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Synthesis of 4-Hydroxymethylene-1,3(2*H*,4*H*)-isoquinolinediones and Related Compounds

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Vilsmeier–Haack reactions of 1,3(2*H*,4*H*)-isoquinolinediones (**1a**, **b**) with dimethylformamide and $POCl_3$ afforded 4-hydroxymethylene-1,3(2*H*,4*H*)-isoquinolinediones (**2a**, **b**) in good yields. Similar reactions of **1a**, **b** using formanilides instead of *N*,*N*-dimethylformamide gave the 4-anilinomethylene compounds (**3a**, **b**). Chlorinations of **2a**, **b** with $POCl_3$ in $CHCl_3$ or tetrahydrofuran gave the 4-chloromethylene compounds **4a**, **b**. Treatment of **2a** with $POCl_3$ in the absence of solvent afforded **4a** and 1,3-dichloro-4-(dichloromethyl)isoquinoline (**5**). Compound **2b** reacted with various amines including ketone reagents to form the corresponding 4-aminomethylene compounds **7a**—**e**, and **7a**—**e** as well as **3a**, **b** could also be prepared from the reactions of **4b** with appropriate amines. Catalytic hydrogenation of **2b** resulted in the formation of 2,4-dimethyl-1,3(2*H*,4*H*)-isoquinolinedione (**8**) and 2,2′,4,4′-tetramethyl[4,4′-biisoquinoline]-1,1′,3,3′(2*H*,2′*H*,4*H*,4′*H*)-tetrone (**9**).

Keywords——Vilsmeier–Haack reaction; 1,3(2*H*,4*H*)-isoquinolinedione; 4-hydroxymethylene-1,3(2*H*,4*H*)-isoquinolinedione; 4-chloromethylene-1,3(2*H*,4*H*)-isoquinolinedione; 4-aminomethylene-1,3(2*H*,4*H*)-isoquinolinedione; 4,4′-biisoquinoline-1,1′,3,3′(2*H*,2′*H*,4*H*,4′*H*)-tetrone

We have been investigating the synthesis of novel 4-substituted isoquinoline compounds[1-3] by taking advantage of the reactivity at the 4-position of 1,3(2*H*,4*H*)-isoquinolinediones (trivial name; homophthalimide) (**1a**, **b**). This paper is concerned with the Vilsmeier–Haack reactions of **1a**, **b** and also presents some results on the reaction products, 4-hydroxymethylene-1,3(2*H*, 4*H*)-isoquinolinediones (**2a**, **b**).

The Vilsmeier–Haack reactions of **1a**, **b** using *N*,*N*-dimethylformamide (DMF) in tetrahydrofuran (THF) gave **2a**, **b** in 96 and 75% yields, respectively. In these reactions, it is considered that the initially formed Vilsmeier products (**2′a**, **b**) underwent hydrolysis during work-up to form **2a**, **b**. The products obtained were clearly in the hydroxymethylene form on the basis of spectral data. In the same reactions of **1b** using formanilide and *N*-methylformanilide in place of DMF, hydrolysis did not occur, and the 4-anilinomethylene compounds **3a**, **b** were obtained in 96 and 84% yields, respectively. Wolfbeis *et al.*[4,5] reported that the condensation of **1b** with trimethoxymethane and aniline afforded **3a** and the alkaline hydrolysis of **3a** produced **2b**, each in 69% yield. The products **2b** and **3a** obtained by them are consistent with those obtained in the present experiment.

Chlorinations of **2a**, **b** with $POCl_3$ in chloroform or THF gave the 4-chloromethylene compounds **4a**, **b** in yields of 61 and 97%, respectively. Treatment of **2a** ($R=H$) with $POCl_3$ in the absence of solvent afforded **4a** and 1,3-dichloro-4-(dichloromethyl)isoquinoline (**5**) in yields of 20 and 44%, respectively. These chloro compounds **4a**, **b** have very high reactivity and were converted into 4-methoxymethylene compounds[5] **6a**, **b** merely by refluxing in methanol. The same compound **6b** was also obtained by treatment of **2b** with diazomethane.

