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Synthesis of Dibenzo[*b*,*f*]cycloprop[*d*]azepine Derivatives. I. Introduction of a Cyclopropane Ring by the Use of Simmons-Smith Reagent[1]

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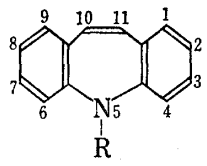
The Simmons-Smith reaction of 5*H*-dibenz[*b*,*f*]azepine (**4**) and 5-methyl-5*H*-dibenz[*b*,*f*]azepine (**5**) yielded 1,1a,6,10b-tetrahydro-6-methyldibenzo[*b*,*f*]cycloprop[*d*]azepine (**6**), which represents synthesis of a novel condensed ring system. **6** was demethylated via the formamide derivative **7** to give 1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine (**8**), which was converted into pharmacologically active 6-dialkylaminoalkyl (**9**) and 6-carbamoyl (**17**) derivatives.

Cyclopropanation of 5-(3-halopropyl)-5*H*-dibenz[*b*,*f*]azepines (**11**) with the Simmons-Smith reagent, however, led to additional reactions in the side chain to yield **12**, **13**, **14**, and **15**.

5*H*-Dibenz[*b*, *f*]azepines (**1**) and 10,11-dihydro-5*H*-dibenz[*b*, *f*]azepines (**2**) have aroused interest of medicinal chemists because of their prominent pharmacological effects on the central nervous system, and thus a great number of derivatives have been synthesized[3] for this reason. Carbamazepine[4] (**1**, R=$CONH_2$) and imipramine[5] (**2**, R=$-(CH_2)_3N(CH_3)_2 \cdot HCl$), for example, have been widely used for therapeutic purposes as anti-convulsive and anti-depressive drugs, respectively.



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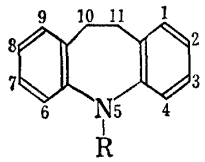

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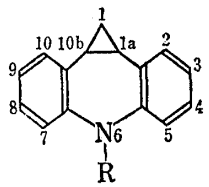

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The fact that not a single derivative of 1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepines (**3**) has been recorded[6–8] prompted us to synthesize these azepines and test their pharmacological activities.[9]

1) A part of the present study has been described in the following patents. *a*) K. Morita and K. Kawashima, Japan. Patent 659215 (1972); *b*) *Idem*, *ibid.* 659216 (1972); *c*) *Idem*, *ibid.* 774337 (1975); *d*) *Idem*, *ibid.* 774338 (1975); *e*) *Idem*, *ibid.* 705739 (1973); *f*) *Idem*, *ibid.* 705738 (1973); *g*) For foreign patents see, for example: *Idem*, Ger. Patent 2020315 (1970) [*C.A.*, **74**, 53573y (1971)].
2) Location: *17–85, Juso-honmachi 2-chome, Yodogawa-ku, Osaka, 532, Japan.*
3) F. Häfliger and V. Burckhardt, "Psychopharmacological Agents," Vol. 1, ed. by M. Gordon, Academic Press Inc., London, 1964, p. 35.
4) N. Delgado and E.I. Isaacson, "Medicinal Chemistry," 3rd ed., Part 2, ed. by A. Burger, John Wiley and Sons, Inc., New York, 1970, p. 1386.
5) C. Kaiser and C.L. Zirkle, "Medicinal Chemistry," 3rd ed., Part 2, ed. by A. Burger, John Wiley and Sons, Inc., New York, 1970, p. 1470.
6) Chemistry and pharmacology of 1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cycloheptene derivatives, which are carbon analogs of **3**, have been recorded (ref. 7, 8).
7) R.F. Childs, M.A. Brown, F.A.L. Anet, and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2175 (1972).
8) Merck and Co, Inc., U.S. Patent 3475438 (1969); *Idem*, Ger. Patent 1964548 (1970); G.D. Searle and Co., Brit. Patent 1246210 (1971) [*C.A.*, **75**, 140561g (1971)]; W.E. Coyne and J.W. Cusic, *J. Med. Chem.*, **17**, 72 (1974).
9) For pharmacology of some of the new compounds described in this report see ref. 1e, f and Y. Nagawa, unpublished.

Synthesis of 1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine[1a,b,d] (8)

Cyclopropanation by the Simmons-Smith reaction[10] was applied to the C10—C11 double bond of a 5*H*-dibenz[*b*, *f*]azepine derivative (**1**). When 5*H*-dibenz[*b*, *f*]azepine[11] (**4**) was subjected to the reaction using diiodomethane and zinc-copper couple prepared by the method of Simmons and co-workers, only N-methylation took place to yield **5**. The use of a modified catalyst of LeGoff,[12] which is of higher reactivity, enabled one to obtain the expected product **6** in 19% yield. On the other hand, the Simmons-Smith reaction of N-acetyl[11] (**1**, R=$COCH_3$) and N-benzyl (**1**, R=$CH_2C_6H_5$) derivatives failed to give the desired products and the starting materials were recovered unchanged. A carbenoid intermediate in the Simmons-Smith

