Studies on Synthesis of the Antibacterial Agent NM441. II.[1] Selection of a Suitable Base for Alkylation of 1-Substituted Piperazine with 4-(Bromomethyl)-5-methyl-1,3-dioxol-2-one

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Diisopropylamine (DIPA), *N,N*-diisopropylethylamine (DIPEA), tributylamine (TNBA) and 7-(1-piperazinyl)-4-quinolone-3-carboxylic acid (2) were titrated in water–dimethylformamide (DMF) mixtures containing 45—98% DMF. Apparent pK_a values in anhydrous DMF (pK_{DMF}) were calculated by extrapolation from the variation in the half-neutralization pH values in aqueous DMF. The validity of the relative basicity derived from the pK_{DMF}s was confirmed by examination of the kinetics of esterification of a derivative of 2 with 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (DMDO-Br). Relative basicities in DMF were: the carboxylate anion of 2 ≫ DIPA > DIPEA > TNBA > the amino group in the piperazinyl part of 2. This order is clearly different from that observed in water. We concluded that DIPEA is a suitable agent to suppress the undesired esterification during the reaction to mask the amino group of 2 with a DMDO group, because it does not remove a proton from the carboxyl group, but only from the protonated amino group.

Key words 7-(1-piperazinyl)-4-quinolone-3-carboxylic acid; pK_a; alkylation; 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one; dimethylformamide; deprotonation agent

6-Fluoro-1-methyl-7-{4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl}-4-oxo-1*H*,4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylic acid (**1**; NM441) is an effective antibacterial agent. As a prodrug, the amino group in its piperazinyl part is masked by a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (DMDO) group in order to improve oral absorption.[2] This antibacterial agent is obtained from the reaction between 6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**2**) and 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (DMDO-Br) in dimethylformamide (DMF). Previously, we elucidated the structures of impurities generated in this reaction, and studied the kinetics of the formation of **1** and by-products.[1] The main reaction consists of two steps as shown in Chart 1.

The first step is rate-determining, and the kinetics is second-order; first-order in both **2** and DMDO-Br. The equilibrium in the second step is shifted markedly toward the formation of protonated **2**. Protonated **1** generated in the first step rapidly transfers a proton to a molecule of **2** in the second step. The yield of **1** does not exceed about 50% in the absence of another base. Consequently, to obtain **1** in reasonable yield, it is necessary to add a base in order to remove the proton from the protonated **2**.

In the reaction of **2** with DMDO-Br, not only the amino group in the piperazinyl part but also the carboxyl group can be masked by the DMDO group. However, the esterification with DMDO-Br did not readily occur in DMF unless a strong base, such as potassium bicarbonate, was added.[3] To obtain **1** while suppressing the undesired esterification, use of a strong base as a deprotonation agent is undesirable. On the other hand, a nucleophilic deprotonation agent interferes with the reaction by attacking DMDO-Br. Therefore, the base used as a deprotonation agent should have no nucleophilicity toward DMDO-Br, but its basicity should be moderately large.

By using potassium hydrogencarbonate, we have suc-

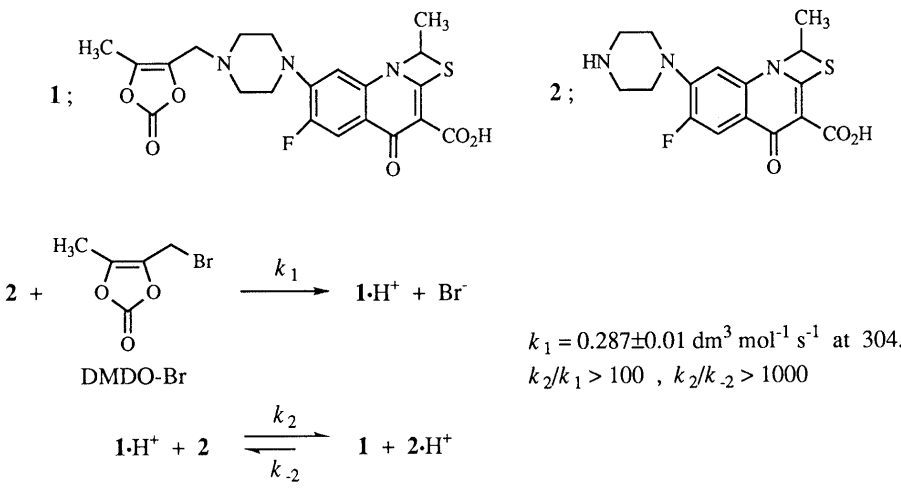

Chart 1

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ceeded in obtaining **1** in reasonable yield.[1] But, potassium hydrogencarbonate has several disadvantages in industrial synthesis. Thus, the base must be milled and added in large excess, and a long time is needed to complete the reaction, because it is poorly soluble in DMF. We therefore examined amines as deprotonation agents in the place of inorganic bases. Diisopropylamine (DIPA), *N*,*N*-diisopropylethylamine (DIPEA) and tributylamine (TNBA) appeared to meet the requirements concerning nucleophilicity and basicity, because they are strong bases in water and their nucleophilicity seems to be depressed by steric hindrance between the unshared electron pair of the nitrogen atom and the large alkyl groups. We studied the usefulness of these amines as deprotonation agents for the title reaction.

