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Acid-Catalyzed Double-Cyclization Reactions of *N,N*-Dibenzylaminoacetaldehyde Dialkyl Acetals and Related Compounds: General Synthesis of 7,12-Dihydro-5*H*-6,12-methanodibenz-[*c,f*]azocines and Related Compounds

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A number of *N,N*-dibenzylaminoacetaldehyde dialkyl acetals (**1**) double-cyclized in 70% perchloric acid or triflic acid (trifluoromethanesulfonic acid) to give good yields of 7,12-dihydro-5*H*-6,12-methanodibenz[*c,f*]azocines (**2**) even when a powerful electron-withdrawing substituent, for example a nitro group, was present on the benzene ring. Triflic acid treatment of α-dibenzylaminoketones (**3**) caused double-cyclization to give 12-substituted derivatives of **2**.

Keywords——Friedel–Crafts type cyclization; perchloric acid (70%); triflic acid; *N,N*-dibenzylaminoacetaldehyde dialkyl acetal; α-dibenzylaminoketone; dibenzazocine; dibenzazonine; isopavine; nitrobenzene

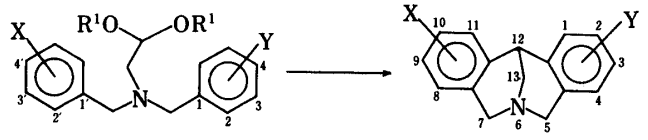
As a modification of the Pomeranz–Fritsch reaction,[1] previous reports have described the acid-catalyzed Friedel–Crafts type intramolecular cyclization of *N*-(1,2-diphenylethyl)-aminoacetaldehyde dialkyl acetal to 10,11-dihydro-10,5-(iminomethano)-5*H*-dibenzo[*a,d*]cycloheptene (isopavine alkaloid),[2] that of *N*-benzyl-*N*-phenylethylaminoacetaldehyde dialkyl acetal to 6,7,8,13-tetrahydro-5*H*-6,13-methanodibenz[*c,f*]azonine,[2b-e] and that of *N,N*-dibenzylaminoacetaldehyde dialkyl acetal to 7,12-dihydro-5*H*-6,12-methanodibenz[*c,f*]azocine,[3] usually by using 6 N hydrochloric acid as a catalyst. However, the cyclization could proceed only when electron-releasing substituents such as methoxy, methylenedioxy, and hydroxy groups were present on the benzene rings.[2,3]

We report here that *N,N*-dibenzylaminoacetaldehyde dialkyl acetals (**1**), α-dibenzylaminoketones (**3**) and related compounds are effectively double-cyclized by using 70% perchloric acid or triflic acid (trifluoromethanesulfonic acid) as a cyclization catalyst to give 7,12-dihydro-5*H*-6,12-methanodibenz[*c,f*]azocines (**2**, **4**) and the corresponding bicyclic amines, respectively, without any requirement for electron-releasing substituents, and even when electron-withdrawing groups such as halogens and nitro are present.[4,5] The scope and limitations, and mechanistic aspects of the present double-cyclization are also discussed.

Results and Discussion

Double-Cyclizations of the Acetals (1) with 70% Perchloric Acid

Treatment of 1 mmol of **1a** (R^1 = Et, X = Y = H) with 1 ml of 70% perchloric acid at room temperature for 12 h gave the bicyclic amine (**2a**) in 95% isolated yield. The structural proof of **2a** was based on the spectral data, and was confirmed by the Hofmann degradation of its *N*-methyl quaternary salt (**5**) to the dibenz[*c,f*]azocine derivative (**6**). The proton nuclear



1 : R^1=Me or Et
X, Y=H, halogen or nitro

2

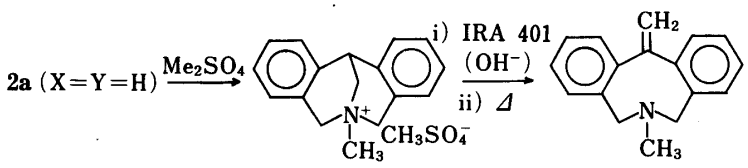


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Chart 1

TABLE I. Reactions of the Acetals (1) with 70% Perchloric Acid

Acetal (1)				Yield[a] (%)	Bicyclic amine (2)		
	X	Y	R			X	Y
1a	H	H	Et	95[b]	**2a**	H	H
1b	H	3,4-OCH_2O	Et	72[b]	**2b**	H	3,4-OCH_2O
1c	H	3-OCH_3	Et	80[b]	**2c**	H	3-OCH_3
1d	3′-Cl	3-Cl	Et	33[b]	**2d**	9-Cl	3-Cl
				82[c]	**2d**		
1e	3′-F	3-F	Et	87[c]	**2e**	9-F	3-F
1f	4′-Br	4-Br	Me	89[c]	**2f**	10-Br	2-Br
1g	4′-Cl	4-Cl	Me	74[c]	**2g**	10-Cl	2-Cl
1h	4′-OCH_3	4-Cl	Et	76[c]	**2h**	10-OCH_3	2-Cl
1i	2′-Cl	2-Cl	Me	78[c]	**2i**	8-Cl	4-Cl
1j	4′-Cl	2-Cl	Et	79[c]	**2j**	10-Cl	4-Cl
1k	H	4-NO_2	Me	0[d]	**2k**	H	2-NO_2

a) Isolated yield. *b*) The reaction was carried out at room temperature. *c*) The reaction was carried out at 80 °C for 3 h. *d*) The reaction was carried out at various temperatures.

magnetic resonance (^{1}H-NMR) spectrum ($CDCl_3$/TMS) of **2a** was characteristic, and it showed an eight-proton multiplet due to the aromatic protons at δ 7.10, a one-proton triplet (J=1.8 Hz) due to H-12 (bridge head) at δ 3.38, a two-proton doublet (J=1.8 Hz) due to H-13 (bridge methylene) at δ 3.73, and a pair of doublets due to the four protons on C-5 and C-7 at δ 3.93 and 4.57 (J=17.5 Hz). In general, the bicyclic amines (**2b—j**) (see Table I) exhibit this characteristic pair of doublets as an AB-type signal in the region of δ 3.5—4.8, assignable to the protons on the methylene group between the nitrogen and the benzene ring.

The effectiveness of 70% perchloric acid as a catalyst for the double-cyclization reaction of the acetals was examined with a series of acetals (**1d—k**) having benzene rings with halogens or a nitro group. While the double-cyclizations of **1a—c** were virtually completed at room temperature, those of the halo-substituted acetals (**1d—j**) required heating at 80 °C for 3 h in order to reach completion. The yields of the bicyclic amines (**2b—j**) were excellent, as shown in Table I.

To test whether this reaction of **1a** depends on the kind of acid or the acidity (Hammett acidity function; H_0),[6] a series of Brønsted acids was examined. The yields of **2a** after treatment of **1a** with 10 molar equiv. of each acid at room temperature for 3 h are shown in Table II. Sulfuric acid at more than 75% concentration (H_0 = −6.71) gave **2a** in 90% or higher

TABLE II. Reactions of the Acetal (**1a**) with 10 Molar Equiv. of Aqueous Acids

Acid	H_0 value[a]	Prod. No.	Yield[b] (%)	Acid	H_0 value[a]	Prod. No.	Yield[b] (%)
				98% H_2SO_4	−10.27	**2a**	98.4
				90% H_2SO_4	−9.03	**2a**	98.5
				85% H_2SO_4	−8.29	**2a**	97.0
70% $HClO_4$	−7.75	**2a**	98.2				
				80% H_2SO_4	−7.52	**2a**	98.1
				75% H_2SO_4	−6.71	**2a**	90.5
				70% H_2SO_4	−5.92	**2a**	58.8
65% $HClO_4$	−6.63—−6.39	**2a**	24.8				
				65% H_2SO_4	−5.18	**2a**	24.8
						7	63.2
60% $HClO_4$	−5.06	**2a**	0.3				
		7	95.0	60% H_2SO_4	−4.51	**2a**	4.6
36% HCl	−4.41—−3.99	**2a**	0				
60% HNO_3	−3.72—−3.42	**2a**	0				
47% HBr	−2.11—−1.93	**2a**	0				

a) The Hammett acidity function.[6] *b*) The yields were checked by GC.

yield. In contrast, with 60% perchloric acid ($H_0 = -5.06$) as a catalyst, the yield of **2a** was only 0.3%, and the hydrolyzed *N*,*N*-dibenzylaminoacetaldehyde (**7**) was obtained in 95% yield. In the cases of other acids such as 36% hydrochloric acid, 48% hydrobromic acid, and 60% nitric acid, the double-cyclization of **1a** did not proceed at all. These results suggest that the acidity governs the yield of **2a**, and the acidity of the catalyst for double-cyclization should correspond to an H_0 value of less than −6.7.