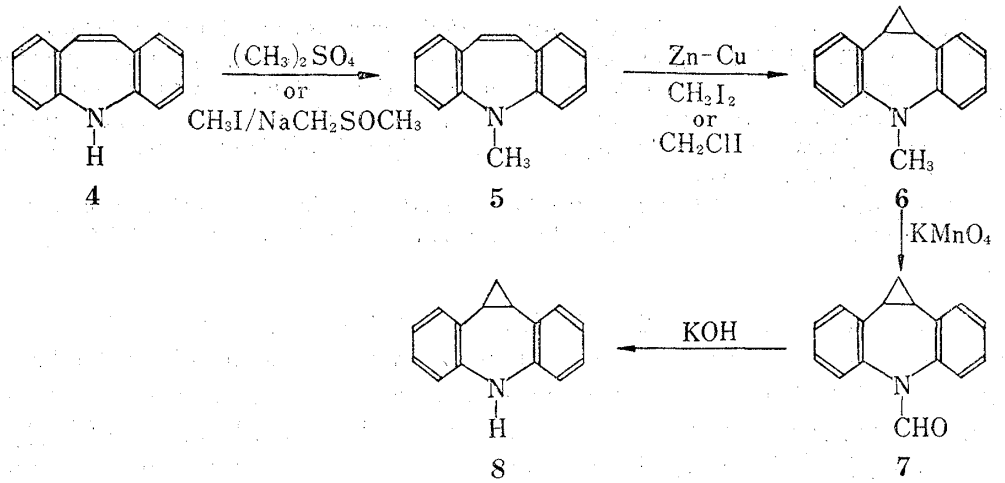


Chart 1

reaction is essentially electrophilic[10] and, therefore, 5-methyl-5*H*-dibenz[*b*, *f*]azepine[13] (**5**) was chosen as a substrate because the N-methyl group should increase the electron density at the C10—C11 double bond. **5** was prepared with ease and in high yields by methylating **4** with dimethyl sulfate or methyl iodide as shown in Chart 1. Although **5** was recovered unchanged under the standard conditions for the Simmons-Smith reaction, *i.e.* refluxing in diethyl ether,[10] modified reaction conditions after extensive screening of solvents and reaction temperature led us to obtain **6** in 55% yield when a large excess of diiodomethane was employed in refluxing dioxane. This appears to be due to the decomposition of the heat-labil carbenoid, ICH_2ZnI,[10] under the reaction condition. An intramolecular hydroxyl group is known to accelerate the Simmons-Smith reaction of olefins; the co-ordination of oxygen atom to zinc atom is believed to be responsible for the rate acceleration (Fig. 1).[10] By analogy with this, it might be reasonable to assume that a co-ordination effect of the lone pair electrons of the nitrogen atom as depicted in Fig. 1 could have contributed to the success of cyclopropanation of **5**.

Of several other dihalomethanes investigated, chloroiodomethane led to a successful result, although the yield of **6** was lowered to 39%. **6** is a colorless crystalline substance melting at 120—122°. The nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$, at 100 MHz) exhibits the following signals for hydrogen atoms attached to the cyclopropane ring[14]:

10) H.E. Simmons and R.D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958); *Idem*, *ibid.*, **81**, 4256 (1959); E.P. Blanchard and H.E. Simmons, *ibid.*, **86**, 1337 (1964); H.E. Simmons, E.P. Blanchard, and R.D. Smith, *ibid.*, **86**, 1347 (1964).
11) W. Schindler and H. Blattner, *Helv. Chim. Acta*, **44**, 753 (1961).
12) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).
13) R. Huisgen, E. Laschtuvka, and F. Bayerlein, *Chem. Ber.*, **93**, 392 (1960).
14) J.W. Emsley, J. Feeney, and L.H. Sutchiffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., New York, 1966, p. 690.

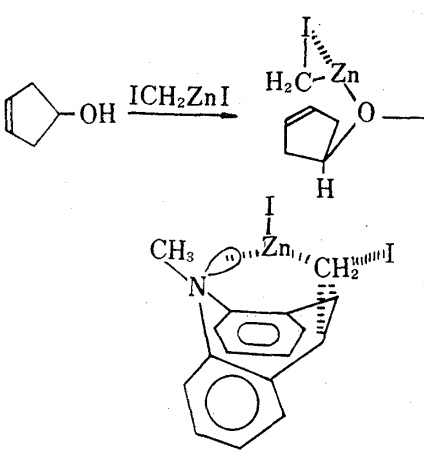


Fig. 1

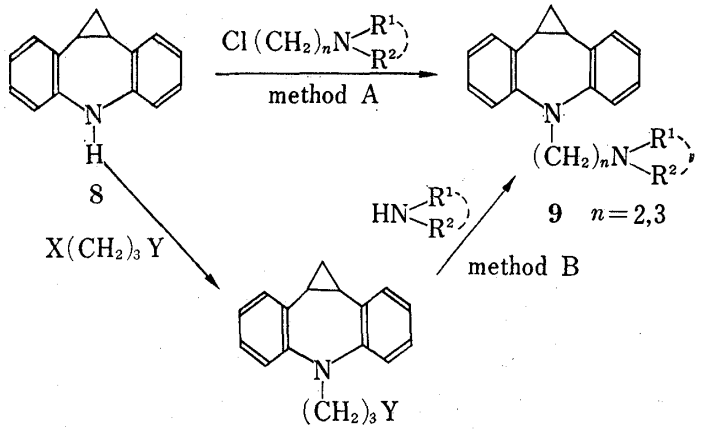


Chart 2

Methylene hydrogens at δ 0.95 (1H, $J_{gem.}=4$ Hz; $J_{vic.}=9$ Hz) and at δ 3.14[15] (1H, $J_{gem.}=4$ Hz; $J_{vic.}=6$ Hz), and methine hydrogens at δ 2.10 (2H, $J_{vic.}=9$ and 6 Hz).

Demethylation of **6** was effected by two steps after several unsuccessful attempts. Thus cyanogen bromide[16] did not react with **6**, and dealkylation with sulfur[17] and oxidation with mercuric acetate[18] met with failure. However, potassium permanganate oxidation[19] of **6** led us to obtain the formamide derivative **7** (68% yield), which was hydrolyzed with potassium hydroxide to afford 1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepine (**8**) (88% yield).

8 is a highly stable crystalline substance and melts at 119—120°. When gaseous hydrogen chloride is introduced to a solution of **8** in benzene, the hydrochloride precipitated, which is somewhat unstable and turns back to the free amine **8** upon contact with water.

Synthesis of 6-Dialkylaminoalkyl-1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]cycloprop[*d*]azepines[1b,f] (9)

6-Dialkylaminoalkyl derivatives (**9**), which were expected to possess anti-depressant activity, have been prepared in two ways starting from **8** as shown in Chart 2.

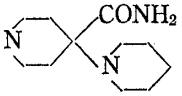
Method A——**8** was alkylated with dialkylaminoalkyl chloride to give **9**. The standard procedure for the alkylation[20] using sodium amide as a condensing agent in a solvent such

Table I. 6-Dialkylaminoalkyl-1,1a,6,10b-tetrahydrodibenzo[*b*, *f*]-cycloprop[*d*]azepines (**9**) prepared by Method A

Compd. No.	n	$N\begin{matrix}R^1\\R^2\end{matrix}$	Salt with	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
9a	2	$N(CH_3)_2$	1 eq. Maleic acid	158—159°	59	$C_{23}H_{26}O_4N_2$	70.03 (70.14)	6.64 (6.79)	7.10 (7.05)
9b	2	$N(C_2H_5)_2$	(free base)	(oil)	76	$C_{21}H_{26}N_2$	82.31 (81.94)	8.55 (8.51)	9.14 (9.03)
9c	3	$N(CH_3)_2$	1 eq. Maleic acid	159—160°	87	$C_{24}H_{28}O_4N_2$	70.56 (70.29)	6.91 (7.03)	6.86 (6.61)

15) Detailed interpretation of the NMR spectra of the related compounds including abnormality in chemical shift of this proton is given separately: K. Kawashima and E. Mizuta, *Chem. Pharm. Bull.* (Tokyo), **24**, 2761 (1976).
16) H.A. Hageman, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, p. 198.
17) N.P. Buu-Hoï and G. Saint-Ruf, *J. Chem. Soc.* (*C*), **1966**, 924.
18) N.J. Leonard and D.F. Morrow, *J. Am. Chem. Soc.*, **80**, 371 (1958).
19) O. Achmatowicz, Jr., Y. Tsuda, and L. Marion, *Can. J. Chem.*, **43**, 2336 (1965).
20) P.N. Craig, B.M. Lester, A.J. Saggiomo, C. Kaiser, and C.L. Zirkle, *J. Org. Chem.*, **26**, 135 (1961).