Results and Discussion

Relative Nucleophilicity of Amines Nucleophilic reactivities of DIPA, DIPEA and TNBA toward DMDO-Br were studied initially to evaluate the importance of the side reaction between the amines and DMDO-Br. These amines were reacted with DMDO-Br in DMF at 304 K, and the decrease in concentration of DMDO-Br was followed. The pseudo-first-order rate constants were measured, from which second-order rate constants were calculated.

The calculated second-order rate constants are $(2.18 \pm 0.01) \times 10^{-3}$, $(9.12 \pm 0.22) \times 10^{-4}$ and $(4.15 \pm 0.05) \times 10^{-4}$ $dm^3\,mol^{-1}\,s^{-1}$ for TNBA, DIPA and DIPEA, respectively. Since the rate constant for the main reaction of **2** with DMDO-Br is 0.287 ± 0.01 $dm^3\,mol^{-1}\,s^{-1}$ in DMF at 304 K,[1] nucleophilicities of the amines toward DMDO-Br appear to be about 130—690 times smaller than that of **2**. Thus, it has been confirmed that the side reaction need not be taken into consideration in the base-catalysis by these amines.

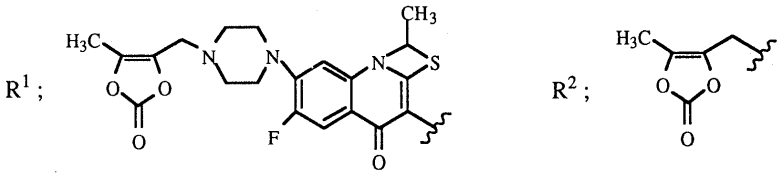
Relative Basicity in Anhydrous DMF As mentioned above, when **2** is reacted with DMDO-Br in DMF, not only alkylation of the amino group but also esterification of the carboxyl group occurred in the presence of a strong base. (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6-fluoro-1-methyl-7-{4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl}-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**3**), which is formed by masking the amino and carboxyl groups of **2** with DMDO groups, is an important by-product in the synthesis of **1**. However, it should be noted that the reaction of **1** or **2** with DMDO-Br in DMF does not afford the ester, **3**, in the absence of a base. Consequently, the mechanism of the formation of **3** in DMF is presumed to be as represented in Chart 2.

A suitable deprotonation agent for the synthesis of **1** would not remove a proton from the carboxyl group, but only from the protonated amino group. Therefore, in order to evaluate the suitability of the above amines, their basicities have to be compared with those of the amino and carboxyl groups of **2**.

DIPA, DIPEA, TNBA and **2** were each dissolved in water–DMF mixtures containing 45—98% DMF, and the solutions were titrated with perchloric acid or sodium hydroxide at 298 K. The pHs at the half equivalence point were measured with a glass electrode (Figs. 1, 2). The assignment of half-neutralization pH for the amino and carboxyl groups of **2** was done by comparison with similar titration of other carboxylic acids, such as acetic acid, in aqueous DMF.

The plots experimentally obtained revealed an apparently linear relationship between the half-neutralization pH and DMF content under all the conditions studied. Figure 3 shows pK_as in water and apparent pK_as in anhydrous DMF, pK_{DMF}s, obtained by extrapolation of data illustrated in Figs. 1 and 2 to 100% DMF content.

Interestingly, several of the lines cross each other, *e.g.*, those for DIPA and DIPEA, and for the amino and carboxyl groups of **2**. Consequently, the order of pK_as in water and DMF is reversed. It is also noteworthy that the carboxyl group (an acid) and the amino moiety (a base) show opposite changes with the change in DMF content in water. There are several reports on reversed pK_a in aqueous and organic solvents and the phenomenon has been interpreted in terms of different solvation modes of water and organic molecules toward the ions.[5] The effect of steric hindrance on the solvation becomes greater in DMF because of the difference in the molecular size of DMF and water. Consequently, it is considered that the conjugate acid of DIPEA, *i.e.*, the diisopropylethylammonium ion, is not appreciably solvated in DMF and is more unstable than that of DIPA, because the DIPEA molecule is bulkier than the DIPA molecule. This steric