Furthermore, we examined the reaction under anhydrous conditions. In 100% phosphoric acid ($H_0 = -5.25$) the reaction did not proceed, whereas in 65% sulfuric acid ($H_0 = -5.2$) the yield of **2a** was 25%. In the case of methanesulfonic acid ($H_0 = -7.85$), the yield was only 11.3%. The strongest acid, triflic acid ($H_0 = -13.0$[7]), catalyzed the reaction virtually to completion.

Double-Cyclizations of the Acetals (1) with Triflic Acid

In view of the acidity effect on the double-cyclization, the reaction of a series of acetals (**1**) having a halogen substituent at the *meta*-position to the cyclization position on each benzene ring was examined (Table III). As expected, triflic acid caused effective double-cyclization at room temperature. The yields of the halo-substituted bicyclic amines were higher than those in 70% perchloric acid. Furthermore, treatment of the nitro-substituted acetal (**1k**) with triflic acid at 40 °C gave the corresponding bicyclic amine (**2k**) in 81% isolated yield. The structure assignment of **2k** was based on the spectral and analytical data. The double-cyclization of the mononitro acetal (**1p**) also proceeded smoothly (Table IV). It is noteworthy that these reactions involve the first successful Friedel–Crafts type alkylation of nitro-substituted benzene. On the other hand, the dinitro acetal (**1q**) gave a mono-cyclized product (**8**) in 95% isolated yield, without formation of the corresponding bicyclic amine (**2q**). The structure assignment of **8** was based on its ^{1}H-NMR spectrum. This reaction should be useful for the synthesis of 1,2,3,4-tetrahydroisoquinolines.

Double-Cyclization of α-Dibenzylaminoketones

In order to enlarge the scope of the double-cyclization, a series of α-dibenzylaminoketone derivatives (**3**), which have a potential double-carbocation, was prepared. Thus, treatment of **3a** with 70% perchloric acid at 80 °C gave the 12-methyl bicyclic amine (**4a**) in 75% yield. The

TABLE III. Reactions of the Halo-Substituted Acetals (1) with Triflic Acid

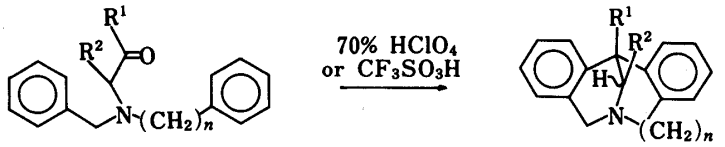
Acetal (1)				Yield[a] (%)	Bicyclic amine (2)		
	X	Y	R			X	Y
1f	4′-Br	4-Br	Me	92 (89)[b]	**2f**	10-Br	2-Br
1g	4′-Cl	4-Cl	Me	93 (74)[b]	**2g**	10-Cl	2-Cl
1i	2′-Cl	2-Cl	Me	87 (78)[b]	**2i**	8-Cl	4-Cl
1m	H	2-Cl	Et	95 (90)[b]	**2m**	H	4-Cl
1n	H	4-Cl	Et	96 (93)[b]	**2n**	H	2-Cl

a) Isolated yield. *b*) Isolated yield in the case of treatment of the acetal with 70% perchloric acid at 80 °C for 3 h.

TABLE IV. Reactions of the NO_2-Substituted Acetals (1) with Triflic Acid

Acetal (1)				Yield[a] (%)	Product		
	X	Y	R			X	Y
1k	H	4-NO_2	Me	81	**2k**	H	2-NO_2
1p	4′-NO_2	4-Cl	Et	73	**2p**	10-NO_2	2-Cl
1q	4′-NO_2	4-NO_2	Me	0	**2q**	10-NO_2	2-NO_2
				95	**8**		

a) Isolated yield.

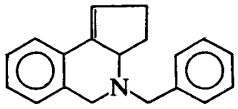


3: R^1 = alkyl or phenyl, R^2 = H or alkyl, $n=1$ — **4**: $n=1$
15: R^1 = phenyl, R^2 = H, $n=2$ — **16**: $n=2$

Chart 2

structure assignment of **4a** was based on the spectral and analytical data. The ketones, **3b** and **3c**, were also double-cyclized to the corresponding bicyclic amines, **4b** and **4c**, respectively. In the reaction of the cyclic ketone (**3d**) with 70% perchloric acid, the double-cyclized **4d** was a minor product (>20%), and the mono-cyclized **9** was isolated as a major product (60%). Fortunately, when the ketone (**3d**) was treated with triflic acid at room temperature, the bicyclic amine (**4d**) was formed in 95% yield. Furthermore, as the double-cyclization of *N*,*N*-dibenzylphenacylamine (**3e**) with 70% perchloric acid was unsuccessful, the reaction of **3e** was performed in triflic acid and the 12-phenyl bicyclic amine (**4e**) was obtained in 95% isolated yield. The phenacylamine derivatives (**3f** and **3g**) in triflic acid were also effectively cyclized to

TABLE V. Reactions of α-Dibenzylaminoketones (3) with Acids

Aminoketone			Conditions			Yield[a] (%)	Product		
	R^1	R^2	Acid	Temp. (°C)	Time (h)			R^1	R^2
3a	CH_3	H	70% $HClO_4$	80	3	75	**4a**	CH_3	H
3c	CH_3	CH_3	70% $HClO_4$	80	3	80	**4b**	CH_3	CH_3
3c	$-(CH_2)_4-$		70% $HClO_4$	80	3	92	**4c**	$-(CH_2)_4-$	
3d	$-(CH_2)_3-$		70% $HClO_4$	80	3	20<	**4d**	$-(CH_2)_3-$	
									
						60	**9**		
			CF_3SO_3H	r.t	o.n[b]	95	**4d**	$-(CH_2)_3-$	
3e	Ph	H	70% $HClO_4$	80	o.n	0	**4e**		
			CF_3SO_3H	r.t	o.n	95	**4e**	Ph	H
3f	*p*-Br-Ph	H	CF_3SO_3H	r.t	o.n	95	**4f**	*p*-Br-Ph	H
3g	*p*-NO_2Ph	H	CF_3SO_3H	r.t	o.n	74	**4g**	*p*-NO_2Ph	H

a) Isolated yields. *b*) The abbreviation o.n stands for overnight.

the corresponding bicyclic amines (**4f** and **4g**).

Further Applications

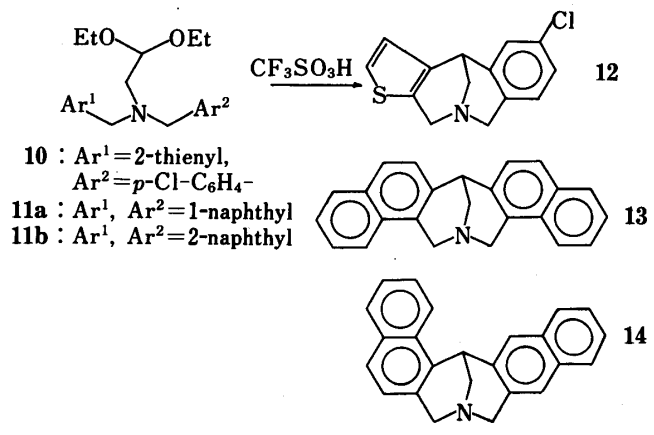


Chart 3

Thus, we have developed a facile and general synthesis of 7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocines and related compounds. This method could be applied to double-cyclizations of aminoacetals having aromatic substituents other than benzene. Thus, treatment of the thiophene-substituted acetal (**10**) with triflic acid at room temperature gave the corresponding bicyclic amine (**12**) in 85% yield. Under the same conditions, double-cyclizations of the naphthalene-substituted acetals (**11a** and **11b**) were examined. The reaction of **11a** afforded the symmetrical bicyclic amine (**13**) in 48% yield. On the other hand, that of **11b** afforded the unsymmetrical product (**14**) in 83% yield. The ^{1}H-NMR of **13** showed a two-proton doublet (J=1.5 Hz) at δ 3.45 due to the bridge methylene protons, but in the ^{1}H-NMR spectrum of **14** the bridge methylene proton signals appeared as two double-doublets (J=2.5 and 12.5 Hz) at δ 3.55 and 3.40. The ^{1}H-NMR spectra, as well as elemental analyses, are consistent with the structures **13** and **14**.

