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# Synthesis and Antimicrobial Activity of some New 2-Indolinone Derived Oximes and Spiro-Isoxazolines

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The synthesis and spectral analysis of some new 1,3-dihydro-3-hydroxy-3-[2-hydroxyimino-2-(substituted phenyl)ethyl]-2*H*-indol-2-ones (**21-32**) and spiro[3*H*-indol-3,5`-(4`*H*)-isoxazol]-2(1*H*)-ones (**33-44**) are described. Sixteen of the synthesized compounds were screened *in vitro* for their growth inhibitory activity against thirteen species of microorganisms, *viz, S. aureus, S. epidermidis, S. faecalis, B. subtilis, B. cereus, E. aerogens, E. coli, P. aeruginosa, P. vulgaris, A. baumonia, A. faecalis, C. albicans* and *S. cervicae*. Most of the compounds exhibited significant antimicrobial activity especially the oximes **28** and **29**.

**Key words:** Indoline-2,3-dione derivatives, Oximes, Spiro-isoxazolines, Antimicrobial activity

## INTRODUCTION

Intensive research in the field of antibacterial and antifungal agents has continued to grow in the recent years because of the increasing resistance of microorganisms to antibiotics and other antimicrobial drugs. The bacterial resistance may arise by selection or adaptation as well as bacterial mutation (Simon *et al.*, 1985).

Isatin and its derivatives represent one of the most active class of compounds possessing antimicrobial activity (Joshi *et al.*, 1992; Piscopo *et al.*, 1987a; Piscopo *et al.*, 1987b; Gupta and Gupta, 1983). Various spiro[indoline-pyrazolines] and spiro[indoline-isoxazolines] have been synthesized and screened for antibacterial and antifungal activities (Ankhiwala, 1990). Moreover, oximes and hydroxamic acid derivatives were found to be useful in the treatment of urinary tract infections caused by urea-splitting bacteria (Abou-Sier *et al.* 1995).

In extension to our earlier work (El-Gendy *et al.*, 1995) concerning synthesis and biological activities of various isatin derivatives and in view of the above mentioned observations, it seemed of interest to synthesize some new 2-indolinone derived oximes and spiro-isoxazolines for possible antimicrobial activity.

## MATERIALS AND METHODS

### Chemistry

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Melting points were determined on Gallenkamp apparatus and are uncorrected. $^1$H-NMR spectra were measured on Varian GEMINI 200 (200MHz), using TMS as internal standard (chemical shifts in δ, ppm). IR spectra were recorded in KBr using Shimadzu IR 435 spectro-photometer (ν` in $cm^{-1}$). Mass spectra were recorded on Hewlett-Packard HP 5988 (70 eV). Elemental analyses were carried out at the Microanalytical unit, Cairo University.

### General procedure for preparation of 1,3-Dihydro-3-hydroxy-3-[2-(subst. Phenyl)-2-oxoethyl]-2*H*-indol-2-ones(9-20)

A mixture of the appropriate indole-2,3-dione **1-6** (0.02 mol), appropriate acetophenone **7** and **8** (0.02 mol) and diethylamine or piperidine (1 ml) in ethanol (60 ml) was heated under reflux for 30-60 min. and then left for 3-4 days when a white compound separated out which was filtered and recrystallized from ethanol (Table I).

### General procedure for preparation of 1,3-Dihydro-3-hydroxy-3-[2-hydroxyimino-2-(subst. Phenyl)ethyl]-2*H*-indol-2-ones (21-32)

A mixture of the appropriate phenacylindolinone **9-20** (0.01 mol), hydroxylamine hydrochloride (0.7 g, 0.01 mol), sodium carbonate (1.06 g, 0.01 mol), ethanol (10 ml) and water (2 ml) was heated under reflux for 8 h. The reaction mixture was diluted with water (20 ml) and the formed white compound was filtered and recrystallized from ethanol (Table I).

