REACTIONS OF 3-SUBSTITUTED QUINOLINE 1-OXIDES
WITH ACYLATING AGENTS

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Abstract — Reactions of 3-fluoro- (1a), 3-bromo- (1b), 3-methyl- (1c), 3-methoxy- (1d) and 3-acetamidoquinoline 1-oxides (1e) with acylating agents (POCl₃, Ac₂O, TsCl and PhCOCl) were examined (Table). While only 2-substituted quinolines were obtained from 1a and 1b, fair amounts of 4-substituted products were formed in reactions of 1d, the sole formation of the 4-acetoxyquinoline (6) with Ac₂O being the most significant result. 2-Chloroquinolines, 4-chloroquinolines and 2-tosyloxyquinolines were formed (and sometimes predominate) in addition to 2-quinolinones in reactions with TsCl.

In our search for effective medicines for dementia of Alzheimer type, we have synthesized a number of 4-aminopyridine and 4-aminquinoline derivatives. During the course of this work we examined reactions of 3-substituted quinoline 1-oxides with acylating agents in connection with synthesis of 2,3-disubstituted 4-aminquinolines. Although there are a few reports on such reactions,¹ no coherent studies have not be done. We chose 3-fluoro- (1a), 3-bromo- (1b), 3-methyl- (1c), 3-methoxy (1d), and 3-acetamidoquinoline 1-oxides (1e) as 3-substituted quinoline 1-oxide and studied their deoxygenative substitution with phosphoryl chloride (POCl₃), acetic anhydride (Ac₂O), tosyl chloride (TsCl), and benzoyl chloride (PhCOCl). The reaction conditions and results are summarized in Table.
Table. Reactions of 3-Substituted Quinoline 1-Oxides (1) with Acylating Agents

Reagents and conditions: 1) POCl₃, 90°C, 1 h; 2) Ac₂O, reflux, 2 h; 3) TsCl-CHCl₃, 10% K₂CO₃, room temperature, 3 h; 4) TsCl, CHCl₃, reflux, 1 h; 5) PhCOCl-CHCl₃, 10% K₂CO₃, room temperature, 3 h

<table>
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<tr>
<th>Run</th>
<th>1</th>
<th>Reaction</th>
<th>2-Substituted Product (%)</th>
<th>4-Substituted Product (%)</th>
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<td>3c (34)</td>
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<td>25</td>
<td>5</td>
<td>4e (23)</td>
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\[ a: R=F, \quad b: R=Br, \quad c: R=Me, \quad d: R=OMe, \quad e: R=NHAc \]
Reactions of 3-fluoroquinoline 1-oxide (1a) proceeded regioselectively and afforded exclusively 2-substituted quinolines (2a and 4a) in generally good yields. Thus, the reaction with POCl₃ afforded only 2-chloro-3-fluoroquinoline (2a) without simultaneous formation of the 4-chloro isomer, and it was found that the reaction with TsCl gave 2a alone not only under reflux in chloroform but also at room temperature in the presence of 10% potassium carbonate (K₂CO₃), the corresponding 2-quinolinone being not isolated.

The reaction of 3-bromoquinoline 1-oxide (1b) gave also only 2-substituted quinolines (2b, 4b and 7). While Ochiai and Okamoto reported that 3-bromo-2-quinolinone (4b) was formed in 70% yield upon heating 1b with Ac₂O at 130-140°C in a sealed tube, heating 1b at reflux with Ac₂O for 2 h resulted in the formation of 4b in a small yield of 10% with a major formation of N-(3-bromo-2-quinoly)3-bromo-2-quinolinone (7; 42%). Reactions with TsCl yielded the 2-chloroquinoline (2b) and the 2-quinolinone (4b) differently from those of 1a.

Although Lyle and coworkers reported that 3-methylquinoline 1-oxide (1c) gave 2-chloro-3-methylquinoline (2c) in 87% yield when heated at reflux with POCl₃, we obtained practically the same amounts of 2c (31%) and the 4-chloro isomer (3c; 34%) from the reaction at 90°C for 1 h. Such an inconsistency remains to be explored further. Whereas the reaction of 1c with TsCl and 10% K₂CO₃ gave 3-methyl-2-quinolinone (4c) as the sole product, 4c and 3-methyl-2-tosyloxyquinoline (5c) were obtained under reflux with TsCl in chloroform, no formation of the 2-chloroquinoline (2c) being noticed in these cases.

