SYNTHESIS OF NEW HETEROCYCLIC RING SYSTEMS: INDENO[2,1-b]-BENZO[g]INDOLIZINE AND INDENO[1',2':5,4]PYRROLO[2,1-a]PHTHALAZINE

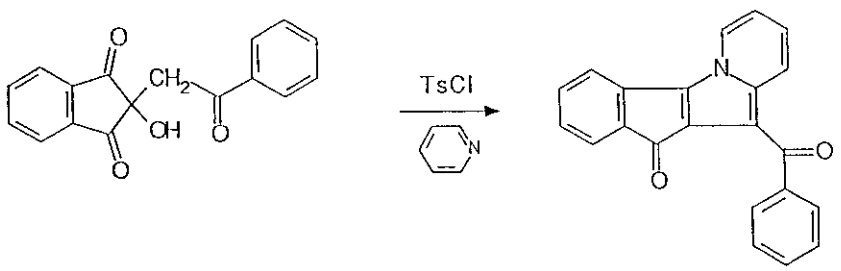
Francesco Campagna*, Angelo Carotti, Giovanni Casini, and Maria Macripò

Dipartimento Farmaco-chimico dell'Università, Via Amendola 173, 70126 BARI, Italy

Abstract - Some derivatives of the title heterocycles have been prepared by a "one step" synthesis from 2-hydroxy-2-acylmethylene-1,3-indandiones, tosyl chloride and isoquinoline or phthalazine. The synthesis of new indeno[2,1-b]indolizine derivatives performed by using pyridine as base is also reported.

During the exploration of synthetic methodology that could provide novel heterocycles and as a part of a program intended to produce DNA-interacting (probably intercalating) compounds, we became interest in the synthesis of novel polycondensed heterocyclic derivatives containing bridgehead nitrogen atoms.[1-8]

In this context, we have recently described the "one-step" synthesis of 11-benzoyl-10H-indeno[2,1-b]indolizin-10-one 2a throughout a simple reaction of 2-hydroxy-2-phenacyl-1,3-indanedione 1a with tosyl chloride (TsCl) in anhydrous pyridine (Scheme 1).

