Journal of the Chinese Chemical Society, **2001**, *48*, 921-927

Synthesis of Some New Spiro, Isolated and Fused Heterocycles Based on 1*H*-indole-2-one

T. I. El-Emary*[†], R. A. Ahmed and E. A. Bakhite
Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

The reaction of 3-benzoylcyanomethylidine-1(*H*)-indole-2-one (**1**) with a variety of active methylene compounds, thioglycolic acid, glycine, hydrazine hydrate and phenyl hydrazine led to the formation of compounds **4a-d-10**. 3-Thiosemicarbazide-1(*H*)-indole-2-one **2** on reaction with α-halocarbonyl compounds gave compounds **11a-c**, **12a-c**. The latter compounds on heating with phosphoryl chloride, cyclization takes place *via* losing water to give the angular tetracyclic compounds **13a**,**b** and **14a-c**. Cyanoacetic hydrazone derivative **3** readily cyclized upon heating in triethyl orthoformate to give the tricyclic system, oxopyridazino indole **15**.

On the other hand, the reaction of **3** with benzylidine malononitrile and benzylidene ethylcyanoactate gave the pyranyl hydrazone derivatives **16a**,**b**.

INTRODUCTION

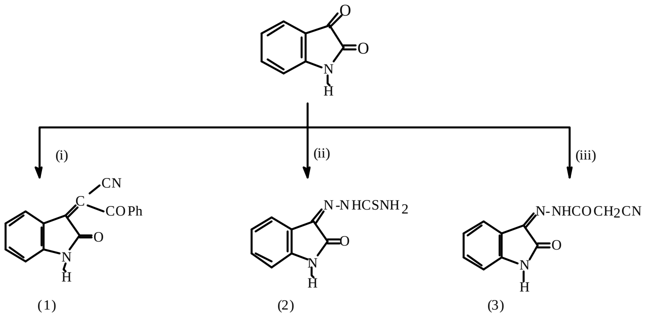
A review describing preparations and reactions of indolin-2(3*H*)-ones was published few years ago.[1] Numerous isatin derivatives exhibit significant biological, medicinal and pharmacological activities,[2-4] such as antituberculous, antihypoxing agent, anticonvulsant, antihyperglycemic; active against salmonella, typhi and against vibrio cholerae. Besides, they are used in treating and preventing pestvirus.[5] Moreovere, they show antifertility activity.[6]

From all the mentioned above and in continuation of the previous work in the synthesis of heterocyclic compounds containing indole moiety,[2c] herein we wish to report synthesis of some new spiro, isolated and fused heterocycles based on 1*H*-indole-2-one.

RESULTS AND DISCUSSION

1*H*-Indole-2,3 dione was readily condensed with benzoylacetonitrile[7] and with thiosemicarbazide[8] in boiling ethanol to give 3-benzoylcyanomethylidine-1(*H*)-indole-2-one **1** and 3-thiosemicarbazide-1(*H*)-indole-2-one **2**, respectively. Its reaction with cyanoacetic hydrazide gave 2-cyano-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)hydrazide **3**.[9]

Scheme I



(i) $CH_2(CN)(COPh)$
(ii) $NH_2NHCSNH_2$
(iii) $NH_2NHCOCH_2CN$

In this paper, a series of new spiro, isolated and fused heterocycles based on 1*H*-indole-2-one were prepared using the ylidene **1** and a variety of active methylene compounds. Thus, subjecting compound **1** to react with, malononitrile, ethyl cyano acetate, ethyl acetoacetate, acetylacetone, 1-phenyl-2*H*-3,5-pyrazoline-dione, 3-methyl-1-phenyl-2-pyrazoline-5-one and thiobarbituric acid in ethanol containing a catalytic amount of triethyl amine produce the spiro pyrano indole derivatives **4a-d-7**, respectively.

The reaction of thioglycolic acid and/or glycine with the ylidene **1** in boiling acetic acid led to the formation of the spiro-thieno-indole and the spiro-pyrrolo-indole derivatives **8a**,**b**.

