[Chem. Pharm. Bull.
29(7)1900—1911(1981)]

Spirocyclopropane Compounds. I. Synthesis and Reactivity of Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones

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(Received January 24, 1981)

A spirocompound, 1′-acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-1), was synthesized from anthranilic acid in three steps, which involve the condensation of anthranilic acid with α-bromo-γ-butyrolactone, followed by spiroannelation with acetic anhydride and triethylamine, and subsequent decarboxylation in the presence of sodium chloride to afford III-1 in good yield. Various derivatives (III-2—III-9) were similarly prepared. Some compounds of this series showed an intense fluorescence in solution. The reactivities of III-1 to electrophiles and nucleophiles, as well as its reaction with reducing agents, were investigated.

Keywords——spirocyclopropanes; 1′-acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one; reactivity with electrophiles and nucleophiles; reduction; fluorescence

In nature, several biologically-active spirocompounds, such as griseofulvin,[1] are known to exist. Various synthetic methods for spiro-linkage formation[2-13] have been developed. Although a single report[14] described the synthesis of indole derivatives bearing a strained cyclopropane ring at the 2-position, the method did not seem to be generally applicable. In this paper, we present a facile synthetic method for spiro[cyclopropane-1,2′-[2H]indol]-3′-(1′H)-ones (III) and describe their reactivities to electrophiles, nucleophiles and reducing agents.

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

Recently, it was reported that decarboxylation of α-acyl-γ-butyrolactones (**1**) in the presence of alkali metal halides in a dipolar aprotic solvent[15,16] led to cyclopropylketones (**3**), and that this reaction proceeded under neutral conditions probably through an intermediary carbanion (**2**). In the light of these results, attempts were made to synthesize spiro [cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III) by a similar reaction of 4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-diones (II) (Chart 1). Although the compound II-7 had been synthesized in 12.5% yield by the treatment of α-(*o*-nitrobenzoyl)-γ-butyrolactone (**4**) with triethylphosphite,[17,18] we obtained II from anthranilic acids in good yields by an alternate synthetic route similar to the synthesis of ethyl 3-oxo (2H)-indole-2-carboxylate (**5**).[19] Thus, condensation of anthranilic acids or N-methylanthranilic acid with α-bromo-γ-butyrolactone in an aqueous alkaline solution in the presence of sodium carbonate, followed by acidification to pH 1.0 with dilute hydrochloric acid afforded 2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic acids (I-1—I-6, Table I). Heating of I-1 in a mixture of acetic anhydride and triethylamine at 130 °C for 3 h gave colorless non-acidic crystals which exhibited strong infrared (IR) absorption bands at 1780 (γ-butyrolactone), 1710 (5-membered ketone) and 1690 cm^{-1} (N-COCH$_3$). These absorptions and the absence of the absorption due to carboxylic acid suggested the formation of the desired spirolactone (II-1). The structure of II-1 thus obtained was confirmed by comparing the spectral data and melting point of its hydrolysis product (II-7) with those of an authentic sample reported by Kametani *et al.*[18] Formylation of I-1 with formic acid–acetic anhydride, followed by a similar cyclization gave the N-formyl derivative (II-8). The substituted spirolatones (II-2—II-6) were similarly derived from the

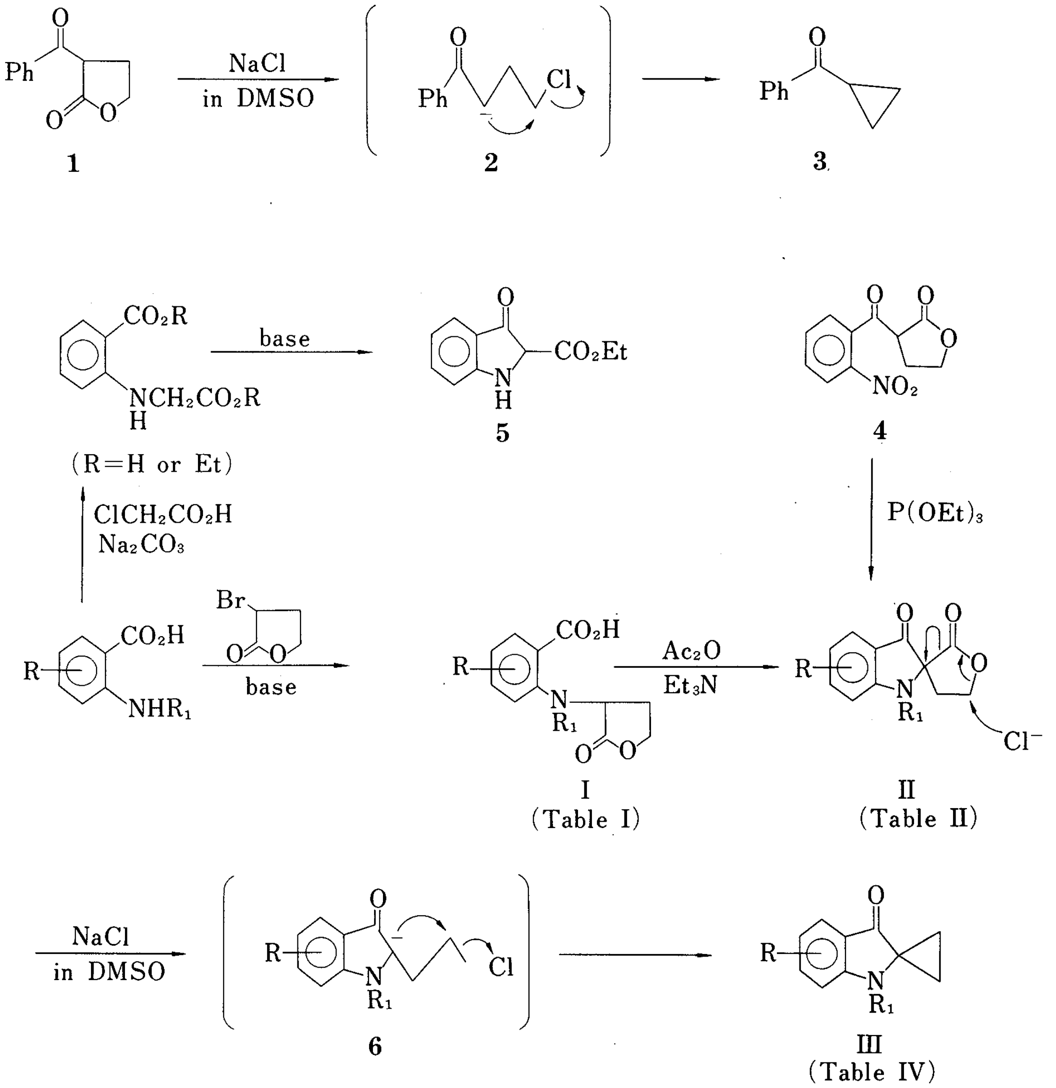
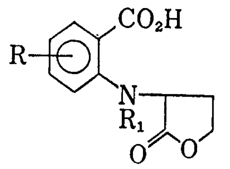