Table II. 6-Dialkylaminoalkyl-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]-cycloprop[*d*]azepines (**9**) prepared by Method B

Compd. No.	*n*	NR^1R^2	Salt with	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl
9c	3	$N(CH_3)_2$	1 eq. Maleic acid	159—160°	34	$C_{24}H_{28}O_4N_2$	70.56 (70.29)	6.91 (7.03)	6.86 (6.61)	— (—)
9d	3		1 eq. Maleic acid	154—156°	72	$C_{27}H_{32}O_4N_2$	72.29 (72.26)	7.19 (7.21)	6.25 (6.47)	— (—)
9e	3		1/2 eq. Oxalic acid	232° (decomp.)	58	$C_{20}H_{32}O_3N_2Cl$	71.48 (71.56)	6.40 (6.45)	5.56 (5.65)	7.03 (6.86)
9f	3		2eq. HCl	280° (decomp.)	48	$C_{29}H_{49}ON_4Cl_2$	65.52 (65.32)	7.59 (7.62)	10.54 (10.42)	13.34 (13.07)
9g	3		2 eq. Oxalic acid	224—225° (decomp.)	47	$C_{27}H_{33}O_8N_3$	61.47 (61.92)	6.31 (5.40)	7.97 (7.71)	— (—)
9h	3		2 eq. Oxalic acid	215—216° (decomp.)	36	$C_{28}H_{35}O_9N_3$	60.31 (60.13)	6.33 (6.28)	7.54 (7.56)	— (—)

as toluene has several disadvantages; it requires generally long time and yields are modest. However, the use of dimsylsodium $NaCH_2SOCH_3$ in dimethyl sulfoxide was found to effect the alkylation in good yields under mild conditions. The compounds **9** prepared by method A are summarized in Table I.

Method B——In this method, **8** was first converted into the 3-halopropyl derivative (**10**), which was then treated with various secondary amines to yield **9** (Table II). When **8** was treated with 1-bromo-3-chloropropane using sodium amide as a condensing agent, a mixture of 3-chloropropyl **10** (Y=Cl) and 3-bromopropyl **10** (Y=Br) derivatives was obtained in a mole ratio of 6:1. The mixture was inseparable and therefore subjected directly to the reaction with amines. When 1,3-dichloropropane and 1,3-dibromopropane were used as the alkylating agent, **8** was converted into **10** (Y=Cl and Br) in poor yields (14.3 and 17.2%, respectively). In these haloalkylations, an allyl derivative **14** was also obtained although in poor yields. Reactions between **10** and secondary amines were effected by potassium carbonate in the presence of sodium iodide.

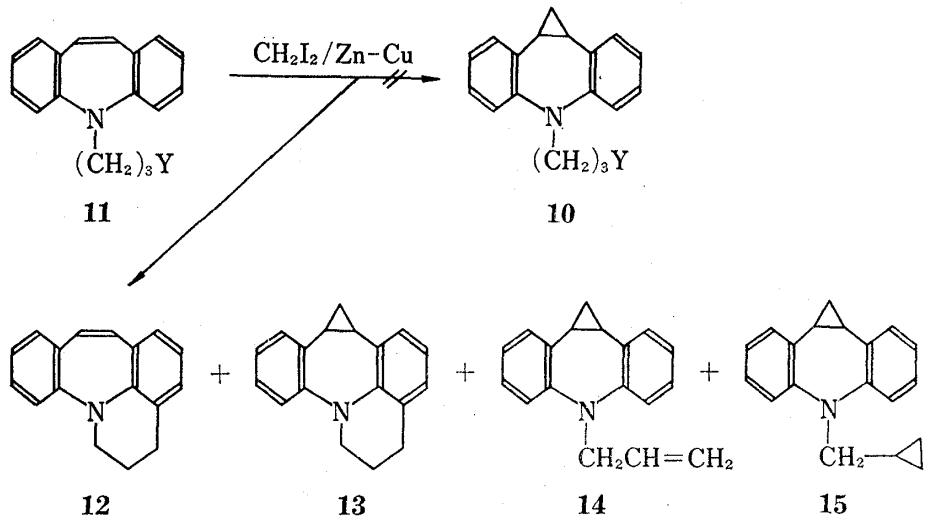


Chart 3

Simmons-Smith Reaction of 5-(3-Halopropyl)-5*H*-dibenz[*b*,*f*]azepines (11)

All attempts to achieve the Simmons-Smith reaction of **11** to obtain **10** were unsuccessful. A mixture of 3-chloropropyl[21] and 3-bromopropyl derivatives (**11**) was obtained by alkylation of **4** with 1-bromo-3-chloropropane. From the reaction of **11** and the Simmons-Smith reagent were obtained **12** (6% yield), **13** (48%), **14** and **15** (12% together), but not **10** as shown in Chart 3. These products all contained the modified side chains. **12** and **13** were considered to have arisen from the Friedel-Crafts reaction catalyzed by zinc iodide formed by decomposition of the carbenoid ICH_2ZnI. Elimination of hydrogen halide from the side chain of **10** can account for the formation of **14**, which could be converted into **15** on further cyclopropanation.

Synthesis of 1a,10b-Dihydrodibenzo[*b*, *f*]cycloprop[*d*]azepine-6(1*H*)-carboxamides[1c,e] (17)

Since we had a good reason to assume that the carbamoyl derivatives (**17**) would exhibit anti-convulsant activity,[4] we have attempted the synthesis by the two methods[22] (Chart 4 and Table III).

