A New Method for the Synthesis of 6*H*,11*H*-Indolo[3,2-*c*]-isoquinolin-5-ones/thiones and their Reactions

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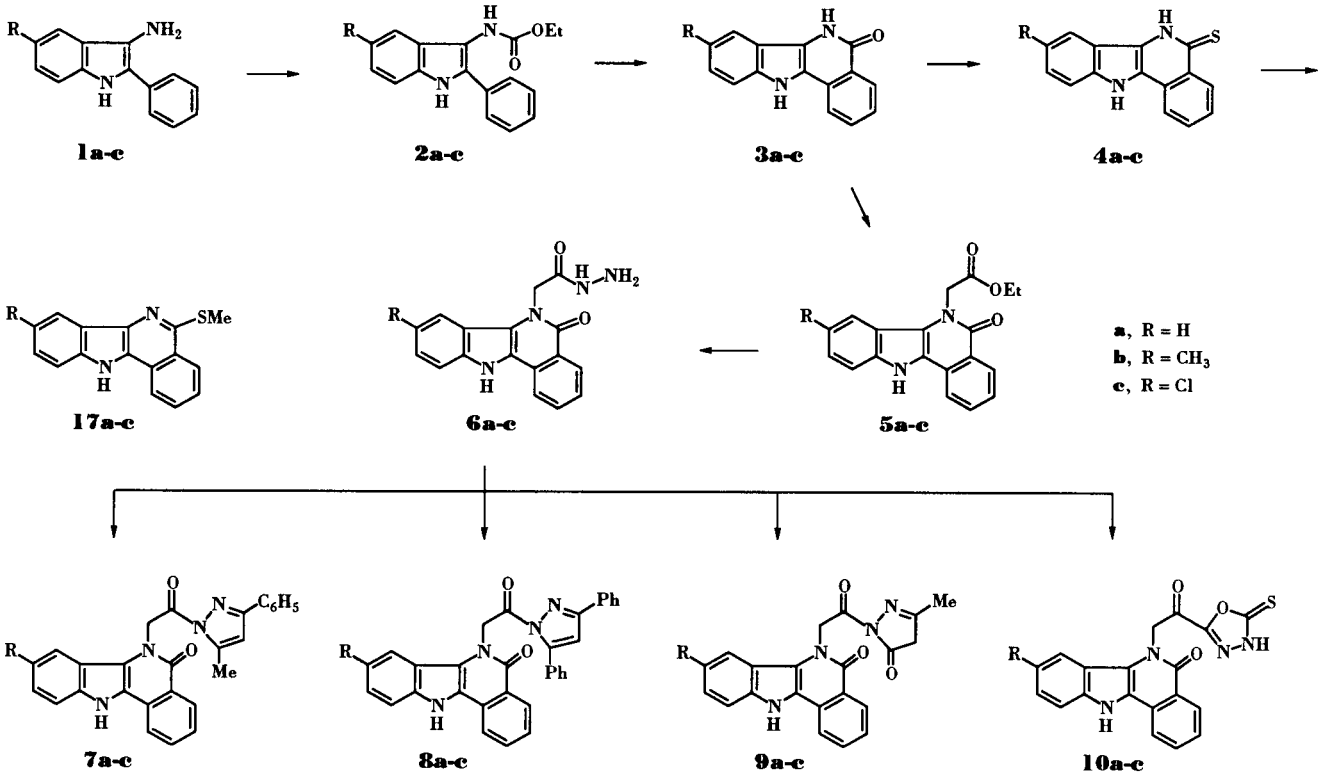
Received March 26, 1992

