UNEXPECTED REARRANGEMENT OF 2-CARBOXYMETHYLENE-INDAN-1-ONE ARYLHYDRAZONES TO SPIRO[INDAN-2,4'-QUINOLINE] KETO LACTAMS

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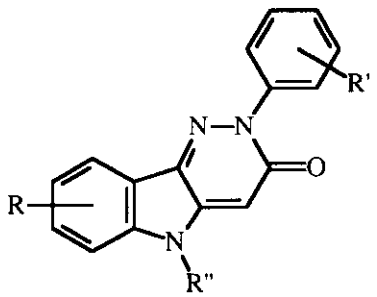
Abstract- The reaction of 1-keto-2-indanylacetic acid (**3**) with substituted phenylhydrazine hydrochlorides (**4**) yielded the spiro[indan-2,4'-quinoline] keto lactams (**6**). The structures of compounds (**6**) were assigned on the basis of ^{1}H- and ^{13}C-NMR analyses. A possible reaction mechanism is proposed .

Our continuing interest in the synthesis of biologically active nitrogen heterocycles led us recently to report on 2-arylpyridazinoindolones (**1**), a new and interesting class of benzodiazepine receptor ligands.[1,2] Different substitution in the pyridazinoindole nucleus and the 2-phenyl ring results in a complete spanning of the pharmacological activity from agonist to inverse agonist.[2]



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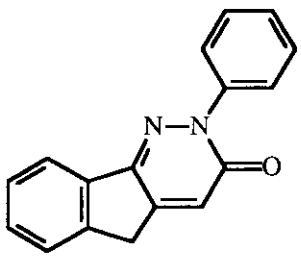

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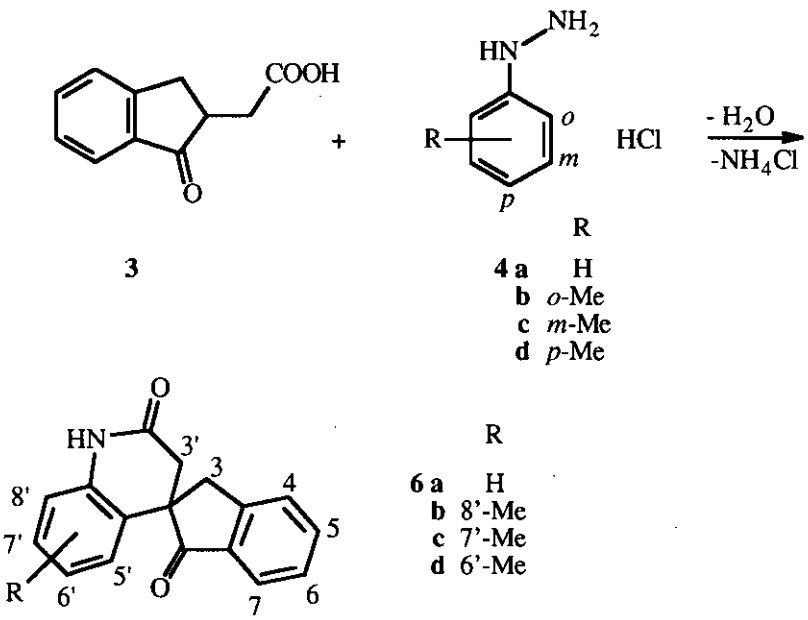
In order to examine closely the importance of the indolic NH function in such ligands we planned the synthesis of 2-phenyl-2,5-dihydroindeno[1,2-*c*]pyridazin-3(3*H*)-one (**2**), which contains the indane nucleus instead of the indole nucleus. A survey of the literature revealed that a series of 2-substituted phenyl-2,4,4a,5-tetrahydroindeno[1,2-*c*]pyridazin-3(3*H*)-ones, have been synthesized and tested for their ability to displace [^{3}H]diazepam from rat brain membranes.[3] Furthermore several indeno[1,2-*c*]pyridazinones, lacking the phenyl substituent at N-2, have been prepared by refluxing 1-keto-2-indanylacetic acid (**3**)[4] with hydrazine hydrate in ethanol.[5,6] Since 2-phenyl-2,4,4a,5-tetrahydroindeno[1,2-*c*]pyridazin-3(3*H*)-one[3] could be easily transformed into **2** by bromination-dehydrobromination, we tried to prepare it by treating **3** with phenylhydrazine hydrochloride (**4a**) instead of the free base. By studying the first step of the planned reaction the unexpected formation of compound (**6a**) containing a spiro ring system was revealed (Scheme 1).