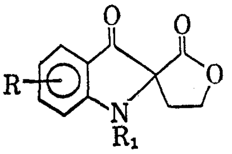
Chart 1

Table I. Physicochemical Properties of 2-[(Tetrahydro-2-oxo-3-furanyl)amino]benzoic Acids (I)



No.	R	R_1	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
I-1	H	H	74	197—199	$C_{11}H_{11}NO_4$	59.72	5.01	6.33	59.32	4.99	6.18
I-2	5-CH_3	H	47	199—200	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.13	5.61	5.99
I-3	5-CH_3O	H	54	207—208	$C_{12}H_{13}NO_5$	57.31	5.22	5.58	57.22	5.37	5.50
I-4	4,5-diCH_3O	H	55	214	$C_{13}H_{15}NO_6$	55.51	5.38	4.98	55.59	5.30	4.97
I-5	5-I	H	39	215—218	$C_{11}H_{10}INO_4$	38.06	2.90	4.40	38.38	2.85	4.07
I-6	H	CH_3	21	113—114	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.37	5.59	5.85

Table II. Physicochemical Properties of 4,5-Dihydrospiro[furan-3(2H), 2′-[2H]indole]-2,3′(1′H)-dinoes (II)

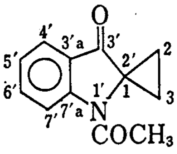


No.	R	R₁	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
II-1	H	CH_3CO	91	159—160	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.76	4.43	5.63
II-2	5′-CH_3	CH_3CO	83	176—177	$C_{14}H_{13}NO_4$	64.86	5.05	5.40	64.66	4.95	5.43
II-3	5′-CH_3O	CH_3CO	78	136—138	$C_{14}H_{13}NO_5$	61.09	4.76	5.09	61.13	4.66	4.96
II-4	5′,6′-diCH_3O	CH_3CO	65	226—228	$C_{15}H_{15}NO_5$	59.09	4.95	4.59	58.88	4.74	4.55
II-5	5′-I	CH_3CO	63	228—230	$C_{13}H_{10}INO_4$	42.07	2.72	3.77	42.19	2.74	3.74
II-6	H	CH_3	83	184—185	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.38	4.71	6.30
II-7	H	H	93	140—141	$C_{11}H_9NO_3$	65.02	4.46	6.89	64.68	4.33	6.81
II-8	H	CHO	87	199—201	$C_{12}H_9NO_4$	62.34	3.92	6.06	62.56	3.87	5.96

corresponding substituted 2-[(tetrahydro-2-oxo-3-furanyl)amino]benzoic acids (I-2—I-6). The physical data for 4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-diones (II-1—II-8) thus obtained are summarized in Table II. Heating of II-1 at 150—155 °C in dimethyl sulfoxide (DMSO) in the presence of sodium chloride under a nitrogen stream generated carbon dioxide and gave colorless needles, mp 156—157 °C, with the molecular formula $C_{12}H_{11}NO_2$ as judged from elementary analysis data and the mass spectrum (MS), m/e=201.0834 (M^+). This compound did not show IR absorption bands due to γ-lactone, unlike II-1. It revealed signals of a 5-membered ketone (1705 cm^{-1}) and an N-acetyl group (1665 cm^{-1}) in its IR spectrum, and two multiplet signals at δ 1.3—1.6 ppm (2H) and δ 2.35—2.65 ppm (2H) assignable to four methylenic AA′BB′ protons on the cyclopropane ring in its proton magnetic resonance (PMR) spectrum. From these data, its structure was considered to be the ring-contracted spirocyclopropane, 1′-acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-1). This structure was confirmed by measurement of the carbon magnetic resonance (CMR) spectrum, in which the eleven signals could be reasonably assigned as shown in Table III. A large (167 Hz) ^1H-^{13}C coupling constant due to two equivalent C-2 and C-3 methylenic signals was observed at 16.5 ppm, in good agreement with results reported for known cyclopropanes.[20,21] The reaction appears to have proceeded through a nucleophilic attack of chloride anion on C-5 of II-1. followed by decarboxylation and cyclization involving the intramolecular S_N2 reaction of the intermediary carbanion (Chart 1). A similar decarboxylation of II-2—II-8 proceeded regardless of the substituents on the phenyl ring and 1′-nitrogen atom to give the spirocyclopropane derivatives (III-2—III-8) in fairly good yields. The physical data for spiro-[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones thus obtained are summarized in Table IV.

In vinylcyclopropanes and acylcyclopropanes, bathochromic shift of the n-π^* band in the ultraviolet (UV) spectra, shift of $\nu_{C=O}$ to lower wave numbers in the IR spectra, and downfield shifts of the PMR signals of the protons on the cyclopropane ring are known to occur, and have been explained in terms of conjugation between the C–C double bond or the carbonyl group and the cyclopropane ring.[22,23] In comparison with spectral data of 2,2-dimethyl-3-indolinone (XVI)[19] and its cycloalkyl analogs (XIV and XV),[9,13] spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-7) showed a shift of the $\nu_{C=O}$ band to lower wave numbers in its IR spectrum (Table V). In the PMR spectrum, cyclopropyl protons of III-1 were observed downfield by *ca.* 1.0 ppm from those of spirans[22] which have no vinyl or acyl group at the α-position . These

Table III. CMR Spectral Data for 1′-Acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-1)

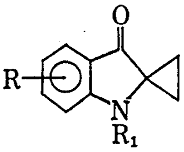


III-1

C-4′	C-5′	C-6′	C-7′	C-7′a	C-3′a	C-3′	C-2′(1)	C-2	C-3	$\underline{C}OCH_3$	$CO\underline{C}H_3$
123.4	123.2	135.2	115.7	151.0	123.6	196.2	52.9	16.5	16.5	167.3	26.7

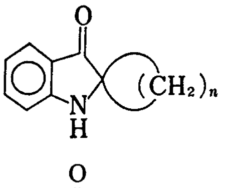
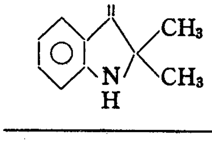
ppm (δ) in $CDCl_3$.