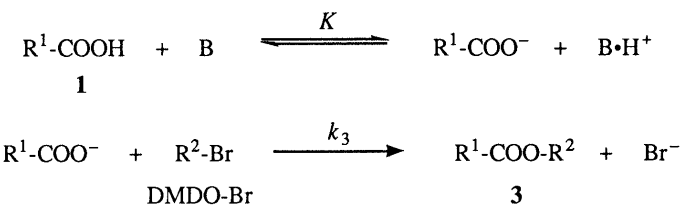


Chart 2

solvent effect is supposed to be responsible for the reversed basicities of DIPA and DIPEA. On the other hand, both the carboxylate anion and proton produced in the dissociation of the carboxyl group are solvated by amphiprotic water, but the negatively charged ion is little solvated and is unstable in a basic solvent such as DMF. Thus the dissociation of the carboxyl group might be depressed by DMF and the acidity might be greatly reduced.

Of course, pK_{DMF} itself may not be identical to the intrinsic basicity of a base in DMF, because the value is affected by many factors such as acidity and basicity of the solvent and liquid junction potentials at the electrode boundaries.[6] However, esterification of **1** by DMDO-Br in the presence of an amine is best explained on the basis of pK_{DMF}, as will be described below. Thus, the orders of basicity in DMF evaluated from kinetic and thermodynamic data show excellent agreement. This result strongly suggests that the relative basicities of the bases in DMF can be evaluated appropriately from the difference in pK_{DMF}.

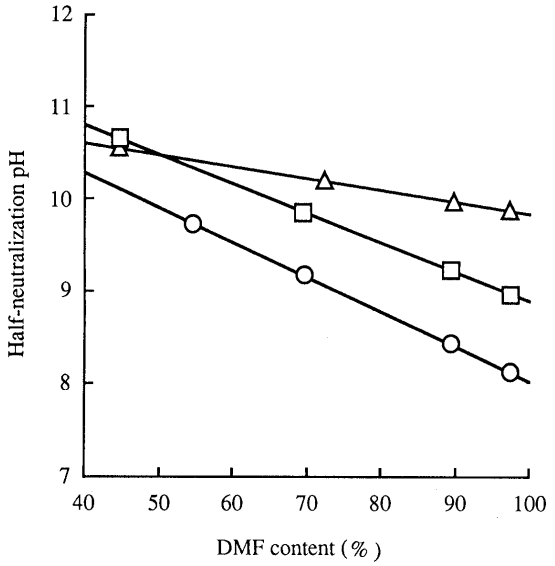


Fig. 1. Plots of Half-Neutralization pH *vs.* DMF Content for TNBA, DIPEA and DIPA

○, TNBA; □, DIPEA; △, DIPA.

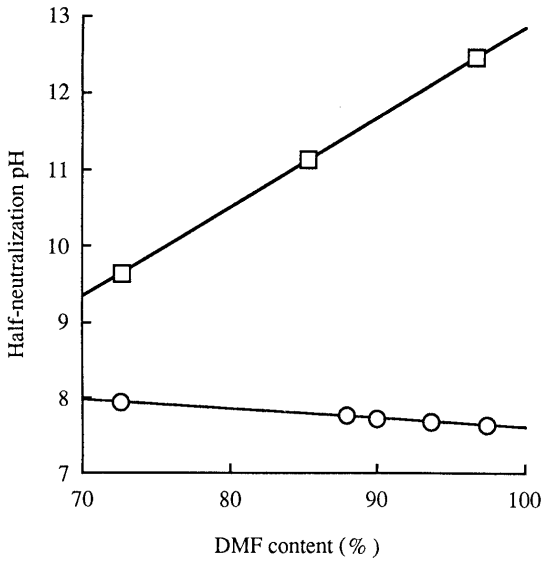


Fig. 2. Plots of Half-Neutralization pH *vs.* DMF Content for **2**

○, the amino group in the piperazinyl moiety; □, the carboxyl group.

Reaction between 2 and DMDO-Br in the Presence of Amine As mentioned above, in the reaction between **2** and DMDO-Br shown in Chart 1, the first step is a simple bimolecular reaction, which is rate-determining. In the presence of an ideal deprotonation agent, which removes a proton only from the protonated amino group of **1** before it transfers the proton to **2** but has no nucleophilicity toward DMDO-Br, the reaction rate is given by Eq. 1.

$$\frac{d[\mathbf{1}]}{dt}=-\frac{d[\mathbf{2}]}{dt}=-\frac{d[\text{DMDO-Br}]}{dt}=k_1[\mathbf{2}][\text{DMDO-Br}] \quad (1)$$

Integration of Eq. 1 affords

$$\frac{1}{b-1}\ln\frac{b-x}{b(1-x)}=[\mathbf{2}]_0k_1t \quad (2)$$

where x is the proportion of consumed **2**, $1-[\mathbf{2}]/[\mathbf{2}]_0$, and b stands for $[\text{DMDO-Br}]_0/[\mathbf{2}]_0$.