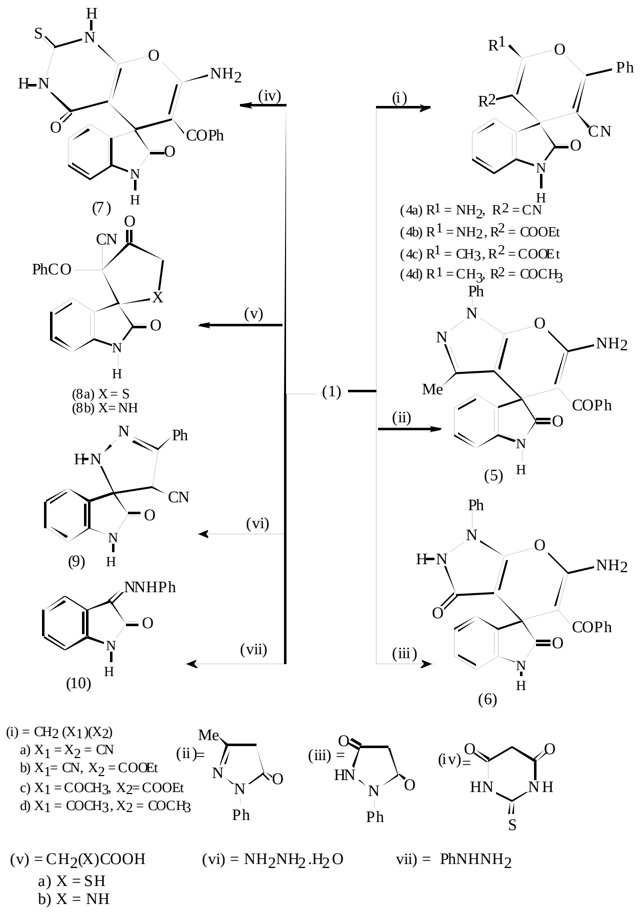
On the other hand, when **1** was treated with hydrazine hydrate in ethanol, the spiro pyrazolo indole derivative **9** was produced, while when phenyl hydrazine was used instead, ylidenic bond cleavage[10] takes place to give 3-phenyl hydrazone **10**.

The thiazolidine and thiazolidinone derivatives **11a-c** and **12a-c** were produced when the thiosemicarbazone **2** was refluxed with α-haloketones and/or α-haloestres in ethanol and in the presence of sodium acetate. The α-haloketones and

---

† Current Address: Al Jouf Teachers College, P.O. Box: 269, Al Jouf, Saudi Arabia

Scheme II



α-haloesters used were: phenacyl bromide, chloroacetone, chloroacetyl ethylacetoacetate, 2-bromo methylpropiopante, chloroacetic acid and bromodiethylmalonate.

On heating compounds **11a**,**b** and **12a-d** with phosphoryl chloride, cyclization takes place *via* losing water to give the angular tetracyclic compounds, thiazolo-triazino-indole and thiazolo-triazino-indole-2-one **13a**,**b** and **14a-c**.

Cyanoacetic hydrazone derivative **3** obtained from condensation of 1(*H*) indolin-2,3-dione with cyanoacetic hydrazide readily cyclized upon heating in triethyl orthformate to give the tricyclic system, oxopyridazino indole **15**.

On the other hand, the reaction of **3** with benzylidine malononitrile and benzylidene ethylcyanoacetate gave the pyranyl hydrazone indolone derivatives **16a**,**b**.

EXPERIMENTAL SECTION

The melting points were determined with a Buchi 500 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 Infrared Spectrophotometer (KBr wafer technique). ^{1}H-NMR spectra were measured on a Varian Associate EM-390 (90 MHz) spectrometer, chemical shifts are reported in ppm, internal standard was tetramethylsilane (δ scal). Mass spectra were measured on a Varian HP Model (MS 5988) at 70 eV with temperature 160-400 °C.

3-Benzoylcyanomethylidine-1(*H*)-indole-2-one (1), indoline-2,3-dione-3-thiosemicarbazone (2), and indoline-2,3-dione-3-cyanoacetic acid (3a)

Were prepared according to methods reported in the literature.[7-9]

Indoline-2,3-dione-3-phenylhydrazone (10)

Was found to be identical to that reported in the literature.[7]

Reactions of compound (1) with, malononitrile, ethylcyanoacetate, ethylacetoacetate, acetylacetone, 1-phenyl-2*H*-3,5-pyrazoline-dione, 3-methyl-1-phenyl-2-pyrazoline-5-one, thiobarbituric acid: Formation of compounds 4a-d-7

General procedure

A mixture of compound **1** (0.002 mole) and the previously mentioned compounds in ethanol containing a catalytic amount of triethyl amine was heated under reflux for 1-3 h. The precipitate that formed was collected by filtration and crystallized from the proper solvent to give compounds **4a-d-7**, respectively. The physical and spectral data are given in Table 1.

