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Studies on the Oxidation of N-Substituted-dibenz[*b*, *f*]azepines I.[1] Oxidation with *m*-Chloroperbenzoic Acid[2]

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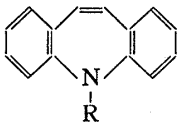
Oxidation of various N-substituted-dibenz[*b*,*f*]azepines with *m*-chloroperbenzoic acid (*m*-CPBA) was examined. Oxidation of N-acyldibenz[*b*,*f*]azepines (If—k) gave the 10,11-oxide (XVIIf—k). Oxidation of N-alkyldibenz[*b*,*f*]azepines (Ia—c) gave the diphenylamine (IIa—c) and 9-acridone (IIIa—c). Oxidation of N-methyldibenz[*b*,*f*]-azepine (Id) gave the N-oxide (IX) as a main product. In the case of oxidation of N-phenyldibenz[*b*,*f*]azepine (Ie), hydroxylation of the phenyl nucleus occurred to give N-(*o*-hydroxy)phenyldibenz[*b*,*f*]azepine (XII). In addition, further oxidation of XII proceeded to give diphenylamine (IIe).

The rates of oxidation of N-substituted-dibenz[*b*,*f*]azepines (Ia—c) having an N-alkyl group were faster than those of If—k (having an N-acyl group).

Keywords——N-substituted-dibenz[*b*,*f*]azepine; N-acyl-10,11-dihydro-dibenz[*b*,*f*]-azepin-10,11-oxide; N-substituted-2-formyl-2′-hydroxydiphenylamine; N-alkyl-9-acridone; N-methyldibenz[*b*,*f*]azepine-N-oxide; oxidation rate; *m*-chloroperbenzoic acid

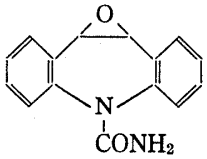
Many dibenz[*b*,*f*]azepine derivatives having pharmacological activities (opipramol, dehydroimipramine, carbamazepine, *etc.*) are known (Chart 1). Although they have been widely used in clinical practice, little work has been done on their metabolic fates.[4] In particular, the oxidative metabolism of the dibenz[*b*, *f*]azepine skeleton has been investigated only in the case of carbamazepine, which has an N-carbamoyl group. That is, Frigerio *et al.*[5] reported that carbamazepine-10,11-oxide was detected in urine as a metabolite of carbamazepine. No work on the oxidative metabolism of N-alkyl derivatives such as opipramol or dehydroimipramine has been reported yet.



opipramol R = $CH_2CH_2CH_2N\langle\rangle NCH_2CH_2OH$

dehydroimipramine R = $CH_2CH_2CH_2N(CH_3)_2$

carbamazepine R = $CONH_2$



carbamazepine oxide

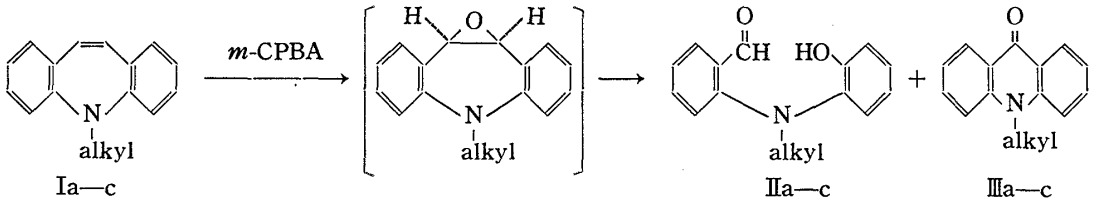
Chart 1

During the course of our chemical studies on drug metabolism, we have been interested in the effects of N-substituents on metabolism. To elucidate these effects we have examined the results of chemical oxidation. In the present paper the oxidative behavior of several N-substituted-dibenz[*b*,*f*]azepines with *m*-chloroperbenzoic acid (*m*-CPBA) is described.

The Oxidation Products of N-Substituted-dibenz[*b*, *f*]azepine Derivatives

Dibenz[*b*,*f*]azepines which have N-alkyl (Ia—d), N-aryl (Ie) or N-acyl (If—k) groups were treated with 1—4 eq mol of 85% *m*-CPBA in CH_2Cl_2–saturated aq. $NaHCO_3$ at room temperature. Several oxidized products were obtained, depending on the nature of the N-substituents.

Namely, oxidation of N-alkyldibenz[*b*, *f*]azepines (Ia—c) with *m*-CPBA gave N-alkyl-2-formyl-2′-hydroxydiphenylamines (IIa—c) and N-alkyl-9-acridones (IIIa—c) (Chart 2).



a: alkyl=n-C_3H_7
b: alkyl=$CH_2CH_2CH_2OH$
c: alkyl=$CH_2C_6H_5$

Chart 2

The structures of IIa—c and IIIa—c were determined on the basis of instrumental analysis data. In addition, the structure of IIa was confirmed by an alternative synthesis (shown in Chart 3). Namely the reduction of IIa with $LiAlH_4$ at 90° gave 2-hydroxy-2′-hydroxymethyl-N-propyldiphenylamine (IV) and 2-hydroxy-2′-methyl-N-propyldiphenylamine (V). O-Methylation of V with dimethyl sulfate gave 2-methoxy-2′-methyl-N-propyldiphenylamine (VI). On the other hand, VI was derived from 2-methoxy-2′-methyldiphenylamine (VIII) by reaction with 1-bromopropane; VIII was itself obtained by the reduction of N-acetyl-2-methoxy-2′-methyldiphenylamine (VII)[6] with $LiAlH_4$. Infrared (IR) and nuclear magnetic resonance (NMR) spectra of VI derived from IIa and VIII were identical.