Table IV. Physicochemical Properties of Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-ones (III)



No.	R	R_1	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C			Found C		
						C	H	N	C	H	N
III-1	H	CH_3CO	94	156—157	$C_{12}H_{11}NO_2$	71.62	5.51	6.96	71.33	5.55	6.68
III-2	5′-CH_3	CH_3CO	87	137—138	$C_{13}H_{13}NO_2$	61.16	4.30	6.02	60.74	4.28	5.94
III-3	5′-CH_3O	CH_3CO	85	169—172	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.61	5.55	6.05
III-4	5′,6′-diCH_3O	CH_3CO	75	174—176	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.36	5.74	5.32
III-5	5′-I	CH_3CO	75	129—131	$C_{12}H_{10}INO_2$	44.06	3.08	4.28	43.95	2.99	4.39
III-6	H	CH_3	90	73—75	$C_{11}H_{11}NO$	76.27	6.40	8.09	76.45	6.19	8.15
III-7	H	H	93	110—111	$C_{10}H_9NO$	75.45	5.70	8.80	75.23	5.49	8.54
III-8	H	CHO	90	122—123	$C_{11}H_9NO_2$	70.58	4.85	7.48	70.63	4.89	7.33
III-9	5′-NO_2	CH_3CO	44	149—151	$C_{12}H_{10}N_2O_4$	58.53	4.09	11.38	58.30	3.94	11.28

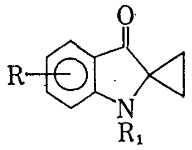
Table V. UV and IR Spectral Data for Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-7) and Related Compounds

Compound		UV λ_{max}^{EtOH}, nm (log ε)	IR cm^{-1} (CO)
	n=2 (III-7)	235(4.4), 258(3.9), 390(3.6)	1660 (KBr)
	n=4 (XIV)[9]	231(4.3), 258(3.7), 398(3.6)	1700 (in $CHCl_3$)
	n=5 (XV)[13]	230(4.34), 252(3.79), 391(3.58)	1680 (KBr)
	(XVI)[19]	230(4.33), 253(3.79), 391(3.60)	1675 (KBr)

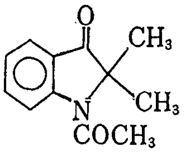
spectral features of III-7 can be explained in terms of the sp^5 hybrid orbitals[22] of the cyclopropane ring being fixed in the perpendicular conformation to the planar 3-indolinone ring, interacting with π-electrons of the phenyl ring and carbonyl group, and the lone pair of nitrogen.

Most of the spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-ones (III) described in this paper showed intense fluorescence. Excitation maxima, emission maxima and relative intensities of their fluorescence in ethanol are shown in Table VI. The intensities of fluorescences appear to be dependent on the nature of the substituents at the phenyl ring and 1'-nitrogen atom, and decreased in the following order: $OCH_3>CH_3>H\gg I>NO_2$ for substituents at the 5'-position, and $CH_3>H>COCH_3>CHO$ on substituents at the 1'-position. Further, structure transformation of 2,2-dimethyl-3-indolinone (XVI) to III-1 led to enhancement of the fluorescence. These results show that the fluorescence may be correlated predominantly with the electron density on the 1'-nitrogen atom. Introduction of the iodo or nitro group at the 5'-position resulted in a marked decrease of the fluorescence, probably due to the heavy atom effect and the tendency to interconvert into the metastable transition state,[24] respectively.

TABLE VI. Fluorescence of Substituted Spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-ones (III) and Related Compounds



III



XVI

Compound			Fluorescence[a] (nm)			
No.	R	R_1	Excitation	Emission	Δ	Relative intensity
III-1	H	$COCH_3$	345	405	60	100
III-6	H	CH_3	410	470	60	991
III-7	H	H	390	455	65	805
III-8	H	CHO	345	400	55	63
III-2	5'-CH_3	CH_3CO	350	410	60	293
III-3	5'-CH_3O	CH_3CO	370	440	70	861
III-5	5'-I	CH_3CO	355	415	60	0.8
III-9	5'-NO_2	CH_3CO	380	435	55	0.1
1-Acetyl-2,2-dimethyl-3-indolinone (XVI)[19]			345	410	65	32

a) The fluorescences of ethanol solutions of the compounds were determined with a Shimadzu corrected recording spectrofluorophotometer, type Rf-502. Wavelengths (nm) of maximal excitation and maximal emission, and their difference ($\triangle$) are shown. Relative intensity is shown as a percentage of the intensity of III-1.

Reaction of Spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-one (III-1) with Electrophiles, Nucleophiles and Reducing Agents

Cyclopropanes are well known to undergo ring cleavage upon treatment with protic or Lewis acids[25] and upon nucleophilic attack.[26,27] However, the cyclopropane ring of III bears a 3-indolinone skeleton and is activated by the carbonyl group at the α-position. Therefore, we investigated the reaction of III-1 with some reagents.

Nitration of III-1 with cupric nitrate in acetic anhydride at 60 °C gave the 5'-nitro compound (III-9) without cleavage of the cyclopropane ring. The structure was established mainly on the basis of PMR spectral data. On the other hand, the Friedel -Crafts reaction of III-1 using acetyl chloride in dichloroethane afforded two ring-opened products, IV-1 and V (Chart 2). Compound IV-1 showed strong absorption bands due to enol acetate (1770 cm^{-1}) and amide (1695 cm^{-1}) in the IR spectrum. In the PMR spectrum, there were signals (δ

