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Synthesis of 1,3-Oxazino[5,6-*c*]isoquinolines and Related Compounds

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Mannich reaction of 1-chloro-4-isoquinolinol (**1**) with dimethylamine and formalin afforded the base, 1-chloro-3-dimethylaminomethyl-4-isoquinolinol (**2**), and a by-product, 1,1′-dichloro-3,3′-methylenedi-4-isoquinolinol (**3**). The reaction of **1** with formalin in H_2SO_4 gave 6-chloro-1,3-dioxino[5,6-*c*]isoquinoline (**4**). The reactions of **1** with formalin and primary amines, and of **1** with acetaldehyde ammonia afforded the corresponding products, 1,3-oxazino[5,6-*c*]isoquinolines (**5**—**7**), in fair yields.

Methyl 4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (**8**) was converted into the carboxamide (**9**), which, on heating with a mixture of $POCl_3$ and PCl_5, afforded two chloro-cyano compounds **10** and **11** in a ratio of *ca.* 1 : 2. The reaction of **11** with hydrazine hydrate gave the 1-hydrazino compound (**13**).

Keywords——1-chloro-4-isoquinolinol; Mannich reaction; 3-dimethylaminomethylisoquinoline; 3,3′-methylenedi-isoquinoline; 1,3-dioxino[5,6-*c*]isoquinoline; 1,3-oxazino[5,6-*c*]isoquinoline; 1,4-dichloroisoquinoline-3-carbonitrile

Isoquinoline derivatives such as papaverine and many other alkaloids are well known to possess potent pharmacological properties. In connection with our continuing studies on the synthesis of condensed quinoxalines[1] for pharmacological evaluation, we became interested in the synthesis of new heterocyclic systems based on the potentially pharmacologically active isoquinoline skeleton. The present paper describes the synthesis of 1,3-dioxino[5,6-*c*] isoquinoline and 1,3-oxazino[5,6-*c*]isoquinoline derivatives, together with some results obtained in an attempt to synthesize the pyrazolo-isoquinoline system.

A Mannich base at the 3-position of 1-chloro-4-isoquinolinol (**1**) has been obtained by Pesson and Richer.[2] Compound **1** was prepared by the method of Gabriel and Colman.[3] We carried out a similar reaction on **1** using dimethylamine and formalin, and obtained the corresponding Mannich base (**2**) together with a by-product (**3**) having mp 251 °C. The structure of the Mannich base (**2**) was confirmed by the infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra and analytical data. The product (**3**) showed signals at δ 4.58 (2H, s) due to CH_2 protons, at 7.65—8.40 (8H, m) due to aromatic protons and at 10.30 (2H, br, disappeared with D_2O) due to two OH protons in the ^{1}H-NMR spectrum. In addition to the above evidence, the mass spectrum (MS) of **3** showed the molecular ion peak (M^+) at *m/z* 370 and a diagnostic peak at *m/z* 179 corresponding to the mass of **1** with loss of one hydrogen radical. These results and the analytical data supported the structure of **3** as 1,1′-dichloro-3,3′-methylenedi-4-isoquinolinol.

Compound **1** was allowed to react with 30% formalin in sulfuric acid, and colorless needles of **4** were obtained in 73% yield. The product **4** showed M^+ at *m/z* 221 in the MS, and the ^{1}H-NMR spectrum showed two singlets (each 2H) at δ 5.02 and 5.42 attributable to two