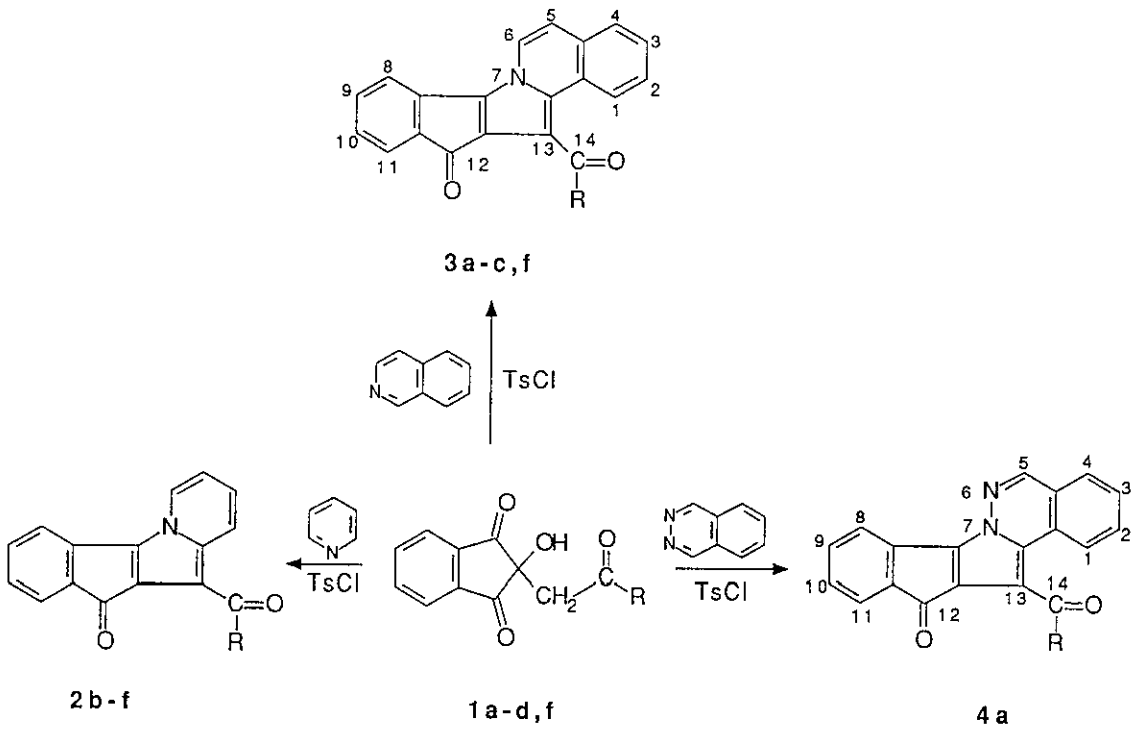


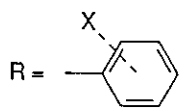
1a 2a

Scheme 1

A possible pathway of this new cyclocondensation reaction and single crystal X-ray diffraction analysis for compound **2a** were reported in that paper.[6]

In order to explore the limitations and applicability of this reaction scheme in the synthesis of derivatives of potential pharmacological interest, we reacted first similar starting ketones **1b-f** with pyridine and then with isoquinoline and phthalazine (Scheme 2)



R =  ; a : X = H; b : X = 3-NO_2; c : X = 4-NO_2 ; d : X = 4- $NHCOOCH_2C_6H_5$;

e : X = 4-NH_2; f : R = $CH_2CH(CH_3)_2$

Scheme 2

As expected the indeno[2,1-b]indolizine derivatives **2b-f** were obtained in fairly good yields. More interestingly also the indeno[2,1-b]benzo[g]indolizine derivatives **3a-c,f** as well as the indeno[1',2':5,4]pyrrolo[2,1-a]phthalazine **4a** were easily formed.

It is important to underline that, to the best of our knowledge, compounds **3** and **4** contain unreported heterocyclic ring systems. The analytical and spectroscopic data of compounds **3a-c,f** are fully consistent with the proposed structures. Furthermore careful analysis of ^{1}H-nmr data allowed a complete proton assignments as indicated for compound **3c** in Table 1.

The ^{1}H-nmr signal patterns are in good agreement with those observed in the simpler structure **2a**.

Similarly, a complete proton assignment has been made for compound **4a** which contained simplified signal patterns due to the presence of a second nitrogen atom in the heterocyclic ring system (Table 2).

A pharmacological screening was carried out on some selected heterocyclic derivatives **2**, **3** and **4**; a limitation for biological activity could arise from their solubility. However compound **2f** displayed weak analgesic (MAD 100 mg/Kg/PO in the acetic acid test) and antiacid (MAD 100 mg/Kg/IP) activities. For **3a** a borderline antiarythmic activity was observed at 100 mg/Kg/IP.

Also some selected 2-hydroxy-2-phenacyl-1,3-indandiones **1** were tested in view of the reported multiple pharmacological properties of 1,3-indandiones,[9,10] which have drawn our interest and attention in the past.[11-13]

Compound **1c** showed a rather unexpected antihypertensive activity (MAD=50mg/Kg/PO) when tested in the Spontaneous Hipertensive Rat.