By using DIPA, DIPEA and TNBA as the deprotonation agents, **2** was reacted with DMDO-Br in DMF at 304 K. The conversion ratio, x, calculated from the concentrations of **2** obtained experimentally, and the proportion of **3** formed in these reaction are plotted in Fig. 4.

The solid lines calculated from Eq. 2 show that the present reactions proceed with ideal deprotonation characteristics, in practical terms. The experimental x values for DIPA and DIPEA are situated approximately on the lines, but those for TNBA are located somewhat below. Since the difference in pK_{DMF}s of TNBA and the amino group of **2** is about 0.4, the base strength of TNBA

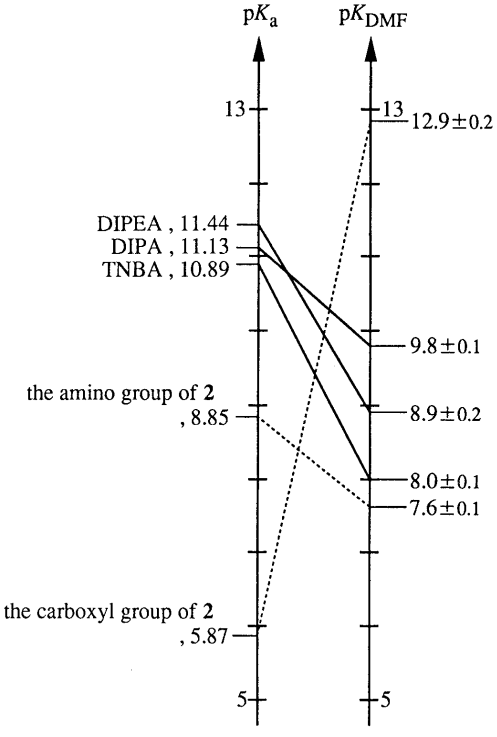


Fig. 3. pK_a Values in Water and Apparent pK_a Values in Anhydrous DMF, pK_{DMF}, at 298 K

The pK_a values of DIPA and TNBA are taken from ref. 4, and that of DIPEA was determined by the potentiometric method.

seems to be insufficient to remove the proton in comparison with DIPA and DIPEA. Consequently, it is suggested that incomplete deprotonation is responsible for the deviation of the points for TNBA from the ideal line. The proportion of **3** in the product increases appreciably in the order of DIPA > DIPEA > TNBA. If the mechanism of the formation of **3** is as represented by Chart 2, this result can be also readily understood from pK_{DMF}s.

It has become apparent that DMF reverses the basicities of the carboxyl group and the amino moiety, and favors the selective alkylation of the aminocarboxylic acid by suppressing esterification. In choosing a base-catalyst, it is important to note that basicities in organic solution are different from those in aqueous solution even in case of similar amines. This observation is of interest in relation to the relative acidities and/or basicities of functional groups in enzymes, where the environment is expected to be hydrophobic.[7]

Esterification of 1 with DMDO-Br Substrate **1** was reacted with DMDO-Br in DMF at 298 K in the presence of DIPEA. Esterification was followed by observing the increase in concentration of **3**. The measured reaction rate constant, $k_{3,obsd}$, is based on the stoichiometric concentration of the carboxyl group of **1**, [**1**].

$$r = k_{3,obsd}[\mathbf{1}][\text{DMDO-Br}] \quad (3)$$

Table 1 lists the $k_{3,obsd}$ values at various initial concentrations of **1** and DIPEA.