Scheme 1



3

R

4 a H
b *o*-Me
c *m*-Me
d *p*-Me

R

6 a H
b 8'-Me
c 7'-Me
d 6'-Me

To generalize this interesting transformation, a series of spiro compounds (**6b-d**) was also prepared in one step by treatment of **3** with an equimolecular amount of substituted phenylhydrazine hydrochlorides (**4b-d**) under reflux in ethanol (Scheme 1). The reaction products were assigned to the structures (**6a-d**) on the basis of ^{1}H- and ^{13}C-NMR spectral data (Tables 1 and 2, respectively). In particular, the signal at 51 ppm in the ^{13}C-NMR spectum was attributed to a quaternary carbon as suggested by the APT spectrum and confirmed by the HETCOR experiment. The proton signals of the two CH_2 groups were

correlated ($^2J_{H,C}$) with this quaternary carbon by INEPTL measurements, which also revealed a $^3J_{H,C}$ connectivity of both the methylenes with C-1 and C-6' carbons. Only the lowfield methylene signals were correlated to C-7a and were attributed to the 3-CH_2. Accordingly, a DIF NOE experiment on the 3-CH_2 protons produced an enhancement of the H-4 and H-5' signals, whereas selective irradiation of the 3'-CH_2 signal did not reveal the presence of neighbouring protons.

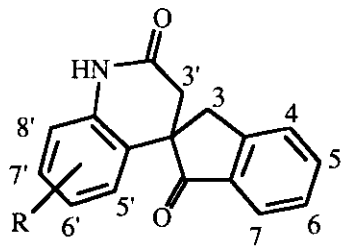


Table 1. ^{1}H-NMR spectral data of compounds (6a-d) [a]

	6a	6b	6c	6d
3-HA	3.38(br d,J=17)	3.34(2H,s)	3.35(br d,J=17)	3.37(br d,J=17)
3-HB	3.33(br d,J=17)		3.31(br d,J=17)	3.31(br d,J=17)
4-H	7.62(br d,J=7.5)	7.62(br d,J=7.5)	7.62(br d,J=7.5)	7.62(br d,J=7.5)
5-H	7.75(dt,J=7.5x2, 1.5)	7.76(dt,J=7.5x2, 1.5)	7.75(dt,J=7.5x2, 1.5)	7.76(dt,J=7.5x2, 1.5)
6-H	7.49(br t,J=7.5)	7.49(dt,J=7.5x2, 1.5)	7.48(dt,J=7.5x2, 1.5)	7.50(dt,J=7.5x2, 1.5)
7-H	7.70(br d,J=7.5)	7.71(br d,J=7.5)	7.69(br d,J=7.5)	7.71(br d,J=7.5)
NH	10.14(br s)	9.43(br s)	10.05(br s)	10.07(br s)
3'-HA	2.73(d,J=16)	2.73(d,J=16)	2.70(d,J=16)	2.69(d,J=16)
3'-HB	2.66(d,J=16)	2.62(d,J=16)	2.63(d,J=16)	2.59(br d,J=16)
5'-H	6.71(dd,J=7.5, 2)	6.56(dd,J=7.5, 1.5)	6.58(d,J=8)	6.52(d,J=2)
6'-H	6.81(dt,J=7.5x2, 2.2)	6.74(t,J=7.5)	6.62(dd,J=8, 2)	-
7'-H	7.15(dt,J=7.5x2, 2.2)	7.02(br dd,J=7.5, 1.5)	-	6.96(br dd,J=8, 2)
8'-H	6.95(dd,J=7.5, 2)	-	6.75(d,J=2)	6.84(d,J=8)
Me	-	2.25(s)	2.19(s)	2.08(s)

