

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

Yutaka Miura,* Sakae Takaku, Yoshiharu Nawata, and
Masatomo Hamana

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

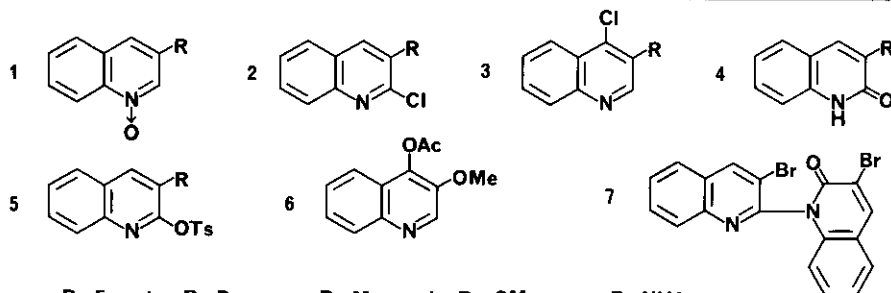
Abstract — Reactions of 3-fluoro- (**1a**), 3-bromo- (**1b**), 3-methyl- (**1c**), 3-methoxy- (**1d**) and 3-acetamidoquinoline 1-oxides (**1e**) with acylating agents (POCl_3 , Ac_2O , TsCl and PhCOCl) were examined (Table). While only 2-substituted quinolines were obtained from **1a** and **1b**, fair amounts of 4-substituted products were formed in reactions of **1d**, the sole formation of the 4-acetoxyquinoline (**6**) with Ac_2O 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-aminoquinoline 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-aminoquinolines. 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 (POCl_3), acetic anhydride (Ac_2O), 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) POCl_3 , 90°C , 1 h; 2) Ac_2O , reflux, 2 h;
3) TsCl-CHCl_3 , 10% K_2CO_3 , room temperature, 3 h; 4) TsCl , CHCl_3 ,
reflux, 1 h; 5) PhCOCl-CHCl_3 , 10% K_2CO_3 , room temperature, 3 h

Run	1	Reaction	2-Substituted Product (%)	4-Substituted Product (%)	Other
1		1)	2a (83)	---	
2	1a (R=F)	2)	4a (70)	---	
3		3)	2a (49)	---	
4		4)	2a (54)	---	
5		5)	4a (48)	---	
6	1b (R=Br)	1)	2b (78)	---	
7		2)	4b (10)	---	7 (42)
8		3)	2b (18), 4b (36)	---	
9		4)	2b (51), 4b (20)	---	
10		5)	4b (58)	---	
11	1c (R=Me)	1)	2c (31)	3c (34)	
12		2)	4c (55)	---	
13		3)	4c (50)	---	
14		4)	4c (20), 5c (19)	---	
15		5)	4c (55)	---	
16	1d (R=OMe)	1)	2d (43)	3d (23)	
17		2)	---	6 (65)	
18		3)	2d (45), 4d (20)	3d (30)	
19		4)	2d (25), 4d (17)	3d (21)	
20		5)	---	---	
21	1e (R=NHAc)	1)	2e (16)	---	
22		2)	4e (29)	---	
23		3)	4e (40)	---	
24		4)	2e (18), 4e (25) 5e (37)	---	
25)		5)	4e (23)	---	



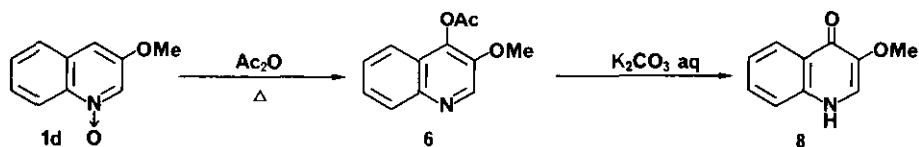
a: R=F, b: R=Br, c: R=Me, d: R=OMe, e: R=NHAc