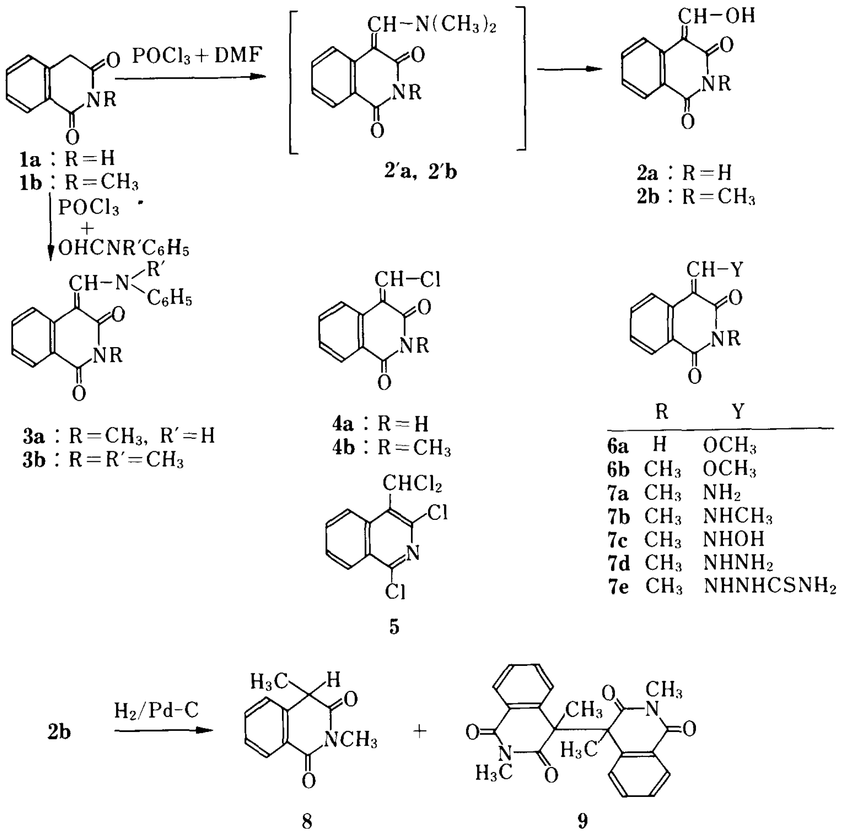

Chart 1

The above results and the electronic character of compounds **2a**, **b** and **4a**, **b** strongly suggested the possibility that other nucleophilic substitutions would take place at the 4-exo-methylene carbon of these compounds. We adopted the N-methyl compounds **2a** and **4b** as reactants in the following reactions.

Compound **2b** readily reacted with various amines, *i.e.*, NH_3, H_2NCH_3, H_2NOH, $NH_2-NH_2 \cdot H_2O$, $H_2NHNCSNH_2$, to form the corresponding 4-aminomethylene compounds **7a**—**e** in good yields. The products **7a**—**e** and **3a**, **b** could also be prepared from the reactions of **4b** with appropriate amines. The products **3a**, **b** were identical with the samples prepared by the foregoing Vilsmeier reactions. The corresponding reactions of N-non-substituted **2a** and **4a** were not examined in detail, because some of the reactions gave slightly soluble products and some were obtained in comparatively low yields.

Finally, the catalytic hydrogenation of **2b** ($R=CH_3$) using Pd–C was carried out. About two molar equivalents of hydrogen uptake gave a mixture of two products, **8** and **9**. However, the formation ratio of these products depended on the solvent used, *viz.* the hydrogenations of **2b** using THF and methanol gave **8** and **9** in ratios of 1.2 : 1 and 19 : 1 (by weight), respectively.

