Linz, Austria, for helpful discussion. Thanks are also due to Prof. *T. Izumi*, Department of Chemistry and

Chemical Engineering, Faculty of Engineering, Yamagata University, Yonezawa 992-8510, Japan, for her kind assistance, Assiut University, Assiut and to the Chemistry Department, 71516, Egypt, for support of this work.

References

[1] a) Fernandez-Alvarez E, Lone M, Monge A (1969) Bull Soc Chim Fr 1932; b) Marco JL (1998) J Heterocycl Chem **35**: 475
[2] a) Perez S, Lasheras B, Oset C, Monge A (1997) J Heterocycl Chem **34**: 1527; b) Cruces MA, Elorriaga C, Fernandes-Alvarez E (1991) Eur J Med Chem **26**: 33; c) Cruces MA, Elorriaga C, Fernandes-Alvarez E (1990) Biochem Pharmacol **40**: 535
[3] Monge Vega A, Palop JA, Gracia CI, Fernandez AE (1982) An Acad Farm **48** (2): 213
[4] Kasahara A (1987) Jpn Kokai Tokkyo Koho JP 62, 153, 271
[5] Ebright RH, Wong JR (1981) Proc Natl Acad Sci USA **78** (7): 4011
[6] Alemany A, Bernabè M, Elorriaga C, Fernandez-Alvarez E, Tamayo ML, Lopez ON (1966) Bull Soc Chim Fr 2486
[7] a) Doyle FP, Ferrier W, Holland DO, Mehta MD, Nayler JHC (1956) J Chem Soc 2853; b) Kelarev VI, Shvekhgeimer GA (1982) Chem Heterocycl Compd (Engl Transl) **18** (3): 258
[8] a) Nogrady T, Morris L (1969) Can J Chem **47**: 1999; b) Monge Vega A, Aldana I, Fernandez-Alvarez E (1978) Eur J Med **13**: 573; c) Kobayashi G, Furukawa S (1964) Chem Pharm Bull **12**: 1129; d) Monge Vega A, Huarte V, Palop JA, Martinez MT, Fernandez-Alvarez E (1977) Ann Quim **73**: 278; e) Monge Vega A, Palop JA, Martinez MT, Fernandez-Alvarez E (1979) Ann Quim **75**: 889
[9] Monge A, Aldana I, Lezamiz I, Fernandez-Alvarez E (1984) Synthesis 160

Received October 17, 2000. Accepted (revised) December 12, 2000