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# Synthesis of novel 6′-amino-1, 3-dihydro spiro [3H-indol-3, 4′(1′H)-pyrano (2,3-c) pyrrol]-2-Oxo-5′-carboxyethylester

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## ABSTRACT

Novel spiro indole derivatives incorporating pyranopyrroles **(5)** have been synthesized by the reaction of 1,3-dihydro-3-carboethoxycyanomethylene-2H-indol-2-one **(3)** with 2- pyrrolidone **(4)** under thermal and microwave irradiation conditions. Compound **(3)** was synthesized by the knoevenagel condensation of indole-2, 3-dione **(1)** and ethylcyanoacetate **(2)**. All the synthesized compounds have been characterized by IR, $^1$HNMR studies and elemental analyses. Few compounds have also been screened for anti-tubercular, antifungal and herbicidal activities.

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## KEYWORDS

Spiro indole derivatives;
Pyranopyrroles;
Microwaves;
Knoevenagel condensation;
Antitubercular;
Antifungal;
Herbicidal activities.

## INTRODUCTION

Heterocyclic compounds play an important role in organic chemistry as synthetic auxiliaries leading to important compounds of industrial and medicinal value. Among nitrogen-containing heterocycles, the indole is of great value in the field of medicine and biochemistry. The indole ring system not only display interesting chemistry as individual ring system but also may lead to large number of fascinating ring systems by incorporating more than one moiety. The research on the chemistry of indoles has been a focus of attention for chemists for a long time, due to their diversified biological activities[1-4]. Furthermore, those compounds in which indole-3 carbon is in the form of spiro atom exhibit enhanced bioactivity[5-7]. Several naturally occurring compounds e.g., elegantine, rhynchophylline and surgatoxin are heterocyclic compounds with a Spiro atom at position 3 of the 2- indolinone skeleton. Fredricamycin-A, spiro heterocycle is an antitumor antibiotic agent. Strychofline, isolated from strychnos usambarensis has been found to exhibit antimitotic activity of cancer cell culture[8]. Spiro [indole- pyrans] also display useful bioactivities as muscle relaxants[9], hypnotics[9] and anti-inflammatory agents[10]. Spiro [indole-pyrrolidines] also exhibit binding affinity to glycine receptors[11], local anesthetic[12], anticonvulsant[13] and other pharmacological activities[14]. The diverse biological activities reported for pyran and pyrrole derivatives prompted the interest to synthesize some novel Spiro indole derivatives incorporating these ring systems at position 3- of 2-indolinone skeleton and to study their antitubercular, antifungal and herbicidal activities

The application of microwaves to organic synthesis is well known[15]. Recently reactions under dry conditions using inorganic reagents[16] are gaining more attention because of their enhanced selectivity and milder conditions than those associated with conventional homogeneous reaction procedures.

Earlier, we studied the reaction of 3- dicyano

methylene-2H-indol-2-ones with 4-hydroxy coumarin, 2-pyrrolidone and 1-phenyl-2-thiohydantoin and reaction of 3-carboethoxycyanomethylene-2H-indol-2-ones with 1-phenyl-2-thiohydantoin under conventional heating and under microwave irradiation[17]. In yet another attempt to study the role of substituent at the olefinic carbon of ylidine derivatives, we explored the reaction of 3-carboethoxycyanomethylene-2H-indol-2-ones **(3)** with 2- pyrrolidone **(4)**. Role of substituent at indole ring has been observed earlier[18], but the role of substituent at the olifinic carbon of ylidine derivative e.g., was not studied.

