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Michael Reactions of 3-Acylmethyleneoxindoles with Active Methylene Compounds

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3-Acylmethyleneoxindoles (Ia—d) reacted with active methylene compounds (IIa—d) in EtOH, in the presence of $NaOC_2H_5$ as a catalyst at room temperature, to afford the corresponding normal Michael adducts (IIIa—f). The reactions of Ia with IIa, Ic with IIa and Id with IIa in EtOH under reflux, in the presence of Et_2NH as a catalyst, produced the corresponding 2′,4′-substituted 3-(5′-amino-2′*H*-furan-3′-ylidene)oxindoles (IVa—c), while the reactions of Ib with IIa, Ib with IIb and Ic with IIb afforded the 2′,4′-substituted 3-(5′-amino-3′-furyl)oxindole compounds (Va—c), respectively. The Michael adducts (IIIa—c), on being refluxed in EtOH with base catalyst, gave IVa, Vb and IVb, respectively, in high yields, whereas IIId—f did not change at all. X-Ray crystallographic analyses of IVb and Vb were performed.

Keywords——3-acylmethyleneoxindole; active methylene compound; Michael reaction; 1-(3-oxindolyl)acetonylmalononitrile; 3-(2′*H*-furan-3′-ylidene)oxindole; 3-(3′-furyl)oxindole; X-ray structure analysis

In connection with our studies on the synthesis of spiro[oxindole-3,4′-(4′*H*-pyran)] and spiro[oxindole-3,4′-(1′,4′-dihydropyridine)] compounds,[1,2] we further investigated the synthesis of the homologous spiro-systems by employing the Michael reaction of 3-acylmethyleneoxindoles with active methylene compounds. Although we could not obtain the desired compounds by this method, some unexpected results were obtained and are reported in this paper.

The reaction of 3-acetonylideneoxindole[3] (Ia) with malononitrile (IIa) in ethanol, in the presence of a catalytic amount of sodium ethoxide at room temperature (method A), afforded colorless crystals (IIIa) in 76% yield. Michael reaction of the deep red-colored Ia gave a colorless product, which suggested that the conjugated oxindolylidene system changed into an unconjugated oxindole.[1-5] The mass spectrum (MS) of IIIa showed the molecular ion peak (M^+) at m/z 253, corresponding to the Michael adduct, and the infrared (IR) spectrum of IIIa showed a weak peak at 2250 cm^{-1} due to a non-conjugated CN group. The proton magnetic resonance (^1H-NMR) spectrum of IIIa showed a set of signals at δ 4.22 (1H, d, $J=3.7$ Hz), 4.23 (1H, dd, $J=3.7$ and $J=8.2$ Hz) and 5.1 (1H, d, $J=8.2$ Hz), which could be assigned to a >CH–ĊH–CH< unit. From the above results and the analytical data, the structure of IIIa was designated as 1-(3-oxindolyl)acetonylmalononitrile. Thus, the product IIIa can be regarded as a normal Michael adduct formed by attack of the carbanion of the active methylene group at the *exo*-methylene carbon of Ia. The similar reactions of Ia—d with active methylene compounds, such as IIa, ethyl cyanoacetate (IIb), cyanoacetamide (IIc) and diethyl malonate (IId), afforded the corresponding products IIIb—f. Some of the reactions gave amorphous and unworkable products or high-molecular-weight solids of unknown structure. The results thus obtained are summarized in Tables I and II. Compounds IIIa—f could have four or eight diastereomers due to the chiral carbons, but the products obtained (IIIa—f) each showed a clear ^{1}H-NMR signal pattern of the $>\mathrm{CH}-\overset{|}{\mathrm{C}}\mathrm{H}-\mathrm{CH}<$ moiety, which indicated the presence of a single isomer.

