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Note

Synthesis, C-13 NMR and anticonvulsant activity of new isatin-based spiroazetidinones

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A series of 1-aryl/cyclohexyl-3, 3-diphenyl-1'-(diphenylacetyl)-2-oxospiro[azetidin-4,3'-indolin-2'-ones] **4a-h** has been synthesized by the reaction of diphenylketene, generated *in situ* from the thermal decomposition of 2-diazo-1,2-diphenylethanone **1** with 3-N-aryl/cyclohexyliminoindolin-2-ones **2a-h** in 2:1 molar ratio. These spiroazetidinones, also obtainable by an equimolar reaction of diphenyketene with 1-diphenylacetyl derivatives **3** of the latter, have been characterized on the basis of elemental and spectral (IR, ^{1}H and ^{13}C NMR and mass) analyses and screened for their anticonvulsant activity. Two compounds **4e** and **4h** exhibit highly significant activity against MES.

Isatin derivatives constitute an important class of heterocycles with a broad range of biological activities[1], such as anticonvulsant, anti-inflammatory and CNS depressant activities which prompted us to investigate the reaction of its 3-N-substituted imines with 2-diazo-1,2-diphenylethanone **1**, a precursor of diphenylketene. Ketenes are known to afford azetidinones[2], lactones and amides[3] by reactions with the substrates containing C=N, C=O and N-H groups, respectively. However, these reactions often depend on structural environment of the molecule, e.g., reaction of diphenylketene with N-benzhydrylidene-N'-phenylurea[4], fluorinone-N-benzoylhydrazone[5] and benzophenone-N-diphenylacetyl hydrazone[6] occurred at C=N group leading to the formation of azetidinones in first two cases and diazopropanones were obtained in the third case. The reaction of phenoxyketene with benzophenone-N-phenylhydrazones has been reported to occur at N-H group of the latter[7].

We have recently reported an equimolar reaction of **1** with 3-N-substituted isatinimines **2** leading to an exclusive formation of the corresponding N-diphenylacetyl derivatives **3**[8]. In continuation to this study, we wish to report the synthesis of new 1-aryl/cyclohexyl-3,3-diphenyl-1'-(diphenylacetyl)-2-oxospiro[azetidin-4,3'-indolin-2'-one] **4a-h** from the reaction of diphenylketene, obtained by thermal decomposition of **1** with 3-N-aryl/cyclohexyliminoindolin-2-ones **2a-h** in 2:1 molar ratio (Scheme I). The spiroazetidinones **4a-h**, also obtainable from an equimolar reaction of **1** with **3a-h**, have been screened for their activity against MES and Chemoshock induced seizures. Only a few spiroazetidinones are known in the literature which have been obtained from the reactions of (i) acid chlorides with anils[9]; (ii) isocyanates with olefins[10]; and dipenylketene with hydrazones and ketoimines[11].

The spiroazetidinones **4a-h** obtained above were crystallized from ethanol in good yields and their structures were characterized on the basis of their physical (Table I) and spectral (IR, ^{1}H and ^{13}C NMR and mass) data (Table II). The IR spectra exhibited three strong absorption bands at 1765±5 (C=O,γ-lactam), 1747±3 (C=O, β-lactam) and 1716 (COCH) cm^{-1}. The ^{13}C NMR spectra showed three carbonyl carbons in range of 175.10-172.70 (β-lactam carbonyl carbon) 172.89-172.52 (*sd*, J_2C-H=7.27 Hz, COCH) and 167.95-165.41 ppm (γ-lactam carbonyl carbon). It showed two signals at about δ78.00 and 72.00 ppm which were assignable to C-3', 4 and C-3 carbons, respectively. The methine carbon appearaed as a doublet at δ57.00 ppm. The proton at this carbon appeared as a singlet at δ6.31 ppm in the ^{1}H NMR spectra. The mass spectra showed the respective M^+ peaks and a fragment at 194 (Ph_2C=C–O) as a base peak. The other main fragments correspond to M^+-Ph_2C=C=O, 4-Ph_2COCH and Ph_2CH.