Table 1. 200 MHz ^{1}H-Nmr data of compound 3c

Protons	Mt [a]	δ, ppm	J H-H		J Hz [b]
1	m [c]	8.66	1,2 1,3	(e) (e)	5.00 2.95
17,19	dt [d]	8.32	17,16(19,20)		8.80 2.10
16,20	dt [d]	8.12	16,17(20,19)		8.80 2.10
6	d	7.90	6,5		7.40
4	m [c]	7.67	4,3 4,2	(f) (f)	6.35 3.10
3	m	7.54	3,4(3,2)	(f)	6.35
2	m	7.52	2,3 2,4	(f) (f)	6.35 3.10
10	td	7.35	10,9 or 11 10,8		7.40 1.35
8	dt	7.32	8,9 8,10 or 11		7.40 1.35
11	dt	7.26	11,10 11,9 or 8		7.40 1.35
5	d	7.20	5,6		7.40
9	td	7.13	9,8 or 10 9,11		7.40 1.35

a) Mt=Multiplicity; b) Values approximated to 0.05 Hz; c) The system was not easily interpretable through a first-order approximation because of para coupling and long range coupling, detected by COSY spectrum; d) The expected A_2B_2 system appears as a couple of double triplets; e) The coupling constants have been determined from the spectrum recorded after irradiation of the H-4 multiplet at 7.67 ppm; f) the coupling constants have been determined from the spectrum recorded after irradiation of the H-1 multiplet at 8.65 ppm.

Table 2. 200 MHz ^{1}H-Nmr data of compound 4a

Protons	Mt[a]	δ, ppm	J H-H	J Hz[b]
5	s	8.58		
1	dd	8.56	1,2 1,3	8.25 1.50
16,20	dt	8.00	16,17(20,19) 16,18 or 19(20,18 or 17)	7.50 1.50
3	m	7.69	3,2 3,4 3,1	8.25 7.70 1.50
2	td	7.65	2,1 2,4	8.25 1.55
4	dd	7.65	4,3 4,2	7.70 1.55
18	tt	7.59	18,19 or 17 18,16 or 20	7.50 1.45
11	dd	7.60	11,10 11,9	7.50 1.05
17,19	td[c]	7.48	17,18(19,18) 17,20(19,16)	7.50 1.50
8	dd	7.35	8,9 8,10	7.50 1.25
10	td	7.34	10,11 or 9 10,8	7.50 1.25
9	td	7.12	9,8 or 10 9,11	7.50 1.05

a) Mt=multiplicity; b) The coupling constants were approximated to 0.05 Hz; c) Signal with additional splittings.

ACKNOWLEDGEMENTS

We wish to thank the Lipha (Lyonnaise Industrielle Pharmaceutique) for the pharmacological screening on some compounds described herein.

EXPERIMENTAL

Melting points were determined by the capillary method on Electrothermal (Mark II) apparatus and are uncorrected. Elemental analyses were made on a Carlo Erba 1106 C,H,N analyzer. Ir spectra were recorded using KBr disks on a Perkin-Elmer 283 spectrophotometer, only the most significant and diagnostic absorption bands being reported. ^{1}H-Nmr specra were recorded on a Varian EM 390 or XL-200 using TMS as internal standard, chemical shifts were expressed in δ (ppm) and the coupling constants J in Hz. Exchange with deuterium oxide (D_2O) was used to identify -OH and -NH protons. A careful ^{1}H-nmr spectral analysis of 11-benzoyl-10H-indeno[2,1-b]-indolizin-10-one 2a has been reported in full details in reference 6 and therefore the same analysis wasn't repeated here for compounds 2b-f whose structures are very close to that of 2a. Chromatographic separations were carried out on silica gel columns (230-400 mesh, Aldrich-Chemie) by using the "flash" technique.