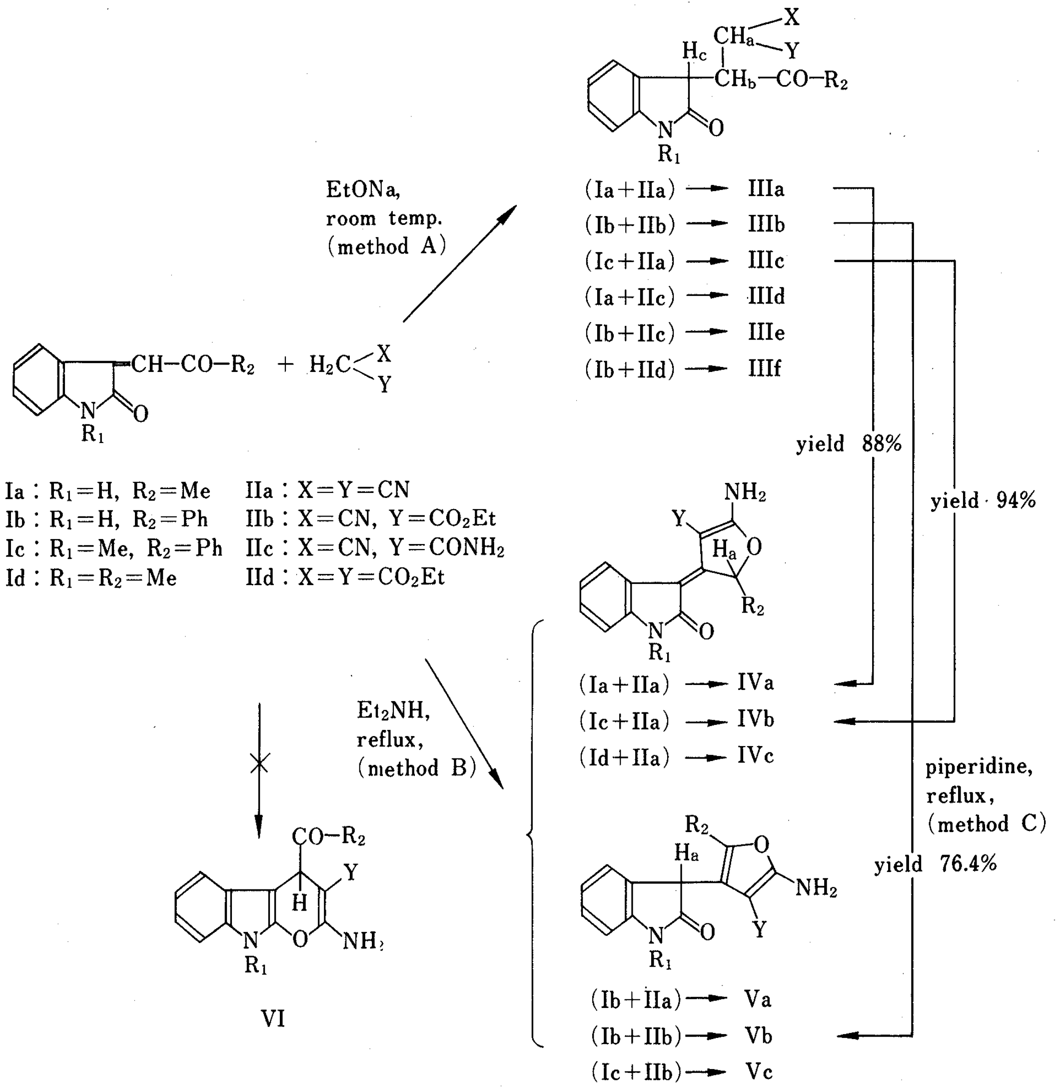

Chart 1

On the other hand, the same reaction of Ia with IIa in ethanol under reflux, in the presence of diethylamine as a catalyst (method B), gave a sole product as yellow needles (IVa) in 40% yield. This product showed the same M$^+$ as IIIa in the MS. The IR spectrum of IVa showed an absorption peak at 1680 cm^{-1} due to C=O of oxindole, a strong peak at 2190 characteristic of a conjugated CN group, and NH and NH$_2$ bands at 3450—3300. The presence of NH$_2$ was also observed in the ^{1}H-NMR spectrum as a singlet at δ 9.18 which disappeared in the presence of D$_2$O. The ^{1}H-NMR spectrum also showed a set of signals at δ 1.56 (3H, d, J=6 Hz) and 6.39 (1H, q, J=6 Hz), indicating a $\mathrm{CH_3}-\mathrm{CH}<$ unit in the molecule. In view of these spectral and analytical data, the above yellow product was assumed to be 3-(5′-amino-2′-methyl-2′*H*-furan-3′-ylidene)oxindole-4′-carbonitrile (IVa). This might be formed as a result of cyclo-addition between one of the CN groups and the enolized OH group of the normal Michael adduct IIIa. Malononitrile (IIa) reacted with Ic and Id to afford the similar compounds IVb and IVc, respectively, as yellow products. An alternative structure VI for the compounds IVa—c was ruled out by the absence of an R$_2$–CO– signal, which usually appears at below 200 ppm, in the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra.