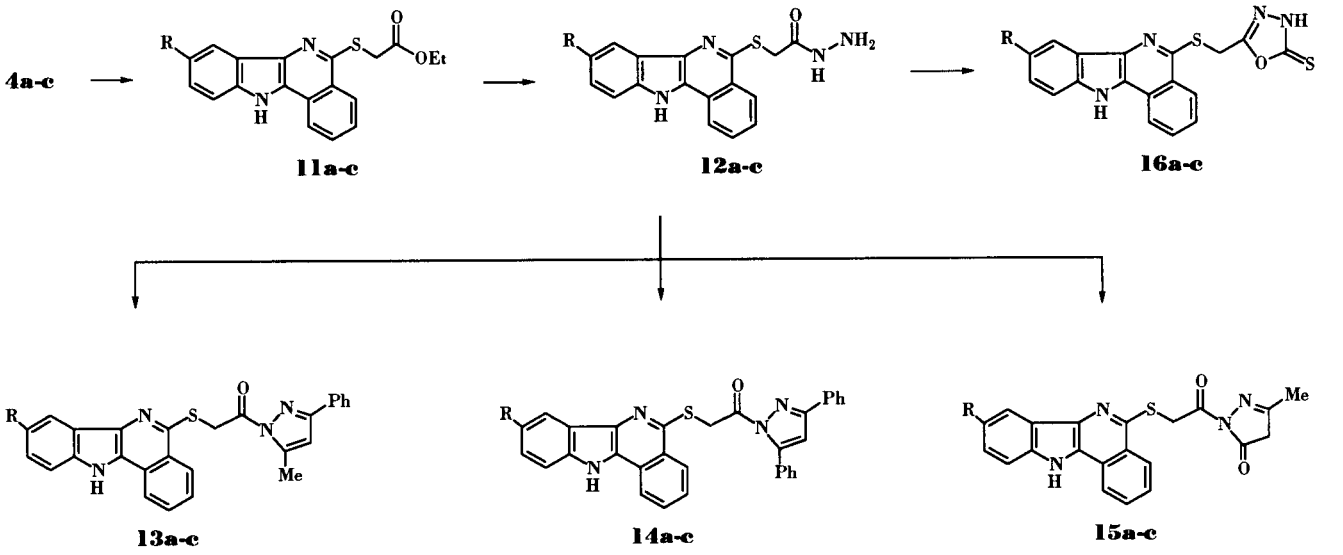
The synthesis of 8-substituted and unsubstituted 6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-ones/thiones **3a-c** and **4a-c** and their derivatives *viz*, ethyl (8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetates **5a-c**, (8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl hydrazides **6a-c**, 3,5-disubstituted-pyrazoles **7a-c** and **8a-c**, 3-substituted-pyrazol-5-ones **9a-c** and 5-(8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)methyl-1,3,4-oxadiazole-2-thiones **10a-c**, also ethyl (8-substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetates **11a-c**, (8-substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl hydrazides **12a-c**, 3,5-disubstituted-pyrazoles **13a-c** and **14a-c**, 3-substituted-pyrazol-5-ones **15a-c** and 5-(8-substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-yl)thiomethyl-1,3,4-oxadiazole-2-thiones **16a-c** is described.

J. Heterocyclic Chem., **30**, 603 (1993).

Indole and its derivatives possess a wide spectrum of biological activity. A literature survey revealed that the 11*H*-indolo[3,2-*c*]isoquinoline system was first synthesized by the cyclization of 3-acetamido-2-phenylindole using phosphorus pentoxide in nitrobenzene [1]. 5-Phenyl-11*H*-indolo[3,2-*c*]isoquinoline [2,3] was obtained as one of the by-products from the Schmidt reaction of 2,3-diphenylindone with hydrazoic acid in acetic acid and sulphuric acid. The same compound was also synthesized by the cyclization of 3-benzamido-2-phenylindole using phosphorus pentoxide in boiling nibrobenzene. 11*H*-Indolo[3,2-*c*]isoquinoline was also prepared by dehydrogenation of the corresponding 7,8,9,10-tetrahydro compound which had in turn been obtained by cyclization of the 4-isoquinolylhydrazone of cyclohexanone using fused zinc chloride [4]. The synthesis of 11*H*-indolo[3,2-*c*]isoquinolines, by cyclization of 2-phenylindole-3-carboxaldoximes in sulphoric acid, has been reported earlier [5] from this laboratory.

In continuation of our work on the synthesis of polyheterocyclic systems containing the indole nucleus [6-9], we now report a convenient method for the synthesis of the 11*H*-indolo[3,2-*c*]isoquinoline system with either an one or a thione function at the 5-position. These previously unreported compounds have been obtained by the thermal cy-





clization of ethyl 2-phenylindole-3-carbamates **2a-c** in boiling diphenyl ether followed by the reaction of the products with phosphorus pentasulphide in refluxing pyridine. These 5-ones/thiones were subsequently used in the preparation of disubstituted pyrazoles, pyrazolones and 1,3,4-oxadiazolethione groups at their 6- and 5-positions respectively.

The 8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-ones **3a-c** were obtained by thermal cyclization of ethyl 5-substituted-2-phenylindole-3-carbamates **2a-c** which had been prepared by a literature method [9]. The ir spectrum of **3c** displayed bands at 3425 (NH), 3150 (NH), 1640 (NH-C=O) cm^{-1}. Compounds **3a-c**, when refluxed with phosphorus pentasulphide in pyridine for 4 hours, afforded the corresponding 5-thiones **4a-c** in good yield. The ir spectrum of compound **4c** showed absorption bands at 3400 (NH), 3150 (NH-C=S), 1210 (C=S) cm^{-1}. The mass spectrum of **4c** showed the molecular ion M^+ at m/z 284 and 286 ($M^+ + 2$). Fragmentation of the molecular ion gave peaks at m/z 269, 271, 234 and 189 due to the sequential expulsion of NH, Cl and C=S fragment. Peaks were also observed at m/z 249, 189 and 164 due to the loss of Cl, NCS, and C_6H_4CS fragments, respectively, from the molecular ion. In case the compound **2c** had undergone thermal cyclization by abstracting hydrogen at 4-position of indole, the fragmentation pattern of the corresponding thione **4c** would have been different. This is in conformity with the structure assigned for **3c** and **4c**.

