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Studies on the Oxidation of *N*-Substituted-dibenz[*b*,*f*]azepines. II.[1] Syntheses and Reactions of 5*H*-Dibenz[*b*,*f*]azepine 10,11-Oxides[2]

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The oxidation of various 5*H*-*N*-alkyl-10,11-substituted-dibenz[*b*,*f*]azepines with *m*-chloroperbenzoic acid (*m*-CPBA) was examined. The oxidation of 5*H*-*N*-benzyl-10-substituted-dibenz[*b*,*f*]azepine (V) gave *N*-benzyl-9-formyl-9-substituted-9*H*,10*H*-acridine (VI), while the oxidation of 5*H*-*N*-benzyl-10,11-disubstituted-dibenz[*b*,*f*]azepine (VII) gave the corresponding 10,11-oxide (VIII).

The chemical reactivities with several nucleophiles and the acid-catalyzed reactions of 5*H*-dibenz[*b*,*f*]azepine 10,11-oxides are also discussed.

Keywords——*m*-chloroperbenzoic acid (*m*-CPBA); 5*H*-*N*-alkyl-10,11-dihydro-10,11-disubstituted-dibenz[*b*,*f*]azepine 10,11-oxide; 9-acyl-*N*-alkyl-9,10-dihydro-9-substituted-9*H*,10*H*-acridine; 5*H*-*N*-acyl-10,11-dihydrodibenz[*b*,*f*]azepine 10,11-oxide; oxidation; acidic hydrolysis; rate constant; nucleophilic reaction

We have been studying the influence of the nature of the N-substituted group on the chemical reactivities of 5*H*-dibenz[*b*,*f*]azepines. In the previous paper,[1b] we reported that the oxidation of 5*H*-*N*-acyldibenz[*b*,*f*]azepines (Ia) with *m*-chloroperbenzoic acid (*m*-CPBA) gave 5*H*-*N*-acyldibenz[*b*,*f*]azepine 10,11-oxides (II), while the oxidation of 5*H*-*N*-alkyldibenz[*b*,*f*]azepines (Ib) gave *N*-alkyl-9(10*H*)-acridones (III) and *N*-alkyl-2-formyl-2′-hydroxydiphenylamines (IV) (Chart 1).

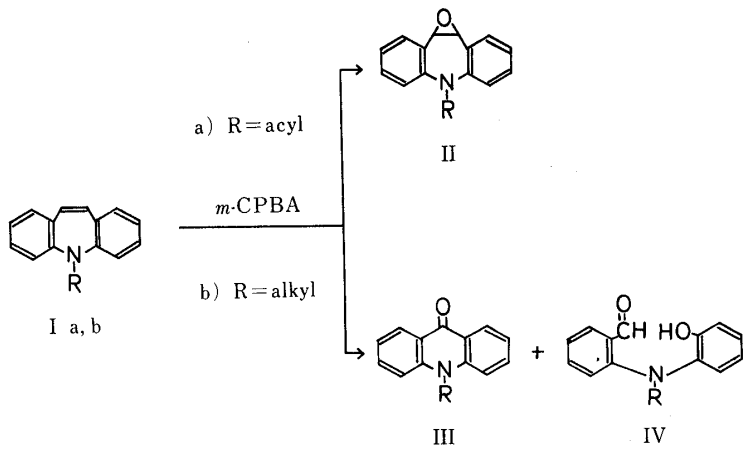
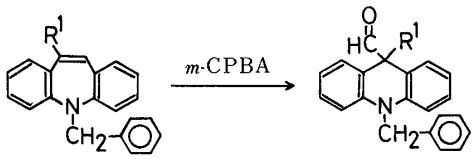


Chart 1

In this paper, we report the results of oxidation of various 5*H*-*N*-alkyl-10 and/or 11-substituted-dibenz[*b*,*f*]azepines with *m*-CPBA and the reactivities of 5*H*-dibenz[*b*,*f*]azepine 10,11-oxides.

Oxidation of Dibenz[*b*,*f*]azepines with *m*-CPBA

First, we studied the oxidation of 5*H*-dibenz[*b*,*f*]azepines having a substituent group at the 10 position. The oxidation of 5*H*-*N*-benzyl-10-substituted-dibenz[*b*,*f*]azepines (Va and Vb) with 1 eq. mol of 85% *m*-CPBA in CH_2Cl_2–saturated aq. $NaHCO_3$ at room temperature afforded *N*-benzyl-9-formyl-9-substituted-9*H*,10*H*-acridines (VIa and VIb), in 63 and 43% yields, respectively. The structures were determined on the basis of instrumental analysis data. Namely, the nuclear magnetic resonance (NMR) spectra of VIa and VIb showed a singlet signal due to the formyl group at about 9.8 ppm, and the infrared (IR) spectra showed the presence of a carbonyl group at about 1720 cm^{-1}. The elemental analyses also supported the structures of VIa and VIb. These formyl-9*H*,10*H*-acridines are a new type of oxidation product which is not obtained by the oxidation of dibenz[*b*,*f*]azepines having no 10-substituent group. Further oxidized products such as acridone and diphenylamine derivatives, which are obtained in the oxidation of 5*H*-dibenz[*b*,*f*]azepines having no 10-substituent group, were not obtained (Chart 2).