The reaction sequence for the formation of **4a-h**

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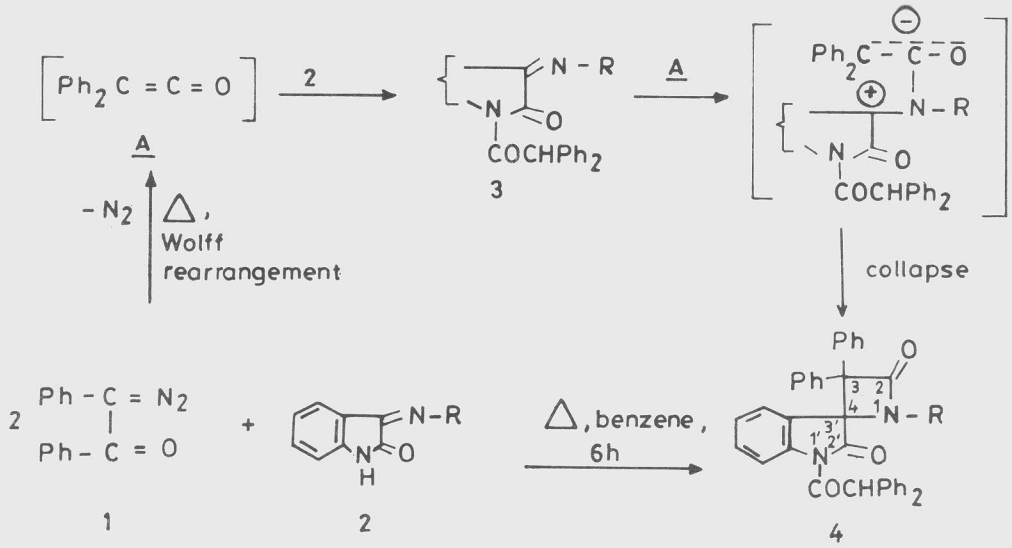

Scheme I

Table I—Physical data of spiroazetidinones **4a-h**

Compd	R	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N
4a	Phenyl	66	142-43	$C_{42}H_{30}N_2O_3$	82.73 (82.62	4.93 4.91	4.60 4.59)
4b	4-Methylphenyl	69	188-89	$C_{43}H_{32}N_2O_3$	82.45 (82.69	5.26 5.12	4.35 4.48)
4c	4-Methoxyphenyl	73	198	$C_{43}H_{32}N_2O_4$	80.69 (80.62	5.09 5.00	4.33 4.37)
4d	4-Ethoxyphenyl	78	186-87	$C_{44}H_{34}N_2O_4$	80.70 (80.73	5.21 5.19	4.25 4.28)
4e	4-Chlorophenyl	59	208-9	$C_{42}H_{29}N_2O_3Cl$	78.15 (78.26	4.62 4.50	4.37 4.34)
4f	4-Nitrophenyl	61	233-34	$C_{42}H_{29}N_3O_5$	76.73 (76.94	4.45 4.42	6.40 6.41)
4g	Cyclohexyl	75	184-85	$C_{42}H_{36}N_2O_3$	82.02 (81.81	6.10 5.84	4.46 4.54)
4h	I-Naphthyl	77	217-18	$C_{46}H_{32}N_2O_3$	83.75 (83.63	4.86 4.84	4.16 4.24)

is shown in Scheme I. Thermal decomposition of **1** with extrusion of N_2 yields diphenylketene as a result of wolff-rearrangement of the resulting benzoylphenylcarbene. The diphenylketene reacts preferentially with amido nitrogen of **2** giving rise to its corresponding N-diphenylacetyl derivative **3**. An imino nitrogen in the latter reacts with a second molecule of diphenylketene to give a possible *zwitterionic* intermediate which finally cyclizes to furnish spiroazetidinones **4a-h**. The formation of similar *zwitterions* have been proposed earlier in the synthesis of azetidinones[4,11].

Anticonvulsant activity. The screening of compounds **3a-h** by maximal electroshock (MES)[12] and chemoshock methods[13] showed a profile of anticonvulsant activity. The compounds **4h** with naphthyl substituent showed 100% protection at the dose level of 200 mg/kg, i.p. which was similar to the activity of standard drug phenobarbitone. However, its LD_{50} value of 150 mg/kg was less in comparison with the standard drug (270 mg/kg).

p-Chlorosubstituted spiroazetidinone **4e** protected 80% animals while other compounds of the series showed 30-60% protection. All the compounds of the series, however, responded insignificantly (0-30%) to picrotoxin and strychnine induced seizures.