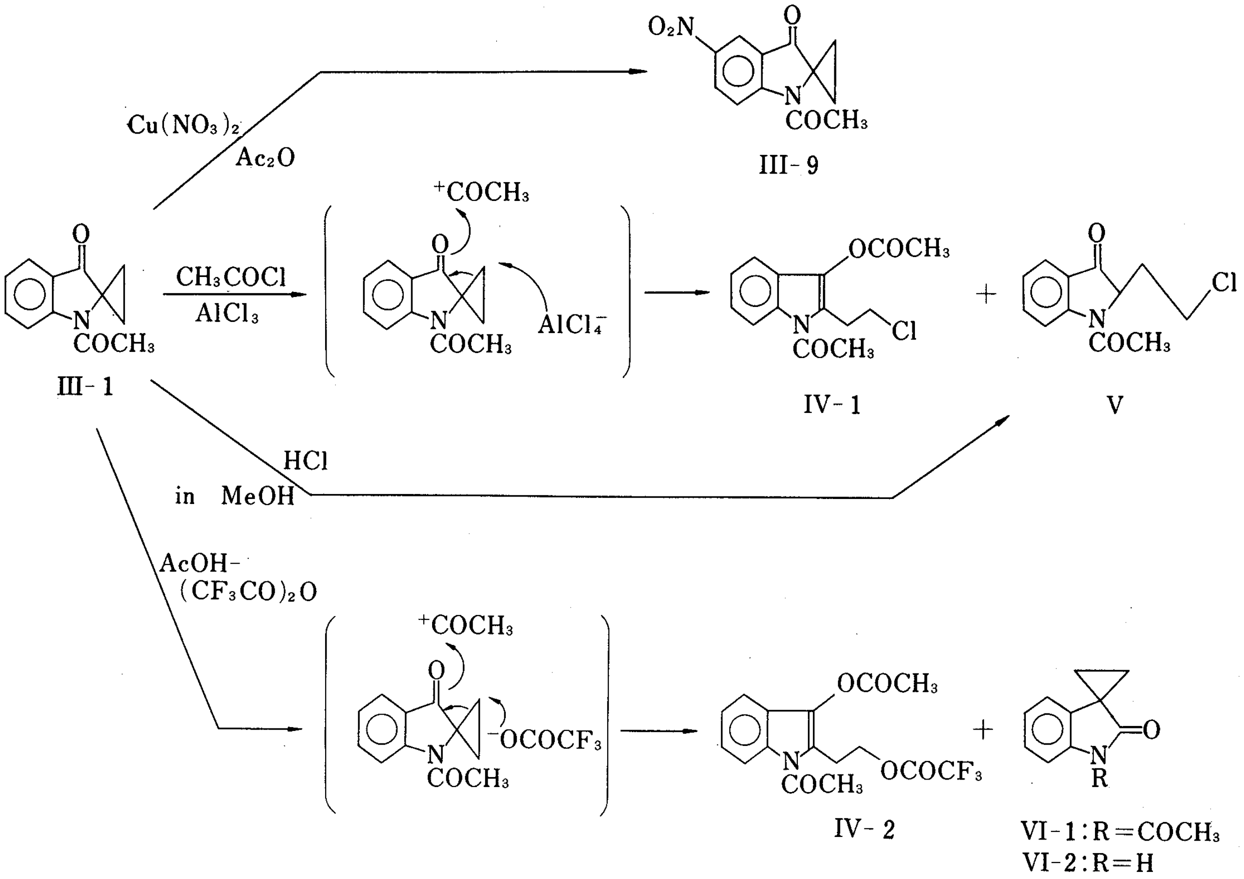
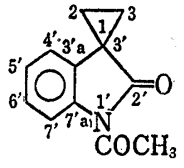


Chart 2

3.15—3.55 ppm, 2H, multiplet and δ 3.60—4.00 ppm, 2H, multiplet) assignable to the methylenic protons of the chloroethyl group. Compound V showed 5-membered ketone (1705 cm^{-1}) and amide (1680 cm^{-1}) signals in the IR spectrum and a double doublet peak at δ 4.40 ppm (J=13 and 8 Hz) assignable to the methine proton on C-2 of 3-oxo(2H)-indole, besides the two methylenic signals of the chloroethyl moiety, in the PMR spectrum. From these spectral data, these products were assigned as 3-acetoxy-1-acetyl-2-(2-chloroethyl)-indole (IV-1) and 1-acetyl-2-(2-chloroethyl)-3-oxo(2H)-indole (V), respectively. Compound V was also obtained by the treatment of III-1 with methanolic hydrogen chloride at room temperature in 37% yield (Chart 2), whereas the Friedel–Crafts reaction of III-1 using acetic acid and trifluoroacetic anhydride afforded a ring-opened product (IV-2) and a rearranged product, VI-1 (Chart 2). Compound IV-2 showed strong absorption bands due to enol acetate and trifluoroacetate (1775 cm^{-1}), and amide (1703 cm^{-1}) in the IR spectrum. In its PMR spectrum, there were signals (δ 3.32 ppm, 2H, triplet, J=8.4 Hz and δ 4.59 ppm, 2H, triplet, J=8.4 Hz) assignable to the methylenic protons of the trifluoroacetoxyethyl group. Its MS showed a molecular ion peak at 357 ($C_{16}H_{14}F_3NO_5$). Compound VI-1 showed strong absorption bands due to 5-membered amide (1745 cm^{-1}) and usual amide (1680 cm^{-1}) in its IR spectrum. The high resolution MS of VI-1 showed a molecular ion peak at 201.0786 ($C_{12}H_{11}NO_2$). In its PMR spectrum, there were signals in the range of δ 6.65—7.45 (3H, multiplet) and 8.15—8.4 (1H, multiplet) assignable to protons of the aromatic ring, at δ 2.69 ppm (3H, singlet) assignable to the protons of the acetyl group and two multiplet signals (δ 1.35—1.7 ppm, 2H and 1.7—2.05 ppm, 2H) assignable to the methylene protons of the cyclopropane ring. Furthermore, the CMR spectrum showed eleven signals which were assigned as shown in Table VII. A signal observed at δ 21.4 ppm showed a large ^{1}H-^{13}C spin-spin coupling constant (J=167 Hz) corresponding to that of cyclopropanes, as mentioned above. From these spectral data, the structures of

Table VII. CMR Spectral Data for 1′-Acetylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (VI-1)



VI-1

C-4′	C-5′	C-6′	C-7′	C-7′a	C-3′a	C-3′(1)	C-2	C-3	C-2′	$\underline{C}OCH_3$	$CO\underline{C}H_3$
124.5	117.5	126.5	116.2	139.4	129.5	27.6	21.4	21.4	177.3	170.4	26.3

ppm (δ) in $CDCl_3$.

