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Spirocyclopropane Compounds. II.$^{1)}$ Synthesis and Biological Activities of Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones

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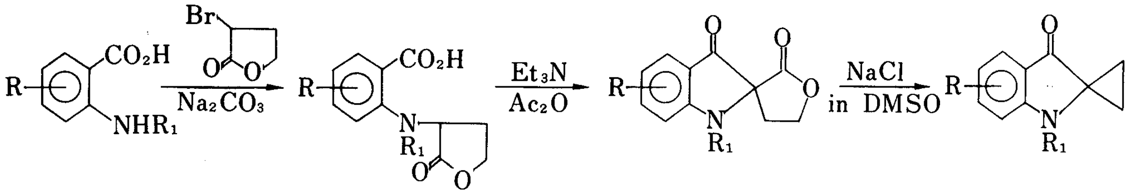
Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones with various substituents on the benzene ring and at the 1′-position were synthesized. Investigation of their biological activities revealed that significant anti-inflammatory and analgesic activities were exhibited by some compounds of this series. Their structure–activity relationships are discussed.

Keywords——Spirocyclopropanes; spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones; anti-inflammatory action; analgesic action

In the previous paper,$^{1)}$ we described a facile synthesis of 1′-acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one and its derivatives, as well as the reactivities of these compounds, and their anti-inflammatory and analgesic activities. We were considerably interested in the pharmacological activities of the derivatives and their structure–activity relationships, and in this report, we describe the synthesis of derivatives with various kinds of substituents on the benzene ring and at the 1′-position, and their effects on carrageenin-induced edema in rats as well as on phenylquinone-induced writhing in mice.



I II III

No.	R	R_1	No.	R	R_1	No.	R	R_1
I-1	H	H	Ⅱ-1	H	$COCH_3$	Ⅲ-1	H	$COCH_3$
I-2	5-CH_3	H	Ⅱ-2	5′-CH_3	$COCH_3$	Ⅲ-2	5′-CH_3	$COCH_3$
I-3	5-CH_3O	H	Ⅱ-3	5′-CH_3O	$COCH_3$	Ⅲ-3	5′-CH_3O	$COCH_3$
I-4	4,5-diCH_3O	H	Ⅱ-4	5′,6′-diCH_3O	$COCH_3$	Ⅲ-4	5′,6′-diCH_3O	$COCH_3$
I-5	5-I	H	Ⅱ-5	5′-I	$COCH_3$	Ⅲ-5	5′-I	$COCH_3$
I-6	H	CH_3	Ⅱ-6	H	CH_3	Ⅲ-6	H	CH_3
I-7	5-Cl	H	Ⅱ-7	5′-Cl	$COCH_3$	Ⅲ-11	H	CHO
I-8	4-Cl	H	Ⅱ-8	6′-Cl	$COCH_3$	Ⅲ-14	H	H
I-9	5-Br	H	Ⅱ-9	5′-Br	$COCH_3$	Ⅲ-15	5′-NO_2	$COCH_3$
			Ⅱ-10	5′-Cl	CHO			
			Ⅱ-11	H	CHO			
			Ⅱ-12	5′CH_3CO	$COCH_3$			
			Ⅱ-13	5′-H_2NSO_2	$COCH_3$			
			Ⅱ-14	H	H			

For III-7, III-8, III-10, III-12, III-13, III-16—III-34, see Table I.

Chart 1

Synthesis of Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones

5′-Chloro (III-7), 6′-chloro (III-8) and 5′-bromo (III-9) derivatives were synthesized from substituted anthranilic acids in three steps (Chart 1) mainly according to the method described in the previous paper.[1] Substituted anthranilic acids were allowed to react with α-bromo-γ-butyrolactone in an aqueous solution containing sodium carbonate or sodium hydroxide, yielding 2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic acids (I). The compounds (I) were spiro-annelated by treatment with acetic anhydride and triethylamine, and then the resulting 1′-acetyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indol]-2,3′(1′H)-diones (II) were decarboxylated by heating at 150—155 °C in the presence of an alkali metal halide to obtain the desired compounds (III) in good yields (Table I). The 5′-chloro derivative (III-7) could alternatively be synthesized by chlorination of II-1 with chlorine or sodium hypochlorite–hydrogen chloride in aqueous solution, followed by decarboxylation of the resulting 5′-chlorospirolactone (II-7). The position of chlorination was confirmed by comparing the melting point and the spectral data with those of II-7 and III-7 which were derived from 5-chloroanthranilic acid. Similarly, the 5′-chloro-1′-formyl (III-10) derivative was prepared by chlorination of II-11 with sodium hypochlorite–hydrogen chloride in an aqueous solution and then decarboxylated as described above. Thus, it was ascertained that electrophilic substitution on II-1 took place at the 5′-position. Previously, we reported that attempted substitution reactions on III-1 with nucleophiles or electrophiles brought about ring opening of the cyclopropane[1] or Wagner–Meerwein rearrangement.[2] Therefore, 5′-acetyl (III-12) and 5′-sulfamoyl (III-13) derivatives were prepared by the corresponding substitution reaction on II-1, followed by decarboxylation of the resulting spirolactones (II-12 and II-13, respectively). That is, acetylation of II-1 using acetic acid and polyphosphoric acid (PPA), and chlorosulfonylation of II-1 with chlorosulfonic acid, followed by treatment of the resulting 5′-chlorosulfonyl derivative with aqueous ammonia afforded 5′-acetyl (II-12) and 5′-sulfamoyl (II-13) spirolactones, respectively. These electrophilic substitution reactions on II-1 were assumed to occur at the 5′-position on the basis of proton magnetic resonance (PMR) spectral data for the aromatic protons. Subsequent decarboxylation of the resulting spirolactones (II-12 and II-13) afforded the corresponding spirocyclopropanes (III-12 and III-13).