Method A——**8** was treated with phosgene in a benzene solution to yield **16**, whereby

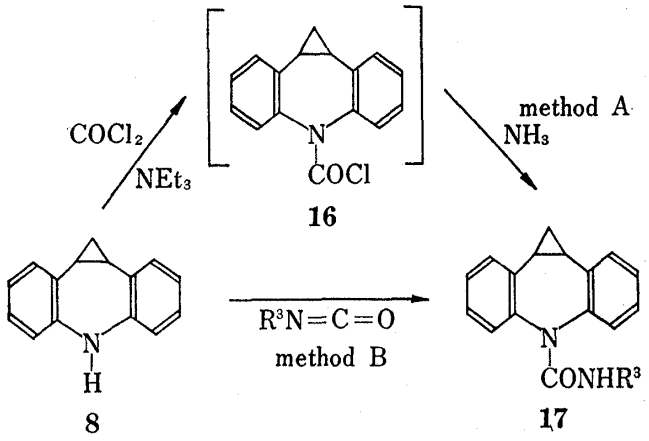


Chart 4

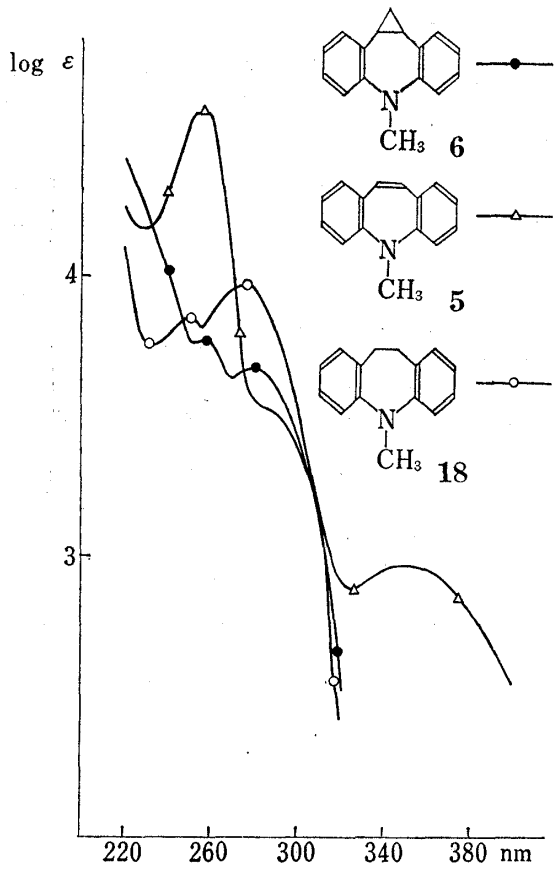


Fig. 2. UV Spectra of 1,1a,6,10b-Tetrahydro-6-methyldibenzo[*b*,*f*]cycloprop[*d*]azepine (**6**), 5-Methyl-5*H*-dibenz[*b*,*f*]azepine (**5**), and 10,11-Dihydro-5-methyl-5*H*-dibenz[*b*,*f*]-azepine[a] (**18**) in Ethanol

a) ref. 13

Table III. 1a,10b-Dihydrodibenzo[*b*,*f*]cycloprop[*d*]azepine-6(1*H*)-carboxamides (**17**)

Compd. No.	R^3	mp (°C)	Yield (%)	Method	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
17a	H	209—211°	83	A	$C_{16}H_{14}ON_2$	76.78	5.64	11.19	76.10	5.40	10.72
17b	CH_3	167—168°	58	B	$C_{17}H_{16}ON_2$	77.25	6.10	10.60	77.18	6.01	10.51
17c	C_6H_5	155—156°	28	B	$C_{22}H_{18}ON_2$	80.95	5.56	8.58	80.66	5.50	8.52

21) J.R. Geigy A.-G., Ger. Patent 1132556 (1962) [*C. A.*, **58**, 5702*b* (1963)].
22) W. Schindler, U.S. Patent 2948718 (1960) [*C. A.*, **55**, 1671*b* (1961)]; *idem*, Japan Patent 287395 (1961).

the hydrogen chloride liberated was conveniently trapped with a tertiary amine; otherwise the hydrochloride of **8** precipitated to lower the yield. Of the amines examined triethylamine gave the most satisfactory result. Treatment of the intermediate **16**, of which the appearance of the absorption maximum at 1745 cm^{-1} in infrared (IR) spectrum had evidenced its formation, with ammonia led to **17a**.

Method B——**8** was treated with methyl and phenyl isocyanates to give directly **17b** and **17c**, respectively.

Ultraviolet (UV) Spectrum of 1,1a,6,10b-Tetrahydro-6-methyldibenzo[*b*,*f*]cycloprop[*d*]azepine (6)

The UV spectrum of 1,1a,6,10b-tetrahydro-6-methyldibenzo[*b*, *f*]cycloprop[*d*]azepine (**6**) is shown in Fig. 2 in comparison with those of 5-methyl-5*H*-dibenz[*b*, *f*]azepine (**5**) and 10,11-dihydro-5-methyl-5*H*-dibenz[*b*, *f*]azepine (**18**). It is interesting to note that the UV spectrum of **6** is similar to but not superimposable with that of **18**, in which the conjugation is insulated at the C10—C11 single bond. The cyclopropane ring in **6**, therefore, appears to exert some influence[23] on the diphenylamine conjugation system.

Experimental

Melting points are uncorrected. The UV and IR spectra were taken with Perkin-Elmer 450 and Hitachi EPI-S2 models, respectively. NMR spectra[15] were recorded with Varian T-60 (60 MHz) and HR-100 (100 MHz) models, the chemical shifts being expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra were measured with a Hitachi RMU-6D double focussing mass spectrometer.

5-Methyl-5*H*-dibenz[*b*,*f*]azepine (5)——**5** was prepared conveniently by methylating 5*H*-dibenz[*b*,*f*]-azepine (**4**) in two ways, while the literature[13] described the dehydrogenation of 10,11-dihydro-5-methyl-5*H*-dibenz[*b*,*f*]azepine (**18**) to yield **5**.

a) A mixture of 5*H*-dibenz[*b*,*f*]azepine (**4**) (25.15 g; 130 mmole) and dimethyl sulfate (18.06 g; 143 mmole) in a round-bottomed flask was heated at 100° (bath temperature) for 30 min in an atmosphere of nitrogen. Saturated Na_2CO_3 aq. (97 ml; 260 mmole) was added with stirring to liberate **5** from the salt. Filtration of the precipitate followed by washing with water and drying yielded a crude product (27.3 g), to which was added hot AcOEt (164 ml). A large amount of insoluble material was removed by filtration and washed with hot AcOEt (50 ml). A combined filtrate and washing was treated with charcoal (0.55 g), filtered, and concentrated. Crystals formed after cooling were collected by filtration. Yield, 22.60 g (83.8%), mp 144—145° (lit.[13] 143—144.5°).

b) Sodium hydride containing *ca.* 50% mineral oil (108 g; 2.25 mole) was placed in a 5-liter four-necked flask equipped with a mechanical stirrer, a thermometer, a condenser, and a gas inlet, and flushed with nitrogen. The mineral oil was washed off three times with hexane (300 ml) by decantation. Dimethyl sulfoxide (3.0 liters) and then 5*H*-dibenz[*b*,*f*]azepine (**4**) (289.5 g; 1.5 mole) were added and the mixture was stirred at room temperature for 2 1/4 hr to give a dark green solution. To this was added methyl iodide (426 g; 3.0 mole) over a period of 40 min, when the temperature rose to 75°. After an additional stirring for 1 1/3 hr at room temperature EtOH (300 ml) was added and stirred for 1 hr to decompose the excess sodium hydride. A crystalline powder formed upon pouring the reaction mixture into ice-water (6 liters), was collected by filtration, washed six times with water (1 liter), and dried at 70° under reduced pressure to yield practically pure **5** (315 g, quantitative yield).