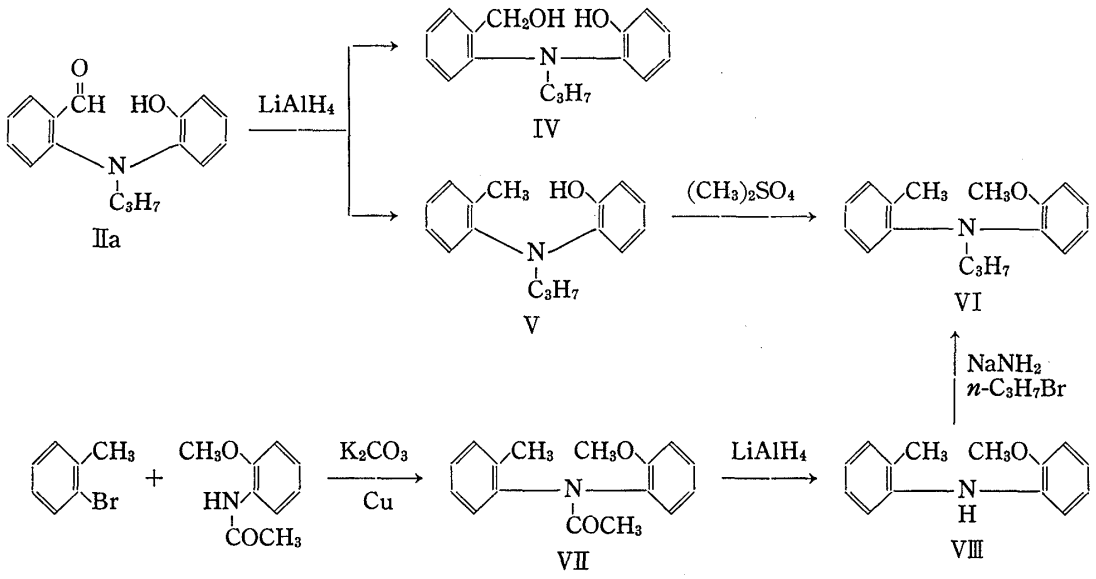


Chart 3

The mechanism of formation of IIa—c and IIIa—c from Ia—c is still uncertain. However, our further experiments have revealed that the 10,11-dialkyl-10,11-epoxides were obtained in 33% yield as oxidation products when 10,11-dialkyl-N-alkyldibenz[b,f]azepines were treated with m-CPBA in the same manner, and the isolated 10,11-epoxides were easily converted to N-alkylacridine derivatives by ring contraction upon treatment with an acid.[7] Thus, a plausible mechanism for the formation of IIa—c and IIIa—c is as follows. That is, Ia—c are first oxidized to their 10,11-epoxides, which are converted to the acridine derivatives, followed by further oxidation to IIa—c and IIIa—c. These results and related reactions will be reported in subsequent papers.

When the N-substituent was a methyl group, N-oxidation occurred mainly. Namely, oxidation of N-methyldibenz[b,f]azepine (Id) with m-CPBA gave N-methyldibenz[b,f]azepine-N-oxide (IX), 2-formyl-2′-hydroxy-N-methyldiphenylamine (IId) and N-methyl-9-acridone

(IIId) in 66.0, 10.3 and 1.2% yields, respectively (Chart 4). The structural determination of IX was carried out by NMR spectrometry and by consideration of the chemical transformations summarized in Chart 5. The methyl protons of IX were observed as a singlet peak at δ 3.54 ppm, at lower field than that (δ 3.30 ppm) of Id and the δ value of aromatic protons of IX was the same as that of Id. Reduction of IX with Na_2SO_3 gave the deoxygenated compound (Id). Catalytic reduction of IX over 10% palladium on charcoal (Pd-C) gave N-methyl-10,11-dihydrodibenz[*b*,*f*]azepine (X). Heating of IX at 160° for 20 min gave dibenz[*b*,*f*]azepine (XI) and Id. These results indicate that the oxidation proceeds preferentially on the nitrogen atom to yield the N-oxide.[8] When IX was further treated with *m*-CPBA, IId, IIId or more oxidized products were not obtained.

