

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

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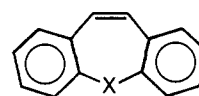
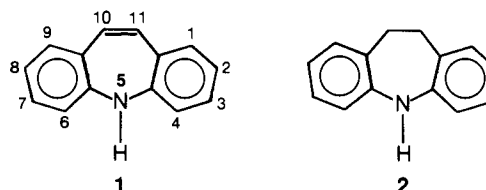
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I. Introduction

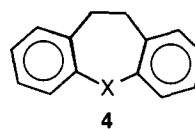
The 5*H*-dibenz[*b,f*]azepine nucleus (1) has been known since 1899 when Thiele and Holzinger¹ prepared 10,11-dihydrodibenz[*b,f*]azepine (2) (hereafter iminobibenzyl) from *o,o'*-diaminobibenzyl hydrochloride; however, over 50 years was to elapse before derivatives of this ring system were prepared 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

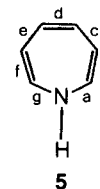


3a, X = CH₂ d, X = Se
b, X = O e, X = GeMe₂
c, X = S f, X = SiMe₂

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 iodopinium cation (4j) have also been reported.⁸



4a, X = CH₂ f, X = SiH₂
b, X = O g, X = GeMe₂
c, X = S h, X = SnMe₂
d, X = Se i, X = PbMe₂
e, X = BH j, X = I⁺



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. morphanthridine¹⁰), and -[*b,d*] annelated¹¹ 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 Burckhardt¹² 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

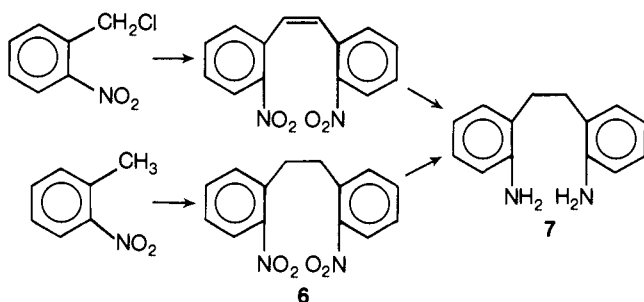
A. Synthesis of 10,11-Dihydrodibenz[*b,f*]azepines

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

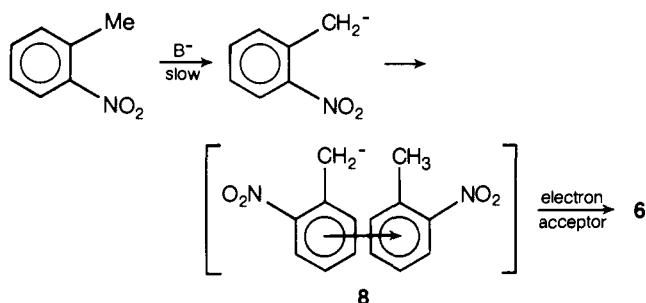
The principal route to the iminobibenzyl nucleus is via cyclization of *o,o'*-diaminobibenzyls (7), which may be

obtained by reduction of *o,o'*-dinitrostilbenes or *o,o'*-dinitrobenzyls. 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-air²⁵ 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 un-ionized nitrotoluene molecule or oxygen) to form the bibenzyl (6) (Scheme I).

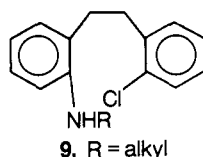


Cyclization of *o,o'*-diaminobenzyls to iminobenzyls is achieved by heating bis salts of the appropriate *o,o'*-diamine. The original synthesis of the parent compound¹ involved heating *o,o'*-diaminobenzyl with its dihydrochloride, but this route proved untenable for substituted derivatives and has been superseded by the bis-methanesulfonate 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(methanesulfonate) alone, above 295°.

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

2. Cyclization of *o*-Amino-*o'*-chlorobenzyls

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

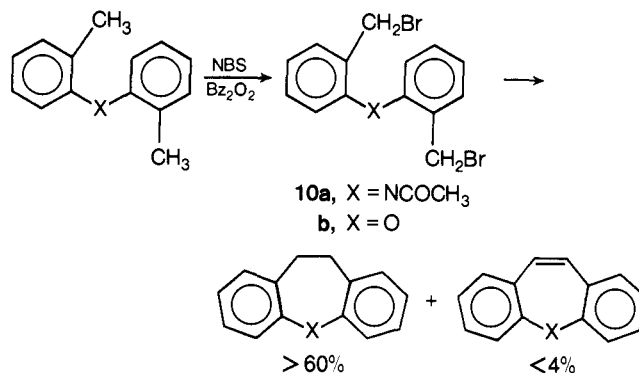


3. Hydrogenation of 5*H*-Dibenz[*b,f*]azepines

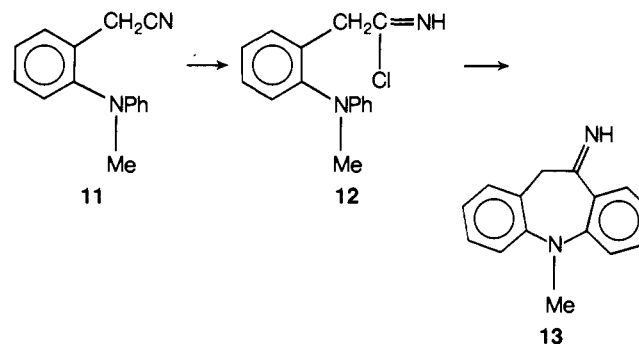
Hydrogenation of iminostilbenes,^{29,30} especially those derived from acridine methanol derivatives (*vide infra*), provides a route to iminobenzyls having a pattern of substitution otherwise difficultly accessible. The hydrogenation is carried out at room temperature and atmospheric pressure using platinum oxide²⁹ or platinum-charcoal³¹ 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-chloroiminobenzyl from 3,7-dichloroiminobenzyl.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 iminobenzyl. Analogously, 10,11-dihydrodibenz[*b,f*]oxepin may be prepared from *o*-ditolyl ether.



Recently, Japanese workers³⁶ 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

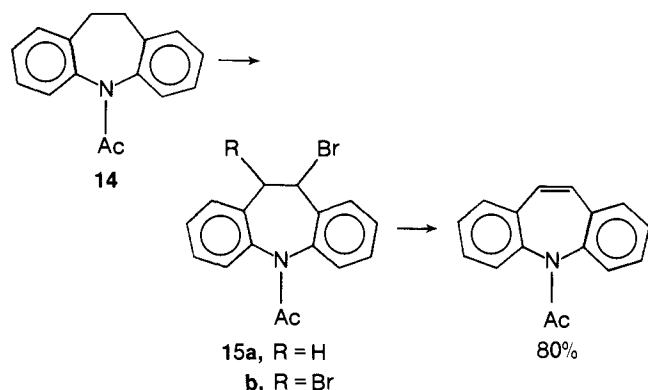
1. Dehydrogenation of 10,11-Dihydrodibenz[*b,f*]azepines

Dehydrogenation of iminobenzyls 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

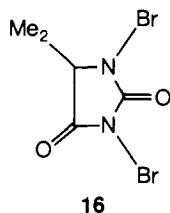
Gas-phase dehydrogenation of iminobibenzyl at 400° using a ferric oxide catalyst [per cent composition of catalyst: Fe₂O₃ (54), Cr₂O₃ (3), CaO (10), K₂CO₂ (33)] is used commercially for the production of iminostilbene. The crude product is contaminated with acridine and 9-methylacridine (see section VIII.B).^{37,38}

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

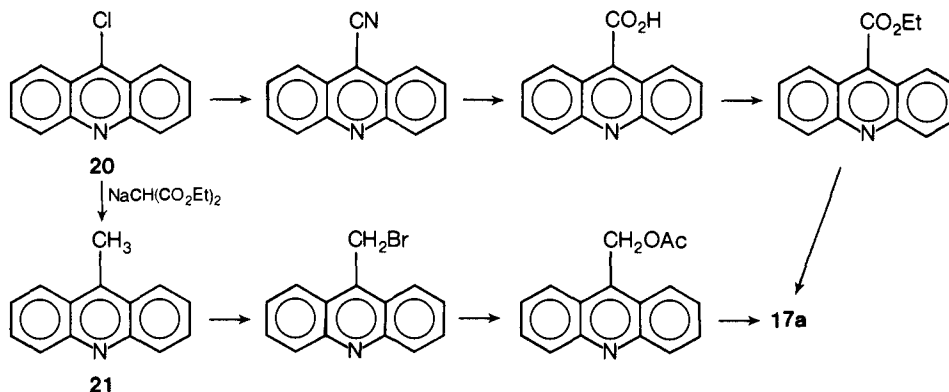
Dehydrobromination of 10-bromo- (15a) and 10,11-dibromoiminobibenzyls (15b) affords iminostilbene derivatives in good yields.^{31,43-48} The replacement by bromine of a benzylic proton of iminobibenzyl having the imino group protected by an acetyl group is most usually accomplished using *N*-bromosuccinimide (NBS)/benzoyl peroxide, although *N*-bromophthalimide, *N*-bromoacetam-