The 5′-amino derivative (III-16) was prepared by catalytic hydrogenation of the 5′-nitro compound (III-15).[1] The 5′-acetylamino (III-17) and 5′-mesylamino (III-18) derivatives were obtained by N-acetylation or N-mesylation of III-16. Replacement of the 5′-iodo moiety of III-5[1] with a cyano or trifluoromethyl group was carried out by the treatment of III-5 with cuprous cyanide in DMF or with trifluoromethyliodide and active copper metal[3] in DMF to give the 5′-cyano (III-19) or 5′-trifluoromethyl (III-20) derivative, respectively.

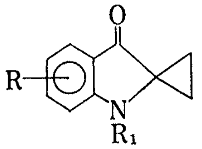
The 1′-N-acyl (III-21—III-23), 1′-N-sulfonyl (III-24 and III-25) and 1′-N-alkoxycarbonyl (III-26—III-30) derivatives were prepared by acylation of III-14[1] with acid chlorides in basic media, sulfonylation of III-14 with sulfonyl chlorides in basic media, and by alkoxycarbonylation of III-14 with chlorocarbonates in the presence of a base, respectively. 1′-N-Alkylation of III-4 with alkyl halides in the presence of sodium hydride in DMSO gave III-31—III-33. The ureido (III-34) derivative was obtained by the treatment of III-14 with methyl isocyanate.

The physical data for spiro[cyclopropane-1,2′-[2H]indol]-3′-(1′H)-one derivatives thus obtained are summarized in Table I.

Anti-inflammatory and Analgesic Activities of Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III) (Table II)

Anti-inflammatory activity was determined by the use of carrageenin-induced acute edema in the hind paw in rats.[4] Analgesic activity was determined by measuring the inhibition of phenylquinone-induced (PQ) writhing in mice.[5] The inhibitory effects were represented as percent inhibition. In these assays, some of these spiro[cyclopropane-1,2′-[2H]indol]-3′-(1′H)-ones were found to have significant anti-inflammatory and analgesic activities. The

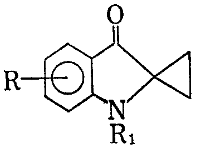
TABLE I. Physicochemical Properties of Spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-ones (III)