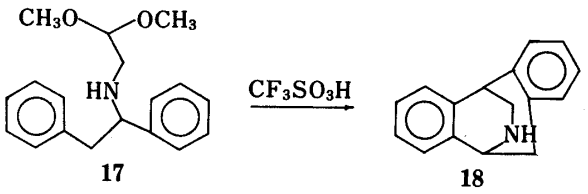


Chart 4

Furthermore, the synthesis of the azonine (**16**) from **15** (Chart 2) and of the isopavine (**18**) from **17** could be achieved by this method.

Mechanism and Conclusion

In order to investigate the mechanism of the double-cyclization of **1a**, the following experiments were carried out. Treatment of **1a** with 70% perchloric acid at 0 °C gave four products. These products were *N*-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**19**) (27%), *N*,*N*-dibenzylaminoacetaldehyde (**7**) (20%), *N*-benzyl-4-ethoxy-1,2,3,4-tetrahydroisoquinoline (**20**) (19%) and the bicyclic amine (**2a**) (20%). On further treatment with 70% perchloric acid at room temperature, two intermediates, **7** and **19**, were readily converted to **2a** in high yields, while the third intermediate **20** gave **2a** in only 40% yield, accompanied by **19** (40%) and the starting **20** (20%) was recovered. From these results, it appears that the reaction proceeds not only *via* the 4-hydroxy intermediate (**19**) but also *via* the 4-alkoxyl intermediate (**9**). Therefore, the mechanism of the reaction is postulated to be as shown in Chart 5.

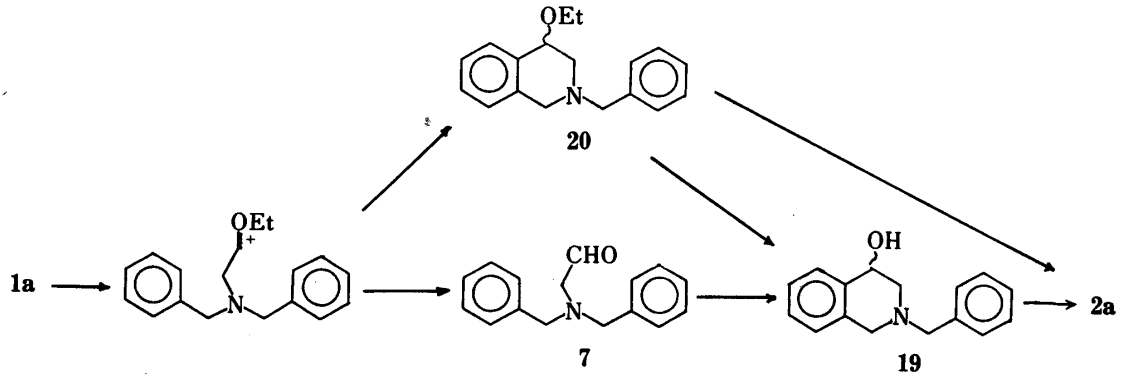


Chart 5

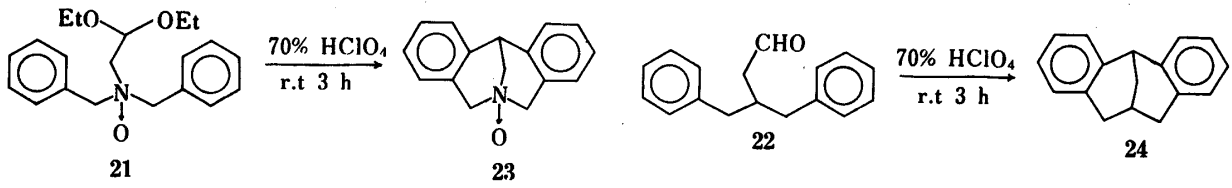


Chart 6

To investigate the contribution[8,9] of the nitrogen of **1a** to the reaction, the *N*,*N*-dibenzylaminoacetal *N*-oxide (**21**) and 3-benzyl-4-phenylbutanal (**22**) were prepared. Under the same conditions as described for the reaction of **1a**, the *N*-oxide (**21**) smoothly produced the corresponding bicyclic amine *N*-oxide (**23**) in 72% yield. The structure of **23** was supported by the ^{1}H-NMR spectrum and was confirmed by the synthesis of **23** by treatment of **2a** with *m*-chloroperbenzoic acid. The C-analogue (**22**) of the aldehyde (**7**) also afforded **24** in 90% yield. Compound **24** was concluded to be a symmetrical bicyclic hydrocarbon from an

inspection of its carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum. These results suggest that the contribution of the nitrogen to the reaction is negligible.

In conclusion, a facile and general synthesis of 7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine and related compounds having electron-withdrawing groups such as halogens and even nitro on the aromatic rings, was established by using 70% perchloric acid and/or triflic acid as a cyclization catalyst. Further studies on the synthesis of bicyclic amines are in progress.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi 215 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian XL-100 (100 MHz) spectrometer and the chemical shifts are reported as δ ppm using tetramethylsilane (TMS) as an internal standard. Mass (MS) spectra were recorded with a JEOL JMS-D 300 GC-MS instrument with an interfaced computer. Microanalyses were done by the Analytical Center, Faculty of Pharmaceutical Sciences, the University of Tokyo.

Preparation of *N*,*N*-Dibenzylaminoacetaldehyde Dialkyl Acetals (1) and Related Compounds (10 and 11)——All of these compounds were prepared by general method A or B. Method A is exemplified by the preparation of **1g**, and method B is exemplified by that of **1j**. In all cases, ^{1}H-NMR and MS spectra of the products were consistent with the proposed structures. The yields, boiling points, ^{1}H-NMR, and MS spectra are given in Table VI.

(a) Method A: Preparation of *N*,*N*-Bis(*p*-chlorobenzyl)aminoacetaldehyde Dimethyl Acetal (1g)——*p*-Chlorobenzyl chloride (3.24 g, 20 mmol) was added to a solution of aminoacetaldehyde dimethyl acetal (1.05 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) in ethanol–water [2 : 1 (v/v), 45 ml], and the mixture was refluxed for 6 h, at the end of which time thin-layer chromatography indicated the absence of the halide. Then, the mixture was cooled and diluted with water (10 ml), and the organic solvent was evaporated off. The product was extracted with methylene chloride (3 × 30 ml) and the extract was washed with brine, and dried over Na_2SO_4. After removal of the solvent, vacuum distillation of the residue gave **1g** (2.97 g).

(b) Method B: Preparation of *N*-(*o*-Chlorobenzyl)-*N*-(*p*-chlorobenzyl)aminoacetaldehyde Diethyl Acetal (1j)——*p*-Chlorobenzaldehyde (10.06 g, 100 mmol) and aminoacetaldehyde diethyl acetal (13.20 g, 100 mmol) were refluxed in ethanol (150 ml) for 3 h and then cooled. The mixture was concentrated by evaporation and the resulting solution was added dropwise to a solution of $NaBH_4$ (5 g) in methanol (100 ml) at room temperature. The whole was stirred at the same temperature for 2 h, and then water (100 ml) was introduced. The organic solvent was evaporated off, and the product was extracted with ether (2 × 100 ml). The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, vacuum distillation of the residue gave *N*-(*p*-chlorobenzyl)aminoacetaldehyde diethyl acetal (23.20 g, 90%). *o*-Chlorobenzyl chloride (1.61 g, 10 mmol) was added to a solution of *N*-(*p*-chlorobenzyl)aminoacetaldehyde diethyl acetal (2.58 g, 10 mmol) and K_2CO_3 (0.69 g, 5 mmol) in ethanol–water [2 : 1 (v/v), 30 ml], and the mixture was refluxed for 4 h, then cooled, and diluted with water (10 ml). The organic solvent was evaporated off, the product was extracted with methylene chloride (3 × 30 ml) and the extract was washed with brine then dried over Na_2SO_4. The solvent was evaporated off and vacuum distillation of the residue gave **1j** (3.31 g).