Treatment of compounds **3a-c** with ethyl chloroacetate in acetone, anhydrous potassium carbonate, under reflux conditions for 8 hours, afforded ethyl (8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetates **5a-c**. The ir spectrum of compound **5a** showed absorption peaks at 3475 (NH), 1740, 1670 (C=O) cm^{-1}. These esters **5a-c** react with hydrazine hydrate (99-100%) in ethanol under reflux conditions to yield the corresponding hydrazides **6a-c**. The ir spectrum of **6a** displayed bands at 3475 (NH), 3150, 3100 (NH/NH_2), 1670, 1630 (C=O) cm^{-1}. The mass spectrum of **6a** showed a molecular ion M^+ at m/z 306. These hydrazides reacted with the diketones, benzoyl acetone, dibenzoyl methane and ethyl acetoacetate in methanol containing a catlytic amount of concentrated hydrochloric acid to give the pyrazoles **7a-c** and **8a-c** and the pyrazol-5-ones **9a-c**, respectively. The ir spectrum of **7a** showed absorption peaks at 3475 (NH), 1670, 1630 (C=O) and 1580 (C=N) cm^{-1}. Compound **8a** displayed bands at 3475 (NH), 1750, 1650 (C=O), and 1620 (C=N) cm^{-1} in its ir spectrum. Compound **9a** showed bands in its ir spectrum at 3475 (NH), 1650, 1640, 1620 (C=O) and 1560 (C=N) cm^{-1}.

The hydrazides **6a-c** on reaction with methanolic potassium hydroxide and carbon disulphide at reflux conditions for 48 hours, afforded 5-(8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)methyl-1,3,4-oxadiazole-2-thiones **10a-c**. Compound **10a** displayed bands in the ir spectrum at 3475 (NH), 3100 (NH), 1640 (C=O), 1220 (C=S) cm^{-1}.

Reaction of 6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thiones **4a-c** with ethyl chloroacetate under the conditions described for compounds **5a-c** gave the thioacetates **11a-c** in high yield. The ir spectrum of **11b** showed absorption bands at 3375 (NH), 1740 (C=O), 1640 (C=N) cm^{-1} and the absence of band at 1220 cm^{-1} due to (C=S) stretching vibration observed in **4b**. The ^1H nmr spectrum showed signals at δ 12.2 (s, 1H, NH), 7.2-8.5 (m, 7H, Ar-H), 4.2 (q, 4H, -O-CH_2 and -S-CH_2), 1.29 (t, 6H, -OCH_2-CH_3 and -CH_3). The mass spectrum of **11b** showed molecular ion M^+ at m/z 350 and further peaks at 305, 231 and 216 due to sequential expulsion of fragments -OC_2H_5, -S-CH_2CO and -CH_3, respectively. Also a peak at 263 was observed due to the loss of -CH_2-C=O from fragment having m/z

305.

Treatment of the esters **11a-c** with hydrazine hydrate (99-100%) afforded the (8-substituted-11*H*-indolo[3,2-*c*]-isoquinolin-5-ylthio)acetylhydrazides **12a-c**. The ir spectrum of compound **12a** showed bands at 3300 (NH), 3250, 3150 (NH/NH_2), 1670 (C=O) and 1620 (C=N) cm^{-1}. The mass spectrum showed a molecular ion M^+ at m/z 322 from which peak at m/z 291 was obtained due to loss of -$NH-NH_2$. Subsequent simultaneous expulsion of C=O, -CH_2-CO and -S-CH_2-CO gave peaks at m/z 263, 249 and 217, respectively. These hydrazides **12a-c**, on reaction with benzoylacetone, dibenzoylmethane and ethyl acetoacetate furnished the corresponding pyrazoles **13a-c** and **14a-c** and pyrazolones **15a-c**, respectively. Compounds **13a** and **14a** displayed bands in their ir spectrum at about 3350 (NH), 1740 (C=O), 1620 (C=N) cm^{-1}. Similarly, compound **15a** displayed bands at 3350 (NH), 1735 and 1640 (C=O), 1560 (C=N) cm^{-1}. Absence of absorption peak at 3250, 3150 cm^{-1} due to NH/NH_2 and 1670 cm^{-1} due to amide carbonyl function provided strong evidence that cyclization had accured as depicted. The ^1H nmr of **13a-c**, **14a-c** and **15a-c** could not be recorded because of their insolubility in common solvents.

The hydrazides **12a-c** on reaction with methanolic potassium hydroxide and carbon disulphide under reflux conditions afforded 5-(8-substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-yl)thiomethyl-1,3,4-oxadiazole-2-thiones **16a-c**. Compound **16a** displayed bands in the ir spectrum at 3300 (NH), 3175 (NH-C=S), 1640 (C=N), 1170 (C=S) cm^{-1}. *S*-Methylation of thiones **4a-c** with methyl iodide gave the 8-substituted-5-methylthio-11*H*-indolo[3,2-*c*]isoquinolines **17a-c**. Compound **17c** displayed bands at 3450 (NH), 1620 (C=N) cm^{-1} in its ir spectrum. The ^1H nmr spectrum showed peaks at δ 12.0 (s, 1H, indole NH), 7.2-8.5 (m, 7H, Ar-H), 2.7 (s, 3H, -S-CH_3).