In the reaction of 3-methoxyquinoline 1-oxide (1d) the reactivity of the 4-position apparently appeared. Fair amounts of 4-chloro-3-methoxyquinoline (3d) were obtained together with the 2-chloro isomer (2d) not only in the reaction with POCl₃ but also in those with TsCl; the latter reaction gave additionally 2-quinolinone (4d) but in rather small yields. Particularly noteworthy is the exclusive formation of 4-acetoxy-3-methoxyquinoline (6) in 65% yield in the reaction with Ac₂O. Treatment of 6 with K₂CO₃ solution smoothly led to 3-methoxy-4-quinolinone (8). The reaction of 1d with PhCOCl gave rise to much resinification, no definite products being obtained.
Reactions of 3-acetamidoquinoline 1-oxide (1e) gave only 2-substituted products in consistently rather low yields. While the reaction with TsCl in the presence of 10% K$_2$CO$_3$ gave only 3-acetamido-2-quinolinone (4e), a fair amount of the 2-tosyloxyquinoline (5e) was formed together with 4e and the 2-chloroquinoline (2e) in the reaction in boiling chloroform. The structures of these products were assigned on the basis of elemental analyses and $^1$H-nmr spectra, and the structure of 6 was further confirmed X-ray diffraction study.

Among the above-mentioned reactions, the exclusive formation of 4-acetoxy-3-methoxyquinoline (6) from 1d and Ac$_2$O is most significant, because the reaction of Ac$_2$O with quinoline 1-oxide having no 2-substituent did not produce 4-substitution products, with one exception of the formation of a minute amount of 6-methoxy-4-quinolinol (0.5%) from 6-methoxyquinoline 1-oxide. The reaction of quinoline 1-oxides with TsCl or PhCOCl, especially in the presence of an alkaline solution, has been efficiently applied to the preparation of 2-quinolinones, but some other products have been isolated in some cases. In fact, while the reaction with PhCOCl provided only the corresponding 2-quinolinones (4a,b,c,e) apart from the resinification in the case of 1d, the reaction with TsCl gave rise to other products in all cases. Thus, 2-tosyloxyquinolines (5c and 5e) were formed in reactions of 1c and 1e, and the deoxygenative chlorination occurred in reactions of 1a, 1b, 1d, and 1e. The formation of 2-acyloxyquinolines from quinoline 1-oxides and acylating agents has been previously observed in reactions of 6-methoxy-, 6-acetamido- and 4-methylquinoline 1-oxides with TsCl or PhCOCl in the presence of bases, and electron-donating substituent seems to promote this type of reactions but its essential features are not yet clear. The deoxygenative chlorination by means of TsCl has been also described in a few cases. However, it is very noticeable that the reaction of the 1a with TsCl afforded exclusively the 2-chloroquinoline (2a) independently of the presence or absence of K$_2$CO$_3$ solution. We obtained the quinolylquinolinone (7) only from the reaction of 1b.
with \( \text{Ac}_2\text{O} \); similar quinolylquinolinones were shown to be given also from reactions of some quinoline 1-oxides with TsCl and PhCOCl.\(^3\,4\)

**EXPERIMENTAL**

All melting points are uncorrected.\(^1\)\(\text{H-Nmr} \) spectra were recorded on a Hitachi R8-24 spectrometer using tetramethylsilane as an internal standard. X-Ray diffraction data were obtained from a Enraf-Nonius CAD 4 diffractometer.

**Reaction with \( \text{POCl}_3 \)** — A solution of la-e (2 g) in \( \text{POCl}_3 \) (10 ml) was heated at 90°C for 1 h. Excess \( \text{POCl}_3 \) was distilled off, and the residue was poured into \( \text{H}_2\text{O} \), neutralized with 10% \( \text{K}_2\text{CO}_3 \) and extracted with \( \text{CHCl}_3 \). The residue from the \( \text{CHCl}_3 \) extract was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

**Reaction with \( \text{Ac}_2\text{O} \)** — A solution of la-e (2 g) in \( \text{Ac}_2\text{O} \) (10 ml) was heated at reflux for 2 h. Excess \( \text{Ac}_2\text{O} \) was evaporated under reduced pressure, and the residue was poured into \( \text{H}_2\text{O} \), neutralized with 10% \( \text{K}_2\text{CO}_3 \) and extracted with \( \text{CHCl}_3 \). The residue from the \( \text{CHCl}_3 \) extract was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