ide,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



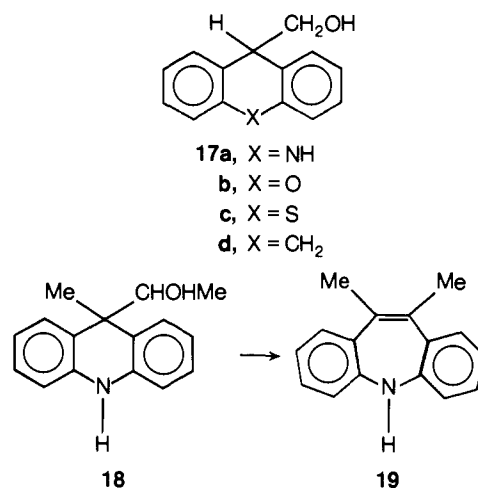
SCHEME II



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



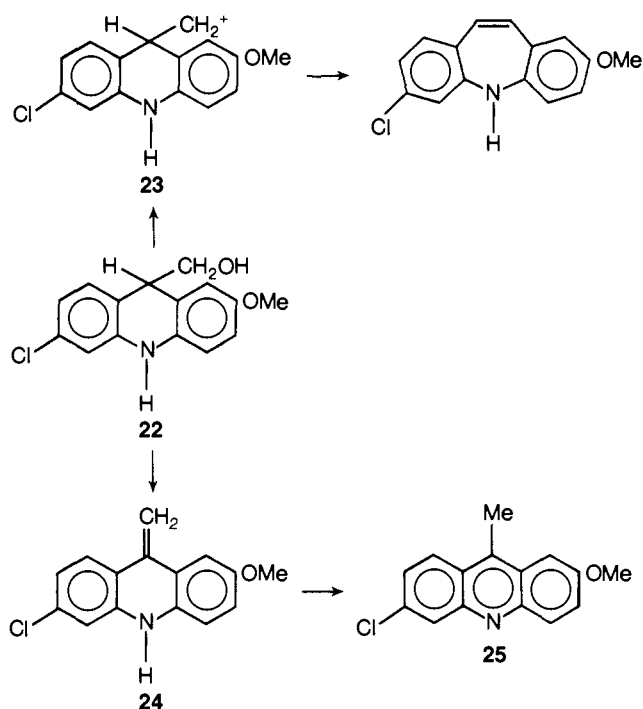
This ring expansion is general and may be used to prepare dibenz[*b,f*]oxepins, dibenzo[*b,f*]thiepins, and dibenzo[*a,d*]cycloheptenes from the corresponding methanols 17b–d, severally.

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 (LiAlH₄). 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 Berntsen reaction.⁵⁸

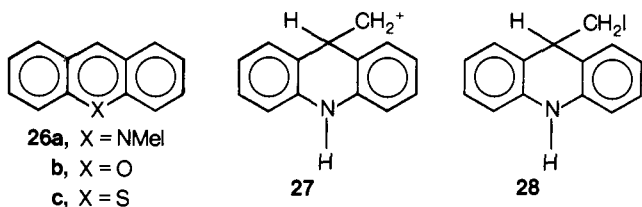
The dehydration–rearrangement is usually carried out by heating the acridine methanol with phosphorus pentoxide in xylene, and, although this is the preferred reagent, various workers have reported that the reaction is erratic and other reagents, e.g., phosphorus oxychloride, and PPA have been cited.⁴⁰

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 prepared⁵² 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-

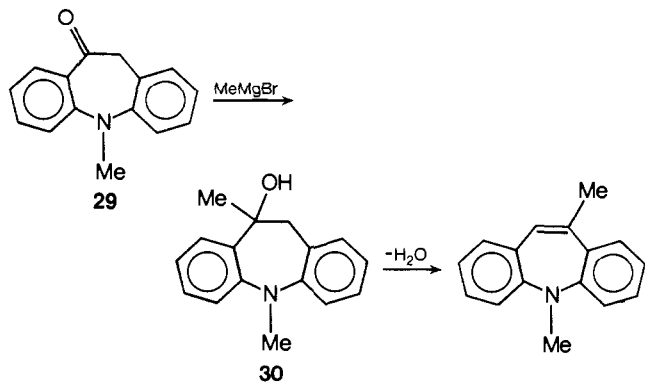


iodomethyl-9-methylacridan (**28**), which arises via capture of an iodide ion by the intermediate carbonium ion **27**. This complication is not such a marked feature of reactions of xanthylium (**26b**) and thioxanthylium perchlorate (**26c**) which, upon exposure to diazomethane in ether at 0°, afford 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.



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

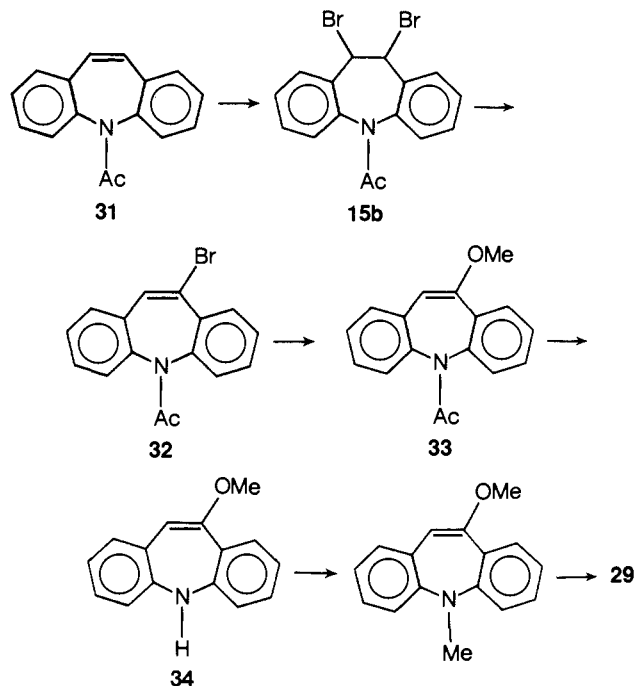
5,10-Disubstituted iminostilbenes are prepared by the reaction of the azepinone **29** with a Grignard reagent and subsequent dehydration of the secondary alcohol **30**. The dehydration step may be accomplished in a variety of ways, *i.e.*, by vacuum distillation, treatment with hydrochloric or polyphosphoric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



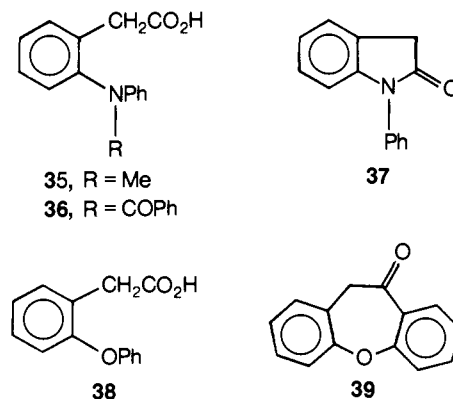
C. Synthesis of 5*H*-Dibenz-*[b,f]*azepin-10-ones

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

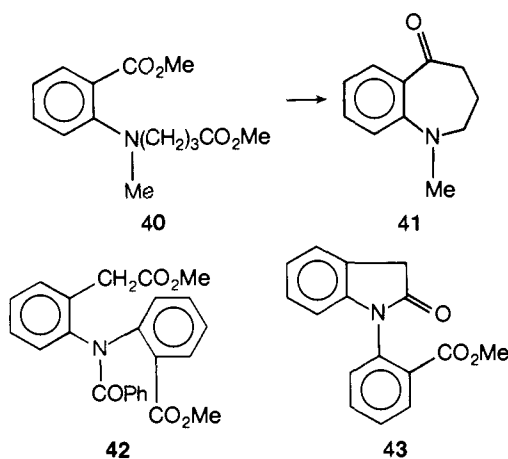
SCHEME III



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



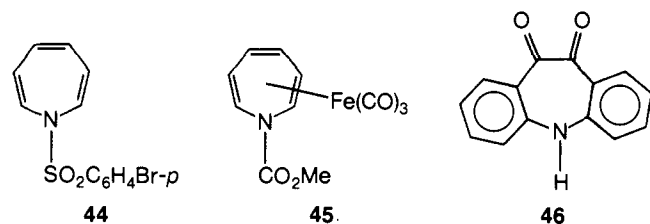
Dieckmann ring closure of diesters, a reaction employed for the synthesis of monobenzazepinones, *e.g.*, **40** → **41**,⁷⁴ is unsuitable for the preparation of dibenzazepinones; attempted cyclization of the diester **42** leads to the oxindole **43**.⁷⁵



III. Physical Properties and Structural Parameters of 5*H*-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 conformation⁷⁶ (cf. cycloheptatriene and related tricyclic molecules^{7,77,78}), and the molecular dimensions indicate substantial sp^2 character for the nitrogen atom.⁷⁶



Denne and Mackay⁷⁹ 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 tran-

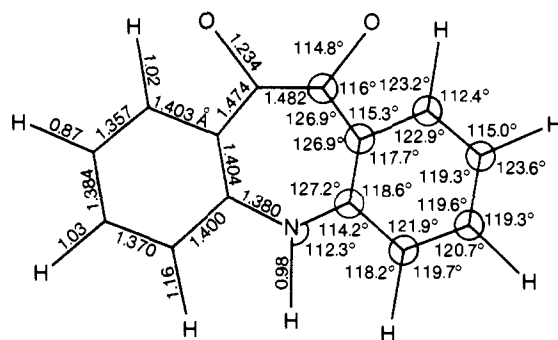


Figure 1.

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 _a	2220 _b	14.18
	94.1 _a	2930 _b	
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 $\Sigma = 5150$.

sition 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.

Related studies⁸⁰ of *N*-acyl phenothiazines and carbazoles indicate that these molecules display entropies, and temperatures, of fusion characteristic of oblate spheroids.

C. Molecular Orbital Calculations and Electronic Spectra

Molecular orbital calculations for the dibenz[*b,f*]azepine system have been carried out by Schmid⁸² using the simple Hückel LCAO–MO method; however, the latter has been shown to be unreliable for heteroaromatic systems⁸³ 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.

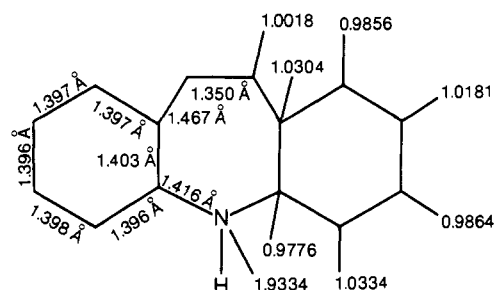


Figure 2. Estimated bond lengths and electron densities for iminostilbene.