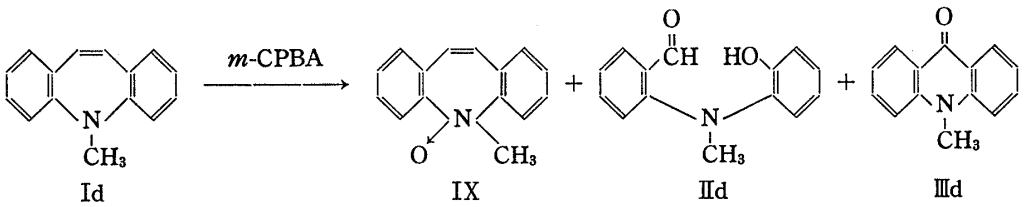


Chart 4

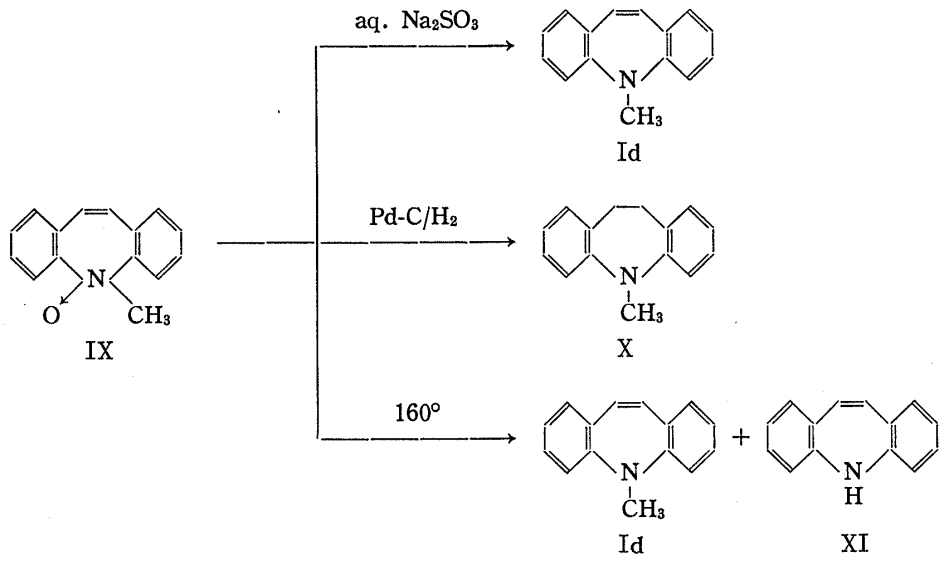


Chart 5

This result suggests that the formation of IId and IIId does not occur through IX and that the 10,11-double bond is not oxidized by *m*-CPBA after N-oxidation. Other N-alkyldibenz[*b*,*f*]azepines (Ia—c) did not afford their N-oxide derivatives under the same reaction conditions. It is presumed that oxidation of the N-atom of I occurs easily as well as that of its 10,11-double bond, but the N-oxidation is affected by the steric hindrance of N-substituents.

Oxidation of N-phenyldibenz[*b*,*f*]azepine (Ie) with *m*-CPBA gave N-(*o*-hydroxyphenyl)-dibenz[*b*,*f*]azepine (XII). The location of the hydroxy group of XII was deduced from the results of the following reactions. As shown in Chart 7, XII was treated with dimethyl sulfate to give N-(*o*-methoxyphenyl)dibenz[*b*,*f*]azepine (XIII). The catalytic hydrogenation of XIII on Pd-C gave N-(*o*-methoxyphenyl)-10,11-dihydrodibenz[*b*,*f*]azepine (XVI). IR and NMR spectra and physical data of XVI agreed with those of the product obtained by the coupling of 10,11-dihydrodibenz[*b*,*f*]azepine (XIV) with iodoanisole (XV).

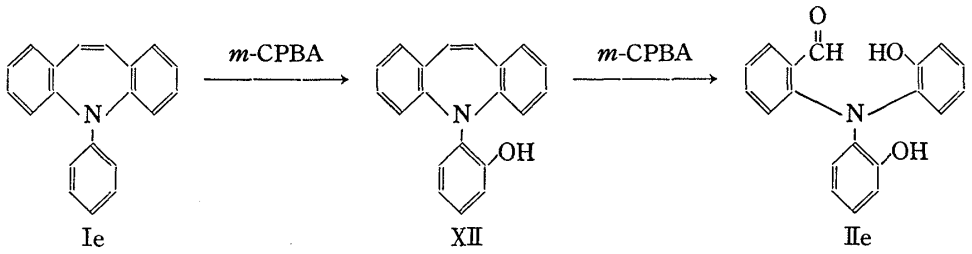


Chart 6

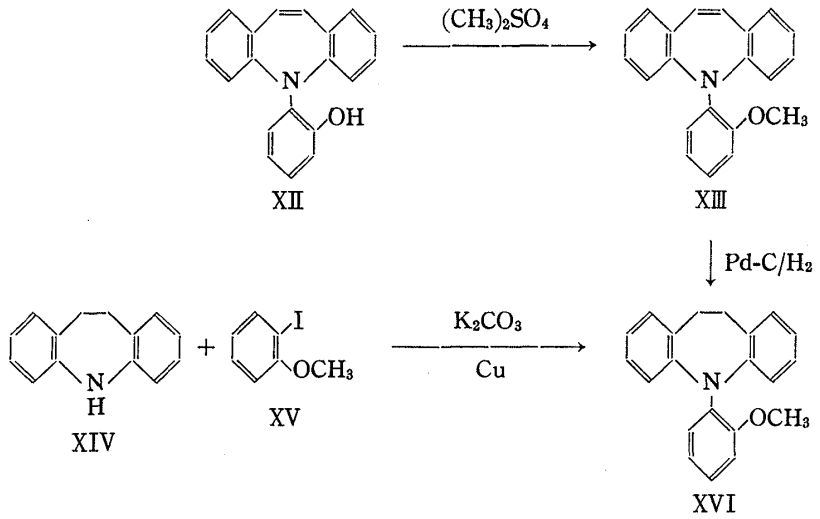


Chart 7

The regioselective hydroxylation at the *ortho*-position is particularly interesting. As regards the formation of XII, we propose that Ie was oxidized to the N-oxide initially, followed by the rearrangement of an oxygen atom to the *ortho*-position of the benzene ring.[9] In addition, further oxidation of XII with *m*-CPBA occurred to give 2-formyl-2′-hydroxy-N-(*o*-hydroxyphenyl)diphenylamine (IIe), which is similar to the oxidation products obtained from Ia—d (Chart 6).

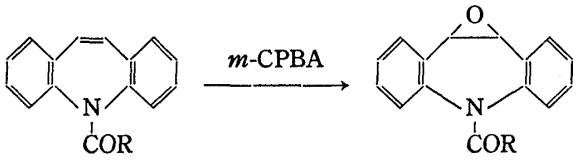
Oxidation of N-acyldibenz[*b*, *f*]azepines (If—k) with *m*-CPBA afforded the corresponding N-acyldibenz[*b*, *f*]azepine-10,11-oxides (XVIIf—k).[10] These N-acyl-epoxides were extremely stable and further oxidized products such as acridones were not afforded, in contrast to the oxidation of N-alkyl- and N-aryl-dibenz[*b*, *f*]azepines. The physical and spectral data of the epoxides (XVII) are summarized in Table I.