1,1a,6,10b-Tetrahydro-6-methyldibenzo[*b*,*f*]cycloprop[*d*]azepine (6)——a) $Cu(OAc)_2 \cdot H_2O$ (18.8 mg) was dissolved in hot 95% (v/v) AcOH aq. (1.88 ml), and sandy Zn (1.31 g) was added with stirring whereby Cu deposited on Zn and the color of Cu ion disappeared. After the AcOH aq. had been removed by decantation, AcOH (1.88 ml) was added, stirred, and removed by decantation. The residue was similarly treated three times with dry ether (1.88 ml). Zn–Cu couple thus obtained[12] contained *ca.* 0.5 mole % Cu and 20 mmole of Zn. To this were added 5*H*-dibenz[*b*,*f*]azepine (**4**) (0.482 g; 2.5 mmole), diiodomethane (5.35 g; 20 mmole), and dry dioxane (12 ml), and the mixture was heated under reflux for 75 min. Ether (12 ml) was added after cooling, and NH_3 gas was passed into the mixture for 30 min. The inorganic salt precipitated was filtered off and washed four times with ether (5 ml). The combined filtrate and washing was washed twice with (1 : 1) NH_3 aq. (5.5 ml and 2 ml), then four times with water (5 ml), and finally with saturated NaCl aq. (4 ml). Drying of the solution over Na_2SO_4 and evaporation of the solvent under reduced pressure afforded a crude oil (0.725 g). Crystallization of the oil from isopropyl ether afforded 0.104 g of **6** (18.9%), mp 120—122°. UV λ_{max}^{EtOH} nm (ε): 258 (5.93×10^3), 281 (4.63×10^3) (Fig. 2). IR ν_{max}^{Nujol} cm^{-1}: 1573 (aromatic). *Anal.* Calcd. for $C_{16}H_{13}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.73; H, 6.57; N, 6.18.

23) R.C. Hahn, P.H. Howard, S.-M. Kong, and G.A. Lorenzo, *J. Am. Chem. Soc.*, **91**, 3558 (1969).

b) Zn–Cu couple containing 0.1 mol % Cu and 3.6 mole of Zn, 5-methyl-5*H*-dibenz[*b*,*f*]azepine (**5**) (124.2 g; 0.6 mole), dioxane (3.0 liters), and diiodomethane (965 g; 3.6 mole) were placed in a 5-liter flask. When a vigorous reaction was started by heating the mixture for a while, the heater was removed. After vigorous refluxing had subsided in *ca.* 15 min, the mixture was heated again and refluxed for 1 3/4 hr and cooled to precipitate a large amount of ZnI_2. After NH_3 gas was passed into the mixture for 70 min under ice cooling, the precipitate was filtered off and washed four times with benzene (3 liters in all). The combined filtrate and washings was shaken with a mixture of conc. NH_3 aq. (150 g) and water (100 ml). The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to yield 132 g of a solid residue. Crystallization of the solid from isopropyl ether afforded 73.4 g of **6** (55.3%).

c) A mixture of Zn–Cu couple containing 0.1 mole % Cu and 60 mmole of Zn, 5-methyl-5*H*-dibenz[*b*,*f*]-azepine (**5**) (2.07 g; 10 mmole), chloroiodomethane (10.58 g; 60 mmole), $ZnCl_2$ (4.09 g; 30 mmole), and dioxane (25 ml) was refluxed for 2.5 hr. Ether (50 ml) was added to the mixture after cooling and NH_3 gas was introduced into the reaction mixture. A white precipitate formed was filtered off and washed four times with ether (50 ml). The combined filtrate and washings was washed twice with (1: 1) NH_3 aq. (20 ml) and then four times with water (50 ml), and dried over Na_2SO_4. Evaporation of ether followed by recrystallization from isopropyl ether afforded 0.899 g of **6** (39.3%).

1a,10b-Dihydrodibenzo[*b*,*f*]cycloprop[*d*]azepine-6(1*H*)-carboxaldehyde (**7**)——To a solution of **6** (14.4 g; 65.4 mmole) in acetone (433 ml) and water (72 ml) was added $KMnO_4$ (61.9 g; 392 mmole) in portions with stirring, the temperature being kept below 30° by external cooling with ice. It required ca. 20 min to add all the $KMnO_4$. After additional stirring for 1 hr at room temperature, excess $KMnO_4$ was decomposed by adding powdered $Na_2S_2O_3 \cdot 5H_2O$ in portions (35 g). A precipitate of MnO_2 formed was filtered off and washed four times with acetone (100 ml). The combined filtrate and washings was evaporated under reduced pressure and water (72 ml) was added to precipitate crude crystals, which were collected by filtration, washed with water, and recrystallized from EtOH to afford **7** in 68% yield, mp 169—170°. IR ν_{max}^{Nujol} cm^{-1}: 2800, 1680 (N–CHO), 1605, 1582 (aromatic). *Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.37; H, 5.66; N, 5.76.

1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine(**8**)——A mixture of **7** (5.0 g), EtOH (115 ml) and 20% KOH aq. (56 ml) was refluxed gently for 15 hr in an atmosphere of nitrogen. EtOH was evaporated under reduced perssure, and water (50 ml) was added to precipitate crude crystals, which were collected by filtration, washed with water and recrystallized from EtOH to afford **8** in 88%, mp 119—120°. UV λ_{max}^{EtOH} nm (ε): 280 (7.07×10^3). IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH), 1580 (aromatic). *Anal.* Calcd. for $C_{15}H_{13}N$ (**8**): C, 86.92; H, 6.32; N, 6.76. Found: C, 86.86; H, 6.41; N, 6.79.

When HCl gas was passed into a solution of **8** in benzene, the HCl-salt precipitated, mp 180—183° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2800—2100, 1563, (N^+H_2). *Anal.* Calcd. for $C_{15}H_{14}NCl$ (**8**·HCl): C, 73.92; H, 5.79; N, 5.75; Cl, 14.55. Found: C, 74.14; H, 5.65; N, 5.53; Cl, 14.71. Treatment of the HCl-salt with water regenerated **8**.