EXPERIMENTAL

All melting points were taken in an open capillary tube and are uncorrected. The ir spectra were recorded in nujol mulls on Perkin-Elmer Model 297 spectrophotometer. The ^1H nmr were recorded on a Varian EM-60 and Varian EM-390 Model operating at 60 MHz and 90 MHz, respectively, in DMSO-d_6 solution using TMS as the internal standard and chemical shifts are expressed in δ values. The mass spectra were run on a Jeol D-300 instument at 70 eV ionization energy by direct inlet system.

5-Substituted-2-phenyl-3-aminoindoles **1a-c** and ethyl 5-substituted-2-phenylindole-3-carbamates **2a-c** were prepared according to literature procedures [9].

General Procedure for the Preparation of 6*H*,11*H*-Indolo[3,2-*c*]-isoquinolin-5-ones **3a-c**.

Compounds **2a-c** (10.7 mmoles) in freshly distilled diphenyl ether (25 ml) were heated under reflux for 4 hours. The solid which separated on cooling was filtered, washed with petroleum ether (60-80°, 2 ml), dried and then crystallized from suitable solvents.

6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-one (**3a**).

This compound was obtained in 68% yield, mp >360° (from benzene); ir: 3410 (NH), 3210 (NH), 1650 (C=O) cm^{-1}.

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.92; H, 4.27; N, 11.96. Found: C, 76.89; H, 4.23; N, 11.89.

8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-one (**3b**).

This compound was obtained in 72% yield, mp >360° (from benzene); ir: 3450 (NH); 3200 (NH), 1660 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.41; H, 4.83; N, 11.29. Found: C, 77.30; H, 4.62; N, 11.00.

8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-one (**3c**).

This compound was obtained in 67% yield, mp >360° (from benzene); ir: 3425 (NH), 3200 (NH), 1640 (C=O) cm^{-1}.

Anal. Calcd. for $C_{15}H_9N_2OCl$: C, 67.16; H, 3.35; N, 10.44. Found: C, 67.30; H, 3.50; N, 10.33.

General Procedure for the Preparation of 8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thiones **4a-c**.

A mixture of 8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-ones **3a-c** (16.12 mmoles) and phosphorus pentasulphide (16.12 mmoles) in dry pyridine (10 ml) was refluxed for 4 hours. After cooling the reaction mixture was decomposed in ice-cold water (200 ml), the separated yellow solid was filtered off, dried and then recrystallized from suitable solvent.

6*H*,11*H*-Indolo[3,2-*c*]isoquinoline-5-thione (**4a**).

This compound was obtained in 80% yield, mp 255-256° (from aqueous pyridine); ir: 3350 (NH), 3200 (NH), 1200 (C=S) cm^{-1}; ^1H nmr: 13.8 (s, 1H, NH-C=S), 11.8 (s, 1H, NH), 6.8-8.8 (m, 8H, Ar-H).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 72.00; H, 4.00; N, 11.2. Found: C, 71.89; H, 4.12; N, 11.18.

8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thione (**4b**).

This compound was obtained in 82% yield, mp 342-343° (from aqueous pyridine); ir: 3425 (NH), 3275 (NH-C=S), 1220 (C=S) cm^{-1}; ms: m/z (ion, relative intensity), 264 (M^+, 20.09), 249 (7), 240 (6.0), 225 (10.74), 205 (3.2), 190 (11.68), 129 (27.10), 120 (11.68).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.73; H, 4.55; N, 10.60. Found: C, 72.62; H, 4.65; N, 10.42.

8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thione (**4c**).

This compound was obtained in 85% yield, mp >360° (from aqueous pyridine); ir: 3400 (NH), 3150 (NH-C=S) 1210 (C=S) cm^{-1}; ms: m/z (ion, relative intensity), 284 (M^+, 80), 286 (M^++2, 28.57), 269 (100), 271 (32.85), 234 (18.57), 189 (3.57), 164 (2.85).

Anal. Calcd. for $C_{15}H_9N_2SCl$: C, 63.38; H, 3.17; N, 9.86. Found: C, 63.12; H, 3.00; N, 9.79.

General Procedure for the Preparation of Ethyl (8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetates **5a-c**.

A mixture of 8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-ones **3a-c** (10 mmoles), anhydrous potassium carbonate (20 mmoles) and ethyl chloroacetate (10 mmoles) in super dry acetone was refluxed on steam bath for 8 hours. The inorganic solids were filtered while hot, and solvent was removed from the filtrate on rotavapour. The resulting residue was crystallized from suitable solvent.

Ethyl (6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetate (**5a**).

This compound was obtained in 86% yield, mp >360° (from ethanol); ir: 3475 (NH), 1740, 1670 (C=O) cm^{-1}; ms: (ion, relative intensity); m/z 320 (M^+, 100), 247 (95.8) 233 (38.4), 217 (18.7), 205 (6.8).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.25; H, 5.00; N, 8.75. Found: C, 71.05; H, 5.02; N, 8.67.

Ethyl (8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetate (**5b**).