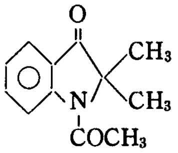
No.	R	R_1	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
Ⅲ-7	5'-Cl	$COCH_3$	94	188—189	$C_{12}H_{10}ClNO_2$	61.15 (61.18	4.28 4.31	5.94 6.16)
Ⅲ-8	6'-Cl	$COCH_3$	67	147—149	$C_{12}H_{10}ClNO_2$	61.15 (60.74	4.28 4.28	5.94 5.94)
Ⅲ-9	5'-Br	$COCH_3$	77	171—172	$C_{12}H_{10}BrNO_2$	51.45 (51.49	3.60 3.49	5.00 5.10)
Ⅲ-10	5'-Cl	CHO	80	185—186	$C_{11}H_8ClNO_2$	59.61 (59.54	3.64 3.53	6.32 6.44)
Ⅲ-12	5'-CH_3CO	$COCH_3$	78	150—151	$C_{14}H_{13}NO_3$	69.12 (69.13	5.39 5.30	5.76 5.65)
Ⅲ-13	5'-H_2NSO_2	$COCH_3$	61	244—247	$C_{12}H_{12}N_2O_4S$	51.41 (51.43	4.32 4.26	10.00 9.98)
Ⅲ-16	5'-H_2N	$COCH_3$	80	230—232	$C_{12}H_{12}N_2O_2$	66.65 (66.62	5.59 5.43	12.96 12.90)
Ⅲ-17	5'-H_3CCONH	$COCH_3$	97	281—284	$C_{14}H_{14}N_2O_2$	65.10 (65.04	5.46 5.38	10.85 10.75)
Ⅲ-18	5'-H_3CSO_2NH	$COCH_3$	83	204—205	$C_{12}H_{12}N_2O_4S$	53.05 (53.14	4.79 4.67	9.52 9.33)
Ⅲ-19	5'-CN	$COCH_3$	69	207—208	$C_{13}H_{10}N_2O_2$	69.01 (69.00	4.46 4.28	12.31 12.41)
Ⅲ-20	5'-F_3C	$COCH_3$	28	128.5—130	$C_{13}H_{10}F_3NO_2$	57.99 (57.63	3.74 3.55	5.20 5.13)
Ⅲ-21	H	$COCH_2CH_3$	77	172.5—173.5	$C_{13}H_{13}NO_2$	72.54 (72.68	6.09 6.11	6.51 6.41)
Ⅲ-22	H	$COCH(CH_3)_2$	38	90—91	$C_{14}H_{15}NO_2$	73.34 (73.29	6.59 6.56	6.11 6.02)
Ⅲ-23	H	 CO- -Cl	86	118—119	$C_{17}H_{12}ClNO_2$	68.58 (68.74	4.06 4.10	4.70 4.39)
Ⅲ-24	H	SO_2CH_3	90	144—145	$C_{11}H_{11}NO_3S$	55.68 (55.74	4.67 4.75	5.90 5.94)
Ⅲ-25	H	 SO_2- $-CH_3$	88	125—126	$C_{17}H_{15}NO_3S$	65.17 (65.37	4.82 4.64	4.47 4.31)
Ⅲ-26	H	CO_2CH_3	11	94—95	$C_{12}H_{11}NO_3$	66.35 (66.24	5.10 5.06	6.45 6.35)
Ⅲ-27	H	$CO_2CH_2CH_3$	81	87.5—88.5	$C_{13}H_{13}NO_3$	67.52 (67.43	5.67 5.63	6.06 5.92)
Ⅲ-28	H	$CO_2CH(CH_3)_2$	10	133—134	$C_{14}H_{15}NO_3$	68.56 (68.44	6.16 6.20	5.71 5.39)
Ⅲ-29	H	$CO_2(CH_2)_3CH_3$	19	37—38	$C_{15}H_{17}NO_3$	69.48 (69.61	6.61 6.75	5.40 5.28)
Ⅲ-30	H	$CO_2CH_2CH=CH_2$	6	56—58	$C_{14}H_{13}NO_3$	69.12 (68.91	5.39 5.37	5.76 5.50)
Ⅲ-31	H	CH_2CH_3	43	oil	$C_{12}H_{13}NO$	76.97 (76.85	7.00 7.06	7.48 7.21)
Ⅲ-32	H	$CH_2CH_2CH_3$	32	oil	$C_{13}H_{15}NO$	77.58 (77.46	7.51 7.55	6.96 6.94)
Ⅲ-33	H	 CH_2- $-OCH_3$	97	66—67	$C_{18}H_{17}NO_2$	77.39 (77.13	6.13 6.15	5.01 4.92)
Ⅲ-34	H	$CONHCH_3$	97	115—116	$C_{12}H_{12}N_2O_2$	66.66 (66.40	5.59 5.54	12.96 12.82)

effects of substitutents at the 1′-position and on the benzene ring on the biological activities are shown in Table II. The activities seem to be greatly influenced by the spatial bulkiness of substituents at the 1′-position. An increase in the size of 1′-substituents resulted in a reduction of the activities. Thus, derivatives with comparatively low molecular weight groups, such as acetyl (III-1), methyl (III-6), ethyl (III-31), fromyl (III-11). methanesulfonyl (III-24) and methoxycarbonyl (III-26) showed significant activities in both assays, and both biological activities tended to decreased upon substitution with comparatively high molecular weight groups such as alkoxycarbonyl (III-27, III-28 and III-29), larger alkyl (III-32), aralkyl (III-33). alkylcarbonyl (III-21 and III-22) and arylcarbonyl (III-23) groups. As regards the substi-

TABLE II. Pharmacological Activities of Spiro[cyclopropane-1,2-[2H]indol]-3′(1′H)-ones and Related Compounds



Ⅲ-1—Ⅲ-33



1-acetyl-2,2-dimethyl-3-indolinone[6]