The Oxidation Rate of N-Substituted-dibenz[*b*, *f*]azepine Derivatives

The nature of the N-substituent of dibenz[*b*, *f*]azepine influences the nature of the oxidation products obtained upon *m*-CPBA treatment. It is presumed that the oxidation proceeds *via* epoxidation of the 10,11-double bond except in the case of N-oxidation. To examine the susceptibility of the 10,11-double bond to oxidation with *m*-CPBA, the oxidation rates of N-substituted-dibenz[*b*, *f*]azepines were investigated. The oxidation rate was determined by measurement of the loss of starting material by high performance liquid chromatography (HPLC), and the rate constants ($k_{obs.}$) were calculated by the usual pseudo-first-order technique.

As shown in Table II, the rate of oxidation of Ic (having an N-alkyl group) was faster than those of Ii, Ik and carbamazepine (having an N-acyl group). Dibenz[*b*, *f*]azepine was also oxidized by *m*-CPBA to 10-formylacridine,[10] but the oxidation rate was too fast to measure even at −15°. It is well known that the rates of epoxidation of double bonds by organic

TABLE I. Yields, Physical and Spectral Data for N-Acyl-10,11-dihydrodibenz[*b*, *f*]azepine-10,11-oxide (XVII)



If—k XVIIf—k

Compd. No.	COR	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (δ, $CDCl_3$) $C_{10,11}$–H	IR ν_{max}^{KBr} cm^{-1} C=O
XVIIf	$COCH_2CH_3$	105	20.0	$C_{17}H_{15}NO_2$	76.96 (76.72	5.70 5.69	5.28 5.11)	4.28	1678
XVIIg	$COCH_2Cl$	132—133	60.1	$C_{16}H_{12}NO_2Cl$	67.26 (67.00	4.23 4.29	4.90 4.91)	4.26	1693
XVIIh	$COCH_2CH_2Cl$	178	59.8	$C_{17}H_{14}NO_2Cl$	68.12 (67.96	4.71 4.81	4.67 4.78)	4.28	1683
XVIIi	COC_6H_5	194—196	52.2	$C_{21}H_{15}NO_2$	80.49 (80.51	4.83 4.85	4.47 4.48)	4.28	1660
XVIIj	$COOC_2H_5$	148—149	43.3	$C_{17}H_{15}NO_3$	72.58 (72.83	5.37 5.41	4.98 5.10)	4.24	1712
XVIIk	$COCH_3$	154—157 (dec.)	53.9	$C_{16}H_{13}NO_2$	76.47 (76.24	5.22 5.31	5.57 5.50)	4.28	1670

TABLE II. Oxidation Rates of N-Substituted-dibenz[*b*, *f*]azepine by *m*-CPBA

Compd. No.	$k_{obs.} \times 10^5 \cdot 1 \cdot mol^{-1} \cdot sec^{-1}$ Reaction temperature (°C) 0	15	30
Ic	100	280	
Ik		22	27
Ii		5	25
Carbamazepine			11

peroxides are dependent on electron density.[11] Therefore, we presume that the oxidation rates of these dibenz[*b*, *f*]azepines on treatment with *m*-CPBA were affected by the electron density of the 10,11-double bond. In fact, ^{1}H-NMR signals[12] of the 10,11-double bond appeared at 6.97—6.84 ppm in N-acyl derivatives, but at 6.73—6.66 ppm in N-alkyl derivatives. These data suggest that the nature of the N-substituted group affects the electron density and the reactivity of 10,11-double bond.

Oxidation of N-substituted-dibenz[*b*, *f*]azepine with *m*-CPBA afforded different products depending on the nature of the N-substituent. It is presumed that oxidation of the 10,11-double bond of dibenz[*b*, *f*]azepines affords the 10,11-oxides, but the oxirane ring of N-alkyl-dibenz[*b*, *f*]azepine-10,11-oxide is labile due to the electron-donating effect of the nitrogen atom, and the compound is further converted to diphenylamine and acridone derivatives.

The correlation between the products of chemical oxidation and those of oxidative metabolism *in vitro* or *in vivo* from N-substituted-dibenz[*b*, *f*]azepines has been investigated. These results will be reported in subsequent 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 using tetramethylsilane as an internal standard (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.

N-Alkyldibenz[*b*,*f*]azepine (Ia, c)——A mixture of dibenz[*b*,*f*]azepine (10 mmol) and sodium amide (16 mmol) in abs. toluene (60 mmol) was stirred under reflux for 2 hr. Alkyl chloride was added to the mixture. After being stirred under reflux for 4 hr, the reaction mixture was poured into ice-water and extracted with benzene. The extract was washed with water, and dried over Na_2SO_4. The residue left after removal of the solvent was chromatographed on silica gel. Elution with CH_2Cl_2–*n*-hexane gave Ia and Ic.

N-*n*-Propyldibenz[*b*,*f*]azepine (Ia):[13] Yellow prisms (recrystallized from *n*-hexane–CH_2Cl_2), mp 81—83°. Yield, 67.4%. *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.81; H, 7.25; N, 5.81. NMR ($CDCl_3$) δ: 0.90 (3H, t, CH_3), 1.56 (2H, m, CH_2), 3.63 (2H, t, NCH_2), 6.66 (2H, s, $C_{10,11}$–H), 6.8—7.3 (8H, m, aromatic H). MS *m/e*: 235 (M^+).

N-Benzyldibenz[*b*,*f*]azepine (Ic): Yellow prisms (recrystallized from *n*-hexane), mp 80°. Yield, 72.4%. *Anal.* Calcd for $C_{21}H_{17}N$: C, 89.10; H, 6.05; N, 4.94. Found: C, 89.28; H, 6.03; N, 5.16. MS *m/e*: 283 (M^+). NMR ($CDCl_3$) δ: 4.93 (2H, s, CH_2N), 6.76 (2H, s, $C_{10,11}$–H), 6.8—7.4 (13H, m, aromatic H).