This compound was obtained in 75% yield, mp >360° (from ethanol-benzene), ir: 3400 (NH), 1740, 1660, (C=O) cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.85; H, 5.38; N, 8.38. Found: C, 71.73; H, 5.41; N, 8.36.

Ethyl (8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetate (**5c**).

This compound was obtained in 80% yield, mp >360° (from benzene); ir: 3400 (NH), 1740, 1650, (C=O) cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_2O_3Cl$: C, 64.40; H, 4.23; N, 7.90. Found: C, 64.23; H, 4.20; N, 7.82.

General Procedure for the Preparation of (8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl Hydrazides **6a-c**.

To a suspension of **4a-c** (5 mmoles) in ethanol (15 ml), hydrazine hydrate (99-100%), 1.5 ml (30 mmoles) was added and the reaction mixture was refluxed on steam bath for 6 hours. After cooling, the resulting crystalline product was filtered, washed with little ethanol, dried and recrystallized from ethanol.

(6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl Hydrazide (**6a**).

This compound was obtained in 62% yield, mp >360° (from ethanol); ir: 3475 (NH), 3150, 3100 (NH/NH_2), 1670 and 1630 (C=O) cm^{-1}; ms: (ion, relative intensity) m/z 306 (M^+, 1.4), 275 (3.3), 247 (4.3), 233 (100), 217 (16.8), 206 (16.2).

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.57; N, 18.30. Found: C, 66.54; H, 4.42; N, 18.10.

(8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl Hydrazide (**6b**).

This compound was obtained in 58% yield, mp >360° (from ethanol); ir: 3475 (NH), 3140, 3100 (NH/NH_2), 1660, 1620 (C=O) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.50; H, 5.0; N, 17.5. Found: C, 67.30; H, 5.21; N, 17.32.

(8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl Hydrazide (**6c**).

This compound was obtained in (70%) yield, mp >360° (from ethanol); ir: 3475 (NH), 3150, 3100 (NH/NH_2), 1670 and 1630 (C=O) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_4O_2Cl$: C, 60.00; H, 3.82; N, 16.47. Found: C, 60.10; H, 3.71; N, 16.25.

General Procedure for the Preparation of 1-(8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3,5-disubstituted-pyrazoles **7a-c** and **8a-c**.

A mixture of hydrazides **5a-c** (10 mmoles) and benzoyl acetone/dibenzoyl methane (10 mmoles) was refluxed in methanol containing 4-5 drops of concentrated hydrochloric acid, for 4 hours on steam bath. The reaction mixture was cooled to room temperature and the separated yellow solid filtered off, washed with little methanol, dried and crystallized from alcohol.

1-(6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-phenyl-5-methylpyrazole (**7a**).

This compound was obtained in 60% yield, mp 350-351° (from benzene-ethanol); ir: 3475 (NH), 1670 and 1630 (C=O), 1580 (C=N) cm^{-1}.

Anal. Calcd. for $C_{27}H_{20}N_4O_2$: C, 75.00; H, 4.62; N, 12.96. Found: C, 74.80; H, 4.60; N, 12.83.

1-(8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-phenyl-5-methylpyrazole (**7b**).

This compound was obtained in 70% yield, mp 318-320° (from ethanol); ir: 3475 (NH), 1660 and 1630 (C=O), 1580 (C=N) cm^{-1}.

Anal. Calcd. for $C_{28}H_{22}N_4O_2$: C, 75.33; H, 4.93; N, 12.55. Found: C, 75.20; H, 4.90; N, 12.50.

1-(8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-phenyl-5-methylpyrazole (**7c**).

This compound was obtained in 63% yield, mp 360° (from ethanol-benzene); ir: 3475 (NH), 1670, 1630, (C=O), 1580 (C=N) cm^{-1}.

Anal. Calcd. for $C_{27}H_{19}N_4O_2Cl$: C, 69.52; H, 4.07; N, 12.01. Found: C, 69.50; H, 4.00; N, 12.00.

1-(6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3,5-diphenyl-pyrazole (**8a**).

This compound was obtained in 67% yield, mp 230-231° (from ethanol-benzene); ir: 3475 (NH), 1750, 1650 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{32}H_{22}N_4O_2$: C, 77.73; H, 4.45; N, 11.33. Found: C, 77.68; H, 4.30; N, 11.22.

1-(8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3,5-diphenylpyrazole (**8b**).

This compound was obtained in 65% yield, mp 348-350° (from ethanol); ir: 3450 (NH), 1760, 1640 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{33}H_{24}N_4O_2$: C, 77.95; H, 4.72; N, 11.02. Found: C, 78.00; H, 4.74; N, 11.22.

1-(8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3,5-diphenylpyrazole (**8c**).

This compound was obtained in 62% yield, mp 293-294° (from ethanol-benzene); ir: 3450 (NH), 1750, 1640, (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{32}H_{21}N_4O_2Cl$: C, 72.72; H, 3.97; N, 10.60. Found: C, 72.60; H, 3.90; N, 10.50.

General Procedure for the Preparation of 1-(8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-methylpyrazol-5-ones **9a-c**.