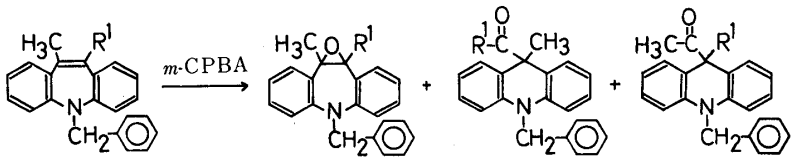


V a, b VI a, b

a: $R^1=CH_3$
b: $R^1=C_6H_5$

Chart 2

Subsequently, we studied the oxidation of 5*H*-dibenz[*b*,*f*]azepines having substituent groups at the 10 and 11 positions. The oxidation of 5*H*-*N*-benzyl-10,11-dimethyldibenz-[*b*,*f*]azepine (VIIa) with *m*-CPBA under the above conditions afforded 5*H*-*N*-benzyl-10,11-dimethyldibenz[*b*,*f*]azepine 10,11-oxide (VIIIa) and 9-acetyl-*N*-benzyl-9-methyl-9*H*,10*H*-acridine (IXa) in 34 and 51% yields, respectively (Chart 3). The structure of VIIIa was determined on the basis of its NMR spectrum (a singlet at 1.77 ppm, 6H, due to 2 methyl groups), IR spectrum (in which the carbonyl group is absent), mass spectrum (MS) (*m*/*e*: 327, M^+), and elemental analysis ($C_{23}H_{21}NO$). This epoxide (VIIIa) is unstable and easily decomposed to IXa. The structure of 9*H*,10*H*-acridine (IXa) was determined on the basis of its NMR spectrum (singlets at 1.69 and 2.07 ppm due to methyl and acetyl groups, respectively), IR spectrum (ν_{max}^{KBr} cm^{-1}: 1710 (C=O)), MS (*m*/*e*: 327, M^+) and elemental analysis ($C_{23}H_{21}NO$). Similarly, the oxidation of 5*H*-*N*-benzyl-10-methyl-11-phenyldibenz[*b*,*f*]azepine (VIIb) afforded 5*H*-*N*-benzyl-10-methyl-11-phenyldibenz[*b*,*f*]azepine 10,11-oxide (VIIIb), *N*-benzyl-9-benzoyl-9-methyl-9*H*,10*H*-acridine (IXb) and 9-acetyl-*N*-benzyl-9-phenyl-9*H*,10*H*-acridine (Xb) in 56, 2 and 12% yields, respectively.



VIIa, b VIIIa, b IXa, b Xb

a: $R^1=CH_3$
b: $R^1=C_6H_5$

Chart 3

Thus, the oxidation of 5*H*-*N*-alkyl-10,11-disubstituted-dibenz[*b*,*f*]azepines afforded the corresponding epoxides, which were not obtained by the oxidation of 5*H*-*N*-alkyldibenz-[*b*,*f*]azepines having or not having a substituent group at the 10 position.

Mechanism of the Oxidation with *m*-CPBA

Since the epoxides (VIIIa and VIIIb) were obtained by the oxidation of VIIa and VIIb having substituent groups at the 10 and 11 positions, it became clear that 5*H*-*N*-alkyl-dibenz[*b*,*f*]azepines were at first oxidized at the 10,11-double bond to form epoxides, as is the case with 5*H*-*N*-acyldibenz[*b*,*f*]azepines (Chart 4).

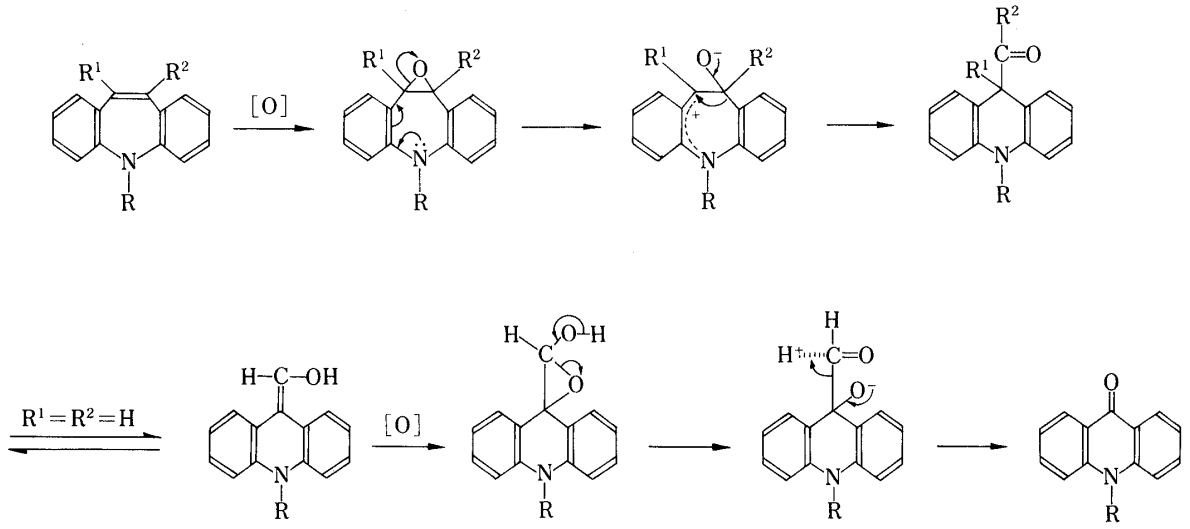


Chart 4

In the case of 5*H*-*N*-alkyldibenz[*b*,*f*]azepines which have no substituent groups at the 10 and 11 positions, or which have a substituent group at the 10 position, the epoxide was not formed, but ring contracted 9*H*,10*H*-acridine derivatives (III, VIa and VIb) were obtained.[1b)]

In the absence of a substituent group at the 10,11-double bond, it is presumed that *N*-alkyl-9-formyl-9*H*,10*H*-acridine isomerized from keto form to enol form, and that the latter was further oxidized to *N*-alkyl-9(10*H*)-acridone (III).