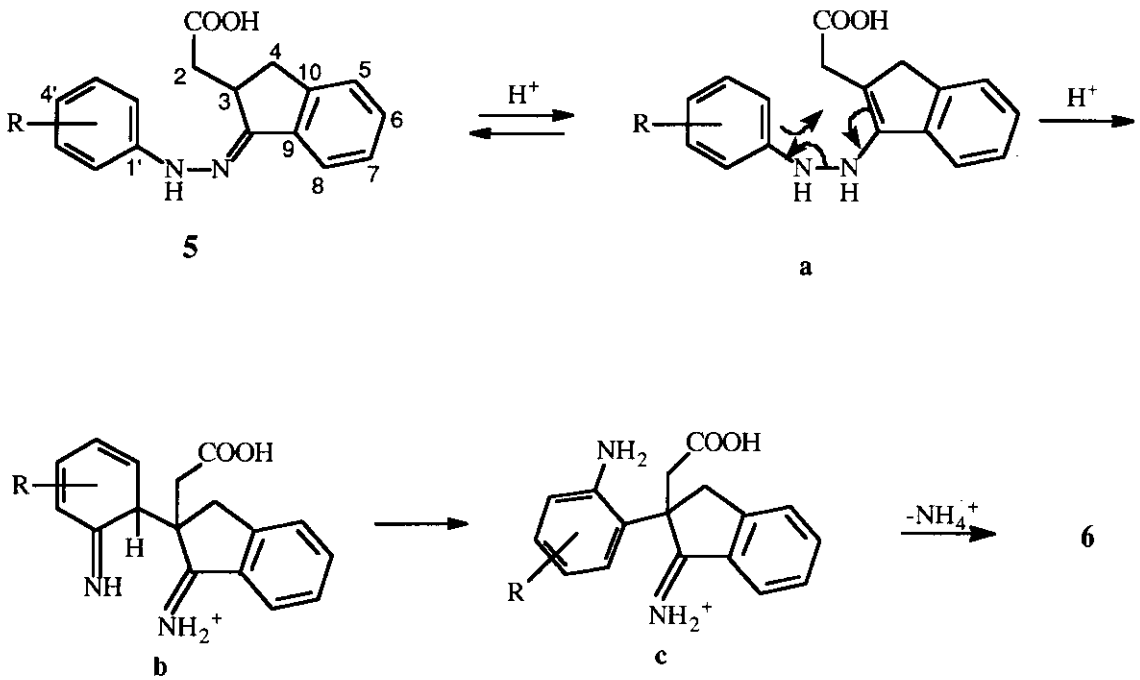
a) In parentheses multiplicities and coupling constants (in Hz).

Table 2. ^{13}C-NMR spectral data of compounds (6a-d)

	6a	6b	6c	6d
1-C	205.38	205.47	205.45	205.55
2:4'-C	51.22	51.31	50.94	51.16
3-C	40.67	40.65	40.67	40.72
3a-C	151.68	151.58	151.66	151.65
4-C	126.60	126.63	126.57	126.64
5-C	135.55	135.54	135.48	135.55
6-C	127.89	127.86	127.85	127.86
7-C	123.88	123.79	123.84	123.84
7a-C	134.14	134.36	134.16	134.21
2'-C	167.63	168.14	167.75	167.41
3'-C	38.20	38.33	38.31	38.53
4'a-C	125.07	126.10	122.19	125.14
5'-C	124.56	122.25	124.42	124.90
6'-C	121.97	121.85	122.62	130.88
7'-C	127.85	129.51	137.32	128.26
8'-C	115.72	124.18	116.13	115.64
8'a-C	138.34	136.38	138.22	135.89
Me	-	17.09	20.34	20.02

To study the mechanism of the reaction we treated **3** with phenylhydrazine in ethanol under reflux. In these conditions only the intermediate phenylhydrazone (**5a**) was formed as checked by TLC. This fact suggested that the spirocyclization occurred in acidic conditions. To support this hypothesis we heated at reflux (**5a**) (easily prepared by treatment of **3** with phenylhydrazine at room temperature, see experimental) in ethanol in the presence of a catalytic amount of HCl. In these conditions the spiro compound (**6a**) was obtained. On the basis of these results we depicted in Scheme 2 a possible reaction mechanism, like that proposed by Robinson for the Fischer indole synthesis,[7] starting from the intermediate phenylhydrazone (**5**).

Scheme 2



The key step is the Claisen-type rearrangement of the indenearylhydrazine intermediate (**a**) which occurs at the free *ortho*-position to yield the diimine intermediate (**b**). The intermediate (**b**) rearranges to the aniline derivative (**c**) which in turn may undergo cyclization to iminolactam and subsequent hydrolysis to the keto lactam (**6**). The reaction with *m*-methylphenylhydrazine, which could yield two possible isomers containing the methyl group in the position 5' and 7' respectively, gave only the 7'-methyl derivative (**6c**). The regiospecific spirocyclization was probably due to the steric hindrance of the methyl group in the key step of the rearrangement hypothesized by us (Scheme 2).

In conclusion we showed that, unlike hydrazine and methylhydrazine,[6,8] substituted phenylhydrazines under reflux with 1-keto-2-indanylacetic acid in ethanol did not give pyridazinone derivatives. However, when the reaction was carried out in the presence of HCl the spiro derivatives (**6a-d**) were formed.

EXPERIMENTAL

Melting points were determined by the capillary method on a Gallenkamp MFB 595 010M apparatus and are uncorrected. Elemental analyses were made on a Carlo Erba 1106 analyser. IR spectra were recorded using potassium bromide disks on a Perkin Elmer 283 spetrophotometer. Only the most significant and

diagnostic absorption bands are reported. Chromatographic separations were carried out on silica gel columns (70-230 mesh, Merck). ^{1}H and ^{13}C-NMR spectra were run with a Varian Gemini spectrometer, working at 300 MHz (^{1}H) and at 75 MHz (^{13}C). The solvent in all measurements was DMSO-d_6 at 60°C. Chemical shifts are reported in ppm by reference to the central peak of the solvent (^{1}H-NMR; δ_H= 2.49ppm and ^{13}C-NMR; δ_C= 39.50 ppm) and the coupling constants (J) are given in Hz. Signal assignment was supported by the following experiments: APT (Attached Proton Test), DIF NOE (Difference Nuclear Overhauser Effect), HETCOR (Heteronuclear Correlation) and INEPTL (Insensitive Nuclei Enhanced by Polarization Transfer Long-range).