70% Perchloric Acid Catalyzed Double-Cyclization of *N*,*N*-Dibenzylaminoacetaldehyde Dialkyl Acetals (1) and Related Compounds——The general procedure with 70% perchloric acid as the catalyst is described for the double-cyclization of **1a** as an example of general procedure A, and that of **1d** as an example of general procedure B.

(a) General Procedure A: Double-Cyclization of *N*,*N*-Dibenzylaminoacetaldehyde Diethyl Acetal (1a) to 7,12-Dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine (2a)——The acetal (**1a**) (313 mg, 1 mmol) was added dropwise to 70% perchloric acid (1 ml) with stirring at *ca.* −30 °C. The mixture was allowed to stand overnight at room temperature. The precipitated perchlorate of **2a** was collected, and then basified with 10% NaOH aq. The product was extracted with methylene chloride and the extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on a short alumina column (benzene) to give **2a** (210 mg, 95%), mp 133—134 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.30—7.20 (8H, aromatic H), 4.57 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.93 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.73 (1H, t, J=1.8 Hz, $PhCHPh$), 3.38 (2H, d, J=1.8 Hz). MS *m*/*e*: 221 (M^+). *Anal.* Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.81; H, 6.84; N, 6.31.

In a similar manner, **1b** and **1c** were double-cyclized to the corresponding products. The physical properties and the spectral data are given below. In all cases, the ^{1}H-NMR and MS spectra were consistent with the proposed structures. The yields are summarized in Table I.

2b: mp 150—151 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.50—6.90 (6H, m, aromatic H), 4.58 (1H, d, J=17.5 Hz, one of NCH_2Ph), 4.46 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.90 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.80 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.58 (1H, t, J=2.1 Hz, $PhCHPh$), 3.33 (2H, d, J=2.1 Hz, NCH_2CH). MS *m*/*e*: 265 (M^+). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.69; N, 5.30.

TABLE VI. *N,N*-Dibenzylaminoacetaldehyde Dialkyl Acetals and Related Compounds

Acetal	bp (°C/mmHg)	Yield[a] (%)	Method	MS *m/e*	^{1}H-NMR δ ($CDCl_3$)
1a	134/0.01	84	A	289 (M^+)	7.30—7.20 (10H, m), 4.42 (1H, t, J=5.0), 3.58 (4H, s), 2.62 (2H, d, J=5.0), 1.10 (6H, t, J=6.0)
1b	193/0.08	82	B	333 (M^+)	7.40—7.05 (5H, m), 6.89 (1H, s), 6.70 (2H, s), 5.78 (2H, s), 4.44 (1H, t, J=5.4), 3.61 (2H, s), 3.52 (2H, s), 3.48 (4H, m), 2.62 (2H, d, J=5.4), 1.11 (6H, t, J=6.6)
1c	142/0.03	86	B	319 (M^+)	7.40—7.10 (6H, m), 6.80—6.70 (3H, m), 4.42 (1H, t, J=5.0), 3.90 (3H, s), 3.59 (2H, s), 3.54 (2H, s), 3.48 (4H, q, J=7.0), 2.60 (2H, d, J=5.0), 1.09 (6H, t, J=7.0)
1d	148/0.001	81	A	357 (M^+) 359 (M^+) 361 (M^+)	7.30—7.10 (8H, m), 4.46 (1H, t, J=5.2), 3.56 (4H, s), 3.49 (4H, q, J=7.0), 2.61 (2H, d, J=5.2), 1.10 (6H, t, J=7.0)
1e	173/0.02	79	A	325 (M^+)	7.30—7.00 (8H, m), 4.48 (1H, t, J=5.2), 3.54 (4H, s), 3.48 (4H, q, J=7.0), 2.62 (2H, d, J=5.2), 1.10 (6H, t, J=7.0)
1f	151/0.008	83	A	417 (M^+) 419 (M^+) 421 (M^+)	7.50—7.10 (8H, m), 4.46 (1H, t, J=5.0), 3.53 (4H, s), 3.31 (6H, s), 2.62 (2H, d, J=5.0)
1g	168—169/0.01	84	A	353 (M^+)	7.30—7.20 (8H, m), 4.50 (1H, t, J=5.0), 3.57 (4H, s), 3.30 (6H, s), 2.60 (2H, d, J=5.0)
1h	133/0.005	84	B	353 (M^+) 355 (M^+)	7.20—6.70 (8H, m), 4.48 (1H, t, J=5.2), 3.59 (2H, s), 3.55 (2H, s), 3.48 (4H, q, J=7.0), 2.61 (2H, d, J=5.2), 1.09 (6H, t, J=7.0)
1i	173/0.02	83	A	329 (M^+) 331 (M^+) 333 (M^+)	7.30—7.10 (8H, m), 4.49 (1H, t, J=5.0), 3.58 (4H, s), 3.32 (6H, s), 2.63 (2H, d, J=5.0)
1j	189—191/0.03	78	B	381 (M^+)	7.80—7.30 (8H, m), 4.59 (1H, t, J=5.0), 3.79 (2H, s), 3.65 (2H, s), 3.50 (4H, m), 2.64 (2H, d, J=5.0), 1.08 (6H, m)
1k	Oil[b]	82	B	306 (M^+)	8.30—7.20 (9H, m), 4.52 (1H, t, J=5.0), 3.82 (2H, s), 3.54 (2H, s), 3.30 (6H, s), 2.66 (2H, d, J=5.0)
1m	165/0.02	86	B	323 (M^+) 325 (M^+)	7.30—7.00 (9H, m), 4.50 (1H, t, J=5.2), 3.59 (2H, s), 3.57 (2H, s), 3.49 (4H, q, J=7.0), 2.63 (2H, d, J=5.2), 1.08 (6H, t, J=7.0)
1n	146/0.008	83	B	323 (M^+) 325 (M^+)	7.30—7.10 (9H, m), 4.52 (1H, t, J=5.0), 3.61 (2H, s), 3.58 (2H, s), 3.48 (4H, q, J=7.0), 2.62 (2H, d, J=5.0), 1.10 (6H, t, J=7.0)
1p	Oil[b]	84	B	368 (M^+) 370 (M^+)	8.30—7.30 (8H, m), 4.65 (1H, t, J=5.0), 3.82 (2H, s), 3.70 (2H, s), 3.57 (4H, q, J=8.0), 2.70 (2H, d, J=5.0), 1.20 (6H, t, J=8.0)
1q	Oil[b]	78	A	351 (M^+)	8.30—7.70 (8H, m), 4.65 (1H, t, J=5.0), 3.84 (4H, s), 3.35 (6H, s), 2.71 (2H, d, J=5.0)
10	120/0.006	79	B	325 (M^+) 327 (M^+)	7.30—6.80 (7H, m), 4.48 (1H, t, J=5.0), 3.90 (2H, s), 3.61 (2H, s), 3.49 (4H, m), 2.76 (2H, d, J=5.0), 1.12 (6H, t, J=7.0)
11a	193/0.01	73	A	413 (M^+)	7.85—7.40 (14H, m), 4.75 (1H, t, J=5.2), 3.90 (4H, s), 3.48 (4H, q, J=7.0), 2.74 (2H, d, J=5.2), 1.16 (6H, t, J=7.0)
11b	183/0.008	79	A	413 (M^+)	7.80—7.40 (14H, m), 4.78 (1H, t, J=5.2), 3.92 (4H, s), 3.51 (4H, q, J=7.0), 2.76 (2H, d, J=5.2), 1.20 (6H, t, J=7.0)

a) The yield is based on the corresponding aminoacetaldehyde dialkyl acetal. *b*) After chromatographic purification (alumina, benzene).

2c: Oil after chromatographic purification (alumina, benzene). ^{1}H-NMR ($CDCl_3$) δ: 7.40—6.90 (7H, m, aromatic H), 4.58 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.84 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.62 (1H, t, J=2.4 Hz, $PhCHPh$), 3.33 (2H, d, J=2.4 Hz, NCH_2CH). MS *m/e*: 251 (M^+).