A mixture of hydrazides **6a-c** (10 mmoles) and ethyl acetoacetate (10 mmoles) was refluxed in methanol containing 4-5 drops of concentrated hydrochloric acid for 4 hours on steam bath. The reaction mixture was cooled to room temperature and the separated yellow solid filtered off washed with little methanol, dried and crystallized from alcohol.

1-(6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-methylpyrazol-5-one (**9a**).

This compound was obtained in 70% yield, mp 342-343° (from ethanol); ir: 3475 (NH), 1650, 1640, 1620 (C=O), 1560 (C=N) cm^{-1}.

Anal. Calcd. for $C_{21}H_{16}N_4O_3$: C, 67.74; H, 4.30; N, 15.05.

Found: C, 67.70; H, 4.25; N, 15.00.

1-(8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-methylpyrazol-5-one (**9b**).

This compound was obtained in 73% yield, mp 342-343° (from ethanol); ir: 3450 (NH), 1660, 1650, 1630 (C=O), 1560 (C=N) cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}N_4O_3$: C, 68.39; H, 4.66; N, 14.50. Found: C, 68.32; H, 4.61; N, 14.32.

1-(8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-3-methylpyrazol-5-one (**9c**).

This compound was obtained in 68% yield, mp 358-360° (from ethanol); ir: 3475 (NH), 1660, 1640, 1620 (C=O), 1570 (C=N) cm^{-1}.

Anal. Calcd. for $C_{21}H_{15}N_4O_3Cl$: C, 62.06; H, 3.69; N, 13.79. Found: C, 62.00; H, 3.65; N, 13.73.

General Procedure for the Preparation of 5-(8-Substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)acetyl-1,3,4-oxadiazole-2-thiones **10a-c**.

A mixture of hydrazide **6a-c** (50 mmoles), potassium hydroxide (50 mmoles) and carbon disulphide (5 ml) in ethanol (50 ml) was refluxed until the evolution of hydrogen sulphide ceased (45-48 hours). The solvent was evaporated and the residue dissolved in ice-water. The resulting clear solution filtered and the filtrate was acidified with dilute hydrochloric acid. The separated solid was filtered, dried and crystallized from ethanol.

5-(6*H*,11*H*-Indolo[3,2-*c*]isoquinolin-5-on-6-yl)methyl-1,3,4-oxadiazole-2-thione (**10a**).

This compound was obtained in 80% yield, mp 350-351° (from ethanol); ir: 3475, 3100 (NH/NH), 1640 (C=O), 1220 (C=S) cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.44; N, 16.09. Found: C, 62.00; H, 3.41; N, 16.04.

5-(8-Methyl-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)methyl-1,3,4-oxadiazole-2-thione (**10b**).

This compound was obtained in (76%) yield, mp 345-346° dec (from ethanol); ir: 3475, 3100 (NH/NH), 1640 (C=O), 1205 (C=S) cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}N_4O_2S$: C, 62.98; H, 3.86; N, 15.46. Found: C, 62.96; H, 3.82; N, 15.41.

5-(8-Chloro-6*H*,11*H*-indolo[3,2-*c*]isoquinolin-5-on-6-yl)methyl-1,3,4-oxadiazole-2-thione (**10c**).

This compound was obtained in 68% yield, mp 314-315° dec (from ethanol); ir: 3475, 3075 (NH/NH), 1630 (C=O), 1160 (C=S) cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}N_4O_2SCl$: C, 56.54; H, 2.87; N, 14.65. Found: C, 56.51; H, 2.85; N, 14.61.

General Procedure for the Preparation of Ethyl (8-Substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetates **11a-c**.

A mixture of 8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thiones **4a-c** (1.00 mmole), anhydrous potassium carbonate (2.00 mmoles) and ethyl chloroacetae (1.00 mmole) in super dry acetone was refluxed on steam bath for 8 hours. The inorganic solids were filtered off and solvent was removed from the filtrate on rotavapour. The resulting residue was crystallized from suitable solvent.

Ethyl (11*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)acetate (**11a**).

This compound was obtained in 90% yield, mp 198-199° (from benzene-ethanol); ir: 3350 (NH), 1725 (C=O), 1630 (C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}N_2O_2S$: C, 67.85; H, 4.76; N, 8.33. Found: C, 67.73; H, 4.72; N, 8.43.

Ethyl (8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetate (**11b**).

This compound was obtained in 92% yield, mp 203-204° (from benzene-ethanol); ir: 3375 (NH), 1740 (C=O), 1640 (C=N) cm^{-1}; ^1H nmr: 12.2 (s, 1H, NH), 7.2-8.5 (m, 7H, Ar-H), 4.2 (q, 4H, $-O-CH_2$ and $-SCH_2$), 1.29 (t, 6H, OCH_2-CH_3 and $-CH_3$), ms: m/z (ion, relative intensity) 350 (M^+, 37.5), 305 (7.5), 277 (100), 263 (12.5), 231 (15), 216 (45).

Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.57; H, 5.14; N, 8.00. Found: C, 68.46; H, 4.98; N, 8.20.