2-Amino-3,5-dicyano-6-phenyl-spiro[indoline-3,4-1′(*H*)pyran]-2′-one (4a)

Was separated from ethanol as colourless crystals (74%).

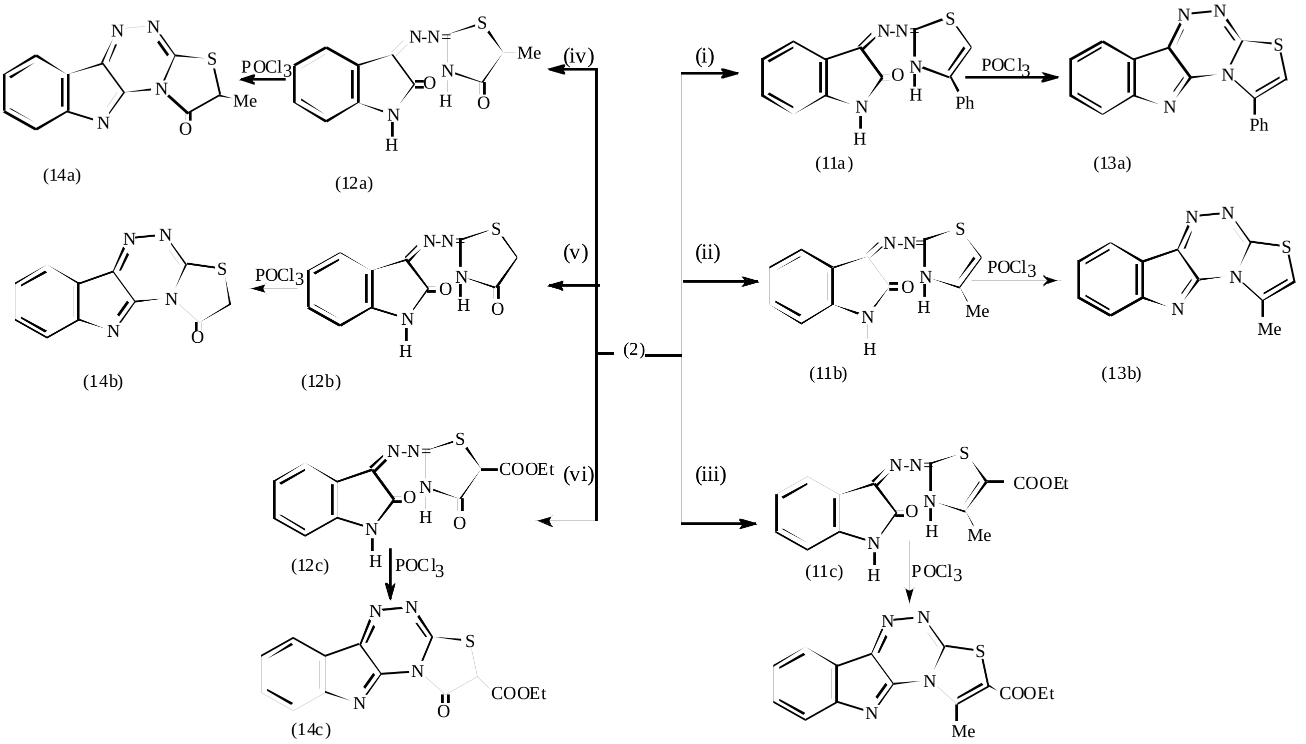
2-Amino-3-carboethoxy-5-cyano-6-phenyl-spiro[indolin-3,4-1′(*H*)pyran]-2′-one (4b)

Was separated from ethanol as colourless crystals (57%).

3-Carboethoxy-5-cyano-3-methyl-6-phenyl-spiro[indolin-3,4-1′(*H*)pyran]-2′-one (4c)

Was separated from ethanol as colourless crystals (42%).