The hydrogenation product **8** thus obtained showed the molecular ion peak (M^+) at m/z 189 in the mass spectrum (MS). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **8** showed a singlet (3H) at δ 3.37 due to NCH_3 protons along with a pair of doublet at 1.67 (3H, $J=7.6$ Hz) and quartet at 3.97 (1H, $J=7.6$ Hz), which are coupled with each other and are assignable to methyl-methine protons. From the above results and by analogy with a similar reaction,[6] the product **8** was assigned as 2,4-dimethyl-1,3(2*H*,4*H*)-isoquinolinedione.[7,8]

The other product **9** showed a very similar infrared (IR) spectrum to that of **8**, and the MS (CI-NH_3) of **9** showed two diagnostic peaks at m/z 394 ($M+NH_4^+$) and 377 ($M+H^+$).

TABLE I. Yields and Elemental Analyses for 4-Hydroxymethylene-1,3-(2*H*,4*H*)-isoquinolinediones and Related Compounds

Compd. No.	Yield (%)	mp °C (Recryst. solv.)	Appearance	Formula	Analysis (%) Calcd (Found)		
					C	H	N
2a	96.0	220	Colorless needles	$C_{10}H_7NO_3$	63.49	3.73	7.41
		(Me_2CO)			(63.97	3.67	7.46)
2b	75.0	206 (lit.[5] mp 205)					
3a	96.2[a]	164 (lit.[5] mp 160)					
3b	84.1[a]	168—171	Yellow needles	$C_{18}H_{16}N_2O_2$	73.95	5.52	9.53
		(Me_2CO)			(74.41	5.58	9.55)
4a	61.0	261 (dec.)	Pale yellow needles	$C_{10}H_6ClNO_2$	57.97	2.90	6.76
		(AcOEt)			(58.25	2.80	6.67)
4b	96.7	124	Colorless needles	$C_{11}H_8ClNO_2$	59.60	3.63	6.31
		(Ligroin)			(59.44	3.49	6.28)
5	44.0	148	Pale yellow prisms	$C_{10}H_5Cl_4N$	42.74	1.79	4.98
		(Ligroin)			(43.04	1.70	5.14)
6a	40.1[b]	260 (lit.[5] mp 259—260)					
6b	68.2[c]	160 (lit.[5] mp 156—157)					
7a	90.0[d]	215	Pale yellow needles	$C_{11}H_{10}N_2O_2$	65.35	4.95	13.86
		(MeOH)			(65.10	4.93	13.56)
7b	72.8[d]	186	Pale yellow needles	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95
		(MeOH)			(66.62	5.53	13.00)
7c	80.0[d]	230	Pale yellow needles	$C_{11}H_{10}N_2O_3$	60.54	4.62	12.84
		(MeOH)			(60.30	4.61	12.50)
7d	80.0[d]	>300	Orange needles	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.35
		(MeOH)			(60.53	5.04	19.30)
7e	96.0[d]	206	Pale yellow needles	$C_{12}H_{12}N_4O_2S$	52.16	4.37	20.27
		(DMSO)			(52.62	4.34	19.87)
8	51.6[e]	58 (lit.[7,8] mp 64—66)					
9	21.6[e]	176—177	Colorless needles	$C_{22}H_{20}N_2O_4$	70.20	5.36	7.44
		(MeOH)			(70.02	5.24	7.57)

a) Based on **1b**. *b*) Based on **4a**. *c*) Based on **4b**. *d*) Based on **2b**. *e*) Solvent, THF. DMSO, dimethylsulfoxide.

The ^1H-NMR spectrum of **9** showed two signals at δ 2.96 and 2.00 (each of 6H, s) attributable to $2 \times NCH_3$ and $2 \times CH_3$ protons. From the above results and analytical data, **9** was concluded to be a dimer, 2,2′,4,4′-tetramethyl[4,4′-biisoquinoline]-1,1′,3,3′(2*H*,2′*H*,4*H*,4′*H*)-tetrone. The mechanism of formation of the dimer is unclear.

Experimental

All melting points are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer and MS with a JEOL D-300 machine at 70 eV. NMR spectra were taken on a JEOL FX-100 spectrometer with tetramethylsilane as the internal standard. The results are summarized in Tables I and II.