### General procedure for preparation of Spiro[3H-indol-3,5`-(4`*H*)-isoxazol]-2(1*H*)-ones(33-44)

A mixture of the appropriate hydroxy-oxime **21-32** (5 mmol) in conc. sulphuric acid (5 ml) was magnetically stirred at room temperature for 5 h. The reaction mixture was cooled and then poured into crushed ice (20 g). The afforded solid product was filtered, washed with water and recrystallized from ethanol (Tables I, II, III).

**1-Acetyl-3-(2-acetoxyimino-2-phenylethyl)-2,3-dihydro-2-oxo-1*H*-indol-3-yl acetic acid ester (45)**

A mixture of the hydroxy-oxime **21** (1.41 g, 5 mmol) and acetic anhydride (20 ml) was heated under reflux for 6 h. The reaction mixture was concentrated under diminished pressure and the residue was triturated with ice cold water. The solution was extracted twice with ether (50 ml). The ether extract was dried ($Na_2SO_4$) and evaporated *in vacuo*. The remaining solid product was recrystallized from benzene/pet. ether 40/60°C as colourless crystals, 1.42 g (70%), mp 120-121°C, IR (KBr): $\nu$ = 1770, 1740, 1710 $cm^{-1}$ (CO), $^1$H-NMR ($CDCl_3$): $\delta$ 2.03 (s, 3H, $NCOCH_3$), 2.31 (s, 3H, $OCOCH_3$), 2.43 (s, 3H,

**Table I.** Yields and Physical Data of Synthesized Compounds

| Compd. No. | R | $R^1$ | $R^2$ | Yield (%) | M.p. °C | Molecular Formula[a] |
|---|---|---|---|---|---|---|
| **9** | H | H | H | - | 168-170[b] | - |
| **10** | Cl | H | H | - | 207-209[c] | - |
| **11** | Br | H | H | - | 216-218[b] | - |
| **12** | $CH_3$ | H | H | - | 185-186[b] | - |
| **13** | H | $CH_3$ | H | - | 170-172[b] | - |
| **14** | $CH_3$ | $CH_3$ | H | 62 | 135-137 | $C_{18}H_{17}NO_3$ |
| **15** | H | H | Br | - | 187-189[d] | - |
| **16** | Cl | H | Br | 65 | 207-209 | $C_{16}H_{11}BrClNO_3$ |
| **17** | Br | H | Br | 71 | 188-190 | $C_{16}H_{11}Br_2NO_3$ |
| **18** | $CH_3$ | H | Br | 68 | 168-170 | $C_{17}H_{14}BrNO_3$ |
| **19** | H | $CH_3$ | Br | - | 160-162[e] | - |
| **20** | $CH_3$ | $CH_3$ | Br | 60 | 131-133 | $C_{18}H_{16}BrNO_3$ |
| **21** | H | H | H | 82 | 197-199 | $C_{16}H_{14}N_2O_3$ |
| **22** | Cl | H | H | 80 | 217-219 | $C_{16}H_{13}ClN_2O_3$ |
| **23** | Br | H | H | 85 | 199-201 | $C_{16}H_{13}BrN_2O_3$ |
| **24** | $CH_3$ | H | H | 72 | 222-224 | $C_{17}H_{16}N_2O_3$ |
| **25** | H | $CH_3$ | H | 72 | 200-202 | $C_{17}H_{16}N_2O_3$ |
| **26** | $CH_3$ | $CH_3$ | H | 65 | 172-174 | $C_{18}H_{18}N_2O_3$ |
| **27** | H | H | Br | 85 | 203-205 | $C_{16}H_{13}BrN_2O_3$ |
| **28** | Cl | H | Br | 73 | 197-199 | $C_{16}H_{12}BrClN_2O_3$ |
| **29** | Br | H | Br | 77 | 207-209 | $C_{16}H_{12}Br_2N_2O_3$ |
| **30** | $CH_3$ | H | Br | 76 | 230-232 | $C_{17}H_{15}BrN_2O_3$ |
| **31** | H | $CH_3$ | Br | 71 | 208-210 | $C_{17}H_{15}BrN_2O_3$ |
| **32** | $CH_3$ | $CH_3$ | Br | 67 | 205-207 | $C_{18}H_{17}BrN_2O_3$ |
| **33** | H | H | H | 64 | 185-187 | $C_{16}H_{12}N_2O_2$ |
| **34** | Cl | H | H | 58 | 212-214 | $C_{16}H_{11}ClN_2O_2$ |
| **35** | Br | H | H | 60 | 245-247 | $C_{16}H_{11}BrN_2O_2$ |
| **36** | $CH_3$ | H | H | 55 | 178-179 | $C_{17}H_{14}N_2O_2$ |
| **37** | H | $CH_3$ | H | 52 | 130-131 | $C_{17}H_{14}N_2O_2$ |
| **38** | $CH_3$ | $CH_3$ | H | 56 | 145-147 | $C_{18}H_{16}N_2O_2$ |
| **39** | H | H | Br | 63 | 226-228 | $C_{16}H_{11}BrN_2O_2$ |
| **40** | Cl | H | Br | 66 | 218-220 | $C_{16}H_{10}BrClN_2O_2$ |
| **41** | Br | H | Br | 72 | 224-226 | $C_{16}H_{10}Br_2N_2O_2$ |
| **42** | $CH_3$ | H | Br | 46 | 217-219 | $C_{17}H_{13}BrN_2O_2$ |
| **43** | H | $CH_3$ | Br | 52 | 198-200 | $C_{17}H_{13}BrN_2O_2$ |
| **44** | $CH_3$ | $CH_3$ | Br | 46 | 235-237 | $C_{18}H_{15}BrN_2O_2$ |