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) nm⁸⁶).

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-

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 -Dimethylaminopropyliminostilbene	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 ₂ NMe 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) ₃ NMe ₂	MeOH	250 (3.75), 290 sh (3.45), 340 (2.85)	91
7-Cl,2-MeO,5-(CH ₂) ₃ NMe ₂	EtOH	260 (4.60), 291 sh (3.90), 357 sh (3.20)	55
(b) Iminostilbenes			
5-H	C ₆ H 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 ₆ H 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 ₆ H 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 ₆ H 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 ₆ H ₁₂	241 (4.18), 286.5 (4.02)	40, 82
3-Cl		262 (4.70), 295 (3.46)	40
5-CO ₂ Et	MeOH	210 (4.53), 233 (4.20), 283 (4.00)	31
3,7-Me ₂	C ₆ H ₁₂	263 (4.67), 297 (3.42), 361 (3.06)	82
2,8-Me ₂	C ₆ H 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 intl (3.53)	64
7-Cl,2-MeO	EtOH	265 (4.60), 303 (3.60), 370 sh (2.90)	55

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

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

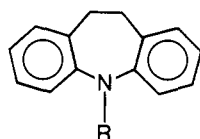
The N-H stretching frequency of unsubstituted iminostilbenes^{16,41,51,55,93} occurs in the region of 3300 cm^{-1} . Absorptions in the infrared spectrum of iminostilbene at 1316 and 760 cm^{-1} are assigned to C-N stretch and ortho-disubstituted benzene ring, respectively.

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 iminobiphenyl 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 iminobiphenyls are collected in Table V. The protons of the etheno and ethano bridge absorb in the region $\tau \sim 3.00$ and ~ 6.9 , respectively.

Absorptions appropriate to the ethano-bridge protons of iminobiphenyl and *N*-alkyliminobiphenyls (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 = COCH₃

47, R = CH₃

48, R = COCH₂Cl

49, R = CO₂CH₂CH₃

acetyliminobiphenyl 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 \rightarrow 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' \rightarrow A₄, the value of

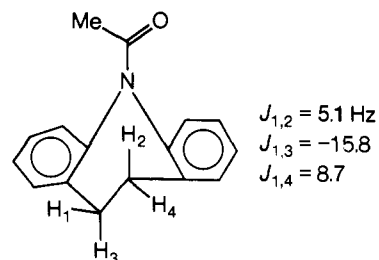


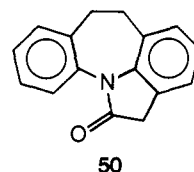
Figure 3.

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

A full analysis of the AA'BB' spectrum provides values for the $^3J_{\text{HH}}$ couplings of the ethano protons (Figure 3). Application of the Karplus-type equation appropriate to rotation of the ethano-bridge fragment⁹⁶ 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 A₄ system.

Since $\delta\nu_{AB}$ for the coalescence ABCD \rightarrow AA'BB' is very much smaller than that of AA'BB' \rightarrow A₄, the process ABCD \rightarrow AA'BB' \rightarrow A₄ 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° .



50

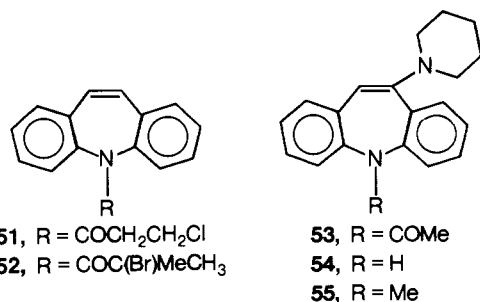
Gipstein, *et al.*,⁹⁸ have reported that *N*- β -chloropropionyl- (51) and *N*- α -bromoisobutyryliminostilbene (52) display temperature-dependant spectra, and these are explained in terms of hindered rotation about the C-N bond and C-C bonds. At room temperature the chloroethyl group of 51 appears as 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 workers⁹⁹ 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. ^1H 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 ₂ Cl	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) ₃ NMe 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) ₃ NMe 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- <i>n</i>	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_2), 9.10 (3 H, t, CH_2CH_3)	100
5-COCH ₂ CH ₂ Cl	3.24 (2 H, d)	2.62–2.75 (8 H, m)	7.21–7.51 and 7.73–8.04 (4 H, $\text{CH}_2\text{CH}_2\text{Cl}$)	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 ₅ H 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



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

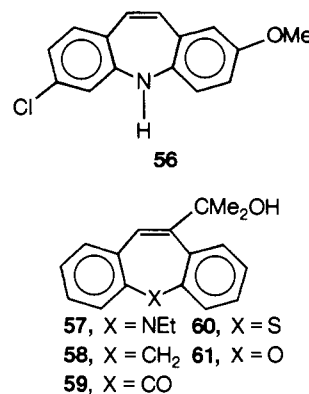


TABLE VI. Spectral Parameters (60 MHz) and Free Energies of Activation (ΔG^*) for Conformational Inversion of Seven-Membered Ring Systems^a

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 ₂ HCl 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 ₆ F ₆	3.5	51	17.7	21.3	4
61	CDCl ₃ -CS ₂ (1:2)	16	-69	10.3	18.3	8

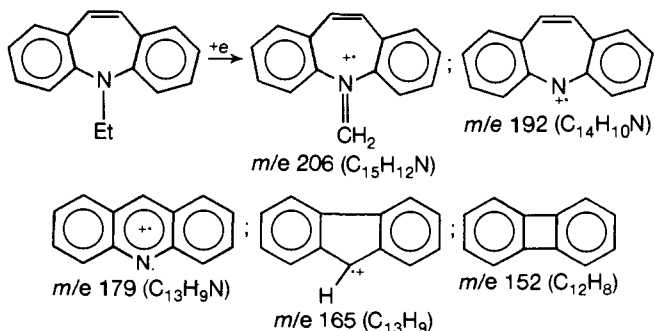
^a Prochiral group, CMe₂.

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 C₁₃H₉N, C₁₃H₉, and C₁₂H₈, 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-

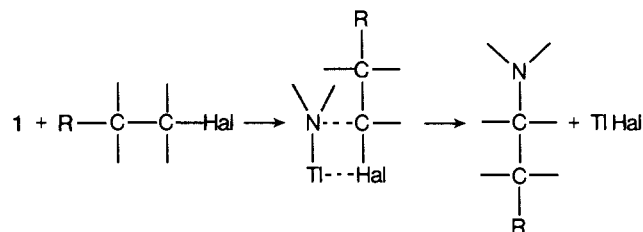


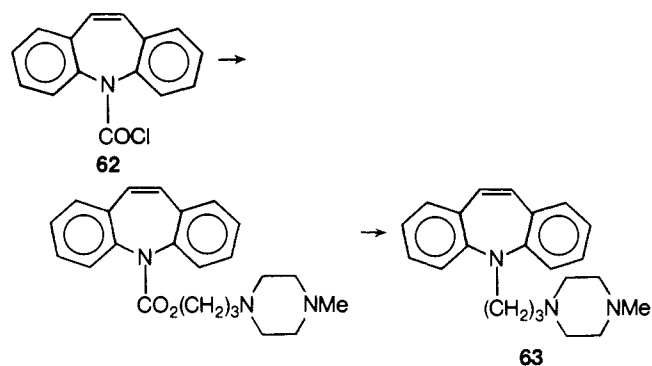
Figure 4.

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 tosylate¹³¹⁻¹³³ and a suitable base, usually in refluxing toluene. Many bases have been cited including alkali metals (K, Na), alkali amides (LiNH₂, NaNH₂, KNH₂), 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}

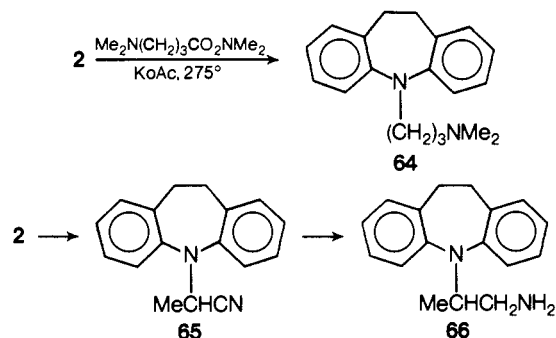
N-Methyl-, *N*-ethyl-, and *N*-propyliminostilbene may be prepared under mild conditions from iminostilbene and the corresponding alkyl iodide using thallium ethoxide as the base. The reaction is thought to proceed via a four-center transition state (Figure 4) and, as such, is subject to severe steric 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 chloro-carbonyl compound and an alcohol, constitutes an important pathway to *N*-alkyliminostilbenes and bibenzyls, *e.g.*, **62** \rightarrow **63**.^{28,124,134,136-146} The decarboxylation is accom-

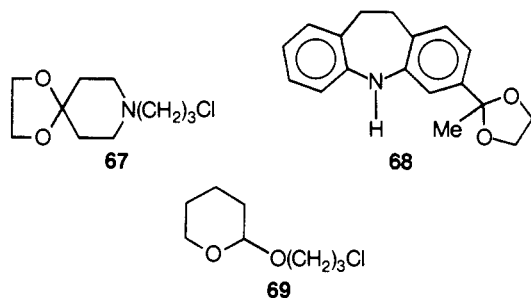


plished either by heating the urethane with copper powder¹³⁷ or alone under reduced pressure. Urethane intermediates are probably involved in the alkylation of iminostilbene and iminobibenzyl with dialkylaminoalkylcarbamates¹⁴⁵ and ethoxycarbonyloxy compounds,^{138,147} *e.g.*, **2** \rightarrow **64**.

