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Spiro Heterocyclic Compounds. III.[1] Synthesis of Spiro[oxindole-3,4′-(4′*H*-pyran)] Compounds

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Spiro[oxindole-3,4′-(4′*H*-pyran)] compounds (IIIa—j), were prepared by the Michael reaction of 3-cyanomethyleneoxindoles (Ia, b) with active methylene compounds. Similarly, the reactions of (Ib, c) with cyclic active methylene compounds, *e.g.* cyclohexane-1,3-dione, 3-methyl-1-phenyl-5-pyrazolone and barbituric acid, afforded the corresponding spiro compounds (V—VII) containing the condensed pyran system.

Keywords——Michael reaction; 3-(carboethoxycyanomethylene)oxindole; 3-(dicyanomethylene)oxindole; active methylene group; spiro[oxindole-3,4′-(2′-amino-4′*H*-pyran)] compound; spiro condensed pyran-oxindole compound

As a part of our continuing studies on the synthesis of spiro heterocyclic compounds for pharmacological evaluation, we investigated the synthesis of a new ring system, spiro-[oxindole-3,4′-(4′*H*-pyran)], by the Michael reaction of 3-cyanomethyleneoxindoles with an active methylene group.

Yokoyama[3] reported that the reaction of isatin with ethyl cyanoacetate, in the presence of piperidine as a catalyst, resulted in the formation of 3-(carboethoxycyano)methylene- (Ia) or 3,3-bis(carboethoxycyanomethyl)oxindole (II),[4] depending on the molar ratios of the reactants, and that II was also obtained from Ia by reaction with the same reagent. This latter reaction is a typical Michael reaction. Therefore, it was expected that oxindolidene compounds, such as Ia, b, having an electron attracting group on the exo-methylene carbon, would similarly react with other active methylene or methyl compounds to give the Michael adducts, which were converted into spiro systems at the C-3 of oxindole. This paper describes the results obtained by the Michael reaction of several 3-cyanomethyleneoxindoles with active methylene compounds.

Compound (Ia) was allowed to react with an equimolecular amount of an active methylene compound, *e. g.* acetylacetone, ethyl acetoacetate, benzoylacetone, ethyl benzoylacetate, or dibenzoylmethane, in EtOH in the presence of piperidine as a catalyst at room temperature for 1—4 hr. The corresponding products (IIIa—d) were obtained as colorless crystals. In the case of Ia with dibenzoylmethane, the reaction produced a solid of unknown structure in poor yield. The analogous sequence of reactions using Ib[5] gave the corresponding products (IIIe—i). The reaction of Ib with methyl pyruvate as a Michael reagent afforded the homologous product (IIIj). The results are summarized in Table I.

Michael reaction of the deep red-violet colored 3-cyanomethyleneoxindoles gave colorless products, which suggested that the conjugated oxindolidene systems were converted into unconjugated oxindoles. All of the products (IIIa—j) gave molecular ions (M^+) corresponding to the Michael adducts in the mass (MS) spectra and showed absorption bands due to NH_2 at 3350—3100 cm^{-1} in the infrared (IR) spectra. The presence of NH_2 was also observed in the proton magnetic resonance (PMR) spectra as a singlet at δ 7.08—7.79 which

1) Part II: H. Otomasu, T. Tanaka, and M. Aoyagi, *Chem. Pharm. Bull.*, **24**, 782 (1976).
2) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo, 142 Japan.*
3) M. Yokoyama, *J. Chem. Soc. Japan*, **57**, 251 (1936).
4) W.C. Sumpter, *Chem. Revs.*, **34**, 393 (1944).
5) W. Walter, *Chem. Ber.*, **35**, 1320 (1902).