[a]Satisfactory elemental analyses for C, H, N; [b]Reported m.p.s, 9, 173-175°C, 11, 220-221°C, 12, 189-190°C, 13, 173-175°C (Popp and Donigan, 1979); [c]Reported m.p. 212-213°C (Pajouhesh *et al.*, 1983), [d]Reported m.p. 178-181°C (Lindwall and Maclennan, 1932); [e]Reported m.p. 159-162°C (Kobayashi and Furukawa, 1964)

**Table II.** $^1$H-NMR Spectral Data of **33-44**

| Compd. No. | DMSO-$D_6$, δ=ppm |
|---|---|
| **33** | 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.86-7.71 (m,9H,ArH), 10.74 (s,1H,NH). |
| **34** | 3.87 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.83-7.76 (m,8H,ArH), 10.74 (s,1H,NH). |
| **35** | 3.78 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.90-7.76 (m,8H,ArH), 10.80 (s,1H,NH). |
| **36** | 2.28 (s,3H,$CH_3$), 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 7.01-7.76 (m,8H,ArH), 10.65 (s,1H,NH). |
| **37** | 3.16 (s,3H,$NCH_3$), 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 7.04-7.81 (m,9H,ArH). |
| **38** | 2.28 (s,3H,$CH_3$), 3.14 (s,3H,$NCH_3$), 3.85 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.97-7.77 (m,8H,ArH). |
| **39** | 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.86-7.70 (m,8H,ArH), 10.63 (s,1H,NH). |
| **40** | 3.88 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.86-7.69 (m,7H,ArH), 10.75 (s,1H,NH). |
| **41** | 3.78 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.86-7.76 (m,7H,ArH), 10.80 (s,1H,NH). |
| **42** | 2.23 (s,3H,$CH_3$), 3.80 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.73-7.69 (m,7H,ArH), 10.52 (s,1H,NH). |
| **43** | 3.15 (s,3H,$NCH_3$), 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.89-7.75 (m,8H,ArH). |
| **44** | 2.29 (s,3H,$CH_3$), 3.15 (s,3H,$NCH_3$), 3.86 (ABq,2H,J=18 Hz,4`-$CH_2$), 6.97-7.77 (m,7H,ArH). |