General Procedure for Vilsmeier–Haack Reaction: Formations of 2a, b and 3a, b——In a typical experiment, $POCl_3$ (7.0 g) was added to a solution of DMF (4.0 g) in THF (30 ml) in small portions over a period of 10 min at 0 °C with stirring, and then **1a** (4.0 g) was added to the stirred mixture under the same conditions. Stirring was continued at 30—35 °C for 4 h, then the mixture was poured into ice–water and kept standing overnight. The solid that separated was collected, washed with water and dried. Recrystallization from acetone gave 4.4 g (96%) of **2a** as colorless needles, mp 220 °C.

The similar reactions of **1b** with formanilide and *N*-methylformanilide instead of DMF produced **3a**, **b**, which were identical with the samples prepared by the reactions of **4b** with anilines, described later.

4-Chloromethylene-1,3(2*H*,4*H*)-isoquinolinediones (4a, b)——In a typical experiment, $POCl_3$ (5.0 g) was added to a solution of **2a** (1.0 g) in THF (80 ml) and the mixture was heated at 100 °C for 2 h. After cooling, the reaction

TABLE II. Spectral Data for 4-Hydroxymethylene-1,3(2*H*,4*H*)-isoquinolinediones and Related Compounds

Compd. No.	IR ν cm^{-1} (Nujol)	^{1}H-NMR ($CDCl_3$); δ ppm, J in Hz
2a	3740 (OH), 3160 (NH), 1690, 1620 (CO)	14.73 (1H, s, br, OH), 8.53 (1H, s, br, NH), 8.53 (1H, s, =CH–)
3b	1680, 1640 (CO)	8.39 (1H, s, =CH–), 3.47 (3H, s, NCH_3), 3.44 (3H, s, NCH_3)
4a	3180, 3070 (NH), 1710, 1680 (CO)	8.28 (1H, s, br, NH), 8.0 (1H, s, =CH–)
4b	1700, 1680 (CO)	7.91 (1H, s, =CH–), 3.40 (3H, s, NCH_3),
5		7.26 (1H, s, $-\mathrm{CH}<$)
7a	3350, 3200 (NH_2), 1660, 1610 (CO)	[a] 9.80 (1H, br, NH_2), 8.76 (1H, s, br, NH_2), 8.37 (1H, m, =CH–), 3.29 (3H, s, NCH_3)
7b	3200 (NH), 1660, 1620 (CO)	10.17 (1H, m, $NHCH_3$), 7.87 (1H, d, $J=13.2$, =CH–), 3.44 (3H, s, NCH_3), 3.24 (3H, d, $J=5.3$, $NHCH_3$)
7c	3210 (NHOH), 1660, 1620 (CO)	[a] 12.26 (1H, s, OH), 10.84 (1H, s, NH), 8.66 (1H, s, =CH–), 3.31 (3H, s, NCH_3)
7d	3300, 3200 ($NHNH_2$)	[a] 11.34 (1H, d, $J=11.4$, NH), 8.44 (1H, d, $J=11.4$, =CH–), 5.56 (2H, s, NH_2), 3.30 (3H, s, NCH_3)
7e	3300, 3150 (NH, NH_2)	[a] 11.27 (1H, d, $J=8.1$, NH), 10.25 (1H, s, NH), 8.32 (1H, d, $J=8.1$, =CH–), 7.98 (2H, s, NH_2), 3.29 (3H, s, NCH_3)
8	1710, 1660 (CO)	3.91 (1H, q, $J=7.6$, $>\mathrm{CH}-$), 1.67 (3H, d, $J=7.6$, CH_3), 3.37 (3H, s, NCH_3)
9	1710, 1660 (CO)	2.96 (6H, s, $2\times NCH_3$), 2.00 (6H, s, $2\times CH_3$)

a) DMSO-d_6.

mixture was poured into ice–water and kept standing overnight. The crude product that precipitated was purified by column chromatography on silica gel with CH_2Cl_2 to give 0.67 g (61%) of **4a** as pale yellow needles. In the case of **4b**, the chromatographic procedure can be omitted.

