

SYNTHESIS OF 2,3-FUSED QUINOLINES FROM 3-SUBSTITUTED QUINOLINE 1-OXIDES. PART III. INTRAMOLECULAR CYCLIZATION OF QUINOLINE 1-OXIDES BEARING ACTIVE METHYLENE GROUPS AT THE 3-POSITION IN THE PRESENCE OF ACETIC ANHYDRIDE

Yutaka Miura*, Yasuo Fujimura, Sakae Takaku, and Masatomo Hamana

Exploratory Laboratories, Chugai Pharmaceutical Co., Ltd.
1-135 Komakado, Gotemba, Shizuoka 412, Japan

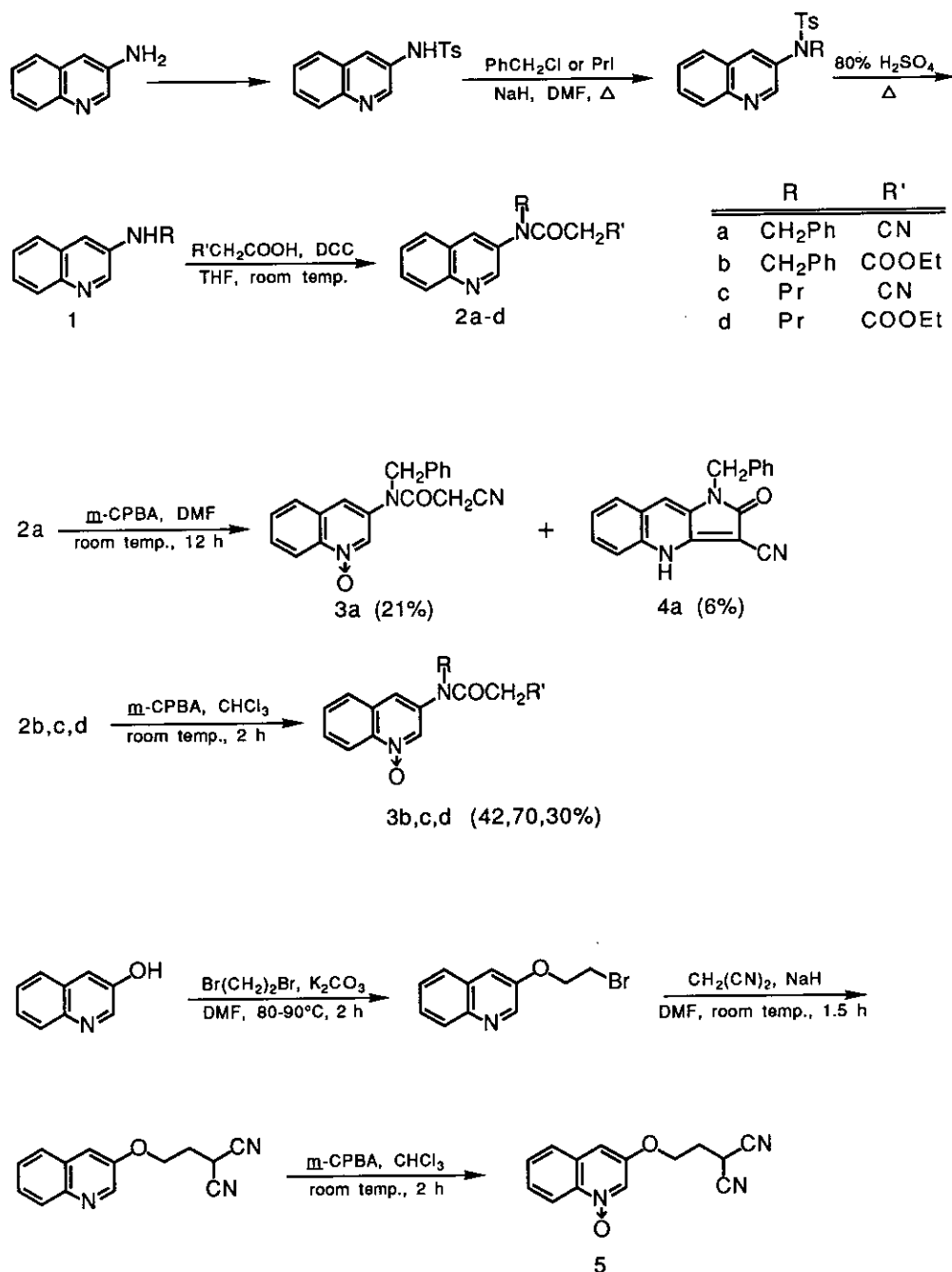
Abstract — 3-*N*-Alkylcyanoacetamidoquinoline 1-oxides (3a and 3c) react with Ac₂O at room temperature in chloroform to afford 1-alkyl-3-cyano-4*H*-pyrrolo[3,2-*b*]quinolin-2-ones (4a and 4c). The cyclization of 3-*N*-alkylethoxycarbonylacetamidoquinoline 1-oxides (3b and 3d) occurs upon heating with Ac₂O at 60°C. 3-(3,3-Dicyanopropoxy)quinoline 1-oxide (5) also cyclizes to the pyranoquinoline (6) when treated with Ac₂O at room temperature in chloroform-DMF.