It is presumed that the oxirane ring of 5*H*-*N*-acyldibenz[*b*,*f*]azepine 10,11-oxides is stable because the lone pair of electrons on the nitrogen atom is conjugated with the carbonyl group, but, in the case of 5*H*-*N*-alkyldibenz[*b*,*f*]azepine 10,11-oxides, these electrons are conjugated with the benzene ring and affect the fission of the oxirane ring. In addition, we presume that the lone pair of electrons on the nitrogen atom contributes to stabilization of the carbonium ion at the 10 position which resulted from fission of the oxirane ring, and ring contraction then occurs to give 9*H*,10*H*-acridine derivatives.

Acid Hydrolysis of 5*H*-Dibenz[*b*,*f*]azepine 10,11-Oxides

It is essential to understand the stability of these epoxides, if they are formed by metabolic oxidation of dibenz[*b*,*f*]azepines, as well as by chemical oxidation. Thus, we investigated the acid hydrolysis of 5*H*-dibenz[*b*,*f*]azepine 10,11-oxides. The acid hydrolysis of 5*H*-*N*-acyldibenz[*b*,*f*]azepine 10,11-oxides(XIa—d) afforded 5*H*-*N*-acyl-10,11-dihydro-*trans*-10,11-dihydroxydibenz[*b*,*f*]azepines (XIIa—d). The *trans* relationship[3)] between the two hydroxyl groups at the 10 and 11 positions was determined from the large values of coupling constants ($J_{10,11}=10$ Hz) between C_{10}–H and C_{11}–H in the NMR spectra of XIIa—d. Treatment of the diol (XIIc) with *p*-nitrobenzoyl chloride afforded the diester (XIIIc). The reduction of XIIc with $LiAlH_4$ afforded 5*H*-*N*-alkyl-10,11-*trans*-10,11-dihydroxydibenz-[*b*,*f*]azepines XIVb and XIVc (Chart 5).

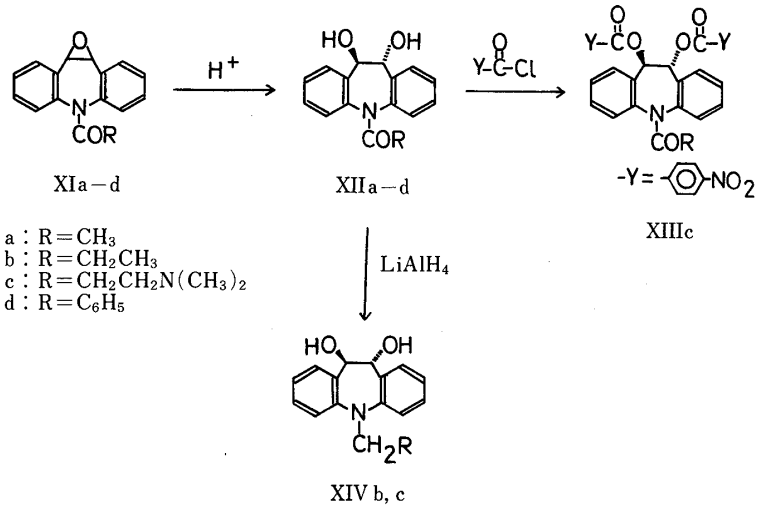


Chart 5

On the other hand, acid hydrolysis of the epoxide (VIIIb) readily afforded 9*H*,10*H*-acridine derivatives (IXb and Xb). Compounds IXb and Xb were identical with the products obtained by the oxidation of VIIb with *m*-CPBA (Chart 6). Thus, it is suggested that 9*H*,10*H*-acridine derivatives (IXb and Xb) are formed *via* the epoxide (VIIIb) when VIIb is oxidized with *m*-CPBA.

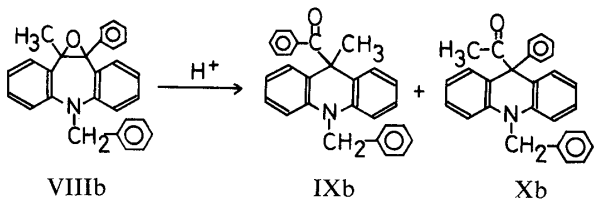


Chart 6

The acid hydrolysis of 5*H*-*N*-substituted-dibenz[*b*,*f*]azepine 10,11-oxides afforded different products depending on the nature of the N-substituent. It is presumed that the oxirane ring of 5*H*-*N*-alkyldibenz[*b*,*f*]azepine 10,11-oxide is affected by an electron-donating group on nitrogen at the 5 position and 9*H*,10*H*-acridine derivatives are obtained, whereas the oxirane ring of 5*H*-*N*-acyldibenz[*b*,*f*]azepine 10,11-oxide is not affected by an electron-attracting group on the nitrogen atom and the diol derivative is obtained.

Kinetic Studies of Acid Hydrolysis of 5*H*-Dibenz[*b*,*f*]azepine 10,11-Oxides

To examine the susceptibility of oxides to acid hydrolysis, the decomposition rates of 5*H*-*N*-acyldibenz[*b*,*f*]azepine 10,11-oxides, phenanthrene oxide, *trans*-stilbene oxide and styrene oxide were compared. The acid hydrolysis rates of these epoxides were determined by following the loss of the compounds in acetone–aq. HCl (1 : 1) at 30 °C. The rate constants ($k_{obs.}$) were calculated by the usual pseudo-first-order technique (Fig. 1).