1,3-Dichloro-4-(dichloromethyl)isoquinoline (5)——A mixture of **2a** (1.0 g) and $POCl_3$ (7.5 g) was heated at 60—70 °C for 2 h. After cooling, the reaction mixture was poured into ice–water and the solid that separated was collected. The product was taken up in CH_2Cl_2 and purified by chromatography on silica gel. The first eluate gave 0.65 g (44%) of **5** as pale yellow prisms. MS *m/z*: 281 (M^+). The last eluate gave 0.22 g (20%) of **4a**.

4-Methoxymethylene-1,3(2*H*,4*H*)-isoquinolinediones (6a, b)——i) In a typical experiment, a solution of **4b** (1.0 g) in MeOH (50 ml) was refluxed for 2 h. The solvent was removed and the residue was purified by column chromatography on silica gel with CH_2Cl_2 to give 0.668 g (68.2%) of **6b**.[5]

ii) An ether solution (50 ml) of diazomethane, prepared from 3.0 g of nitrosomethylurea, was added to a solution of **2b** (1.0 g) in THF (60 ml) over a period of 20 min under ice-cooling and stirring. The reaction mixture was allowed to stand overnight at room temperature, then the solvent was evaporated off and the product **6b** was obtained in nearly theoretical yield. It was identical with the above sample.

Reactions of 2b with Amines: Formation of 4-Aminomethylene-2-methyl-1,3(2*H*,4*H*)-isoquinolinediones (7a—e)——Preparation of **7b**: A mixture of **2b** (0.5 g) and H_2NCH_3 (40%, 1.2 ml) in MeOH (50 ml) was refluxed for 1 h. The reaction mixture was concentrated to dryness *in vacuo*, then the residue was washed with water and dried to give 0.38 g (72.8%) of **7b**.

Preparation of **7c**: A mixture of **2b** (0.5 g), H_2NOH–HCl (0.35 g) and $NaHCO_3$ (1.0 g) in MeOH (50 ml) was refluxed for 1 h. The solvent was removed, then the residue was treated with water and dried to give 0.43 g (80%) of **7c**.

Reactions of 4b with Amines: Formation of 4-Anilinomethylene- (3a,b) and 4-Aminomethylene-2-methyl-1,3-(2*H*,4*H*)-isoquinolinediones (7a—e)——In a typical experiment, a mixture of **4b** (0.5 g) and aniline (0.22 g) in benzene (50 ml) was refluxed for 1 h. The solvent was removed and the residue was recrystallized from MeOH to give pale yellow needles of **3a**,[4,5] mp 164 °C, in almost theoretical yield.

Compounds **7a**—**e** were also obtained from the reactions of **4b** with appropriate amines. The results were similar to those obtained by the reactions of **2b** with amines.

Catalytic Hydrogenation of 2b: Formation of 2,4-Dimethyl-1,3(2*H*,4*H*)-isoquinolinedione (8) and 2,2′,4,4′-tetramethyl[4,4′-biisoquinoline]-1,1′,3,3′(2*H*,2′*H*,4*H*,4′*H*)-tetrone (9)——A mixture of **2b** (1.0 g) and Pd–C (10%, 0.2 g) in THF (100 ml) was shaken in hydrogen at room temperature and atmospheric pressure. When the absorption of hydrogen ceased, the mixture was filtered and the filtrate was evaporated to dryness. The resulting products were subjected to column chromatography on silica gel with benzene. The first eluate gave 0.48 g of **8**.[7,8] MS *m*/*z*: 189 (M^+).

The last eluate gave 0.40 g of **9**. MS (CI-NH_3) *m*/*z*: 394 ($M+NH_4^+$), 377 ($M+H^+$). When this hydrogenation was carried out in THF as the solvent, the formation ratio of **8** and **9** was 19 : 1 by weight.

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