Dibenz[*b,f*]azepines and Related Ring Systems

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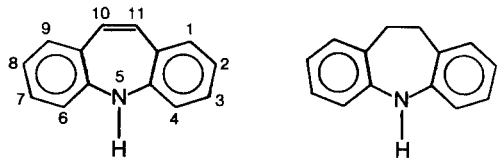
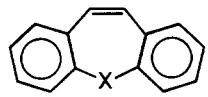
I. Introduction

The 5*H*-dibenz[*b,f*]azepine nucleus (**1**) has been known since 1899 when Thiele and Holzinger[1] prepared 10,11-dihydrodibenz[*b,f*]azepine (**2**) (hereafter iminobibenzyl) from *o,o'*-diaminobibenzyl hydrochloride; however, over 50 years was to elapse before derivatives of this ring system were prepared and characterized.[2]

Other heterocyclic analogs of the dibenzo[*a,d*]cycloheptene (**3a**) and 10,11-dihydrodibenzo[*a,d*]cycloheptene (**4a**) ring systems are known, namely, dibenzo[*b,f*]oxepin (**3b**),[3] -thiepin (**3c**),[4] -selenepin (**3d**),[5] their 10,11-dihydro derivatives (**4b–d**), and 10,11-dihydrodibenzo[*b,f*]borepin (**4e**).[6] Corey, *et al.*,[7] have described

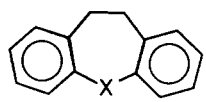


1 **2**



3a, X = CH_2 **d**, X = Se
b, X = O **e**, X = $GeMe_2$
c, X = S **f**, X = $SiMe_2$

the synthesis of dibenzo[*b,f*]metalepins of the group IV elements, *e.g.*, 10,11-dihydrodibenzo[*b,f*]silepin (**4f**), -germepin (**4g**), -stannepin (**4h**), -plumbepin (**4i**), and the unsaturated germepin (**3e**) and silepin (**3f**) analogs. Salts of the iodepinium cation (**4j**) have also been reported.[8]



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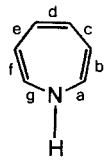
4a, X = CH_2 **f**, X = SiH_2
b, X = O **g**, X = $GeMe_2$
c, X = S **h**, X = $SnMe_2$
d, X = Se **i**, X = $PbMe_2$
e, X = BH **j**, X = I^+



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The present coverage of the literature, up to 1973, is restricted to 5*H*-dibenz[*b,f*]azepine and excludes the dibenzo[*c,e*],[9] -[*b,e*] (*cf.* morphanthridine[10]), and -[*b,d*] annelated[11] analogs of the azepine nucleus (**5**).

The approved (*Chemical Abstracts*) numbering of the ring positions of 5*H*-dibenz[*b,f*]azepine (iminostilbene) is as shown in structure **1**. A particular difficulty in surveying the chemistry of 5*H*-dibenz[*b,f*]azepines is the apparently proprietary nature of the physical and chemical properties of many of the derivatives, and in this respect the present coverage confines itself solely with authenticated compounds.

Previously, Häfliger and Burckhardt[12] have reviewed the pharmacology and synthesis of 5*H*-dibenz[*b,f*]azepines, and elsewhere other authors have discussed briefly some derivatives of this ring system.[13,14]

II. Synthesis

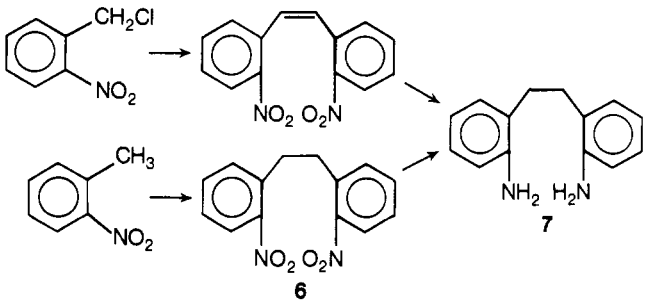
A. Synthesis of 10,11-Dihydrodibenz[*b,f*]azepines

1. Cyclization of *o,o'*-Diaminobibenzyls

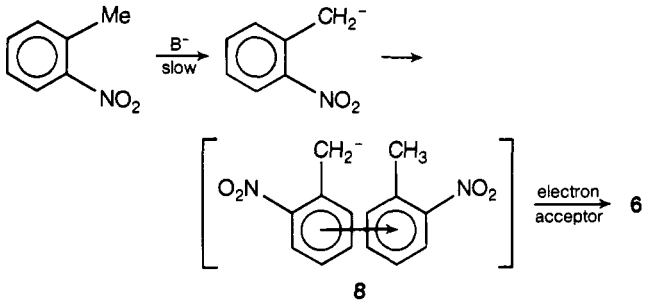
The principal route to the iminobibenzyl nucleus is *via* cyclization of *o,o'*-diaminobibenzyls (**7**), which may be

obtained by reduction of *o,o'*-dinitrostilbenes or *o,o'*-dinitrobibenzyls. The latter materials are available by Wurtz coupling of *o*-nitrobenzyl chloride[15,16] and by base-catalyzed coupling of *o*-nitrotoluenes,[17-24] respectively.

SCHEME I



Sodium ethoxide–isoamyl nitrite is commonly used as the basic catalyst for the coupling of nitrotoluenes, although sodium ethoxide–ethyl formate and methanolic potassium hydroxide–air[25] are similarly effective. Russell, *et al.*,[26] have extensively investigated the base-catalyzed coupling of nitrotoluenes and propose that the coupling proceeds through an intermediate charge-transfer complex (**8**) which reacts with an electron acceptor (an unionized nitrotoluene molecule or oxygen) to form the bibenzyl (**6**) (Scheme I).

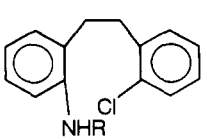


Cyclization of *o,o'*-diaminobibenzyls to iminobibenzyls is achieved by heating bis salts of the appropriate *o,o'*-diamine. The original synthesis of the parent compound[1] involved heating *o,o'*-diaminobibenzyl with its dihydrochloride, but this route proved untenable for substituted derivatives and has been superseded by the bis-methanosulfonate route.[27] The latter forms the basis of the commercial route to iminobibenzyl and involves heating either the diamine in the presence of an aliphatic or aromatic sulfonic acid, or the diamine bis(methanosulfonate) alone, above 295°.

Polyphosphoric acid (PPA) may also be used as a cyclization agent for *o,o'*-diaminobibenzyls; alternatively the diphosphate salt may be isolated and allowed to react separately with PPA.[16]

2. Cyclization of o-Amino-o'-chlorobibenzyls

Iminobibenzyl derivatives may be prepared from *o*-amino-*o'*-chlorobibenzyls (**9**) *via* dehydrochlorination using potassium carbonate together with catalytic quantities of copper powder or copper bronze, in refluxing *N,N*-dimethylformamide (DMF).[21,28]



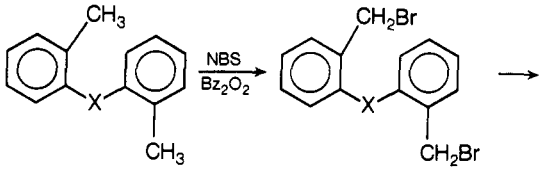
9, R = alkyl

3. Hydrogenation of 5H-Dibenz[b,f]azepines

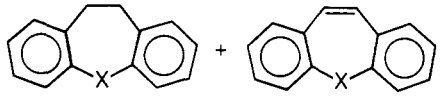
Hydrogenation of iminostilbenes,[29,30] especially those derived from acridine methanol derivatives (*vide infra*), provides a route to iminobibenzyls having a pattern of substitution otherwise difficultly accessible. The hydrogenation is carried out at room temperature and atmospheric pressure using platinum oxide[29] or platinum–charcoal[31] as the catalyst. Platinum oxide is favored over Raney nickel as a catalyst as the latter has the disadvantage of effecting dechlorination;[32] however, this has been effectively utilized for the preparation of 3-chloroiminobibenzyl from 3,7-dichloroiminobibenzyl.[33] Sodium in ethanol may also be used to reduce the etheno-bridge of iminostilbene derivatives.[31]

4. Cyclization of Diphenylamine Derivatives

Internal coupling of *N*-acetyl-2,2'-di(bromomethyl)diphenylamine (**10a**) using phenyllithium has been successfully employed by Bergmann, *et al.*,[34,35] to prepare iminobibenzyl. Analogously, 10,11-dihydrodibenz[*b,f*]oxepin may be prepared from *o*-ditolyl ether.

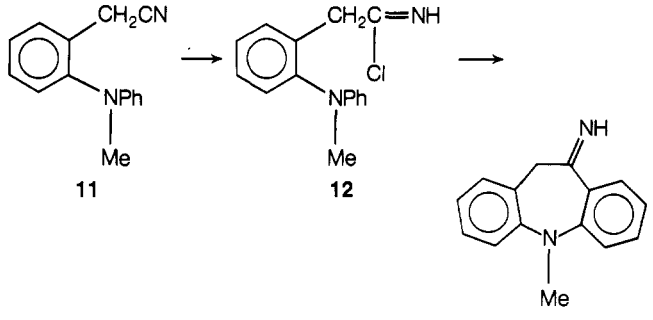


10a, X = $NCOCH_3$
b, X = O



>60% <4%

Recently, Japanese workers[36] report that *o*-(*N*-methyl-*N*-phenylamino)phenylacetonitrile (**11**) upon treatment with hydrogen chloride below 0° affords the imine **13**, presumably *via* the imido chloride **12**.



B. Synthesis of 5*H*-Dibenz[*b,f*]azepines

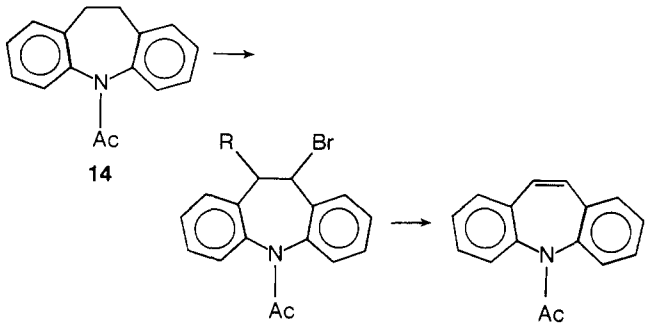
1. Dehydrogenation of 10,11-Dihydrodibenz[b,f]azepines

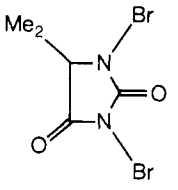
Dehydrogenation of iminobibenzyls is the main route to iminostilbene derivatives.[37-42] Palladium on charcoal is the preferred catalyst, although other reagents and catalysts have been used, *e.g.*, concentrated sulfuric acid,[16] sulfur, selenium,[19] and ferric oxide.[37,38] Typically the bibenzyl is sublimed through an electrically heated glass column packed with glass wool on which has been sprinkled 20–30% palladium/charcoal;[19,21] alternatively the bibenzyl may be heated with the dehydrogenation catalyst, either alone or in a high-boiling solvent such as diphenyl ether or dimethylaniline.[39]

Gas-phase dehydrogenation of iminobibenzyl at 400° using a ferric oxide catalyst [per cent composition of catalyst: Fe_2O_3 (54), Cr_2O_3 (3), CaO (10), K_2CO_2 (33)] is used commercially for the production of iminostilbene. The crude product is contaminated with acridine and 9-methylacridine (see section VIII.B).[37,38]

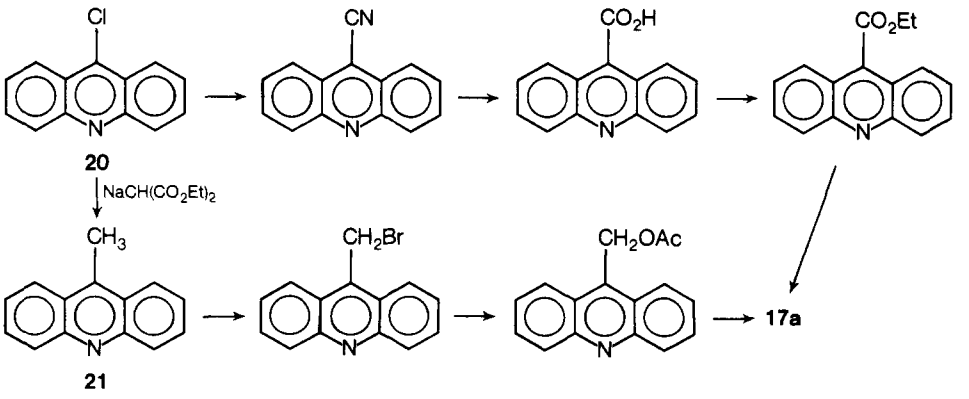
2. *Dehydrobromination of 10-Bromo-10,11-dihydrodibenz[b,f]azepines*

Dehydrobromination of 10-bromo- (**15a**) and 10,11-dibromoiminobibenzyls (**15b**) affords iminostilbene derivatives in good yields.[31,43-48] The replacement by bromine of a benzylic proton of iminobibenzyl having the imino group protected by an acetyl group is most usually accomplished using *N*-bromosuccinimide (NBS)/benzoyl peroxide, although *N*-bromophthalimide, *N*-bromoacetamide,[49] or 1,3-dibromo-5,5-dimethylhydantoin (**16**) may be used as the brominating agent.[50] Elimination of hydrogen bromide from **15a** is achieved using potassium hydroxide[31,44] or, under more forcing conditions, by means of a tertiary organic base, *e.g.*, collidine.[49]



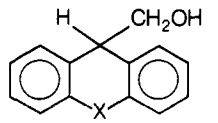


SCHEME II

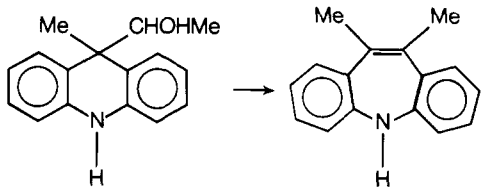


3. *Ring Expansion of Acridine-9-methanol Derivatives*

Wagner–Meerwein rearrangement of 9-hydroxymethyl-9,10-dihydroacridine (**17a**) represents a useful route to the 5*H*-dibenz[*b,f*]azepine ring system[29,40,51-57] and especially ring and etheno-bridge substituted derivatives, *e.g.*, **18** → **19**.[55]



17a, X = NH
b, X = O
c, X = S
d, X = CH_2



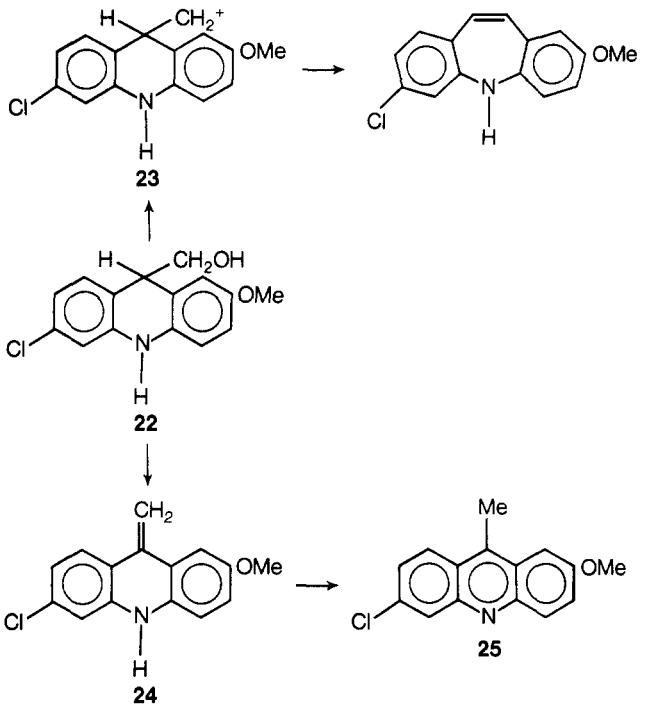
This ring expansion is general and may be used to prepare dibenz[*b,f*]oxepins, dibenzo[*b,f*]thiepins, and dibenzo[*a,d*]cycloheptenes from the corresponding methanols **17b–d**, severally.