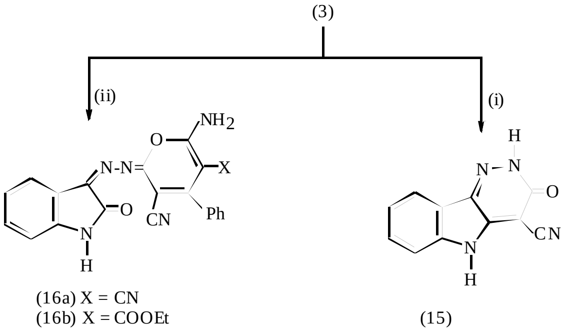
Scheme III



(i) $PhCOCH_2Br$ (ii) CH_3COCH_2Cl (iii) $ClCH(COCH_3)(COOEt)$

(iv) $CH_3CH(Br)(COOMe)$ (v) $ClCH_2COOH$ (vi) $BrCH(COOEt)_2$

Scheme IV



(i) = $CH(EtO)_3$

(ii) = $PhCH{=}C(X)(CN)$

a) X = CN

b) X = COOEt

3-Acetyl-5-cyano-2-methyl-5-phenyl-spiro[indolin-3,4-1′(*H*)pyran]-2′-one (4d)

Was separated from diluted ethanol as colourless crystals (36%).

5-Benzoyl-6-cyano-3-methyl-2′-oxo-phenyl-spiro[pyrano-[2,3-c]pyrazole-4(1*H*)-3′-[2]indoline] (5)

Was separated from ethanol as colourless crystals (52%).

5-Benzoyl-6-cyano-3,2′-dioxo-phenyl-spiro[pyrano[2,3-c]-pyrazole-4(1*H*)-3′-[2]indoline] (6)

Was separated from benzene-petroleum ether (60/80 °C)(1:1) as colourless crystals (38%).

5-Benzoyl-6-cyano-4,2′-dioxo-2-thioxo-spiro[pyrano[2,3-c]-pyrimidine-4(1*H*)-3′-[2]indoline] (7)

Was separated from dioxan-water (3:1) as colourless crystals (43%).

Reaction of compound (1) with thioglycolic acid and glycine: Formation of Compounds (8a,b)

General procedure

A mixture of compound **1** (0.001 mole) and thioglycolic acid/or glycine (0.001 mole) in acetic acid (20 mL)

Table 1.