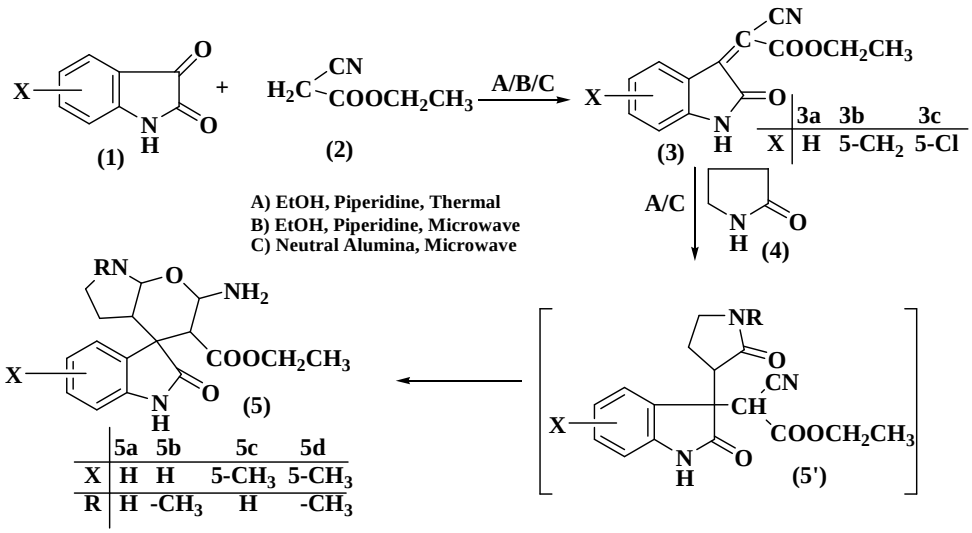
Hence, as a part of our continuing interest on the synthesis of biodynamic heterocycles[19] under conventional heating and microwave irradiation, we have now investigated the reaction of indole-2, 3-dione **(1)** with ethylcyanoacetate **(2)** resulting in the formation of 3-carboethoxycyanomethylene-2H-indol-2-ones **(3)**. The Michael reaction of **(3)** having an electron attracting group on exomethylene carbon is interesting as it can afford either a Michael adduct (5') which can exist as such or converted into Spiro pyran system of oxindole (SCHEME 1). Reaction of **(3)** with 2-pyrrolidone **(4)** lead to the formation of 6'amino-1, 3-dihydro Spiro [3Hindol-3, 4'(1'H)-pyrano (2,3-c) pyrrol] –2-oxo-5'-carboxyethylester in support of the earlier reports of the formation of spiroindolines in the reaction of 3 with heterocyclic ketones under classical conditions[20]. Compound **(3)** has been synthesized earlier under classical conditions by the Knoevenagel condensation of indole-2, 3-dione **(1)** with ethyl cyanoacetate **(2)** in the presence of piperidine. We have improved its synthesis under microwave irradiation without using any catalyst, which yield crystalline product of sufficient purity in enhanced yield with no need of further purification. Encouraging results have been obtained using ethanol as energy transfer medium in the absence of any catalyst.

One Spiro compound **(5a)** has also been synthesized under microwave irradiation using neutral alumina as inorganic solid support. Neutral alumina efficiently catalyzed the Michael condensation in dry media under microwave irradiation. Moreover, a reaction is fast, procedure is simple and have low cost and it is possible to work under ecofriendly mild neutral conditions. Few compounds have also been screened for antifungal, antitubercular and herbicidal activities.

## EXPERIMENTAL

### Chemicals and apparatus

Chemicals were purchased from Aldrich, Fluka and Merch Chemical Companies. Infrared spectra were recorded on Perkin-Elmer (model-577) and Testscan FTIR 8000 series in KBr pellets and $^1$H NMR on Jeol (model Fx-90Q) using $CDCl_3$ at 89.55 MHz and on Bruker WM-400 FTNMR spectrometer (400 MHz) using TMS as internal reference. Melting points were recorded in open capillary tubes and are uncorrected. All the compounds were found homogeneous on TLC in various solvent systems. The induced microwave convection system has been used where microwaves




SCHEME 1

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**TABLE 1: Physical and analytical data of 1,3-dihydro-3-carboethoxycyanomethylene-2H-indol-2-one (3a-c) and 6' amino-1, 3-dihydro Spiro [3H-indol-3, 4'(1'H) pyrano [2,3-c] pyrrol]-2-oxo-5'-carboxyethylesters (5a-d)**

| Compd. no. | X | R | Reaction time | Yield (%) | M.P. (ºC) | Molecular formula | Analysis (%) carbon found/calculated | Analysis (%)nitrogen found/calculated |
|---|---|---|---|---|---|---|---|---|
| (3a) | H | - | 4hrs | 65 | 213 | $C_{13}H_{10}N_2O_3$ | 64.50/64.46 | 11.04/11.57 |
| (3b) | 5-$CH_3$ | - | 4hrs | 63.6 | 210 | $C_{14}H_{12}N_2O_3$ | 65.72/65.62 | 10.90/10.93 |
| (3c) | 5-Cl | - | 4hrs | 64 | 206 | $C_{13}H_9ClN_2O_3$ | 56.09/56.41 | 9.58/10.14 |
| (5a) | H | H | 7.00 | 57.8 | 149-150 | $C_{17}H_{17}N_3O_4$ | 62.35/62.38 | 12.85/12.84 |
| (5b) | H | $CH_3$ | 9.00 | 59 | 155 | $C_{18}H_{19}N_3O_4$ | 63.30/63.34 | 12.36/12.31 |
| (5c) | 5-$CH_3$ | H | 12.00 | 55.2 | 229-230 | $C_{18}H_{19}N_3O_4$ | 63.36/63.34 | 12.28/12.31 |
| (5d) | 5-$CH_3$ | $CH_3$ | 13.00 | 58.9 | 242 | $C_{19}H_{21}N_3O_4$ | 64.15/64.22 | 11.70/11.83 |

**Compounds (3a-c) and (5a-d) were synthesized by conventional method. (3a) and (5a) have also been synthesized by microwave irradiation method**

are generated at a frequency of 2450 MHz. The oven has a output range of 700 watts.