Acridine methanols are available from 9-chloroacridine (**20**) (Scheme II). Cyanation of **20**, hydrolysis, and treatment of the intermediate amide with nitrous acid give acridine-9-carboxylic acid, from which acridine methanol is prepared by esterification and subsequent reduction of the ester with lithium aluminum hydride ($LiAlH_4$). An alternative route starting from 9-methylacridine (**21**) is also outlined in Scheme II, the acridine **21** being prepared either by treatment of 9-chloroacridine with sodium diethyl malonate or *via* the Bernthsen reaction.[58]

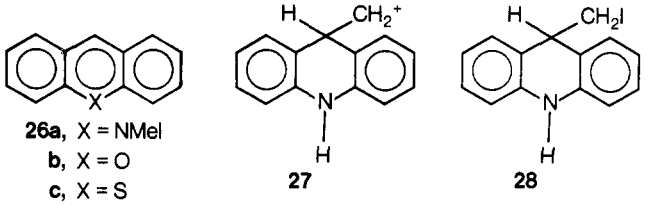
The dehydration–rearrangement is usually carried out by heating the acridine methanol with phosphorus pentoxide in xylene, and, although this is the preferred reagent, various workers have reported that the reaction is erratic and other reagents, *e.g.*, phosphorus oxychloride, and PPA have been cited.[40]

A side reaction which occurs with acridine methanols bearing a hydrogen at the 9 position is dehydration without rearrangement (**22** → **24**), with the intermediate 9-methylene-9,10-dihydroacridine (**24**) rearranging to the isomeric 9-methylacridine (**25**).[55]

Acridylmethyl carbonium ions, *e.g.*, **27**, can also be prepared[52] by treatment of *N*-methylacridinium iodide (**26a**) with diazomethane. This method is of little value since rearranged products account for only a small fraction of the total yield, and the principal product is 9-



iodomethyl-9-methylacridan (**28**), which arises *via* capture of an iodide ion by the intermediate carbonium ion **27.** This complication is not such a marked feature of reactions of xanthylium (**26b**) and thiaxanthylium perchlorate (**26c**) which, upon exposure to diazomethane in ether at 0°, afford the ring expansion products dibenz[*b,f*]oxepin and dibenzo[*b,f*]thiepin in yields of 61 and 22%, respectively. *N*-Methylacridinium perchlorate does not react with ethereal diazomethane, possibly owing to the insolubility of the former in ether.

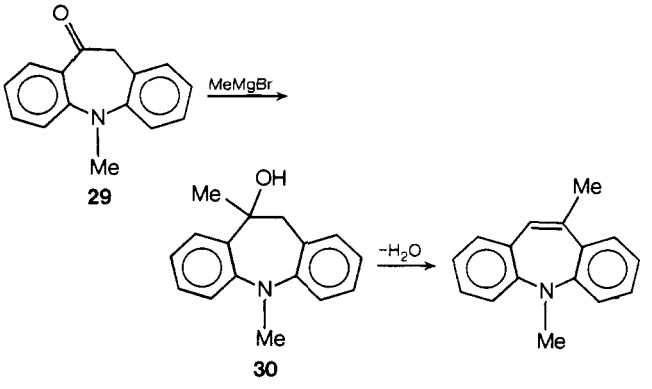


26a, X = NMeI
b, X = O
c, X = S

27 **28**

4. *Dehydration of 10,11-Dihydro-10-hydroxydibenz[b,f]azepines*

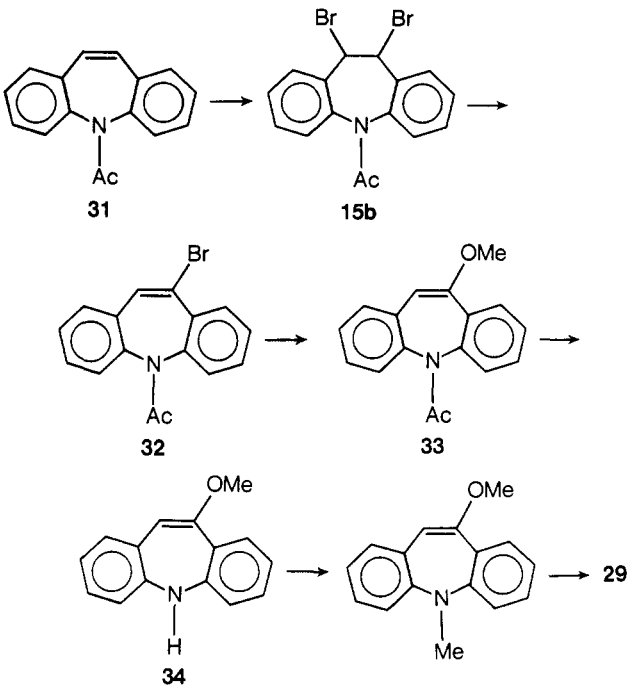
5,10-Disubstituted iminostilbenes are prepared by the reaction of the azepinone **29** with a Grignard reagent and subsequent dehydration of the secondary alcohol **30.** The dehydration step may be accomplished in a variety of ways, *i.e.,* by vacuum distillation, treatment with hydrochloric or polyphosphoric acid, or heating with toluenesulfonic acid in benzene.[59]



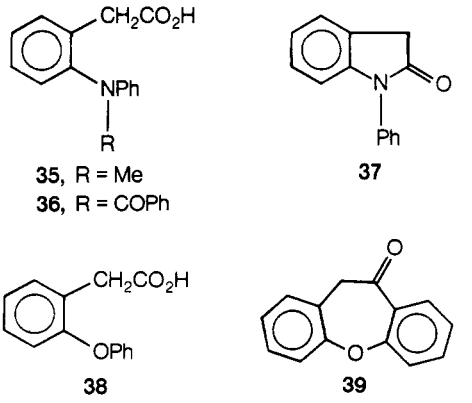
C. Synthesis of 5*H*-Dibenz[*b,f*]azepin-10-ones

Scheme III outlines the principal route to derivatives of 5*H*-dibenz[*b,f*]azepin-10-one. The enol ether **33** may be prepared by nucleophilic substitution of the vinylic bromide **32** or in a single step by reaction of the dibromide **15b** with methanolic potassium hydroxide.[59-69] Modification of the nitrogen substituent is carried out at the enol ether stage (**34**) owing to the reactivity of the protons at the 11 position in the ketonic product **29.**[70]

SCHEME III



5-Methyldibenz[*b,f*]azepin-10-one (**29**) has also been prepared by the dehydration–cyclization of *N*-methyl-*N*-phenylaminoacetic acid (**35**) using either PPA or tris(dimethylamino)phosphine oxide.[71] Previously, other workers had unsuccessfully attempted to cyclize the *N*-benzoyl analog **36** by treatment with thionyl chloride followed by aluminum trichloride.[72] The only product isolated from this reaction was the oxindole **37.** In contrast, an analogous reaction with the ether **38** affords the oxepinone **39.**[73]

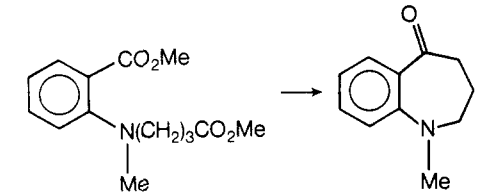


35, R = Me
36, R = COPh

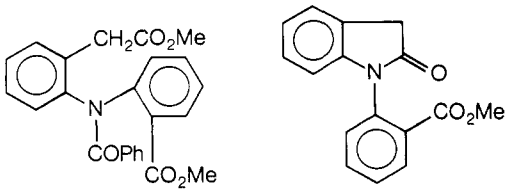
37

38 **39**

Dieckmann ring closure of diesters, a reaction employed for the synthesis of monobenzazepinones, *e.g.,* **40** → **41,**[74] is unsuitable for the preparation of dibenzazepinones; attempted cyclization of the diester **42** leads to the oxindole **43.**[75]



40 41

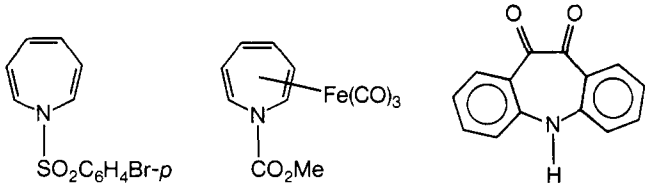


42 43

III. Physical Properties and Structural Parameters of 5H-Dibenz[b,f]azepines

A. X-Ray Studies

To date there have been no X-ray studies of 5*H*-dibenz[*b*,*f*]azepines or of 10,11-dihydrodibenz[*b*,*f*]azepine derivatives. Studies of the related noncondensed azepines **44** and **45** reveal that the ring adopts a boat conformation[76] (*cf.* cycloheptatriene and related tricyclic molecules[7,77,78]), and the molecular dimensions indicate substantial sp^2 character for the nitrogen atom.[76]



44 45 46

Denne and Mackay[79] have studied 5*H*-10,11-dioxo-10,11-dihydrodibenz[*b*,*f*]azepine (**46**) which was found to belong to the space group *Pccn* (*a* = 5.07, *b* = 14.05, *c* = 13.78 Å). This molecule is not quite planar, but "propeller-like" in shape, with atoms other than oxygen lying in two planes inclined at 8.4° to each other about the molecular twofold axis. The bond angles and bond lengths are displayed in Figure 1, and it is interesting that the C(1)–C(2) and C(7)–N bonds are shorter than expected, suggesting some π-electron delocalization in the seven-membered ring; these authors believe that the azepine ring is better described as a combination of two vinylogous amides rather than as an aromatic system.

B. Thermal Properties

The transition enthalpies (ΔH) and transition temperatures (T_m) have been obtained for a series of *N*-acyliminostilbenes (Table I) by differential scanning calorimetry.[80,81] A plot of entropy of fusion (ΔS) against transition temperature revealed that the iminostilbenes shown in Table I formed two sets of uniquely oblate spheroid molecules falling on two straight lines converging at a transition temperature of 144° and an entropy of fusion of 18.6 cal mol^{-1} K^{-1}. The series showing the largest entropy change with increasing melting point contains *N*-formyl-, *N*-isobutyryl-, *N*-bromoacetyl-, and *N*-methacrylyliminostilbene.

The general tendency toward decreasing melting point with increasing acyl chain length indicated that the chain is progressively shifting the overall molecular conformation toward a more spherical geometry. Indeed, the transition entropy of *N*-decanoyliminostilbene is comparable with that of the truly spherical molecules carbon tetrachloride and neopentane, suggesting that in the solid phase the decanoyl chain is folded over the iminostilbene nucleus.

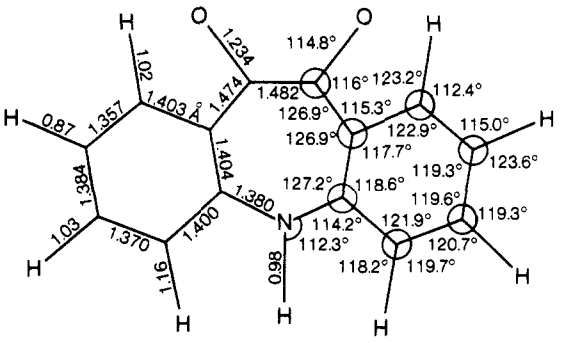


Figure 1.

TABLE I. Thermodynamic Properties of *N*-Acyliminostilbenes

N substituent	T_m, °C	ΔH, cal mol^{-1}	ΔS, cal mol^{-1} K^{-1}
Formyl	133.5	5092	12.5
Acetyl	112.1	5847	15.1
Propionyl	75.7	3904	11.2
Isobutyryl	140.4	6890	16.7
Chloropropionyl	129.3	6707	16.7
Chlorobutyryl	86.3	4188	11.7
Bromoacetyl	136.8	5856	14.3
Bromoisobutyryl	86.3, 94.1 [a]	2220, 2930 [b]	14.18
Trifluoroacetyl	99.2	4910	13.2
Acrylyl	121.9	5202	13.2
Methacrylyl	138.3	6435	15.6
Chloroacetyl	143.2	5847	14.1
Decanoyl	3.30	1001	3.66
H	198.0	6840	14.5

[a] Two peaks on first melt. [b] Σ = 5150.

C. Molecular Orbital Calculations and Electronic Spectra

Molecular orbital calculations for the dibenz[*b*,*f*]azepine system have been carried out by Schmid[82] using the simple Hückel LCAO–MO method; however, the latter has been shown to be unreliable for heteroaromatic systems[83] and has been superseded by a semiempirical SCF–MO approach developed by Dewar, *et al.*[84]

Calculated heats of atomization, resonance energies, and ionization potentials for azepine and its mono- and dibenzo analogs are shown in Table II.[85] The resonance energies indicate that azepine is nonaromatic, the estimated bond lengths being appropriate to a structure having localized bonds, while benzo-, and dibenzoazepines have resonance energies almost the same as that of a corresponding number of benzene molecules. The calculated ionization potential for dibenz[*b*,*f*]azepine (**1**) is not in good agreement with the experimental value available from photoelectron spectroscopy (Table III). Estimated bond lengths and electron densities are presented in Figure 2, from which it is predicted that electrophilic attack should occur preferentially at the positions ortho and para to the nitrogen atom.

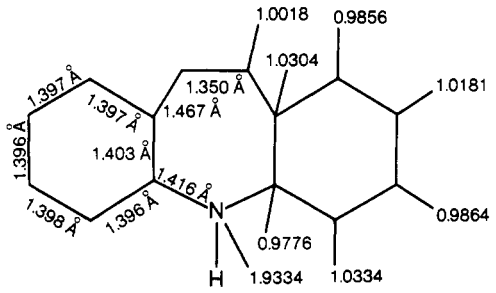


Figure 2. Estimated bond lengths and electron densities for iminostilbene.

Uv spectra of a series of iminobibenzyls and iminostilbenes are collected in Table IV. The spectra of iminobibenzyls bear resemblances to those of diphenylamine (*cf.* Ph_2NH: λ_{max} (EtOH) 237 sh (log ϵ 3.72), 286 (4.38) nm[86]).