N-Methyldibenz[*b*,*f*]azepine (Id)[14]——A mixture of dibenz[*b*,*f*]azepine (10 mmol) and dimethyl sulfate (15 mmol) was stirred at 100° for 3 hr. Water was added to the reaction mixture and this solution was neutralized, and extracted with CH_2Cl_2. The solvent layer was dried over Na_2SO_4 and evaporated to dryness. The residual crystals were recrystallized from CH_3OH to give Ia as yellow prisms, mp 148°. Yield, 70.4%. *Anal.* Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.79; H, 6.40; N, 6.75. NMR ($CDCl_3$) δ: 3.30 (3H, s, CH_3), 6.60 (2H, s, $C_{10,11}$–H), 6.8—7.3 (8H, m, aromatic H).

N-(3-Hydroxypropyl)dibenz[*b*,*f*]azepine (Ib)——Ib was prepared as described previously.[15] Pale yellow prisms (recrystallized from *n*-hexane–ether), mp 117°. *Anal.* Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.08; H, 6.52; N, 5.46. NMR ($CDCl_3$) δ: 1.80 (2H, m, CH_2), 2.78 (1H, broad s, OH), 3.70 (2H, m, CH_2O), 3.92 (2H, t, CH_2N), 6.73 (2H, s, $C_{10,11}$–H), 6.8—7.3 (8H, m, aromatic H).

10,11-Dihydro-N-phenyldibenz[*b*,*f*]azepine (XVIII)——A mixture of 10,11-dihydrodibenz[*b*,*f*]azepine (8 g), iodobenzene (16 g), anhydrous K_2CO_3 (11.2 g), and Cu powder (200 mg) in nitrobenzene (50 ml) was stirred under reflux for 14 hr, diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with *n*-hexane–CH_2Cl_2 (4: 1 v/v) gave XVIII (6 g, 54.1%), mp 86—88° (from *n*-hexane), colorless prisms. *Anal.* Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16. Found: C, 88.44; H, 6.39; N, 5.39. NMR ($CDCl_3$) δ: 3.00 (4H, s, CH_2), 6.5—7.5 (13H, m, aromatic H).

N-Phenyldibenz[*b*,*f*]azepine (Ie)——A solution of XVIII (5 g) in diethyl maleate (50 ml) was vigorously stirred with Pd-C (5 g) at 210° for 5 hr. The mixture was filtered. The filtrate was evaporated to dryness and the residue was recrystallized from methanol to give colorless prisms, mp 127—128°. Yield, 4.4 g (88.7%). *Anal.* Calcd for $C_{20}H_{15}N$: C, 89.10; H, 5.61; N, 5.20. Found: C, 88.97; H, 5.79; N, 5.41. NMR ($CDCl_3$) δ: 6.76 (2H, s, $C_{10,11}$–H), 6.2—7.5 (13H, m, aromatic H).

N-Acyldibenz[*b*,*f*]azepine (If—i, k)——A mixture of dibenz[*b*,*f*]azepine (30 mmol) and acid chloride (30 mmol) in abs. benzene (60 ml) was refluxed for 3 hr. The reaction mixture was washed with water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave I, which was recrystallized.

N-Propionyldibenz[*b*,*f*]azepine (If):[12a] mp 67—68° (from *n*-hexane). Yield, 91.4%. *Anal.* Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.73; H, 5.98; N, 5.75. IR ν_{max}^{KBr} cm^{-1}: 1679 (C=O).

N-Chloroacetyldibenz[*b*,*f*]azepine (Ig):[16] mp 144—146° (from methanol). Yield, 94.3%. *Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.08; H, 4.58; N, 5.17. NMR ($CDCl_3$) δ: 3.84 (2H, q, CH_2), 6.94 (2H, s, $C_{10,11}$–H), 7.25—7.5 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O).

N-(3-Chloropropionyl)dibenz[*b*,*f*]azepine (Ih): mp 128° (from methanol). Yield, 91.3%. *Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.90; H, 5.04; N, 5.04. MS *m/e*: 283 (M^+). NMR ($CDCl_3$) δ: 6.90 (2H, s, $C_{10,11}$–H), IR ν_{max}^{KBr} cm^{-1}: 1671 (C=O).

N-Benzoyldibenz[*b*,*f*]azepine (Ii):[12a] mp 132—133° (from *n*-hexane–ether). Yield, 85.6%. *Anal.* Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.09; N, 4.71. Found: C, 84.61; H, 5.10; N, 4.71. NMR ($CDCl_3$) δ: 6.97 (2H, s, $C_{10,11}$–H), 7.0—7.4 (13H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1658 (C=O). MS *m/e*: 297 (M^+).

N-Acetyldibenz[*b*,*f*]azepine (Ik):[10] mp 118—121° (from ether–*n*-hexane). Yield, 91.4%. *Anal.* Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.53; H, 5.90; N, 5.95. NMR ($CDCl_3$) δ: 1.84 (3H, s, CH_3), 6.92 (2H, s, $C_{10,11}$–H), 7.2—7.6 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). MS *m/e*: 235 (M^+).

N-Ethoxycarbonyldibenz[*b*,*f*]azepine (Ij)[17]——A mixture of dibenz[*b*,*f*]azepine (30 mmol) and sodium amide (40 mmol) in abs. toluene was stirred under reflux for 2 hr. Ethoxycarbonyl chloride (30 mmol) was added to the mixture. After being stirred under reflux for 3 hr, the reaction mixture was washed with water,

and dried over Na_2SO_4. Removal of the solvent by evaporation gave Ij, which was recrystallized from ether. mp 124—125°. Yield, 69.7%. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.72; H, 5.75; N, 5.30. NMR ($CDCl_3$) δ: 1.15 (3H, t, CH_3), 2.12 (2H, q, CH_2), 6.85 (2H, s, $C_{10,11}$–H), 7.0—7.5 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O).