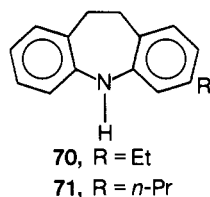
N- α -Cyanoalkyliminobibenzyls (**65**) may be obtained by condensation of the parent compound with an aldehyde in the presence of cyanide ions. The cyano group is reduced to an amine (**66**) in the usual manner either by LiAlH₄¹⁴⁸ or hydrogen and Raney nickel.¹⁴⁹



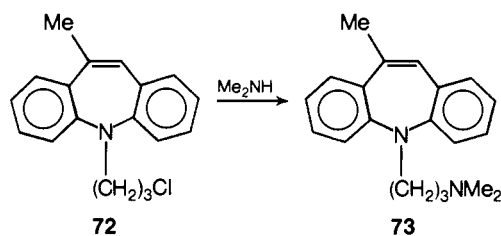
Alkyl groups and dibenzazepines bearing labile substituents must be protected prior to N-alkylation. *N*-3-Chloropropylpiperidone¹²⁷ and the acetyl group of 3-acetylaminobibenzyl must be converted to their respective ketals **67** and **68**, before N-alkylation may be attempted.¹⁵⁰⁻¹⁵² Hydroxypropyl 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.



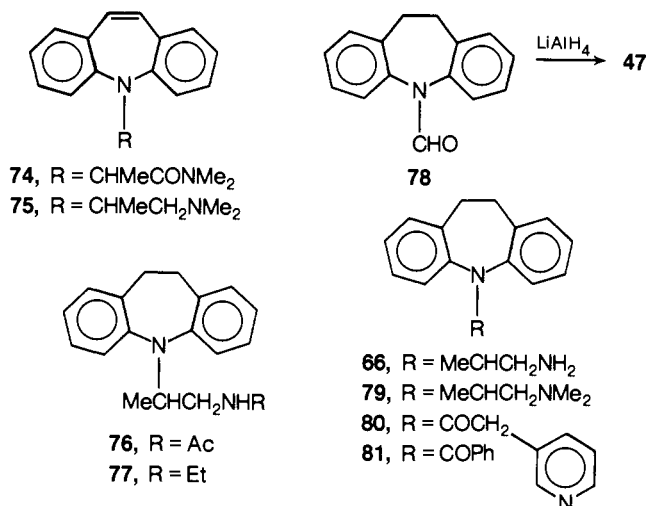
Ring alkylation of iminostilbene is outlined in section V.A. 3-Ethyl- (**70**) and 3-propyliminobibenzyl (**71**) are synthesized by reduction of the corresponding 3-acetyl and 3-propionyl derivatives with hydrazine hydrate.⁴⁴



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** \rightarrow **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 LiAlH₄,¹⁵⁷⁻¹⁵⁹ and this reagent also reduces *N*-formyl substituents to *N*-methyl groups, **78** \rightarrow **47**,¹⁴⁹ as does diborane.¹⁶⁰



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

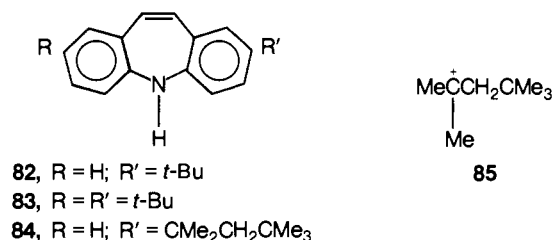
Iminostilbene and iminobibenzyl undergo acylation¹⁶³⁻¹⁷⁰ in the normal manner (compare the preparation of nicotyliminobibenzyl (**80**) from **2** and nicotiny chloride¹⁶³) and also, under Schotten–Bauman conditions, *N*-benzoylation, e.g., **81**.

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

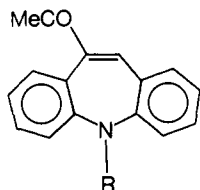
Friedel–Crafts alkylation of iminostilbene at 180–190° with diisobutylene (a 3:1 mixture of 2,4,4-trimethylpent-1- and -2-enes) produces 2-*tert*-butyl- (**82**) and 2,8-di-*tert*-butyliminostilbene (**83**). Under different conditions 2-(1,1,3,3-tetramethylbutyl)iminostilbene (**84**) is produced.¹⁷¹ 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



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

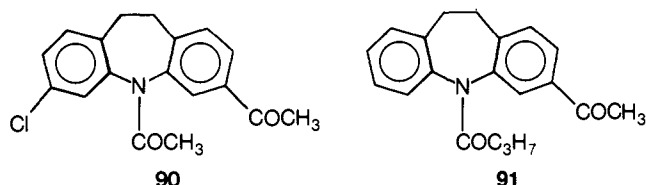
withdrawal from the nitrogen atom renders the nitrogen atom electron deficient and nondirecting (*vide infra*).

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 = COCH₃
87, R = COPh
88, R = COEt
89, R = COCH₂Cl

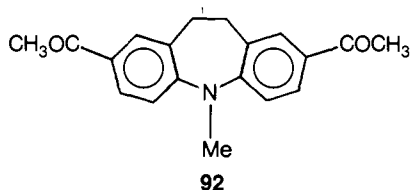
Several catalysts have been utilized in the Friedel-Crafts acylation of *N*-acyliminobibenzyls, *e.g.*, aluminum trichloride,^{44,174} iodine,¹⁶⁰ and ferric chloride.⁴⁴ The acyl group enters the nucleus at the 3 position; *cf.* formation of 7-chloro-3,5-diacetyl- (**90**) and 5-butyryl-3-acetyliminobibenzyl (**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-diacetylated 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



90

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.

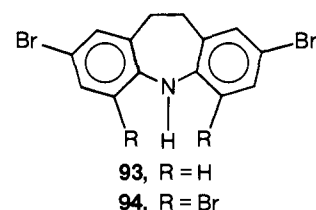


92

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

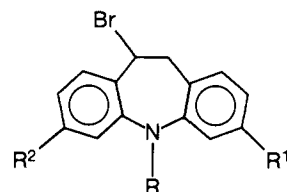
B. Halogenation

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 alkyl⁴⁴ ring substituents to give the 10-bromides **95**–**97**. A second bromine atom



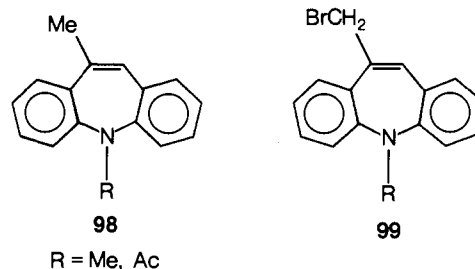
95, R = Ac; R¹ = SO₂NMe₂; R² = H
96, R = Ac; R¹ = Et; R² = H
97, R = Ac; R¹ = R² = Cl

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}

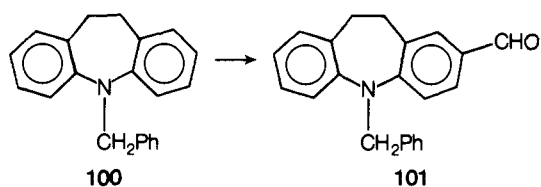


98
R = Me, Ac

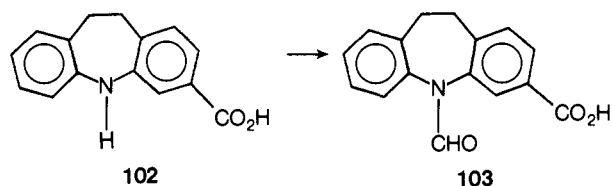
99

C. Formylation

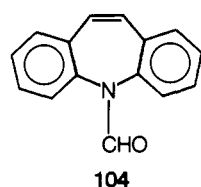
A formyl group may be introduced into the aromatic ring of an iminobibenzyl derivative by means of the Vilsmeier reaction,^{53,179-181} *i.e.*, *N,N*-dimethylformamide- or *N*-methylformanilide-phosphorus oxychloride. In agreement with electron density calculations, the formyl group enters the 2 position, **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



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

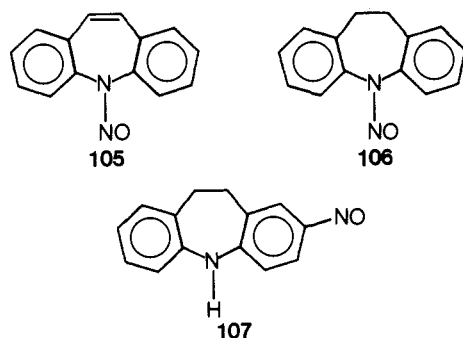


(**103**), and *N*-formyliminostilbene (**104**) is available by treatment of **1** with refluxing formic acid.^{81,160}



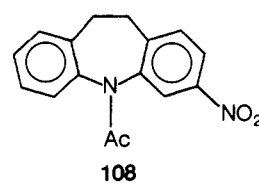
D. Nitrosation and Nitration

N-Nitrosoiminostilbene (**105**) has been prepared by nitrosation of the parent compound using acidified ethanolic sodium nitrite solution.⁹³ Similarly *N*-nitrosoiminobenzyl (**106**) is available by reaction of iminobenzyl with either ethereal amyl nitrite¹⁸² or sodium nitrite in DMF-hydrochloric acid.^{183,184} A nitroso group may be introduced into the 2 position of iminobenzyl by means of the Fisher-Hepp rearrangement;¹⁸⁵ thus upon treatment with hydrogen chloride, **106** rearranges to form 2-nitrosoiminobenzyl (**107**). The latter material is also available from the reaction of iminobenzyl with a mixture of thionyl chloride and sodium nitrite.¹⁸²



N-Nitrosoiminobenzyl 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

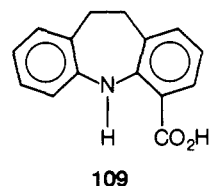
Nitration of *N*-acetyliminobenzyl (**14**) at low temperatures using concentrated sulfuric acid-nitric acid^{186,187} affords 3-nitroiminobenzyl (**108**), the product of substitution meta to the nitrogen atom (section IV.A). Alternatively, **14** may be treated at room temperature with concentrated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