The order of acid hydrolysis of epoxides and the relative rates were as follows:[4] phenanthrene oxide 13000 > styrene oxide 6800 > stilbene oxide 60 > 5*H*-*N*-acyldibenz-[*b*,*f*]azepine oxides 1—2. 5*H*-*N*-Acyldibenz[*b*,*f*]azepine oxides were found to be more stable than the arene oxide and the other epoxides in acidic solution. Thus, it is suggested that 5*H*-*N*-acyldibenz[*b*,*f*]azepine oxides can exist stably when these epoxides are formed metabolically.

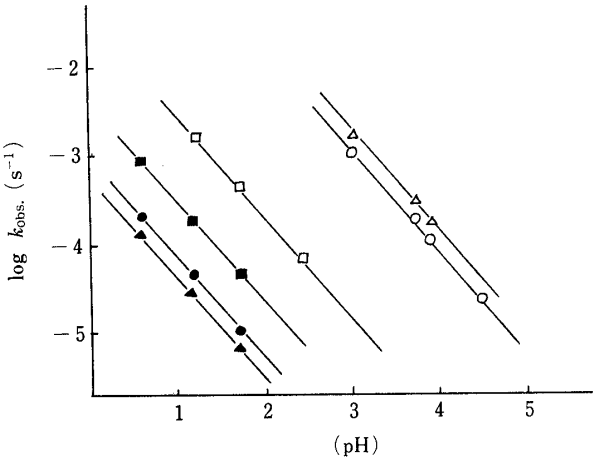


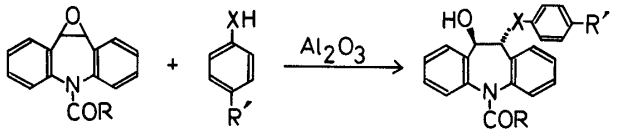
Fig. 1. Acid Hydrolysis Rates of Oxides Plots of log $k_{obs.}$ *vs.* pH at 30 °C in Acetone : Aq.-HCl (1 : 1)

—△—, phenanthrene 9,10-oxide; —○—, styrene oxide; —□—, stilbene oxide; —■—, carbamazepine 10,11-oxide; —●—, 5*H*-*N*-acetyldibenz[*b*,*f*]azepine 10,11-oxide (XIa); —▲—, 5*H*-*N*-(3-dimethylaminopropionyl)dibenz[*b*,*f*]azepine 10,11-oxide(XIc).

Nucleophilic Substitution Reactions of 5*H*-Dibenz[*b*,*f*]azepine 10,11-Oxides

Several metabolically formed oxides are well known to be electrophilically active intermediates. Therefore, it is important to investigate the reaction of 5*H*-dibenz[*b*,*f*]azepine oxides with nucleophilic reagents.

The reaction of epoxides XIa and XIc with *p*-toluidine in the presence of Al_2O_3[5] in abs. ether at room temperature afforded the corresponding 5*H*-*N*-acyl-10,11-dihydro-*trans*-10-hydroxy-11-(*p*-methylanilino)dibenz[*b*,*f*]azepines (XVa and XVb). The *trans* conformation of XV was established on the basis of the large values of coupling constants between C_{10}–H and C_{11}–H in the NMR spectrum. Namely, the spectrum of XVa showed two doublet signals due to C_{10}–H and C_{11}–H at 4.94 and 5.28 ppm and the coupling constants were 10 Hz. Similarly, the reaction of the epoxide XIc with thiophenol afforded 5*H*-*N*-(3-dimethylaminopropionyl)-10,11-dihydro-*trans*-10-hydroxy-11-phenylthiodibenz[*b*,*f*]azepine (XVc) (Chart 7).



XIa, c XVa—c

a: R = CH_3
c: R = $CH_2CH_2N(CH_3)_2$

	R	X	R′
a:	CH_3	NH	CH_3
b:	$CH_2CH_2N(CH_3)_2$	NH	CH_3
c:	$CH_2CH_2N(CH_3)_2$	S	H

Chart 7

5*H*-Dibenz[*b*,*f*]azepine oxides reacted easily with nucleophilic reagents under mild conditions. On the basis of these results, it is presumed that these epoxides will react easily with bio-molecules *in vivo* if the epoxides are administered[6] or are formed metabolically.

The oxidation of 5*H*-dibenz[*b*,*f*]azepines afforded different products. Namely, 5*H*-*N*-acyldibenz[*b*,*f*]azepines were oxidized to give epoxides and 5*H*-*N*-alkyldibenz[*b*,*f*]azepines were oxidized to give acridone and diphenylamine derivatives as previously reported.[1b] In the present work, it became apparent that 5*H*-*N*-alkyl-10-substituted-dibenz[*b*,*f*]azepines were oxidized to give 9*H*,10*H*-acridine derivatives and that 5*H*-*N*-alkyl-10,11-disubstituted-dibenz[*b*,*f*]azepines were oxidized to give epoxides which were less stable than phenanthrene oxide, though 5*H*-*N*-acyldibenz[*b*,*f*]azepine epoxides were more stable than the other epoxides.