No.	R	R₁	% inhibition, *p.o.* Carrageenin edema in rats 25 mg/kg	50 mg/kg	150 mg/kg	Phenylquinone writhing in mice 12.5 mg/kg	25 mg/kg	50 mg/kg
Ⅲ-1[a]	H	$COCH_3$	37.3[c]			67.2[c]	81.6[c]	84.2[c]
Ⅲ-2	5′-CH_3	$COCH_3$		10.7			42.5	
Ⅲ-3	5′-CH_3O	$COCH_3$		9.1				31.0
Ⅲ-4	5′,6′-diCH_3O	$COCH_3$		11.7				45.2
Ⅲ-5	5′-I	$COCH_3$		23.4			85.6[c]	
Ⅲ-6	H	CH_3		28.3[c]		5.4	57.0	78.2[c]
Ⅲ-7	5′-Cl	$COCH_3$		20.6[b]		57.1[c]	68.9[c]	
Ⅲ-8	6′-Cl	$COCH_3$	31.0[c]			18.8	41.6[b]	
Ⅲ-9	5′-Br	$COCH_3$		13.5			34.5	
Ⅲ-10	5′-Cl	CHO	45.9[c]			57.4[b]	73.8[c]	
Ⅲ-11	H	CHO	42.7[c]			35.8	67.6[c]	85.6[c]
Ⅲ-12	5′-CH_3CO	$COCH_3$	6.0					69.2[c]
Ⅲ-13	5′-H_2NSO_2	$COCH_3$	7.1	30.2[c]				
Ⅲ-14	H	H		10.1			21.1	69.0[b]
Ⅲ-15	5′-O_2N	$COCH_3$	35.9[c]			76.4[c]	90.6[c]	
Ⅲ-18	5′-H_3CSO_2NH	$COCH_3$					38.2	
Ⅲ-19	5′-NC	$COCH_3$	17.9	25.2[b]		56.8[b]	71.6[b]	
Ⅲ-20	5′-F_3C	$COCH_3$	14.5	30.3[c]		27.4	48.0[b]	
Ⅲ-21	H	$COCH_2CH_3$		10.7			30.0	
Ⅲ-22	H	$COCH(CH_3)_2$		6.7			4.0	
Ⅲ-23	H	CO--Cl		13.8				30.9
Ⅲ-24	H	SO_2CH_3	25.9[c]	35.2[c]		79.6[c]	87.7[c]	
Ⅲ-26	H	CO_2CH_3	41.0[c]	57.2[c]		74.4[b]	87.8[c]	
Ⅲ-27	H	$CO_2CH_2CH_3$		10.7		52.3[b]	52.6[c]	
Ⅲ-29	H	$CO_2(CH_2)_3CH_3$		11.2				15.1
Ⅲ-31	H	CH_2CH_3		33.9[c]			23.0	79.4[c]
Ⅲ-32	H	$CH_2CH_2CH_3$		37.3[c]				31.0
Ⅲ-33	H	CH_2--O CH_3		14.8				20.1
1-Acetyl-2,2-dimethyl-3-indolinone[6]					32.5[c]			25.0

a) III-1—III-6, III-14 and III-15 were synthesized as described previously.[1]
b) $p<0.05$.
c) $p<0.01$.

tuents on the benzene ring, introduction of the nitro (III-15) group, which is a strongly electron-withdrawing group, led to a slight increase in both activities, and introduction of chloro (III-7, III-8 and III-10), cyano (III-19) and trifluoromethyl (III-20) groups, which are electron-withdrawing groups, resulted in retention of the activities. Similarly, introduction of the sulfamoyl (III-13) group, a rather strongly electron-withdrawing group, led to a fairly significant anti-inflammatory activity but reduced the analgesic activity, while the iodo (III-5) group gave significant analgesic activity but reduced the anti-inflammatory activity, and the bromo (III-9) group gave weak activity in both cases. Introduction of electron donating substituents, such as methyl (III-2) and methoxy (III-3 and III-4) groups, led to a significant decrease in both activities. The cyclopropane ring was important for the anti-inflammatory and analgesic activities, because 1-acetyl-2,2-dimethyl-3-indolinone[6] (Table II) had very weak activities. From these results, it was concluded that the biological activities were influenced by the spatial bulk and electronic effects of substituents at the 1′-position and on the benzene ring, and that the spirocyclopropane ring was required for the activities.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The following instruments were used to obtain physical data; PMR spectra, Varian A-60A and Varian HA-100 spectrometers; IR spectra, a Hitachi 215 grating infrared spectrophotometer; UV spectra, a Perkin-Elmer 450 UV-visible-NIR spectrophotometer; mass spectra, a Hitachi RMU-6D mass spectrometer and a JMS-01SC mass spectrometer (Japan Electron Optics Co.). In the PMR spectra, chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. The following abbreviations are used; s = singlet, b.s = broad singlet, d = doublet, d.d = double doublet, t = triplet, q = quartet, m = multiplet.

5-Chloro-2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic Acid (I-7)——α-Bromo-γ-butyrolactone (12.37 g) was added to a solution of 5-chloroanthranilic acid (4.3 g) and NaOH (3.22 g) in H_2O (100 ml) at 0°C with stirring. After being stirred at room temperature overnight, the mixture was treated with a solution of KOH (1.1 g) in H_2O (20 ml) at room temperature with stirring. Additional α-bromo-γ-butyrolactone (4.15 g) was added at room temperature with stirring. After being stirred at room temperature overnight and at 5°C for an additional 3 days, the mixture was filtered and the filtrate was acidified with conc. HCl (50 ml) at room temperature. The resulting precipitate was collected, washed with H_2O, dried, and recrystallized from AcOEt to give I-7 (1.5 g, 23%) as colorless prisms, mp 228—229°C. *Anal.* Calcd for $C_{11}H_{10}ClNO_4$: C, 51.67; H, 3.94; N, 5.48. Found: C, 51.45; H, 3.85; N, 5.62. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3340 (NH), 1770 (lactone), 1660 (COOH). PMR (DMSO-d_6) δ: 1.5—3.1 (2H, m, $NCHC\underline{H}_2CH_2O$), 4.0—4.85 (3H, m, $NC\underline{H}CH_2C\underline{H}_2O$), 6.88 (1H, d, J=8.4, C_6-H), 7.40 (1H, d.d, J=8.4 and 2.4, C_5-H), 7.77 (1H, d, J=2.4, C_3-H).