**Table III.** Mass Spectral Data of **33-44** (m/z, % relative abundance)

| ($M^+$-$R^2C_6H_4CNO$) | ($M^+$-CO) | Compd. No. $M^+$ |
|---|---|---|
| 145 | 236(29.0) | 33 294(39.3) |
| 179/181(31.0) | 270(18.8)/272(8.2) | 34 298(43.3)/300(13.3) |
| 223/225(95.5) | 314(21.6)/316(18.7) | 35 342(31.4)/344(31.2) |
| 159 | 250(13.2) | 36 278(33.8) |
| 159 | 250(10.2) | 37 278(20.7) |
| 173 | 264(2.9) | 38 292(33.4) |
| 145 | 314(21.6)/316(16.1) | 39 342(20.3)/344(19.2) |
| 179/181(33.5) | 348(13.1)/350(12.4)/ 352(3.0) | 40 376(13.0)/378(15.7)/ 380(4.5) |
| 223/225(98.4) | 392(16.3)/394(19.1)/ 396(8.6) | 41 420(14.7)/422(29.0)/ 424(13.8) |
| 159 | 328(9.5)/330(7.2) | 42 356(17.1)/358(16.6) |
| 159 | 328(9.4)/330(7.1) | 43 356(17.1)/358(16.6) |
| 173 | 342(2.3)/344(2.2) | 44 370(7.2)/372(7.5) |

$NOCOCH_3$), 3.62 (s, 2H, $CH_2$), 6.82-7.71 ppm (m, 9H, ArH). MS (m/z, %): 409 (7.5) [$M^+$+1], 408 (6.5) [$M^+$], 367 (41.7), 307 (14.3), 265 (45.4), 237 (14.3), 237 (41.7), 209 (20.1), 163 (19.1), 146 (100), 133 (62.7), 117 (43.5), 90 (46.5), 77 (40.1), 51 (22.5). *Anal.* Calcd. For $C_{22}H_{20}N_2O_6$ (408.4): C, 64.69, H, 4.93, N, 6.86, Found C, 64.40, H, 5.00, N, 6.60.

## Microbiological activity

### Microorganisms

*In vitro* antimicrobial activity of the tested compounds was determined by the agar serial microdilution method (Ahmedy *et al.*, 1985). Microorganisms: *Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* NCIMB 9992, *Streptococcus faecalis* NCTC 755, *Bacillus subtilis* NCTC 10075, *Bacillus cereus* NCTC 7464, *Enterobacter aerogens* NCTC 5055, *Escherichia coli* ATCC 10536, *Pseudomonas aeruginosa* CNCMA 21, *Proteus vulgaris* NCTC 4175, *Acetobacter baumonia* CIP 7034, *Alkaligenes faecalis* NCTC 775, *Candida albicans* NCTC 3179 and *Saccharomyces cervicae* IMI 080178.

### Culture media

Mueller-Hinton agar was used for diluting the bacteria suspension and for two-fold dilution of the compounds. Sabouraud liquid medium was used for yeast-like fung.