Table II—Spectral Data of Spiroazetidinones **4a-h**

Compd	^{1}H NMR ($CDCl_3$, δppm)	^{13}C NMR ($CDCl_3$, δppm)	MS m/z (r.i)
4a	8.45(d,*J*=8.24 Hz,1 H, arom), 7.23(m,21 H, arom), 6.98(m, 3 H, arom), 6.83(td,*J*=6.60, 0.99 Hz,1 H, arom), 6.31(s,1 H, CH), 7.48(m,2 H, arom), 6.28(dd,*J*=6.60, 0.99 Hz,1 H, arom)	173.31, 172.85(sd,*J*=7.27 Hz), 165.67, 140.19, 137.07, 137.99, 137.34, 136.60, 136.01, 131.09, 11.0.3, 129.21, 129.09, 128.67, 128.60, 128.40128.05, 127.95, 127.64, 127.45, 127.37126.52, 126.32, 125.01, 124.86, 122.20, 122.14, 117.34, 116.99, 78.22, 71.84, 56.94(dm, CH)	610(M^+, 15), 416(15, M^+ Ph_2C=C=O), 222(10, $MCOCHPh_2$), 194(100), 166(30), 77(8)
4b	8.44(d,*J*=8.24 Hz, 1 H, arom), 7.26(m, 25 H, arom), 6.82(td, 1H, arom), 6.32(s, 1H, CH), 628(dd, 1 H, arom), 2.24(s, 3 H, CH_3)	173.42, 172.84 (sd,*J*=7.93 Hz), 165.47, 140.21, 138.09, 138.07, 137.39, 136.70, 134.63, 133.49, 131.01, 129.70, 129.19., 129.10, 128.66, 128.57, 128.36, 128.31, 128.06, 127.88, 127.57, 127.43, 127.29, 126.53, 126.29, 124.96, 122.30, 117.45, 116.95, 78.18, 71.88, 56.85, 20.85	624(M,15), 430(60), 236(82), 208(25), 194(100), 165(58), 139, 115, 91, 65
4c	8.43(d,*J*=8.24 Hz, 1 H, arom), 7.28(m,21 H, arom), 6.92, (dd,2 H, arom), 6.84 (t,1 H, arom), 6.63(dd,2 H, arom), 6.31(s,1 H, CH), 6.28 (d,*J*=7.22 Hz, 1 H, arom), 3.69(s,3 H, OMe)	173.51, 172.82(sd,*J*=7.93 Hz), 165.42, 156.77, 140.31, 138.10, 138.05, 137.48, 136.79, 131.04, 129.20, 129.11, 128.66, 128.58(two C), 128.37, 128.31128.07, 127.88, 127.57, 127.43, 127.31, 126.54, 126.32, 124.96, 122.31, 119.45, 116.93, 114.42, 78.33, 72.18, 56.91, 55.34 (q, OMe)	640(M^+, 2), 446(70), 418(2), 296(3), 252(100), 224(20), 194(35), 165(38), 139, 83
4d	8.44(d,*J*=8.24 Hz, 1 H, arom), 7.27(m, 21 H, arom), 6.92(dd, 2 H, arom), 6.88(td,1 H, arom), 6.60(dd, 2 H, arom), 6.32(s, 1 H, CH), 6.26(dd,1 H, arom) 3.90(q,2 H, OCH_2), 1.31(t,3 H, CH^3)	173.3, 172.83(sd,*J*=7.93 Hz), 165.41, 156.17, 140.31, 138.10, 138.05, 137.49, 136.80, 131.02, 129.20, 129.11, 129.07, 128.67, 128.58(two C), 128.38, 128.08, 127.88, 127.51, 127.44, 127.32, 126.55, 126.33, 124.94, 122.34, 119.47, 116.94, 115.00, 78.32, 72.19, 63.58, 56.91, 14.71	654(M^+5), 460(55), 296, 266(100), 238(20), 194(40), 165(38), 139, 83
4e	8.44(d,*J*=8.24 Hz,1 H, arom), 7.15(m,26 H, arom), 6.34(s, 1 H, CH), 6.31(dd,1 H, arom)	173.09, 172.78(sd,*J*=7.93 Hz), 165.68, 140.24, 137.96, 137.79, 137.18, 136.41, 134.53, 131.32, 130.05, 129.32, 129.19, 129.06, 128.66(two C), 128.47, 128.31, 128.05, 127.97, 127.74, 127.47, 127.45, 126.43, 126.27, 125.08, 121.83, 118.58, 117.01, 78.55, 71.95, 57.06	644(M^+, 8), 450(5), 421, 393, 296, 256, 228, 194(100), 166(30), 111, 78