(b) General Procedure B: Double-Cyclization of *N,N*-Di(*p*-chlorobenzyl)aminoacetaldehyde Diethyl Acetal (1d) to 3,9-Dichloro-7,12-dihydro-5*H*-6,12-methanodibenz[*c,f*]azocine (2d)——The acetal (**1d**) (1.08 g, 2.8 mmol) was added dropwise to 70% perchloric acid (2.8 ml) with stirring at *ca.* −30 °C. The mixture was allowed to warm up to room temperature over a period of 2 h, then heated at 80 °C for 3 h and cooled. The reaction mixture was poured onto cracked ice (*ca.* 10 g) and basified with 2 N NaOH aq., then the product was extracted with methylene chloride (3 × 30 ml). The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on alumina (10 g) with benzene as the eluent to give **2d** (665 mg, 82%), mp 161—162 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.10—6.80 (6H, m, aromatic H), 4.45 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.78 (2H. d, J=18.0 Hz, one of NCH_2Ph), 3.55 (1H, t, J=2.0 Hz, $PhCHPh$), 3.15 (2H, d, J=2.0 Hz, NCH_2CH). MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{16}H_{13}Cl_2N$: C, 66.23; H, 4.51; N, 4.83. Found: C, 66.20; H, 4.52; N, 4.58.

In a similar manner, **1e**, **1f**, **1g**, **1h**, **1i**, and **1j** were double-cyclized to the corresponding products. The physical properties and the spectral data are given below, and the yields are summarized in Tables I and IV.

2e: mp 166—168 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.30—6.80 (6H, m, aromatic H), 4.54 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.88 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.71 (1H, t, J=1.5 Hz, $PhCHPh$), 3.33 (2H. d, J=1.5 Hz, NCH_2CH). MS *m/e*: 257 (M^+). *Anal.* Calcd for $C_{16}H_{13}F_2N$: C, 74.69; H, 5.09; N, 5.44. Found: C, 74.62; H, 5.01; N, 5.49.

2f: mp 193—195 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.40 (2H, m, aromatic H), 7.24 (2H, d, J=7.0 Hz, aromatic H), 6.86 (2H, d, J=7.0 Hz, aromatic H), 4.49 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.80 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.64 (1H, t, J=1.5 Hz, $PhCHPh$), 3.32 (2H, d, J=1.5 Hz, NCH_2CH). MS *m/e*: 377 (M^+). *Anal.* Calcd for $C_{16}H_{13}Br_2N$: C, 50.69; H, 3.46; N, 3.69. Found: C, 50.61; H, 3.42; N, 3.74.

2g: mp 173—174 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.20—7.10 (8H, m, aromatic H), 4.50 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.81 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.58 (1H, t, J=2.0 Hz, $PhCHPh$), 3.20 (2H, d, J=2.0 Hz, NCH_2CH). MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{16}H_{13}Cl_2N$: C, 66.23; H, 4.51; N, 4.83. Found: C, 66.29; H, 4.49; N, 4.71.

2h: mp 179—182 °C (dec.) as the iodomethylate (ethanol). ^{1}H-NMR ($CDCl_3$) (free base) δ: 7.10—6.80 (6H, m, aromatic H), 4.60 (2H, d, J=17.0 Hz, one of NCH_2Ph), 3.80 (2H, d, J=17.0 Hz, one of NCH_2Ph), 3.70 (3H, s, OCH_3), 3.62 (1H, t, J=1.5 Hz, $PhCHPh$), 3.30 (2H, d, J=1.5 Hz, NCH_2CH). MS *m/e*: 285 (M^+). *Anal.* Calcd for $C_{17}H_{16}ClNO \cdot CH_3I$: C, 50.55; H, 4.48; N, 3.27. Found: C, 50.49; H, 4.45; N, 3.28.

2i: mp 165—166 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.10—6.90 (6H, m, aromatic H), 4.45 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.95 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.70 (1H, t, J=2.0 Hz, $PhCHPh$), 3.30 (2H, d, J=2.0 Hz, NCH_2CH). MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{16}H_{13}Cl_2N$: C, 66.23; H, 4.51; N, 4.83. Found: C, 66.18; H, 4.50; N, 4.76.

2j: mp 150—151 °C (acetone–ethanol). ^{1}H-NMR ($CDCl_3$) δ: 7.20—6.80 (6H, m, aromatic H), 4.46 (1H, d, J=18.0 Hz, one of NCH_2Ph), 4.40 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.89 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.85 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.63 (1H, t, J=2.0 Hz, $PhCHPh$), 3.24 (2H, d, J=2.0 Hz, NCH_2CH). MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{16}H_{13}Cl_2N$: C, 66.23; H, 4.51; N, 4.83. Found: C, 66.18; H, 4.42; N, 4.85.

The Hofmann Degradation of 7,12-Dihydro-5*H*-6,12-methanodibenz[*c,f*]azocine (2a)——Dimethyl sulfate (6.30 g, 50 mmol) was added dropwise to a solution of **2a** (1.11 g, 5 mmol) in benzene (50 ml), then the mixture was allowed to stand overnight at room temperature. The *N*-methyl quaternary salt (**5**) that precipitated was collected and washed with a small amount of chloroform. An aqueous solution of **5** was treated with Amberlite IRA-401 (OH^-) (80 ml) by passing it through a column of the resin with water (100 ml) as the eluent. After removal of water *in vacuo*, the residue was heated at 190 °C under reduced pressure (0.1 mmHg) and distilled. The distillate was chromatographed on alumina with hexane–AcOEt [2 : 1 (v/v)] as the eluent to give **6** (0.60 g, 51%) as an unstable oil. ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.10 (8H, m, aromatic H), 5.39 (2H, s, $C=CH_2$), 3.57 (4H, br s, NCH_2Ph), 2.33 (3H, s, NCH_3). MS *m/e*: 235 (M^+). Furthermore, **6** was characterized as its hydrogenated product (palladium catalytic hydrogenation/95% ethanol), 1,5-dimethyl-dibenzo[*c,f*]-1,2,4,7-tetrahydroazocine, mp 131—132.5 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.00 (8H, m, aromatic H), 4.83 (1H, q, J=7.4 Hz, $PhCHPh$), 4.79 (2H, d, J=15.0 Hz, one of NCH_2Ph), 3.88 (2H, d, J=15.0 Hz, one of NCH_2Ph), 1.90 (3H, s, Ph_2NCH_3), 1.79 (3H, d, J=7.4 Hz, Ph_2CHCH_3). MS *m/e*: 237 (M^+). *Anal.* Calcd for $C_{17}H_{19}N$: C, 85.68; H, 8.02; N, 5.91. Found: C, 85.69; H, 8.13; N, 5.83.

Reaction of *N,N*-Dibenzylaminoacetaldehyde Diethyl Acetal (1a) with 70% Perchloric Acid at 0 °C——The acetal (**1a**) (313 mg, 1 mmol) was added dropwise to 1 ml of 70% perchloric acid at −30 — −35 °C with stirring. Then the reaction mixture was allowed to warm up to 0 °C. After standing at this temperature for a further 1 h, the reaction mixture was basified with 20% NaOH aq., while keeping the temperature at 5—7 °C. The products were extracted with methylene chloride (3 × 12 ml) and the extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on alumina with methylene chloride and hexane [1 : 4—1 : 2 (v/v)] as eluents to give *N*-benzyl-4-ethoxy-1,2,3,4-tetrahydroisoquinoline (**20**) (46 mg, 19%), *N,N*-dibenzylaminoacetaldehyde (**7**) (44 mg, 20%), **2a** (40 mg, 20%), and *N*-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoqui-

noline (**19**) (58 mg, 27%). The spectral data for the products are given below.

20: ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.00 (9H, m, aromatic H), 4.55 (1H, t, J=5.0 Hz, C^4-H), 3.64 (2H, s, benzyl H), 4.00—3.50 (4H, m, C^1-H and OCH_2CH_3), 2.85 (2H, d, J=5.0 Hz, C^3-H), 1.25 (3H, t, J=6.0 Hz, OCH_2CH_3). MS m/e: 267 (M^+).

7: ^{1}H-NMR ($CDCl_3$) δ: 9.54 (1H, t, J=2.0 Hz, CHO), 7.50—7.15 (10H, m, aromatic H), 3.68 (4H, s, benzyl H), 3.18 (2H, d, J=2.0 Hz, NCH_2CHO). MS m/e: 239 (M^+).