Compd. No	Mp °C (Yield%)	Mol. Formula (M.Wt)	IR/Cm^{-1}	^{1}H NMR/δ	MS *m/z* (%)
4a	264-265 (74)	$C_{20}H_{12}N_4O_2$ (340.3)	3300-3180 (NH_2 + NH), 2200 (CN), 1650 (CO)	(d_6-DMSO): 3.3 (s,2H,NH_2), 6.85-7.85, (m,9H,Ar-H), 11.8 (NH)	340 (20)
4b	226-227 (57)	$C_{22}H_{17}N_3O_4$ (387.3)	3300-3180 (NH_2 + NH), 2210 (CN), 1720, 1650 (2CO)	(CF_3COOD): 0.8-1.0 (t,3H,$\underline{CH_3}CH_2$), 3.85-4.0 (q,2H,$\underline{CH_2}CH_3$), 7.0-7.85 (m,9H,Ar-H)	387 (18)
4c	227-228 (42)	$C_{23}H_{18}N_2O_4$ (386.3)	3300 (NH), 2200 (CN), 1780, 1650 (2CO)	(d_6-DMSO): 0.9-1.1 (t,3H,$\underline{CH_3}CH_2$), 2.5 (s,3H,CH3), 3.85-4.0 (q,2H,$\underline{CH_2}CH_3$), 7.1-7.9 (m,9H,Ar-H), 11.5 (s,1H,NH)	386 (22)
4d	216-218 (36)	$C_{22}H_{16}N_2O_3$ (356.3)	3250 (NH), 2220 (CN), 1760, 1720, 1650 (3CO)	(d_6-DMSO): 2.4 (s,3H,CH_3), 3.2 (s,3H,$COCH_3$), 7.1-7.9 (m,9H,Ar-H), 11.8 (s,1H,NH)	
5	268-270 (52)	$C_{27}H_{20}N_4O_3$ (448.4)	3400-3300 (NH_2 + NH), 1720, 1650 (2CO)	(CF_3COOD): 2.8 (s,3H,CH_3), 7.8-8.0 (m,14H,Ar-H)	
6	247-248 (38)	$C_{26}H_{18}N_4O_4$ (450.3)	3380-3220 (NH_2 + 2NH), 1700, 1660, 1640 (3CO)	(CF_3COOD): 7.9-8.1 (m,14H,Ar-H)	
7	196-197 (43)	$C_{21}H_{14}N_4O_4S$ (418.3)	3360-3200 (NH_2 + 3NH), 1720, 1660, 1640 (3CO)	(CF_3COOD): 7.8-8.0 (m,9H,Ar-H)	
8a	143-145 (27)	$C_{19}H_{12}N_2O_3S$ (348.2)	3300 (NH), 2210 (CN), 1720, 1700, 1650 (3CO)	(d_6-DMSO): 4.1 (s,2H,CH_2), 7.1-7.7 (m,9H,Ar-H), 11.5 (s,1H,NH)	
8b	160-162 (34)	$C_{19}H_{13}N_3O_3$ (331.2)	3400-3200 (2NH), 2200 (CN), 1720, 1690, 1640 (3CO)	(d_6-DMSO): 4.2 (s,2H, CH_2), 7.2-7.8 (m,9H,Ar-H), 11.5, 11.8 (2s,2H,2NH)	
9	176-178 (62)	$C_{17}H_{11}N_4O$ (287.2)	3300-3150 (2NH), 2200 (CN), 1650 (CO)	(d_6-DMSO): 6.8 (s,1H,NH), 7.1-7.8 (m,9H,Ar-H), 11.2, 12.5 (2s,2H,2NH)	287 (18)
11a	273-275 (78)	$C_{17}H_{12}N_4OS$ (320.4)	3300-3250 (2NH), 1660 (CO)	(d_6-DMSO): 6.5-7.6 (m,10H, Ar-H,-CH=), 10.9, 11.8 (2s,2H,2NH)	320 (28)
11b	256-258 (61)	$C_{12}H_{10}N_4OS$ (258.3)	3400-3300 (2NH), 1650 (CO)	(d_6-DMSO): 2.5 (s,3H,CH_3), 6.7-7.8 (m,10H,Ar-H,-CH=), 11.2, 11.8 (2s, 2H,2NH)	258 (11)
11c	216-218 (48)	$C_{15}H_{14}N_4O_3S$ (330.4)	3400-3150 (2NH), 1690, 1650 (2CO)	(d_6-DMSO): 1.2-1.3 (t,3H, $CH_2\underline{CH_3}$), 2.5 (s,3H,CH_3), 3.5-3.7 (q,3H,$\underline{CH_2}CH_3$), 6.8-7.8 (m,4H,Ar-H), 11.5, 12.6 (2s, 2H,2NH)	
12a	273-275 (52)	$C_{12}H_{10}N_4O_2S$ (274.3)	3250-3150 (2NH), 1690, 1640 (2CO)	(d_6-DMSO): 2.5 (s,3H,CH_3) 6.7-7.8 (m,5H,Ar-H,-CH), 10.8, 11.6 (2s,2H,2NH)	
12b	290-292 (66)	$C_{11}H_8N_4O_2S$ (260.3)	3300-3150 (2NH), 1680, 1650 (2CO)	(d_6-DMSO): 4.2 (s,3H,CH_2), 6.9-7.8 (m,4H,Ar-H), 10.2, 11.5 (2s, 2H,2NH).	260 (24)
12c	223-225 (58)	$C_{14}H_{12}N_4O_4S$ (332.4)	3380, 3250 (2NH), 1720, 1680, 1640 (3CO)	(d_6-DMSO): 1.1-1.2 (t,3H,-CH_2-$\underline{CH_3}$), 4.0-4.2 (q,2H,$\underline{CH_2}$-CH_3), 7.0-7.8 (m,4H,Ar-H).	
13a	> 300 (62)	$C_{17}H_{10}N_4S$ (302.3)	3050 (CH,aliph.), 2900 (CH,arom.)	(CF_3COOD): 7.8-8.1 (m,10H,Ar-H+ -CH=)	302 (18)
13b	> 300 (52)	$C_{12}H_8N_4S$ (240.3)	3020 (CH,aliph.), 2930 (CH,arom.)	(CF_3COOD): 2.8 (s,3H,CH_3), 7.8-8.1 (m,4H,Ar-H).	
13c	> 300 (41)	$C_{15}H_{12}N_4O_2S$ (312.4)	3010 (CH,aliph.), 2920 (CH,arom.), 1730 (CO)	(CF_3COOD): 1.2-1.3 (t,3H,CH_2-$\underline{CH_3}$), 3.0 (s,3H,CH_3), 3.6-3.8 (q,2H,$\underline{CH_2}$-CH_3), 7.7-7.9 (m,4H,Ar-H)	
14a	> 300 (48)	$C_{12}H_8N_4OS$ (256.3)	3010 (CH,aliph.), 2920 (CH,arom.), 1670 (CO)	(CF_3COOD): 2.7 (s,3H,CH_3), 7.8-8.0 (m,4H,Ar-H)	