4-Chloro-2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic Acid (I-8)——a) α-Bromo-γ-butyro-lactone (16.5 g) was added to a solution of 4-chloroanthranilic acid (5.7 g) and NaOH (5.35 g) in H_2O (250 ml) at room temperature with stirring. After being stirred at room temperature for 24 h and then at 50°C for 26 h, the mixture was filtered and the filtrate was acidified with conc. HCl (100 ml) at room temperature. The resulting precipitate was collected, washed with H_2O, dried, and recrystallized from EtOH to give I-8 (1.3 g, 15%) as a colorless crystalline powder, mp 280—282.5°C. *Anal.* Calcd for $C_{11}H_{10}ClNO_4$: C, 51.67; H, 3.94; N, 5.48. Found: C, 51.78; H, 4.04; N, 5.46. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3340 (NH), 1762 (lactone), 1660 (COOH). PMR (DMSO-d_6) δ: 1.9—3.1 (2H, m, $CHC\underline{H}_2CH_2O$), 4.0—4.9 (3H, m, $C\underline{H}CH_2C\underline{H}_2O$), 6.67 (1H, d.d, J=8.4 and 1.8, C_4-H), 6.90 (1H, d, J=1.8, C_6-H), 7.81 (1H, d, J=8.4, C_3-H), 8.22 (1H, d, J=7.2, NH).

b) α-Bromo-γ-butyrolactone (9.9 g) was added to a solution of 4-chloroanthranilic acid (3.4 g) and Na_2CO_3 (5.3 g) in H_2O (100 ml) at room temperature with stirring. After being stirred at 50°C for 2 d the mixture was filtered and the filtrate was acidified with conc. HCl (50 ml) at room temperature. The resulting precipitate was collected, washed with H_2O, dried, and recrystallized from EtOH to give I-8 (1.35 g, 27%).

5-Bromo-2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic Acid (I-9)——α-Bromo-γ-butyrolactone (15.35 g) was added to a solution of 5-bromoanthranilic acid (5.0 g) and NaOH (4.65 g) in H_2O (100 ml) at room temperature with stirring. After being stirred at 50°C for 22 h, the mixture was filtered and the filtrate was acidified with conc. HCl (80 ml) at room temperature. The resulting precipitate was worked up in a usual manner to give I-9 (1.3 g, 17%) as a colorless crystalline powder (from AcOEt), mp 233—235°C. *Anal.* Calcd for $C_{11}H_{10}BrNO_4$: C, 44.18; H, 3.36; N, 4.68. Found: C, 43.97; H, 3.32; N, 4.83. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3345 (NH), 1765 (lactone), 1660 (COOH). PMR (DMSO-d_6) δ: 1.85—3.1 (2H, m, $CHC\underline{H}_2CH_2O$), 4.05—4.8 (3H, m, $C\underline{H}CH_2C\underline{H}_2O$), 6.82 (1H, d, J=9, C_7'-H), 7.50 (1H, d.d, J=9 and 2.4, C_6'-H), 7.88 (1H, d, J=2.4, C_4'-H), 7.95—8.2 (1H, m, NH).

1′-Acetyl-5′-chloro-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-7)——a) A mixture of I-7 (1.0 g) in Ac_2O (20 ml) and Et_3N (4 ml) was heated at 130°C for 30 min under a stream of N_2 gas with stirring. The mixture was evaporated to dryness *in vacuo*, and the residue was triturated with cold EtOH. The resulting precipitate was collected and treated with charcoal, then recrystallized from EtOH to give II-7 (448 mg, 41%) as colorless needles, mp 179—180°C. IR ν_{max}^{KBr} cm^{-1}: 1775 (lactone), 1720 (5-membered ketone), 1675 (amide). PMR (DMSO-d_6) δ: 2.4—3.1 (2H, m, $C\underline{H}_2CH_2O$), 2.57 (3H, s, $COCH_3$), 4.60 (2H, t, $J=7.8$, $CH_2C\underline{H}_2O$), 7.7—7.9 (3H, m, Ar.H).

b) A solution of II-1[1] (4.91 g) in CH_3CN (50 ml) was treated with a solution of Cl_2 in CH_3CN at 0°C with stirring. After being stirred at 0°C for 2 h and at room temperature for an additional 16 h, the mixture was evaporated to dryness *in vacuo*. The resulting residue was recrystallized from EtOH to give II-7 (4.2 g, 75%).

c) A mixture of II-1[1] (100 g) in AcOH (1 l) and conc. HCl (300 ml) was treated with a solution of $NaClO_3$ (46 g) in H_2O (200 ml) at 10°C with stirring. After being stirred at room temperature for 3 h, the mixture was poured into ice–H_2O. The resulting precipitate was worked up in a usual manner to give II-7 (106 g, 94%).