19: ^{1}H-NMR ($CDCl_3$) δ: 7.50—7.00 (9H, m, aromatic H), 4.60 (1H, t, J=4.0 Hz, C^4-H), 3.80 (1H, d, J=16.0 Hz, one of C^1-H), 3.70 (2H, s, benzyl H), 3.40 (1H, d, J=16.0 Hz, one of C^1-H), 3.10 (1H, br s, OH, exchangeable with D_2O), 2.95 (1H, dd, J=4.0 and 12.0 Hz, one of C^3-H), 2.65 (1H, dd, J=4.0 and 12.0 Hz, one of C^3-H). MS m/e: 238 (M^+).

Reaction of *N*-Benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (19) with 70% Perchloric Acid at Room Temperature——The treatment of **19** (30 mg, 0.13 mmol) with 70% perchloric acid (0.13 ml) at room temperature for 3 h followed by chromatographic purification of the products as described above gave **2a** (24 mg, 87%) and **19** (3 mg).

Reaction of *N*,*N*-Dibenzylaminoacetaldehyde (7) with 70% Perchloric Acid at Room Temperature——The treatment of **7** (239 mg, 1 mmol) with 70% perchloric acid (1 ml) at room temperature for 3 h under nitrogen gave 197 mg (89%) of **2a**.

Reaction of *N*-Benzyl-4-ethoxy-1,2,3,4-tetrahydroisoquinoline (20) with 70% Perchloric Acid at Room Temperature——The treatment of **20** (25 mg, 0.094 mmol) with 70% perchloric acid (0.1 ml) at room temperature for 3 h followed by chromatographic purification of the products as described above gave **20** (5 mg, 20%), **19** (8 mg, 37%) and **2a** (8 mg, 39%).

Double-Cyclization of *N*,*N*-Dibenzylaminoacetaldehyde Diethyl Acetal *N*-Oxide (21)——By general procedure A described above, 1.70 g (72%) of 7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine *N*-oxide (**23**) was obtained from 3.30 g (10 mmol) of **21** and 10 ml of 70% perchloric acid. mp 232—234 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.40—6.90 (8H, m, aromatic H), 5.05 (2H, d, J=17.5 Hz, one of NCH_2Ph), 4.94 (2H, d, J=17.5 Hz, one of NCH_2Ph), 4.34 (1H, t, J=2.0 Hz, PhCHPh), 4.05 (2H, d, J=2.0 Hz, NCH_2CH). MS m/e: 237 (M^+). IR ($CHCl_3$): 970 (N-O) cm^{-1}. *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.30; N, 5.87.

Double-Cyclization of 3-Benzyl-4-phenylbutanal (22)——The aldehyde (**22**) (120 mg, 0.5 mmol) was added to 70% perchloric acid (0.5 ml) at *ca.* −35 °C, and the mixture was allowed to stand overnight at room temperature. The usual work-up followed by silica gel chromatographic purification [hexane–benzene 2 : 1 (v/v)] gave **24** (100 mg, 90%), mp 64—65.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.35—6.88 (8H, m, aromatic H), 3.96 (1H, t, J=3.0 Hz, PhCHPh), 3.30 (2H, dd, J=7.0 and 17.5 Hz, one of $PhCH_2CH$), 2.70 (2H, d, J=17.5 Hz, one of $PhCH_2CH$), 2.85—2.53 (2H, m, $CHCH_2CH$), 2.08 (1H, t, J=3.0 Hz, $CHCH_2$). ^{13}C-NMR ($CDCl_3$/TMS) δ: 142.19 (s), 134.77 (s), 129.40 (d), 127.68 (d), 125.89 (d), 125.70 (d), 40.07 (d), 37.02 (t), 29.01 (t), 25.43 (d). MS m/e: 220 (M^+).

Triflic Acid-Catalyzed Double-Cyclizations of *N*,*N*-Dibenzylaminoacetaldehyde Dialkyl Acetals and Related Compounds——The double-cyclization of **1m** with triflic acid as the catalyst is described as an example of general procedure C, and the procedure for the nitro-substituted acetal (**1k**) is described individually.

(a) General Procedure C: Double-Cyclization of *N*-Benzyl-*N*-(*o*-chlorobenzyl)aminoacetaldehyde Diethyl Acetal (1m) to 4-Chloro-7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine (2m)——The acetal (**1m**) (6.54 g, 18.8 mmol) was added dropwise to 18.8 ml of triflic acid at *ca.* −40 °C with stirring under a nitrogen atmosphere. Then the reaction mixture was allowed to warm up to room temperature over a period of 2 h. After being stirred at this temperature for an additional 3 h, the reaction mixture was diluted with water (*ca.* 20 ml) and basified with 2 N NaOH aq., while keeping the temperature below 10 °C. The product was extracted with methylene chloride (3 × 30 ml), and the extract was washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was chromatographed on alumina (70 g) with benzene as the eluent to give **2m** (4.56 g, 95%), mp 115—116 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.20—6.80 (7H, m, aromatic H), 4.55 (1H, d, J=18.0 Hz, one of NCH_2Ph), 4.45 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.90 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.68 (1H, t, J=2.0 Hz, PhCHPh), 3.35 (2H, d, J=2.0 Hz, NCH_2CH). MS m/e: 255 (M^+). *Anal.* Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.16; H, 5.48; N, 5.46.

In a similar manner, **10**, **11a**, and **11b** were double-cyclized. The physical properties and the spectral data are given below.

12: mp 195—196 °C (dec.) as HCl salt (ethanol). ^{1}H-NMR (free base) ($CDCl_3$) δ: 7.10—6.60 (5H, m, aromatic H), 4.45 (2H, d, J=18.0 Hz, one of NCH_2Ph), 3.85 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.78 (1H, d, J=18.0 Hz, one of NCH_2Ph), 3.60 (1H, t, J=2.0 Hz, PhCHPh), 3.15 (2H, d, J=2.0 Hz, NCH_2CH). MS m/e: 261 (M^+). *Anal.* Calcd for $C_{14}H_{12}ClNS \cdot HCl$: C, 56.38; H, 4.93; N, 4.70. Found: C, 56.31; H, 4.89; N, 4.74.

13: mp 182—183 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.70—7.10 (12H, m, aromatic H), 4.85 (2H, d, J=18.0 Hz, one of NCH_2Ar), 4.35 (2H, d, J=18.0 Hz, one of NCH_2Ar), 3.75 (1H, t, J=1.5 Hz, ArCHAr), 3.45 (2H, d, J=1.5 Hz, NCH_2CH). MS m/e: 321 (M^+). *Anal.* Calcd for $C_{24}H_{19}N$: C, 89.68; H, 5.96; N, 4.36. Found: C, 89.60; H, 5.97; N, 4.33.

14: mp 159—161 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 8.55 (1H, m, aromatic H), 7.90—6.90 (11H, m, aromatic H), 4.70 (1H, d, J=17.5 Hz, one of NCH_2Ar), 4.68 (1H, d, J=17.5 Hz, one of NCH_2Ar), 4.65 (1H, t, J=2.5 Hz,

ArCH$_2$Ar), 4.15 (1H, d, J=17.5 Hz, one of NCH$_2$Ar), 4.05 (1H, d, J=17.5 Hz, one of NCH$_2$Ar), 3.55 (1H, dd, J=2.5 and 12.5 Hz, one of NCH$_2$CH), 3.40 (1H, dd, J=2.5 and 12.5 Hz, one of NCH$_2$CH). MS *m/e*: 321 (M^+). *Anal.* Calcd for $C_{24}H_{19}N$: C, 89.68; H, 5.96; N, 4.36. Found: C, 89.69; H, 5.98; N, 4.36.

(b) Double-Cyclization of *N*-Benzyl-*N*-(*p*-nitrobenzyl)aminoacetaldehyde Dimethyl Acetal (1k) to 2-Nitro-7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine (2k)——The acetal (**1k**) (1.000 g, 3.0 mmol) was cooled until it solidified at *ca.* −60 °C under a nitrogen atmosphere. A magnetic stirrer bar was put in place, then triflic acid (3.0 ml) was added slowly over the cold surface of the reaction flask with stirring at this temperature. Then the mixture was allowed to warm up slowly to room temperature over a period of 6 h with stirring. After being stirred at 40 °C for an additional 24 h, the reaction mixture was poured onto cracked ice (*ca.* 10 g) and basified with 1 N NaOH aq. The product was extracted with methylene chloride (3 × 30 ml), and the extract was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was chromatographed on alumina (10 g) with benzene as the eluent to give **2k** (652 mg, 81%), mp 135—136 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 8.20—7.80 (2H, m, aromatic H), 7.40—6.90 (5H, m, aromatic H), 4.63 (1H, d, J=18.8 Hz, one of NCH$_2$Ph), 4.58 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 4.03 (1H, d, J=18.8 Hz, one of NCH$_2$Ph), 3.95 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 3.85 (1H, t, J=1.5 Hz, PhCHPh), 3.38 (2H, d, J=1.5 Hz, NCH$_2$CH). IR ($CHCl_3$): 1520 (NO_2), 1340 cm^{-1}. *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.13; H, 5.29; N, 10.54. When the acetal (**1k**) was added dropwise to triflic acid at −40 °C, the yield of **2k** was 53%.