14b	> 300 (57)	$C_{11}H_6N_4OS$ (242.3)	3050 (CH,aliph.), 2920 (CH,arom.), 1690 (CO)	(CF_3COOD): 4.3 (s,2H,CH_2), 7.7-7.9 (m,4H,Ar-H)	242 (18)
14c	> 300 (42)	$C_{14}H_{10}N_4O_3S$ (314.4)	3040 (CH,aliph.), 2910 (CH,arom.), 1680 (CO)	(CF_3COOD): 1.2-1.3 (q,2H,$\underline{CH_2}$-CH_3), 2.1 (s,1H,CH), 3.8-3.9 (t,2H,$\underline{CH_2}CH_3$), 7.8-8.0 (m,4H,Ar-H)	
15	> 300 (38)	$C_{11}H_6N_4O$ (210.2)	3300 (NH), 2220 (CN), 1660 (CO)	(CF_3COOD): 7.7-7.9 (m,4H,Ar-H)	
16a	> 300 (59)	$C_{21}H_{12}N_6O_2$ (380.4)	3400-3250 (NH_2 + NH), 2220 (CN), 1660 (CO)	(CF_3COOD): 7.8-8.1 (m,9H,Ar-H)	
16b	> 300 (36)	$C_{23}H_{17}N_5O_4$ (427.4)	3400-3200 (NH_2 + NH), 2210 (CN), 1650 (CO)	(CF_3COOD): 1.3-1.4 (t,3H,CH_2-$\underline{CH_3}$), 3.8-4.0 (q,2H,$\underline{CH_2}CH_3$), 7.8-8.0 (m,4H,Ar-H)	

was heated under reflux overnight; the solvent was removed under reduced pressure and the residue was triturated with hot water. The solid product was collected and crystallized from the proper solvent to give compounds **8a**,**b**, respectively. The physical and spectral data are given in Table 1.

3-Benzoyl-3-cyano-4,2′-dioxo-spiro[indolin-3,2-1′(*H*)tetrahydrothiophine] (8a)

Was separated from dioxan-water (1:1) as colourless crystals (27%).

3-Benzoyl-3-cyano-4,2′-dioxo-spiro[indolin-3,2-1′(*H*)pyrrol] (8b)

Was separated from dioxan-water (1:1) as colourless crystals (34%).

Reaction of compound (1) with hydrazine hydrate: Formation of compound (9)

A mixture of compound **1** (0.001 mole) and hydrazine hydrate (1 mL) was heated in ethanol (20 mL) under reflux for 1 h. The solution was concentrated and the product obtained was filtered, washed with water, dried. The physical and spectral data are given in Table 1.

4-Cyano-3-phenyl-2′-oxo-spiro[indolin-3,2-1′(*H*)-1(*H*)-pyrazol] (9)

Was separated from ethanol-water (1:1) as colourless crystals (62%).

Reaction of compound (3) with α-halocarbonyl compounds: formation of compounds (11a,b) and (12a-d)

General procedure

A mixture of compound **2** (0.005 mole) and α-halocarbonyl compound (0.005 mole) and fused sodium acetate (0.01 mole) in ethanol (30 mL) was heated under reflux for 1-4 h. The solid product was filtered off and crystallized from the proper solvent to give compounds **11a**,**b** and **12a-d**. The physical and spectral data are given in Table 1. The α-haloketones and α-haloesters used were: phenacyl bromide, chloro acetone, chloroacetyl ethylacetoacetate, 2-bromo methylpropiopante, chloro acetic acid and bromo diethyl malonate.

1(*H*)-3-hydrazono-4′-phenyl-3′(*H*)thiazolyl-indolin-2-one (11a)

Was separated from ethanol as orange crystals (78%).

1(*H*)-3-hydrazono-4′-methyl-3′(*H*)thiazolyl-indolin-2-one (11b)

Was separated from ethanol as orangish-brown crystals (61%).

5′-Ethyl-3-hydrazono-4′-methyl-3′(*H*)thiazolyl-indolin-2-one-carboxylate (11c)

Was separated from ethanol as orangish-red crystals (48%).

1(*H*)-3-hydrazono-5′-methyl-4′-oxo-3′(*H*)thiazolyl-indolin-2-one (12a)

Was separated from ethanol as yellowish-orange crystals (52%).