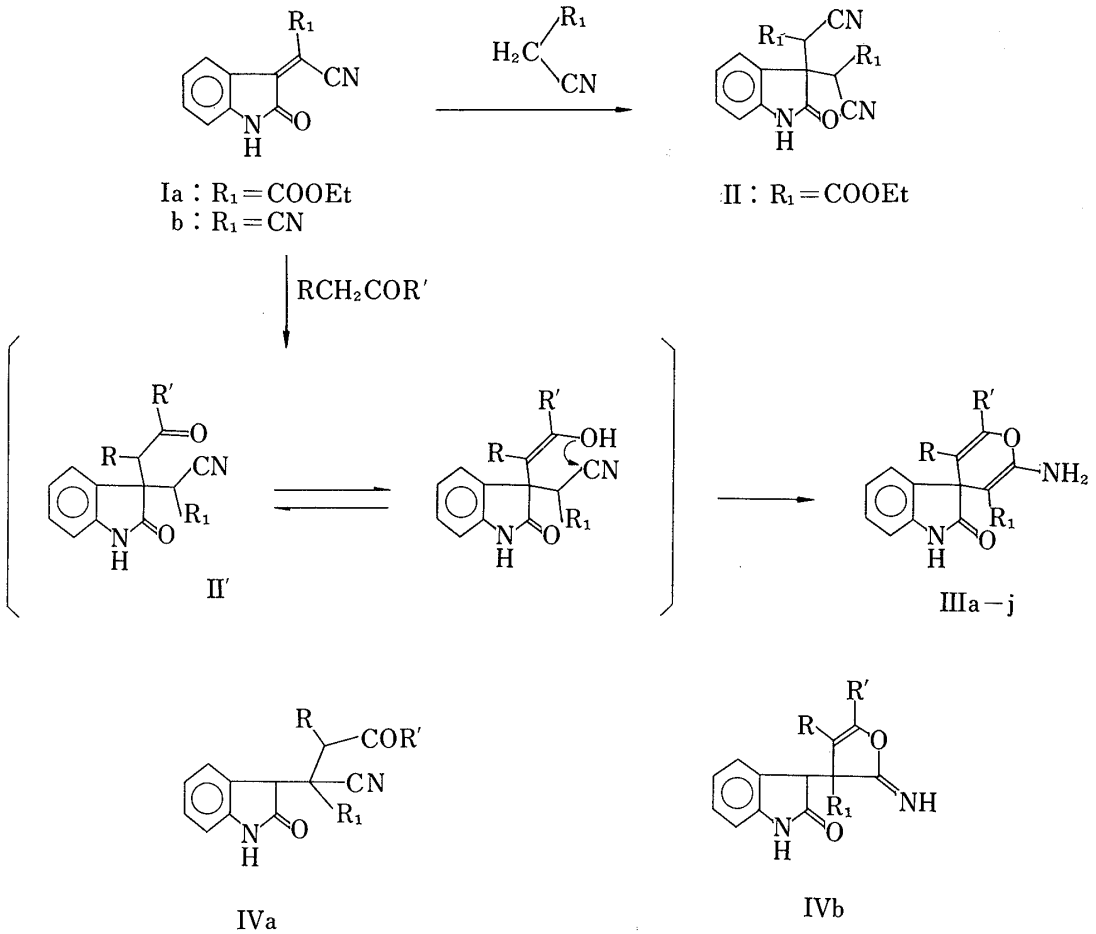


Chart 1

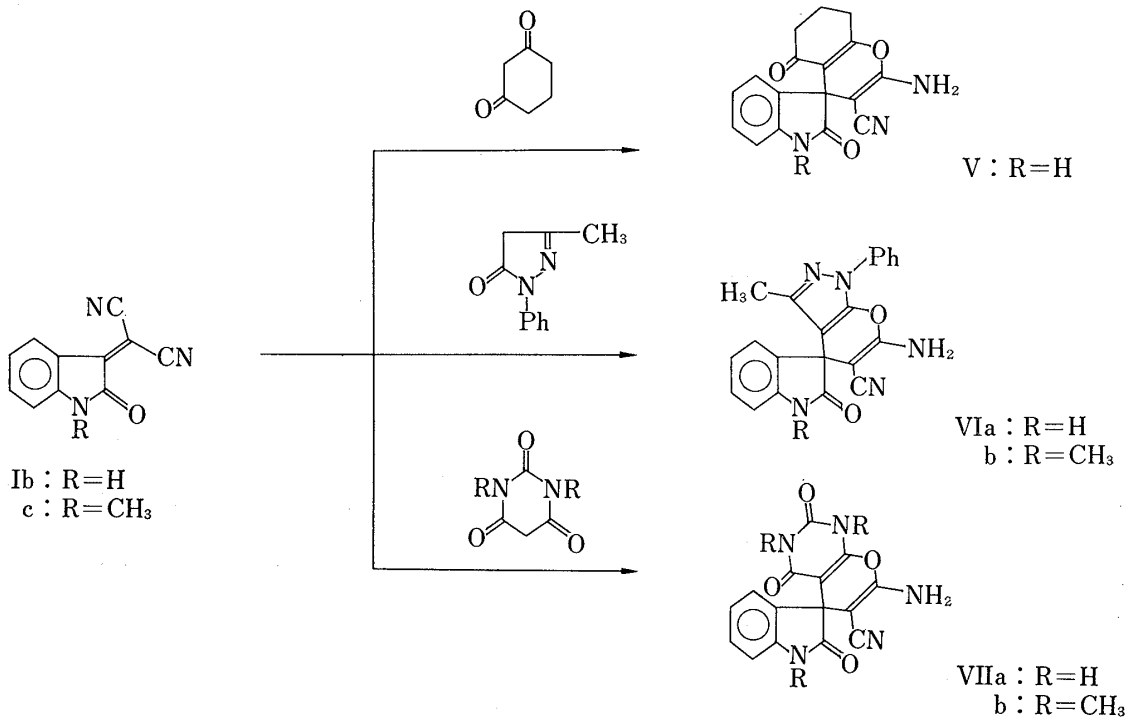
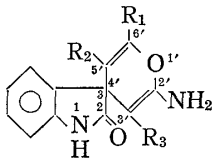


Chart 2

disappeared in D_2O. Compounds IIIe—j, which were formed from Ib, showed a strong peak at 2190—2180 cm^{-1} ascribable to the conjugated CN group in the IR spectra. These results and the analytical data were in good accord with the proposed spiro[oxindole-3,4′-(2′-amino-4′*H*-pyran)] structures (IIIa—j).

A possible mechanism for the formation of spiro-pyran compounds is as follows. As shown in Chart 1, the nucleophillic attack of the active methylene group on the C-3 carbon of Ia, b produces the normal Michael adducts (II′), which enolize and then undergo cyclo-addition between the OH and CN groups to form the 2′-amino-4′*H*-pyran compounds (III). If the reaction involved carbanion attack on the exo-methylene carbon of I, IVa or IVb would

Table I. Spiro[oxindole-3,4′-(4′H-pyran)] Compounds