6-[3-(Dimethylamino)propyl]-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine Maleate (1:1)(9c)——a) Sodium hydride (1.529 g containing *ca.* 53% mineral oil; 30 mmole) was washed three times with ether (3 ml) and dimethyl sulfoxide (31 ml) was added. The mixture was heated at 70° for 45 min in an atmosphere of nitrogen to dissolve the sodium hydride. After removing the heater, a solution of **8** (4.14 g; 20 mmole) in dimethyl sulfoxide (41 ml) was added to give an orange yellow solution. To this was added a solution of 3-chloro-N,N-dimethylpropylamine (3.65 g; 30 mmole) in dimethyl sulfoxide (4 ml), the temperature being raised from 44° to 53°. The mixture was stirred at room temperature for 1 3/4 hr, and poured into ice-water (*ca.* 75 ml). An oil separated was extracted with ether, and the extract was washed four times with water (40 ml). A basic substance was transferred into 1 N HCl aq. (24 ml) and washed with ether (8 ml). Addition of 40% NaOH aq. (2.8 ml) separated an oil which was reextracted with ether (50 ml). The extract was washed twice with water (30 ml) and then with saturated NaCl aq. (30 ml), dried over Na_2SO_4 and evaporated under reduced pressure to give an oil (6.3 g). To a solution of the oil in AcOEt (13 ml) was added maleic acid (2.32 g; 20 mmole) in AcOEt (70 ml) to precipitate a maleate, which was collected and recrystallized from EtOH to give 6.59 g of **9c** (80.7%), mp 161—163°. IR ν_{max}^{Nujol} cm^{-1}: 2800—2100 (CO_2H, NH^+), 1685 (CO_2H), 1616 ($-CO_2^-$). *Anal.* see Table I.

b) A mixture of the crystals consisted of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6: 1 (0.290 g; 1.0 mmole), 40% dimethylamine aq. (0.455 g containing 4.04 mmole of the amine), K_2CO_3 (0.276 g; 2.0 mmole), NaI (0.150 g; 1.0 mmole) and 2-butanone (5.8 ml) was heated for 7.5 hr under reflux. The solvent was evaporated under reduced pressure, and AcOEt (10 ml) and water (4 ml) were added. The organic layer was separated and washed twice with water (5 ml). A basic substance was transferred into 0.52 N HCl aq. (2.7 ml) and washed with AcOEt (2 ml). Addition of 10% NaOH aq. (0.7 ml) separated the base, which was extracted with AcOEt (10 ml). The extract was washed with water (5 ml) and then with saturated NaCl aq. (5 ml), dried over Na_2SO_4 and evaporated under reduced pressure to give 0.10 g of an oily 6-[3-(dimethylamino)-propyl] derivative (34%), which was converted into the maleate (1: 1) in a similar manner as described in a).

6-[2-(Dimethylamino)ethyl]-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine Maleate (1: 1)(9a)——6-[2-(Dimethylamino)ethyl] derivative was obtained as an oil from the reaction of **8** and 2-chloro-N,N-dimeth-

ylethylamine in 59% yield in a similar manner as in the case of **9c** (method a). Maleate (1: 1), mp 158—159° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2100, 1700 (CO_2H). *Anal.* see Table I.

6-[2-(Diethylamino)ethyl]-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepine(9b)——**9b** was obtained as an oil by the reaction of **8** and 2-chloro-N,N-diethylethylamine in 76% yield in a similar manner as in the case of **9c** (method a). IR ν_{max}^{Liquid} cm^{-1}: 1576 (aromatic). *Anal.* see Table I.

6-(3-Chloropropyl)-(10, Y=Cl), 6-(3-Bromopropyl)-(10, Y=Br) and 6-Allyl-1,1a,6,10b-tetrahydrodibenzo-[*b*,*f*]cycloprop[*d*]azepine(14)——a) **8** (1.036 g; 5 mmole) was converted into the Na-salt by allowing it to react with $NaNH_2$ (0.390 g; 10 mmole) in dry refluxing xylene (20 ml) for 2 hr in an atmosphere of nitrogen. To this was added 1-bromo-3-chloropropane (3.148 g; 20 mmole) and the mixture was refluxed for 7 hr. After cooling the reaction mixture was poured into ice-water (20 ml) and the organic phase was separated and washed twice with water (10 ml) and then with saturated NaCl aq. (10 ml). Drying of the solution over Na_2SO_4 followed by evaporation under reduced pressure yielded 1.914 g of a crude product, which was separated by column chromatography on silica-gel (52 g). From a fraction eluted with hexane–benzene (90: 10 v/v) was obtained first 0.128 g of **14** (10.3%), mp 116—118° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1642 (C=C), 1572 (aromatic). *Anal.* Calcd. for $C_{18}H_{17}N$ (**14**): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.40; H, 7.01; N, 5.77. From a fraction eluted with the same mixed solvent were next obtained 0.849 g (58.5%) of mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6: 1, mp 102—103° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1574 (aromatic). *Anal.* Calcd. for 6 $C_{18}H_{18}NCl$ (**10**, Y=Cl)·$C_{18}H_{18}NBr$ (**10**, Y=Br): C, 74.50; H, 6.25; N, 4.83; Halogen, 3.45 μmole/mg. Found: C, 74.53; H, 6.35; N, 4.83; Halogen, 3.39 μmole/mg. Benzene eluted 0.276 g of **8** (26.7% recovery).

b) **8** was allowed to react with 1,3-dichloropropane in a similar manner as in a) to afford **14** and **10** (Y=Cl) in 3.4 and 14.3% yields, respectively, 59.6% of **8** being recovered. **10** (Y=Cl), mp 101—102° (from EtOH). UV λ_{max}^{EtOH} nm (ε): 256 (5.80×10^3). IR ν_{max}^{Nujol} cm^{-1}: 1573 (aromatic). *Anal.* Calcd. for $C_{18}H_{18}NCl$ (**10**; Y=Cl): C, 76.18; H, 6.39; N, 4.94; Cl, 12.49. Found: C, 75.93; H, 6.39; N, 4.92; Cl, 11.39.

c) **8** was allowed to react with 1,3-dibromopropane in a similar manner as in a) to afford **14** and **10** (Y=Br) in 9.7 and 17.2% yields, respectively, 51.7% of **8** being recovered. **11** (Y=Br), mp 109—110° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1575 (aromatic). *Anal.* Calcd. for $C_{18}H_{18}NBr$ (**10**, Y=Br): C, 65.86; H, 5.53; N, 4.27; Br, 24.35. Found: C, 65.55; H, 5.37; N, 4.24; Br, 23.68.

