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

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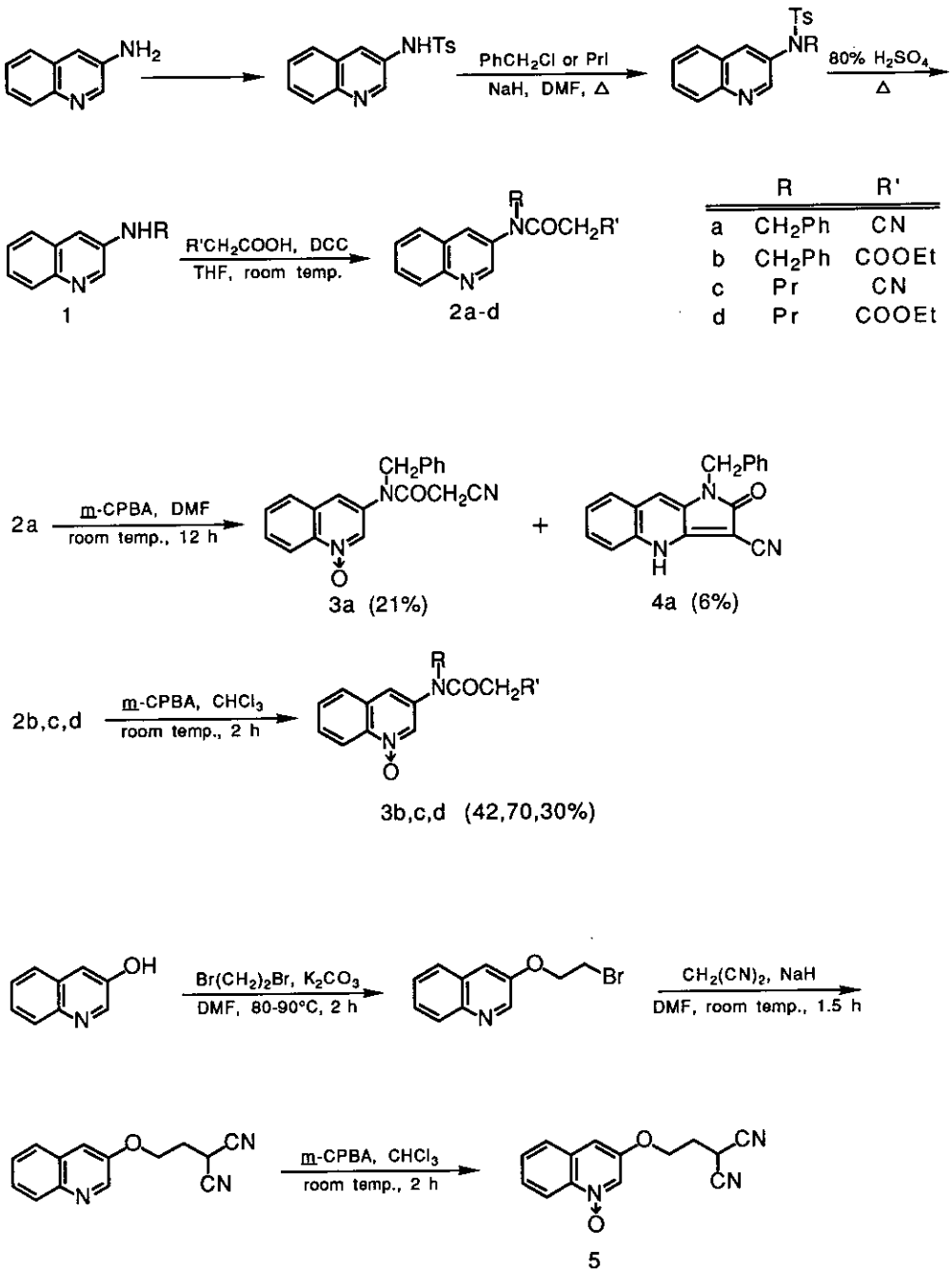
Abstract — 3-*N*-Alkylcyanoacetamidoquinoline 1-oxides (**3a** and **3c**) react with Ac_2O at room temperature in chloroform to afford 1-alkyl-3-cyano-4*H*-pyrrolo[3,2-*b*]quinolin-2-ones (**4a** and **4c**). The cyclization of 3-*N*-alkylethoxycarbonylacetamidoquinoline 1-oxides (**3b** and **3d**) occurs upon heating with Ac_2O at 60°C. 3-(3,3-Dicyanopropoxy)quinoline 1-oxide (**5**) also cyclizes to the pyranoquinoline (**6**) when treated with Ac_2O 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 (Ac_2O) 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 Ac_2O-mediated intramolecular cyclization reactions of some quinoline 1-oxides bearing active CH-groups at the 3-position.