The rate constant, $k_{3,obsd}$, does not appear as a constant under the conditions employed. Assuming bimolecular reaction between carboxylate anion of **1**, R^1-COO^-, and DMDO-Br, we obtain Eq. 4.

$$r = k_3[R^1\text{-}COO^-][\text{DMDO-Br}] \quad (4)$$

The initial concentration of R^1-COO^- can be expressed by Eq. 5 with the equilibrium constant, K, defined by Eq. 6.

$$[R^1\text{-}COO^-] = \frac{K([B]_0+[\mathbf{1}]_0) - \sqrt{K^2([B]_0+[\mathbf{1}]_0)^2 - 4(K-1)K[B]_0[\mathbf{1}]_0}}{2(K-1)} \quad (5)$$

$$K = \frac{[R^1\text{-}COO^-][B\cdot H^+]}{[\mathbf{1}][B]} \quad (6)$$

Finally, we obtain Eq. 7 for true rate constant, k_3.

$$k_3 = \frac{k_{3,obsd}[\mathbf{1}]}{\dfrac{K([B]_0+[\mathbf{1}]_0) - \sqrt{K^2([B]_0+[\mathbf{1}]_0)^2 - 4(K-1)K[B]_0[\mathbf{1}]_0}}{2(K-1)}} \quad (7)$$

Since the basicity of the carboxylate anion of **1** can be assumed to be the same as that of **2**, the equilibrium constant, K, between the carboxyl group of **1** and DIPEA in DMF can be calculated from the difference in pK_{DMF}s of the carboxylate anion of **2** and DIPEA to be about $10^{-4.0}$, or $-\log K \approx 4.0$. The true rate constant, k_3, calculated based on this equilibrium constant appears to be essentially constant, as shown in Table 1.

Likewise, **1** was reacted with DMDO-Br in the presence of DIPA or TNBA. On the basis of k_3 determined for DIPEA, the $-\log K$s for the amines were calculated and the values are given in Table 2.

The differences in pK_{DMF}s of the carboxylate anion of **2** and DIPA or TNBA are about 3.1 or 4.9, respectively. These values are in good agreement with the $-\log K$s listed in Table 2, which confirms the validity of the proposed mechanism shown in Chart 2 and Eq. 7.

Conclusion

The relative basicities in DMF have been found to be in the following order: the carboxylate anion of **2** ≫ DIPA > DIPEA > TNBA > the amino group in the piperazinyl part of **2**. This is clearly different from that observed in aqueous solution, where the order is DIPEA ≈ DIPA ≈ TNBA ≫ the amino group of **2** ≫ the carboxylate anion of **2**. As the relative basicity in DMF suggests, TNBA did not cause the undesired **3** to be formed, but the main reaction did not go to completion. DIPA has a satisfactory deprotonation ability, but accelerated the undesired esterification. Therefore, of the amines studied, DIPEA is the most suitable base in the reaction to mask the amino group of **2** with a DMDO group, because its basicity in

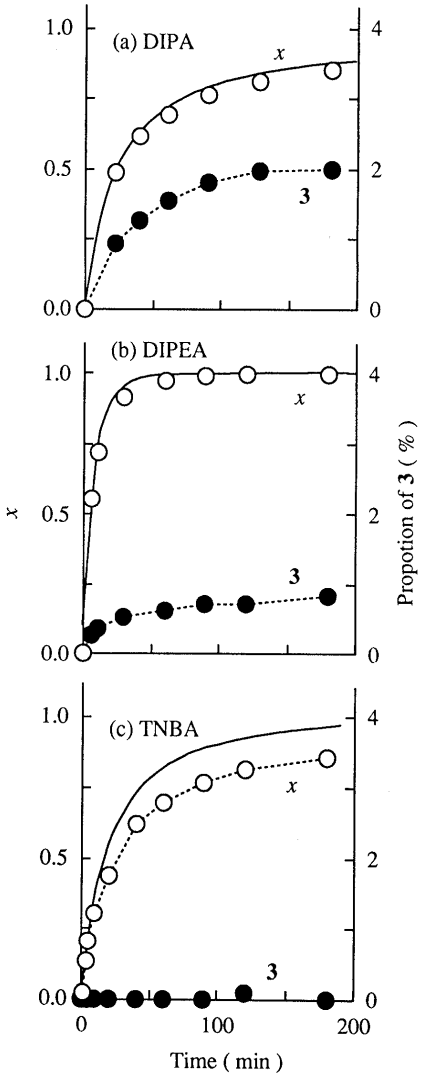


Fig. 4. Plots of the Conversion Ratio of **2**, x, and the Proportion of **3** in the Product *vs.* Time for the Reaction of **2** with DMDO-Br in the Presence of Amines

The proportion of **3** was determined by HPLC. (a) $[\mathbf{2}]_0 = 2.63 \times 10^{-3}$ mol d m^{-3}, $b = 0.966$, $[\text{DIPA}]_0/[\mathbf{2}]_0 = 1.17$. (b) $[\mathbf{2}]_0 = 8.22 \times 10^{-3}$ mol d m^{-3}, $b = 1.46$, $[\text{DIPEA}]_0/[\mathbf{2}]_0 = 1.21$. (c) $[\mathbf{2}]_0 = 2.71 \times 10^{-3}$ mol d m^{-3}, $b = 1.19$, $[\text{TNBA}]_0/[\mathbf{2}]_0 = 1.15$. ○, the experimental values of x; solid line, the calculated values of x; ●, the proportion of **3** in the product.