4f	8.47(d,*J*=7.92 Hz,1 H, arom), 7.95(dd,2 H, arom), 7.27(m, 23 H, arom), 6.82(td,1 H, arom), 6.25(s, 1 H, CH), 6.23(dd,1 H, arom)	172.70, 172.57, 166.18, 147.73, 141.16, 140..25, 137.78, 137.53, 136.85, 135.94, 131.75, 129.19, 129.02, 128.81, 128.75, 121.24, 117.12, 116.93, 78.94, 72.0857.32	655(M^+,1), 491, 461, 431, 404, 358, 297, 280, 267, 251, 237, 220, 194(100), 166(45), 15.2, 76
4g	8.29(d,*J*=7.92 Hz,1 H, arom), 7.19(m,21 H, arom), 6.84(td, 1 H, arom), 6.32(s,1 H, CH), 6.23(dd,1 H, arom), 3.20(m,1 H, N-CH), 1.45(m,10 H, 5 CH_2)	175.10, 172.89, 167.95, 140.16, 138.23, 138.16, 137.88, 137.35, 130.68, 129.29, 129.14, 128.58, 128.54, 1`28.46, 128.31, 128.12, 127.64, 127.39, 127.35, 127.29, 126.56, 126.44, 124.63, 123.60, 116.70, 77.70, 71.79, 57.26(d), 54.17(dm), 31.83, 30.36, 25.13, 25.09, 25.04, 24.86	616(M^+, 10), 491(2), 422(5), 297(6), 267, 228, 194(100), 166(35), 145, 55
4h	8.24(d,*J*=8.24 Hz,1 H, arom), 8.09(d,*J*=8.90 Hz,1 H, arom), 7.70(d,*J*=7.26 Hz,1 H, arom), 7.59(d,*J*=8.25 Hz,1 H, arom), 7.42(m,4 H, arom), 7.16(m,20 H, 6.90(t,*J*=8.00 Hz,1 H, arom), 6.67(m,1 H, arom), 6.30(dd, 1 H, arom), 6.28(s,1 H, CH)	174.35, 172.79, 167.17, 140.98, 138.45, 138.17, 137.87, 137.46, 134.24, 131.06, 130.73, 129.60, 129.30, 129.08, 128.69, 128.63, 128.59, 128.50, 129.31, 128.17, 128.12, 127.96, 127.54, 127.44, 127.25, 126.91, 126.90, 126.49, 126.45, 125.09, 124.71, 123.61, 122.60, 122.26, 116.77, 78.15, 75.15, 57.27	660(M^+, 5), 491, 466(80),437, 296, 272(100), 243, 220, 194(40), 165(45), 127(15), 82

Experimental Section

Melting points have been determined on a Buchi apparatus and are uncorrected. The IR spectra were recorded in KBr on a Perkin-Elmer 720 spectrophotometer; ^{1}H and ^{13}C NMR spectra in $CDCl_3$ on Geol FX 270 MHz and 67.8 MHz spectrometers, respectively using TMS as an internal standard, and mass spectra on Hitachi Perkin-Elmer model RMU-6E spectrometer at 70 ev.

2-Diazo-1,2-diphenylethanone **1** was prepared by well-known method and ketoimines **2a-h** were prepared by the literature procedure[14].

Synthesis of 4a-h. General procedure. A mixture of **1** (2.22 g, 10 mmoles) and **2a-h** (5 mmoles) was heated to reflux in dry benzene (80 mL) for 6 hr under a stream of nitrogen. The solvent was removed on rotatory evaporator and the residue crystallised from ethanol to give spiroazetidinones **4a-h**.

Similarly the reaction of **1** (1.11 g, 5 mmoles) with an equimolar amount of **3a-h** as described above gave **4a-h**.

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