1,1a,6,10b-Tetrahydro-6-[3-(1-piperidyl)propyl]dibenzo[*b*,*f*]cycloprop[*d*]azepine Maleate (1:1) (9d)——A mixture of the mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6: 1 (0.284 g; 0.98 mmole), piperidine (0.170 g; 2.0 mmole), K_2CO_3 (0.276 g; 2.0 mmole), NaI (0.150 g; 1.0 mmole), and 2-butanone (4 ml) was heated for 8.5 hr under reflux. The precipitate was filtered off and washed three times with 2-butanone (4 ml in all). The combined filtrate and washings were evaporated under reduced pressure. To the residue was added ether (20 ml) and water (4 ml) and the organic layer was separated and washed with water (5 ml). A basic substance was transferred into 0.5 N HCl aq. (2.5 ml) and washed with ether (1 ml). Addition of 10% NaOH aq. (0.5 ml) liberated the base, which was extracted with ether (10 ml). The extract was washed with water (5 ml) and then with saturated NaCl aq. (5 ml), dried over Na_2SO_4 and evaporated to give an oily 6-[3-(1-piperidyl)propyl] derivative (0.240 g; 72% yield). The maleate (1: 1) (**9d**) was obtained by the usual method, mp 154—156° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2100 (CO_2H, NH^+), 1694 (CO_2H), 1614 ($-CO_2^-$). *Anal.* see Table II.

6-[3-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidyl]propyl]-1,1a,6,10b-tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]-azepine Oxalate (2: 1) (9e)——A mixture of the mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6: 1 (0.290 g; 1.0 mmole), 4-(4-chlorophenyl)-4-hydroxypiperidine (0.212 g; 1.0 mmole), K_2CO_3 (0.138 g; 1.0 mmole), NaI (0.150 g; 1.0 mmole), and 2-butanone (4.2 ml) was heated for 8 hr under reflux. The precipitate was filtered off and washed five times with 2-butanone (1 ml). The combined filtrate and washings were evaporated under reduced pressure. To the residue was added ether (12 ml) and water (4 ml) and the organic layer was separated and washed three times with water and once with saturated NaCl aq. (4 ml). The ether solution was dried with Na_2SO_4 and evaporated to yield 0.440 g of an amorphous substance, which was dissolved in EtOH (2 ml) and treated with oxalic acid (0.036 g; 0.4 mmole) in EtOH (1 ml). The precipitated crude oxalate was collected and recrystallized from THF to yield 0.292 g of **9e** (58% yield), mp 232° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3050 (OH), 1620 ($-CO_2^-$). *Anal.* see Table II.

1′-[3-(1,1a,6,10b-Tetrahydrodibenzo[*b*,*f*]cycloprop[*d*]azepin-6-yl)propyl]-[1,4′-bipiperidine]-4′-carboxamide Dihydrochloride (9f)——A mixture of the mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6: 1 (2.03 g; 7.0 mmole), 1.4′-bipiperidine-4′-carboxamide[24] (1.48 g; 7.0 mmole), K_2CO_3 (1.94 g; 14.0 mmole), NaI (1.05 g; 7.0 mmole), and 2-butanone (29 ml) was heated for 8 hr under reflux. The precipitate was filtered off and washed five times with 2-butanone (5 ml). The combined filtrate and washings were evaporated under reduced pressure. To the residue was added AcOEt (60 ml) and water (10 ml) and the organic layer was separated and washed four times with water (10 ml). A basic substance was transferred into 1N HCl aq. (14 ml) and the solution was concentrated under reduced pressure. Crystalline precipitates formed were collected by filtration and washed with EtOH. The crude product was recrystallized from MeOH to yield

24) C. van de Westeringh, P.V. Daele, B. Hermans, C.V. der Eycken, J. Boey, and P.A.J. Janssen, *J. Med. Chem.*, 7, 619 (1964).

1.78 g of **9f** (48% yield), mp 280° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3600—2100 (NH^+). 1689, 1622 ($CONH_2$). *Anal.* see Table II.

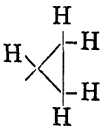
1,1a,6,10b-Tetrahydro-6-[3-(4-methyl-1-piperazinyl)propyl]dibenzo[*b,f*]cycloprop[*d*]azepine Oxalate (1:2) (9g)——A mixture of the mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6:1 (0.500 g), N-methylpiperazine (0.353 g), NaI (0.264 g), and 2-butanone (30 ml) was heated for 10 hr under reflux. To the mixture was added water (30 ml) and the aqueous layer was separated and extracted with $CHCl_3$. The combined extracts were dried with $MgSO_4$ and evaporated to yield an oil, which was treated with oxalic acid (0.318 g) in ether. Crystals precipitated were collected and recrystallized from 90% EtOH aq. to yield 0.440 g of **9g** (47% yield) as colorless fine crystals, mp 224—225° (decomp.). *Anal.* see Table II.

1,1a,6,10b-Tetrahydro-6-[3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl]dibenzo[*b,f*]cycloprop[*d*]azepine Oxalate (1:2) (9h)——A mixture of the mixed crystals of **10** (Y=Cl) and **10** (Y=Br) in a mole ratio of 6:1 (0.500 g), N-2-hydroxyethylpiperazine (0.460 g), NaI (0.264 g), and 2-butanone (30 ml) was heated for 18 hr under reflux. The solvent was evaporated and the residue was treated with water (30 ml) and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to yield an oil, which was treated with oxalic acid (0.318 g) in ether. Crystals precipitated were collected and recrystallized from dilute MeOH aq. to yield 0.350 g of **9h** (36% yield) as colorless fine crystals, mp 215—216° (decomp.). *Anal.* see Table II.