Compd. No.	R_1	R_2	R_3	Yield (%)	mp °C (solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	Me	COMe	COOEt	75.0	238 (EtOH)	$C_{18}H_{18}N_2O_5$	63.15 (62.87	5.30 5.00	8.18 7.69)
IIIb	Me	COOEt	COOEt	84.9	184 (C_6H_6)	$C_{19}H_{20}N_2O_6$	61.28 (61.12	5.41 5.27	7.52 7.14)
IIIc	Me	COPh	COOEt	74.1	254 (**)[a]	$C_{23}H_{20}N_2O_5$	68.30 (68.40	4.99 5.01	6.93 7.22)
IIId	Ph	COOEt	COOEt	74.1	180 (C_6H_6)	$C_{24}H_{22}N_2O_6$	66.35 (66.23	5.10 5.09	6.45 6.59)
IIIe	Me	COMe	CN	85.9	258 (MeOH)	$C_{16}H_{13}N_3O_3$	65.08 (64.78	4.44 4.40	14.23 13.90)
IIIf	Me	COOEt	CN	93.0	264 (EtOH)	$C_{17}H_{15}N_3O_4$	62.76 (62.76	4.65 4.70	12.92 12.41)
IIIg	Me	COPh	CN	71.7	264 (MeOH)	$C_{21}H_{15}N_3O_3$	70.58 (70.36	4.23 4.40	11.76 11.54)
IIIh	Ph	COOEt	CN	91.7	254 (EtOH)	$C_{22}H_{17}N_3O_4$	68.31 (68.23	4.41 4.40	10.85 10.50)
IIIi	Ph	COPh	CN	91.2	265 (MeOH)	$C_{26}H_{17}N_3O_3$	74.45 (74.39	4.09 4.07	10.02 9.90)
IIIj	COOMe	H	CN	64.8	249 (MeOH)	$C_{15}H_{11}N_3O_4$	60.60 (60.32	3.73 3.82	14.14 13.92)