Table I. Michael Reactions of 3-Acylmethyleneoxindoles (Ia—d) with Active Methylene Compounds (IIa—d)

Compd. No.	R_1	R_2	X	Y	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
									C	H	N
IIIa	H	Me	CN	CN	76.2	171	CH_2Cl_2	$C_{14}H_{11}N_3O_2$	66.39	4.38	16.59
									(66.14	4.73	16.80)
IIIb	H	Ph	CN	COOEt	41.0	152	MeOH	$C_{22}H_{20}N_2O_4$	69.60	5.00	7.34
									(70.03	5.00	7.49)
IIIc	Me	Ph	CN	CN	70.0	182	CH_2Cl_2	$C_{20}H_{15}N_3O_2$	72.93	4.59	12.76
									(72.99	4.69	12.57)
IIId	H	Me	CN	$CONH_2$	87.0	267	B+M	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49
									(61.66	4.54	15.60)
IIIe	H	Ph	CN	$CONH_2$	73.4	196	B+M	$C_{19}H_{15}N_3O_3$	68.46	4.54	12.61
									(68.04	4.40	12.27)
IIIf	H	Ph	COOEt	COOEt	55.6	105	Ether	$C_{23}H_{23}NO_6$	67.46	5.66	3.42
									(67.54	5.72	3.23)
IVa	H	Me		CN	40.6	320	EtOH	$C_{14}H_{11}N_3O_2$	66.39	4.38	16.59
									(66.02	4.28	16.60)
IVb	Me	Ph		CN	63.0	227	B+M	$C_{20}H_{15}N_3O_2$	72.93	4.59	12.76
									(73.24	4.84	12.69)
IVc	Me	Me		CN	42.6	248	B+M	$C_{15}H_{13}N_3O_2$	67.40	4.90	15.72
									(67.65	4.71	15.78)
Va	H	Ph		CN	40.0	253	B+M	$C_{19}H_{13}N_3O_2$	72.37	4.16	13.33
									(72.12	4.39	13.13)
Vb	H	Ph		COOEt	48.0	252	EtOH	$C_{21}H_{18}N_2O_4$	69.60	5.00	7.73
									(69.37	5.04	7.52)
Vc	Me	Ph		COOEt	58.0	185	EtOH	$C_{22}H_{20}N_2O_4$	70.20	5.36	7.44
									(69.91	5.57	7.52)

B+M; benzene–methanol (1 : 1).

However, the formation of this type of compound was limited to the above reactions. The reactions of Ib with IIa, Ib with IIb and Ic with IIb under the same reaction conditions afforded the colorless products Va—c, respectively. All of the products Va—c showed M^+ corresponding to the Michael adducts and are assumed to be the saturated oxindole compounds as judged from their ultraviolet (UV) spectra. Their IR spectra showed the presence of an NH group and a conjugated CN group, and their ^{1}H-NMR spectra showed a singlet due to NH_2 and a methine proton in the region of δ 4.74—4.89, which could be assigned to 3-H of oxindole. In the case of the reactions of Ia, b with IIc by method B, the results were the same as those obtained by method A. Thus, the spectral and analytical data supported the structures of Va—c as 2′,4′-substituted 3-(5′-amino-3′-furyl)oxindole compounds.

The fact that the different products III and IV or V were formed depending on the reaction conditions suggested that the initially formed III was transformed into IV or V. When IIIa—f were refluxed in ethanol using less volatile piperidine as a catalyst (method C), IIIa—c changed into IVa, Vb and IVc in yields of 88, 76 and 94%, respectively, whereas IIId—f did not change at all. Attempts to interconvert IV and V were unsuccessful.