In general, the spectra >230 nm of iminostilbenes consist of three major bands comprising a strong absorption in the 241–265-nm region, a medium intensity band at 282–313 nm (frequently only seen as a shoulder), and a weak band at 343–403 nm. This long-wavelength band extends to about 420 nm and accounts for the yellow-orange color of iminostilbene and many of its derivatives. Molecular orbital calculations (see section III.H) disclose that the long-wavelength band is associated with the promotion of an electron from the highest occupied to the

TABLE II. Calculated Heats of Atomization, Resonance Energies, and Ionization Potentials

Compound	—(Heat of atomization), eV	Resonance energy, kcal mol^{-1}	Ionization potential, eV
Azepine (**5**)	63.083	—1.80	8.21
Benz[*d*]azepine	96.621	17.53	8.20
Benz[*c*]azepine	96.127	—0.78	7.61
Benz[*b*]azepine	96.567	18.36	8.19
Dibenz[*b,e*]azepine	130.006	19.49	7.62
Dibenz[*b,f*]azepine (**1**)	130.826	38.40	8.19
Dibenz[*c,e*]azepine	129.208	1.08	7.20

TABLE III. Ionization Potentials for Iminostilbene and Iminobibenzyl Derivatives

Compound	Vertical ionization potentials, eV (adiabatic potentials)
1	7.10 (6.65), 8.13 (7.90), 8.99, 10.46
31	8.13, 8.77, 9.40, 10.78
5-Methyliminostilbene	7.02 (6.60), 7.90 (7.65), 8.98, 10.46
5-γ-Dimethylaminopropyl-iminostilbene	6.92 (6.55), 7.95, 9.63
2	7.00 (6.70), 8.71 (8.30), 10.45
14	8.65, 9.91
47	7.10 (6.74), 8.56 (8.00), 9.91 (9.60)

TABLE IV. Uv Spectra of Iminobibenzyls and Iminostilbenes

Compound	Solvent	λ_{max}, nm (log ϵ)	Ref
		(a) Iminobibenzyls	
5-H	EtOH	206 (4.54), 287 (4.29)	16, 40, 87, 88
5-Ac		233 sh (3.97), 270 (2.88)	40
2-NO_2	MeOH	261 (3.68), 419 (3.81)	89
4-NO_2	MeOH	283 (3.72), 460 (3.08)	89
3-Et	MeOH	210 (4.54), 290 (4.33)	31
5-c-$PrCH_2NMe_2$	EtOH	244 (4.02)	90
7-Cl,3-MeO	EtOH	290 (...)	55
5-Ac,10-Br	MeOH	280 sh (3.2)	31
5-Ac,3-Et	EtOH	293 sh (3.77), 269.5 (3.02)	31
6,9-H_2,5-$(CH_2)_3NMe_2$	MeOH	250 (3.75), 290 sh (3.45), 340 (2.85)	91
7-Cl,2-MeO,5-$(CH_2)_3NMe_2$	EtOH	260 (4.60), 291 sh (3.90), 357 sh (3.20)	55
		(b) Iminostilbenes	
5-H	C_6H_{12}	258.5 (4.65), 293 (3.43), 365 (2.89)	16, 40, 51, 82, 92
	MeOH	258 (4.62), 292 (3.45), 355 sh (2.86)	
5-Me	C_6H_{12}	258 (4.60), 285 sh (3.52), 355 (2.99)	82
	MeOH	256 (4.58), 284 sh (3.52), 349 (2.98)	
10-Me	C_6H_{12}	254.5 (4.57), 287 sh (3.48), 343 (3.08)	82
	MeOH	252 (4.55), 285 sh (3.54), 355 sh (3.09)	
3-Et	C_6H_{12}	262 (4.65), 290 sh (3.60), 367 (3.0)	31
2-NO_2	MeOH	258 (4.48), 318 (4.08), 403 (3.80)	93
5-NO	MeOH	222 (4.26), 231 (4.26), 288 (3.94)	93
5-Ac	C_6H_{12}	241 (4.18), 286.5 (4.02)	40, 82
3-Cl		262 (4.70), 295 (3.46)	40
5-CO_2Et	MeOH	210 (4.53), 233 (4.20), 283 (4.00)	31
3,7-Me_2	C_6H_{12}	263 (4.67), 297 (3.42), 361 (3.06)	82
2,8-Me_2	C_6H_{12}	261 (4.66), 293 sh (3.48), 362 (2.86)	82
3,7-Cl_2	EtOH	241 (4.33), 267 (4.73), 304 (3.38)	31
5-Me,10-Pr	EtOH	255 (4.28), 284 sh (3.84), 340 sh (2.95)	55
5-Me,10-Ph	$CHCl_3$	264 (4.30), 290 sh (4.08), 370 sh (2.70)	55
3-Cl,10-MeO	MeOH	216 (4.28), 244 (4.51), 274 (4.04), 368 (3.74)	64
3-Cl,11-MeO	MeOH	261 (4.56), 290 infl (3.53)	64
7-Cl,2-MeO	EtOH	265 (4.60), 303 (3.60), 370 sh (2.90)	55

lowest unoccupied molecular orbital of iminostilbene, and comparison of the contribution of the nitrogen lone-pair electrons to these MO's shows that the transition has considerable charge-transfer character. The observed hypsochromic shift (blue shift) of this band (*ca.* 10 nm) in polar solvents is in agreement with the foregoing.[82]

N-Acylation of iminostilbene has the effect of localizing the nitrogen lone-pair electrons in the *N*-acyl moiety and explains the lack of color, and similarity of the spectrum of *N*-acetyliminostilbene with that of *cis*-stilbene [*cf.* λ_{max} (EtOH) 280 nm (4.02)].

D. Infrared Spectra

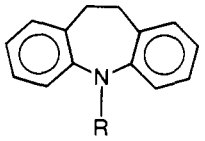
The N–H stretching frequency of unsubstituted iminostilbenes[16,41,51,55,93] occurs in the region of 3300 cm^{-1}. Absorptions in the infrared spectrum of iminostilbene at 1316 and 760 cm^{-1} are assigned to C–N stretch and ortho-disubstituted benzene ring, respectively.

Schmid has compared the intensity of the N–H stretching band of iminostilbene, 2.953 μ (log intensity 0.8), with the intensities of similar absorptions in other nitrogen heterocycles, *e.g.*, indole 2.865 μ (5.7), carbazole 2.876 μ (4.8), and iminobibenzyl 2.920 μ (1.3). The comparatively low intensity of this band is indicative of a high electron density at the nitrogen atom of iminostilbene, since the intensity is inversely proportional to the charge density at the nitrogen atom.[94]

E. Nuclear Magnetic Resonance Spectra

Spectra of a series of iminostilbenes and iminobibenzyls are collected in Table V. The protons of the etheno and ethano bridge absorb in the region τ ~3.00 and ~6.9, respectively.

Absorptions appropriate to the ethano-bridge protons of iminobibenzyl and *N*-alkyliminobibenzyls (**47**) appear as a singlet down to −100°, indicating that the barrier to ring inversion for these nonplanar molecules is very small.[95] Delocalization of the nitrogen lone-pair electrons (*e.g.*, formation of an amide bond) introduces an extra conformational barrier as evidenced by the complexity of the absorptions of the ethano protons in the N-acylated derivatives **14**, **48**, and **49**. The ^1H nmr spectrum of *N*-



14, R = $COCH_3$
47, R = CH_3
48, R = $COCH_2Cl$
49, R = $CO_2CH_2CH_3$

acetyliminobibenzyl shows a remarkable variation with temperature. At −60° all the protons of the ethano bridge are nonequivalent and thus form an ABCD system which gives rise to two groups of peaks centered at δ *ca.* 2.8 and 3.3. As the temperature is raised, the ABCD spectrum is transformed into an AA′BB′ system (T_c *ca.* room temperature) which appears as two symmetrical groups of absorptions at δ 2.85 and 3.43. A further increase in temperature leads to a broadening of the AA′BB′ absorptions which eventually coalesce to a single absorption (T_c 112°).

Of the two coalescence processes involved, the first, ABCD → AA′BB′, is complex and ill-defined, and it was not possible to determine a value for the activation energy; however, for the process AA′BB′ → A_4, the value of

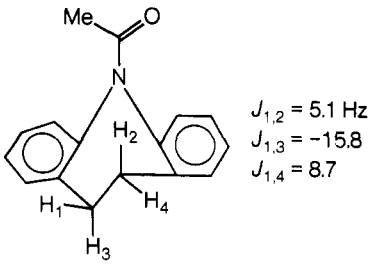


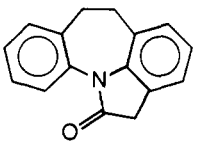
Figure 3.

$\delta\nu_{AB}$ was found to be 56.7 Hz, and from this and the coalescence temperature, the free energy of activation (ΔG^*) for the process may be calculated as 19.9 kcal mol^{-1}.

A full analysis of the AA′BB′ spectrum provides values for the $^3J_{HH}$ couplings of the ethano protons (Figure 3). Application of the Karplus-type equation appropriate to rotation of the ethano-bridge fragment[96] between two equivalent conformations gives a dihedral angle (ϕ) of *ca.* 45°. This value indicates that the ethano bridge is twisted out of a symmetrical staggered conformation; *cf.* metacyclophane.[97]

These spectra have been interpreted in terms of restricted rotation about the amide C–N bond and an inversion of the central seven-membered azepine ring. At low temperatures the amide moiety adopts a fixed planar conformation which has the effect of "freezing" the conformation of the seven-membered ring. This follows since ring flip would involve gross steric interaction between the planar amide group and the abutting aromatic protons at the 4 and 6 positions. As the temperature is raised, the amide rotational barrier is overcome, removing the steric restrictions imposed on the ring inversion by the planar amide group; rapid ring flip occurs, resulting in the collapse of the AA′BB′ to an A_4 system.

Since $\delta\nu_{AB}$ for the coalescence ABCD → AA′BB′ is very much smaller than that of AA′BB′ → A_4, the process ABCD → AA′BB′ → A_4 may equally well be considered as a cooperative phenomenon in which ring-flip must be preceded by rotation of the amide group to a nonplanar conformation. When the amide group is held in a rigidly planar conformation, as in the annelated derivative **50**, ring inversion involves mainly the ethano bridge and the least substituted aromatic ring. There is no longer a requirement for movement of the planar amide group across the interfering ortho protons and, in agreement with prediction, the ^1H nmr spectrum of **50** shows the ethano-bridge protons as a single line down to −60°.



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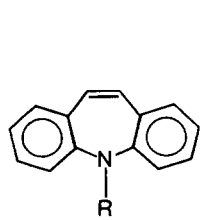
Gipstein, *et al.*,[98] have reported that *N*-β-chloropropionyl- (**51**) and *N*-α-bromoisobutyryliminostilbene (**52**) display temperature-dependant spectra, and these are explained in terms of hindered rotation about the C–N bond and C–C bonds. At room temperature the chloroethyl group of **51** appears as two multiplets from τ 7.21 to 7.51 and 7.73 to 8.04. Upon heating to 110° the multiplets collapse to the expected triplets.

Other workers[99] have described similar phenomena. The proton at the 10 position of the ene-amine **53** appears as a doublet as does the methyl group of the nitrogen substituent. This is thought to be due to restricted

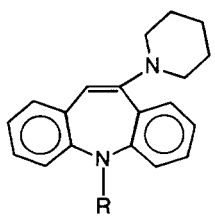
TABLE V. ^{1}H Nmr Spectral Data for Iminostilbene and Iminobibenzyl Derivatives

Compound	10,11 protons	Aromatic protons	Other	Ref
		(a) Iminobibenzyls		
5-H	7.17 (4 H, s)	3.0–3.6 (8 H, m)	4.4 br (1 H, NH)	101
5-Me	7.00 (4 H, s)	2.9–3.4 (8 H, m)	6.85 (3 H, s, NCH_3)	
5-Et	6.90 (4 H, s)	2.6–3.1 (8 H, m)	6.24 (2 H, q, $J = 8$ Hz, NCH_2), 8.87 (3 H, t, CH_3)	
5-COMe	6.6–7.5 (4 H, m)	2.8–3.1 (8 H, m)	8.10 (3 H, s, $COCH_3$)	
5-COEt	6.5–7.5 (4 H, m)	2.6–3.1 (8 H, m)	7.5–8.1 (2 H, m, $COCH_2$), 8.95 (3 H, t, $J = 7$ Hz, CH_3)	
5-$COCH_2Cl$	6.5–7.5 (4 H, m)	2.9–3.1 (8 H, m)	6.17 (2 H, s, $COCH_2Cl$)	
5-COPh	6.4–7.5 (4 H, m)	2.6–3.2 (13 H, m)		
3-COMe	7.14 (4 H, s)	2.2–3.2 (7 H, m)	7.60 (3 H, s, $COCH_3$)	
3,5-$(COMe)_2$	6.5–7.5 (4 H, s)	2.0–2.8 (7 H, m)	7.45 (3 H, s, $COCH_3$), 7.99 (3 H, s, $NCOCH_3$)	
2-NO_2	6.9 (4 H, s)	2.01–2.03 (2 H, m, 1- and 3-H), 2.8–3.2 (4 H, m), 3.27 (1 H, d, 4-H)	3.45 (1 H, NH)	89
4-NO_2	6.84 (4 H, s)	1.98 (1 H, d, 3-H), 2.7–3.45 (5 H, m), 3.33 (1 H, d, 2-H)	−0.72 (1 H, NH)	89
5-$(CH_2)_3NMe_2$-1,4-H_2		2.9 (4 H, m)	4.16 br (2 H, s, vinyl H's)	91
2,4,6,8-Br_4	7.24 (4 H, s)	2.8–3.3 (6 H, m)		
2,8-Br_2,5-Me	6.95 (4 H, s)	2.5–3.2 (6 H, m)	6.75 (3 H, s, NCH_3)	
2,8-$(COCH_3)_2$,5-Me	6.95 (4 H, s)	2.2–3.1 (6 H, m)	6.69 (3 H, s, NCH_3), 7.60 (6 H, s, $COCH_3$)	
3,7-Cl_2,5-$(CH_2)_3NMe_2$	6.92 (4 H, s)	2.6–3.1 (6 H, m)	6.28 (2 H, t, $J = 7$ Hz, NCH_2) 7.8 br (2 H, NCH_2), 7.85 (6 H, s, NCH_3), 8.3 br (2 H, CH_2)	
		(b) Iminostilbenes		
5-Et	3.32 (2 H, s)	2.7–3.2 (8 H, m)	4.26 (2 H, q, NCH_2), 8.82 (3 H, t, CH_2CH_3)	100
5-Pr-*n*	3.45 (2, H, s)	2.8–3.5 (8 H, m)	6.40 (2 H, t, NCH_2), 8.45 (2 H, m, CH_2CH_3), 9.10 (3 H, t, CH_2CH_3)	100
5-$COCH_2CH_2Cl$	3.24 (2 H, d)	2.62–2.75 (8 H, m)	7.21–7.51 and 7.73–8.04 (4, H, CH_2CH_2Cl)	98
5-$COCH{=}CH_2$	3.20 (2 H, d)	2.92–2.70 (8 H, m)	3.68 (1 H, β-vinyl H), 4.2 and 4.6 (3 H, m, vinyl)	98
5-$COCMe{=}CH_2$	3.04 (2 H, d)	2.58–2.76 (8 H, m)	7.02 (2 H, β-vinyl H), 8.24 (3 H, m, OMe)	98
5-$COCMeBrCH_3$	3.05 (2 H, d)	2.83–2.31 (8 H, m)	8.42 (3 H, s, CH_3)	98
5-$COCH_3$,10-$C_5H_{10}N$ (piperidyl)	3.75 and 3.85 (2 H, s)	2.6 (8 H, m)	7.0 (4 H, NCH_2), 8.10 (3 H, Me), 8.35 (6 H, CH_2)	99
5-NO	3.18 (2 H, s)	2.3–3.0 (8 H, m)		93
2-NO_2,5-$COCH_3$	2.98, 3.00 (2 H, s)	1.68–1.80 (2 H, m, 1- and 3-H), 2.46 (1 H, d, 4-H), 2.56 (4 H, m)	8.12 (3 H, s, $COCH_3$)	93

rotational isomerism involving the amide group. Restricted rotation about the C–N bond at the 11 position was discounted since the proton at the 10 position appears as a singlet in both **54** and **55**.[99]



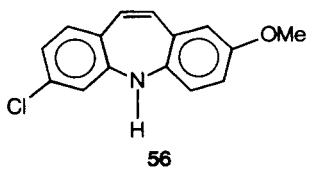
51, R = $COCH_2CH_2Cl$
52, R = $COC(Br)MeCH_3$



53, R = COMe
54, R = H
55, R = Me

Bergmann, *et al.*,[55] have noted that the 10,11 protons of 2-methoxy-7-chloroiminostilbene (**56**) are not equivalent and appear as part of the aromatic multiplet, the aromatic protons being shielded by the methoxyl and imino groups.