Compd. No.	IR cm^{-1} (Nujol) NH_2, NH	CN	C=O	PMR (d_6-DMSO) δ ppm NH	NH_2	R_1	R_2
IIIa	3250—3100		1710, 1700, 1670	10.17	7.73	1.99	1.88
IIIb	3250—3100		1720, 1700, 1680	10.15	7.74	2.15	0.87(t), 3.76(q) $J=7$
IIIc	3350—3100		1720, 1690	10.07	7.79	1.61	arH
IIId	3350—3100		1720, 1710, 1680	10.25	7.84	arH	0.74(t), 3.72(q) $J=7$
IIIe	3350—3130	2180	1700, 1670	10.37	7.08	2.28	2.07
IIIf	3300—3150	2180	1710, 1680	10.37	7.11	2.31	0.79(t), 3.76(q) $J=7$
IIIg	3320—3150	2190	1720, 1680	10.34	7.18	1.69	arH
IIIh	3320—3170	2190	1725, 1690	10.49	7.27	arH	0.59(t), 3.40(q) $J=7$
IIIi	3300—3150	2180	1720, 1700	10.46	7.19	arH	arH
IIIj	3350—3200	2180	1720, 1680	10.32	7.30	3.75	5.98

a) MeOH and C_6H_6 1:1.

have been obtained predominantly. However, inspection of the PMR spectra of the crude products produced no evidence for the formation of such compounds.

Subsequently, in the expectation of obtaining other spiro-system pyran compounds, the reactions of Ib, c with cyclic active methylene compounds were carried out.

The reactions of Ib, c with cyclic active methylene compounds, *e. g.* cyclohexane-1,3-dione, 3-methyl-1-phenyl-5-pyrazolone and barbituric acid, in EtOH solution in the presence of piperidine as a catalyst at room temperature afforded the corresponding spiro condensed pyran compounds (V—VII) as sole products. All of the products obtained were colorless crystals which showed a strong peak at 2200—2190 cm^{-1} due to conjugated CN in the IR spectra and a singlet at δ 7.62—7.26 due to NH_2 which disappeared on deuteration in the PMR spectra. These results and the elemental analysis data supported the view that the products, (V—VII), were spiro condensed pyran compounds.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer. MS spectra were taken with a JEOL JMS-D300 instrument at 70 eV. PMR spectra were determined with a JEOL FX-100 spectrometer using tetramethylsilane as an internal standard.

Starting materials Ia—c were prepared according to the methods of Yokoyama[3] and Walter.[5]

Preparation of IIIa—j: Spiro[oxindole-3,4′-(ethyl 5′-acetyl-2′-amino-6′-methyl-4′*H*-pyran-3′-carboxylate)] (IIIa)——A solution of Ia (2.4 g, 0.01 mol) and acetylacetone (1.0 g, 0.01 mol) in EtOH (20 ml) was treated with 2 drops of piperidine, and the mixture was stirred at room temperature for 3 hr. After removal of EtOH, the residue was rinsed with CH_2Cl_2 and the insoluble solid was recrystallized from EtOH to give colorless prisms of IIIa. Data for the products (IIIa—j) are listed in Table I.

Spiro[(2-amino-3-cyano-5,6,7,8-tetrahydro-4*H*-chromene-5-one)-4,3′-oxindole] (V)——A solution of Ib (2.0 g) and cyclohexane-1,3-dione (1.15 g) in EtOH (20 ml) was treated with 2 drops of piperidine, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was treated as described for the preparation of IIIa to give 3.02 g (95.9%) of V as colorless needles, mp 280° (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3350—3150 (NH_2, NH), 2180s (CN), 1710, 1680 (C=O). MS *m/e*: 307 (M^+). PMR (d_6-DMSO) δ: 10.37 (1H, s, 1′-NH–), 7.19 (2H, s, 2-NH_2), 7.15—6.73 (4H, m, arH), 2.65 (2H, m, 6-CH_2–), 2.22 (2H, m, 7-CH_2–), 1.92 (2H, m, 8-CH_2–). *Anal.* Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.56; H, 4.40; N, 13.41.