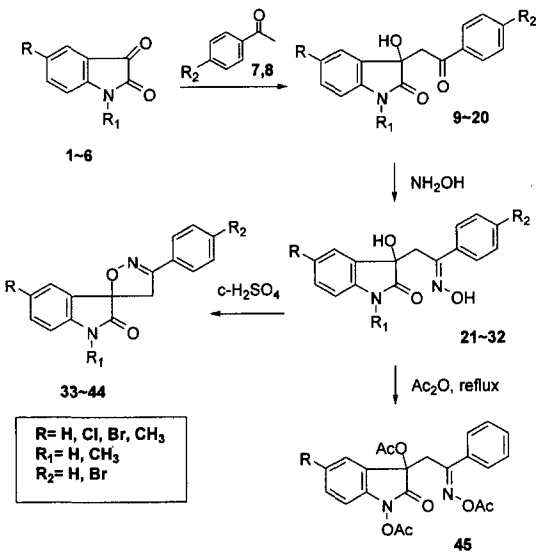
### *In vitro* antibacterial assay

A series of two-fold agar dilution for each compound (0.25,0.5,1,2,4,.....256 μg/ml) was made by dispensing the stock solutions to the remaining wells. The inoculum was prepared by diluting the overnight culture of each microorganism to $10^6$ CFU/ml, and 10 μl of each culture media were transferred on the surface of the dried plates ($10^4$ CFU/inoculum). The plates were incubated at 37°C for 24 h for bacteria and at 25°C for 48 h for yeasts. Rifamycin SV sodium for bacteria as well as Amphotericin B for yeasts were tested under the same conditions and were used as positive control. The minimal inhibitory

concentration (MIC) was determined and compared to that obtained using the positive control.

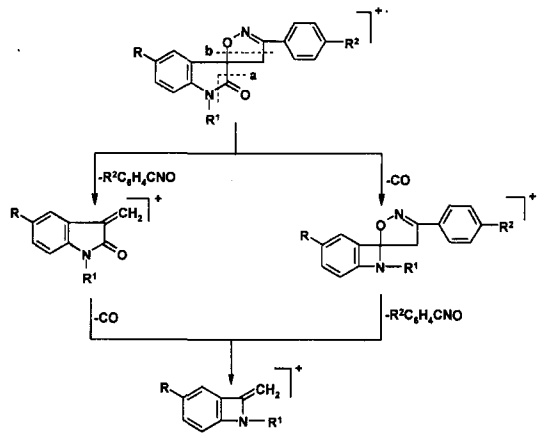
## RESULTS AND DISCUSSION

### Chemistry




**Scheme 1.** Syntheses of New 2-Indolinones

The synthesis of the compounds of this study are illustrated in Scheme 1. Reaction of indoline-2,3-dione and its derivatives **1-6** with acetophenones **7** and **8** in presence of diethylamine or piperidine base gave 3-hydroxy-3-phenacylindolin-2-ones (**9-20**). Condensation of **9-20** with hydroxylamine hydrochloride in equimolecular amounts in the presence of aqueous ethanolic alkali afforded the hydroxy-oximes **21-32**. Trials to convert **21** to the corresponding spiro-indoline-isoxazoline **33** by heating under reflux with acetic anhydride led to acetyla-