Barriers to inversion of a range of fused seven-membered ring systems (**57**–**61**) have been determined by variable-temperature nmr spectroscopy.[102] The degenerate ring inversion process was followed by observing the absorptions of the methyl groups of the prochiral 1-hydroxyisopropyl group, and the results are presented in Table VI. Ring inversion may be considered to proceed through a planar transition state in which π-electron delocalization is more efficient than in the nonplanar ground



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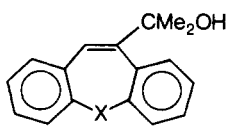


57, X = NEt **60**, X = S
58, X = CH_2 **61**, X = O
59, X = CO

TABLE VI. Spectral Parameters (60 MHz) and Free Energies of Activation (ΔG*) for Conformational Inversion of Seven-Membered Ring Systems[a]

Compd	Solvent	ν_{AB}, Hz	T_c, °C	ΔG* at T_c, kcal mol^{-1}	E_{inv} (calcd), kcal mol^{-1}	E_{inv} (calcd) − ΔG*, kcal mol^{-1}
57	C_2HCl_5	2.4	116	21.7	22.1	0.4
58	$CDCl_3$	2.6	44	17.5		
59	CS_2		<−90	<9	15.3	>6
60	C_6F_6	3.5	51	17.7	21.3	4
61	$CDCl_3$–CS_2(1:2)	16	−69	10.3	18.3	8

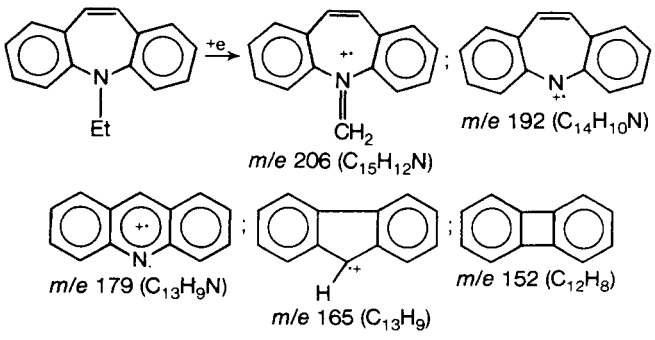
[a] Prochiral group, CMe_2.

state. The three main sources of π-electron delocalization are (a) cis-stilbenoid conjugation, (b) π–p or π–π conjugation involving the benzene rings and the atom or group joining the rings, and (c) antiaromatic character associated with the seven-membered ring. The activation energy [E_{inv}(calcd)] for each of the compounds **57** and **59–61** was obtained by summation of the activation energy of the reference compound, 5*H*-dibenzo[*a,d*]cycloheptene (**3a**), the estimated change in transition state angle strain relative to **3a**, and the appropriate nonbonded interactions. Differences between the experimental and calculated activation energies provide a measure of the stabilization of the transition state by π-electron delocalization other than cis stilbenoid, and from these differences it was concluded that compounds **59, 60,** and **61** did not show a significant increase or decrease in delocalization energy which could have been a consequence of cyclic conjugation in the planar seven-membered ring. An exception is the azepine **57,** but this anomaly was tentatively attributed to large steric interactions between the nitrogen substituent and abutting aromatic protons, rather than antiaromatic character.

The very much lower barrier to inversion for the seven-membered ring of *N*-alkyliminobibenzyls compared to *N*-alkyliminostilbenes is noteworthy.

F. Mass Spectra

Mass spectral data for dibenzazepine derivatives have been recorded in several instances. Iminostilbene fragments under electron impact to produce three principal fragment ions at *m/e* 179, 165, and 152. Accurate mass measurements of these ions indicate the molecular formulas $C_{13}H_9N$, $C_{13}H_9$, and $C_{12}H_8$, severally. The fragmentation, together with the proposed structural assignments of the fragments, for 5-ethyliminostilbene is shown below.[103]



IV. Substitution at the Nitrogen Atom

A. Alkylation

Descriptions of N-alkylation procedures comprise the major part of the extant literature relating to the di-

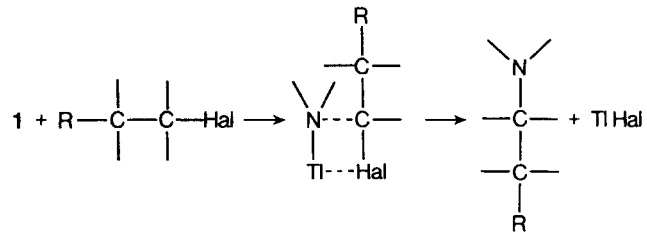


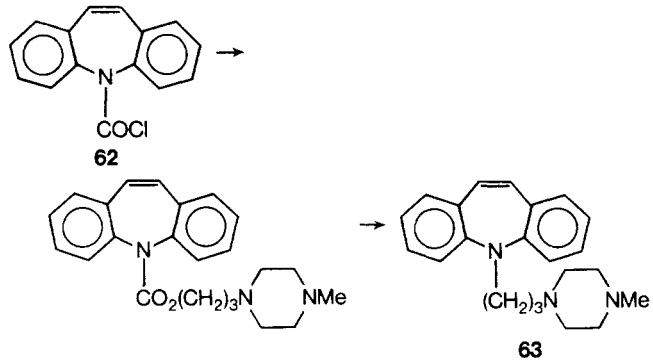
Figure 4.

benz[*b,f*]azepine ring system.[104-130] Alkylation of iminostilbene or iminobibenzyl is effected by reacting the free base with an alkyl halide, preferably a chloride, bromide, or a tosylate[131-133] and a suitable base, usually in refluxing toluene. Many bases have been cited including alkali metals (K, Na), alkali amides ($LiNH_2$, $NaNH_2$, KNH_2), alkali hydrides (LiH, NaH), and metal alkyls and metal aryls (Li-*n*-Bu, Na-octyl, Li-Ph, Na-Ph).[134] Sodium amide is most commonly used, but butyllithium has been shown to be most effective for the introduction of small groups at the nitrogen atom. Metal salts, analogous to potassium carbazole, have not been isolated for either ring system **1** or **2.** Methyl sulfate may be used to N-methylate iminobibenzyl, but butyllithium or phenyllithium/methyl iodide affords better yields.[16]

When ω-dialkylaminoalkyl groups are to be introduced at the nitrogen atom, it is usual to use the corresponding hydrochloride and 2 equiv of base, rather than isolate the free α-halo-ω-dialkylaminoalkane.[21,109,135]

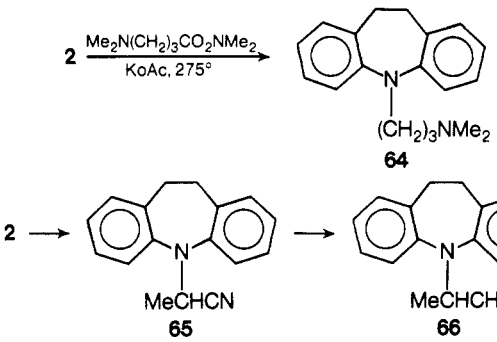
N-Methyl-, *N*-ethyl-, and *N*-propyliminostilbene may be prepared under mild conditions from iminostilbene and the corresponding alkyl iodide using thallium ethoxide as the base. The reaction is thought to proceed *via* a four-center transition state (Figure 4) and, as such, is subject to severe steric restraints; *i.e.*, only small primary alkyl groups may be introduced at the nitrogen atom. This procedure is unsuitable for iminobibenzyl owing to decreased ring coplanarity and increased steric restrictions imposed by the ethano bridge.[100]

Decarboxylation of urethanes, prepared from a chlorocarbonyl compound and an alcohol, constitutes an important pathway to *N*-alkyliminostilbenes and bibenzyls, *e.g.*, **62** → **63.**[28,124,134,136-146] The decarboxylation is accom-

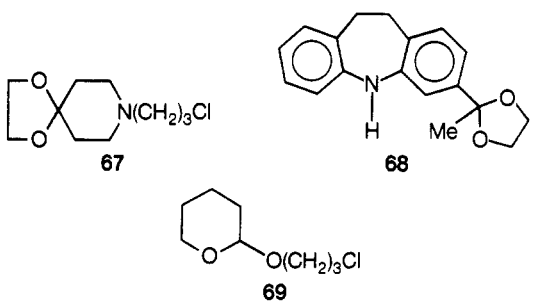


plished either by heating the urethane with copper powder[137] or alone under reduced pressure. Urethane intermediates are probably involved in the alkylation of iminostilbene and iminobibenzyl with dialkylaminoalkylcarbamates[145] and ethoxycarbonyloxy compounds,[138,147] *e.g.*, **2** → **64.**

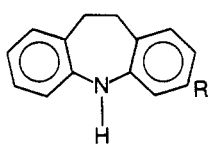
N-α-Cyanoalkyliminobibenzyls (**65**) may be obtained by condensation of the parent compound with an aldehyde in the presence of cyanide ions. The cyano group is reduced to an amine (**66**) in the usual manner either by $LiAlH_4$[148] or hydrogen and Raney nickel.[149]



Alkyl groups and dibenzazepines bearing labile substituents must be protected prior to N-alkylation. *N*-3-Chloropropylpiperidone[127] and the acetyl group of 3-acetyliminobibenzyl must be converted to their respective ketals **67** and **68**, before N-alkylation may be attempted.[150-152] Hydroxypropyl groups cannot be introduced directly at the nitrogen atom of the dibenzazepine nucleus; instead the hydroxy group must be protected with a tetrahydropyranyl group (**69**),[152] which is subsequently removed by acid hydrolysis.

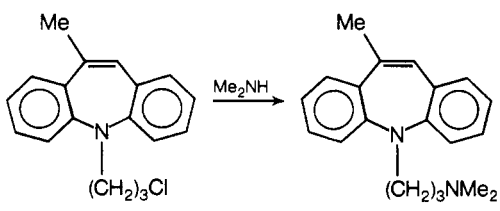


Ring alkylation of iminostilbene is outlined in section V.A. 3-Ethyl- (**70**) and 3-propyliminobibenzyl (**71**) are synthesized by reduction of the corresponding 3-acetyl and 3-propionyl derivatives with hydrazine hydrate.[44]

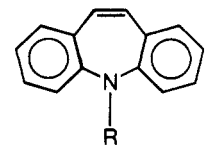


70, R = Et
71, R = *n*-Pr

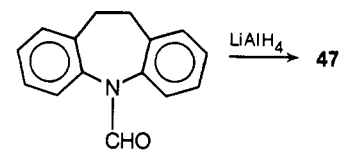
Much of the literature of dibenz[*b,f*]azepine chemistry dwells upon the modification of nitrogen substituents, especially the introduction and modification of amino groups. An amino group may be introduced into a 5-alkyl substituent *via* nucleophilic substitution, by an amine, of the appropriate halide, **72** → **73**.[153] Terminal amino groups are methylated by dimethyl sulfate[149,154,155] or formaldehyde–Raney nickel;[152] if in the latter the formaldehyde is replaced by propionaldehyde, then N-butylation occurs.[156]



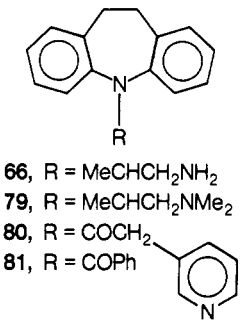
N-Acyl derivatives **74** and **76** are reduced to their respective saturated analogs **75** and **77** by $LiAlH_4$,[157-159] and this reagent also reduces *N*-formyl substituents to *N*-methyl groups, **78** → **47**,[149] as does diborane.[160]



74, R = $CHMeCONMe_2$
75, R = $CHMeCH_2NMe_2$



76, R = Ac
77, R = Et



Reductive methylation of 5-α-cyanoethyliminobibenzyl using formaldehyde–hydrogen and a Raney nickel catalyst produces a mixture of the primary and tertiary amines **66** and **79**, which may be retreated with dimethylamine–Raney nickel to afford **79** as the major product.[161,162]

B. Acylation

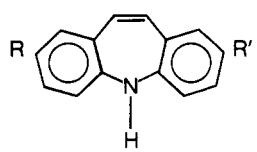
Iminostilbene and iminobibenzyl undergo acylation[163-170] in the normal manner (compare the preparation of nicotinyliminobibenzyl (**80**) from **2** and nicotinyl chloride[163]) and also, under Schotten–Bauman conditions, N-benzoylation, *e.g.*, **81**.

V. Electrophilic and Related Substitution Reactions

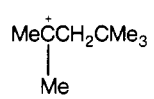
Electrophilic substitution of dibenzazepines is predicted by MO calculations to occur at the 2 and 4 positions (section III.C), although no systematic study has been reported; likewise, there have been no reports of nucleophilic substitutions. Examples of electrophilic substitution reactions are to be found in the following sections A–E.

A. Electrophilic Alkylation and Acylation

Friedel–Crafts alkylation of iminostilbene at 180–190° with diisobutylene (a 3:1 mixture of 2,4,4-trimethylpent-1- and -2-enes) produces 2-*tert*-butyl- (**82**) and 2,8-di-*tert*-butyliminostilbene (**83**). Under different conditions 2-(1,1,3,3-tetramethylbutyl)iminostilbene (**84**) is produced.[171] The reaction proceeds *via* protonation of diisobutylene and reaction of the secondary carbonium ion (**85**) with iminostilbene or fragmentation of the carbonium ion (**85**) to give isobutylene and a *tert*-butyl carbonium ion which becomes the active electrophilic species.[172]



82, R = H; R' = *t*-Bu
83, R = R' = *t*-Bu
84, R = H; R' = $CMe_2CH_2CMe_3$

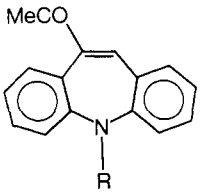


85

Introduction of an acyl group at the nitrogen atom of condensed N-heteroaromatic molecules profoundly affects its directing influence toward electrophiles. Electron

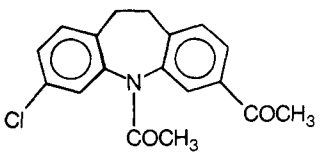
withdrawal from the nitrogen atom renders the nitrogen atom electron deficient and nondirecting (*vide infra*).

Acetylation of *N*-acyliminostilbenes under Friedel–Crafts conditions has been described by Ledwith, *et al.*[173] In agreement with MO calculations and in contrast to the electrophilic substitution of iminostilbene, substitution of *N*-acyliminostilbenes takes place at the 10(11) position; thus 5-acetyliminostilbene reacts with acetyl chloride–aluminum trichloride to produce 5,10-diacetyliminostilbene (**86**). 5-Benzoyl-, 5-propionyl-, and 5-chloroacetyliminostilbene similarly undergo acetylation to afford the methyl ketones **87**, **88**, and **89**, respectively.