General Method for the Preparation of Ketones 1a-d,f

Compound 1a was prepared according to the procedure described previously.[6]

Compounds 1b-d,f were prepared as follows:

A solution of appropriate ketone (30 mmol) and ninhydrin (5.34 g, 30 mmol) in glacial acetic acid (70 ml) was kept under reflux for 4 h. The solvent was evaporated *in vacuo* and the residue was crystallized or separated by chromatography on a silica gel column to give:

2-Hydroxy-2-[3'nitrophenacyl]-1,3-indanedione 1b (70% yield) mp 162-164 °C from ether, ir, ν max: 3420 br, 1750, 1710, 1680, 1610, 1590 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 4.14(s, 2H, $-CH_2$), 5.81(s, 1H, -OH, exch. with D_2O), 7.86(t, 1H, H-5', J=8.00), 8.05-8.08(m,4H , arom, indanedione moiety), 8.40(dt, 1H, H-6',J=8.00 and 1.20), 8.51(dt, 1H, H-4',J=8.00 and 1.20), 8.65-8.70(m, 1H, H-2'). Anal. Calcd for $C_{17}H_{11}NO_6$: C, 62.77; H, 3.41; N, 4.31. Found: C, 62.46; H, 3.60; N, 4.28.

2-Hydroxy-2-[4'-nitrophenacyl]-1,3-indanedione 1c (40% yield) mp 145-147 °C, from chloroform-hexane, ir, ν max: 3400 br, 1750, 1715, 1695, 1605 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 3.45(s, 1H, -OH, exch. with D_2O), 3.95(s, 2H, $-CH_2$), 7.80-8.40(m, 8H arom, indanedione and phenacyl moieties). Anal. Calcd for $C_{17}H_{11}NO_6$: C, 62.77; H, 3.41; N, 4.31. Found: C, 62.40; H, 3.65; N, 4.20.

2-Hydroxy-2-[(4'-benzyloxycarbonylamino)phenacyl]-1,3-indanedione 1d (47% yield) mp 165-167°C, after column chromatography (ethyl acetate/hexane 1:1 as eluant) and crystallization from the same solvents mixture, ir, ν max: 3380 br, 1750, 1710, 1665, 1585 cm^{-1}; ^{1}H-nmr (acetone-d_6) δ : 4.00(s, 2H, -CH_2), 5.20 (s, 2H, -OCH_2), 5.65-5.85(br, 1H, -OH, exch. with D_2O), 7.30-7.50(m, 5H, arom, -C_6H_5), 7.70(dt, 2H, arom, J=8.90 and 1.90), 7.92(dt, 2H, arom, J=8.90 and 1.90), 7.98-8.15(m, 4H arom, indanedione moiety), 9.19(s, 1H, -NH, exch. with D_2O). Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.82; H, 4.46; N, 3.26. Found: C, 70.16; H, 4.20, N, 3.14.

2-Hydroxy-2-[2'-oxo-4'-methylpentan-1'-yl]-1,3-indanedione 1f (49% yield) mp 89-90 °C, from ether-hexane, ir, ν max: 3400 br, 1750, 1710, 1605 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 0.86(d, 6H, 2-CH_3, J=6.00), 1.75-2.40(m, 1H, -CH_2-CH), 2.26(d, 2H, -CH_2-CH, J=6.00, overlapped to the -CH-CH_2 signal), 3.10-4.00(br, 1H, -OH, exch. with D_2O), 3.23(s, 2H, -CH_2-C=O, overlapped to the -OH signal), 7.70-8.15(m,4H, arom, indanedione moiety). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.08; H, 6.22.

Preparation of 4-Benzyloxycarbonylaminoacetophenone

Benzyl chloroformate (8.5 ml, 55 mmol) was added dropwise to the ice-cooled solution of 4-aminoacetophenone (5 g, 37 mmol) in anhydrous pyridine (20 ml) with vigorous stirring. The reaction mixture was then allowed to warm to room temperature, refluxed for 2 h and after cooling poured into a cold aqueous solution of 3N HCl (110 ml). The mixture was extracted with chloroform and the residue obtained after drying the organic phase over Na_2SO_4 and elimination of the solvent in vacuo was crystallized from ethyl acetate-hexane (7.4 g, 50% yield), mp 118-119°C, ir, ν max: 3295, 1725, 1670, 1590 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 2.54(s, 3H, -CH_3), 5.20(s, 2H, -CH_2), 7.20(s, 1H, -NH, exch. with D_2O), 7.30-7.54(m, 5H , -C_6H_5), 7.49(dt, 2H, arom, J=8.70 and 2.00), 7.90(dt, 2H, arom, J=8.70 and 2.00).