These results demonstrate that the 10,11-double bond of 5*H*-dibenz[*b*,*f*]azepines is generally oxidized to the epoxide, and it is further oxidized to 9*H*,10*H*-acridine, acridone and diphenylamine derivatives by *m*-CPBA.

The correlation of product patterns in the chemical oxidation and the oxidative metabolism of 5*H*-*N*-substituted-dibenz[*b*,*f*]azepines has also been investigated. The results will be reported in succeeding papers.

Experimental

All melting points are uncorrected. IR spectra were determined with a JASCO DS-701G spectrometer, and NMR spectra with a JEOL JNM-4H-100 spectrometer (chemical shifts are in δ units, in $CDCl_3$). Mass spectra (MS) were recorded on a JEOL SG-01 spectrometer using the direct insertion technique. For spectroscopic data, the following abbreviations are used: d = doublet, m = multiplet, q = quartet, s = singlet, and t = triplet. Neutral silica gel (Kieselgel 60, Art. 7734) was used, purchased from Merck Japan Ltd.

5*H*-*N*-Benzyl-10-methyldibenz[*b*,*f*]azepine (Va)——A mixture of 5*H*-*N*-benzyl-10,11-dihydrodibenz[*b*,*f*]azepin-10-one[7] (300 mg) and CH_3MgI [prepared from Mg (81 mg) and CH_3I (474 mg)] in abs. benzene was stirred under a nitrogen atmosphere at room temperature for 18 h. After the addition of 10% NH_4Cl, the reaction mixture was extracted with benzene. The extract was dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue. A suspension of the residue in acetone (5 ml) and 10% HCl (4 ml) was stirred under reflux. After 1 h, water was added to the reaction mixture, and this solution was extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown oily residue, which was chromatographed on silica gel and eluted with *n*-hexane to afford Va as a pale yellow viscous oil (259 mg, 86.9%). NMR: 2.36 (3H, s, CH_3), 4.92 (2H, s, CH_2), 6.6—7.5 (14H, m, aromatic H).

5*H*-*N*-Benzyl-10-phenyldibenz[*b*,*f*]azepine (Vb)[7]——Vb was prepared from 5*H*-*N*-benzyl-10,11-dihydrodibenz[*b*,*f*]azepin-10-one and phenyl magnesium bromide in the same manner as Va. Yellow viscous oil. Yield, 35.8%. NMR: 5.00 (2H, q, CH_2), 6.7—7.5 (19H, m, aromatic H). MS *m/e*: 359 (M^+).

5*H*-*N*-Benzyl-10,11-dimethyldibenz[*b*,*f*]azepine (VIIa)[8]——VIIa was prepared from 5*H*-*N*-benzyl-10,11-dihydro-10-methyldibenz[*b*,*f*]azepin-10-one and CH_3MgI in the same manner as Va. Colorless prisms (recrystallized from CH_3OH). mp 125—126 °C. Yield, 40.6%. *Anal.* Calcd for $C_{23}H_{21}N$: C, 88.70; H, 6.80; N, 4.50. Found: C, 88.47; H, 6.83; N, 4.49. NMR: 2.29 (6H, s, $CH_3 \times 2$), 4.86 (2H, s, CH_2), 6.7—7.5 (13H, m, aromatic H).

5*H*-*N*-Benzyl-10-methyl-11-phenyldibenz[*b*,*f*]azepine (VIIb)——VIIb was prepared from 5*H*-*N*-benzyl-10,11-dihydro-10-methyldibenz[*b*,*f*]azepin-11-one and phenyl magnesium bromide in the same manner as Va. Colorless viscous oil. Yield, 106 mg (22.2%). NMR: 2.20 (3H, s, CH_3), 4.95 (2H, q, CH_2), 6.5—7.5 (18H, m, aromatic H). MS *m/e*: 373 (M^+).

Oxidation of Va——A mixture of Va (240 mg) and 85% *m*-CPBA (164 mg) in CH_2Cl_2 (24 ml)–saturated aq. $NaHCO_3$ (10 ml) was stirred for 2 h at room temperature. The reaction mixture was washed with 10% Na_2SO_3 and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was chromatographed on neutral silica gel and eluted with *n*-hexane–CH_2Cl_2 (10 : 3) to afford *N*-benzyl-9,10-dihydro-9-formyl-9-methylacridine (VIa) as colorless prisms, mp 129—130 °C (recrystallized from *n*-hexane–ether). Yield, 158 mg (62.5%). *Anal.* Calcd for $C_{22}H_{19}NO$: C, 84.31: H, 6.11; N, 4.47. Found: C, 84.57; H, 6.20; N, 4.66. NMR: 1.66 (3H, s, CH_3), 5.12 (2H, s, CH_2), 6.7—7.5 (18H, m, aromatic H), 9.78 (1H, s, CHO). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

Oxidation of Vb——Vb was oxidized in the same manner as Va. After 24 h, the reaction mixture was worked up as usual and the residue was chromatographed on neutral silica gel and eluted with CH_2Cl_2–*n*-hexane (1 : 1) to afford *N*-benzyl-9,10-dihydro-9-formyl-9-phenylacridine (VIb) as colorless prisms, mp 185—188 °C (recrystallized from CH_2Cl_2–ether). Yield, 43.1%. *Anal.* Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.11; H, 5.75; N, 3.96. NMR: 5.12 (2H, s, CH_2), 6.7—7.4 (13H, m, aromatic H), 9.76 (1H, s, CHO). IR ν_{max}^{KBr} cm^{-1}: 1724 (C=O).