86, R = $COCH_3$
87, R = COPh
88, R = COEt
89, R = $COCH_2Cl$

Several catalysts have been utilized in the Friedel–Crafts acylation of *N*-acyliminobibenzyls, *e.g.*, aluminum trichloride,[44,174] iodine,[160] and ferric chloride.[44] The acyl group enters the nucleus at the 3 position; *cf.* formation of 7-chloro-3,5-diacetyl- (**90**) and 5-butyryl-3-acetyliminobibenzyl (**91**). Several groups of workers[31,101] have reported that a second acyl group cannot be introduced into the unsubstituted ring of a 3,5-diacylated iminobibenzyl. It has been proposed that 3,5-diacetyliminobibenzyl adopts a conformation in which the *N*-acyl group is coplanar with the unsubstituted benzene ring, thus causing deactivation; *cf.* *N*-acetyldiphenylamine.[175]



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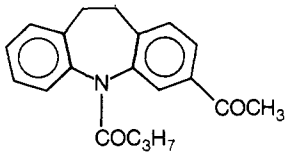
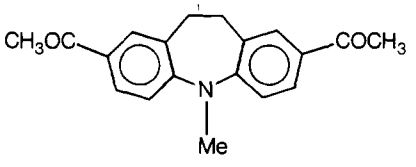


91

N-Methyliminobibenzyl reacts with acetyl chloride–aluminum chloride in carbon disulfide to produce 2,8-diacetyl-5-methyliminobibenzyl (**92**).[101] The positions occupied by the acetyl groups were established from an examination of the 100-MHz ^1H nmr spectrum.

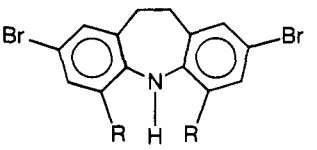


92

Intramolecular electrophilic alkylation involving 5-chloroacetyliminobibenzyls is discussed elsewhere (section XII).

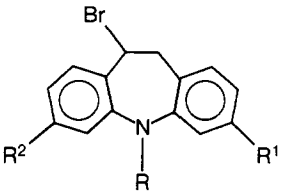
B. Halogenation

Bromination of iminobibenzyl by bromine in acetic acid, chloroform, or carbon disulfide occurs at the positions ortho and para to the nitrogen atom; 2 equiv and 4 equiv of bromine afford the dibromide **93** and tetrabromide **94**, respectively.[16,101] The former product may also be formed by the interaction of iminobibenzyl and *N*-bromosuccinimide (NBS)–benzoyl peroxide.



93, R = H
94, R = Br

Irradiation of a mixture of *N*-acetyliminobibenzyl and NBS in carbon tetrachloride gives 10-bromo-5-acetyliminobibenzyl, the product of benzylic bromination.[31] This procedure may also be carried out on derivatives carrying chloro,[43,49] sulfonyl,[47] and alkyl[44] ring substituents to give the 10-bromides **95–97**. A second bromine atom



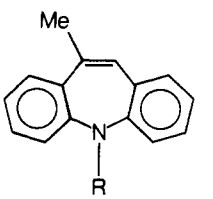
95, R = Ac; $R^1 = SO_2NMe_2$; R^2 = H
96, R = Ac; R^1 = Et; R^2 = H
97, R = Ac; $R^1 = R^2$ = Cl

may be introduced at the 11 position using bromine–potassium hydroxide, *e.g.*, **15a** → **15b**.[99] Replacement of benzylic protons is also brought about by 1,3-dibromo-5,5-dimethylhydantoin.[50]

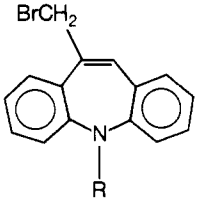
Direct halogenation of iminostilbene has not been described, although halo-iminostilbenes may be prepared from ring-halogenated acridine methanols and iminobibenzyls by rearrangement and dehydrogenation reactions, respectively (section II.B). It is reported that iminostilbene reacts with iodine in dimethyl sulfoxide, but iodo derivatives were not among the products.[176,177] Acid-catalyzed rearrangements frustrate the electrophilic bromination of iminostilbene and its *N*-alkyl derivatives.[103]

Bromination of *N*-acetyliminostilbene with bromine in chloroform occurs with great facility (*cf.* the stilbenoid nature of *N*-acyliminostilbenes, section III.C), producing the 10,11-dibromide (**15b**) which may be converted by dehydrobromination with potassium hydroxide or dibutylamine to the 10-bromoiminostilbene (**32**).[61,64,99]

Allylic bromination of 10-alkyliminostilbenes is effected by NBS, *e.g.*, **98** → **99**.[67,70,178]



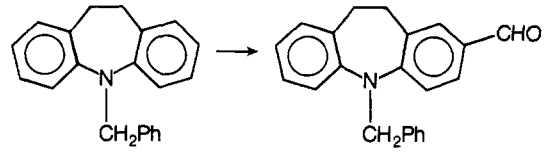
98
R = Me, Ac



99

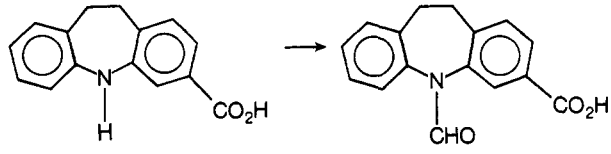
C. Formylation

A formyl group may be introduced into the aromatic ring of an iminobibenzyl derivative by means of the Vilsmeier reaction,[53,179-181] *i.e.*, *N,N*-dimethylformamide- or *N*-methylformanilide–phosphorus oxychloride. In agreement with electron density calculations, the formyl group enters the 2 position, **100** → **101**, but if the nitrogen atom is unsubstituted, then an *N*-formyl derivative is preferentially formed, *e.g.*, *N*-formyliminobibenzyl (**78**) from **2**.[160]



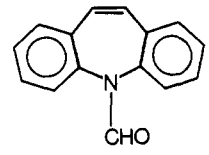
100 101

Formic acid and a mixture of formic acid and acetic anhydride have been used as N-formylating reagents; reaction of the latter with iminobibenzyl-3-carboxylic acid (**102**) affords *N*-formyliminobibenzyl-3-carboxylic acid



102 103

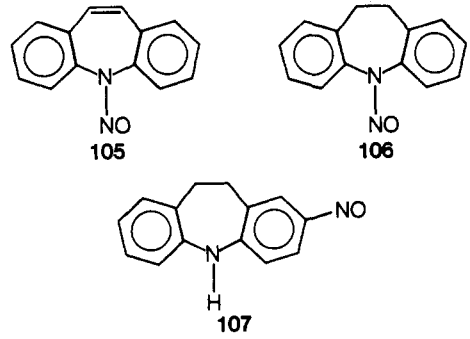
(**103**), and *N*-formyliminostilbene (**104**) is available by treatment of **1** with refluxing formic acid.[81,160]



104

D. Nitrosation and Nitration

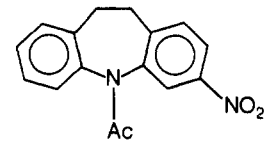
N-Nitrosoiminostilbene (**105**) has been prepared by nitrosation of the parent compound using acidified ethanolic sodium nitrite solution.[93] Similarly *N*-nitrosoiminobibenzyl (**106**) is available by reaction of iminobibenzyl with either ethereal amyl nitrite[182] or sodium nitrite in DMF–hydrochloric acid.[183,184] A nitroso group may be introduced into the 2 position of iminobibenzyl by means of the Fisher–Hepp rearrangement;[185] thus upon treatment with hydrogen chloride, **106** rearranges to form 2-nitrosoiminobibenzyl (**107**). The latter material is also available from the reaction of iminobobenzyl with a mixture of thionyl chloride and sodium nitrite.[182]



105 106 107

N-Nitrosoiminobibenzyl has been used as a nitrosation agent, converting 7-phenyl-3-methyl-5-pyrazolone into the 4-isonitroso derivative, and as a diazotization reagent, producing a diazonium cation in acidified aniline solutions.[182]

Nitration of *N*-acetyliminobibenzyl (**14**) at low temperatures using concentrated sulfuric acid–nitric acid[186,187] affords 3-nitroiminobibenzyl (**108**), the product of substitution meta to the nitrogen atom (section IV.A). Alternatively, **14** may be treated at room temperature with concentrated nitric acid in glacial acetic acid to produce a material formulated as a nitrate salt of *N*-acetyliminobibenzyl. This salt upon treatment with concentrated sulfuric acid forms the 3-nitro derivative **108**.[187]

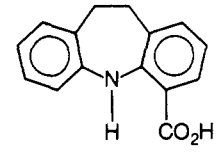


108

Formation of 2-nitroiminostilbene and 2- and 4-nitroiminobibenzyl via irradiation of the respective *N*-nitroso derivatives **105** and **106** is outlined in section IX.[93]

E. Metalation

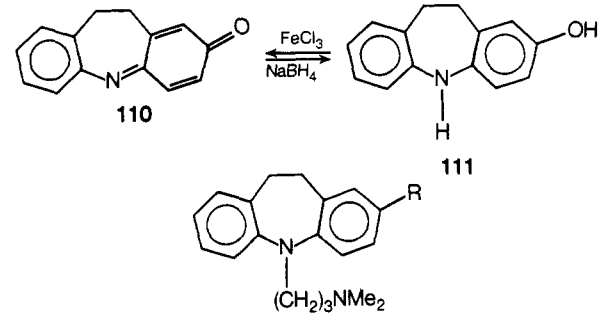
Ring lithiation of iminobibenzyl apparently occurs at the 4 position. In the single instance reported,[188] reaction of **2** with butyllithium followed by carbonation gave iminobibenzyl-4-carboxylic acid (**109**); *cf.* the analogous formation of carbazole-1-carboxylic acid.[189]



109

VI. Oxidation and Hydroxylation of Dibenz[b,f]azepines

2-Oxo-10,11-dihydro-2*H*-dibenz[*b,f*]azepine (**110**) is the major product from the oxidation of iminobibenzyl at pH 8 with potassium nitrosodisulfonate (Fremy's salt); at lower pH values acridine-9-carboxaldehyde is also produced.[88,190,196] The oxo derivative (**110**) is readily reduced to 2-hydroxyiminobibenzyl (**111**) using either sodium borohydride or sodium dithionite[88] or by hydrogenation in the presence of a Lindlar catalyst.[190] Oxidation of imipramine (**64**) with Fremy's salt in the presence of a phosphate buffer[191] leads to hydroxylation in the 2 position, and the product (**112**) is also available in moderate yield by oxygenation of an EDTA solution containing **64**, ferrous sulfate, and ascorbic acid.[190] The tribromo analog



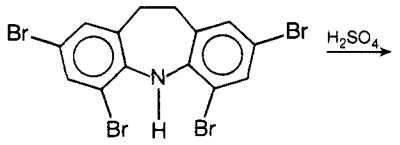
110 111

64, R = H
112, R = OH

113 of the quinone imide **110** is prepared by reaction of 2,4,6,8-tetrabromoiminobibenzyl (**94**) with concentrated sulfuric acid.[88] Reduction of this compound (**113**) with sodium dithionite leads to the 2-hydroxy derivative **114**, which is reconverted to the quinone imide **113** by ferric chloride.

Lead tetraacetate is reported[88] as being unreactive toward iminobibenzyl, while selenium dioxide oxidizes the benzylic protons of 5-acetyliminobibenzyl to give, after hydrolysis, 5*H*-10,11-dioxodihydrodibenz[*b,f*]azepine (**46**) (ref 192).

A hydroxy group may be introduced at the 3 position of iminobibenzyl *via* hydrolysis of the appropriate diazonium salt, *e.g.*, **115** → **116**.[191]



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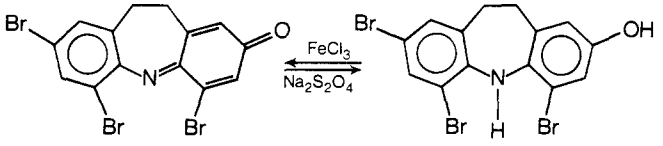
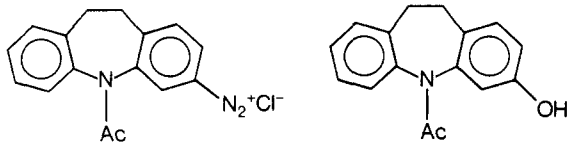
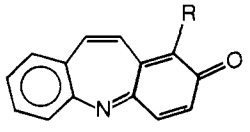


113 114

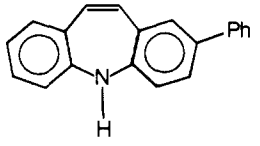


115 116

Proctor, *et al.*,[176,193] have described the synthesis and properties of dibenz[*b*,*f*]azepin-2 one (**117**). This material is photostable in benzene and unreactive toward dienophiles, *e.g.*, dimethyl acetylenedicarboxylate and maleic anhydride. Nitration using $Cu(NO_3)_2$–acetic anhydride affords the 7-nitro derivative **118**, and halogenation by means of *N*-chlorosuccinimide– and *N*-bromosuccinimide–benzoyl peroxide produces the respective 7-chloro (**119**) and 7-bromo compounds (**120**). The position occupied by the substituents was determined by nmr spectroscopy. It was necessary to employ the shift reagent tris(dipivalomethanato)praseodymium in order to resolve the complex spectra of **117** and its derivatives. Phenyllithium reacts with **117** in benzene at 80° to produce, in low yield, a material tentatively identified as 2-phenyliminostilbene (**121**).



117, R = H
118, R = NO_2
119, R = Cl
120, R = Br

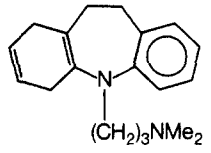


121

VII. Reduction of Dibenz[b,f]azepines

Reduction of iminostilbenes to iminobibenzyls and the reduction of ring substituents are discussed elsewhere (sections II.A.3 and IV).

6,9-Dihydro-5-γ-dimethylaminopropyliminobibenzyl (**122**) has been prepared by reduction of imipramine (**64**)



122

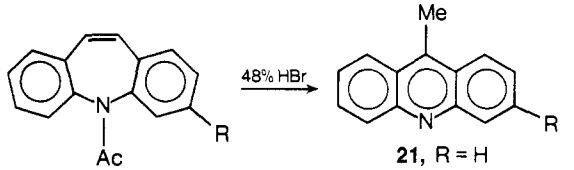
with lithium–methanol in liquid ammonia. The 6,9-dihydro compound is isolated as an oil from a mixture of reduction products by chromatography and is best stored under nitrogen below 5°. Nmr spectroscopy of **122** indicated only two vinylic absorptions, thus excluding other nonconjugated isomers.[91]

No other examples of iminobibenzyls or iminostilbenes are known in which the fused benzene rings are reduced or partially reduced.

VIII. Rearrangement of Dibenz[b,f]azepines

A. Acid Catalyzed

The acid-catalyzed rearrangement of iminostilbenes to 9-methylacridines[31,92,194] was first demonstrated by Schindler and Blattner,[31] who treated 5-acetyl- (**31**) and 5-acetyl-3-ethyliminostilbene (**123**) with 48% hydrobromic acid and obtained 9-methyl- (**21**) and 3-ethyl-9-methylacridine (**124**), respectively. Rumpf and Reynaud[92] investigated the mechanism of this rearrangement and concluded that the reaction proceeded *via* the quinone imonium ion **125** (Scheme IV). In mild conditions (treatment with 0.15 *N* hydrochloric acid) the major rearrangement product of iminostilbene was acridine, whereas in more vigorous conditions (5 *N* HCl), 9-methylacridine predominated. Acridine was seen to arise *via* the reaction of cation **126** with oxygen, and it was proposed that the carbon fragment was expelled as a hydroperoxymethylene species.