Table 1. Observed Rate Constants, $k_{3,obsd}$, and Calculated Rate Constants, k_3, for the Esterification of **1** with DMDO-Br in DMF at 298 K[a]

$[\mathbf{1}]_0 \times 10^2$ (mol dm^{-3})	$[DIPEA]_0 \times 10^2$ (mol dm^{-3})	$k_{3,obsd} \times 10^3$ (dm^3 mol^{-1} s^{-1})	$k_3 \times 10^{2}$[b] (dm^3 mol^{-1} s^{-1})
2.00	4.01	1.11 ±0.06	8.0±0.4
5.00	3.99	0.714±0.050	8.1±0.6
2.00	10.0	1.80 ±0.09	8.2±0.4

a) $[DMDO\text{-}Br]_0 = 1.01 \times 10^{-2}$ mol dm^{-3}. *b*) k_3 values were calculated from Eq. 7 with $-\log K = 4.0$.

Table 2. Observed Rate Constants, $k_{3,obsd}$, and Calculated Equilibrium Constants, K, for the Esterification of **1** with DMDO-Br in DMF at 298 K[a]

Amine	$[\mathbf{1}]_0 \times 10^2$ (mol dm^{-3})	$[Amine]_0 \times 10^2$ (mol dm^{-3})	$k_{3,obsd} \times 10^3$ (dm^3 mol^{-1} s^{-1})	$-\log K$[b]
DIPA	1.00	1.00	2.74 ±0.40	2.9±0.1
TNBA	2.00	8.61	0.442±0.030	5.2±0.1

a) $[DMDO\text{-}Br]_0 = 1.01 \times 10^{-2}$ mol dm^{-3}. *b*) K values were calculated from Eq. 7 as $k_3 = 8.1 \times 10^{-2}$ dm^3 mol^{-1} min^{-1}.

Table 3. Typical Composition of the Reaction Products

Base	Time (h)	Molar ratio	Products, yield/%[b]			
		2[a]: DMDO-Br: Base	**1**	**2**	**3**	Others
$KHCO_3$	3	1.00: 1.22: 2.32	89.9	0.9	1.6	7.6
DIPEA	1	1.00: 1.16: 1.14	93.7	1.0	0.8	4.5

a) $[\mathbf{2}]_0 = 0.309$ mol dm^{-3}. *b*) Analyzed by HPLC.

DMF occupies a moderate position between those of the amino and carboxyl groups of **2**. The yields of products from the reaction of **2** and DMDO-Br in the presence of DIPEA are given in Table 3. It is clear that a superior yield can be obtained by using DIPEA.

Experimental

Materials 6-Fluoro-1-methyl-7-{4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl}-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**1**), 6-fluoro-1-methyl-7-(1-piperazinyl)-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**2**), and DMDO-Br were prepared as described previously.[2,3b]

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6-Fluoro-1-methyl-7-{4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl}-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (3) DMDO-Br (1.15 g, 5.96 mmol) was added dropwise at room temperature to a DMF suspension (60 ml) of **1** (1.83 g, 3.97 mmol) and K_2CO_3 (1.10 g, 7.96 mmol). The reaction mixture was stirred at 313 K for 3 h, then filtered, and the filtrate was concentrated under reduced pressure until 50 ml of DMF had been collected. Acetonitrile (30 ml) was added to the DMF suspension. The resulting precipitate was collected by filtration and dried in a desiccator to yield a crude solid. The solid was dissolved in CH_2Cl_2 (123 ml) at 303 K, and the solution was filtered. The filtrate was concentrated until 100 ml of CH_2Cl_2 had been removed. Acetonitrile (15 ml) was then added to the suspension, and the resulting precipitate was collected by filtration and dried in a desiccator to yield a solid (1.63 g, 72%): mp 234—236 °C (dec.); *Anal.* Calcd for $C_{26}H_{24}FN_3O_9S$: C, 54.45; H, 4.22; N, 7.33%; Found: C, 54.35; H, 4.40; N, 7.33%. IR (KBr) 1815, 1727, 1670, 1629, 1610, 1498 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, d, J=7 Hz , 1-CH_3), 2.38 (6H, s, dioxol $CH_3 \times 2$), 2.50—3.87 (8H, m, piperazine), 3.43 (2H, s, dioxol CH_2N), 5.03 (2H, s, dioxol CH_2OCO), 6.10 (1H, q, J=7 Hz, 1-H), 6.30 (1H, d, J=7 Hz, 8-H), 7.71 (1H, d, J=12 Hz, 5-H).