Preparation of Indenoindolizine Derivatives 2b-d,f

Tosyl chloride (0.40 g, 2.1 mmol) was added portionwise to a solution of 1b,d,f (2 mmol) in anhydrous pyridine (5 ml); [for 1c a mixture of anhydrous pyridine dioxane in 1:1 ratio (10 ml) was used]. The reaction mixture was kept under stirring at 50°C overnight and then poured on a cold 2N HCl aqueous solution (10 ml).

The aqueous solution from 1c gave a dark brown precipitate, whereas the aqueous solutions from 1b,d,f were extracted with chloroform. The crude residue 2c and 2b,d, obtained after drying the organic phase over Na_2SO_4 and elimination of the solvent in vacuo, were purified on a silica gel column to give:

11-[4'-Nitrobenzoyl]-10H-indeno[2,1-b]indolizin-10-one 2c (20% yield) chloroform as eluant, mp 260°C dec., ir, ν max: 1715, 1630, 1590 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6) δ : 7.10-7.25(m, 3H, H-3, H-7 and H-2), 7.30-7.50(m, 2H, H-6 and H-8), 7.70(d, 1H, H-9, $J_{9,8}$=7.20), 7.94(d, 2H, H-2' and H-6', $J_{2',3'}=J_{6',5'}$=8.60), 8.21(d, 1H, H-4, $J_{4,3}$= 8.00), 8.27(d, 2H, H-3' and H-5', $J_{3',2'}=J_{5',6'}$=8.60 partially overlapped to the signals of H-4), 8.73(d, 1H, H-1, $J_{1,2}$=8.00). Anal. Calcd for $C_{22}H_{12}N_2O_4$: C,71.73; H, 3.28; N, 7.61. Found: C, 71.42; H, 3.18; N, 7.50.

11-[3'-Nitrobenzoyl]-10H-indeno[2,1-b]indolizin-10-one 2b (20% yield) chloroform/methanol 99:1 as eluant, mp 313-315°C dec., ir, ν max: 1710, 1610, 1600 cm^{-1}; ^{1}H-nmr (chloroform-d) δ : 7.04(td, 1H, H-3, $J_{3,2}=J_{3,4}$=7.00, $J_{3,1}$=1.30), 7.10-7.25(m, 3H, H-7, H-2 and H-9), 7.30-7.40(m, 2H, H-8 and H-6), 7.66(t, 1H, H-5', $J_{5',6'}$=7.95), 8.09(dt, 1H, H-4, $J_{4,3}$=7.00, $J_{4,2}=J_{4,1}$=1.20), 8.15(dt, 1H, H-6', $J_{6',5'}$=7.95, $J_{6',4'}$=1.30), 8.40(dt, 1H, H-1, $J_{1,2}$=7.80, $J_{1,3}$, $J_{1,4}$=1.20-1.30), 8.44(dt, 1-H, H-4', $J_{4',5'}$=7.95, $J_{4',2'}=J_{4',6'}$=1.30), 8.65(t, 1H, H-2', $J_{2',4'}=J_{2',6'}$=1.30). Anal. Calcd for $C_{22}H_{12}N_2O_4$: C, 71.73; H, 3.28; N, 7.61. Found: C, 71.37; H, 3.26; N, 7.47.