Since it was found in 1963 that quinoline 1-oxides react with some active methylene compounds in the presence of acetic anhydride (Ac₂O) to give 2-substituted quinolines,¹ this and analogous reactions of aromatic *N*-oxides with carbon nucleophiles in the presence of acylating agents are established as one of the most effective methods for introducing carbon-substituents

into the α -position of N-heteroaromatic nuclei.² As a further extension of our studies on the synthesis of 2,3-fused quinolines from 3-substituted quinoline 1-oxides,^{3,4} we investigated Ac₂O-mediated intramolecular cyclization reactions of some quinoline 1-oxides bearing active CH-groups at the 3-position.

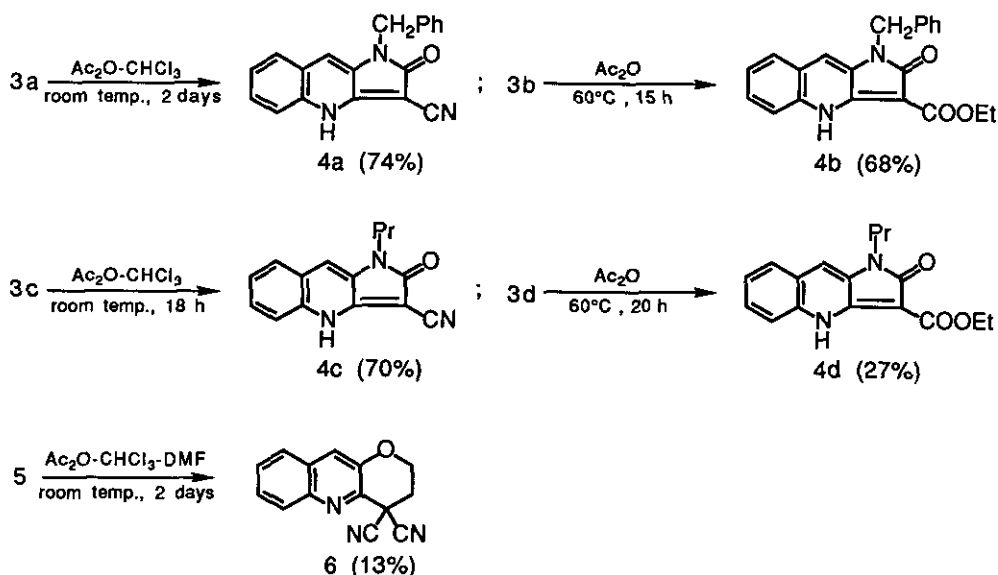
The relevant 3-substituted quinoline 1-oxides were prepared by the reaction sequences shown in Scheme 1, starting from 3-aminoquinoline and 3-quinolinol. Thus 3-aminoquinoline was first tosylated to 3-N-tosylaminoquinoline,³ which was alkylated with benzyl chloride or propyl iodide in the presence of sodium hydride (NaH) followed by detosylation by means of hot 80% sulfuric acid to give the corresponding 3-N-alkylaminoquinoline (1). Treatment of 1 with cyanoacetic acid or monoethyl malonate in the presence of dicyclohexylcarbodiimide (DCC) gave 3-N-alkylacetamidoquinoline derivatives (2a-d) in generally good yields (68-76%). When a solution of 3-N-benzylcyanoacetamidoquinoline (2a) and m-chloroperbenzoic acid (m-CPBA, 1.2 equiv) in dimethylformamide (DMF) was stirred at room temperature for 12 h, not only the expected 1-oxide (3a) but also its cyclization product (4a) were formed in 21 and 6% yields, respectively. This result is significantly interest, however to simplify the problem avoiding the formation of cyclization product we attempted the oxidation of 2b-d with m-CPBA using chloroform as the solvent and successfully obtained only the corresponding 1-oxides (3b-d).