In a similar manner, 2.19 g (73%) of **2p** was obtained from **1p** (3.93 g, 10.0 mmol) and 10 ml of triflic acid, mp 197—198 °C (hexane–acetone). ^{1}H-NMR ($CDCl_3$) δ: 8.10—7.70 (3H, m, aromatic H), 7.20—6.80 (3H, m, aromatic H), 4.58 (1H, d, J=18.0 Hz, one of NCH$_2$Ph), 4.50 (1H, d, J=18.0 Hz, one of NCH$_2$Ph), 3.95 (1H, d, J=18.0 Hz, one of NCH$_2$Ph), 3.84 (1H, d, J=18.0 Hz, one of NCH$_2$Ph), 3.78 (1H, t, J=2.0 Hz, PhCHPh), 3.30 (2H, d, J=2.0 Hz, NCH$_2$CH). MS *m/e*: 300 (M^+). IR ($CHCl_3$): 1520 (NO_2), 1320 cm^{-1}. *Anal.* Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.32. Found: C, 64.01; H, 4.44; N, 9.27.

Triflic Acid-Catalyzed Reaction of *N*,*N*-Bis(*p*-nitrobenzyl)aminoacetaldehyde Dimethyl Acetal (1q) to *N*-(*p*-Nitrobenzyl)-4-methoxy-1,2,3,4-tetrahydroisoquinoline (8)——By the procedure described above, 3.36 g (95%) of **8** was obtained from **1q** (3.75 g, 10.0 mmol) and 10 ml of triflic acid. Oil (chromatographic purification). ^{1}H-NMR ($CDCl_3$) δ: 8.35—7.80 (4H, m, aromatic H), 7.60—7.40 (2H, m, aromatic H), 7.10 (1H, m, aromatic H), 4.42 (1H, t, J=5.0 Hz, C^4-H), 3.85 (2H, s, benzyl H or C^1-H), 3.70 (2H, s, C^1-H or benzyl H), 3.50 (3H, s, OCH$_3$), 2.90 (2H, d, J=5.0 Hz, C^3-H). MS *m/e*: 343 (M^+). IR ($CHCl_3$): 2810 (OCH_3), 1520 (NO_2), 1340 cm^{-1}.

Preparation of α-Dibenzylaminoketone (3)——All of the ketones were prepared by method C or D. The preparation of α-dibenzylaminoacetophenone (**3e**) is described as an example of method C, and that of 3-dibenzylamino-2-butanone (**3b**) as an example of method D. In all cases, ^{1}H-NMR and MS spectra of the products were consistent with the proposed structures.

(a) Method C: Preparation of α-Dibenzylaminoacetophenone (3e)——Phenacyl bromide (19.9 g, 0.10 mol) was added to a two-phase solution of dibenzylamine (19.7 g, 0.1 mol) and Na_2CO_3 (25.1 g, 0.25 mol) in methylene chloride and water [1 : 1 (v/v), 200 ml], and the mixture was vigorously stirred at room temperature for 4 h. The organic layer was separated, washed with brine, and dried over Na_2SO_4. After removal of the solvent, 26.4 g (84%) of **3e** was obtained by recrystallization (methanol), mp 81.5—82.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.00—7.80 (2H, m, aromatic H), 7.60—7.30 (13H, m, aromatic H), 3.85 (2H, s, NCH$_2$COPh), 3.80 (4H, s, benzyl H). MS *m/e*: 315 (M^+).

By means of method C, **3a**, **3f**, and **3g** were prepared from the corresponding α-haloketones and dibenzylamine.

(b) Method D: Preparation of 3-Dibenzylamino-2-butanone (3b)——Acetoin (6.16 g, 70 mmol) was added to a solution of dibenzylamine (13.75 g, 70 mmol) in 35 ml of dry benzene, and the mixture was refluxed with a Dean-Stark separator for 3.5 h. After removal of the solvent, vacuum distillation of the residue gave **3b** (13.82 g, 74%), bp 120—122 °C (0.003 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 7.50—7.20 (10H, m, aromatic H), 3.70 (2H, d, J=15.0 Hz, one of NCH$_2$Ph), 3.45 (2H, d, J=15.0 Hz, one of NCH$_2$Ph), 3.30 (1H, q, J=8.0 Hz, NCHCO), 2.20 (3H, s, COCH$_3$), 1.15 (3H, d, J=8.0 Hz, CHCH$_3$). MS *m/e*: 267 (M^+).

In a similar manner, **3c** and **3d** were prepared from the corresponding cyclic ketones and dibenzylamine.

Double-Cyclization of α-Dibenzylaminoketones (3)——The 70% perchloric acid-catalyzed double-cyclization of **3b** is described as an example of the reaction of α-dibenzylaminoketones, and the triflic acid procedure is exemplified by the case of **3g**.

(a) 70% Perchloric Acid-Catalyzed Double-Cyclization of 3-Dibenzylamino-2-butanone (3b) to 12,13-Dimethyl-7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine (4b)——The dibenzylaminoketone (**3b**) (4.45 g, 16.7 mmol) was dissolved in 16.7 ml of 70% perchloric acid at below *ca.* 0 °C with stirring, and the mixture was allowed to stand overnight at room temperature. After being heated at 80 °C for 3 h, the reaction mixture was poured onto cracked ice (*ca.* 20 g) and basified with 10% NaOH aq. The product was extracted with methylene chloride (3 × 50 ml), and the extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on alumina (50 g) with benzene as the eluent to give **4b** (3.33 g, 80%), mp 71—72 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.20—7.00 (8H, m, aromatic H), 4.67 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 4.59 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 3.98 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 3.83 (1H, d, J=17.5 Hz, one of NCH$_2$Ph), 3.30 (1H, q, J=7.0 Hz, NCH(CH$_3$)C), 1.73 (3H, s, Ph$_2$CCH$_3$), 1.18 (3H, d, J=7.0 Hz, NCH(CH$_3$)C). MS *m/e*: 249 (M^+). *Anal.*

Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.72; H, 7.62; N, 5.67.

In a similar manner, **3a** and **3c** were double-cyclized to the corresponding products (**4**). The yields are summarized in Table V, and the physical properties and spectral data for the products are given below.

4a: mp 124—125 °C (ether). ^{1}H-NMR ($CDCl_3$) δ: 7.20—7.00 (8H, m, aromatic H), 4.69 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.95 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.26 (2H, s, NCH_2C), 1.72 (3H, s, CH_3). MS *m/e*: 235 (M^+). *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.81; H, 7.24; N, 5.98.

4c: bp 163—166 °C (0.005 mmHg). mp > 300 °C as the perchlorate. ^{1}H-NMR ($CDCl_3$) (free base) δ: 7.50—6.90 (8H, m, aromatic H), 4.68 (1H, d, J=17.5 Hz, one of NCH_2Ph), 4.57 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.95 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.82 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.24 (1H, m, NCH), 3.11 (1H, m, one of cyclic CH_2), 1.90—1.20 (7H, m, cyclic CH_2). MS *m/e*: 285 (M^+). *Anal.* Calcd for $C_{20}H_{21}N \cdot HClO_4$: C, 63.91; H, 5.90; N, 3.73. Found: C, 63.88; H, 5.94; N, 3.69.

(b) Reaction of 2-Dibenzylaminocyclopentanone (3d) with 70% Perchloric Acid——By the procedure described above, 52 mg (20%) of 7,12-dihydro-5*H*-6,12-methano-6,13-propanodibenz[*c*,*f*]azocine (**4d**) and 157 mg (60%) of *N*-benzyl-3,3a,4,5-tetrahydro-2*H*-cyclopent[*c*]isoquinoline (**9**) were obtained from **3d** (279 mg, 1 mmol) by using 1 ml of 70% perchloric acid.