Finally, in order to verify the above structural assignments of IV and V, X-ray crystallographic analyses of IVb and Vb were performed. Bond lengths and angles for IVb and Vb are listed in Tables III and IV and perspective drawings of IVb and Vb are shown in Figs. 1 and 2, respectively. It is clear that sp^2 and sp^3 carbons are located at the 3- and 2′-

Table II. UV, IR and ^{1}H-NMR Spectral Data for Michael Products III—V

Compd. No.	UV λ_{max}^{EtOH} nm (log ε)			IR cm^{-1} (Nujol)				
				NH_2NH	CN	C=O		
IIIa				3150	2250 (w)	1720	1700	
IIIb				3150	2250 (w)	1720	1700	1680
IIIc					2250 (w)	1710	1690	
IIId				3450—3150	2250 (w)	1700	1690	1670
IIIe				3450—3250	2250 (w)	1720	1690	1680
IIIf				3350		1740	1720	1680
IVa	245 (5.11)	287 (5.07)	388 (5.45)	3450—3300	2190 (s)	1680		
IVb	247 (5.05)	289 (4.98)	387 (5.26)	3400—3300	2190 (s)	1700		
IVc	246 (5.16)	289 (5.14)	386 (5.42)	3400—3250	2200 (s)	1670		
Va	237 (5.07)	258 (5.18)	303 (5.27)	3450—3150	2200 (s)	1700		
Vb	236 (5.05)	250 (5.05) 293 (5.27)	303 (5.27)	3400—3150		1690	1670	
Vc	238 (4.89)	257 (5.09) 294 (5.27)	303 (5.27)	3430—3250		1700	1670	

Compd. No.	^{1}H-NMR (DMSO-d_6); δ ppm, J in Hz						
	R_1	R_2	H_a	H_b	H_c	NH_2	X or Y
IIIa	10.74 (1H, s, NH)	2.22 (3H, s, CH_3)	4.22 (d)	4.23 (dd)	5.01 (d, $J_{ab}=3.7$, $J_{bc}=8.2$)		
IIIb	8.08 (1H, s, NH)	Ar-H	3.86 (d)	4.55 (dd)	4.44 (d, $J_{ab}=2.0$, $J_{bc}=6.4$)		1.22 (3H, t) 4.17 (2H, q,[a] $J=7.1$, OCH_2CH_3)
IIIc	3.01 (3H, s, CH_3)	Ar-H	4.00 (d)	4.55 (dd)	5.01 (d, $J_{ab}=5.6$, $J_{bc}=6.4$)		[a]
IIId	10.49 (1H, s, NH)	1.31 (3H, s, CH_3)	3.70 (d)	3.30 (dd)	4.31 (d, $J_{ab}=3.33$, $J_{bc}=2.1$)		
IIIe	10.51 (1H, s, NH)	Ar-H	3.56 (d)	3.41 (dd)	4.27 (d, $J_{ab}=2.8$, $J_{bc}=11.1$)		9.37 (2H, s, $CONH_2$)
IIIf	8.72 (1H, s, NH)	Ar-H	3.74 (d)	5.07 (dd)	4.34 (d, $J_{ab}=2.1$, $J_{bc}=11.5$)		1.12 (6H, t) 4.05 (4H, q,[a] $J=7.1$, OCH_2CH_3)
IVa	10.24 (1H, s, NH)	1.56 (3H, d, $J=6.0$, $C\underline{H}_3CH$)	6.38 (1H, q, $J=6.0$, $CH_3C\underline{H}$)			9.18	
IVb	3.25 (3H, s, CH_3)	Ar-H	7.22 (s)			9.27	
IVc	3.15 (3H, s, NH)	1.55 (3H, d, $J=6.3$, $C\underline{H}_3CH$)	6.39 (1H, q, $J=6.3$, $CH_3C\underline{H}$)			9.21	
Va	10.70 (1H, s, NH)	Ar-H	4.89 (s)			7.55	
Vb	10.43 (1H, s, NH)	Ar-H	4.74 (s)			7.21	0.85 (3H, t) 3.77 (2H, q, $J=7.0$, OCH_2CH_3)
Vc	3.20 (3H, s, CH_3)	Ar-H	4.83 (s)			7.20	0.75 (3H, t) 3.67 (2H, q, $J=6.8$, OCH_2CH_3)

[a] In $CDCl_3$.

positions of IV, but at 2′- and 3-positions in V, respectively. Consequently, it was concluded that the initially assumed structures for IV and V are correct.