Starting from 3-quinolinol, 3-(3,3-dicyanopropoxy)quinoline 1-oxide (5) was prepared as follows. 3-Quinolinol was treated with 1,2-dibromoethane in the presence of potassium carbonate followed by the action of malononitrile and NaH on the formed 3-(3-bromoethoxy)quinoline to give 3-(3,3-dicyanopropoxy)quinoline, which was oxidized with m-CPBA to its 1-oxide (5).



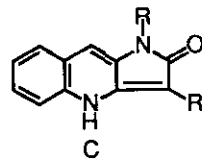
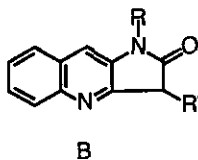
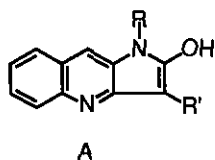
Scheme 1

When a solution of **3a** and Ac_2O in chloroform was stirred at room temperature, a reaction apparently occurred and the solution turned pale yellow. Stirring was continued for 2 days and a precipitate formed was filtered and recrystallized from dimethyl sulfoxide-methanol to afford the intramolecular cyclization product, 1-benzyl-3-cyano-4H-pyrrolo[3,2-b]quinolin-2-one (**4a**) in 74% yield. A similar reaction of 3-N-propylcyanoacetamidoquinoline 1-oxide (**3c**) for 18 h gave the 1-propylpyrroloquinoline (**4c**) in 70% yield. However, the 3-ethoxycarbonylacetylamidoquinoline 1-oxides (**3b** and **3d**) were almost inert under the above conditions, but reactions took place upon heating with Ac_2O alone at 60°C to provide the corresponding cyclization products (**4b** and **4d**) in 68 and 27% yields after 15 h's and 20 h's reactions, respectively. The low yield of **4d** may be partly due to the difficulty of purification of **3d** owing to its highly hygroscopic property (Scheme 2).



Scheme 2

As **5** is scarcely soluble in chloroform, it was dissolved in a mixture of chloroform and DMF (4:1), and this solution was stirred with Ac₂O at room temperature for 2 days to give 4,4-dicyano-2,3-dihydropyrano[3,2-*b*]quinoline (**6**) in a low yield of 13% with fair amounts of **5** being recovered (Scheme 2). Structures of these products were assigned on the basis of elemental analyses and the nmr spectroscopies.⁵ Three isomeric structures (**A**, **B** and **C**) are conceivable for **4a-d**. Among these structures, the enamine form **C** was shown to be most predominant by their ¹H-nmr spectra, which showed the respective 4-NH proton signal as a broad singlet at δ 13.89 (**4a**), 11.14 (**4b**), 13.77 (**4c**) and 11.14 (**4d**).⁵ The ¹³C-nmr spectra were also in agreement with the enamine form **C**, and further X-ray diffraction study of **4a** confirmed this conclusion.