11-[4'-Benzyloxycarbonylaminobenzoyl]-10H-indeno[2,1-b]indolizin-10-one 2d (60% yield) chloroform/methanol 98:2 as eluant, mp 192-193°C, ir, ν max: 3320 br, 1705, 1605 cm^{-1}; ^{1}H-nmr (chloroform-d) δ : 5.18(s, 2H, $-CH_2$), 6.88-6.98(m, 2H, H-3 and H-7), 7.00-7.20(m, 3H, H-2, H-9 and H-8), 7.28-7.40(m, 6H, H-6 and $-C_6H_5$), 7.48(d, 2H, H-3' and H-5', $J_{3',2'}=J_{5',6'}$=8.60), 7.86(d, 2H, H-2' and H-6', $J_{2',3'}=J_{6',5'}$=8.60), 7.99(d, 1H, H-4, $J_{4,3}$=6.90), 8.20(d, 1H, H-1, $J_{1,2}$=8.95). Anal. Calcd for $C_{30}H_{20}N_2O_4$: C, 76.26; H, 4.27, N, 5.93. Found: C, 75.90; H, 4.37; N, 6.25.

11-[3'-Methylbutanoyl]-10H-indeno[2,1-b]indolizin-10-one 2f was obtained after concentration of dried organic phase (30% yield), mp 130-131°C, ir, ν max: 3450 br, 1715, 1705, 1645, 1605 cm^{-1}; ^{1}H-nmr (chloroform-d) δ : 1.02(d, 6H, $-CH-(CH_3)_2$, J=6.60), 2.08-2.30(m, 1H, $-CH-(CH_3)_2$), 3.07(d, 2H, CH_2-CH, J= 7.10), 6.88(td, 1H, H-3, $J_{3,4}$=6.90, $J_{3,1}$=1.30), 6.95-7.20(m, 3H, H-7, H-2 and H-9), 7.28(td, 1H, H-8,

$J_{8,7}=J_{8,9}=8.60$, $J_{8,6}=1.30$), 7.42(dt, 1H, H-6, $J_{6,7}=7.70$, $J_{6,8}=1.30$), 7.89(dt, 1H, H-4, $J_{4,3}=6.90$, $J_{4,1}=1.20$), 8.46(dt, 1H, H-1, $J_{1,2}=9.20$, $J_{1,3}=J_{1,4}=1.20$). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.85; H, 5.56; N, 4.48.

Preparation of 11-[4'-Aminobenzoyl]-10H-indeno[2,1-b]indolizin-10-one 2e

Compound 2d (0.47 g, 1 mmol) was treated with HBr (20 wt. % solution in acetic acid, 10 ml). The reaction mixture was kept under stirring at room temperature overnight and after the addition of ether, the precipitate was collected, suspended in a saturated aqueous $NaHCO_3$ solution and extracted with chloroform. The organic layer was dried on anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Crystallization from chloroform-hexane gave a pure dark red solid (0.24 g, 70% yield), mp 266-268°C, ir, νmax: 3360 br, 1710, 1605, 1595 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6) δ : 5.40-6.40(br, 2H, $-NH_2$, exch. with D_2O), 6.54(d, 2H, H-3' and H-5', $J_{3',2'}=J_{5',6'}=8.20$), 6.90-7.20(m, 3H, H-3, H-7 and H-2), 7.25-7.45(m, 3H, H-9, H-8 and H-6), 7.60(d, 2H, H-2' and H-6', $J_{2',3'}=J_{6',5'}=8.20$), 7.80(d, 1H, H-4, $J_{4,3}=8.40$), 8.48(d, 1H, H-1, $J_{1,2}=6.75$). Anal. Calcd for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28. Found: C, 77.93; H, 4.40; N, 7.94.

Preparation of Indeno[2,1-b]benzo[g]indolizine Derivatives 3a-c,f

A mixture of tosyl chloride (0.40 g, 2.1 mmol), isoquinoline (2.58 g, 20 mmol) and appropriate ketone 1 (2 mmol) was kept under stirring at 50°C for 18 h. The work-up was made according to method A_1 or A_2.