General method for the preparation of spiro[indan-2,4'-quinoline] keto lactams (6a-d).

A solution of the appropriate phenylhydrazine hydrochloride (1.2 mmol) in ethanol/water 1:1 (6 mL) was added to a solution of 1-keto-2-indanylacetic acid (**3**) (0.190 g; 1 mmol) in ethanol (16 mL) and the reaction mixture was refluxed for 7 h. Work-up was performed as indicated below.

Spiro[indan-1-one-2,4'-1',2',3',4',-tetrahydroquinolin-2'-one] (6a).

The final solution was concentrated under reduced pressure to give a precipitate which was filtered and crystallized from ethanol to afford **6a** (0.105 g, 40%); mp 267-269°C. IR, ν cm^{-1}: 3190, 1705, 1675. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.31. Found: C, 77.94; H, 5.23; N, 5.37.

Spiro[indan-1-one-2,4'-8'-methyl-1',2',3',4',-tetrahydroquinolin-2'-one] (6b).

After cooling the reaction mixture yielded a precipitate which was collected and recrystallized from ethanol to afford **6b** (0.083 g; 30%); mp 241-243°C. IR, ν cm^{-1}: 3300, 1705, 1675. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 78.22; H, 5.80; N, 5.41.

Spiro[indan-1-one-2,4'-7'-methyl-1',2',3',4',-tetrahydroquinolin-2'-one] (6c).

After removal of the solvents under reduced pressure, the crude residue was chromatographed on silica gel (8:2 chloroform/ethyl acetate; Rf=0.22) and recrystallized from ethanol to afford (**6c**) (0.058 g; 21%). mp 240-241°C. IR, ν cm^{-1}: 3200, 1700, 1685. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 78.29; H, 5.62; N, 5.06.

Spiro[indan-1-one-2,4'-6'-methyl-1',2',3',4',-tetrahydroquinolin-2'-one] (6d).

After cooling the reaction mixture yielded a precipitate which was collected and recrystallized from ethanol to afford **6d** (0.083g; 30%); mp 243-245°C. IR, ν cm^{-1}: 3200, 1705, 1670. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 78.33; H, 5.78; N, 5.19.

2-Carboxymethylen-indan-1-one phenylhydrazone (5a).

A solution of **3** (0.190 g; 1 mmol) and phenylhydrazine (0.118 mL; 1.2 mmol) in anhydrous methanol (3 mL) was stirred at rt for 3 h. The precipitate was collected and recrystallized from methanol to give the phenylhydrazone (**5**) (0.190 g, 68%), mp 149-150°C. IR, ν cm^{-1}: 3280, 1700, 1595. ^{1}H-NMR (DMSO-d_6, 60°C): δ 12.18 (1H, br s, OH), 9.24 (1H, s, NH), 7.60 (1H, m, H-8), 7.30, 7.27, 7.24 (1H each, m, H-5, H-6, H-7), 7.20, 6.74 (4H, 1H, m, Ph), 3.71 (1H, dddd, J= 10.5, 8, 3.5 and 1.5 Hz, H-3), 3.33 (1H, dd, J= 17 and 8 Hz, H-4A), 2.88 (1H, dd, J= 16.5 and 3.5 Hz, H-2A), 2.80 (1H, dd, J=17 and 1.5 Hz, H-4B), 2.12 (1H, dd, J=16.5 and 10.5 Hz, H-2B); ^{13}C-NMR: δ 172.92 (s, C=O), 151.04 (s, C=N), 145.96 (s, C-1'), 144.28 (s, C-10), 138.34 (s, C-9), 128.52, 118.51, 112.51 (dx2, d, dx2, NHPh), 128.46 (d, C-6), 126.66, 125.32 (d each, C-5, C-7), 120.11 (d, C-8), 35.99 (t, C-4), 34.75 (t, C-2), 34.44 (d,C-3). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 10.00. Found: C, 72.45; H, 5.91; N, 10.04

Spirocyclization of 5a to 6a.

A catalytic amount of conc. HCl was added to a solution of **5a** (0.280 g; 1 mmol) in ethanol/water 87:13 (20 mL) and then the mixture was refluxed for 7 h. The reaction mixture was cooled to rt and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate/petroleum ether 55:45 as eluent) to afford **6a** (0.050 g, 18% ; Rf=0.35).

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