5-(3-Chloropropyl)-(11, Y=Cl), 5-(3-Bromopropyl)-5*H*-dibenz[*b,f*]azepine (11, Y=Br), and 1,3-Bis(5*H*-dibenz[*b,f*]azepin-5-yl)propane (19)——5*H*-Dibenz[*b,f*]azepine (**4**) (5.80 g; 30 mmole) was converted into the Na-salt by allowing it to react with $NaNH_2$ (2.34 g; 60 mmole) in refluxing xylene (116 ml) for 2 hr in an atmosphere of nitrogen. To this was added 1-bromo-3-chloropropane (18.91 g; 120 mmole) and the mixture was refluxed for 9 hr. After cooling, the reaction mixture was poured into water (100 ml), the organic phase being separated, and washed first with water (100 ml) and then with saturated NaCl aq. (50 ml). Drying the solution with Na_2SO_4 followed by evaporation under reduced pressure yielded 5 g of a crude product, which was separated by column chromatography on silica-gel (150 g). From a fraction eluted with hexane–benzene (70:30 v/v) were obtained 4.038 g (46.7%) of mixed crystals of **11** (Y=Cl)[20] and **11** (Y=Br) in a mole ratio of 6:4, mp 46—51° (from hexane). IR ν_{max}^{Nujol} cm^{-1}: 1593, 1570 (aromatic). NMR (60 MHz) δ^{CDCl_3}: 1.7—2.1 (m, $-CCH_2C-$), 3.3—4.0 (m, $N-CH_2$, CH_2Y), 6.63 (s, $-CH=CH-$), 6.8—7.4 (m, aromatic). *Anal.* Calcd. for $6C_{17}H_{16}NCl$ (**11**, Y=Cl)·$4C_{17}H_{16}NBr$ (**11**, Y=Br): C, 71.00; H, 5.61; N, 4.87; Halogen, 3.48 μmole/mg. Found: C, 71.44; H, 5.69; N, 4.99; Halogen, 3.43 μmole/mg. Mass Spectrum *m/e*: 269, 271; 313, 315 (M^+).

From a fraction eluted with hexane–benzene (30:70 v/v) was first obtained 0.842 g (13.2%) of **19**, 1.533 g (26.4%) of **4** being eluted by the same mixed solvent. **19**, mp 163—166° (from benzene). NMR (60 MHz) δ^{CDCl_3}: 1.72 (quintet J=6 Hz, $-CCH_2C-$), 3.78 (t, J=6 Hz NCH_2), 6.47 (s, $-CH=CH-$), 6.6—7.3 (m, aromatic). *Anal.* Calcd. for $C_{31}H_{26}N_2$ (**19**): 87.29; H, 6.14; N, 6.57. Found: C, 87.73; H, 6.26; N, 6.00. Mass Spectrum *m/e*: 426 (M^+).

Simmons-Smith Reaction of 5-(3-Halopropyl)-5*H*-dibenz[*b,f*]azepines (11)——A mixture of Zn–Cu couple containing 0.1 mole % Cu and 12 mmole of Zn, the mixed crystals of **11** (Y=Cl) and **11** (Y=Br) in a mole ratio of 6:4 (0.576 g; 2 mmole), dioxane (5.0 ml), and diiodomethane (3.22 g; 12 mmole) was refluxed for 2 hr. The usual work-up yielded 0.754 g of a crude product, which was purified by column chromatography on silica-gel (23 g). From fractions eluted with hexane–benzene (90:10 v/v) were obtained first 0.061 g (*ca.* 12%) of a mixture of **14** and **15** (mole ratio of *ca.* 2:3) and next 0.237 g (47.9%) of **13**. From a fraction eluted with hexane–benzene (50:50 v/v) was obtained 0.028 g (6.0%) of **12**.

The mixture of **14** and **15**, IR ν_{max}^{Nujol} cm^{-1}: 1573 (aromatic). NMR (100 MHz) δ^{CDCl_3}: 0.3—0.7 (m, 

15), 1.01 (double t, J=4; 9 Hz 

), 2.17 (double d, J=6; 9 Hz 

), 3.45 (d, J=6 Hz, CH_2 **15**), 3.60 (double t, J=4; 6 Hz 

14), 3.79 (double t, J=4; 6 Hz 

15), 4.25 (d, J=6 Hz $N-CH_2$ **14**), 5.2 (m, $=CH_2$ **14**), 5.7 (m, $-CH=$ **14**), 6.7—7.5 (m, aromatic).

13, mp 155—156° (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1572 (weak, aromatic). *Anal.* Calcd. for $C_{16}H_{17}N$ (**13**): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.59; H, 7.03; N, 5.71.

12, IR ν_{max}^{Nujol} cm^{-1}: 1572 (weak, aromatic). NMR (60 MHz) δ^{CCl_4}: 2.15 (m, $N-C-C-CH_2$), 2.81 (t, J=6 Hz $C-CH_2-C$), 3.62 (m, $N-CH_2$), 6.36 (s, $-CH=CH-$), 6.5—7.2 (m, aromatic).

1a,10b-Dihydrodibenzo[*b,f*]cycloprop[*d*]azepine-6(1*H*)-carboxamide (17a)——$COCl_2$ gas (1.4 g; 14 mmole) was passed into a solution of **8** (1.036 g; 5 mmole) and NEt_3 (0.506 g; 5 mmole) in dry benzene (10 ml) and the mixture was left standing for 2 hr at room temperature. NEt_3·HCl was filtered off and washed five times with ether (1 ml). The combined filtrate and washings were evaporated at room temperature to yield 1.346 g (99.5%) of the 6(1*H*)-carbonyl chloride **16** (IR ν_{max}^{Nujol} cm^{-1}: 1745). When NH_3 gas was introduced into a refluxed suspension of **16** in EtOH (10 ml), crystals of **17a** separated after initial dissolution of the starting material. After refluxing for 1 hr, the mixture was allowed to cool and the precipitate was collected by filtration, and washed first with EtOH and then with water to yield 0.928 g of **17a**. Additional crop of crystals (0.104 g) was obtained from the mother liquor, the total yield being 82.5%, mp 209—211° (from EtOH).

UV λ_{max}^{EtOH} nm (ε): 271 (9.05×10^2). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3400—3050 (NH_2), 1735 (weak), 1718 (weak), 1673, 1597 ($NCONH_2$). *Anal.* see Table III.

1a,10b-Dihydro-N-methyldibenzo[*b*,*f*]cycloprop[*d*]azepine-6(1*H*)-carboxamide (17b)——A solution of **8** (2.48 g; 12 mmole) and methyl isocyanate (3.42 g; 60 mmole) in dry xylene (24 ml) was refluxed for 24 hr. The mixture was evaporated under reduced pressure and the residue was dissolved in benzene (60 ml). The benzene solution was washed three times with 5% KOH aq. and dried over Na_2SO_4. Evaporation of benzene afforded 2.0 g of white crystals (58% yield), mp 167—168°. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1645 (NCONH). *Anal.* see Table III.

1a,10b-Dihydro-N-phenyldibenzo[*b*,*f*]cycloprop[*d*]azepine-6(1*H*)-carboxamide (17c)——A solution of **8** (0.414 g; 2 mmole) and phenyl isocyanate (0.572 g; 4.8 mmole) in dry benzene (5 ml) was refluxed for 8 hr. After adding benzene (5 ml), the solution was washed three times with 5% KOH aq. and dried over Na_2SO_4. Evaporation of benzene followed by purification by column chromatography on silica-gel afforded 0.182 g of white crystals (27.9% yield), mp 155—156°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 1680 (NCONH). *Anal.* see Table III.

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