Kinetic Procedures. Reaction between Amine and DMDO-Br DMDO-Br was dissolved in DMF to an appropriate concentration (between 0.01 and 0.015 mol dm^{-3}). TNBA, DIPEA or DIPA, at about a 20-fold molar excess over DMDO-Br, was added at 304 K to the DMDO-Br solution in a flask equipped with a stirrer and thermometer. To measure the concentration of DMDO-Br at appropriate time intervals, aliquots of the solution were pipetted out and diluted with acetonitrile, and the solutions were subjected to HPLC. Analytical conditions will be described below. Pseudo-first-order plots are shown in Fig. 5. The rate constants were calculated from the slopes of the lines.

Reaction between 1 and DMDO-Br Substrate **1** was dissolved in DMF at an appropriate concentration (between 0.01 and 0.05 mol dm^{-3}). DMDO-Br was dissolved separately in DMF. The solution of DMDO-Br and amine were added to the solution of **1**. The concentration of **3** was determined at appropriate time intervals as described for the reaction between amine and DMDO-Br. Data plotted as [**3**] *vs.* time, where [**3**] is the concentration of **3** at the appropriate time, gave a good linear relation. The initial reaction rates were calculated by linear least-squares fitting.

Reaction between 2 and DMDO-Br Substrate **2** was dissolved in DMF at an appropriate concentration (between 2.7×10^{-3} and 8.2×10^{-3} mol dm^{-3}). DMDO-Br was dissolved separately in DMF. The solution of DMDO-Br and amine were added to the solution of **2**. The concentrations of **1** and **2** were determined at appropriate time intervals as described for the reaction between amines and DMDO-Br.

Determination of the Concentrations of DMDO-Br, 1, 2 and 3 The HPLC operating conditions were as follows. Apparatus: an L-6000 system (Hitachi Co., Tokyo, Japan) equipped with a UV detector (L-4200, Hitachi), and an integrated data analyzer (D-2500, Hitachi). Stationary phase: Cosmosil 5C18-AR packed in a 25 cm × 4.6 mm i.d. stainless steel column (Nacalai Tesque, Inc., Kyoto, Japan). Column temperature: 298 K. Detection: UV 220 nm for DMDO-Br, and UV 275 nm for **1**, **2** and **3**. Internal standard: ethyl 4-hydroxybenzoate. Mobile phase: 1 mol dm^{-3} H_3PO_4: 1 mol dm^{-3} sodium 1-pentanesulfonate : water : acetonitrile = 22 : 20.3 : 507 : 1473 (v/v). Flow rate 0.9 ml min^{-1}.

Formation of 1 from 2 and DMDO-Br Using DIPEA DMDO-Cl (2.28 g, 14.5 mmol) was dissolved in 5.5 ml DMF and NaBr (2.94 g, 28.6 mmol) was added to the solution. The reaction mixture was stirred at 303 K for 1 h, then acetone (11 ml) was added and DMDO-Cl was allowed to react with NaBr for 1 h. The reaction solution was filtered and the filtrate was concentrated under reduced pressure to remove the acetone. The solution contained 13.4 mmol of DMDO-Br. Substrate **2** (5.00 g, 11.6 mmol) had previously been suspended in 32 ml of DMF and the solution containing DMDO-Br was added to this suspension. DIPEA (1.76 g, 13.2 mmol) was added dropwise to the reaction solution for

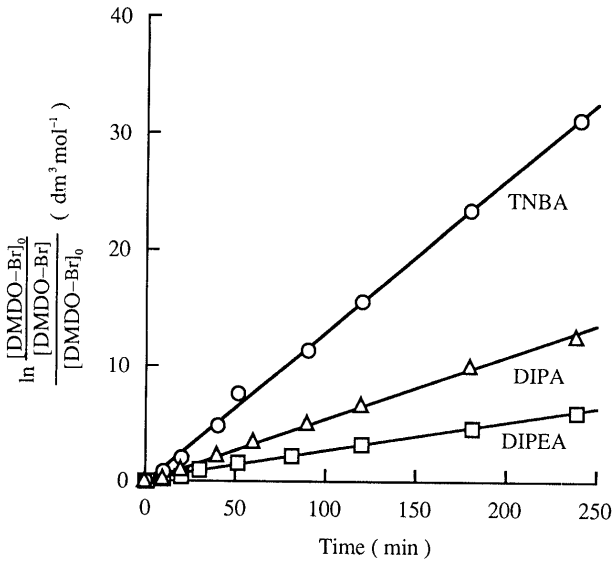


Fig. 5. Plots of $\{\ln([DMDO\text{-}Br]_0/[DMDO\text{-}Br])\}/[DMDO\text{-}Br]_0$ *vs.* Time for the Reaction of Amine with DMDO-Br