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

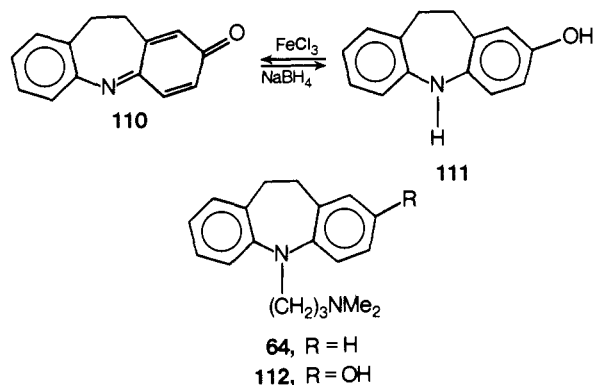
E. Metalation

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



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

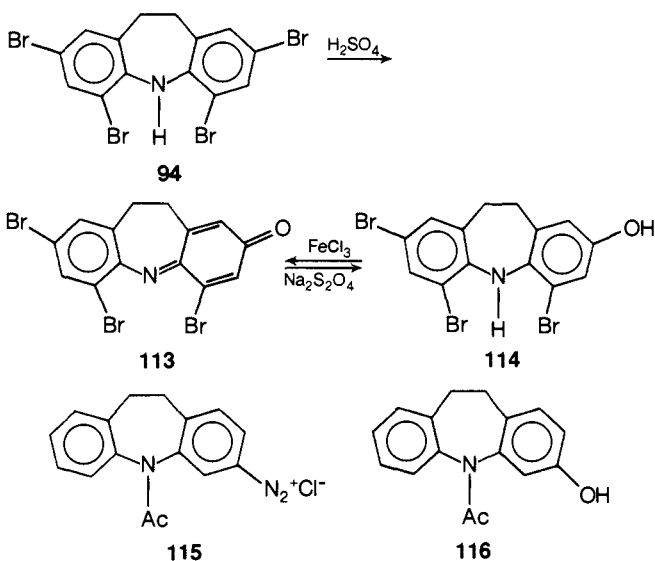
2-Oxo-10,11-dihydro-2*H*-dibenz[*b,f*]azepine (**110**) is the major product from the oxidation of iminobenzyl at pH 8 with potassium nitrosulfonate (Fremy's salt); at lower pH values acridine-9-carboxaldehyde is also produced.^{88,190,196} The oxo derivative (**110**) is readily reduced to 2-hydroxyiminobenzyl (**111**) using either sodium borohydride or sodium dithionite⁸⁸ 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 buffer¹⁹¹ 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



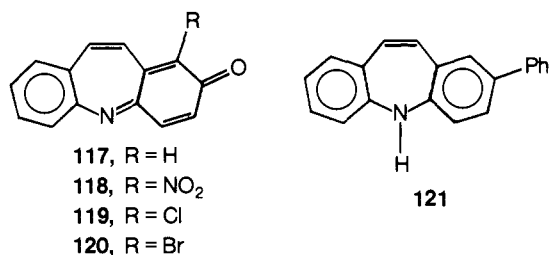
113 of the quinone imide **110** is prepared by reaction of 2,4,6,8-tetrabromoiminobenzyl (**94**) with concentrated sulfuric acid.⁸⁸ Reduction of this compound (**113**) with sodium dithionite leads to the 2-hydroxy derivative **114**, which is reconverted to the quinone imide **113** by ferric chloride.

Lead tetraacetate is reported⁸⁸ as being unreactive toward iminobenzyl, while selenium dioxide oxidizes the benzylic protons of 5-acetyliminobenzyl 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 iminobenzyl *via* hydrolysis of the appropriate diazonium salt, e.g., **115** \rightarrow **116**.¹⁹¹



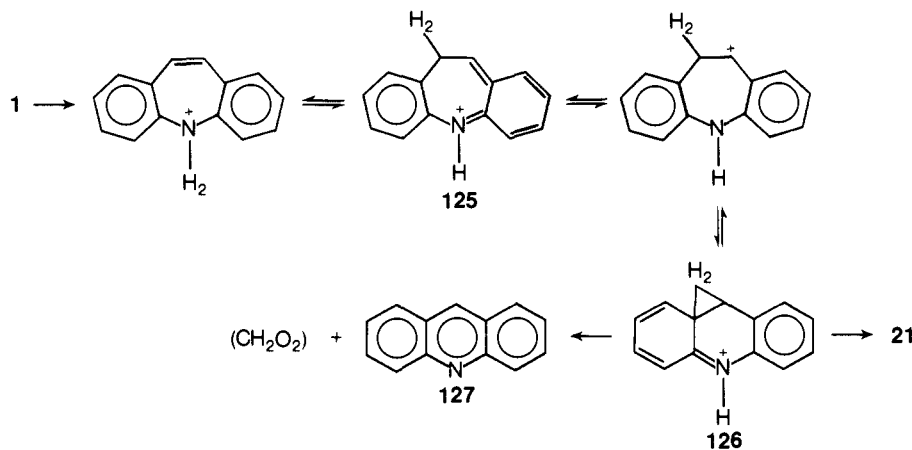
Proctor, *et al.*,^{176,193} have described the synthesis and properties of dibenz[*b,f*]azepin-2 one (117). This material is photostable in benzene and unreactive toward dienophiles, *e.g.*, dimethyl acetylenedicarboxylate and maleic anhydride. Nitration using $\text{Cu}(\text{NO}_3)_2$ -acetic anhydride 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).



VII. Reduction of Dibenz[*b,f*]azepines

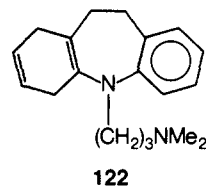
Reduction of iminostilbenes to iminobibenzyls and the

SCHEME IV



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)



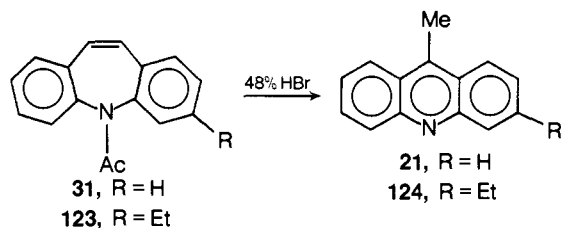
with lithium-methanol in liquid ammonia. The 6,9-dihydro compound is isolated as an oil from a mixture of reduction products by chromatography and is best stored under nitrogen below 5°. Nmr spectroscopy of 122 indicated only two vinylic absorptions, thus excluding other nonconjugated isomers.⁹¹

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 Reynaud⁹² in-



vestigated the mechanism of this rearrangement and concluded that the reaction proceeded *v/a* 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 *v/a* the reaction of cation 126 with oxygen, and it was proposed that the carbon fragment was expelled as a hydroperoxymethylene species.

TABLE VII. Thermal and Acid-Catalyzed Reactions of Iminostilbenes

Substrate	Reaction conditions	Products ^a						Other products
		1	127	21	133	129	105	
1	5 N HCl, 100° (1 hr)	48	tr	24	tr			MeONO, HCO ₂ Me, N ₂ O
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 ₂ Et, N ₂ O
105	HCl/Me ₂ CO, 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 study⁸⁹ 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.

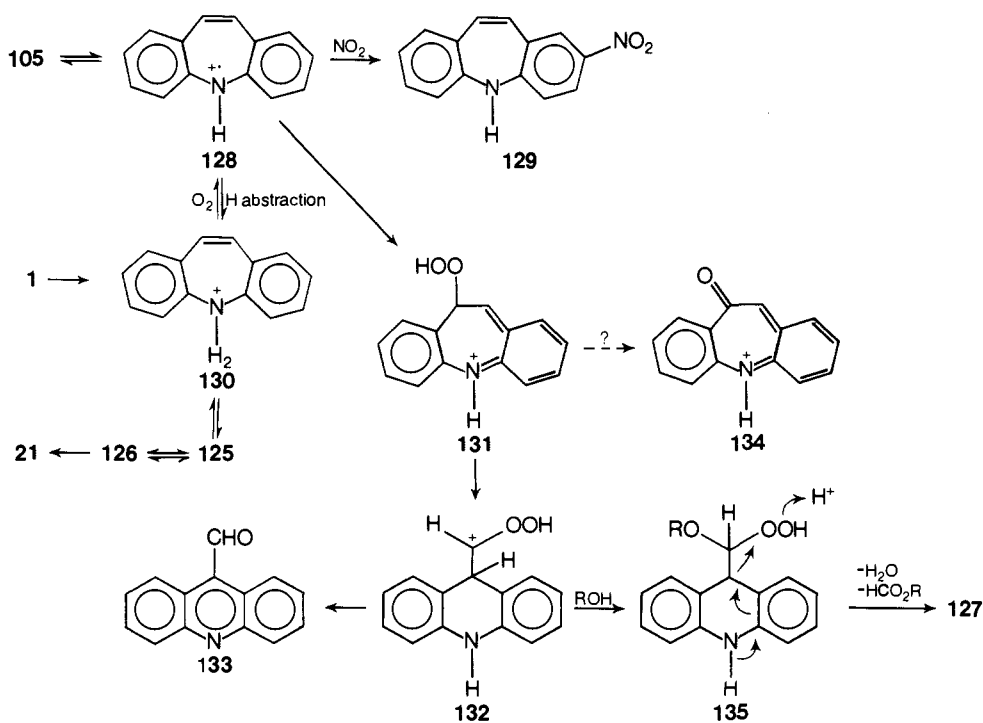
A mechanistic scheme to account for the acid-catalyzed rearrangement of iminostilbene and 5-nitrosoiminostilbene is shown (Scheme V). The reactions of 1 and 105 in acidic media are most probably mediated by the protonated species 130, which under forcing conditions rearranges via the quinone imonium ion 125 to the valence tautomer 126, while at lower temperatures 128 undergoes slow aerial oxidation to the iminium radical