Ethyl (8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetate (**11c**).

The compound was obtained in 90% yield, mp 238-239° (from benzene-ethanol); ir: 3350 (NH), 1730 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_2O_2SCl$: C, 61.62; H, 4.05; N, 7.56. Found: C, 61.60; H, 4.13; N, 7.49.

General Procedure for the Preparation of (8-Substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl Hydrazides **12a-c**.

These compounds were prepared according to the procedure described for (**6a-c**) starting from (**11a-c**).

(11*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl Hydrazide (**12a**).

This compound was obtained in 86% yield, mp 220-221° dec; ir: 3300 (NH), 3250, 3150, (NH/NH_2), 1670 (C=O), and 1620 (C=N) cm^{-1}; ms: m/z (ion, relative intensity) 322 (M^+, 47.5), 291 (42), 263 (44), 249 (100), 217 (12), 191 (42), 115 (12).

Anal. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.35; H, 4.34; N, 17.39. Found: C, 63.25; H, 4.40; N, 17.50.

(8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl Hydrazide (**12b**).

This compound was obtained in 85% yield, mp 246-247° dec; ir: 3325 (NH), 3275, 3175 (NH/NH_2), 1680 (C=O), 1630 (C=N) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.28; H, 4.76; N, 16.66. Found: C, 64.19; H, 4.62; N, 16.52.

(8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl Hydrazide (**12c**).

This compound was obtained in 88% yield, mp 278-279° dec; ir: 3300 (NH), 3275, 3150 (NH/NH_2), 1700 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_4OSCl$: C, 57.30; H, 3.65; H, 15.73. Found: C, 57.43; H, 3.55; N, 15.80.

General Procedure for the Preparation of 1-(8-Substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3,5-substituted-pyrazoles **13a-c** and **14a-c**.

These compounds were synthesized by following the procedure described for **7a-c** and **8a-c** starting from **12a-c**.

1-(11-*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-phenyl-5-methylpyrazole (**13a**).

This compound was obtained in 78% yield, mp 199-200° dec; ir: 3350 (NH), 1740 (C=O), 1630 (C=N) cm^{-1}.

Anal. Calcd. for $C_{27}H_{20}N_4OS$: C, 72.32; H, 4.46; N, 12.50.

Found: C, 72.28; H, 4.39; N, 12.60.

1-(8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-phenyl-5-methylpyrazole (**13b**).

This compound was obtained in 75% yield, mp 257-258° dec; ir: 3325 (NH), 1730 (C=O), 1630 (C=N) cm^{-1}.

Anal. Calcd. for $C_{28}H_{22}N_4OS$: C, 72.72; H, 4.76; N, 12.12. Found: C, 72.80; H, 4.50; N, 12.00.

1-(8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-phenyl-5-methylpyrazole (**13c**).

This compound was obtained in 80% yield, mp 245-246° dec; ir: 3360 (NH), 1720 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{27}H_{19}N_4OSCl$: C, 67.21; H, 3.94; N, 11.61. Found; C, 67.11; H, 3.83; N, 11.70.

1-(11*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3,5-diphenylpyrazole (**14a**).

This compound was obtained in 91% yield, mp 198-199° dec; ir: 3350 (NH), 1740 (C=O), 1620 (C=N) cm^{-1}; ^1H nmr: 7.0-8.5 (m, 19H, 18 Ar-H, 1-NH), 3.65 (s, 2H, $-SCH_2$), 4.25 (s, 1H, =C-H).

Anal. Calcd. for $C_{32}H_{22}N_4OS$: C, 75.29; H, 4.31; N, 10.98. Found: C, 75.35; H, 4.21; N, 10.82.

1-(8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3,5-diphenylpyrazole (**14b**).

This compound was obtained in 79% yield, mp 253-254° dec; ir: 3375 (NH), 1730 (C=O), 1630 (C=N) cm^{-1}.

Anal. Calcd. for $C_{33}H_{24}N_4OS$: C, 75.57; H, 4.58; N, 10.68. Found: C, 75.43; H, 4.6; N, 10.70.

1-(8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3,5-diphenylpyrazole (**14c**).

This compound was obtained in 91% yield, mp 232-233° dec; ir: 3350 (NH), 1720 (C=O), 1620 (C=N) cm^{-1}.

Anal. Calcd. for $C_{32}H_{21}N_4OSCl$: C, 70.58; H, 3.86; N, 10.29. Found: C, 70.62; H, 3.72; N, 10.15.

General Procedure for the Preparation of 1-(8-Substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-methylpyrazol-5-ones **15a-c**.

These compounds were obtained in good yield by following the procedure described for **9a-c** starting from **12a-c**.

1-(11*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-methylpyrazol-5-one (**15a**).

This compound was obtained in 85% yield, mp 195-196°; ir: 3350 (NH), 1735, 1640 (C=O), 1560 (C=N) cm^{-1}.

Anal. Calcd. for $C_{21}H_{16}N_4O_2S$: C, 64.94; H, 4.12; N, 14.43. Found: C, 64.83; H, 4.01; N, 14.51.