IV-2 and VI-1 were assigned as 3-acetoxy-1-acetyl-2-(2-tri-fluoroacetoxyethyl)indole and 1-acetylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one, respectively. The structure of VI-1 was confirmed by comparing the melting point of the hydrolysis product (VI-2), which was prepared by the treatment of VI-1 with 6 N methanolic hydrogen chloride, with that of an authentic sample.[28] The intramolecular rearrangement of III-1 to VI-1 might have proceeded through a Wagner–Meerwein shift.[10]

The treatment of III-1 with nucleophilic reagents afforded three products as illustrated in Chart 3. When III-1 was heated in piperidine, the ring-opended product, 1-acetyl-2-(2-N-piperidinoethyl)-3-oxo-(2H)-indole (VII), was isolated in 77% yield. Its structure was confirmed on the basis of its spectral similarity to V. That is, the PMR spectrum of VII showed a double doublet peak due to C-2 methine proton at δ 4.42 ppm (J=7 and 8 Hz), and its IR spectrum revealed the presence of a 5-membered ketone (1720 cm^{-1}) and an N-acetyl group (1680 cm^{-1}). When III-1 was treated with potassium hydroxide in methanol or sodium methoxide in tetrahydrofuran (THF), the hydrolyzed compound (III-7) was obtained in almost quantitative yield. On the other hand, Grignard reagents (phenylmagnesium bromide and benzylmagnesium chloride) selectively attacked the 3′-carbonyl carbon of III-1 to give

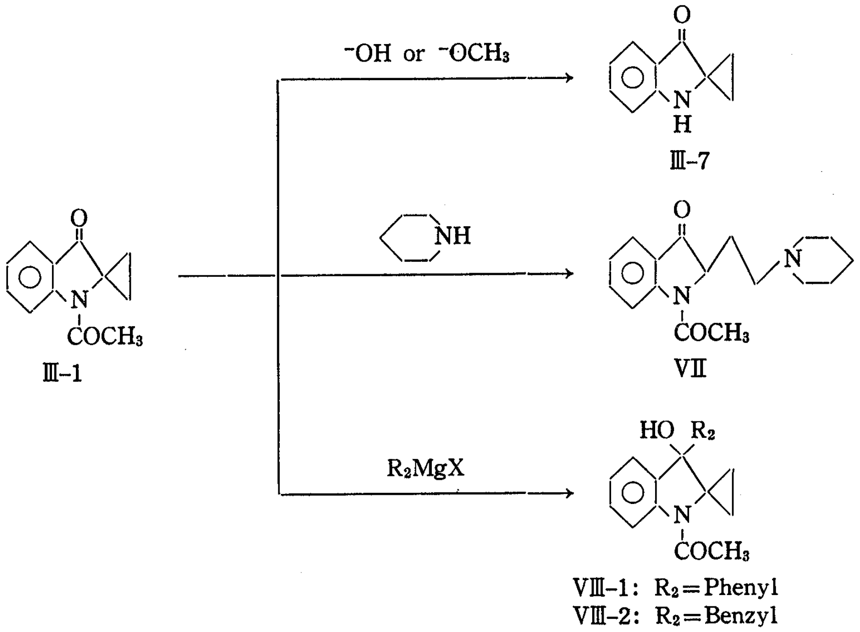


Chart 3

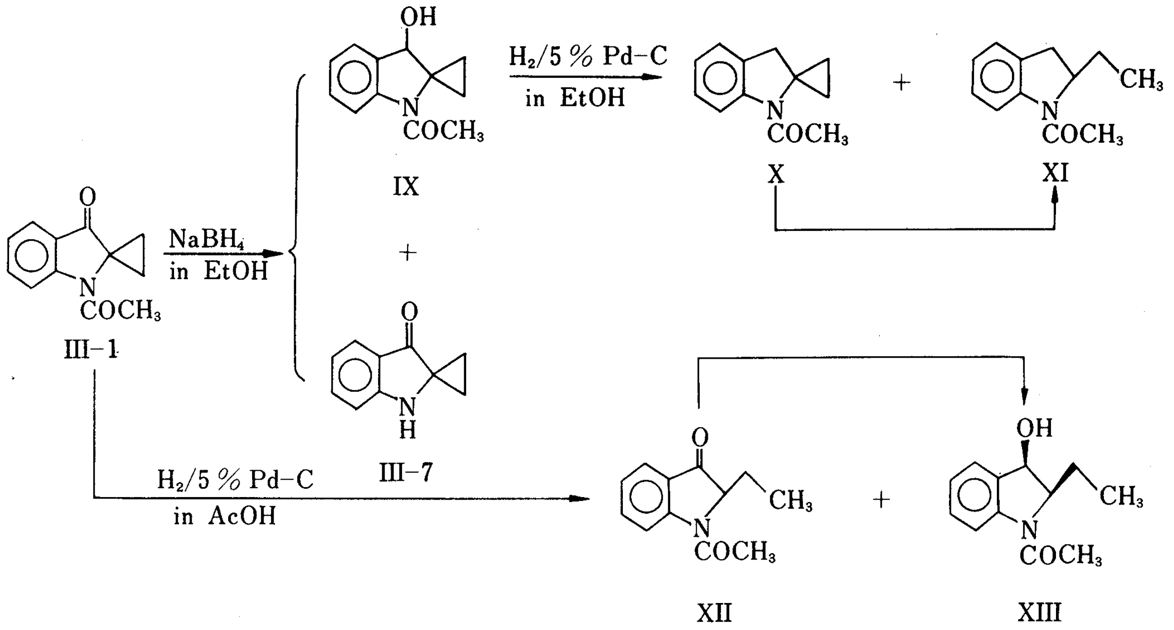


Chart 4

the 3'-hydroxy derivatives (VIII-1 and VIII-2) in 67 and 79% yields, without opening the cyclopropane ring, respectively.