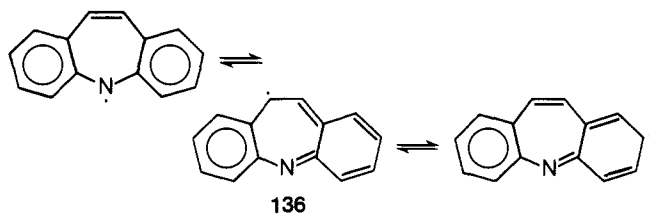
128. This may then react with oxygen to form the peroxide 131, and subsequent Wagner–Meerwein rearrangement affords the cation 132, which in hydroxylic solvents is trapped as 135 and subsequently fragments to acridine and a formate ester. In nonhydroxylic solvents deprotonation of 132 results in acridine-9-carboxaldehyde, 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



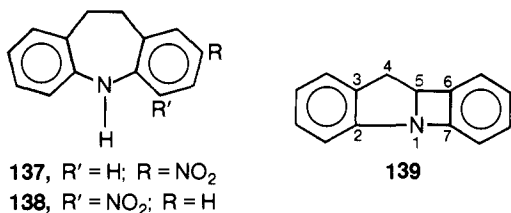


duce the peroxide **131**. In hydroxylic solvents hydrogen abstraction builds up a concentration of radicals RCHOH which react with nitric oxide to form eventually nitrous and nitric acids. The fate of **131** in this eventually is as outlined previously (Scheme V), and the isolation of acridinium nitrate 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.

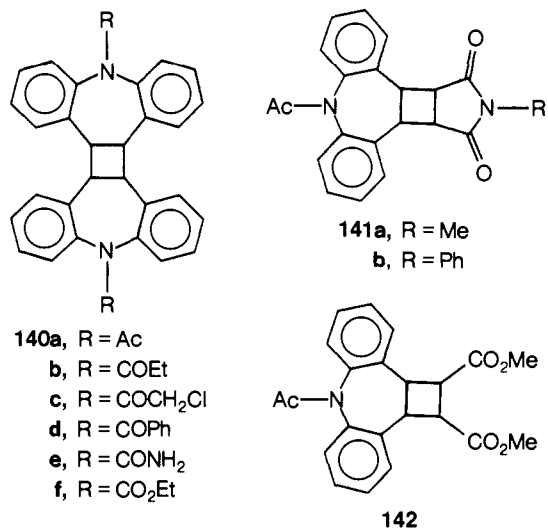
The irradiation of a solution of *N*-nitrosoiminobibenzyl in benzene under oxygen at 5–10° gave a mixture of products, including iminobibenzyl (2%) and 2-nitro- (**137**, 28%) and 4-nitroiminobibenzyl (**138**, 21%).



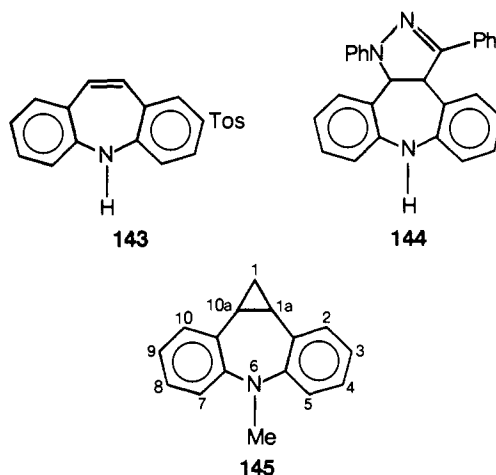
The expectation that irradiation of an acid solution of **105** would lead to a transannular addition of the intermediate aminium radical to the electron-rich 10,11 double bond to afford a derivative of the unknown 2,3:6,7-dibenzo-7-azabicyclo[3.2.0]heptane ring system (**139**) was not realized, since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



tion occupied by the tosyl group was assumed by analogy with related photo-Fries rearrangements of sulfoanilides, shown to yield exclusively *p*-tosylanilines.¹⁹⁵

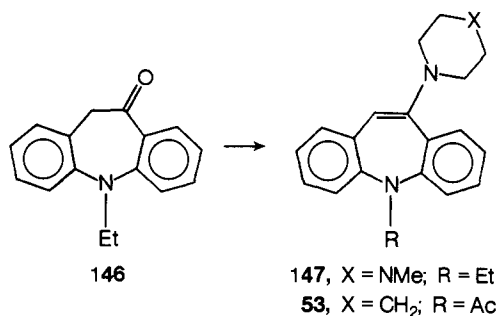


Huisgen, *et al.*,¹⁹⁶ have described the reaction *in situ* of iminostilbene with the 1,3-dipolarophile diphenylnitrile-imine (PhC≡N⁺—N⁻Ph), which produces a 1:1 adduct, 1,3-diphenyldibenzo[*b,f*]pyrazolo[3,4-*d*]azepine (**144**).

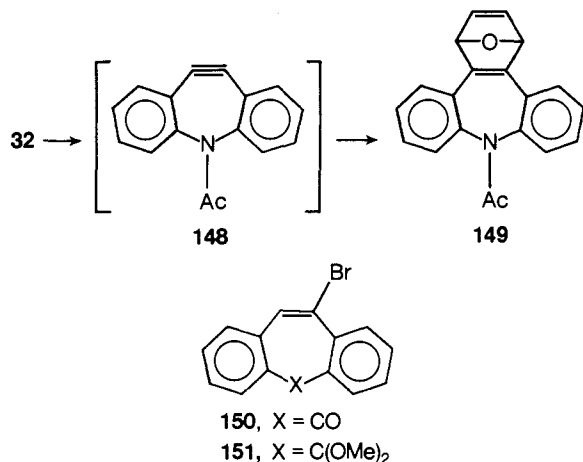
The etheno bridge is also susceptible to attack by methylene (generated from diiodomethane-iodine and a zinc-copper couple). Reaction of 5-methyliminostilbene with methylene affords the 1,1a,6,10b-tetrahydrocyclopropa[*d*]dibenzo[*b,f*]azepine derivative (**145**).¹⁹⁷

X. Aminodibenz[*b,f*]azepines

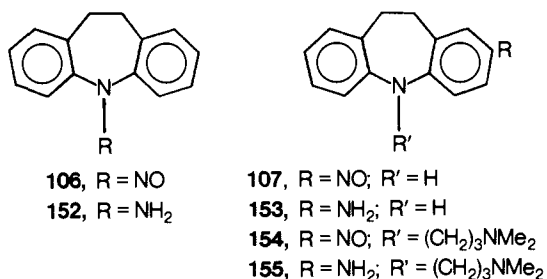
No examples of amino-substituted iminostilbenes are as yet known, but 10-cycloalkylamino derivatives may be prepared by the acid-catalyzed condensation of dibenz[*b,f*]azepin-10-ones with cycloalkylamines;¹⁹⁸ e.g., condensation of **146** with *N*-methylpiperazine affords *N*-(5-ethylidibenz[*b,f*]azepin-10-yl)-*N'*-methylpiperazine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



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



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 workers¹⁸² claim that attempts to reduce the *N*-nitroso compound (**106**) leads to cleavage of the *N*-*N* bond.

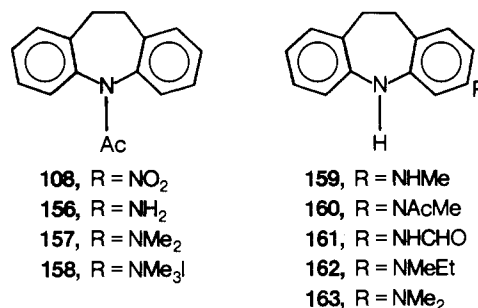


2-Nitrosoiminobibenzyl (**107**), available *via* Fisher-Hepp rearrangement of **106**, is reduced to produce 2-aminoiminobibenzyl (**153**), and similarly reduction of 5- γ -dimethylaminopropyl-2-nitrosoiminobibenzyl (**154**) affords the air-sensitive 2-amino derivative **155**. Bechamp reduction (iron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

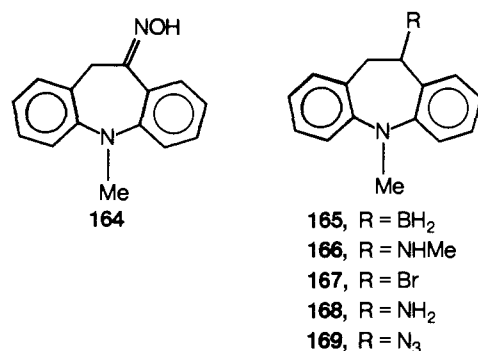
Dialkylamino groups can be introduced at the 3 position by reductive methylation of a 3-nitro compound using formaldehyde–hydrogen and a Raney nickel catalyst, e.g., **108** \rightarrow **157**.²⁰¹ A nitro group may also be transformed into an *N,N*-dimethylamino group by potassium carbonate–methyl iodide 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** \rightarrow **159**; likewise *N*-ethylation is effected *via* *N*-acetylation (**160** \rightarrow **162**). An alternative *N*-methylation procedure²⁰² 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