Substituted 4,5-Dihydrospiro[furan-3(2H),2′-[2H]indol]-2,3′(1′H)-diones (II-8 and II-9)——These compounds were prepared in the manner described for II-1 except for the use of the appropriate substituted 2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic acids (I-8 and I-9).

II-8: Colorless needles (from H_2O–EtOH (5: 4, v/v)), mp 153—154°C. IR ν_{max}^{KBr} cm^{-1}: 1770 (lactone), 1715 (5-membered ketone), 1670 (amide). PMR ($CDCl_3$) δ: 2.25—3.15 (2H, m, $C\underline{H}_2CH_2O$), 2.51 (3H, s, $COCH_3$), 4.45—4.80 (2H, m, $CH_2C\underline{H}_2O$), 7.15 (1H, d.d, $J=8.4$ and 1.8, C_5'–H), 7.5—7.7 (2H, m, C_4'–H and C_7'–H). *Anal.* Calcd for $C_{13}H_{10}ClNO_4$: C, 55.82; H, 3.60; N, 5.01. Found: C, 55.94; H, 3.60; N, 4.90.

II-9: Pale yellow needles (from EtOH), mp 207—210.5°C. IR ν_{max}^{KBr} cm^{-1}: 1770 (lactone), 1710 (5-membered ketone), 1663 (amide). PMR (DMSO-d_6) δ: 2.5—3.0 (2H, m, $C\underline{H}_2CH_2O$), 2.56 (3H, s, $COCH_3$), 4.4—4.8 (2H, m, $CH_2C\underline{H}_2O$), 7.6—8.1 (3H, m, Ar.H). *Anal.* Calcd for $C_{13}H_{10}BrNO_4$: C, 48.17; H, 3.11; N, 4.32. Found: C, 47.91; H, 3.05; N, 4.36.

5′-Chloro-1′-formyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]2,3′(1′H)-dione (II-10)——Compound II-10 was prepared in the manner described for II-7 by treatment of II-14 with $NaClO_3$–conc. HCl in aqueous solution. Colorless prisms (from EtOH), mp 204—205°C. *Anal.* Calcd for $C_{12}H_8ClNO_4$: C, 54.25; H, 3.04; N, 5.27. Found: C, 54.43; H, 3.30; N, 5.40.

1′,5′-Diacetyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-12)——A mixture of II-1[1] (5.0 g) in AcOH (3 ml) and polyphosphoric acid (100 g) was heated at 90°C for 5 h with stirring. After being cooled, the mixture was diluted with ice–H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel eluting with $CHCl_3$–AcOEt (10: 1, v/v) to give II-12 (560 mg, 9%) as colorless prisms (from EtOH), mp 150—151°C. *Anal.* Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.88. Found: C, 62.77; H, 4.77; N, 4.93. IR ν_{max}^{KBr} cm^{-1}: 1770 (lactone), 1720, 1670. PMR ($CDCl_3$) δ: 2.4—3.3 (2H, m, $C\underline{H}_2CH_2O$), 2.65 (6H, s, $COCH_3$), 4.73 (2H, t, $J=8$, $CH_2C\underline{H}_2O$), 7.80 (1H, d, $J=9$, C_7'–H), 8.17 (1H, d, $J=2$, C_4'–H), 8.25 (1H, d.d, $J=9$ and 2, C_6'–H).

1′-Acetyl-5′-sulfamoyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-13)——Compound II-1[1] (25 g) was added in small portions to $ClSO_3H$ (50 ml) at 0°C under an N_2 atmosphere with stirring. After being stirred at 50°C for 45 min, the mixture was poured into ice–H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness *in vacuo* to give crude 1′-acetyl-5′-chlorosulfonyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (14.6 g, 42%). A solution of the resulting crude 5′-chlorosulfonyl compound (14.0 g) in THF (100 ml) was treated with 14% NH_4OH (3 ml) at 0°C with stirring. After being stirred at 0°C for 10 min, the mixture was treated with Na_2SO_4. The insoluble inorganic precipitate was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was recrystallized from EtOH to give II-13 (2.9 g, 49%) as colorless needles, mp 222—224°C. *Anal.* Calcd for $C_{13}H_{12}N_2O_6S$: C, 48.18; H, 3.73; N, 8.64. Found: C, 47.89; H, 3.60; N, 8.82. IR ν_{max}^{KBr} cm^{-1}: 1770 (lactone), 1725 (5-membered ketone), 1675 (amide). PMR (DMSO-d_6) δ: 2.64 (3H, s, $COCH_3$), 2.81 (2H, t, $J=7$, $C\underline{H}_2CH_2O$), 4.63 (2H, t, $J=7$, $CH_2C\underline{H}_2O$), 7.54 (2H, b.s, SO_2NH_2), 8.02 (1H, d, $J=9$, C_7'–H), 8.16 (1H, d, $J=2$, C_4'–H), 8.27 (1H, d.d, $J=9$ and 2, C_6'–H).