○, $[TNBA]_0 = 5.88 \times 10^{-2}$ mol dm^{-3}, $[DMDO\text{-}Br]_0 = 8.36 \times 10^{-3}$ mol dm^{-3}; □, $[DIPEA]_0 = 2.93 \times 10^{-1}$ mol dm^{-3}, $[DMDO\text{-}Br]_0 = 1.48 \times 10^{-2}$ mol dm^{-3}; △, $[DIPA]_0 = 1.94 \times 10^{-1}$ mol dm^{-3}, $[DMDO\text{-}Br]_0 = 9.83 \times 10^{-3}$ mol dm^{-3}.

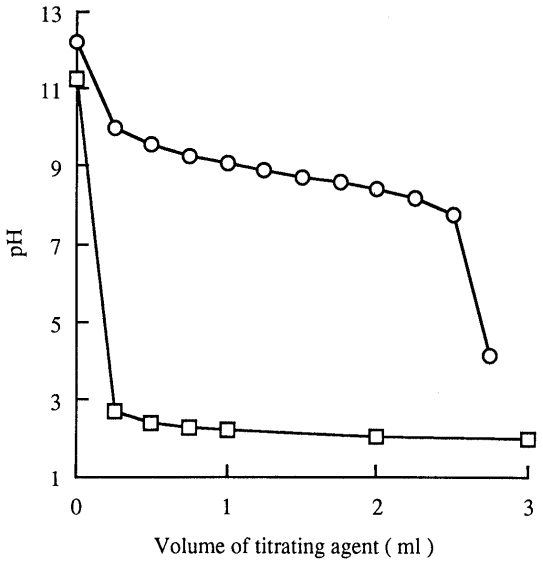


Fig. 6. Typical Titration Curve for Water–DMF Mixture

The titrating agent was 0.2 M $HClO_4$ ($f=1.0478$). The water content was 2.02%. The titration temperature was 298 K. ○, [DIPEA] $=2.83\times10^{-1}$ mol dm^{-3}; □, blank.

10 min. The mixture was stirred at 304 K for 1 h, then poured into ice-water (120 ml). The resulting precipitate was collected by filtration and dried in a desiccator to yield **1** (4.76 g). In order to check the purity of **1**, a portion of the product was dissolved in acetonitrile, and its composition was analyzed by HPLC. The analytical conditions for HPLC were the same as described above.

Measurement of pK_a in Water–DMF Mixtures A pH meter, which consisted of a meter (Toa, HM-5ES) and a composite glass electrode (Toa, No. 201F5328), was calibrated with phosphate and tetraborate standard pH solutions. Distilled water was mixed with DMF, which contained 0.029% water, to obtain mixtures with a water content of 2—55%. A base was dissolved in 100 ml of a water-DMF mixture at an appropriate concentration (between 2.0 and 2.5 mmol dm^{-3}), and the solution was titrated at 298 K. Amines were titrated with 0.2 M perchloric acid. The carboxyl group of **2** was titrated with 0.2 M sodium hydroxide. Figure 6 shows a typical titration curve.

Determination of pK_a of DIPEA in Water pK_a was determined by the potentiometric titration method.[8] The pH meter used was the same as that used in the titration of water–DMF mixtures. DIPEA was dissolved in 200 ml of distilled water at a concentration of 3.83×10^{-3} mol dm^{-3}. The solution was titrated with 0.1 M HCl at 298 K. The pK_a was calculated from the experimental titration curve and the result is given in Table 4.

Table 4. Titration of DIPEA in Water at 298 K

Titrating agent[a] (ml)	pH	[Y] $\times10^3$[b] (mol dm^{-3})	[X] $\times10^3$[c] (mol dm^{-3})	$\frac{[Y]-[X]-[OH^-]}{[X]+[OH^-]}$	pK_a
0	11.33	3.83	0	0.781	11.44
1.0	11.24	3.82	0.498	0.698	11.40
2.0	11.19	3.80	0.991	0.489	11.50
3.0	11.07	3.78	1.48	0.419	11.45
4.0	10.97	3.76	1.96	0.296	11.50
5.0	10.79	3.74	2.44	0.222	11.44
6.0	10.56	3.72	2.92	0.135	11.43
7.0	10.13	3.71	3.38	0.053	11.41
8.0	5.43	3.69	3.85		

a) Aqueous 0.1 M HCl ($f=1.0148$). b) [Y] is the concentration of DIPEA. c) [X] is the concentration of HCl.

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