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 POCl_3 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 (K_2CO_3), 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^{1a} reported that 3-bromo-2-quinolinone (**4b**) was formed in 70% yield upon heating **1b** with Ac_2O at 130–140°C in a sealed tube, heating **1b** at reflux with Ac_2O for 2 h resulted in the formation of **4b** in a small yield of 10% with a major formation of *N*-(3-bromo-2-quinoly1)-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 POCl_3 ,^{1f} we obtained practically the same amounts of **2c** (31%) and the 4-chloro isomer² (**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% K_2CO_3 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 POCl_3 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 Ac_2O . Treatment of **6** with K_2CO_3 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_2CO_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 ^1H -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_2O is most significant, because the reaction of Ac_2O 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.³ 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.³⁻⁶ 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-,³ 6-acetamido-³ and 4-methylquinoline 1-oxides⁵ 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.^{3,4,6} 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_2CO_3 solution. We obtained the quinolylquinolinone (**7**) only from the reaction of **1b**

with Ac_2O ; 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. ^1H -Nmr spectra were recorded on a Hitachi RB-24 spectrometer using tetramethylsilane as an internal standard. X-Ray diffraction data were obtained from a Enraf-Nonius CAD 4 diffractometer.

Reaction with POCl_3 —A solution of **1a-e** (2 g) in POCl_3 (10 ml) was heated at 90°C for 1 h. Excess POCl_3 was distilled off, and the residue was poured into H_2O , neutralized with 10% K_2CO_3 and extracted with CHCl_3 . The residue from the CHCl_3 extract was chromatographed on silica gel column, and the products were recrystallized from appropriate solvents.

Reaction with Ac_2O —A solution of **1a-e** (2 g) in Ac_2O (10 ml) was heated at reflux for 2 h. Excess Ac_2O was evaporated under reduced pressure, and the residue was poured into H_2O , neutralized with 10% K_2CO_3 and extracted with CHCl_3 . The residue from the 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 Ac_2O (10 ml) was heated at reflux for 2 h, and then excess Ac_2O was evaporated under reduced pressure and the residue was dissolved in CHCl_3 . The CHCl_3 solution was washed successively with aq. NaHCO_3 and H_2O . The residue from the CHCl_3 solution was recrystallized from CHCl_3 -ether to give 17 g (69%) of **6**, colorless needles, mp 115 – 116°C . Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.34; H, 5.07; N, 6.41. ^1H -Nmr (CDCl_3) δ : 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 MeOH (40 ml) was added 10% K_2CO_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 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. ^1H -Nmr (CDCl_3) δ : 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 **1a-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 **1a-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 **1a-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) δ: 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) δ: 7.30–8.01 (4H, m, H₅₋₈), 8.28 (1H, s, H₄).

2c^{1f} (Run 11): Colorless scales, mp 80–81°C (hexane). Anal. Calcd for C₁₀H₈NCl: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.86; H, 4.43; N, 7.85. ¹H-Nmr (CDCl₃) δ: 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 C₁₀H₈NCl: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.23; H, 4.09; N, 7.25. ¹H-Nmr (CDCl₃) δ: 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) δ: 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 C₁₀H₈NCl:

C, 67.62; H, 4.54; N, 7.89. Found: C, 67.66; H, 4.44; N, 7.85. $^1\text{H-Nmr}$ (CDCl_3) δ : 2.50 (3H, s, CH_3), 7.40 (4H, m, H_{5-8}), 8.61 (1H, s, H_2).

3d (Runs 16, 18 and 19): Colorless needles, mp 73–74°C (hexane). Anal. Calcd for $\text{C}_{10}\text{H}_8\text{NOCl}$: C, 63.03; H, 4.16; N, 7.23. Found: C, 62.15; H, 4.06; N, 7.10. $^1\text{H-Nmr}$ (CDCl_3) δ : 4.10 (3H, s, OCH_3), 7.40–8.25 (4H, m, H_{5-8}), 8.75 (1H, s, H_2).

2-Quinolinones

4a (Runs 2 and 5): Colorless needles, mp 244°C (CHCl_3 -MeOH). Anal. Calcd for $\text{C}_9\text{H}_6\text{NOF}$: C, 66.26; H, 3.71; N, 8.59. Found: C, 66.39; H, 3.69; N, 8.56. $^1\text{H-Nmr}$ (CDCl_3) δ : 6.99–7.85 (5H, m, H_{4-8}), 12.31 (1H, br s, NH).

4b^{1a} (Runs 7, 8, 9 and 10): Colorless prisms, mp 250–251°C (CHCl_3 -MeOH). Anal. Calcd for $\text{C}_9\text{H}_6\text{NOBr}$: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.27; H, 2.61; N, 6.36. $^1\text{H-Nmr}$ (CDCl_3) δ : 6.96–7.65 (4H, m, H_{5-8}), 8.25 (1H, s, H_4), 12.25 (1H, br s, NH).