Oxidation of VIIa——A mixture of VIIa (71 mg) and 85% *m*-CPBA (47 mg) in CH_2Cl_2 (10 ml)–saturated aq. $NaHCO_3$ (5 ml) was stirred at room temperature. After 1 h, 85% *m*-CPBA (47 mg) was added to the reaction mixture. After a further 1 h, the reaction mixture was washed with 10% Na_2SO_3 and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was chromatographed on neutral silica gel (5 g). The first elute with *n*-hexane–CH_2Cl_2 (5 : 1) yielded recovered starting material (VIIa). The second eluate gave 9-acetyl-*N*-benzyl-9,10-dihydro-9-methylacridine (IXa) as colorless prisms, mp 180 °C (recrystallized from *n*-hexane–ether). Yield, 38 mg (50.9%). *Anal.* Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.37; H, 6.50; N, 4.55. NMR: 1.69 (3H, s, CH_3), 2.07 (3H, s, $COCH_3$), 5.10 (2H, s, CH_2), 6.6—7.2 (13H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). MS *m/e*: 327 (M^+). The last eluate gave 5*H*-*N*-benzyl-10,11-dimethyldibenz[*b*,*f*]azepine 10,11-oxide (VIIIa) as a colorless viscous oil. Yield, 25 mg (33.5%). NMR: 1.77 (6H, s, $CH_3 \times 2$), 4.88 (2H, s, CH_2), 6.8—7.8 (13H, m, aromatic H). MS *m/e*: 327 (M^+).

Oxidation of VIIb——A mixture of VIIb (50 mg) and 85% *m*-CPBA (41 mg) in CH_2Cl_2 (10 ml)–saturated aq.

$NaHCO_3$ (4 ml) was stirred at room temperature. After 1.5 h, 85% *m*-CPBA (41 mg) was added to the reaction mixture. Stirring was continued for 5 h, then the reaction mixture was worked up as usual and the residue was chromatographed on neutral silica gel (3.5 g) and eluted with *n*-hexane–CH_2Cl_2 (10 : 1). The first eluate gave 9-benzoyl-*N*-benzyl-9,10-dihydro-9-methylacridine (IXb) as colorless prisms, mp 178—180 °C. Yield, 1 mg (1.9%). *Anal.* Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.49; H, 5.90; N, 3.63. IR ν_{max}^{KBr} cm^{-1}: 1685 (C=O). MS *m/e*: 389 (M^+), 284 ($M^+ - COC_6H_5$). The second eluate gave 5*H*-*N*-benzyl-10-methyl-11-phenyldibenz[*b*,*f*]azepine 10,11-oxide (VIIIb) as white crystals, mp 144—146 °C (recrystallized from *n*-hexane). Yield, 29 mg (55.6%). *Anal.* Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.48; H, 5.91; N, 3.74. NMR: 1.41 (3H, s, CH_3), 4.95 (2H, s, CH_2), 6.7—7.5 (18H, m, aromatic H). MS *m/e*: 389 (M^+). The last eluate gave 9-acetyl-*N*-benzyl-9,10-dihydro-9-phenylacridine (Xb) as colorless needles, mp 149 °C (recrystallized from CH_3OH). Yield, 6 mg (11.5%). *Anal.* Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.17; H, 5.99; N, 3.66. NMR: 2.17 (3H, s, $COCH_3$), 5.12 (2H, s, CH_2), 6.6—7.4 (18H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). MS *m/e*: 346 ($M^+ - COCH_3$).

5*H*-*N*-Acetyldibenz[*b*,*f*]azepine 10,11-Oxide (XIa), 5*H*-*N*-Propionyldibenz[*b*,*f*]azepine 10,11-Oxide (XIb) and 5*H*-*N*-Benzoyldibenz[*b*,*f*]azepine 10,11-Oxide (XId)——These compounds were prepared by the method described previously.[1b]

5*H*-*N*-(3-Dimethylaminopropionyl)dibenz[*b*,*f*]azepine 10,11-Oxide (XIc)——A solution of *N*-(3-chloropropionyl)dibenz[*b*,*f*]azepine 10,11-oxide[1b] (3.16 g) and 50% aq. dimethylamine (50 ml) in CH_2Cl_2 (200 ml) was stirred at room temperature for 8 h. The reaction mixture was separated and the solvent layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residual crystals were recrystallized from ether to afford colorless prisms (2.6 g, 80%), mp 146—147 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.71; H, 6.46; N, 9.01. NMR: 2.15 (6H, s, $CH_3 \times 2$), 2.0—2.8 (4H, m, $CH_2 \times 2$), 4.24 (2H, s, $C_{10,11}$–H), 7.2—7.5 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). MS *m/e*: 308 (M^+).

Acid Hydrolysis of 5*H*-*N*-Acyldibenz[*b*,*f*]azepine 10,11-Oxide (XI)——A solution of XI (100 mg) in acetone (10 ml)–H_2O (10 ml) containing a small amount of 1 N HCl (0.5 ml) was stirred at room temperature for 20—24 h. Water was added to the reaction mixture, and this solution was neutralized with 10% NaOH, then extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was chromatographed on silica gel and eluted with CH_2Cl_2–CH_3OH.

5*H*-*N*-Acetyl-10,11-dihydro-*trans*-10,11-dihydroxydibenz[*b*,*f*]azepine (XIIa)——Colorless prisms (recrystallized from CH_2Cl_2–ether), mp 170—173 °C (dec.). Yield, 26.6%. *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.12; H, 5.51; N, 5.06. NMR: 1.96 (3H, s, CH_3), 2.45 (2H, s, OH × 2), 4.42 (1H, t, C_{10}–H, $J_{10,11} = 10$ Hz), 5.15 (1H, t, C_{11}–H, $J_{10,11} = 10$ Hz), 7.0—7.8 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1654 (C=O).