The reduction of III-1 with sodium borohydride in ethanol at room temperature afforded the 3'-hydroxy derivative (IX, 49%), which was labile to acid, and the hydrolyzed compound (III-7, 40%), which was resistant to reduction under the conditions used (Chart 4). Catalytic hydrogenation of IX using 5% palladium charcoal in ethanol gave the 3'-methylenic compound (X) with a cyclopropane ring (PMR spectrum: δ 3.10 ppm, 2H, singlet, C-3'–CH$_2$) and the ring-opened product (XI). Monitoring of this reaction by thin–layer chromatography (TLC) demonstrated that X was the main product at the early stage of the reduction, but that the ratio of XI to X increased after prolonged hydrogenation. On the contrary, the direct hydrogenation of III-1 using 5% palladium charcoal in acetic acid yielded 1-acetyl-2-ethyl-3-oxo(2H)-indole (XII), which was formed by the reductive cleavage of the cyclopropane ring. Its structure was confirmed by analysis of its spectral data. The compound XII revealed the absorption due to a 5-membered ketone (1720 cm^{-1}) in the IR spectrum, and signals due to the 2-ethyl moiety and the 2-methine proton (δ 4.23 ppm, double doublet, J=5.4 and 4.2 Hz) in the PMR spectrum. Further reduction of the ketone (XII) produced *cis*-1-acetyl-2-ethylindolin-3-ol (XIII), the stereostructure of which was deduced by comparing the coupling constant of the C-3 proton in the PMR spectrum (δ 5.56 ppm, doublet, J=8.4 Hz) with those of N-acylated 3-hydroxy-indolines.[29–31]

Some of the spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-ones prepared in this paper were found to have significant anti-inflammatory and analgesic activities. These pharmacological properties will be described in the following paper.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The following instruments were used to obtain the 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.); CMR spectra, a Varian XL-100-12 spectrometer. 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.

2-[(Tetrahydro-2-oxo-3-furanyl)amino]benzoic Acid (I-1)——a) α-Bromo-γ-butyrolactone (103.2 g) was added to a solution of anthranilic acid (68.6 g) and Na_2CO_3 (132.2 g) in H_2O (400 ml) at 0°C with stirring. After being stirred at 0°C for 5 h and at room temperature for an additional 24 h, the mixture was acidified with conc. HCl to pH 1.0 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 triturated with Et_2O and recrystallized from EtOH to give I-1 (52.0 g, 47%) as colorless needles.

b) In the above procedure, after addition of α-bromo-γ-butyrolactone, the mixture was stirred at room temperature for 1 h and at 40—50°C for an additional 8 h. After being cooled, the mixture was acidified with conc. HCl to pH 0.5—1.0 and stirred overnight. The resulting precipitate was collected, washed with H_2O, dried and recrystallized from EtOH to give I-1 (82 g, 74%) as colorless needles.

Substituted 2-[(Tetrahydro-2-oxo-3-furanyl)amino]benzoic Acids (I-2—I-6) (Table I)——These compounds were prepared in the manner described for I-1 except for the use of the appropriate substituted anthranilic acids.

1-Acetyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-1)——A solution of I-1 (6.64 g) in Ac_2O (90 ml) and Et_3N (181 ml) was heated at 130°C for 3 h under an N_2 atmosphere, and then evaporated to dryness *in vacuo*. The resulting residue was triturated with H_2O. The resulting precipitate was collected, washed with H_2O, dried and recrystallized from EtOH to give II-1 (6.7 g, 91%) as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 1775 (lactone), 1720, 1675, 1610. PMR ($CDCl_3$) δ: 2.5—3.1 (2H, m, $C\underline{H}_2CH_2O$), 2.56 (3H, s, $COCH_3$), 4.5—4.8 (2H, m, $CH_2C\underline{H}_2O$), 7.1—7.9 (4H, m, Ar. H).

Substituted 4,5-Dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-diones (II-2—II-6) (Table II)——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-2—I-6).

4,5-Dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-7) (Table II)——After N-trifluoroacetylation, I-1 was worked up by the procedure applied in the case of II-1. The reaction mixture was poured into ice-H_2O. The resulting precipitate was washed with H_2O, dried and recrystallized from EtOH to yield II-7.

1′-Formyl-4,5-dihydrospiro[furan-3(2H),2′-[2H]indole]-2,3′(1′H)-dione (II-8) (Table II)——After N-formylation, I-1 was treated in the manner described for II-1 to yield II-8. It was alternatively prepared by formylation of II-7 with formic acid-acetic anhydride.

1′-Acetylspiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-1)——A mixture of II-1 (491 mg) and NaCl (129 mg) in DMSO (2 ml) was heated at 155—160°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-1 (380 mg, 94%) as colorless prisms (from EtOH). UV λ_{max}^{EtOH} nm (ε): 238 (3.48×10^4), 255 (shoulder, 1.51×10^4), 262 (shoulder, 1.30×10^4). IR ν_{max}^{KBr} cm^{-1}: 1705, 1665. PMR ($CDCl_3$) δ: 1.3—1.6 (2H, m, cyclopropane CH_2), 2.35—2.65 (2H, m, cyclopropane CH_2), 2.60 (3H, s, $COCH_3$). MS *m/e*: 201.0834 (M^+), 159.0678 ($M^+ - COCH_3 + 1$), 130.0647 ($M^+ - COCH_3 - CHO + 1$), 103.76.

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

Spiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-7)——This compound was also prepared by the following methods.

a) A solution of III-1 (12.1 g) in THF (200 ml) was treated with 28% NaOMe in MeOH (12.8 g) at 0°C with stirring. After being stirred at 0°C for 1 h, the mixture was evaporated to dryness *in vacuo*. Ice-H_2O was added to the resulting residue and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The resulting residue was recrystallized from iso-Pr_2O to give III-7 (9.48 g, 99%) as yellow prisms. IR ν_{max}^{KBr} cm^{-1}: 3275 (NH), 1660. PMR ($CDCl_3$) δ: 1.35—1.65 (4H, m, 2 cyclopropane CH_2), 5.35 (1H, b.s, NH), 6.65—7.75 (4H, m, 4 Ar–H).

b) A solution of III-1 (3.0 g) in MeOH (15 ml) was treated with 20% KOH in MeOH (5 ml) at room temperature with stirring. After being stirred for 30 min, the mixture yielded III-7 (2.36 g, 99%) on the usual work-up as described above.

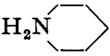
1′-Acetyl-5′-nitrospiro[cyclopropane-1,2′-[2H]indol]-3′(1′H)-one (III-9)——$Cu(NO_3)_2 \cdot 3H_2O$ (5.0 g) was added in small portions to a solution of III-1 (1.5 g) in Ac_2O (25 ml) at 60°C with stirring. After being stirred at 60°C for 1.5 h and then cooled, the mixture was poured into ice-H_2O. The resulting precipitate was collected, washed with H_2O, dried and subjected to column chromatography on silica gel eluting with CCl_4–AcOEt (3: 1, v/v) to give III-9 (788 mg, 44%) as colorless needles (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1710, 1690, 1520, 1330. PMR ($CDCl_3$) δ: 1.4—1.7 (2H, m, cyclopropane CH_2), 2.35—2.65 (2H, m, cyclopropane CH_2), 7.91 (1H, d, *J* = 9, C_7'-H), 8.55 (1H, d.d, *J* = 9 and 2.4, C_6'-H), 8.63 (1H, d, *J* = 2.4, C_4'-H).