4c (Runs 12, 13, 14 and 15): Yellow needles, mp 240–242°C (CHCl_3). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.55; H, 5.70; N, 8.75. $^1\text{H-Nmr}$ (CDCl_3) δ : 2.14 (3H, s, CH_3), 6.90–7.73 (5H, m, H_{4-8}), 12.10 (1H, br s, NH).

4d (Runs 18 and 19): Colorless needles, mp 189–190°C (CHCl_3 -MeOH). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_2$: C, 68.15; H, 5.15; N, 7.95. Found: C, 68.68; H, 5.04; N, 8.01. $^1\text{H-Nmr}$ (CDCl_3) δ : 3.83 (3H, s, OCH_3), 6.95–7.60 (5H, m, H_{4-8}), 12.02 (1H, br s, NH).

4e (Runs 22, 23, 24 and 25): Colorless crystals, mp 230°C (CHCl_3 -MeOH). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.40; H, 4.83; N, 13.76. $^1\text{H-Nmr}$ (CDCl_3) δ : 2.17 (3H, s, COCH_3), 6.95–7.65 (5H, m, H_{4-8}), 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). $^1\text{H-Nmr}$ (CDCl_3) δ : 2.30 (3H, s, 3-CH_3), 2.70 (3H, s, $\text{CH}_3\text{-Ph-}$), 7.09–7.81 (4H, ABq, $J=8.0$ Hz, $\text{Ph-H}_{2,3,5,6}$), 7.93–8.60 (4H, m, H_{5-8}), 9.37 (1H, s, H_4).

5e (Run 24): Colorless needles, mp 157–158°C (MeOH-ether). $^1\text{H-Nmr}$ (CDCl_3) δ : 2.24 (3H, s, $\text{CH}_3\text{-Ph-}$), 2.27 (3H, s, COCH_3), 6.96–7.37 (4H, ABq, $J=8.0$ Hz, $\text{Ph-H}_{2,3,5,6}$), 7.55–8.45 (4H, m, H_{5-8}), 9.60 (1H, s, H_4), 10.15 (1H, br s, NHAc).

Quinolyquinolinone 7 (Run 7): Brown prisms, mp 249–250°C (CHCl_3 -ether). Anal. Calcd for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{OBr}_2$: C, 50.27; H, 2.34; N, 6.51. Found: C, 50.43; H, 2.29; N, 6.71. $^1\text{H-Nmr}$ (CDCl_3) δ : 7.20–8.35 (9H, m, Ar-H), 8.65 (1H, s, H_4).

REFERENCES

1. a) E. Ochiai and T. Okamoto, Yakugaku Zasshi, 1948, **68**, 88; b) E. Ochiai, C. Kaneko, and J. Inamoto, ibid., 1958, **78**, 584; c) C.E. Kaslow and B. Buchner, J. Org. Chem., 1958, **23**, 271; d) T. Kaufmann and J. Schulz, Chem. Ber., 1966, **99**, 1837; e) Y. Kobayashi, I. Kumadaki, and S. Taguchi, Chem. Pharm. Bull., 1969, **17**, 2335; f) R. E. Lyle, D. E. Portlock, M. J. Kane, and J. A. Bristol, J. Org. Chem., 1972, **37**, 3967.
2. E.A. Steck, L.L. Hallock, and A.J. Holland, J. Am. Chem. Soc., 1946, **68**, 129.
3. M. Hamana and I. Kumadaki, Yakugaku Zasshi, 1966, **86**, 1090.
4. G. Jones and D. J. Baty, "The Chemistry of Heterocyclic Compounds, Vol. 32, Quinoline N-Oxides", ed. by G. Jones, John Willey & Sons Ltd., New York, 1982, pp. 491-492.
5. E. Ochiai, T. Watanabe, and S. Suzuki, Yakugaku Zasshi, 1956, **76**, 1321.
6. M. Hamana and O. Hoshino, Yakugaku Zasshi, 1964, **84**, 34.
7. a) K. Shichiri, K. Funakoshi, and M. Hamana, Chem. Pharm. Bull., 1980, **28**, 424; b) Idem, ibid., 1980, **28**, 493.

Received, 7th June, 1991