1(*H*)-3-hydrazono-5′-oxo-3′(*H*)thiazolyl-indolin-2-one (12b)

Was separated from ethanol as brownish-orange crystals (66%).

5′-Ethyl-3-hydrazono-4′-oxo-3′(*H*)thiazolyl-indolin-2-one-carboxylate (12c)

Was separated from ethanol as reddish-orange crystals

(58%).

Heating of compounds (11a,b) and (12a-d) in phosphoryl chloride. Formation of compounds (13a,c) and (14a-c)

A mixture of compound **11a-c** or **12a-c** and $POCl_3$ was heated on a water bath for 1 h. After cooling, the reaction mixture was poured into ice-water; the solid product formed was filtered off, washed with water, dried and crystallized from the proper solvent to give compounds **13a-c** and **14a-c**. The physical and spectral data are given in Table 1.

3-Phenyl-thiazolo[2′,3′:3,4]-1,2,4-triazino[5,6-b]indole (13a)

Was separated from dioxan-water (1:1) as brownish-violet crystals (62%).

3-Methyl-thiazolo[2′,3′:3,4]-1,2,4-triazino[5,6-b]indole (13b)

Was separated from dioxan-water (1:1) as reddish-brown crystals (52%).

2-Ethoxycarbonyl-3-methyl-thiazolo[2′,3′:3,4]-1,2,4-triazino-[5,6-b]indole (13c)

Was separated from dioxan-water (1:1) as brown crystals (41%).

2-Methyl-thiazolo[2′,3′:3,4]-1,2,4-triazino[5,6-b]indole-3(2*H*)-one (14a)

Was separated from dioxan-water (1:1) as brown crystals (48%).

[2′,3′:3,4]-1,2,4-triazino[5,6-b]indole-3(2*H*)-one (14b)

Was separated from DMF-water (1:1) as brownish-violet crystals (57%).

2-Ethoxycarbonyl-thiazolo[2′,3′:3,4]-1,2,4-triazino[5,6-b]-indole-3(2*H*)-one (14c)

Was separated from dioxan-water (1:1) as brown crystals (48%).

Heating of compound (3) in triethyl orthoformate. Formation of 4-cyano-2,3,5-trihydro-3-oxopyridazino[4,3-b]-indole (15)

A mixture of compound **3** (0.002 mole) and triethyl orthoformate (10 mL) was heated on a water bath for 6 h. After cooling the reaction mixture was poured into ice-water, the solid product was filtered, washed with water, dried and crystallized from dioxan-water (3:1) (38%). The physical and spectral data are given in Table 1.

Reaction of compound (3) with benzylidinemalononitrile, benzylidine ethylcyanoacetate: Formation of compounds (16a,b)

General procedure

A mixture of compound **3** (0.002 mole) and benzylidinemalononitrile or benzylidine ethylcyanoacetate (0.002 mole) in ethanol (30 mL) was heated under reflux for 3-5 h. The solid product obtained was filtered, washed with water, dried and cryslallized from the proper solvent to give compounds **16a,b**. The physical and spectral data are given in Table 1.

3-(2′-amino-3′,5′-dicyano-4′-phenyl-pyran-6′-yl)hydrazono-2,3-dihydroindoline-2-one (16a)

Was separated from dioxan-water (1:1) as brown crystals (59%).

3-(2′-amino-3′-carboethoxy-5′-cyano-4′-phenyl-pyran-6′-yl)hydrazono-2,3-dihydroindoline-2-one (16b)

Was separated from dioxan-water (1:1) as brown crystals (37%).

Received February 2, 2001.

Key Words

Synthesis; Indole derivatives.