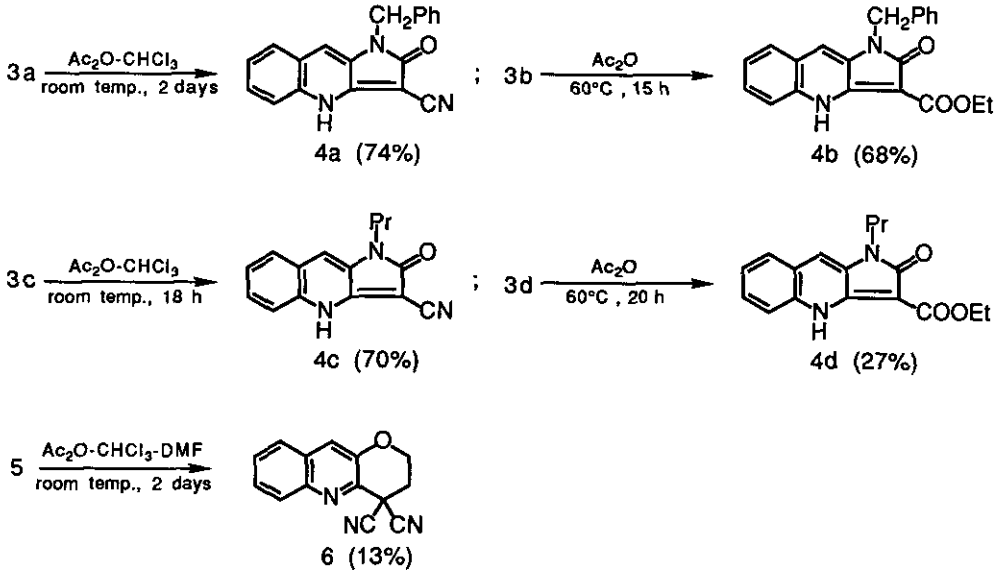
The relevant 3-substituted quinoline 1-oxides were prepared by the reaction sequences shown in Scheme 1, starting from 3-aminoquinoline and 3-quinolinol. Thus 3-aminoquinoline was first tosylated to 3-N-tosylaminoquinoline,[3] which was alkylated with benzyl chloride or propyl iodide in the presence 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 molonate 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**).


NH2
NHTs
PhCH2Cl or PrI
NaH, DMF, Δ
Ts
NR
80% H2SO4
Δ
NHR
R'CH2COOH, DCC
THF, room temp.
1
NCOCH2R'
2a-d
R R'
a CH2Ph CN
b CH2Ph COOEt
c Pr CN
d Pr COOEt
2a
m-CPBA, DMF
room temp., 12 h
CH2Ph
NCOCH2CN
3a (21%)
+
CH2Ph
O
CN
H
4a (6%)
2b,c,d
m-CPBA, CHCl3
room temp., 2 h
3b,c,d (42,70,30%)
OH
Br(CH2)2Br, K2CO3
DMF, 80-90°C, 2 h
Br
CH2(CN)2, NaH
DMF, room temp., 1.5 h
CN
m-CPBA, CHCl3
room temp., 2 h
5

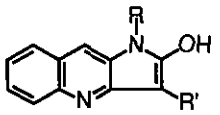
Scheme 1

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-ethoxycarbonylacetamidoquinoline 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).

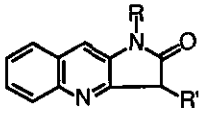


Scheme 2

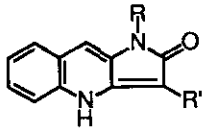
As **5** is scarcely soluble in chloroform, it was dissolved in a mixture of chloroform and DMF (4:1), and this solution was stirred with Ac_2O at room temperature for 2 days to give 4,4-dicyano-2,3-dihydropyrano[3,2-b]quinoline (**6**) in a low yield of 13% with fair amounts of **5** being recovered (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 ^{1}H-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 ^{13}C-nmr spectra were also in agreement with the enamine form **C**, and further X-ray diffraction study of **4a** confirmed this conclusion.



A



B



C

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5. **4a**: Colorless needles, mp >300°C (DMSO-MeOH). Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.08; H, 4.42; N, 13.93. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 5.09 (2H, s, CH_2-Ph), 7.25-7.82 (10H, m, Ar-H), 13.89 (1H, br s, NH). ^{13}C-Nmr ($CDCl_3$-DMSO-d_6) 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. ^{1}H-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. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 0.90 (3H, t, J=7.3 Hz, CH_3), 1.63-1.73 (2H, m, $CH_2C\underline{H}_2CH_3$), 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. ^{1}H-Nmr ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.43 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.71-1.82 (2H, m, $CH_2C\underline{H}_2CH_3$), 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. ^{1}H-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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