### Synthesis of 6'-amino-1, 3-dihydro Spiro [3H-indol-3, 4' (1'H)-pyrano [2,3-c] pyrrol]-2-oxo-5'-carboxy ethyl ester (5a)

Synthesis of the compound takes place in two steps:

### Synthesis of 1,3-dihydro-3-carboethoxycyano methylene-2H-indol-2one (3a)

This compound was synthesized by conventional and microwave irradiation methods.

### Conventional method

The compound has been synthesized by literature method[21] under classical conditions. A solution of indole-2, 3-dione **(1a)**(0.01mole, 1.47gm) and ethylcy anoacetate (2)(0.01mole, 1.13gm) in absolute ethanol (30ml) containing piperidine (2-3drops) as catalyst was refluxed for 3-4hours.After being chilled overnight, the resulting solid was filtered, washed with cold ether and recrystallised from ethanol. M.p.213$^0$C; Yield 65%

### Microwave irradiation method

Equimolar mixture of **(1a)** and **(2)** (2mmole) in minimum quantity of ethanol required to form a slurry containing piperidine (1drop) was irradiated intermittently inside a microwave oven for a period of 4min. at 240 watts. Progress of the reaction was monitored by TLC. The solid separated on cooling was filtered and recrystallized from ethanol, m. p. 213$^0$C; Yield 82.2%.

Synthesis of the compound **(3a)** has also been carried out in the absence of piperidine by similar procedure in 6 min. at 240 watts. m.p. 213$^0$C; Yield 68 % **3(b,c)** were synthesized by conventional methods. (TABLE 1).

### Synthesis of spiro compound (5a)

Compound **(5a)** has been synthesized by conventional and microwave irradiation methods. **5(b, c)** have been synthesized by conventional methods.

### Conventional method

A solution of 3-carboethoxycyanomethylene-2H-indol-2-ones (0.01mole) and 2-pyrrolidone (0.01mole) in absolute ethanol (40ml) containing 2-3 drops of piperidine as catalyst was refluxed for 7 hours. The reaction mixture was cooled to room temperature. After keeping the mixture under refrigeration overnight, the separated solid was filtered, dried and recrystallised from benzene. (m.p. 150$^0$C; Yield 57.8%)

### Microwave irradiation method

The compound **(5a)** was synthesized under microwave irradiation in the absence of any solvent or catalyst. 3-carboethoxycyanomethylene-2H-indol-2-ones and 2-pyrrolidone (2mmole) were separately dissolved in minimum quantity of methanol and adsorbed on neutral alumina and irradiated inside a domestic microwave oven for appropriate time (8min.) at 480watts. Progress of the reaction was monitored by TLC. The reaction product was extracted using methanol and the product was further recrystallized from methanol, (m.p.150$^0$C; Yield 65%).

## RESULTS AND DISCUSSION

The reaction of **(3)** with 2-pyrrolidone **(4)** afforded **(5)** which displayed characteristic absorption bands at 33320 and 3240cm$^{-1}$,corresponding to the free asymmetric and symmetric stretching due to $NH_2$ group and at 3260-3200,1730,1700 and 1184cm$^{-1}$ corresponding to NH stretching, two >C=O's and pyran ether linkage respectively (TABLE 2). The $^1$HNMRspectra displayed signals at δ6.92-8.00 (m, Ar-H), δ7.7-7.9 (br, s, $NH_2$), δ2.25 (t, $CH_2$-$CH_2$), δ3.35-3.42 (t, $CH_2$-N),

δ8.44(s, pyrrole NH), δ8.53(s, indole NH), δ1.17 (t, $CH_2CH_3$) and δ4.5 (q, $CH_2$-$CH_3$) ppm (TABLE 3).

## Bioassay

### Anti tubercular activity

The Antitubercular screening was carried out by the Tuberculosis Antimicrobial Acquisition and coordinating Facility (TAACF) in USA. Primary screening of the compounds have been conducted at 12.5ug/ml against Mycobacterium tuberculum H37RV in BACTEC 12B medium using BACTEC 460 Radiometric system[22]. Antitubercular activity data were compared with standard drug Rifampin at 0.255ug/mlconcentration that showed 98% inhibition.