31, R = H
123, R = Et

21, R = H
124, R = Et

SCHEME IV

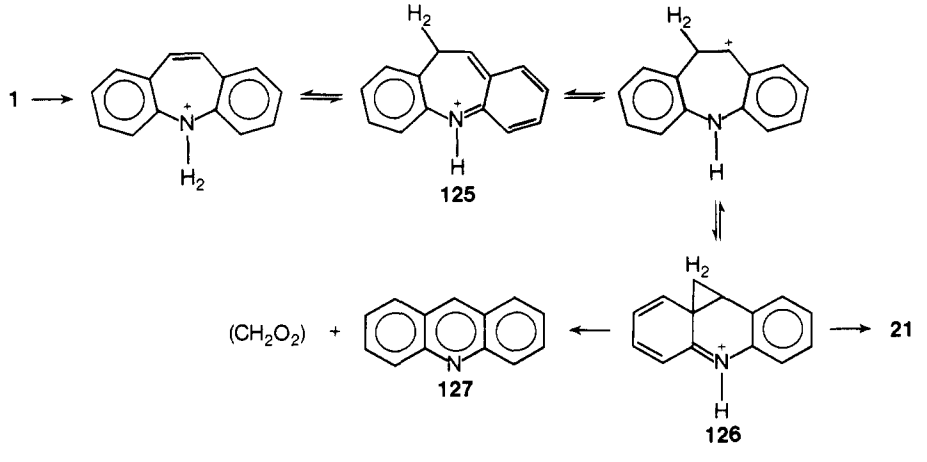


TABLE VII. Thermal and Acid-Catalyzed Reactions of Iminostilbenes

Substrate	Reaction conditions	Products[a] 1	127	21	133	129	105	Other products
1	5 N HCl, 100° (1 hr)	48	tr	24	tr			MeONO, HCO_2Me, N_2O
1	0.15 N HCl/EtOH, 40–50° (30 hr)	<1	49		4			
105	HCl/MeOH, 20° (2 hr)		59	tr		3		
105	HCl/MeOH, under argon		7					
105	HCl/EtOH, 20° (6 hr)		39	tr		4		EtONO, HCO_2Et, N_2O
105	HCl/Me_2CO, 20° (24 hr)	3			57			
105	MeOH, 65° (5 hr)	49	36			4		Acridinium nitrate, tr
105	PrOH, 97° (5 hr)	10	76					
105	PhH, 80° (20 hr)	51	tr		22	4		
105	PhH, 80°/O_2 (20 hr)	41	tr		39	7		
105	MeOH, 65°, est[b] (5 hr)		6		4		66	
105	PhH, 80°, est (20 hr)		5		6	3	79	

[a] tr = trace. [b] est = evacuated sealed tube.

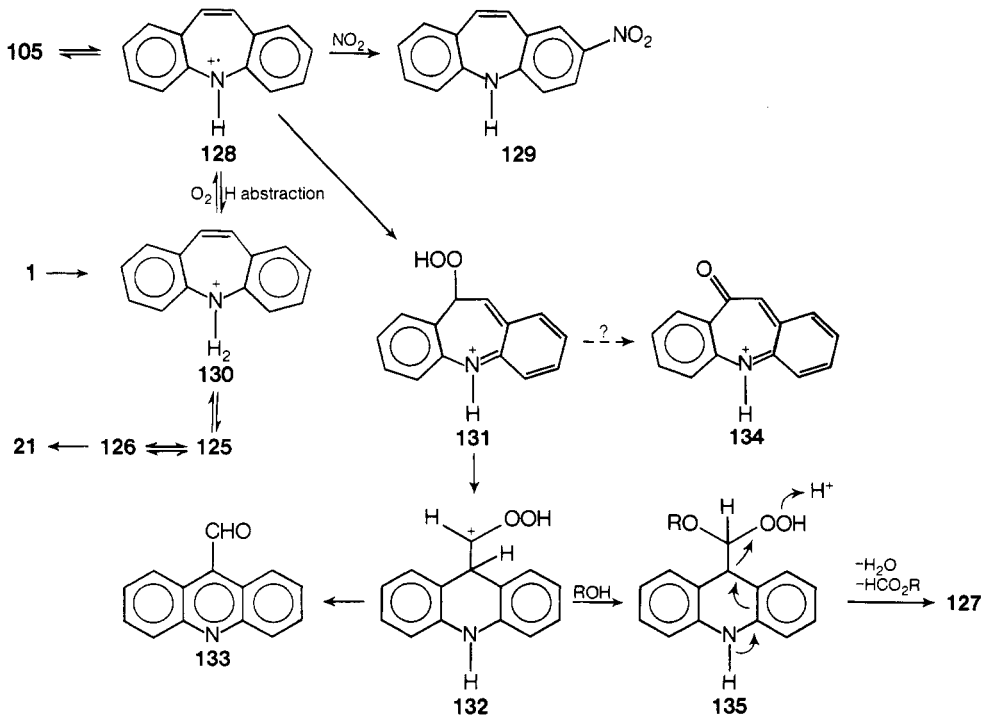
A more recent study[89] of this rearrangement reveals that the products and yields are dependent upon reaction conditions, the nature of the solvent, and in particular the presence or absence of oxygen (see Table VII). The acid-catalyzed rearrangement of *N*-nitrosoiminostilbene (**105**) in hydroxylic solvent (in air) produces acridine together with small amounts of acridine-9-carboxaldehyde (**133**) and 2-nitroiminostilbene (**129**). In nonhydroxylic solvents, *e.g.*, acetone, the major product was the aldehyde **133.** An ir spectral analysis of the vapor present above the reaction mixture from an acidified methanolic solution of **105** indicated the presence of methyl formate, methyl nitrite, and nitrous oxide; ethyl formate and ethyl nitrite were similarly detected when the reaction was conducted in ethanol.

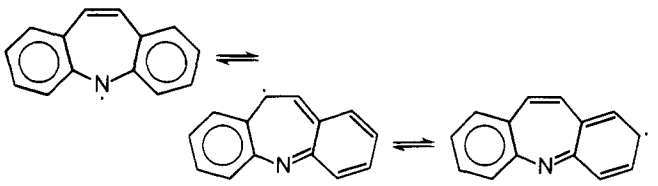
A mechanistic scheme to account for the acid-catalyzed rearrangement of iminostilbene and 5-nitrosoiminostilbene is shown (Scheme V). The reactions of **1** and **105** in acidic media are most probably mediated by the protonated species **130,** which under forcing conditions rearranges *via* the quinone imonium ion **125** to the valence tautomer **126,** while at lower temperatures **128** undergoes slow aerial oxidation to the iminium radical **128.** This may then react with oxygen to form the peroxide **131,** and subsequent Wagner–Meerwein rearrangement affords the cation **132,** which in hydroxylic solvents is trapped as **135** and subsequently fragments to acridine and a formate ester. In nonhydroxylic solvents deprotonation of **132** results in acridine-9-carboxaldehyde, but it is plausible that this compound is formed *via* the azepine **134.**

B. Thermal

Acridine and 9-methylacridine are formed as by-products in the dehydrogenation of iminobibenzyl and these arise presumably *via* thermal rearrangement of the dehydrogenation product iminostilbene,[37] although iminostilbene has been shown to be thermally stable in refluxing propanol and refluxing oxygenated benzene.[89] The thermal rearrangement of 5-nitrosoiminostilbene has been studied extensively (Table VII).[89] The initial step in the rearrangement is assumed to be homolytic cleavage of the *N*-nitrosamine to form the resonance-stabilized radical **136,** and this species may abstract hydrogen atoms forming iminostilbene and/or react with oxygen to pro-

SCHEME V





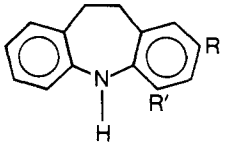
136

duce the peroxide **131.** In hydroxylic solvents hydrogen abstraction builds up a concentration of radicals RCHOH which react with nitric oxide to form eventually nitrous and nitric acids. The fate of **131** in this eventually is as outlined previously (Scheme V), and the isolation of acridinium nitrate in trace quantities from reaction of **105** in methanol and ethanol is taken as evidence for this mechanistic interpretation. In nonhydroxylic solvents no acid is formed and the intermediate peroxide **131** fragments to give the aldehyde **133.**

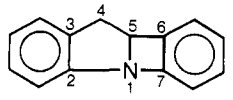
IX. Photochemical Transformations and Addition Reactions

Iminostilbene and 5-nitrosoiminostilbene (**105**) have been found to be stable to irradiation under argon.[89] Irradiation of a benzene solution of iminostilbene in the presence of oxygen affords a considerable amount of a red material, tentatively identified as a dimer of acridine or acridan. Under similar conditions **105** gave acridine-9-carboxaldehyde [**133,** 21%] and 2-nitroiminostilbene (23%). Photolysis of **105** in methanol under oxygen produced acridine (32%) and the aldehyde **2** (18%); a similar photolysis under argon gave the product of N-denitrosation (**1**) (61%) as the only detectable product.

The irradiation of a solution of *N*-nitrosoiminobibenzyl in benzene under oxygen at 5–10° gave a mixture of products, including iminobibenzyl (2%) and 2-nitro- (**137,** 28%) and 4-nitroiminobibenzyl (**138,** 21%).



137, R′ = H; R = NO_2
138, R′ = NO_2; R = H

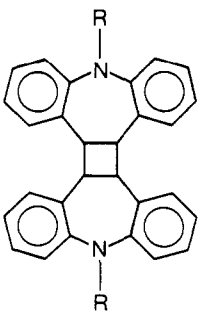


139

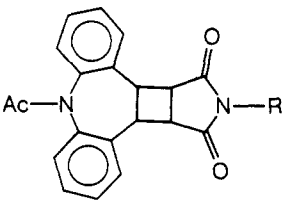
The expectation that irradiation of an acid solution of **105** would lead to a transannular addition of the intermediate aminium radical to the electron-rich 10,11 double bond to afford a derivative of the unknown 2,3:6,7-dibenzo-7-azabicyclo[3.2.0]heptane ring system (**139**) was not realized, since upon acidification **105** underwent a rapid ground-state reaction to produce mainly acridine.

Benzophenone-sensitized irradiation of acetone or benzene solutions of 5-acetyliminostilbene gave the dimer **140a.**[93] Michlers ketone but not fluorenone sensitized the dimerization, indicating that the triplet energy (E_T) for **31** lies in the region 53.3–61.0 kcal mol^{-1}. Similarly sensitized irradiation of 5-propionyl-, 5-chloroacetyl-, 5-benzoyl-, 5-carbamyl-, and 5-carboethoxyiminostilbene gave the dimers **140b, 140c, 140d, 140e,** and **140f,** respectively. The presumed intermediacy of triplet state reactants suggests a stable trans configuration for these cyclodimers. Mixed cyclodimers **141a, 141b,** and **142** have been prepared from similar photosensitized reactions of **31** with *N*-methylmaleimide, *N*-phenylmaleimide, and dimethyl fumarate, severally.

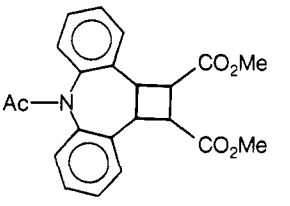
5-Tosyliminostilbene undergoes a photo-Fries rearrangement when irradiated in sensitized and unsensitized conditions to form 2-tosyliminostilbene (**143**). The position occupied by the tosyl group was assumed by analogy with related photo-Fries rearrangements of sulfoanilides, shown to yield exclusively *p*-tosylanilines.[195]



140a, R = Ac
b, R = COEt
c, R = $COCH_2Cl$
d, R = COPh
e, R = $CONH_2$
f, R = CO_2Et



141a, R = Me
b, R = Ph



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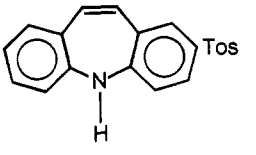

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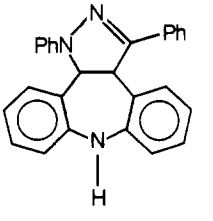

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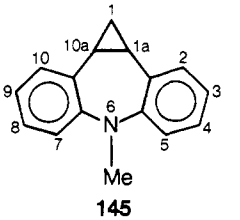


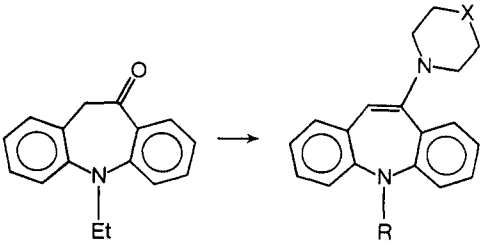
145

Huisgen, *et al.*,[196] have described the reaction *in situ* of iminostilbene with the 1,3-dipolarophile diphenylnitrileimine ($PhC{\equiv}N^{+}{-}N^{-}Ph$), which produces a 1:1 adduct, 1,3-diphenyldibenzo[*b,f*]pyrazolo[3,4-*d*]azepine (**144**).

The etheno bridge is also susceptible to attack by methylene (generated from diiodomethane–iodine and a zinc–copper couple). Reaction of 5-methyliminostilbene with methylene affords the 1,1a,6,10b-tetrahydrocyclopropa[*d*]dibenz[*b,f*]azepine derivative (**145**).[197]

X. Aminodibenz[b,f]azepines

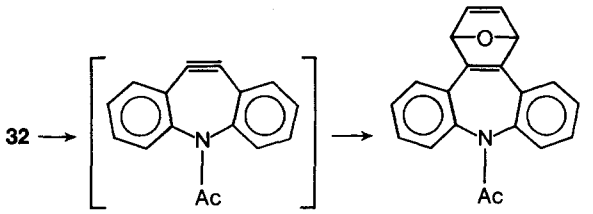
No examples of amino-substituted iminostilbenes are as yet know, but 10-cycloalkylamino derivatives may be prepared by the acid-catalyzed condensation of dibenz[*b,f*]azepin-10-ones with cycloalkylamines;[198] *e.g.*, condensation of **146** with *N*-methylpiperazine affords *N*-(5-ethyldibenz[*b,f*]azepin-10-yl)-*N′*-methylpiperazine (**147**). An



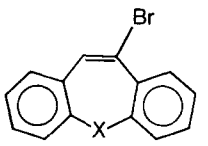
146

147, X = NMe; R = Et
53, X = CH_2; R = Ac

alternative method starts from the bromide **32**.[99,198,199] Conversion of **32** into a cycloalkylamino derivative **53** could not be accomplished by simply heating **32** with the appropriate amine; however, when heated in the presence of potassium *tert*-butoxide, good yields of **53** were obtained. The reaction proceeds *via* a dehydrogenation–addition mechanism, as evidenced by the isolation of the furan adduct **149** from the reaction of furan and 5-acetyl-10-bromodibenz[*b,f*]azepine in the presence of potassium *tert*-butoxide. Precedents for the hetaryne **148** are to be found in the chemistry of the heptanone (**150**) and dimethyl ketal (**151**).[185]

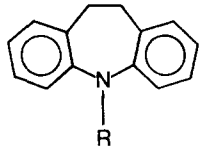


148 **149**

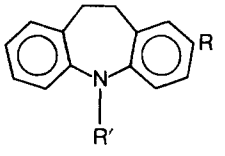


150, X = CO
151, X = $C(OMe)_2$

N-Aminoiminobibenzyl (**152**) may be prepared directly by the reaction *in situ* of the sodium salt of iminobibenzyl and chloramine in dimethyl sulfoxide.[183,200] Alternatively this material (**152**) is obtained by reduction of **106** with *lithium aluminum hydride*,[183] *although Russian workers*[182] claim that attempts to reduce the *N*-nitroso compound (**106**) leads to cleavage of the N–N bond.