The Friedel-Crafts Reaction of III-1 with Acetyl Chloride-Aluminum Chloride——A solution of III-1 (2.0 g) in 1,2-dichloroethane (30 ml) was added to a mixture of AcCl (1.0 g) and $AlCl_3$ (1.6 g) in 1,2-dichloroethane (30 ml) at 0°C with stirring. After being stirred at room temperature for 19 h, the mixture was poured into ice-H_2O 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 silica gel eluting with CCl_4–AcOEt (20: 1, v/v). The first eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from hexane–benzene (2: 1, v/v) to give 3-acetoxy-1-acetyl-2-(2-chloroethyl)-indole (IV-1, 663 mg, 24%) as colorless needles, mp 121—122°C. *Anal.* Calcd for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01; Cl, 12.68. Found: C, 60.25; H, 4.94; N, 5.16; Cl, 12.78. IR ν_{max}^{KBr} cm^{-1}: 1770 (enol acetate), 1695 (amide). PMR ($CDCl_3$) δ: 2.39 (3H, s, $OCOCH_3$), 2.83 (3H, s, $NCOCH_3$), 3.15—3.55 (2H, m, $C\underline{H}_2CH_2Cl$), 3.6—4.0 (2H, m, $CH_2C\underline{H}_2Cl$). The subsequent eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from hexane–benzene (3: 1, v/v) to give 1-acetyl-2-(2-chloroethyl)-3-oxo(2H)-indole (V, 1.23 g, 52%) as colorless needles, mp 71—72°C. *Anal.* Calcd for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.09; N, 5.89; Cl, 14.92. Found: C, 60.72; H, 4.78; N, 5.93; Cl, 14.71. IR ν_{max}^{KBr} cm^{-1}: 1705, 1680. PMR ($CDCl_3$) δ: 2.05—2.90 (2H, m, $C\underline{H}_2CH_2Cl$), 2.43 (3H, s, $COCH_3$), 3.35—4.10 (2H, m, $CH_2C\underline{H}_2Cl$), 4.45 (1H, d.d, $J=13$ and 8, C_2–H).

Reaction of III-1 with Acetic Acid-Trifluoroacetic Anhydride——a) Acetic acid (7 ml) was added to a mixture of III-1 (4.5 g) in trifluoroacetic anhydride (25 g) at 0° with stirring. After being stirred at room temperature for 2 h, the mixture was poured into ice-H_2O. The resulting precipitate was collected, washed with cold H_2O, dried and subjected to column chromatography on silica gel (150 g) eluting with CCl_4–AcOEt (10: 1, v/v). The first eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH–H_2O (4: 3, v/v) to give 1-acetylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (VI-1, 1.8 g, 40%) as colorless prisms, mp 125—127°C. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.64; H, 5.46; N, 6.83. IR ν_{max}^{KBr} cm^{-1}: 1750 (5-membered amide), 1700 (5-membered ketone). PMR ($CDCl_3$) δ: 1.35—2.05 (4H, m, cyclopropane CH_2), 2.69 (3H, s, $COCH_3$), 6.65—7.45 (3H, m, Ar.H), 8.15—8.4 (1H, m, Ar.H). MS *m/e*: 201.0786 (M^+, $C_{12}H_{11}NO_2$). The subsequent eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH–H_2O (2: 1, v/v) to give 3-acetoxyl-1-acetyl-2-(2-trifluoroacetoxyethyl)-indole (IV-2, 2.07 g, 46%) as colorless prisms, mp 100.5—101.5°C. *Anal.* Calcd for $C_{16}H_{14}F_3NO_5$: C, 53.79; H, 3.95; N, 3.92. Found: C, 53.86; H, 3.91; N, 3.90. IR ν_{max}^{KBr} cm^{-1}: 1775 (enol acetate and trifluoroacetate), 1703 (amide). PMR ($CDCl_3$) δ: 2.38 (3H, s, $OCOCH_3$), 2.79 (3H, s, $NCOCH_3$), 3.38 (2H, t, $J=6.6$, $C\underline{H}_2CH_2OCOCF_3$), 4.64 (2H, t, $J=6.6$, $CH_2C\underline{H}_2OCOCF_3$), 7.1—7.8 (3H, m, Ar.H). MS *m/e*: 357 (M^+).

b) Hydrolysis of VI-1: A solution of VI-1 (673.6 mg) in MeOH (140 ml) was treated with 5 N methanolic HCl (7 ml) at room temperature with stirring. After being stirred at 50°C for 30 min, the mixture was evaporated to dryness *in vacuo*. The resulting residue was recrystallized from AcOEt to give spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (VI-2, 466 mg, 87.5%) as colorless needles, mp 184—185°C (lit.[28]) mp 184—185°C). IR ν_{max}^{KBr} cm^{-1}: 3200 (amino), 1700 (5-membered ketone). PMR ($CDCl_3$) δ: 1.36—1.94 (4H, m, cyclopropane CH_2), 4.35 (1H, b.s, NH), 6.65—7.35 (4H, m, Ar.H). CMR ($CDCl_3$) δ: 179.8, 140.7, 131.1, 126.5, 121.7, 118.3, 109.8, 27.6, 19.3 (cyclopropane CH_2, $J=167$).

Reaction of III-1 with Hydrogen Chloride——A solution of III-1 (2.0 g) in 1,2-dichloroethane (50 ml) was treated with 6 N methanolic HCl (10 ml) at room temperature with stirring. After being stirred for 20 h, the mixture was evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel eluting with $CHCl_3$. The first eluate gave unchanged III-1 (400 mg, 20%). The subsequent eluate gave V (888 mg, 37%).

Reaction of III-1 with Piperidine——A solution of III-1 (403 mg) in piperidine (10 ml) was refluxed for 10 h under an N_2 atmosphere. The mixture was evaporated to dryness *in vacuo*. A solution of the resulting residue in AcOEt was treated with a solution of maleic acid (305 mg) in AcOEt at room temperature with stirring. The resulting precipitate was collected, washed with AcOEt, dried and recrystallized from EtOH to give 1-acetyl-2-[2-(1-piperidino)ethyl]-3-oxo(2H)-indole maleate (VII, 622 mg, 77%) as colorless needles, mp 157°C (dec.). *Anal.* Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.53; H, 6.73; N, 6.85. IR ν_{max}^{KBr} cm^{-1}: 1720, 1680. PMR ($CDCl_3$) δ: 2.41 (3H, s, $COCH_3$), 4.42 (1H, d.d, $J=7$ and 5, C_2–H), 6.18 (2H, s, CH_2N), 7.1—8.2 (4H, m, 4 Ar.H).