**Scheme 2.** Fragmentation of $M^+$ of **33-44**

**Table IV.** Antimicrobial Activity of Some Synthesized Compounds[a]

| Compd. No. | Compd. Minimal Inhibitory Concentration (MIC, μg/ml) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I | J | K | L | M |
| **22** | - | - | - | - | - | - | - | - | 128 | 32 | - | 32 | 128 |
| **23** | - | - | 64 | 32 | 64 | - | - | 16 | 16 | 64 | 32 | 8 | 32 |
| **25** | 64 | 64 | - | - | - | 8 | 128 | - | 16 | 8 | 32 | 32 | 128 |
| **27** | - | 128 | 64 | 16 | 64 | - | 64 | 8 | 0.5 | 32 | 32 | 16 | 64 |
| **28** | 8 | 2 | 2 | 4 | 8 | 16 | 8 | 8 | 64 | 16 | 64 | 2 | 2 |
| **29** | 4 | 2 | 2 | 2 | 4 | 8 | 16 | 2 | 16 | 1 | 16 | 2 | 1 |
| **30** | - | - | - | - | - | 32 | 32 | - | 64 | 32 | - | 32 | 128 |
| **31** | - | - | - | 16 | - | 16 | 128 | 16 | - | 16 | 32 | 32 | 64 |
| **33** | 16 | 32 | 64 | 32 | 32 | 16 | - | 64 | 64 | 64 | - | 16 | 128 |
| **34** | - | - | 64 | 64 | - | 16 | 4 | 128 | - | - | - | - | - |
| **35** | - | - | 64 | 64 | - | 16 | 4 | 128 | - | - | - | - | - |
| **39** | - | 8 | 32 | 32 | 64 | - | - | 16 | 32 | 32 | 64 | 32 | 32 |
| **41** | 32 | 32 | 64 | 64 | 64 | 64 | 32 | 16 | 16 | 64 | 64 | 32 | 16 |
| **42** | - | - | 16 | 64 | 32 | - | 64 | 16 | 32 | 16 | 32 | 16 | 32 |
| **43** | 32 | - | 128 | 128 | 64 | - | 32 | 128 | - | 128 | 64 | 8 | 64 |
| **44** | - | - | 64 | 128 | - | - | 64 | 32 | 256 | - | - | 16 | 64 |
| Rifamycin | 0.5 | 2 | 2 | 0.25 | 1 | 32 | 4 | 4 | 1 | 2 | 16 | | |
| Amphotericin B | | | | | | | | | | | | 0.5 | 1 |

[a]Microorganisms selected are: A *(Staphylococcus aureus)*, B *(Staphylococcus epidermidis)*, C *(Streptococcus faecalis)*, D *(Bacillus subtilis)*. E *(Bacillus cereus)*, F *(Enterobacter aerogens)*, G *(Escherichia coli)*, H *(Pseudomonas aeruginosa)*, I *(Proteus vulgaris)*, J *(Acetobacter baumonia)*, K *(Alkaligenes faecalis)*, L *(Candida albicans)* and M (Saccharomyces cervicae).
(-) no activity at MIC>256 μg/ml

tion rather than cyclodehydration and the triacetyl derivative **45** was obtained. The formation of spiro-indoline-isoxazolines **33-44** from the corresponding hydroxy-oximes succeeded only when concentrated sulfuric acid was used as dehydrating agent. The $^1$H-NMR spectra of **33-44** exhibited a signal of AB-type double doublet due to geminal coupling (J=18 Hz) attributable to a methylene protons at the range of δ=3.78-3.88 ppm (Table II). The mass spectra revealed that fragmentation of $M^+$ of **33-44** occurs *via* two characteristic pathways (a) and (b), Scheme 2. In pathway (a), simultaneous loss of CO moiety from the molecular ion is isatin characteristic. In pathway (b), loss of $R^2C_6H_4CNO$ can be explained in terms of simple ring fission of the isoxazoline ring system. The base peak corresponding in all fragmentation patterns was found to be ($M^+$-$R^2C_6H_4CNO$). These spectral data along with elemental analyses are well consistent with the structure of spiro[indoline-isoxazolines]. .

### Antimicrobial activity

Sixteen of the synthesized compounds were evaluated for their in-vitro antimicrobial activity against some Gram-positive, Gram-negative bacteria and two fungi (Table IV). All tested compounds showed moderate or relative high activity. No clear-cut structure-activity relationship was found since each microorganism was selective to certain types of the tested compounds. Compounds **28** and **29** showed significant antimicrobial activity. They showed high antifungal activity against *C. albicans*, having similar Minimal Inhibitory Concentration (MIC) of 2 μg/ml and against *S. cervicae*, having MIC of 2 μg/ml and 1 μg/ml respectively. Under the same experimental conditions using the same strains, Amphotericin B has MIC of 0.5 μg/ml and 1 μg/ml for *C. albicans* and *S. cervicae* respectively. They also showed antibacterial activity, having MIC in the range of 2-64 μg/ml and 2-16 μg/ml respectively. Under the same experimental conditions using the same strains, Rifamycin SV sodium has MIC of 0.25-32 μg/ml. Compounds **34** and **35** showed no activity against fungi.

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