Experimental

All melting points were determined in capillaries and are uncorrected. IR spectra were recorded with a Hitachi model 215 instrument and MS with a JEOL D-300 at 70 eV. Nuclear magnetic resonance (NMR) spectra were taken on a JEOL FX-100 (100 MHz) using tetramethylsilane as an internal standard. The lattice constants and intensity

TABLE III. Bond Lengths and Angles for IVb with Estimated Standard Deviations in Parentheses

Bond length	(Å)	Bond angle	(°)
C2–C3	1.480 (26)	C2–N1–C7a	111.1 (9)
C2–O9	1.237 (12)	C2–N1–C8	124.0 (6)
C2–N1	1.356 (12)	C7a–N1–C8	124.9 (12)
C3–C3a	1.455 (10)	C3–C2–O9	128.3 (10)
C3–C3′	1.365 (10)	C3–C2–N1	107.3 (6)
C3a–C4	1.393 (22)	O9–C2–N1	124.4 (9)
C3a–C7a	1.405 (14)	C2–C3–C3a	105.7 (9)
C4–C5	1.410 (14)	C2–C3–C3′	120.7 (7)
C5–C6	1.396 (16)	C3a–C3–C3′	133.4 (10)
C6–C7	1.397 (23)	C3–C3a–C4	134.7 (6)
C7–C7a	1.377 (14)	C3–C3a–C7a	107.0 (12)
C7a–N1	1.394 (19)	C4–C3a–C7a	118.2 (12)
C8–N1	1.471 (21)	C3a–C4–C5	118.6 (7)
C2′–C3′	1.542 (11)	C4–C5–C6	121.6 (10)
C2′–C6′	1.509 (11)	C5–C6–C7	120.0 (13)
C2′–O1′	1.470 (11)	C6–C7–C7a	117.6 (8)
C3′–C4′	1.432 (23)	C3a–C7a–C7	123.9 (9)
C4′–C5′	1.402 (12)	C3a–C7a–N1	109.0 (13)
C4′–C12′	1.408 (20)	C7–C7a–N1	127.1 (7)
C5′–O1′	1.319 (21)	C2′–O1′–C5′	109.7 (12)
C5′–N14′	1.321 (13)	C3′–C2′–C6′	113.6 (6)
C6′–C7′	1.398 (24)	C3′–C2′–O1′	103.7 (13)
C6′–C11′	1.388 (10)	C6′–C2′–O1′	106.1 (10)
C7′–C8′	1.405 (12)	C3–C3′–C2′	120.6 (12)
C8′–C9′	1.394 (13)	C3–C3′–C4′	134.6 (6)
C9′–C10′	1.400 (24)	C2′–C3′–C4′	105.0 (12)
C10′–C11′	1.400 (12)	C3′–C4′–C5′	108.4 (7)
C12′–N13′	1.157 (19)	C3′–C4′–C12′	131.5 (12)
		C5′–C4′–C12′	120.0 (7)
		C4′–C5′–O1′	112.8 (6)
		C4′–C5′–N14′	131.1 (9)
		O1′–C5′–N14′	116.1 (12)
		C2′–C6′–C7′	119.0 (7)
		C2′–C6′–C11′	120.6 (10)
		C7′–C6′–C11′	120.3 (8)
		C6′–C7′–C8′	119.1 (8)
		C7′–C8′–C9′	120.5 (11)
		C8′–C9′–C10′	120.3 (10)
		C9′–C10′–C11′	119.0 (9)
		C6′–C11′–C10′	120.9 (10)
		C4′–C12′–N13′	175.1 (8)

data were collected on a Rigaku AFC-5 FOS diffractometer using Mo*Kα* radiation monochromated by means of a graphite plate.