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



XI. Sulfonamides, Sulfinic Acids, and Sulfides

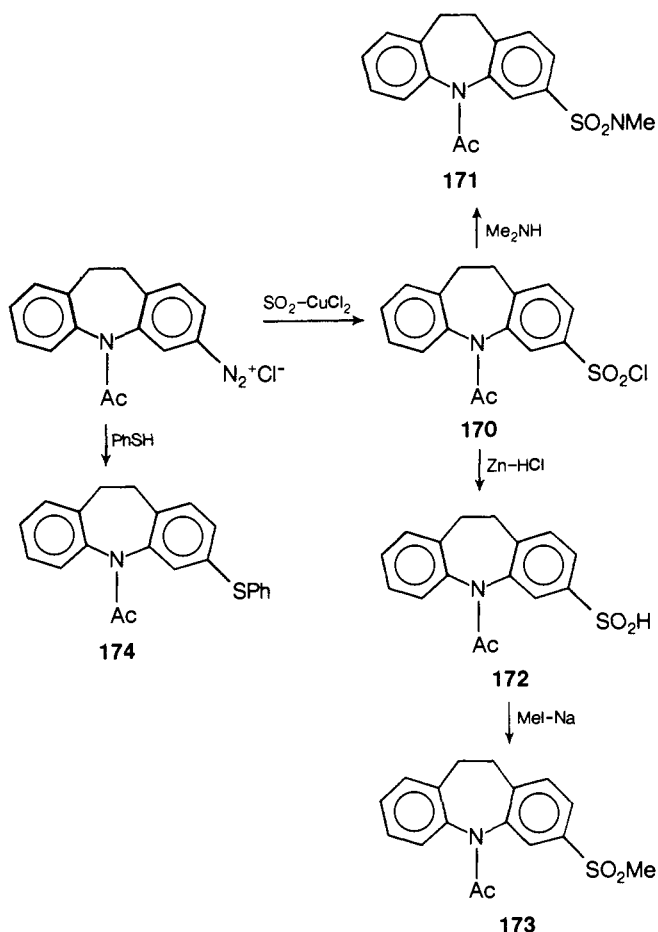
The diazonium salt **115** derived from 5-acetyl-3-aminoiminobibenzyl is a useful intermediate for the preparation of sulfinic acid derivatives (Scheme VI). Treatment of **115** with sulfur dioxide–cupric chloride affords the 3-chlorosulfonyl derivative **170**.^{207,208} This material reacts with amines to form sulfonamides (**171**);^{207,209} reduction of **170** using zinc–hydrochloric acid²⁰⁸ or alkaline sodium sulfite²¹⁰ produces the 3-sulfinic acid **172** which may be esterified by methyl iodide–sodium to give methyl 5-acetylaminobibenzyl-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

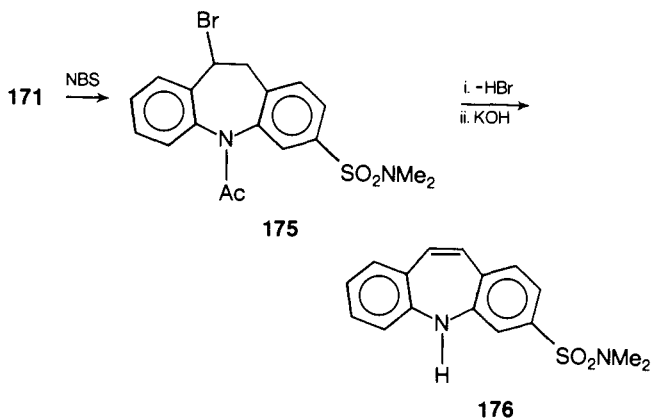
Sulfonamide derivatives of the iminostilbene ring system cannot be prepared directly;^{218,219} instead they are available by dehydrohalogenation of 10-bromoiminobibenzyls, e.g., **175** \rightarrow **176**, and the resulting 3-dimethylamino-sulfonyliminostilbene (**176**) finds use as an antioxidant.⁴⁷

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

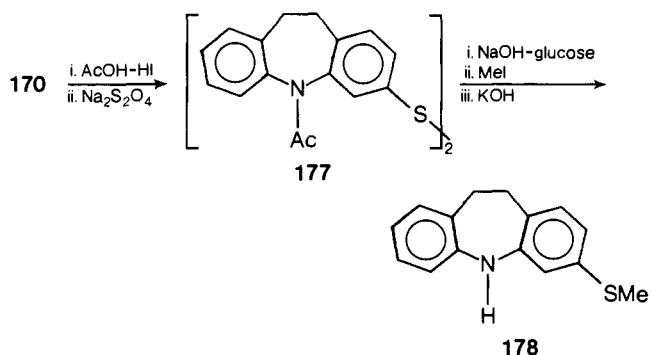
SCHEME VI



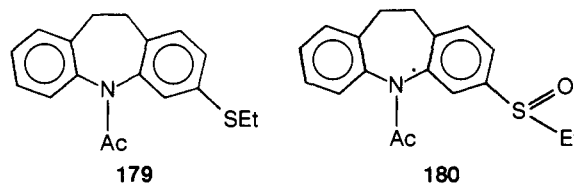
the reductive cleavage and concomitant alkylation of the disulfide **177**, which is available from **170** (Scheme VII).



SCHEME VII



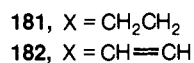
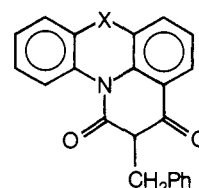
Oxidation of sulfides with sodium periodate produces sulfoxides, e.g., **179** → **180**.²²⁶



XII. Annelation

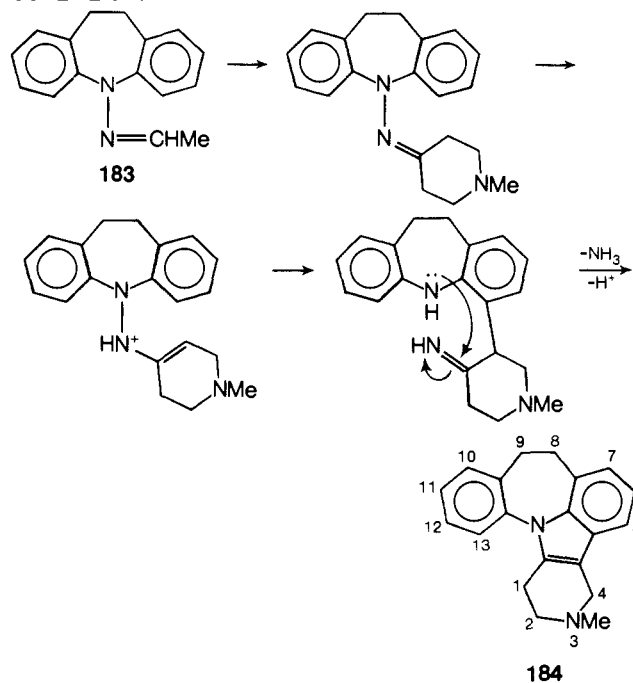
Iminostilbene and iminobiphenyl are the starting points for the synthesis of a variety of polycyclic azepine derivatives.

4,5-Malonyl-10,11-dihydrodibenz[*b,f*]azepine (**181**) may be obtained by reacting iminobiphenyl with bis(2,4-dichlorophenyl)benzylmalonate²²⁷ and distilling off the 2,4-dichlorophenol formed. Similarly, the azepine **182** is available from iminostilbene and benzylmalonic acid-phosphorus oxychloride.²²⁷

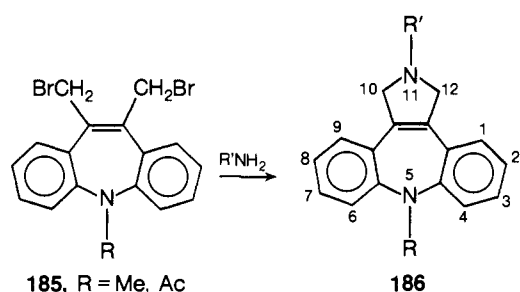


Annelation of the dibenzazepine nucleus may also be achieved by a modification of the Fisher indole synthesis;^{184,228} treatment of 5-nitrosoiminobiphenyl with ethylmagnesium bromide produces the amidine **183** which undergoes acid-catalyzed exchange with *N*-methylpyridone and a subsequent Fisher reaction²²⁹ 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

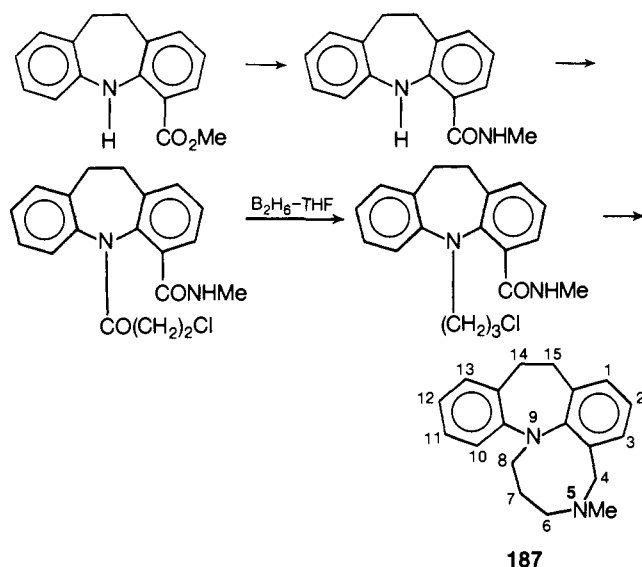


Derivatives of 10,12-dihydrodibenz[*b,f*]pyrrolo[*d*]azepine (**186**) may be prepared by condensation of 10,11-dibromomethyliminostilbene (**185**) and a primary amine (ref 230 and 231).



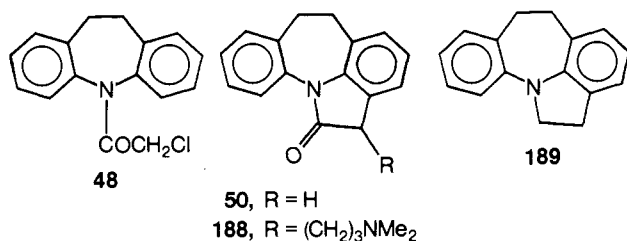
A large saturated nitrogen-containing ring has been attached at the 4 and 5 positions of iminobibenzyl by the synthetic route outlined in Scheme IX. The product, 5-methyl-4*H*-5,6,7,8,14,15-hexahydro-5,9-diazocino[1,2,3-*de*]dibenzazepine (**187**)²³² is reported to have antidepressant properties.