Oxidation of Ia——A mixture of Ia (800 mg) and 85% *m*-CPBA (1.38 g) in CH_2Cl_2 (160 ml)–saturated aq. $NaHCO_3$ (80 ml) was stirred at room temperature. After 18.5 hr, *m*-CPBA (1.38 g) was added to the reaction mixture. After being stirred for 2 hr, the reaction mixture was washed with 10% Na_2SO_3, 10% $NaHCO_3$ and water. It was dried over Na_2SO_4, and the solvent was evaporated off to give a residue, which was chromatographed on silica gel (60 g). Elution with CH_2Cl_2 gave IIa and IIIa.

N-Propyl-2-formyl-2′-hydroxydiphenylamine (IIa): Yellow prisms. mp 85—86°. Yield, 279 mg (32.2%). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.57; H, 6.76; N, 5.67. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O), 3180 (OH). MS *m/e*: 255 (M^+). NMR ($CDCl_3$) δ: 9.85 (1H, s, CHO).

N-Propyl-9-acridone (IIIa): mp 129—130°.[18] Yield, 198 mg (24.5%). *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.42; N, 6.00. IR ν_{max}^{KBr} cm^{-1}: 1626 (C=O).

Oxidation of Ib——The reaction mixture was worked up as described above for the oxidation of Ia. IIb and IIIb were obtained.

N-(3-Hydroxypropyl)-9-acridone (IIIb): Yellow prisms. mp 209—210°. Yield, 12.2%. *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.98; N, 5.47. NMR ($CDCl_3$) δ: 2.16 (2H, m, CH_2), 2.84 (1H, s, OH), 3.84 (2H, t, CH_2), 4.52 (2H, t, CH_2), 7.1—7.7 (6H, m, aromatic H), 8.40 (2H, d, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1625 (C=O), 3370 (OH). MS *m/e*: 253 (M^+).

N-(3-Hydroxypropyl)-2-formyl-2′-hydroxydiphenylamine (IIb): Viscous oil. Yield, 48.1%. NMR ($CDCl_3$) δ: 1.84 (2H, m, CH_2), 3.70 (4H, m, $CH_2 \times 2$), 6.4—7.7 (8H, m, aromatic H), 8.2—9.0 (1H, broad s, OH), 9.80 (1H, s, CHO). IR ν_{max}^{cap} cm^{-1}: 1670 (C=O), 3360 (OH). MS *m/e*: 271 (M^+).

Oxidation of Ic——The reaction mixture was worked up as described above for the oxidation of Ia. IIc and IIIc were obtained and the recovery of Ic was 26.6%.

N-Benzyl-2-formyl-2′-hydroxydiphenylamine (IIc): Yellow viscous oil. Yield, 23.4%. NMR ($CDCl_3$) δ: 4.65 (2H, s, CH_2), 6.7—7.8 (13H, m, aromatic H), 6.81 (1H, s, OH), 9.96 (1H, s, CHO). IR ν_{max}^{cap} cm^{-1}: 1660 (C=O).

2,4-Dinitrophenylhydrazone of IIc: Brown needles (from H_2O–CH_3OH). mp 131—133°. *Anal.* Calcd for $C_{26}H_{21}N_5O_5$: C, 64.59; H, 4.38; N, 14.49. Found: C, 64.40; H, 4.41; N, 14.30.

N-Benzyl-9-acridone (IIIc): mp 177°.[18] Yield, 17.9%. *Anal.* Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.93; H, 5.33; N, 4.99. NMR ($CDCl_3$) δ: 5.78 (2H, s, CH_2), 7.0—7.6 (6H, m, aromatic H), 8.44 (2H, q, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1627 (C=O).

Reduction of IIa——IIa (100 mg) was added to $LiAlH_4$ (120 mg) in dry dioxane (10 ml), and the reaction mixture was stirred at 90° for 12 hr. After cooling, the mixture was poured into ice–water and extracted with CH_2Cl_2. The extract was washed with water, and dried over Na_2SO_4. The residue (75 mg) left after removal of the solvent was chromatographed on silica gel (7 g). Elution with *n*-hexane–CH_2Cl_2 (15: 1) gave V and with CH_2Cl_2 gave IV.

N-Propyl-2-hydroxy-2′-methyldiphenylamine (V): Colorless oil. Yield, 38 mg (40.2%). NMR ($CDCl_3$) δ: 0.94 (3H, t, CH_3), 1.63 (2H, m, CH_2), 2.00 (3H, s, CH_3), 3.32 (2H, t, CH_2), 6.5—7.4 (8H, m, aromatic H).

N-Propyl-2-hydroxy-2′-hydroxymethyldiphenylamine (IV): Colorless prisms (from ether–*n*-hexane). mp 99°. Yield, 22 mg (21.8%). *Anal.* Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.92; H, 7.47; N, 5.64. NMR ($CDCl_3$) δ: 0.94 (3H, t, CH_3), 1.62 (2H, m, CH_2), 3.34 (2H, t, CH_2), 4.60 (2H, s), CH_2 and OH), 6.7—7.3 (8H, m, aromatic H). MS *m/e*: 257 (M^+).

N-Acetyl-2-methoxy-2′-methyldiphenylamine (VII)——A suspension of N-acetyl-*o*-anisidine (1.5 g), *o*-bromotoluene (2.2 g), anhydrous K_2CO_3 (940 mg), Cu powder (60 mg) and I_2 (60 mg) was heated at 200° for 28 hr.[6] The reaction mixture was evaporated to dryness under reduced pressure. Water was added to the residue and the solution was extracted with CH_2Cl_2. The solvent layer was dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown oily residue, which was chromatographed on silica gel. The first elution with *n*-hexane–CH_2Cl_2 (10: 1) gave unchanged N-acetyl-*o*-anisidine. The residue obtained from the second eluate was recrystallized from ether to give 440 mg (19.0%) of VII as colorless prisms, mp 112°. *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.25; H, 6.68; N, 5.40. NMR ($CDCl_3$) δ: 2.00 (3H, s, $COCH_3$), 2.46 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 6.7—7.5 (8H, m, aromatic H).