Reactions of 3-Acylmethyleneoxindoles (Ia—d) with Active Methylene Compounds (IIa—d)——Formation of IIIa—f (Method A): In a typical experiment, a solution of Ia (2.0 g) and malononitrile (IIa, 0.71 g) in EtOH (30 ml) was treated with 0.1 g of $NaOC_2H_5$ and the mixture was stirred at room temperature for 2 h. A colorless solid that separated was collected and recrystallized from CH_2Cl_2. Yield, 2.06 g (76.2%). Analogous products (IIIb—f) obtained are listed in Table I.

Formation of IVa—c and Va—c (Method B): In a typical experiment, a solution of Ia (2.0 g) and malononitrile (0.71 g) in EtOH (30 ml) was treated with 5 drops of Et_2 NH, and the whole was refluxed for 1 h. The solvent was removed and the residual product was treated with a small amount of MeOH to give a yellow solid. Yield, 1.1 g (40.6%).

TABLE IV. Bond Lengths and Angles for Vb with Estimated Standard Deviations is Parentheses

Bond length	(Å)	Bond angle	(°)
C2–C3	1.536 (20)	C2–N1–C7a	110.4 (12)
C2–O8	1.219 (16)	C3–C2–O8	126.4 (9)
C2–N1	1.358 (17)	C3–C2–N1	108.9 (13)
C3–C3a	1.513 (21)	O8–C2–N1	124.6 (12)
C3–C3′	1.493 (15)	C2–C3–C3a	101.3 (12)
C3a–C4	1.380 (16)	C2–C3–C3′	112.3 (9)
C3a–C7a	1.397 (20)	C3a–C3–C3′	119.3 (10)
C4–C5	1.407 (21)	C3–C3a–C4	131.5 (11)
C5–C6	1.398 (23)	C3–C3a–C7a	108.0 (12)
C6–C7	1.409 (18)	C4–C3a–C7a	120.4 (11)
C7–C7a	1.403 (20)	C3a–C4–C5	117.8 (13)
C7a–N1	1.396 (16)	C4–C5–C6	121.6 (13)
C2′–C3′	1.353 (28)	C5–C6–C7	121.2 (12)
C2′–C6′	1.448 (31)	C6–C7–C7a	115.7 (12)
C2′–O1′	1.405 (18)	C3a–C7a–C7	123.3 (11)
C3′–C4′	1.441 (24)	C3a–C7a–N1	110.4 (11)
C4′–C5′	1.360 (12)	C7–C7a–N1	126.3 (12)
C4′–C12′	1.443 (35)	C2′–O1′–C5′	106.9 (12)
C5′–O1′	1.355 (31)	C3′–C2′–C6′	134.3 (14)
C5′–N17′	1.362 (21)	C3′–C2′–O1′	109.4 (11)
C6′–C7′	1.411 (22)	C6′–C2′–O1′	116.3 (12)
C6′–C11′	1.400 (16)	C3–C3′–C2′	123.7 (10)
C7′–C8′	1.405 (31)	C3–C3′–C4′	129.4 (14)
C8′–C9′	1.399 (18)	C2′–C3′–C4′	106.6 (16)
C9′–C10′	1.399 (22)	C3′–C4′–C5′	106.6 (17)
C10′–C11′	1.387 (30)	C3′–C4′–C12′	132.6 (11)
C12′–O13′	1.216 (20)	C5′–C4′–C12′	120.7 (14)
C12′–O14′	1.338 (10)	C4′–C5′–O1′	110.5 (16)
C15′–C16′	1.474 (19)	C4′–C5′–N17′	132.0 (13)
C15′–O14′	1.487 (35)	O1′–C5′–N17′	117.5 (11)
		C2′–C6′–C7′	119.9 (13)
		C2′–C6′–C11′	119.9 (12)
		C7′–C6′–C11′	120.2 (15)
		C6′–C7′–C8′	119.4 (14)
		C7′–C8′–C9′	119.8 (13)
		C8′–C9′–C10′	120.3 (15)
		C9′–C10′–C11′	120.2 (14)
		C6′–C11′–C10′	120.1 (12)
		C4′–C12′–O13′	124.9 (11)
		C4′–C12′–O14′	112.5 (14)
		O13′–C12′–O14′	122.7 (16)
		C12′–O14′–C15′	119.1 (13)
		O14′–C15′–C16′	105.9 (12)

Analogous yellow products (IVa—c) were obtained from the reactions of malononitrile with Ic and Id. From the reactions of Ib + IIa, Ib + IIb and Ic + IIb, the corresponding colorless products (Va—c) were obtained. The reactions of Ia, b with cyanoacetamide (IIc) gave the same products IIIe, d as in method A.