METHOD A_1. At the end of reaction the precipitate formed spontaneously or after dilution with chloroform was collected and washed with chloroform, by this procedure the following compounds were obtained:

13-[3'-Nitrobenzoyl]indeno[2,1-b]benzo[g]indolizin-12-one 3b (84% yield) mp 332-333°C, ir, ν max: 1720, 1610 cm^{-1}; ^{1}H-nmr spectrum was not easily interpretable because of the very low solubility of the compound; saturated solutions in different deuterated solvents give rise to signals almost as low as the noise signal. Anal. calcd for $C_{26}H_{14}N_2O_4$: C, 74.64; H, 3.37; N, 6.70. Found: C, 74.45; H, 3.32; N, 6.77.

13-[4'-Nitrobenzoyl]indeno[2,1-b]benzo[g]indolizin-12-one 3c (60% yield) mp 302°C dec, ir, ν max: 1700, 1630, 1595 cm^{-1}; ^{1}H-nmr data are reported in Table 1. Anal.

Calcd for $C_{26}H_{14}N_2O_4$: C, 74.64; H, 3.37; N, 6.70. Found: C, 74.40; H, 3.25; N, 6.56.

METHOD A_2. The reaction mixture was poured in a cold 2N HCl aqueous solution (20 ml). By this treatment compound 3a was formed as a dark red precipitate, whereas 3f was first extracted from the aqueous solution with chloroform and purified by chromatography on a silica gel column using chloroform/methanol 95:5 as eluant; by this method the following compounds were obtained:

13-Benzoylindeno[2,1-b]benzo[g]indolizin-12-one 3a (51% yield) mp 224-225°C after washing with warm anhydrous ethanol, ir, ν max: 1720, 1620 cm^{-1} ; ^{1}H-nmr(chloroform-d)[15] δ : 7.04(d, 1H, H-5, $J_{5,6}$=8.10), 7.06(td, 1H, H-9, $J_{9,8}$=$J_{9,10}$= 7.20, $J_{9,11}$=1.20), 7.13(dd, 1H, H-11, $J_{11,10}$=7.20, $J_{11,9}$=1.20), 7.26(td, 1H, H-10, $J_{10,11}$=$J_{10,9}$=7.20, $J_{10,8}$=1.20), 7.29(dt, 1H, H-8, $J_{8,9}$=7.20, $J_{8,10}$=1.20), 7.37(m, 1H, H-3, $J_{3,2}$=$J_{3,4}$=6.20), 7.39(dd, 1H, H-2, $J_{2,3}$=6.20, $J_{2,4}$=3.15), 7.46(dt, 2H, H-17 and H-19, $J_{17,18}$=$J_{19,18}$=7.65), 7.54(dd, 1H, H-4, $J_{4,3}$=6.20, $J_{4,2}$=3.15), 7.62(tt, 1H, H-18, $J_{18,19}$=$J_{18,17}$=7.65, $J_{18,16}$=$J_{18,20}$=1.70), 7.75(d, 1H, H-6, $J_{6,5}$=8.10), 8.02(dt, 2H, H-16 and H-20, $J_{16,17}$=$J_{20,19}$=7.65, $J_{16,18}$=$J_{16,19}$=$J_{20,18}$= $J_{20,17}$=1.40), 8.35(m, 1H, H-1, $J_{1,2}$=5.00, $J_{1,3}$=2.90). Anal. Calcd for $C_{26}H_{15}NO_2$: C, 83.63; H, 4.05; N, 3.75. Found: C, 83.70; H, 4.06; N, 3.73.