5*H*-10,11-Dihydro-*trans*-10,11-dihydroxy-*N*-propionyldibenz[*b*,*f*]azepine (XIIb)——Colorless viscous oil. Yield, 15.7%. NMR: 1.05 (3H, t, CH_3), 2.23 (2H, q, CH_2), 4.36 (1H, d, C_{10}–H, $J_{10,11} = 10$ Hz), 5.18 (1H, d, C_{11}–H, $J_{10,11} = 10$ Hz), 4.55 (2H, s, OH × 2), 7.1—7.9 (8H, m, aromatic H).

5*H*-10,11-Dihydro-*trans*-10,11-dihydroxy-*N*-(3-dimethylaminopropionyl)dibenz[*b*,*f*]azepine (XIIc)——Viscous oil. Yield, 47.6%. A mixture of XIIc and *p*-nitrobenzoyl chloride in abs. pyridine was stirred at room temperature for 21 h. The reaction mixture was worked up as usual. XIIIc (the *p*-nitrobenzoyl ester of XIIc) was obtained. XIIIc: NMR: 2.18 (6H, s, $CH_3 \times 2$), 2.3—3.0 (4H, m, $CH_2 \times 2$), 6.68 (1H, d, C_{10}–H, $J_{10,11} = 10$ Hz), 7.05 (1H, d, C_{11}–H, $J_{10,11} = 10$ Hz), 7.2—8.4 (12H, m, aromatic H). The maleate salt of XIIIc was obtained from XIIIc and maleic acid in EtOH. White crystals, mp 218—219 °C. *Anal.* Calcd for $C_{37}H_{32}N_4O_{13}$: C, 60.00; H, 4.35; N, 7.56. Found: C, 59.72; H, 4.27; N, 7.56. IR ν_{max}^{KBr} cm^{-1}: 1678, 1730 and 1741 (C=O), 1354 and 1525 (NO_2).

5*H*-*N*-Benzoyl-10,11-dihydro-*trans*-10,11-dihydroxydibenz[*b*,*f*]azepine (XIId)——Colorless prisms (recrystallized from CH_2Cl_2), mp 199—200 °C (dec.). Yield, 35.1%. *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.23; H, 5.13; N, 4.11. NMR: 4.55 (1H, d, C_{10}–H, $J_{10,11} = 10$ Hz), 5.58 (1H, d, C_{11}–H, $J_{10,11} = 10$ Hz), 5.90 (2H, br s, OH × 2), 6.8—8.0 (13H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1627 (C=O).

5*H*-10,11-Dihydro-*trans*-10,11-dihydroxy-*N*-propyldibenz[*b*,*f*]azepine (XIVb)——A solution of XIIb (80 mg) in abs. ether (2 ml) was added dropwise to a suspension of $LiAlH_4$ (60 mg) in abs. ether (5 ml). The reaction mixture was stirred at room temperature for 20 min, then poured into ice-water. The whole solution was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel to give XIVb as a colorless viscous oil (68 mg, 89.5%). NMR: 0.86 (3H, t, CH_3), 1.1—1.8 (2H, m, CH_2), 3.61 (2H, br s, OH × 2), 3.69 (2H, t, CH_2), 5.03 (2H, s, $C_{10,11}$–H), 6.7—7.7 (8H, m, aromatic H). MS *m/e*: 267 (M^+).

5*H*-10,11-Dihydro-*trans*-10,11-dihydroxy-*N*-(3-dimethylaminopropyl)dibenz[*b*,*f*]azepine (XIVc)——A solution of XIIc (91 mg) in abs. ether (6 ml) was added dropwise to a suspension of $LiAlH_4$ (14 mg) in abs. ether (5 ml). The reaction mixture was stirred under reflux for 10 h then worked up as usual and the residue was chromatographed on silica gel (4 g). Elution with CH_2Cl_2–CH_3OH (50 : 3) gave white crystals (24 mg, 27.0% yield) which were recrystallized from ether, mp 99—101 °C. *Anal.* Calcd for $C_{19}H_{24}N_2O_2 \cdot 1/3H_2O$: C, 71.82; H, 7.61; N, 8.82. Found: C, 71.64; H, 7.48; N, 9.08. NMR: 1.5—1.9 (2H, m, CH_2), 2.16 (6H, s, $CH_3 \times 2$), 2.0—2.7 (2H, m, CH_2), 3.5—3.9 (2H, m, CH_2), 3.72 (2H, s, OH × 2), 4.94 (2H, s, $C_{10,11}$–H), 6.9—7.6 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3360 (OH).

Acid Hydrolysis of VIIIb——A solution of VIIIb (30 mg) in CH_3OH (2 ml) and 10% HCl (0.5 ml) was stirred at room temperature for 10 min. Water was added to the reaction mixture, and the solution was extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was chromatographed on silica gel (9 g). The first eluate with *n*-hexane–CH_2Cl_2 (10 : 1) gave IXb (3 mg, 10% yield). The second eluate gave Xb (18 mg, 60% yield). The IR and NMR spectral and physical data of IXb and Xb were identical with those of IXb and Xb obtained by the oxidation of VIIb with *m*-CPBA.