REFERENCES

1. Karp, G. M. *Org. Prep. Proced. Int.* **1993**, *25(5)*, 481; *Chem. Abstr*. **1994**, *120*, 134153g.
2. (a) Karali, N.; Terzioglu, N.; Gursoy, A. *Arzneim.-Forsch*. **1998**, *48(7)*, 758; *Chem. Abstr*. **1998**, *129*, 133555. (b) Pandeya, S. N.; Sriram, D. *Acta Pharm. Turc.* **1998**, *40(1)*, 33; *Chem. Abstr*. **1998**, *129*, 109060c. (c) El-Emary, T. I. *Polish J. Chem.* **1996**, *70*, 1143. (d) Clow, A.; Davidson, J.; Glover, V.; Halket, J. M.; Milton, A. S.; Sandler, M.; Watkins, P. J. *Neuro Sci. Lett.* **1989**, *107*, 327; *Chem. Abstr*. **1990**, *112*, 116689s. (e) Alam, M.; Ahmad, M.; Rasheed, A.; Saleem, M; Javaid, M. K., Ikram, S. *Indian J. Exp. Biol.* **1990**, *28*, 940; *Chem. Abstr*. **1991**, *114*, 74632b. (f) Meis, R. J.; Condit, R. C. *Virology*. **1991**, *182*, 442; *Chem. Abstr*. **1992**, *116*, 1416r. (g) Bodo, G. *Bid Wiss*. **1972**, 9, 928; *Chem. Abstr*. **1973**, *78*, 2378t. (h) Mohan, J.; Anjaneyulu, G. S. R.; Verma, K.; Verma, P. *Chim. Acta Turc*. **1990**, *18(20)*, 331; *Chem.*

Abstr **1992**, *116*, 59323z. (i) Holla, B.; Shivarama, U.; Udupa, V. *Heterocycles* **1991**, *32(6)*, 1081. (j) Joshi, K. C.; Dandia, A.; Baweja, S. *J. Indian Chem. Soc.* **1989**, *66(8)*, 690. (k) Mohan, J.; Verma, P. *J. Indian Chem. Soc.* **1989**, *66(4)*, 252. (l) Mahmoud, A. M.; Abdel-Rahman, A. E.; El-Naggar, G. M.; EI-Sherief, H.A. *Indian J. Chem*. **1984**, *23B*, 379. (m) Varma, R. S.; Garg, P. K. *Acta Pharm. Jugosl.* **1980**, *30(4)*, 199.

3. Sarangapani, M.; Narayan, A. R.; Jayamma, Y.; Reddy, V. M. *Indian Drugs* **1998**, *35(6)*, 336; *Chem. Abstr.* **1998**, *129*, 216578z. (b). Keller, S. *Mol. Toxicol.* **1987**, *1(2-3)*, 261; *Chem. Abstr.* **1998**, *108*, 17332f. (c) Moldvai, I.; Gacs-Baitz, E; Balazs, M.; Incze, M.; Szantay, C. *Arch. Pharm (Weinheim, Ger.)* **1996**, *329(12)*, 541. (d) Monge, A.; Palop, J.; Ramirez, C.; Font, M.; Fernandez-Alvarez, E. *Eur. J. Med Chem.* **1991**, *26(2)*, 179. (e) Katz, E. *Rev. Clin. Basic Pharmacol.* **1987**, *6(2)*, 119; *Chem. Abstr.* **1988**, *108*, 48704h. (f) Omar, M. B.; Bshba, N. H.; Salama, H. M. *Arch.Pharm. (Weinheim)* **1984**, *317*, 709.
4. Ram, J. V.; Dube, V.; Vlietinck, A. J. *J. Heterocycl. Chem.* **1987**, *24(5)*, 1435. (b) Soliman, F. S. G.; Salama, H. M. *Pharmazie.* **1983**, *38*, 585. (c) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (d) Sweetman, B. J.; Bellas, M.; Field, L. *J. Med. Chem.* **1969**, *12*, 888. (e) Rajopadhye, M.; Popp, F. D. *J. Heterocl. Chem.* **1987**, *24*, 1637. (f) Rajopadhye, M.; Popp, F. D. *J. Med. Chem.* **1988**, *31*, 1001.
5. Pevear, C. D.; Nitz, J. T.; Seipel, M. *PCT Int. Appl. WO **98** 36,752. (Cl.A61K3 1/555)*27 Aug 1998, U S Appl. 12 Feb. **1997**, *803*, 675; *Chem. Abstr* **1998**, *129*, 197982h.
6. Joshi, K. C.; Jam, R.; Chand, P.; Garg, S. *J. Indian Chem. Soc.* **1983**, *LX*, 760.
7. Abdel Lattif, F. F.; Regaila, H. A.; Gohar, A-k. M.; Mohammed, Y. S. *Indian J. Chem.* **1985**, *24B*, 775.
8. Holzbecher, Z. *Chem. Listy* **1950**, *44*, 126; *Chem. Abstr*. **1951**, 8005g.
9. Popp, F. *J. Heterocycl. Chem.* **1984**, *21*, 1641.
10. El-Sakka, I. A.; Kandil A.; El-Moghaer, M. H. *Arch. Pharm.*(Weinheim). **1983**, *316*, 76.