REFERENCES AND NOTE

1. M. Hamana and M. Yamazaki, Chem. Pharm. Bull., 1963, 11, 411 and 415.
2. M. Hamana, Croat. Chem. Acta, 1986, 24, 89.
3. Y. Miura, S. Takaku, Y. Fujimura, and M. Hamana, Heterocycles, 1992, 34, 1055.
4. Y. Miura, M. Yoshida, and M. Hamana, Heterocycles, 1993, in press.
5. **4a**: Colorless needles, mp >300°C (DMSO-MeOH). Anal. Calcd for C₁₉H₁₃N₃O: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.08; H, 4.42; N, 13.93. ¹H-Nmr (CDCl₃-DMSO-d₆) δ : 5.09 (2H, s, CH₂-Ph), 7.25-7.82 (10H, m, Ar-H), 13.89 (1H, br s, NH). ¹³C-Nmr (CDCl₃-DMSO-d₆) δ : 42.33 (t), 63.85 (s), 109.60

(d), 115.24 (s), 116.83 (d), 121.68 (s), 123.73 (d), 126.87 (d), 127.42 (s), 127.44 (d), 128.35 (d), 130.44 (s), 132.95 (s), 136.73 (s), 144.33 (s), 166.24 (s).

4b: Colorless needles, mp 189–191°C (decomp.) (acetone). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.98; H, 5.22; N, 8.05. 1H -Nmr ($CDCl_3$) δ : 1.44 (3H, t, $J=7.1$ Hz, CH_3), 4.43 (2H, q, $J=7.1$ Hz, OCH_2), 5.08 (2H, s, NCH_2), 6.97–7.58 (10H, m, Ar-H), 11.14 (1H, br s, NH). ^{13}C -Nmr ($CDCl_3$) δ : 14.62 (q), 43.12 (t), 60.19 (t), 85.00 (s), 108.35 (d), 116.80 (d), 122.54 (s), 124.12 (d), 127.42 (d), 127.54 (s), 127.79 (d), 128.03 (d), 128.73 (d), 131.79 (s), 132.09 (s), 136.72 (s), 147.23 (s), 165.63 (s), 166.30 (s).

4c: Colorless needles, mp >300°C (DMSO-MeOH). Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.85; H, 5.22; N, 16.76. 1H -Nmr ($CDCl_3$ -DMSO- d_6) δ : 0.90 (3H, t, $J=7.3$ Hz, CH_3), 1.63–1.73 (2H, m, $CH_2CH_2CH_3$), 3.82 (2H, t, $J=7.1$ Hz, NCH_2), 7.36–7.88 (5H, m, Ar-H), 13.77 (1H, br s, NH). ^{13}C -Nmr ($CDCl_3$ -DMSO- d_6) δ : 11.05 (q), 21.24 (t), 40.84 (t), 63.97 (s), 109.29 (d), 115.52 (s), 116.92 (d), 121.99 (s), 123.79 (d), 127.60 (d), 127.97 (d), 130.93 (s), 132.95 (s), 144.33 (s), 166.43 (s).

4d: Colorless prisms, mp 144–145°C (acetone-hexane). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.47; H, 6.13; N, 9.35. 1H -Nmr ($CDCl_3$) δ : 0.97 (3H, t, $J=7.3$ Hz, $CH_2CH_2CH_3$), 1.43 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.71–1.82 (2H, m, $CH_2CH_2CH_3$), 3.86 (2H, t, $J=7.3$ Hz, NCH_2), 4.40 (2H, q, $J=7.1$ Hz, OCH_2), 7.14–7.73 (5H, m, Ar-H), 11.14 (1H, br s, NH). ^{13}C -Nmr ($CDCl_3$) δ : 11.48 (q), 14.62 (q), 21.91 (t), 41.20 (t), 60.12 (t), 85.10 (s), 107.31 (d), 116.83 (d), 122.66 (s), 124.12 (d), 127.67 (d), 127.88 (d), 132.00 (s), 132.37 (s), 147.05 (s), 165.75 (s), 166.40 (s).

6: Colorless needles, mp 163-164°C (EtOH). Anal. Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.62; H, 3.89; N, 17.87. 1H -Nmr ($CDCl_3$ -DMSO- d_6) δ : 3.21 (2H, t, J = 5.2 Hz, C_3 -2H), 4.49 (2H, t, J = 5.2 Hz, C_2 -2H), 7.62-8.09 (5H, m, Ar-H). ^{13}C -Nmr ($CDCl_3$ -DMSO- d_6) δ : 30.21 (t), 62.11 (t), 114.54 (s), 121.82 (d), 126.64 (d), 128.12 (d), 128.32 (d), 129.80 (s), 135.30 (s), 142.47 (s), 146.74 (s).

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