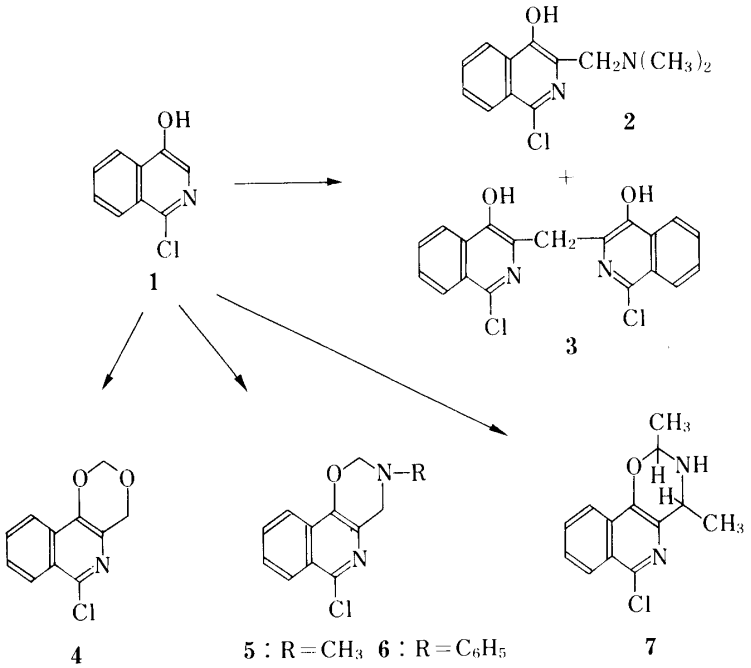

Chart 1

sets of methylene protons. From the above results and by analogy with similar reactions,[4-7] the product **4** was assigned as 6-chloro-1,3-dioxino[5,6-*c*]isoquinoline. Thus, it was found that C-3 of **1** is reactive toward formaldehyde.

Subsequently, we carried out the cyclization between the OH group and 3-position of **1** by Mannich reaction using formalin and primary amines. The reaction of **1** with formalin and methylamine in benzene solution at room temperature gave **5** as orange prisms of mp 125 °C in 82% yield. Similarly, the reaction of **1** with formalin and aniline under reflux gave **6**, yellow prisms of mp 141—142 °C, in 89% yield. The ^{1}H-NMR and MS spectra along with analytical data of these products were consistent with the proposed 3-substituted 6-chloro-3,4-dihydro-2*H*-1,3-oxazino[5,6-*c*]isoquinoline structures **5** and **6**.

In the reaction of **1** with 2 mol eq. of acetaldehyde ammonia in benzene under reflux, a colorless product (**7**) of mp 106 °C was obtained in good yield. The MS of **7** showed M^+ at *m/z* 248 and the ^{1}H-NMR spectrum of **7** showed a quartet at δ 2.45 (1H, J=7 Hz, disappeared with D_2O) due to NH coupled with an adjacent CH (q) proton, two doublets at 1.58 and 1.63 (each of 3H, J=7 Hz) due to two CH_3 protons together with a pair of quartets at 4.17 and 4.45 (each of 1/2 H, J=7 Hz) due to CH and a double-quartet at 5.10 (1H, J=7 and 11 Hz) due to another CH proton; these signals were coupled with each other, indicating two kinds of CH_3CH– group attached to NH in the molecule, as well as 4H (m) of aromatic protons. These results and the analytical data were consistent with the structure of 6-chloro-3,4-dihydro-2,4-dimethyl-2*H*-1,3-oxazino[5,6-*c*]isoquinoline for **7**. The foregoing signals for two CH_3CH protons were correlated to the presence of four CH_3 (q) and four CH (d) carbons in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum. This result indicated that the product **7** was a mixture of four diastereomers due to the 2- and 4-chiral carbons. However, these diastereomers could not be isolated.

The foregoing starting material **1** was derived from methyl 4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylate[3] (**8**). This compound (**8**) seemed to be a suitable material for the synthesis of pyrazolo-isoquinoline structures such as **12**, by analogy with similar reactions previously reported.[1,8,9] Although we could not obtain the desired compound by these methods, unexpected results were obtained, as follows.

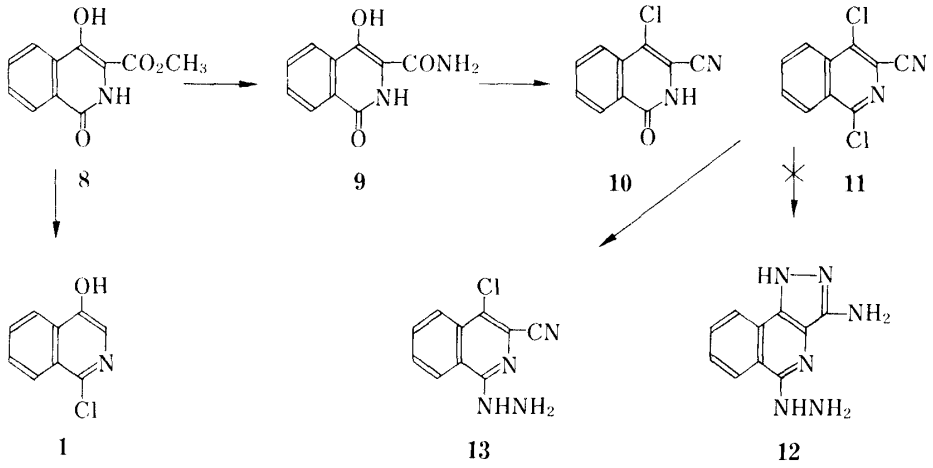

Chart 2

The reaction of **8** with ammonia water afforded the carboxamide (**9**) in 58% yield. When **9** was treated with a mixture of $POCl_3$ and PCl_5, chlorination and dehydration occurred, and two chloro-cyano compounds **10** and **11** were obtained in 28 and 48% yields, respectively. The product **10** did not react with hydrazine hydrate in dioxane under reflux. In contrast to this, the product **11** did not form **12** but merely the 1-hydrazino compound (**13**) in 54% yield.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer and MS with a JEOL D300 spectrometer at 70 eV. ^{1}H- and ^{13}C-NMR spectra were taken on a JEOL FX-100 spectrometer with tetramethylsilane as an internal standard.