Spiro[oxindole-3,4′-(2′-amino-3′-cyano-5′-methyl-7′-phenyl-4′*H*-pyrano[2,3-*c*]pyrazole)] (VIa)——Compound Ib (2.0 g) and 3-methyl-1-phenyl-5-pyrazolone (1.8 g) were treated as described for the synthesis of IIIa to yield 3.69 g (97.6%) of VIa as colorless prisms, mp 237° (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3300—3150 (NH_2, NH), 2190s (CN), 1690 (C=O). MS *m/e*: 369 (M^+). PMR (d_6-DMSO) δ: 10.70 (1H, s, 1-NH–), 7.51 (2H, s, 2′-NH_2), 7.85—6.92 (9H, m, arH), 1.58 (3H, s, 5′-CH_3). *Anal.* Calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found: C, 68.20; H, 4.08; N, 18.68.

Spiro[1-methyloxindole-3,4′-(2′-amino-3′-cyano-5′-methyl-7′-phenyl-4′*H*-pyrano[2,3-*c*]pyrazole)] (VIb)——Compound Ic (2.0 g) and 3-methyl-1-phenyl-5-pyrazolone (1.67 g) were treated as described for the synthesis of IIIa to yield 3.5 g (94.8%) of VIb as colorless needles, mp 227° (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3350—3180 (NH_2, NH), 2200s (CN), 1700 (C=O). MS *m/e*: 383 (M^+). PMR (d_6-DMSO) δ: 7.62 (2H, s, 2′-NH_2), 7.86—7.09 (9H, m, arH), 3.26 (3H, s, 1-NCH_3), 1.50 (3H, s, 5′-CH_3). *Anal.* Calcd for $C_{22}H_{17}N_5O_2$: C, 68.91; H, 4.47; N, 18.27. Found: C, 69.10; H, 4.23; N, 18.08.

Spiro[oxindole-3,4′-(2′-amino-3′-cyano-5′,6′,7′,8′-tetrahydro-4′*H*-pyrano[2,3-*d*]pyrimidine-5′,7′-dione)] (VIIa)——Compound Ib (2.0 g) and barbituric acid (1.32 g) were treated as described for the synthesis of IIIa to yield 3.28 g (99.0%) of VIIa as colorless prisms, mp 266° (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3370—3150 (NH_2, NH), 2200s (CN), 1720, 1690, 1670 (C=O). MS *m/e*: 323 (M^+). PMR (d_6-DMSO) δ: 12.24 (1H, s, 6′-NH–), 11.08 (1H, s, 8′-NH–), 10.44 (1H, s, 1-NH–), 7.32 (2H, s, 2′-NH_2), 7.14—6.74 (4H, m, arH). *Anal.* Calcd for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.69. Found: C, 55.73; H, 3.19; N, 21.18.

Spiro[1-methyloxindole-3,4′-(2′-amino-3′-cyano-6′,8′-dimethyl-5′,6′,7′,8′-tetrahydro-4′*H*-pyrano[2,3-*d*]-pyrimidine-5′,7′-dione)] (VIIb)——Compound Ic (2.0 g) and 1,3-dimethylbarbituric acid (1.5 g) were treated as described for the synthesis of IIIa to yield 3.27 g (93.6%) of VIIb as colorless needles mp 231° (MeOH and C_6H_6 1:1). IR ν_{max}^{Nujol} cm^{-1}: 3380—3150 (NH_2, NH), 2200s (CN), 1720, 1690, 1680 (C=O). MS *m/e*: 365 (M^+). PMR (d_6-DMSO) δ: 7.56 (2H, s, 2′-NH_2), 7.26—6.97 (4H, m, arH), 3.39 (3H, s, NCH_3), 3.16 (3H, s, NCH_3), 3.00 (3H, s, NCH_3). *Anal.* Calcd for $C_{18}H_{15}N_5O_4$: C, 59.17; H, 4.14; N, 19.17. Found: C, 58.97; H, 4.36; N, 18.84.