106, R = NO
152, R = NH_2

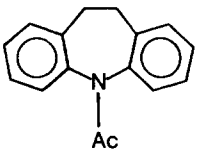


107, R = NO; R′ = H
153, R = NH_2; R′ = H
154, R = NO; R′ = $(CH_2)_3NMe_2$
155, R = NH_2; R′ = $(CH_2)_3NMe_2$

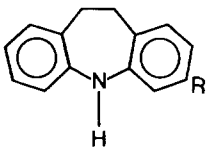
2-Nitrosoiminobibenzyl (**107**), available *via* Fisher-Hepp rearrangement of **106**, is reduced to produce 2-aminoiminobibenzyl (**153**), and similarly reduction of 5-γ-dimethylaminopropyl-2-nitrosoiminobibenzyl (**154**) affords the air-sensitive 2-amino derivative **155**. Bechamp reduction (iron filings–acetic acid) of 3-nitrobibenzyls gives 3-aminobibenzyls; thus reduction of 5-acetyl-3-nitroiminobibenzyl (**108**) affords the 3-amino compound **156**.[187]

Dialkylamino groups can be introduced at the 3 position by reductive methylation of a 3-nitro compound using formaldehyde–hydrogen and a Raney nickel catalyst, *e.g.*, **108** → **157**.[201] A nitro group may also be transformed into an *N,N*-dimethylamino group by potassium carbonate–methyl iodide in acetone.[201]

N-Methylation of an arylamino group is achieved by N-formylation (formaldehyde in pyridine) and subsequent reduction with lithium aluminum hydride, *e.g.*, **161** → **159**; likewise N-ethylation is effected *via* N-acetylation (**160** → **162**). An alternative N-methylation procedure[202] involves refluxing the amino compound in acetone with methyl iodide–potassium carbonate and subsequent hydrolysis of the quaternary iodide; thus 5-acetyl-3-aminoiminobibenzyl (**156**) is transformed *via* the iodide **158** into 3-dimethylaminoiminobibenzyl (**163**).[203]

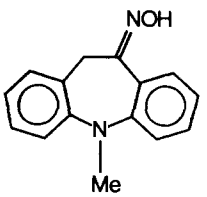


108, R = NO_2
156, R = NH_2
157, R = NMe_2
158, R = NMe_3I



159, R = NHMe
160, R = NAcMe
161, R = NHCHO
162, R = NMeEt
163, R = NMe_2

10-Aminoiminobibenzyls are available by reduction of the hydroxylamine **164** with sodium in butanol.[69,199,204,205] A methylamino group is introduced directly at the 10 position of 5-methyliminobibenzyl by reduction with diborane and reaction of the intermediate borohydride (**165**) *in situ* with methylchloramine.[206] 5-Methyl-10-methylaminoiminobibenzyl (**166**) has also been synthesized *via* nucleophilic displacement of bromine from **167** by treatment with sodium azide and subsequent reduction of the azide **169** with sodium borohydride. The intermediate azides are severe skin irritants and must be handled with care.[22]



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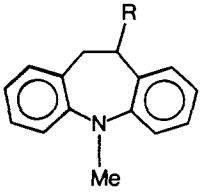


165, R = BH_2
166, R = NHMe
167, R = Br
168, R = NH_2
169, R = N_3

XI. Sulfonamides, Sulfinic Acids, and Sulfides

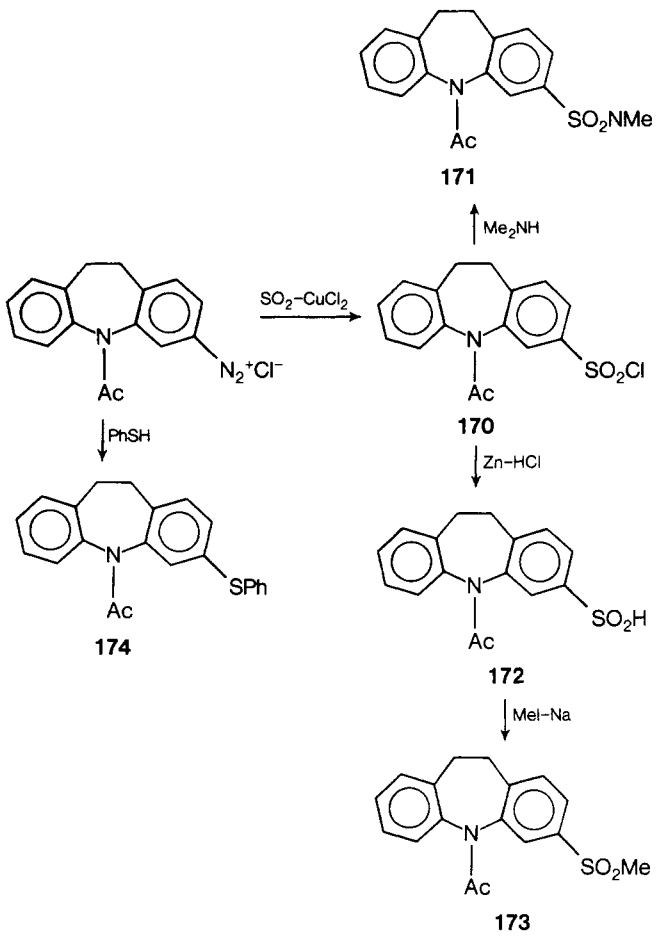
The diazonium salt **115** derived from 5-acetyl-3-aminoiminobibenzyl is a useful intermediate for the preparation of sulfinic acid derivatives (Scheme VI). Treatment of **115** with sulfur dioxide–cupric chloride affords the 3-chlorosulfonyl derivative **170**.[207,208] This material reacts with amines to form sulfonamides (**171**);[207,209] reduction of **170** using zinc–hydrochloric acid[208] or alkaline sodium sulfite[210] produces the 3-sulfinic acid **172** which may be esterified by methyl iodide–sodium to give methyl 5-acetyliminobibenzyl-3-sulfonate (**173**).[208,211] The sulfinic acid **172** is also prepared by treating the diazonium salt **115** with sulfur dioxide–copper powder.[211]

Base-catalyzed hydrolysis of **171** and **173** generates the corresponding 5-unsubstituted compounds, and these may be alkylated at the 5 position by the usual methods.[212-217]

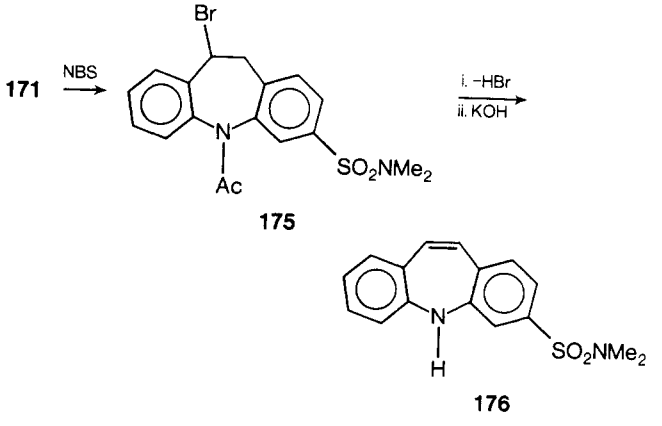
Sulfonamide derivatives of the iminostilbene ring system cannot be prepared directly;[218,219] instead they are available by dehydrohalogenation of 10-bromoiminobibenzyls, *e.g.*, **175** → **176**, and the resulting 3-dimethylaminosulfonyliminostilbene (**176**) finds use as an antioxidant.[47]

5-Acetyl-3-phenylthioiminobibenzyl (**174**) is prepared from the diazonium salt **115** and thiophenol.[220,221] 3-Alkylthioiminobibenzyls (**178**)[221-225] are synthesized *via*

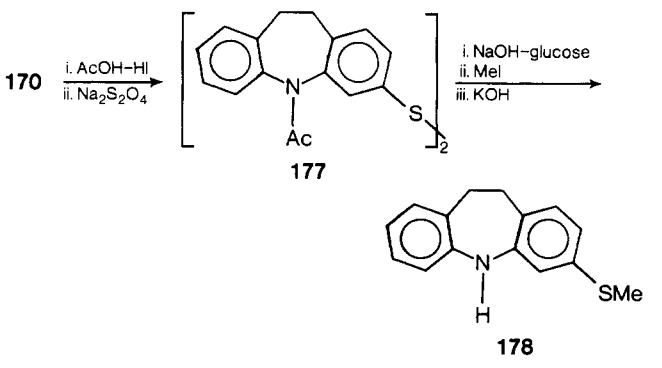
SCHEME VI



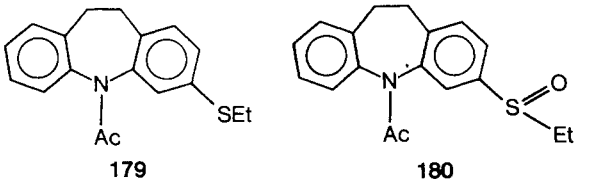
the reductive cleavage and concomitant alkylation of the disulfide **177**, which is available from **170** (Scheme VII).



SCHEME VII



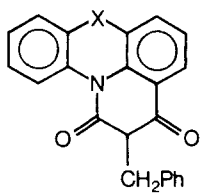
Oxidation of sulfides with sodium periodate produces sulfoxides, *e.g.*, **179** → **180**.[226]



XII. Annelation

Iminostilbene and iminobibenzyl are the starting points for the synthesis of a variety of polycyclic azepine derivatives.

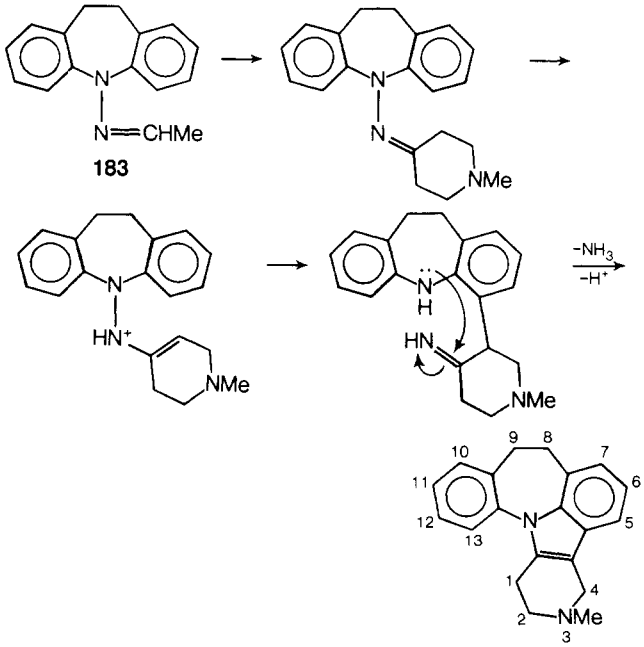
4,5-Malonyl-10,11-dihydrodibenz[*b,f*]azepine (**181**) may be obtained by reacting iminobibenzyl with bis(2,4-dichlorophenyl) benzylmalonate[227] and distilling off the 2,4-dichlorophenol formed. Similarly, the azepine **182** is available from iminostilbene and benzylmalonic acid–phosphorus oxychloride.[227]



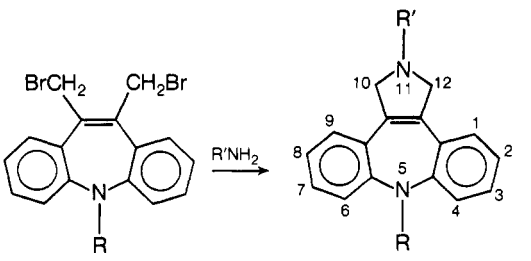
181, X = CH_2CH_2
182, X = CH=CH

Annelation of the dibenzazepine nucleus may also be achieved by a modification of the Fisher indole synthesis;[184,228] treatment of 5-nitrosoiminobibenzyl with ethylmagnesium bromide produces the amidine **183** which undergoes acid-catalyzed exchange with *N*-methylpyridone and a subsequent Fisher reaction[229] to afford 3-methyl-1,2,3,4,8,9-hexahydro-1-benzazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole (**184**) (see Scheme VIII).

SCHEME VIII



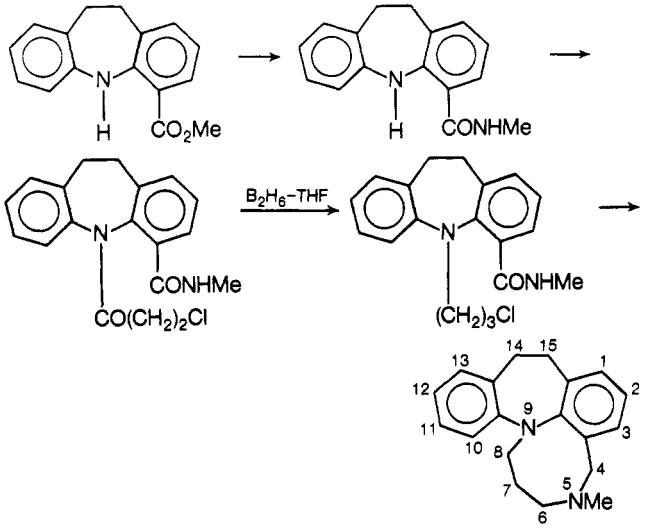
Derivatives of 10,12-dihydrodibenz[*b,f*]pyrrolo[*d*]azepine (**186**) may be prepared by condensation of 10,11-dibromomethyliminostilbene (**185**) and a primary amine (ref 230 and 231).



185, R = Me, Ac 186

A large saturated nitrogen-containing ring has been attached at the 4 and 5 positions of iminobibenzyl by the synthetic route outlined in Scheme IX. The product, 5-methyl-4*H*-5,6,7,8,14,15-hexahydro-5,9-diazocino[1,2,3-*de*]dibenzazepine (**187**)[232] is reported to have antidepressant properties.

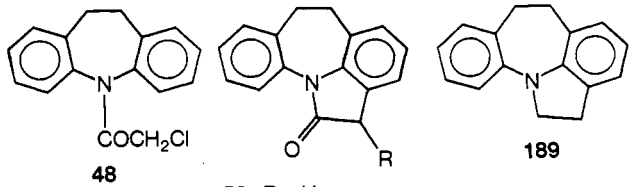
SCHEME IX



187

Examples of the tetracyclic azepine, 1-oxo-1,2,6,7-tetrahydroindolo[1,7-*ab*][1]benzazepine (**50**), are prepared by the intramolecular Friedel–Crafts alkylation of α-haloacetyliminobibenzyls;[233] typically, **50** is obtained by heating together α-chloroacetyliminobibenzyl (**48**) and aluminum trichloride at 120–200°. Cyclizations of this type are not known for the iminostilbene, carbazole, phenothiazine, or dihydroacridine analogs of **48**.