1′-Acetyl-5′-chlorospiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-7)——A mixture of II-7 (2.52 g) and NaCl (0.58 g) in DMSO (30 ml) was heated at 155°C for 2 h under an N_2 atmosphere with stirring. After being cooled, the mixture was poured into ice–H_2O. The resulting precipitate was collected, washed with H_2O, dried and subjected to column chromatography on charcoal eluting with $CHCl_3$ to give III-7 (2.02 g, 95%) as colorless prisms (from EtOH). UV λ_{max}^{EtOH} nm (ε): 240 (3.14×10^4), 267 (1.68×10^4), 348 (4.2×10^3). IR ν_{max}^{KBr} cm^{-1}: 1695 (5-membered ketone), 1660 (amide). PMR ($CDCl_3$) δ: 1.3—1.55 (2H, m, cyclopropane CH_2), 2.25—2.5 (2H, m, cyclopropane CH_2), 2.42 (3H, s, $COCH_3$), 7.45—7.75 (3H, m, Ar.H).

Substituted Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III-8—III-13)——These compounds were prepared in the manner described for III-7 except for the use of the appropriate substituted 4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-diones (II-8—II-13, Table I).

1′-Acetyl-5′-aminospiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-16)——Compound III-15[1] (3.0 g) was hydrogenated in the presence of PtO_2 (306 mg) in MeOH (600 ml) until three moles of H_2 gas had been absorbed. The catalyst was then filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was recrystallized from EtOH to give III-16 (2.1 g, 80%) as pale yellow needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3330 (NH_2), 1675, 1655. PMR ($CDCl_3$) δ: 1.14—1.38 (2H, m, cyclopropane CH_2), 2.2—2.4 (2H, cyclopropane CH_2), 2.41 (3H, s, $COCH_3$), 5.33 (2H, b.s, NH_2), 6.93 (1H, d, $J=2.4$, C_4'-H), 7.18 (1H, d.d, $J=11.4$ and 2.4, C_6'-H), 7.64 (1H, d, $J=11.4$, C_7'-H).

1′-Acetyl-5′-acetylamino[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-17)——Ac_2O (7 ml) was added to a solution of III-16 (704 mg) in AcOH (7 ml) and $CHCl_3$ (7 ml) at room temperature with stirring. After being stirred for 30 min, the mixture was diluted with hexane (100 ml). The resulting precipitate was collected, washed with hexane, dried and recrystallized from AcOH–AcOEt to give III-17 (645 mg, 86%) as a colorless crystalline powder.

1′-Acetyl-5′-mesylaminospiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-18)——Mesyl chloride (666 mg) was added to a solution of III-16 (602 mg) in pyridine (12 ml) at 0°C with stirring. After being stirred at 0°C for 30 min, the mixture was poured into ice–H_2O containing conc. HCl (4 ml) and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on charcoal eluting with $CHCl_3$–acetone (5: 1, v/v) to give III-18 (679 mg, 83%) as colorless needles.

1′-Acetyl-5′-cyanospiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)- one (III-19)——A mixture of III-5 (1.0 g)[1] and CuCN (300 mg) in DMF (6 ml) was heated at 100°C with stirring. After being cooled, the mixture was poured into ice–H_2O. The resulting precipitate was collected, washed with H_2O, dried and recrystallized from EtOH to give III-19 (420 mg, 69%) as colorless plates. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2210 (CN), 1705, 1675. PMR ($CDCl_3$) δ: 1.3—1.8 (2H, m, cyclopropane CH_2), 2.3—2.7 (2H, m, cyclopropane CH_2), 2.51 (3H, s, $COCH_3$), 7.90 (2H, m, C_6'- and C_7'-H), 8.10 (1H, d, $J=2$, C_4'-H).

1′-Acetyl-5′-trifluoromethylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-20)——A mixture of CF_3I (10 g) and activated Cu (prepared from $CuSO_4$, 5.0 g) in hexamethylphosphortriamide (HMPA) (20 ml) was heated at 110°C in a sealed tube for 8 h with stirring, then cooled. III-5 (3.0 g)[1] was added and the whole was heated at 60°C in a sealed tube for an additional 8 h. After being cooled, the mixture was poured into ice–H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting residue was recrystallized from EtOH to give III-20 (601 mg, 28%) as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710, 1680. PMR ($CDCl_3$) δ: 1.40—1.68 (2H, m, cyclopropane CH_2), 2.38—2.64 (2H, m, cyclopropane $C\underline{H}_2$), 2.56 (3H, s, $COCH_3$), 7.82—7.94 and 8.05—8.20 (3H, m, Ar.H).

1′-Propionylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-21)——Propionyl chloride (0.4 g) was added to a solution of III-14 (0.4 g)[1] in pyridine (5 ml) at 0°C with stirring. After being stirred at room temperature for 1.5 h, the mixture was poured into ice–H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel to give III-21 (0.4 g, 73%) as colorless needles. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1705 (5-membered ketone), 1670 (amide). PMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7.5$, $COC\underline{H}_2CH_3$), 1.25—1.65 (2H, m, cyclopropane CH_2), 2.3—2.7 (2H, m, cyclopropane CH_2), 2.76 (2H, q, $J=7.5$, $COC\underline{H}_2CH_3$), 7.0—8.0 (4H, m, Ar.H).