5*H*-*N*-Acetyl-10,11-dihydro-*trans*-10-hydroxy-11-(*p*-methylanilino)dibenz[*b*,*f*]azepine (XVa)——A mixture of XIa (100 mg), Al_2O_3[5] (3 g) and *p*-toluidine (170 mg) in abs. ether (3 ml) was stirred at room temperature for 4 h. CH_2Cl_2 (50 ml) was added to the reaction mixture and Al_2O_3 was removed by filtration. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel (10 g) using CH_2Cl_2 as an eluent to give colorless prisms (121 mg, 84.8%), which were recrystallized from *n*-hexane–CH_2Cl_2, mp 176—177 °C. *Anal.* Calcd for $C_{23}H_{22}N_2O_2 \cdot 1/3H_2O$: C, 75.80; H, 6.27; N, 7.71. Found: C, 76.10; H, 6.14; N, 7.74. NMR: 1.98 (3H, s, CH_3), 2.22 (3H, s, $COCH_3$), 3.28 (1H, br s, OH), 4.94 (1H, d, C_{10}–H, $J_{10,11}=9$ Hz), 5.28 (1H, d, C_{11}–H, $J_{10,11}=9$ Hz), 6.3—7.8 (12H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1639 (C=O), 3210 (OH), 3360 (NH). MS *m/e*: 358 (M^+).

5*H*-10,11-Dihydro-*N*-(3-dimethylaminopropioyl)-*trans*-10-hydroxy-11-(*p*-methylanilino)dibenz[*b*,*f*]azepine (XVb)——A mixture of XIc (100 mg), Al_2O_3 (3.5 g) and *p*-toluidine (139 mg) in abs. ether (4 ml) was stirred at room temperature for 4 h. The reaction mixture was worked up in the same manner as described for XVa. XVb was obtained as colorless crystals (86 mg, 63.8% yield), which were recrystallized from *n*-hexane–ether, mp 114—118 °C. *Anal.* Calcd for $C_{26}H_{29}N_3O_2 \cdot 1/3H_2O$: C, 74.08; H, 7.09; N, 9.97. Found: C, 74.18; H, 7.07; N, 9.80. NMR: 1.84 (1H, s, CH_3), 2.23 (1H, s, CH_3), 4.68 (1H, d, C_{10}–H, $J_{10,11}=10$ Hz), 4.96 (1H, d, C_{11}–H, $J_{10,11}=10$ Hz), 3.90 (1H, br s, OH), 6.3—7.5 (12H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1669 (C=O), 3370 (OH and NH). MS *m/e*: 415 (M^+).

5*H*-10,11-Dihydro-*N*-(3-dimethylaminopropionyl)-*trans*-10-hydroxy-11-phenylthiodibenz[*b*,*f*]azepine (XVc)——A mixture of XIc (80 mg), Al_2O_3 (2.8 g) and thiophenol (114 mg) in abs. ether (3 ml) was stirred at room temperature for 3.5 h. The reaction mixture was worked up in the same manner as described for XVa. XVc was obtained as colorless prisms (90 mg, 82.9% Yield), which were recrystallized from *n*-hexane–CH_2Cl_2, mp 140—142 °C. *Anal.* Calcd for $C_{25}H_{26}N_2O_2S \cdot 1/3H_2O$: C, 71.62; H, 6.42; N, 6.68. Found: C, 71.32; H, 6.30; N, 6.55. NMR: 1.81 (1H, s, CH_3), 3.66 (1H, br s, OH), 4.15 (1H, d, C_{10}–H, $J_{10,11}=10$ Hz), 5.24 (1H, d, C_{11}–H, $J_{10,11}=10$ Hz), 6.9—7.7 (13H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1646 (C=O), 3430 (OH).

Kinetic Measurements of Acid Hydrolysis Rates——Materials: Carbamazepine 10,11-oxide was prepared by Frigerio's method.[9] *trans*-Stilbene oxide was prepared by Reif's method.[10] Styrene oxide was purchased from Tokyo Kasei Co. Phenanthrene 9,10-oxide was prepared by Newman's method.[11].

Instrument and Conditions: High-performance liquid chromatography (HPLC) was carried out with a Milton Roy M-396 pump, a Rheodyne M-7120 injector and a UVIDEC-100 detector (254 nm). Column: Merck Lichrosorb RP-18 (5 μm), 4.3 (ϕ) × 150 mm.

An oxide (0.02 mmol) was dissolved in aceton (1.5 ml), and dil. HCl (1.5 ml) was added to the solution. The mixture was immersed in a thermostated bath controlled at 30±0.1 °C. The reaction mixture was sampled at appropriate intervals and the samples were injected into the HPLC machine. The decrease of the oxide was monitored by HPLC (Table I) and the acid hydrolysis rate constants were calculated from the following pseudo-first-order rate expression;

$$k_{obs.} = 2.303/t \times \log a/x$$

where a is the initial concentration of the oxide (mol/l), and x is the mol number of unchanged oxide at time t.

TABLE I. Acid Hydrolysis Times ($t_{3/4}$ s) of Various Oxides

Compd. No.	pH							
	0.63	1.16	1.64	2.30	2.97	3.57	3.83	4.35
XIc	1780	6850	31600					
XIa	1630	5200	19200					
Carbamazepine 10,11-oxide	409	1430	4780					
trans-Stilbene oxide		272	813	4120				
Styrene oxide					184	842	1570	6600
Phenanthrene 9,10-oxide					130	552	1150	

References and Notes

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