The Grignard Reaction of III-1 with Phenylmagnesium Bromide——A solution of III-1 (900 mg) in dry THF (30 ml) was added to a solution of Grignard reagent [prepared by the usual method from Mg (201 mg) and bromobenzene (1.4 g)] in Et_2O (30 ml) at 0°C under an N_2 atmosphere with stirring. After being stirred at 4°C for 15 h, the mixture was poured into satd. NH_4Cl 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 (5: 1, v/v) to give 1′-acetyl-3′-phenyl-2′,3′-dihydrospiro[cyclopropane-1,2′-[2H]indol]-3′-ol (VIII-1, 842 mg, 67%) as colorless needles, mp 139—140°C. *Anal.* Calcd for $C_{18}H_{17}NO$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.09; H, 6.03; N, 5.21. IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 1640. PMR ($CDCl_3$) δ: 0.00—2.40 (4H, m, 2 cyclopropane CH_2), 2.35 (3H, s, $COCH_3$), 2.91 (1H, s, OH).

The Grignard Reaction of III-1 with Benzylmagnesium Chloride——1′-Acetyl-3′-benzyl-2′,3′-dihydrospiro[cyclopropane-1,2′-[2H]indol]-3′-ol (VIII-2, 1.1 g, 79%) was obtained by the procedure described for VIII-1, from the Grignard reaction of III-1 (0.95 g) with benzylmagnesium bromide, as colorless needles from benzene AcOEt (1: 1, v/v), mp 139—141°C. *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.87; H, 6.52; N, 4.90. IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1640. PMR ($CDCl_3$) δ: 0.57—1.2 (3H, m, cyclopropane CH_2), 1.82 (3H, s, $COCH_3$), 2.31 (1H, s, OH), 2.70—3.05 (1H, m, cyclopropane CH_2), 2.99 (2H, s, Ar.CH_2), 6.65—7.30 (9H, m, 9 Ar.H).

Reduction of III-1 with Sodium Borohydride——$NaBH_4$ (1.9 g) was added in small portions to a solution of III-1 (10.0 g) in EtOH (100 ml) at room temperature with stirring. After being stirred for 4 h, the mixture was poured into ice-H_2O 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 recrystallized from hexane–AcOEt (2: 1, v/v) to give 1′-acetyl-2′,3′-dihydrospiro[cyclopropane-1,2′-[2H]indol]-3′-ol (IX, 4.9 g, 49%) as colorless needles, mp 130—133°C. *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.36; N, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1625. PMR ($CDCl_3$) δ: 0.25—2.55 (4H, m, 2 cyclopropane CH_2), 2.27 (3H, s, $COCH_3$), 2.86 (1H, d, $J=9$, OH), 4.47 (1H, d, $J=9$, $C_{3'}$–H), 6.90—7.60 (4H, m, 4 Ar.H). The hydrolyzed compound (III-7, 3.17 g, 40%) was obtained from the mother liquor of IX.

Catalytic Hydrogenation of IX using 5% Palladium Charcoal in EtOH——Compound IX (1.5 g) was hydrogenated in the presence of 5% Pd-C (wet, 1.5 g) in EtOH (150 ml) for 1 h under atmospheric pressure of H_2 gas with stirring. The catalyst was then filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was subjected to column chromatography on silica gel eluting with CCl_4–AcOEt (5: 1, v/v). The first eluate was evaporated to dryness *in vacuo* to give 1′-acetyl-2′,3′-dihydrospiro-[cyclopropane-1,2′-[2H]indol]-3′-ol (X, 280 mg, 40%) as a colorless oil. MS *m/e*: 187 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 1645. PMR ($CDCl_3$) δ: 0.45—0.75 (2H, m, cyclopropane CH_2), 2.0—2.25 (2H, m, cyclopropane CH_2), 2.34 (3H, s, $COCH_3$), 3.10 (2H, s, Ar.CH_2). The subsequent eluate was evaporated to dryness *in vacuo* to give 1-acetyl-2-ethylindoline (XI, 252 mg, 36%) as a colorless oil. MS *m/e*: 189 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1645. PMR ($CDCl_3$) δ: 0.86 (3H, t, $J=7.2$, $CH_2C\underline{H}_3$), 1.25 (2H, m, $C\underline{H}_2CH_3$), 2.23 (3H, s, $COCH_3$), 2.28 (1H, m, C_2–H), 2.45—3.50 (2H, m, Ar.CH_2).

Catalytic Hydrogenation of III-1 using 5% Palladium Charcoal in AcOH——Compound III-1 (705 mg) was hydrogenated in the presence of 5% Pd-C (wet, 196 mg) in AcOH (70 ml) for 6 h under atmospheric pressure of H_2 gas. The catalyst was then filtered off and the filtrate was 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). The first eluate was evaporated to dryness *in vacuo* and recrystallized from H_2O–MeOH (3: 2, v/v) to give 1-acetyl-2-ethyl-3-oxo(2H)-indole (XII, 390 mg, 55%) as colorless needles, mp 60—62°C. *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.65; H, 6.40; N, 6.73. IR ν_{max}^{KBr} cm^{-1}: 1720, 1670. PMR ($CDCl_3$) δ: 0.79 (3H, t, $J=7$, $CH_2C\underline{H}_3$), 1.8—2.5 (2H, m, $CHC\underline{H}_2CH_3$), 2.73 (3H, s, $COCH_3$), 4.28 (1H, d.d, $J=5.4$ and 4.2, C_2–H). The subsequent eluate was evaporated to dryness *in vacuo* to give *cis*-1-acetyl-2-ethylindolin-3-ol (XIII, 193 mg, 27%) as colorless needles (AcOEt), mp 51.5—53.5°C. MS *m/e*: 205 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 3350 (OH), 1630. PMR ($CDCl_3$) δ: 0.92 (3H, t, $J=7.2$, $CH_2C\underline{H}_3$), 1.35—2.25 (2H, m, $C\underline{H}_2CH_3$), 2.29 (3H, s, $COCH_3$), 3.87 (1H, b.s, OH), 5.56 (1H, d, $J=8.4$, C_3–H).

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