**4-Acetoxy-3-methoxyquinoline (6)** — A solution of 1d (2 g) in \( \text{Ac}_2\text{O} \) (10 ml) was heated at reflux for 2 h, and then excess \( \text{Ac}_2\text{O} \) was evaporated under reduced pressure and the residue was dissolved in \( \text{CHCl}_3 \). The \( \text{CHCl}_3 \) solution was washed successively with aq.\( \text{NaHCO}_3 \) and \( \text{H}_2\text{O} \). The residue from the \( \text{CHCl}_3 \) solution was recrystallized from \( \text{CHCl}_3 \)-ether to give 17 g (69%) of 6, colorless needles, mp 115-116°C. Anal. Calcd for \( \text{C}_{14}\text{H}_{11}\text{NO}_3 \): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.34; H, 5.07; N, 6.41.

\(^1\)\(\text{H-Nmr} \) (\( \text{CDCl}_3 \)) \( \delta \): 2.47 (3H, s, COCH\(_3\)), 4.00 (3H, s, OCH\(_3\)), 7.31-8.12 (4H, m, H\(_{5-8}\)), 8.80 (1H, s, H\(_2\)).

To a solution of 6 (1.65 g) in \( \text{MeOH} \) (40 ml) was added 10% \( \text{K}_2\text{CO}_3 \) (10 ml), and the whole was stirred at room temperature for 1 h and then treated with anhydrous resin amberlyst. The solvent was evaporated and the residue was recrystallized from \( \text{CHCl}_3 \)-MeOH to give 1.3 g (65%) of 3-methoxy-4-quinolinone (8), colorless granules, mp 151-152°C. Anal. Calcd for \( \text{C}_{10}\text{H}_9\text{NO}_2 \): C, 68.17; H, 5.15; N, 7.95. Found: C, 68.35; H, 5.01; N, 8.20. \(^1\)\(\text{H-Nmr} \) (\( \text{CDCl}_3 \)) \( \delta \): 3.80 (1H, s, OCH\(_3\)), 7.15-7.95 (4H, m, H\(_{5-8}\)), 8.30-8.55 (1H, dd, J=1.5 and 8.0 Hz, H\(_2\)), 11.70 (1H, br s, NH).
Reaction with TsCl-10% K₂CO₃ — A solution of la-e (2 g) and TsCl (2.06-2.80 g, 1.2 equiv.) in CHCl₃ (40 ml) was stirred with 10% K₂CO₃ (40 ml) at room temperature for 3 h. The CHCl₃ layer was separated, washed with H₂O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

Reaction with TsCl — A solution of la-e (2 g) and TsCl (2.06-2.80 g, 1.2 equiv.) in CHCl₃ (40 ml) was heated at reflux for 1 h. The reaction mixture was washed with H₂O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

Reaction with PhCOCl-10% K₂CO₃ — A solution of la-e (2 g) and PhCOCl (1.52-2.19 g, 1.2 equiv.) in CHCl₃ (40 ml) was stirred with 10% K₂CO₃ (40 ml) at room temperature for 3 h. The precipitate was filtered off, and the CHCl₃ layer was washed with H₂O and concentrated. The residue was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

2-Chloroquinolines

2a (Runs 1, 3 and 4): Colorless needles, mp 83-84°C (hexane). Anal. Calcd for C₉H₅NFCl: C, 59.53; H, 2.78; N, 7.71. Found: C, 59.50; H, 2.62; N, 7.71. ¹H-Nmr (CDCl₃) 6: 7.40-8.05 (5H, m, H₄-8).

2b (Runs 6, 8 and 9): Colorless needles, mp 91-92°C (hexane). Anal. Calcd for C₉H₅NBrCl: C, 44.58; H, 2.08; N, 5.78. Found: C, 44.87; H, 2.03; N, 5.68. ¹H-Nmr (CDCl₃) 6: 7.30-8.01 (4H, m, H₅-8), 8.28 (1H, s, H₄).