Comversion of IIIa—c into IVa, Vb and IVb (Method C): In a typical experiment, a solution of IIIa (1.0 g) and 3 drops of pipeidine in EtOH (30 ml) was refluxed for 30 min. The solvent was removed, a small amount of MeOH was added to the residual product and the solid that separated was collected. Yield, 88.0%. By similar procedures, IIIb, c were converted into IVb and Vb, respectively. Compounds IIId—f showed no change.

X-Ray Structure Analysis of IVb——The crystal data are: monoclinic, space group $P2_1/c$, $a=9.554$ (2), $b=15.728$ (3), $c=12.289$ (4) Å, $\beta=120.22$ (2)°, $V=1595.6$ (8) Å^3, $z=4$, $D_c=1.37\,\mathrm{g\cdot cm^{-3}}$. A total of 1554 independent

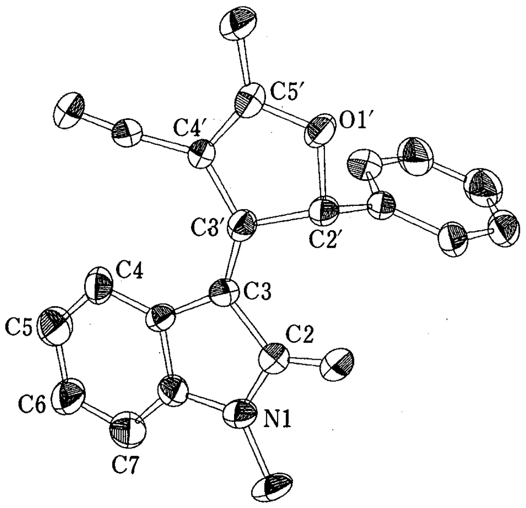

Fig. 1. A Perspective View of IVb

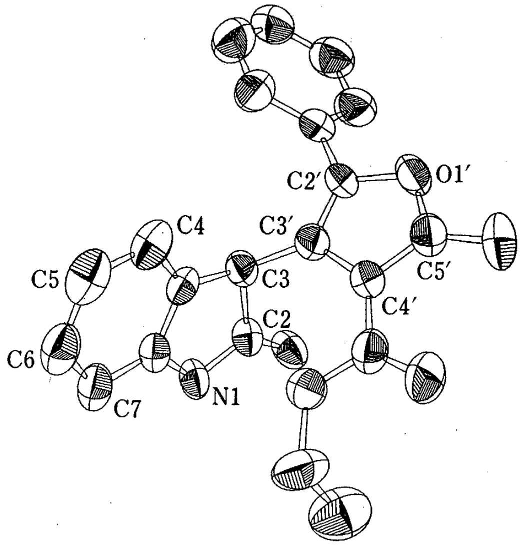

Fig. 2. A Perspective View of Vb

reflections were measured with 2θ less than 46° as above the 2σ (F) level and used in the structural analysis. The structure was solved by the direct method and refined by the block-diagonal least-squares method. The final R factor without hydrogen atoms was 0.082.

X-Ray Structure Analysis of Vb——The crystal data are: triclinic, space group $P\bar{1}$, $a=10.383$ (3), $b=10.523$ (2), $c=9.682$ (3) Å, $\alpha=91.18$ (2), $\beta=114.25$ (2), $\gamma=107.66$ (2)°, $V=906.0$ (5) Å^3, $z=2$, $D_c=1.33\,\mathrm{g\cdot cm^{-3}}$. A total of 1665 independent reflections were measured with 2θ less than 46° as above the 2σ (F) level and used in the structural analysis. The structure was solved by the direct method and refined by the block-diagonal least-squares method. The final R factor without hydrogen atoms was 0.090.

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