4d: mp 161—162 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.50—6.90 (8H, m, aromatic H), 4.73 (1H, d, J=17.5 Hz, one of NCH_2Ph), 4.60 (1H, d, J=17.5 Hz, one of NCH_2Ph), 4.07 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.89 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.41 (1H, m, NCH), 2.85 (1H, m, one of cyclic CH_2), 2.10—1.40 (5H, m, cyclic CH_2). MS *m/e*: 261 (M^+). *Anal.* Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.28; H, 7.30; N, 5.37.

9: Oil (chromatographic purification). ^{1}H-NMR ($CDCl_3$) δ: 7.65—6.80 (9H, m, aromatic H), 6.12 (1H, dd, J=2.5 and 5.0 Hz, ollefinic H), 4.12 (1H, d, J=13.0 Hz, one of NCH_2Ph), 3.72 (1H, d, J=15.0 Hz, one of NCH_2Ph), 3.49 (1H, t, J=6.8 Hz, $NCHC$=), 3.34 (1H, d, J=15.0 Hz, one of NCH_2Ph), 3.13 (1H, d, J=13.0 Hz, one of NCH_2Ph), 2.68—1.68 (4H, m, cyclic CH_2). MS *m/e*: 261 (M^+), 170.

(c) Triflic Acid-Catalyzed Double-Cyclization of *N*,*N*-Dibenzyl-*p*-nitrophenacylamine (3g) to 12-(*p*-Nitrophenyl)-7,12-dihydro-5*H*-6,12-methanodibenz[*c*,*f*]azocine (4g)——The aminoketone (**3g**) (360 mg, 1 mmol) was dissolved in triflic acid (1 ml) at below *ca.* 0 °C, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was diluted with ice-cold water (10 ml) and basified with 2 N NaOH aq. The product was extracted with methylene chloride (3 × 10 ml) and the extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on alumina (5 g) with benzene as the eluent to give **4g** (253 mg, 74%), mp 236—237 °C (methanol–acetone). ^{1}H-NMR ($CDCl_3$) δ: 8.25 (2H, d, J=10.0 Hz, aromatic H), 7.70 (2H, d, J=10.0 Hz, aromatic H), 7.40—7.10 (8H, m, aromatic H), 4.74 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.99 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.34 (2H, s, NCH_2C). MS *m/e*: 324 (M^+). *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.15; H, 5.27; N, 8.47.

In a similar manner, **3d**, **3e**, and **3f** were double-cyclized to the corresponding products. The yields are summarized in Table V and the physical properties and the spectral data for the products, **4e** and **4f** are given below.

4e: mp 138—139°C (methanol) (without chromatographic purification). ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.00 (13H, m, aromatic H), 4.73 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.97 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.34 (2H, s, NCH_2C). MS *m/e*: 297 (M^+). *Anal.* Calcd for $C_{22}H_{19}N \cdot H_2O$: C, 83.81; H, 6.67; N, 4.44. Found: C, 83.82; H, 6.72; N, 4.50. (The sample was dried *in vacuo* at room temperature.)

4f: mp 157—158 °C (methanol–methylene chloride). ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.00 (12H, m, aromatic H), 4.72 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.97 (2H, d, J=17.5 Hz, one of NCH_2Ph), 3.31 (2H, s, NCH_2C). MS *m/e*: 375 (M^+). *Anal.* Calcd for $C_{22}H_{18}BrN$: C, 70.22; H, 4.82; N, 3.72. Found: C, 70.27; H, 4.81; N, 3.82.

Applications

(a) Synthesis of 13-Phenyl-6,7,8,13-tetrahydro-5*H*-6,13-methanodibenz[*c*,*f*]azonine (16)——According to method C, 3.26 g (84%) of *N*-benzyl-*N*-(phenylethyl)phenacylamine (**15**) was obtained from *N*-benzylphenethylamine (2.47 g, 11.7 mmol) and phenacyl bromide (2.33 g, 11.7 mmol) in the presence of K_2CO_3 (0.81 g, 5.9 mmol). Oil (chromatographic purification). ^{1}H-NMR ($CDCl_3$) δ: 7.90—7.10 (15H, m, aromatic H), 3.90 (2H, s, NCH_2CO or NCH_2Ph), 3.80 (2H, s, NCH_2Ph or NCH_2CO), 2.87 (4H, m, NCH_2CH_2Ph). MS *m/e*: 329 (M^+). IR ($CHCl_3$): 1690 cm^{-1}.

13-Phenyl-6,7,8,13-tetrahydro-5*H*-6,13-methanodibenz[*c*,*f*]azonine (**16**) was obtained in 85% yield (1.32 g) from 1.65 g (5 mmol) of **15** in the presence of 5 ml of triflic acid by the method described for the synthesis of **4g**: mp 162—163 °C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.00 (13H, m, aromatic H), 4.40 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.98 (1H, d, J=12.5 Hz, one of bridge CH_2), 3.85 (1H, d, J=17.5 Hz, one of NCH_2Ph), 3.55—3.00 (2H, m, two of NCH_2CH_2Ph), 3.23 (1H, d, J=12.5 Hz, one of bridge CH_2), 2.95—2.70 (2H, m, two of NCH_2CH_2Ph). MS *m/e*: 311 (M^+). *Anal.* Calcd for $C_{23}H_{21}N$: C, 88.70; H, 6.80; N, 4.50. Found: C, 88.59; H, 6.76; N, 4.51.

(b) Synthesis of 10,11-Dihydro-10,5-(iminomethano)-5*H*-dibenzo[*a*,*d*]cycloheptene (18) (Isopavine Alkaloid Derivative)——A solution of benzyl phenyl ketone (7.84 g, 40 mmol) and aminoacetaldehyde dimethyl acetal (4.31 g, 41 mmol) in abs. toluene (60 ml) was refluxed with a Dean–Stark separator for 3 h. After removal of the solvent *in vacuo*, the residue was added dropwise to a solution of $NaBH_4$ (2.5 g) in methanol (50 ml) at room temperature with stirring. The mixture was stirred for 1 h at this temperature and then the solvent was evaporated off. The residue was

diluted with water (*ca.* 30 ml) and the product was extracted with methylene chloride (3 × 50 ml). After being washed with brine, the extract was dried over Na_2SO_4 and evaporated. Vacuum distillation of the residue gave *N*-(1,2-diphenylethyl)aminoacetaldehyde dimethyl acetal (**17**) (9.01 g, 79%), bp 129—132°C (0.02 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 7.25—7.10 (10H, m, aromatic H), 4.25 (1H, t, J=6.0 Hz, C$\underline{H}$(OMe)$_2$), 3.75 (1H, t, J=7.0 Hz, NHC$\underline{H}$), 3.15 (6H, s, OC$\underline{H}_3$), 2.85 (2H, d, J=7.0 Hz, CHC$\underline{H}_2$Ph), 2.45 (2H, d, J=6.0 Hz, NHC$\underline{H}_2$CH(OMe)$_2$), 1.75 (1H, br s, N$\underline{H}$, exchangeable with D_2O). MS *m/e*: 285 (M^+).

According to general procedure C, 690 mg (89%) of 10,11-dihydro-10,5-(iminomethano)-5*H*-dibenzo[*a*,*d*]cycloheptene (**18**) was obtained from 1.000 g (3.5 mmol) of **17** and 3.5 ml of triflic acid. mp 79 °C(benzene–acetone). ^{1}H-NMR ($CDCl_3$) δ: 7.10—6.90 (8H, m, aromatic H), 4.20 (1H, t, J=3.8 Hz, C^{10}-H), 3.80 (1H, dd, J=2.5 and 5.0 Hz, C^5-H), 3.52 (1H, dd, J=2.5 and 12.3 Hz, one of C^{12}-H), 3.25 (1H, dd, J=3.8 and 16.5 Hz, one of C^{11}-H), 3.15 (1H, dd, J=5.0 and 12.3 Hz, one of C^{12}-H), 3.09 (1H, dd, J=3.8 and 16.5 Hz, one of C^{11}-H), 2.32 (1H, br s, N$\underline{H}$, exchangeable with D_2O). MS *m/e*: 221 (M^+). *Anal.* Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.75; H, 6.80; N, 6.39.

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