Replacement of an active methylene proton of **50** is achieved in the usual manner with a base and alkyl halide; *cf.* **50** → **188**.[234] Lithium aluminum hydride reduces the carbonyl group of **50** to a methylene group, *e.g.*, **50** → **189**.[235]

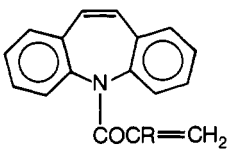


48 50, R = H 189

188, R = $(CH_2)_3NMe_2$

XIII. Polymerization Studies

Thermal and free radical initiated polymerization of the acrylyl monomers **190** and **191** with benzoyl peroxide and azobisisobutyronitrile have been investigated by Gipstein, *et al.*[98,236] 5-Acrylyliminostilbene (**190**) polymerizes to



190, R = H
191, R = Me

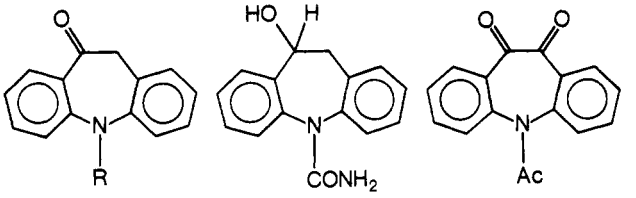
give high molecular weight homopolymers of interest as organic photoconductors;[236] however, all attempts to homopolymerize 5-methacrylyliminostilbene were unsuccessful, a result attributed to steric interference by the bulky dibenzazepine nucleus.

The photo-cross-linking *via* formation of a cyclobutane (*cf.* section IX) of copolymers of **190** with styrene, methyl methacrylate, *N*-vinylcarbazole and maleic anhydride has been investigated by other workers.[237]

XIV. Reactions of 10,11-Dihydrodibenz[*b,f*]azepin-10-ones

The reactions of 10,11-dihydrodibenz[*b,f*]azepin-10-ones with Grignard reagents[59] have already been discussed (section II.B.4).

A variety of reducing agents are effective for the reduction of the carbonyl function to a methylene group, namely, sodium amalgam,[71] sodium borohydride, and $LiAlH_4$,[238,239] and hydrogenation using a copper chromite–barium carbonate catalyst.[62,240-242] Partial reduction to an alcohol (**192** → **194**) is achieved by hydrogenation with a copper chromite catalyst.[243,244]



192, R = $CONH_2$ **194** **195**
193, R = Ac

Oxidation of the 11-methylene group of 5-acetyl-10,11-dihydrodibenz[*b,f*]azepin-10-one is accomplished by selenium dioxide, *e.g.*, **193** → **195**.[192] Replacement of the activated 11-methylene protons is effected in the usual manner.[242]

XV. Pharmacology of Dibenz[*b,f*]azepines

Drugs which affect the mind (psychotropic drugs) may be classified under the following main headings:[245]

(a) *Neuroleptics.* Antipsychotic, ataractic, and tranquillizing agents, *e.g.*, the phenothiazine, butyrophenone, thioxanthene, and reserpine derivatives **196**, **197**, **198**, and **199**, severally.

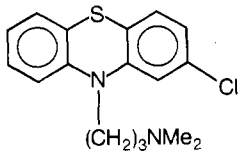
(b) *Axiolytic Sedatives.* These include the barbiturates and derivatives of the benzodiazepine ring system, *e.g.*, diazepam (**200**).

(c) *Psychostimulants. E.g.*, the amphetamines and caffeine derivatives.

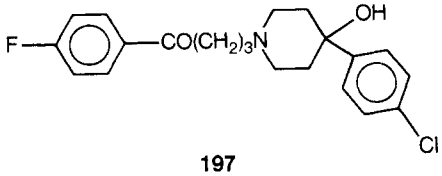
(d) *Psychodysleptics.* Psychedelics, hallucinogens, and psychomimetic drugs, *e.g.*, lysergic acid diethylamide.

(e) *Antidepressants* (*thymoleptics*). Drugs useful against depression may be divided into two classes, the mono-amine oxidase inhibitors, *e.g.*, isocarboxazid (**201**) and, secondly, drugs derived from tricyclic ring systems, especially derivatives of dibenz[*b,f*]azepine.

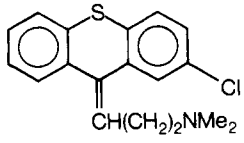
Dibenz[*b,f*]azepine derivatives have been variously reported as having antiallergic activity, specifically antihis-



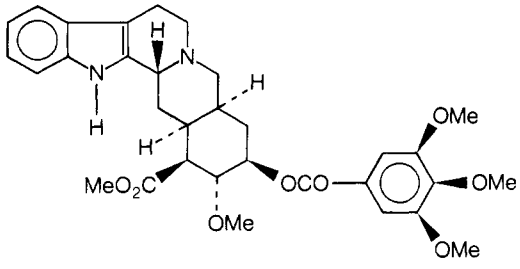
196
Chloropromazine



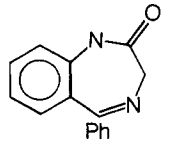
197
Haloperidol



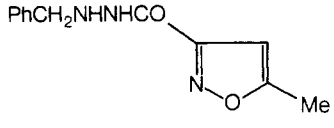
198
Chlorproxithen



199
Deserpidine



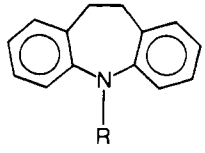
200



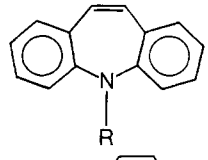
201

taminic activity, spasmolytic, serotonin antagonistic, anticonvulsive, antiemetic, antiepileptic, antiinflammatory, sedative, and fungicidal[246] action. In particular, they potentiate the action of other pharmaceutica, *e.g.*, anesthetics, and antitubercular drugs.[247]

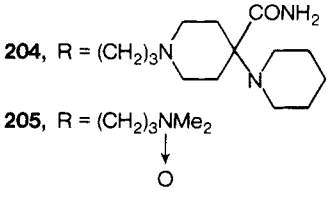
The major dibenz[*b,f*]azepine drugs are imipramine (**64,** Tofranil), desipramine (**202,** Pertofan), trimeprimine (**203,** Surmontil), opipramol (**206,** Ensidone, Insidone), carpipramine (**204**), and carbamazepine (**207,** Tegretol).



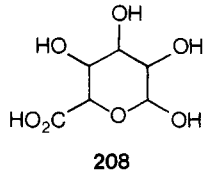
64, R = $(CH_2)_3NMe_2$
202, R = $(CH_2)_3NHMe$
203, R = $CH_2CHMeCH_2NMe_2$



206, R = $(CH_2)_3N$ $N(CH_2)_2OH$
207, R = $CONH_2$



204, R = $(CH_2)_3N$
205, R = $(CH_2)_3NMe_2$



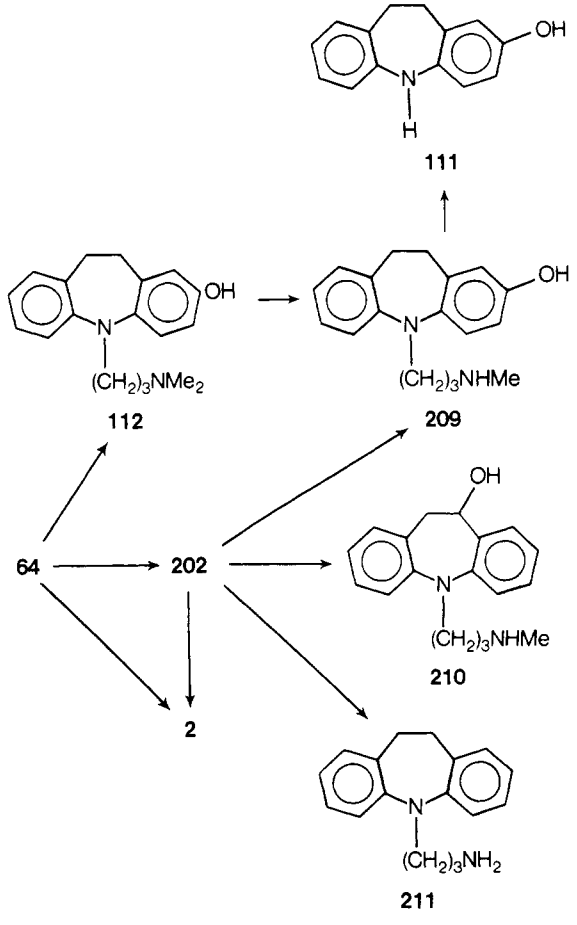
208

No attempt has been made here to cover the extensive literature relating to clinical investigations of dibenzazepine derivatives or to their detection and identification by thin layer chromatography and colorimetric techniques (ref 248–252). Instead the reader is referred to earlier reviews which deal exclusively with the biochemical and pharmacological aspects of dibenzazepines (ref 14, 185, 253–260).

Metabolism of imipramine and related drugs both in man and animals has been extensively studied.[190,261-271] The principal metabolic processes for imipramine are ring hydroxylation, side-chain demethylation, and loss of the side chain to form the respective metabolites **111, 112, 209, 202, 210, 211,** and **2.** A metabolite of minor importance is the *N*-oxide **205.**[265] Hydroxylated metabolites are usually excreted as derivatives of glucuronic acid (**208**).

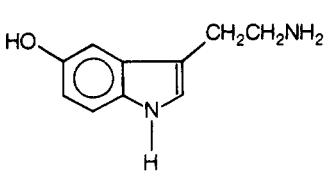
Bickel, *et al.*,[264] have studied the kinetics of the metabolism of imipramine in the rat and propose that metabolism proceeds *via* the routes shown in Scheme X; recent studies with [^{14}C]imipramine support these proposals.[261]

SCHEME X



The therapeutic actions of depressants and antidepressants are not well understood. Antidepressant drugs must be administered in large doses and take up to 2 weeks to become effective. Affective illness (*i.e.*, mania and depression) is thought to be a consequence of changes in the transmission of the amine neurotransmitters [5-hydroxytryptamine (**212**), noradrenaline (**213**), dopamine (**214**)], either by altered synthesis of the neurotransmitters or changes in the postsynaptic receptors.

Curzon[272] has implicated imipramine and/or its metabolites, *e.g.*, demethylimipramine (**202**), in the biosynthetic pathway leading to 5-hydroxytryptamine. This author suggests that in depressive illness the liver enzyme tryptophane pyrrolase is overactive; thus less tryptophan



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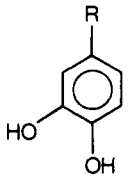
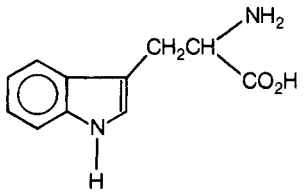


213, R = $CHOHCH_2NH_2$
214, R = $CH_2CH_2NH_2$

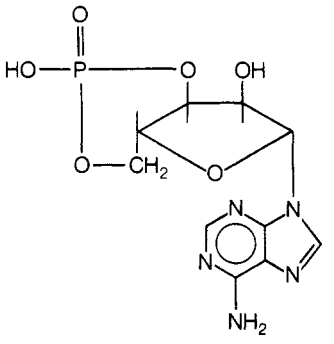


215

(215) is available for the synthesis of the neurotransmitter (212), in which case imipramine may act by inhibiting this enzyme and hence provide a metabolic correction of the depressive illness.

An alternative interpretation is that tricyclic antidepressants rely for their effect on their capacity to block the re-uptake of neurotransmitters released upon stimulation of the nerve terminal, which leads to an accumulation of neurotransmitters at the receptor and a consequent increase in activity.

Defects in the adenosine 3′,5′-monophosphate [**216**, cyclic AMP] system in postsynaptic membranes has also been suggested as a cause of affective illness, since the amount of cyclic AMP excreted in the urine of manic patients is raised above normal, whereas that in depressed patients is reduced.



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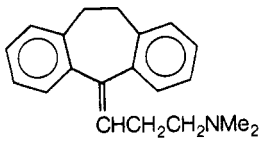

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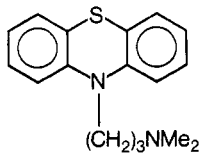


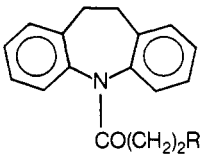
218

The structure of the antidepressant drugs imipramine and amitryptylene (**217**) are very similar to that of the tranquilizing agent **218**, and yet replacement of an ethano bridge by a sulfur bridge causes a complete reversal of pharmacological activity. This dichotomy, as yet unresolved, has led to extensive investigation of possible relationships between structural features and physical properties of drug molecules and pharmacological activity. Russian workers[273] examined the pK_a of a series of iminobibenzyl derivatives (Table VIII) and discovered that antidepressant activity decreased while neuroleptic activity increased with decreasing pK_a. Ionization potentials of drug molecules obtained from studies of charge transfer spectra do not correlate in any significant way with drug activity.[274]

Imipramine is reported as having a considerable radioprotective effect.[275,276] Mice dosed with imipramine were found to survive (60% mortality rate) an otherwise lethal dose of radiation.

Acknowledgments. We are grateful to the SRC for a Research Assistantship (to L. J. K.).

TABLE VIII. pK_a Values for a Series of Iminobibenzyl Derivatives



R	pK_a	R	pK_a
NEt_2	8.37		7.4
NMe_2	8.36		6.02
	8.25		

XVI. Addendum

The conformational equilibria in 5-substituted iminobibenzyls have been studied by variable-temperature ^{13}C nmr spectroscopy, and the nonequivalence of the ethano-bridge carbon atoms has been unequivocally demonstrated. A detailed analysis of the ^1H nmr spectrum of imipramine suggests that this molecule adopts a conformation in which the 5-dimethylaminopropyl substituent is bent toward the tricyclic nucleus.[277]

Huber, *et al.*,[278] have determined the fluorescence and phosphorescence quantum yields and lifetimes in solution at 77°K, and room temperature, for iminobibenzyl and compared these values with those obtained for diphenylamine, carbazole, and acridan. The results indicate that the excited-state behavior of aromatic amines is dominated by the influence of molecular geometry on spin–orbit coupling.

The formation of 2- and 4-acetyliminobibenzyl by irradiation of a solution of 5-acetyliminobibenzyl in ethanol has provided a further example of the photo-Fries rearrangement of iminobibenzyl derivatives (see section IX).[279]

Derivatives of the 10,10′,11,11′-tetrahydrobis(dibenz[*b,f*]azepine) ring system have been prepared by oxidative coupling of iminobibenzyls using sodium dichromate–acetic acid, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone–perchloric acid, or the one-electron oxidants tris(*p*-bromophenyl)aminium perchlorate and hexachloroantimonate.[280]

Heath-Brown, *et al.*,[281] have described the synthesis of derivatives of the 6,7-dihydroindolo[1,7-*ab*][1]benzazepine ring system (see section XII). The parent heterocycle is available by partial reduction of 1-oxo-1,2,5,6-tetrahydroindolo[1,7-*ab*][1]benzazepine with lithium aluminum hydride or by decarboxylation of 6,7-dihydroindolo[1,7-*ab*]-[1]benzazepine-1-carboxylic acid using copper chromate in quinoline.

The monomer 5-methyl-2-vinyliminobibenzyl, available *via* a Wittig reaction of the corresponding 2-aldehyde with methylenetriphenylphosphorane, has been shown to have reactivity in anionic, cationic, and free-radical polymerizations.[282]

XVII. References

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