1′-Isobutyryl- and 1′-*p*-Chlorobenzoylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III-22 and III-23)——These compounds were prepared in the manner described for III-21 except for the use of isobutyryl chloride and *p*-chlorobenzoyl chloride, respectively. Compound III-23 was alternatively prepared by N-benzoylation of II-14 with *p*-chlorobenzoylchloride in the presence of $NaHCO_3$ and $ZnCl_2$, followed by decarboxylation of the resulting N-*p*-chlorobenzoylspirolactone.

1′-Mesylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-24)——Mesyl chloride (688 mg) was added to a solution of III-14 (487 mg)[1] in pyridine (5 ml) at 0°C with stirring. After being stirred at room temperature for 6 h, the mixture was poured into ice–H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on charcoal eluting with $CHCl_3$ to give III-24 (640 mg, 90%) as colorless prisms. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1705 (C=O), 1613, 1356, 1333, 1160. PMR ($CDCl_3$) δ: 1.35—1.65 (2H, m, cyclopropropane CH_2), 1.95—2.25 (2H, m, cyclopropane CH_2), 2.92 (3H, s, CH_3), 7.1—8.0 (4H, m, Ar.H).

1′-*p*-Methylbenzenesulfonylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-25)——This compound was prepared in the manner described for III-24 except for the use of *p*-methylbenzenesulfonyl chloride.

1′-Methoxycarbonylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-26)——A solution of III-14 (6.0 g)[1] in MeOH (40 ml) was treated with 28% NaOMe–MeOH solution (7.8 g) at 10—15°C with stirring. After being stirred at room temperature for 30 min, the mixture was evaporated to dryness *in vacuo*. Next, $ClCO_2CH_3$ (4.2 g) was added to a solution of the resulting residue in DMSO (60 ml) at 10—15°C with stirring. After being stirred at room temperature for 1 h, the mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel eluting with $CHCl_3$ to give III-26 (900 mg, 11%) as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1695 (broad, 5-membered ketone and NCO_2CH_3). PMR ($CDCl_3$) δ: 1.30—1.55 (2H, m, cyclopropane CH_2), 2.1—2.35 (2H, m, cyclopropane CH_2), 7.1—8.25 (4H, m, Ar.H).

1′-Ethoxycarbonyl-, 1′-Isopropyloxycarbonyl-, 1′-Butyloxycarbonyl- and 1′-Allyloxycarbonylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III-27—III-30)——These compounds were prepared in the manner described for III-26, except for the use of the corresponding alkoxy- and allyloxycarbonyl halides.

1′-Ethylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-31)——A solution of III-14 (8 g)[1] in MeOH (50 ml) was treated with 28% NaOMe–MeOH solution (10.4 g) at 10—15°C with stirring. After being stirred at room temperature for 30 min, the mixture was evaporated to dryness *in vacuo*. EtI (8.4 g) was added to a solution of the resulting residue in DMSO (80 ml) at 10—15°C with stirring. After being stirred at room temperature for 1 h, the mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel eluting with ligroin–AcOEt (6: 4, v/v) to give III-31 (4.0 g, 43%) as a yellow oil. IR $\nu_{\max}^{\text{Neat}}$ cm^{-1}: 1680 (C=O). PMR ($CDCl_3$): δ: 1.10 (3H, t, $J=7.2$, $CH_2C\underline{H}_3$), 1.4 (4H, s, 2 cyclopropane CH_2), 3.26 (2H, q, $J=7.2$, $C\underline{H}_2CH_3$), 6.55—7.8 (4H, m, Ar.H).

1′-Propylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-32)——This compound was prepared in the manner described for III-31, except for the use of *n*-PrI.

1′-*p*-Methoxybenzylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-33)——This compound was prepared in the manner described for III-31, except for the use of *p*-methoxybenzyl chloride.

1′-(N-Methylcarbamoyl)spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-34)——CH_3NCO (2.86 g) was added to a solution of III-14 (1.5 g)[1] in dry benzene (30 ml) at room temperature with stirring, and the mixture was refluxed for 24 h. After the addition of CH_3NCO (1.14 g), it was refluxed for an additional 3 h and evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on charcoal eluting with $CHCl_3$ to give III-34 (2.105 g, 97%) as colorless needles. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3300 (NH), 1702 (5-membered ketone), 1675, 1656. PMR ($CDCl_3$) δ: 1.2—1.5 (2H, m, cyclopropane CH_2), 1.95—2.35 (2H, m, cyclopropane CH_2), 2.88 (3H, d, $J=5$, NCH_3), 5.55 (1H, m, NH), 6.8—7.7 (4H, m, Ar.H).

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References and Notes

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