Mannich Reaction of 1 with Dimethylamine and Formalin: Formation of 1-Chloro-3-dimethylaminomethyl-4-isoquinolinol (2) and 1,1′-Dichloro-3,3′-methylenedi-4-isoquinolinol (3)——An aq. solution of dimethylamine (50%, 1 ml) and formalin (35%, 1 ml) were added to a stirred suspension of **1** (1.8 g) in MeOH (30 ml) in small portions at 0—5 °C. Stirring was continued for 2 h, then the reaction mixture was acidified with 10% HCl, and MeOH was evaporated off. The residual product was dissolved in water and an insoluble material was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and concentrated to dryness. Recrystallization from EtOH gave colorless needles of **3**, mp 251 °C. Yield, 1.0 g (27%). MS *m/z*: 370 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3000 (OH), 1440 (CH_2). ^{1}H-NMR (DMSO-d_6) δ: 4.58 (2H, s, CH_2), 7.65—8.40 (8H, m, ArH), 10.30 (2H, br, 2OH). *Anal.* Calcd for $C_{19}H_{12}Cl_2N_2O_2$: C, 61.46; H, 3.23; N, 7.55. Found: C, 61.10; H, 3.19; N, 7.38.

The aqueous solution from the separation of **3** was neutralized with Na_2CO_3 and extracted with CH_2Cl_2. Removal of the solvent followed by recrystallization from petroleum ether gave **2** as colorless prisms of mp 73—74 °C. Yield, 1.35 g (57%). MS *m/z*: 236 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s, $2CH_3$), 3.92 (2H, s, CH_2), 7.50—8.73 (4H, m, ArH), 11.35 (1H, s, OH). HCl-salt, mp 167—168 °C. *Anal.* Calcd for $C_{12}H_{13}ClN_2O \cdot HCl$: C, 52.76; H, 5.17; N, 10.26. Found: C, 53.02; H, 5.01; N, 10.17.

6-Chloro-1,3-dioxino[5,6-*c*]isoquinoline (4)——Formalin (35%, 1.5 ml) and H_2O (2.5 ml) were added to a solution of **1** (1.0 g) in H_2SO_4 (7.5 ml), and the mixture was stirred at 40 °C for 8 h. The reaction mixture was poured into ice water, and the precipitate that separated was collected and recrystallized from acetone to give **4** as colorless needles of mp 117—118 °C. Yield, 0.98 g (73.2 g). MS *m/z*: 221 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 5.02 (2H, s, CH_2), 5.42 (2H, s, CH_2), 7.75—8.30 (4H, m, ArH). *Anal.* Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.37; H, 3.44; N, 6.17.

6-Chloro-3,4-dihydro-3-methyl-2*H*-1,3-oxazino[5,6-*c*]isoquinoline (5)——Methylamine (40%, 279 mg) and formalin (35%, 823 mg) were added to a suspension of **1** (718 mg) in benzene (12 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water, then dried over Na_2SO_4 and the solvent was evaporated off. The residual product was recrystallized from benzene–petroleum ether to give **5** as pale yellow prisms, mp 125 °C. Yield, 772 mg (82.3%). MS *m/z*: 234 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, CH_3), 4.12 (2H, s, CH_2), 4.99 (2H, s, CH_2), 7.42—8.35 (4H, m, ArH). *Anal.* Calcd for $C_{12}H_{11}ClN_2O$: C, 61.42; H, 4.72; N, 11.94. Found: C, 61.36; H, 4.73; N, 11.85.

6-Chloro-3,4-dihydro-3-phenyl-2*H*-1,3-oxazino[5,6-*c*]isoquinoline (6)——Formalin (35%, 617 mg) and aniline (335 mg) were added to a solution of **1** (531 mg) in benzene (10 ml) and the mixture was refluxed for 1 h, then allowed

to cool. The reaction mixture was washed with water, dried over Na_2SO_4 and the solvent was removed. The residual product was recrystallized from benzene–petroleum ether to give **6** as yellowish prisms, mp 141—142 °C. Yield, 510 mg (89%). MS *m/z*: 296 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 4.75 (2H, s, CH_2), 5.45 (2H, s, CH_2), 6.75—8.25 (9H, m, ArH). *Anal.* Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.41; N, 9.44. Found: C, 68.52; H, 4.41; N, 9.19.