2-Methoxy-2′-methyldiphenylamine (VIII)——A solution of VII (216 mg) in abs. THF (2 ml) was added dropwise into a suspension of $LiAlH_4$ (321 mg) in abs. THF (6 ml). The reaction mixture was stirred at room temperature. After 20 min, the mixture was poured into ice-water and extracted with CH_2Cl_2. The solvent layer was washed with water, and dried over Na_2SO_4. The residue left after removal of the solvent was chromatographed on alumina (40 g). The first elution with *n*-hexane gave N-ethyl-2-methoxy-2′-methyldiphenylamine which was isolated as a colorless oil. Yield, 74 mg (36.2%), NMR ($CDCl_3$) δ: 1.12 (3H, t, CH_3), 1.19 (3H, t, CH_3), 3.59 (2H, q, CH_2), 3.69 (3H, s, OCH_3), 6.6—7.4 (8H, m, aromatic H). The second elution gave VIII (colorless oil). Yield, 80 mg (44.3%). NMR ($CDCl_3$) δ: 2.25 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 5.88 (1H, broad s, NH), 6.8—7.5 (8H, m, aromatic H).

2-Methoxy-2′-methyl-N-propyldiphenylamine (VI)——i) Dimethyl sulfate was added to a solution of V in acetone–CH_3OH (1: 1, 2 ml) and 10% NaOH, and the mixture was stirred at room temperature for 20 min. Water was added to the reaction mixture, and this solution was extracted with CH_2Cl_2. The solvent layer 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. Elution with CH_2Cl_2 gave a colorless viscous oil (38 mg, 94.3%). NMR ($CDCl_3$) δ: 0.91 (3H, t, CH_3), 1.60 (2H, m, CH_2), 1.90 (3H, s, CH_3), 3.48 (2H, t, NCH_2), 3.74 (3H, s, OCH_3), 6.5—7.1 (8H, m, aromatic H). MS *m/e*: 255 (M^+).

ii) A suspension of VIII (123 mg) and sodium amide in abs. toluene was stirred under reflux, and after 3 hr 1-bromopropane (1.2 ml) was added to this suspension. The reaction mixture was stirred under reflux at 2 hr, then cooled. Water was then added, and the solution was extracted with benzene. The benzene layer was washed with water and dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown oily residue (160 mg), which was chromatographed on alumina (30 g). Elution with *n*-hexane–CH_2Cl_2 (3: 1) gave a colorless viscous oil (79 mg, 53.7%). NMR, IR and MS spectra of the product obtained by method (i) were identical with those of this oil.

Oxidation of Id——A mixture of Id (400 mg) and 85% *m*-CPBA (780 mg) in CH_2Cl_2 (100 ml)–saturated aq. $NaHCO_3$ (50 ml) was stirred for 4.5 hr at room temperature. The reaction mixture was washed with 10% $NaHCO_3$ and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown residue which was chromatographed on silica gel (15 g). Elution with CH_2Cl_2 gave 62 mg of (A) and elution with CH_2Cl_2–CH_3OH (5: 1) gave 300 mg of IX. Compound (A) was chromatographed on alumina (40 g). Elution with *n*-hexane–CH_2Cl_2 (4: 1) gave IIId and elution with CH_2Cl_2 gave IId.

N-Methyldibenz[*b*,*f*]azepine-N-oxide (IX): mp 151—155° (dec.). Yield, 284 mg (66.0%). *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.41; H, 5.99; N, 6.20. NMR ($CDCl_3$) δ: 3.54 (3H, s, CH_3), 7.1—7.7 (6H, m, aromatic H), 9.0 (2H, d, aromatic H). MS *m/e*: 223 (M^+).

N-Methyl-2-formyl-2′-hydroxydiphenylamine (IId): Yellow oil. Yield, 45 mg (10.3%). NMR ($CDCl_3$) δ: 3.12 (3H, s, CH_3), 6.7—7.7 (8H, m, aromatic H), 9.78 (1H, s, CHO). IR ν_{max}^{cap} cm^{-1}: 1682 (C=O), 3380 (OH). MS *m/e*: 227 (M^+).

N-Methyl-9-acridone (IIId): mp 204—205°.[19] Yield, 5 mg (1.2%). *Anal.* Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.26; H, 5.29; N, 6.88. NMR ($CDCl_3$) δ: 3.77 (3H, s, CH_3), 7.0—8.6 (8H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O).

Reactions of IX——i) An aliquot of 1 N HCl (1.5 ml) was added to a stirred suspension of IX (50 mg) in 10% Na_2SO_3 (1.5 ml). The mixture was stirred for 10 min, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4. Removal of the solvent by evaporation gave Id in 80.5% yield.

ii) A mixture of IX (100 mg) and 10% Pd-C (10 mg) in CH_3OH (10 ml) was stirred under a hydrogen atmosphere at room temperature for 1.5 hr. The catalyst was then removed by filtration. The solution was evaporated to dryness to give 85 mg of N-methyl-10,11-dihydrodibenz[*b*,*f*]azepine (X) as colorless needles (from CH_3OH), mp 106—107°: *Anal.* Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.25; H, 7.25; N, 6.54. NMR ($CDCl_3$) δ: 3.13 (4H, s, $CH_2 \times 2$), 3.31 (3H, s, CH_3), 6.7—7.3 (8H, m, aromatic H). MS *m/e*: 209 (M^+). IR and NMR spectra and physical data of X were identical with those of the product obtained by Huisgen's method.[14]

iii) IX (50 mg) was heated at 160—170° for 20 min. The reaction mixture was chromatographed on silica gel. Dibenz[*b*,*f*]azepine (XI: 5 mg) and Id (15 mg) were obtained.