13-[3'-Methylbutanoyl]indeno[2,1-b]benzo[g]indolizin-12-one 3f (50% yield), mp 162-163°C, ir, ν max: 1700, 1600 cm^{-1}; ^{1}H-nmr (chloroform-d) δ: 1.02(d, 6H, 2-CH , J=8.00), 2.12-2.40(m, 1H, CH -CH), 3.22(d, 2H, -CH -CH, J=8.00), 6.91(d, 1H, H-5, $J_{5,6}$=7.00), 7.05(dd, 1H, H-11, $J_{11,10}$=7.00, $J_{11,9}$=1.20), 7.06(td, 1H, H-9, $J_{9,8}$= $J_{9,10}$=7.00, $J_{9,11}$=1.20), 7.25(td, 1H, H-10, $J_{10,11}$=$J_{10,9}$=7.00, $J_{10,8}$=1.20), 7.30-7.50(m, 4H, H-2, H-3, H-4 and H-8), 7.65(d, 1H, H-6, $J_{6,5}$=7.00), 8.86(dd, 1H, H-1, $J_{1,2}$=6.00, $J_{1,3}$=2.00). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.59; H, 5.34; N, 3.88.

Preparation of 13-Benzoylindeno[1',2':5,4]pyrrolo[2,1-a]phthalazin-12-one 4a

Tosyl chloride (0.29 g, 1.25 mmol) was added portionwise to a solution of 1a (0.88 g, 1 mmol) and phthalazine (0.65 g, 5 mmol) in anhydrous dioxane (15 ml).
The reaction mixture was kept under stirring at 50 C for 5 h. The brown precipitate obtained after partial elimination of the solvent in vacuo was collected and

washed with water. After drying the crude product was purified by chromatography on a silica gel column (chloroform/hexane 9:1 as eluant) to give pure indenopyrrolophthalazine 4a (0.15 g, 29% yield), mp 240°C dec, ir, ν max: 1710, 1635, 1615, 1600 cm^{-1}; ^{1}H-nmr data are reported in Table 2. Anal. Calcd for $C_{25}H_{14}N_2O_2$: C, 80.20; H, 3.76; N, 7.48. Found: C, 79.84; H, 4.14; N, 7.40.

REFERENCES AND NOTES

1. A. Carotti, G. Casini, M. Ferappi, and G. M. Cingolani, J. Heterocycl. Chem., 1980, 17, 1577.
2. A. Carotti, Il Farmaco Ed. Sci., 1981, 36, 146.
3. C. Altomare, A. Carotti, and F. Campagna, J. Heterocycl. Chem., 1983, 20, 1751.
4. C. Altomare, A. Carotti, G. Casini, and M. Ferappi, J.Heterocycl. Chem., 1984, 21, 777.
5. C. Altomare, F. Campagna, A. Carotti, and W. E. Steinmetz, Heterocycles, 1985, 23, 1933.
6. A. Carotti, G. Casini, E.Gavuzzo, and F. Mazza, Heterocycles, 1985, 23, 1659.
7. F. Campagna, C. Altomare, A. Carotti, G. Casini, and M. Ferappi, Steroids, 1986, 47, 307.
8. F. Campagna, A. Carotti, and G. Casini, Heterocycles, 1988, 27, 245.
9. W. TH. Nauta and R. F. Rekker, "Pharmacochemistry of 1,3-Indandiones", Elsevier Publishing Company, Amsterdam, 1981, Chap. 3.
10. D. Deblois, S. Piessard, G. Le Baut, P. Kumar, J. D. Brion, L. Sparfel, R. Y. Sanchez, M. Juge, J. Y. Petit, and L. Welin, Eur. J. Med. Chem., 1987, 22, 229.
11. A. Carotti, M. Ferappi, and G. Casini, Boll. Chim. Farm., 1974, 113, 359.
12. A. Carotti, F. Campagna, G. Casini, M. Ferappi, and D. Giardinà, Gazz. Chim. Ital., 1979, 109, 329.
13. F. Campagna, A. Carotti, G. Casini, and M. Ferappi, Gazz. Chim. Ital., 1983, 113, 507.
14. L. H. Hurley and F. L. Boyld, Trends in Pharm. Sci., 1988, 9, 402.
15. The coupling constants for protons H_1-H_4 were determined after irradiation of the H_1 and H_4 signals at 8.35 and 7.54 ppm respectively.

Received, 31st July, 1989