2clf (Run 11): Colorless scales, mp 80-81°C (hexane). Anal. Calcd for C₁₀H₈NC1: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.86; H, 4.43; N, 7.85. ¹H-Nmr (CDCl₃) 6: 2.43 (3H, s, CH₃), 7.20-8.00 (5H, m, H₄-8).

2d (Runs 16, 18 and 19): Colorless needles, mp 80-81°C (hexane). Anal. Calcd for C₁₀H₈NC1: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.23; H, 4.09; N, 7.25. ¹H-Nmr (CDCl₃) 6: 3.95 (3H, s, OCH₃), 7.30-8.10 (5H, m, H₄-8).

2e (Runs 21 and 24): Orange needles, mp 168-169°C (EtOH). Anal. Calcd for C₁₁H₉N₂OCl: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.94; H, 4.07; N, 12.60. ¹H-Nmr (CDCl₃) 6: 2.30 (3H, s, COCH₃), 7.10-7.90 (5H, m, H₅-8, NHAc), 8.91 (1H, s, H₄).

4-Chloroquinolines

3c² (Run 11): Colorless needles, mp 52-53°C (hexane). Anal. Calcd for C₁₀H₈NC1:
C, 67.62; H, 4.54; N, 7.89. Found: C, 67.66; H, 4.44; N, 7.85.

\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
2.50 (3H, s, CH₃), 7.40 (4H, m, H₅₋₈), 8.61 (1H, s, H₂).

**3d** (Runs 16, 18 and 19): Colorless needles, mp 73-74°C (hexane). Anal. Calcd for C₁₀H₈NOCl: C, 63.03; H, 4.16; N, 7.23. Found: C, 62.15; H, 4.06; N, 7.10.

\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
4.10 (3H, s, OCH₃), 7.40-8.25 (4H, m, H₅₋₈), 8.75 (1H, s, H₂).

**2-Quinolinones**


\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
6.99-7.85 (5H, m, H₄₋₈), 12.31 (1H, br s, NH).

**4b** (Runs 7, 8, 9 and 10): Colorless prisms, mp 250-251°C (CHCl₃-MeOH). Anal. Calcd for C₁₀H₉NOBr: C, 48.25; H, 2.70; N, 6.36. Found: C, 48.27; H, 2.61; N, 6.36.

\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
6.95-7.65 (4H, m, H₅₋₈), 8.25 (1H, s, H₄), 12.25 (1H, br s, NH).

**4c** (Runs 12, 13, 14 and 15): Yellow needles, mp 240-242°C (CHCl₃). Anal. Calcd for C₁₀H₉NO: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.55; H, 5.70; N, 8.75.

\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
2.14 (3H, s, CH₃), 6.90-7.73 (5H, m, H₄₋₈), 12.10 (1H, br s, NH).

**4d** (Runs 18 and 19): Colorless needles, mp 189-190°C (CHCl₃-MeOH). Anal. Calcd for C₁₀H₉N₃O₂: C, 68.15; H, 5.15; N, 7.95. Found: C, 68.68; H, 5.04; N, 8.01.

\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
3.83 (3H, s, CH₃), 6.95-7.60 (5H, m, H₄₋₈), 12.02 (1H, br s, NH).


\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
2.17 (3H, s, COCH₃), 6.95-7.65 (5H, m, H₄₋₈), 9.30 (1H, br s, NHAc), 12.15 (1H, br s, NH).

**2-Tosyloxyquinolines**

**5c** (Run 14): Colorless needles, mp 193-195°C (MeOH-ether). \( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
2.30 (3H, s, J=8.0 Hz, Ph-H₂,3,5,6), 7.93-8.60 (4H, m, H₅₋₈), 9.37 (1H, s, H₄).

**5e** (Run 24): Colorless needles, mp 157-158°C (MeOH-ether). \( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
2.24 (3H, s, CH₃), 2.27 (3H, s, CH₃-Ph-), 6.96-7.37 (4H, ABq, J=8.0 Hz, Ph-H₂,3,5,6), 7.55-8.45 (4H, m, H₅₋₈), 9.60 (1H, s, H₄), 10.15 (1H, br s, NHAc).

**Quinolyquinolinone**


\( ^1H\-N\text{mr} (\text{CDCl}_3) \delta: 
7.20-8.35 (9H, m, Ar-H), 8.65 (1H, s, H₄).
REFERENCES


Received, 7th June, 1991