Oxidation of Ie——A mixture of Ie (500 mg) and 85% *m*-CPBA (377 mg) in CH_2Cl_2 (60 ml)–saturated aq. $NaHCO_3$ (25 ml) was stirred at room temperature. After 3 hr, 85% *m*-CPBA (377 mg) was added to the reaction mixture. After being stirred for 7 hr, the reaction mixture was washed with 10% Na_2SO_3, 10% $NaHCO_3$ and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown residue (530 mg), which was chromatographed on silica gel (40 g). The first elution with *n*-hexane–CH_2Cl_2 (3: 2) provided unchanged Ie (203 mg). The second elution gave N-(*o*-hydroxyphenyl)dibenz[*b*,*f*]azepine (XII) as yellow prisms (from *n*-hexane), mp 150—151°. Yield, 116 mg (21.9%). *Anal.* Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.42; H, 5.39; N, 5.10. NMR ($CDCl_3$) δ: 6.84 (2H, s, $C_{10,11}$–H), 6.9—7.4 (11H, m, aromatic H), 7.84 (1H, q, aromatic H). MS *m/e*: 285 (M^+).

Oxidation of XII——A mixture of XII (116 mg) and 85% *m*-CPBA (165 mg) in CH_2Cl_2 (23 ml)–saturated aq. $NaHCO_3$ (12 ml) was stirred at room temperature. After 19 hr, 85% *m*-CPBA (165 mg) was added to the reaction mixture. After being stirred for 6.5 hr, the reaction mixture was washed with 10% Na_2SO_3, 10% $NaHCO_3$ and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave a brown residue, which was chromatographed on silica gel (5 g). Elution with CH_2Cl_2 gave 2-formyl-2′-hydroxy-N-(*o*-hydroxyphenyl)diphenylamine (IIe) as yellow prisms (recrystallized from *n*-hexane–CH_2Cl_2), mp 169—170°. Yield, 38 mg (30.6%). *Anal.* Calcd for $C_{20}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.76; H, 5.01; N, 4.66. NMR ($CDCl_3$) δ: 6.68—7.72 (12H, m, aromatic H), 9.76 (1H, s, CHO). IR ν_{max}^{KBr} cm^{-1}: 1643 (C=O), 3440 (OH). MS *m/e*: 304 ($M^+ - 1$).

N-(*o*-Methoxyphenyl)dibenz[*b*,*f*]azepine (XIII)——Dimethyl sulfate (120 mg) was added to a solution of XII (60 mg) in acetone (1 ml) and 30% KOH (0.5 ml). The mixture was stirred at room temperature for 30 min. Water was then added, and the solution was extracted with CH_2Cl_2. Removal of the solvent

by evaporation gave crystals, which were recrystallized from CH_3OH to afford colorless needles (45 mg), mp 99°. *Anal.* Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 83.97; H, 5.79; N, 4.85. NMR ($CDCl_3$) δ: 3.41 (3H, s, OCH_3), 6.4—7.5 (12H, m, aromatic H), 6.77 (2H, s, 10,11-double bond).

10,11-Dihydro-N-(*o*-methoxyphenyl)dibenz[*b*,*f*]azepine (XVI)——i) A mixture of XIII (60 mg) and 10% Pd-C (36 mg) in CH_3OH was stirred under a hydrogen atmosphere at room temperature. The catalyst was removed by filtration. The filtrate was evaporated to dryness to give crystals, which were recrystallized from EtOH to afford colorless prisms (54 mg), mp 101—102°. *Anal.* Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.38; N, 4.65. Found: C, 83.40; H, 6.39; N, 4.62. NMR ($CDCl_3$) δ: 3.20 (4H, s, $C_{10,11}$–H), 3.69 (3H, s, OCH_3), 6.7—7.3 (12H, m, aromatic H).

ii) A mixture of 10,11-dihydrodibenz[*b*,*f*]azepine (XIV) (2 g), iodoanisole (XV) (3.2 g), anhydrous K_2CO_3 (1.56 g) and Cu powder (200 mg) in nitrobenzene (10 ml) was stirred under reflux for 20 hr, then diluted with water and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated to dryness to give crystals, which were recrystallized from EtOH to afford colorless prisms (1.07 g). Physical and spectral data for these crystals coincided with those of crystals obtained by method i).

Oxidation of N-Acyldibenz[*b*,*f*]azepine (If—k)——A mixture of I (2 mmol) and 85% *m*-CPBA (4 mmol) in CH_2Cl_2 (60 ml)–saturated aq. $NaHCO_3$ (30 ml) was stirred at room temperature. After 8—10 hr, 85% *m*-CPBA (4 mmol) was added to the reaction mixture. After being stirred for 14—16 hr, the reaction mixture was washed with 10% Na_2SO_3, 10% $NaHCO_3$ and water, and dried over Na_2SO_4. Removal of the solvent by evaporation gave N-acyldibenz[*b*,*f*]azepine-10,11-oxide (XVII). Analytical and physical data are summarized in Table I.

Kinetic Measurements of Oxidation Rates——Instrument and conditions. HPLC was carried out with a Waters 6000A pump, a Shimadzu SIL-1A sample injector and a Waters UV M-440 detector (254 nm). Integrator: Shimadzu Chromatopac-E1A. Column: Merck Lichrosorb RP-18 (5 μm), 4.3(ϕ) × 150 mm. Eluent: CH_3OH–H_2O (9: 1 or 7: 3).

N-Substituted-dibenz[*b*,*f*]azepines (0.02 mmol) were dissolved in CH_2Cl_2 (10 ml) and *m*-terphenyl or biphenyl was added to this solution as an internal standard. The mixture was immersed in a thermostat controlled at 0°, 15° or 30° ± 0.2° and *m*-CPBA (0.2 mmol) was added to the mixture. The reaction mixture was sampled (0.5—1 μl) at appropriate intervals and the samples were injected into the HPLC machine. The decrease of N-substituted-dibenz[*b*,*f*]azepine was monitored by HPLC and the oxidation 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 dibenz[*b*,*f*]azepine (mol/l), and x is the mol number of unchanged dibenz-[*b*,*f*]azepine at the time (t).

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