### Antifungal activity

Antifungal activity was carried out against pathogenic fungus namely "Alternaria alternata"using "Poison Plate Technique". It was carried out at Department of Pathology, Durgapura Agricultural Research station, Jaipur.

The method employed was "Food Poison Technique[23]". The principle involved in this technique is to poison the nutrient medium with a fungi toxicant and then allowing a test fungus to grow on such a medium. Potato dextrose agar medium is prepared in flasks and sterilized. To this medium, a requisite quantity of fungicide is added so as to get certain final concentration. The medium is then poured into petriplates. A culture of test fungus is grown on PDA for 6-7 days. Small disc (4mm) of the fungus culture is cut with a sterile cork borer and above transferred aseptically, upside down in the center of petridishes containing the medium and fungicides. Suitable checks are kept where the culture discs are grown under same conditions on PDA containing only acetone. The colony diameter, with check, is taken as a measure of fungi toxicity. The compounds synthesized were dissolved in acetone and were prepared in 1000, 500 and 250 ppm concentrations. These concentrations were screened against the fungus in three triplicates by the above method. These pathogens were grown on potato dextrose agar medium in which desired amount of test compounds were previously incorporated in 1000 ppm and 500 ppm concentrations. A suitable check of plain PDA with acetone was maintained. Plates were inoculated with the pathogens and incubated at 25±1C for 6 days. Colony diameter was measured and data was statistically analyzed using completely randomized design and averages compared using critical difference at 0.05% probability. The amount of growth inhibition was calculated by the equation:

**% Inhibition=C-T × 100/C**

C = Diameter of fungus colony in control plate, T= diameter of fungus colony in test plate

### Herbicidal activity

Herbicidal activity was carried out against Digitaria sanguinalis, Arabidopsis thaliana, Browallia Americana, Coleus blumei benth, Petunia hybriden and tobaccum Nicotiana Rustica. Seeds were planted into a sandy loam soil and preemergence with test chemicals dissolved in a non-phytotoxic solvent. At the same time, these crops and weed species were also treated post emergence with test chemicals. Plants ranged in height from 2-18cm (one to four leaf stage) for post emergence treatments. Treated plants and untreated controls were maintained in a green house for approximately 11 days after which all species were compared to controls and visually evaluated for injury.

Compounds **(3a)**, **(3b)** were screened for antifungal and antitubercular activity against Alternaria alternata and M. tuberculosis respectively. Compounds **(5a,b)** were screened for herbicidal activity against *Digitaria sanguinalis, Arabidopsis thaliana, Browallia Ameri-*

**TABLE 2: IR spectral data of synthesized compounds**

| Compd. no. | IR ($cm^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| | $\nu NH_2$ | νNH | νNH | νC=O | νC=O | Pyran ether linkage |
| (5a) | 3380 | 3240 | 3040 | 1733 | 1700 | 1184 |
| (5b) | 3320 | 3250 | - | 1730 | 1705 | 1184 |
| (5c) | 3390 | 3259 | 3091 | 1730 | 1700 | 1184 |
| (5d0 | 3380 | 3240 | - | 1733 | 1710 | 1184 |

**TABLE 3: $^1$H NMR spectral data of synthesized compounds**

| Compd. no. | $^1$H NMR (δ ppm) $CDCl_3$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $CH_2CH_3$ | $OCH_2CH_3$ | $CH_2$-$CH_2$ | $CH_2$-N | Ar-H | $NH_2$ | Pyrrole NH | Indole NH |
| (5a) | 1.17(t) | 4.50(q) | 2.25(t) | 3.35(t) | 6.92-8.00(m, Ar-H) | 7.7-7.9(br, s) | 8.44(s) | 8.53(s) |
| (5b) | 1.16(t) | 4.55(q) | 2.24(t) | 3.35(t) | 6.90-8.00(m, Ar-H) | 7.7-7.8(br, s) | - | 8.57(s) |
| (5c) | 1.17(t) | 4.50(q) | 2.24(t) | 3.35(t) | 6.90-8.00(m, Ar-H) | 7.7-7.9(br, s) | 8.44(s) | 8.53(s) |
| (5d) | 1.17(t) | 4.50(q) | 2.25(t) | 3.35(t) | 6.92-8.00(m, Ar-H) | 7.7-7.9(br, s) | - | 8.57(s) |

*cana*, *Coleus blumei benth*, *Petunia hybriden* and *tobaccum Nicotiana Rustica*.None of the compounds showed good activity against the pathogens.

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