1-(8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-methylpyrazol-5-one (**15b**).

This compound was obtained in 85% yield, mp 147-148°; ir: 3350 (NH), 1740, 1660 (C=O), 1590 (C=N) cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}N_4O_2S$: C, 65.67; H, 4.47; N, 13.93. Found: C, 65.56; H, 4.51; N, 14.00.

1-(8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)acetyl-3-methylpyrazol-5-one (**15c**).

This compound was obtained in 77% yield, mp 221-222°; ir: 3350 (NH), 1740, 1640 (C=O), 1600 (C=N) cm^{-1}.

Anal. Calcd. for $C_{21}H_{15}N_4O_2SCl$: C, 59.71; H, 3.55; N, 13.27. Found: C, 59.52; H, 3.60; N, 13.18.

General Procedure for the Preparation of 5-(8-Substituted-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)methyl-1,3,4-oxadiazole-2-thiones **16a-c**.

These compounds were prepared according to the procedure described for **10a-c** starting from **12a-c**.

5-(11*H*-Indolo[3,2-*c*]isoquinolin-5-ylthio)methyl-1,3,4-oxadiazole-2-thione (**16a**).

This compound was obtained in 90% yield, mp 165-166°; ir: 3300 (NH), 3175 (NH), 1640 (C=N), 1170 (C=S) cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_4OS_2$: C, 59.34; H, 3.29; N, 15.38. Found: C, 59.23; H, 3.18; N, 15.26.

5-(8-Methyl-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)methyl-1,3,4-oxadiazole-2-thione (**16b**).

This compound was obtained in 85% yield, mp 189-198°; ir: 3325 (NH), 3225 (NH), 1630 (C=N), 1160 (C=S) cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}N_4OS_2$: C, 60.31; H, 3.70; N, 14.81. Found: C, 60.40; H, 3.89; N, 14.92.

5-(8-Chloro-11*H*-indolo[3,2-*c*]isoquinolin-5-ylthio)methyl-1,3,4-oxadiazole-2-thione (**16c**).

This compound was obtained in 89% yield, mp 199-200°; ir: 3300 (NH), 3175 (NH), 1640 (C=N), 1170 (C=S) cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}N_4OS_2Cl$: C, 54.27; H, 2.76; N, 14.07. Found: C, 54.31; H, 2.62; N, 14.12.

General Procedure for the Preparation of 8-Substituted-5-methylthio-11*H*-indolo[3,2-*c*]isoquinoline **17a-c**.

Methyl iodide (1.1 ml, 17.7 mmoles) was added dropwise to a stirred suspension of 8-substituted-6*H*,11*H*-indolo[3,2-*c*]isoquinoline-5-thiones **4a-c** (17.7 mmoles) and potassium hydroxide (18.00 mmoles) in 50% aqueous methanol (30 ml) at room temperature and stirring is continued for 2 hours, after which two drops of glacial acetic acid were added to this solution. The solid was separated by filtration, washed with water, dried and crystallized from alcohol.

5-Methylthio-11*H*-indolo[3,2-*c*]isoquinoline (**17a**).

This compound was obtained in 83% yield, mp 141-142°; ir: 3450 (NH), 1630 (C=N) cm^{-1}; ^1H nmr: 12.0 (s, 1H, NH), 7.2-8.5 (m, 8H, Ar-H), 2.7 (s, 3H, $-SCH_3$).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.72; H, 4.54; N, 10.60. Found: C, 72.80; H, 4.61; N, 10.75.

8-Methyl-5-methylthio-11*H*-indolo[3,2-*c*]isoquinoline (**17b**).

This compound was obtained in 86% yield, mp 175-176°; ir: 3375 (NH), 1630 (C=N) cm^{-1}; ^1H nmr: 12.1 (s, 1H, NH), 7.1-8.6 (m, 7H, Ar-H), 3.7 (s, 3H, $-SCH_3$), 2.6 (s, 3H, $-CH_3$).

Anal. Calcd. for $C_{17}H_{14}N_2S$: C, 73.38; H, 5.03; N, 10.07. Found: C, 73.41; H, 5.14; N, 10.12.

8-Chloro-5-methylthio-11*H*-indolo[3,2-*c*]isoquinoline (**17c**).

This compound was obtained in 82% yield, mp 160-161°; ir: 3450 (NH), 1620 (C=N) cm^{-1}; ^1H nmr: 12.0 (s, 1H, NH), 7.2-8.3 (m, 7H, Ar-H), 2.7 (s, 3H, $-SCH_3$).

Anal. Calcd. for $C_{16}H_{11}N_2SCl$: C, 64.42; H, 3.69; N, 9.39. Found: C, 64.51; H, 3.61; N, 9.28.

Acknowledgement.

The authors are thankful to Professor Malcolm Hooper and

Dr. Jim Hurst of Sunderland Polytechnic, UK for useful discussions. One of us (ARS) is grateful to UGS, New Delhi for financial assistance. We are thankful to Dr. P. H. Ladawa, Ahmednagar College, Ahmednagar for providing nmr data.

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