SCHEME IX



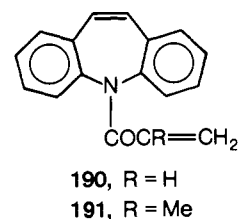
Examples of the tetracyclic azepine, 1-oxo-1,2,6,7-tetrahydroindolo[1,7-*ab*][1]benzazepine (**50**), are prepared by the intramolecular Friedel-Crafts alkylation of α -haloacetylaminobibenzyls;²³³ typically, **50** is obtained by heating together α -chloroacetylaminobibenzyl (**48**) and aluminum trichloride 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** \rightarrow **188**.²³⁴ Lithium aluminum hydride reduces the carbonyl group of **50** to a methylene group, e.g., **50** \rightarrow **189**.²³⁵



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



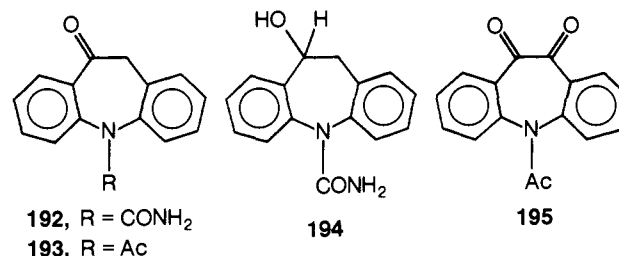
give high molecular weight homopolymers of interest as organic photoconductors;²³⁶ however, all attempts to homopolymerize 5-methacrylyliminostilbene were unsuccessful, a result attributed to steric interference by the bulky dibenzazepine nucleus.

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 reagents⁵⁹ 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** \rightarrow **194**) is achieved by hydrogenation with a copper chromite catalyst.^{243,244}



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** \rightarrow **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 tranquilizing agents, e.g., the phenothiazine, butyrophenone, thioxanthene, and reserpine derivatives **196**, **197**, **198**, and **199**, severally.

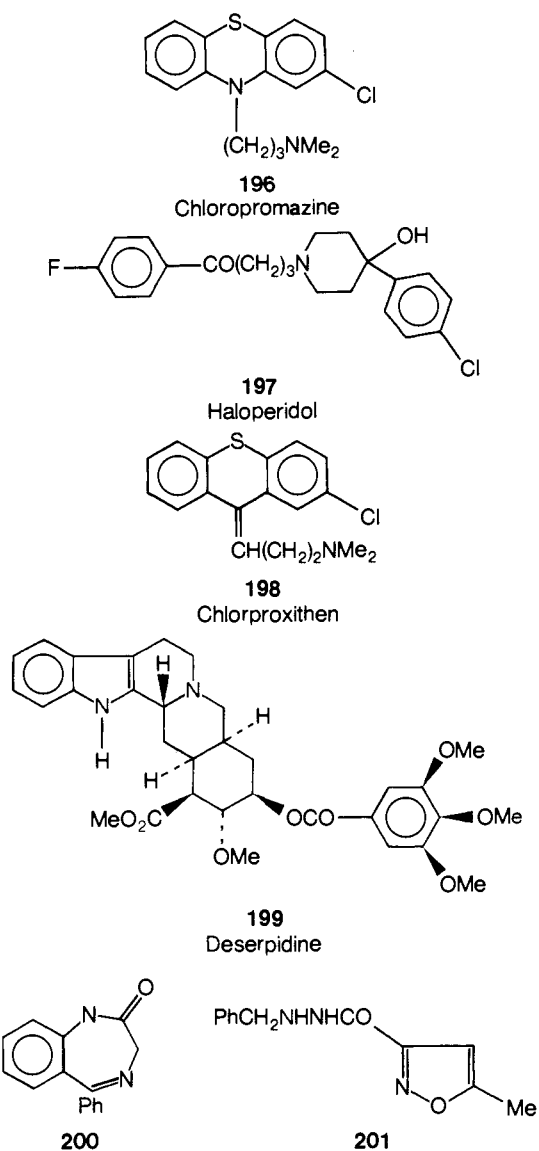
(b) *Anxiolytic Sedatives*. These include the barbiturates and derivatives of the benzodiazepine ring system, e.g., diazepam (**200**).

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

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

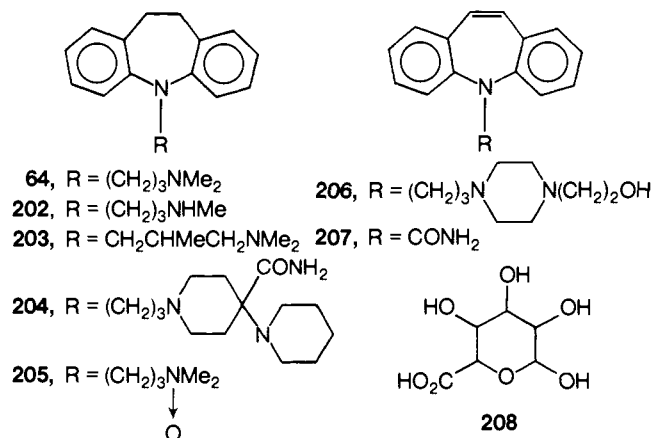
(e) *Antidepressants (thymoleptics)*. Drugs useful against depression may be divided into two classes, the mono-amine oxidase inhibitors, e.g., isocarboxazid (**201**) and, secondly, drugs derived from tricyclic ring systems, especially derivatives of dibenz[*b,f*]azepine.

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



taminic activity, spasmolytic, serotonin antagonistic, anti-convulsive, antiemetic, antiepileptic, antiinflammatory, sedative, and fungicidal²⁴⁶ action. In particular, they potentiate the action of other pharmaceuticals, e.g., anesthetics, and antitubercular drugs.²⁴⁷

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



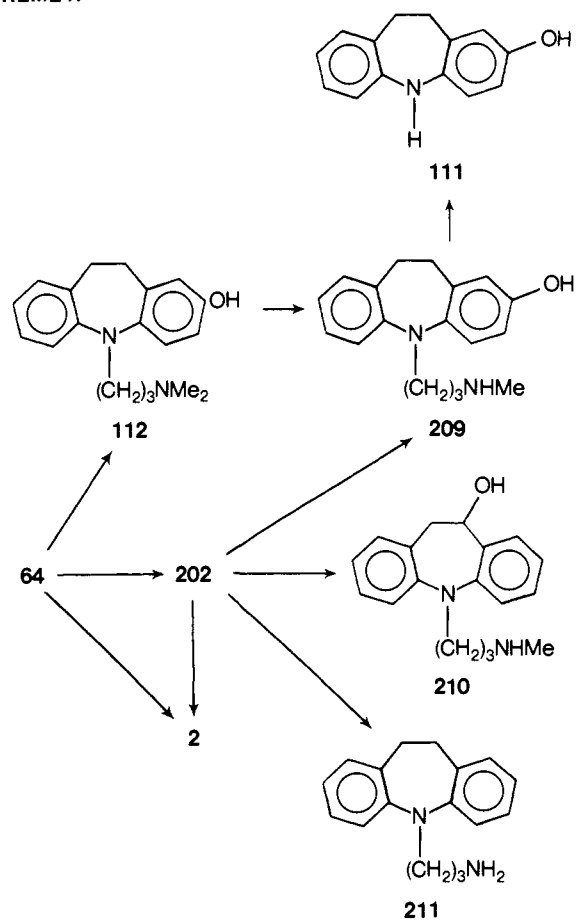
No attempt has been made here to cover the extensive literature relating to clinical investigations of dibenzazep-

ine 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).

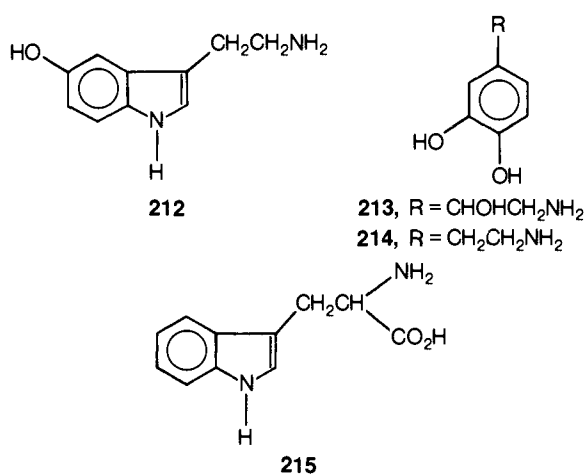
Bickel, *et al.*,²⁶⁴ have studied the kinetics of the metabolism of imipramine in the rat and propose that metabolism proceeds *via* the routes shown in Scheme X; recent studies with [¹⁴C]imipramine support these proposals.²⁶¹

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.

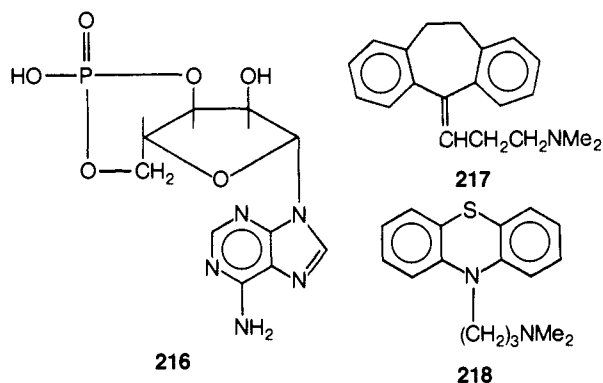
Curzon²⁷² has implicated imipramine and/or its metabolites, e.g., demethylimipramine (202), in the biosynthetic pathway leading to 5-hydroxytryptamine. This author suggests that in depressive illness the liver enzyme tryptophan pyrrolase is overactive; thus less tryptophan



(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.






The structure of the antidepressant drugs imipramine and amitriptylene (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 workers²⁷³ 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 ¹³C 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

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