6-Chloro-3,4-dihydro-2,4-dimethyl-2*H*-1,3-oxazino[5,6-*c*]isoquinoline (7)——Acetaldehyde ammonia (1.46 g) was added to a solution of **1** (1.8 g) in benzene (30 ml), and the mixture was refluxed for 2 h, then allowed to cool. The reaction mixture was washed with 10% NaOH solution, dried over Na_2SO_4 and the solvent was removed. The residual product was recrystallized from petroleum ether to give **7** as colorless needles of mp 106 °C. Yield, 2.0 g (80.3%). MS *m/z*: 248 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH). ^{1}H-NMR ($CDCl_3$) δ: 1.58 (3H, d, J=7 Hz, CH_3CH), 1.63 (3H, d, J=7 Hz, CH_3CH), 2.45 (1H, br, exchangeable with D_2O, NH), 4.17 (1/2 H, q, J=7 Hz, CH_3CH), 4.45 (1/2 H, q, J=7 Hz, CH_3CH), 5.10 (1H, dq, J=7 and 11 Hz, CH_3-CH), 7.45—8.35 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.6 (q), 21.1 (q), 21.3 (q), 22.0 (q), 49.2 (d), 50.8 (d), 80.3 (d), 84.7 (d). *Anal.* Calcd for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26. Found: C, 63.05; H, 5.22; N, 10.78.

4-Hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxamide (9)——A solution of methyl 4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylate[3] (**8**) (4.0 g) in ammonia water (28%, 50 ml) was warmed at 40—50 °C for 5 h and kept standing overnight at room temperature. The reaction mixture was acidified with conc. HCl, and the crystals that separated were filtered off, washed with water and dried. The whole was dissolved in THF (40 ml), and filtered to remove the unreacted **8**, then the filtrate was concentrated to give **9**. Yield, 2.2 g (59.1%). Colorless needles, mp 300 °C (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 3230 (NH), 1670 (CO). MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.01; H, 3.98; N, 13.42.

Reaction of 9 with $POCl_3$ and PCl_5: Formation of 4-Chloro-1-oxo-1,2-dihydroisoquinoline-3-carbonitrile (10) and 1,4-Dichloroisoquinoline-3-carbonitrile (11)——A mixture of **9** (5.0 g), $POCl_3$ and PCl_5 was heated at 130 °C for 1 h, then allowed to cool. The reaction mixture was poured into ice water, and the solid that separated was collected, washed with water and dried. The whole was dissolved in benzene and the insoluble **10** was filtered off. Yield, 1.4 g (28%). Colorless needles, mp 255 °C (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3150 (NH), 2220 (CN), 1680 (CO). MS *m/z*: 205 (M^+). *Anal.* Calcd for $C_{10}H_5ClN_2O$: C, 58.70; H, 2.46; N, 13.69. Found: C, 59.03; H, 2.40; N, 13.90.

The filtrate from the separation of **10** was concentrated to dryness, taken up in CH_2Cl_2 and subjected to column chromatography on silica gel to give **11**. Yield, 2.4 g (48%). Colorless needles, mp 160 °C (benzene). IR ν_{max}^{Nujol} cm^{-1}: 2225 (CN). MS *m/z*: 223 (M^+). *Anal.* Calcd for $C_{10}H_4Cl_2N_2$: C, 53.85; H, 1.81; N, 12.56. Found: C, 53.91; H, 1.88; N, 12.25.

4-Chloro-1-hydrazinoisoquinoline-3-carbonitrile (13)——A mixture of **11** (516 mg) and $NH_2NH_2 \cdot H_2O$ (280 mg) in dioxane (7 ml) was refluxed for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel with a mixed solvent of CH_2Cl_2 and MeOH (20 : 1). The first eluent gave a small amount of unreacted **11**. The second eluent gave **13** as colorless needles of mp 225—227 °C (MeOH). Yield, 271 mg (54%). IR ν_{max}^{Nujol} cm^{-1}: 3350—3250 (NH_2, NH), 2230 (CN). MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{10}H_7ClN_4$: C, 54.93; H, 3.23; N, 25.62. Found: C, 55.21; H, 3.22; N, 25.37.

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