Tricyclic Epines. Novel (*E*)- and (*Z*)-11*H*-Dibenz[*b*,*e*]azepines as Potential Central Nervous System Agents. Variation of the Basic Side Chain†

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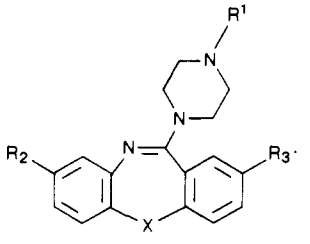
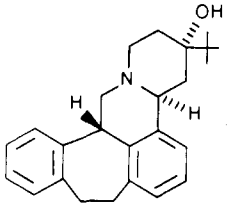
The synthesis and pharmacological activity of new (*E*),(*Z*)-[6-(alkylamino)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]-acetonitriles **12–45** and (*E*),(*Z*)-[6-(aminoalkoxy)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitriles **46–51** are described. The introduction of the cyanomethylene group into the 11-position of the 11*H*-dibenz[*b*,*e*]azepine framework has been carried out by a Wittig–Horner reaction under mild conditions. The (*E*),(*Z*) isomers were separated by fractional crystallization, assignment being achieved by X-ray analysis. A number of (*E*),(*Z*)-[6-(alkylamino)-11*H*-dibenz-[*b*,*e*]azepin-11-ylidene]acetonitriles (**12**, **14**, **16**, **20**) show potent neuroleptic activity (2–7 times that of clozapine) in animal tests. The screening included tests for sedative and anticholinergic activity in mice, apomorphine and tryptamine antagonism in rats, and muscle-relaxing activity in rabbits. The divergence in the activity profile in the case of the separated (*E*),(*Z*) isomers has been observed as an interesting new aspect: the (*Z*) isomers show a significantly higher sedative and muscle-relaxant activity, whereas the (*E*) isomers possess a higher anticholinergic efficacy and somewhat greater apomorphine antagonism. Broad changes in the basic side chain were made in order to investigate structure–activity relationships. The important geometrical parameters for the molecules, obtained by X-ray analysis, were compared with the corresponding features in dopamine agonists and antagonists.

Tricyclic ring systems possessing a dibenzo structure joined to a central seven-membered heterocyclic ring with a basic side chain frequently show effects on the central nervous system. During the last 20 years, a number of dibenzepines have been introduced. Some of these are powerful antipsychotic agents: clotiapine (**1**), metiapine (**2**), and loxapine (**3**) are classical neuroleptics showing a similar pattern of pharmacological activities to the phenothiazines, while amoxapine (**4**) has antidepressant properties and perlapine (**5**) is a hypnotic agent.[1]



	X	R_1	R_2	R_3	
1	S	CH_3	H	Cl	clotiapine
2	S	CH_3	H	CH_3	metiapine
3	O	CH_3	H	Cl	loxapine
4	O	H	H	Cl	amoxapine
5	CH_2	CH_3	H	H	perlapine
6	NH	CH_3	Cl	H	clozapine
7	CH_2	CH_3	F	H	fluperlapine



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Clozapine (**6**) is an exception, since it was the first example of a new class of tricyclic neuroleptics with a novel activity pattern, producing minimal extrapyramidal side effects (EPS) in man.[2]

Pharmacologically it differs from the classical neuroleptics in causing no catalepsy and only moderate apomorphine antagonism in the rat while also showing an anticholinergic effect.[1,3]

Unfortunately, its use was associated with agranulocytosis, a serious side effect.[4] Since then, various new tricyclic epine derivatives carrying a piperazinyl substituent that are structurally related to clozapine have been synthesized in different laboratories,[5-9] but the intended im-

† This paper has been compiled in honor of Professor Ernst Biekert on the occasion of his 60th birthday.

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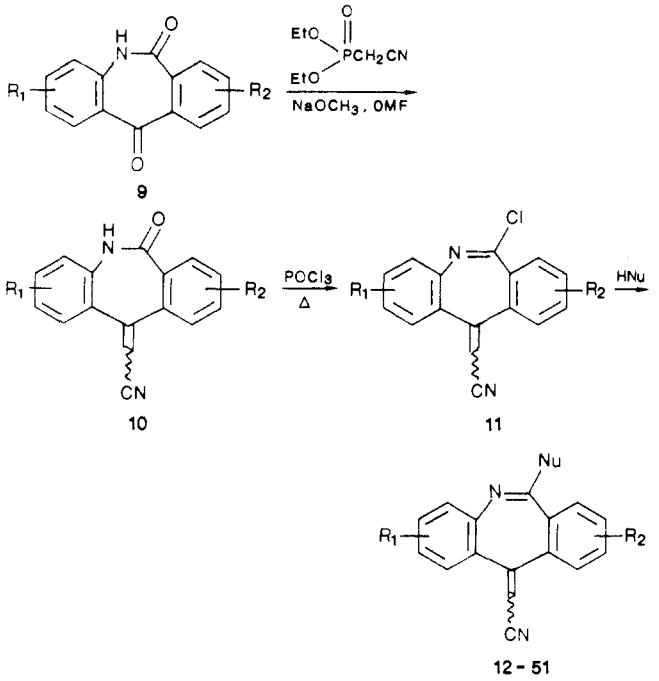
Scheme I



provement of the therapeutic profile and the elimination of EPS could not be achieved in every case, EPS being a persistent problem in the case of, for example, the well-known compound butaclamol (**8**).[10]

Fluperlapine (**7**) is the newest drug with a clozapine-like activity: it is in clinical trial and resembles clozapine qualitatively and quantitatively.[11]

The object of our work was to develop new tricyclic epines whose framework differs from that of clozapine and that have a higher activity and are free from extrapyramidal and possibly other toxic effects. In this paper, we report the synthesis and the pharmacological evaluation of a series of 6-alkylamino- and 6-aminoalkoxy-substituted [11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile derivatives.[12] In order to investigate structure–activity relationships, broad changes in the basic side chain have been made and substituents have been introduced into the aromatic rings.

Chemistry. The synthesis of the 6-substituted [11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile derivatives **12–51** is outlined in Scheme I.

The morphanthridine-6,11(5*H*)-diones **9** were synthesized by ring enlargement of the corresponding anthraquinones via Schmidt reaction with sodium azide in sulfuric acid.[13,14] It was not possible in every case to separate the positional isomers formed in the ring-enlargement reaction (where a maximum of four isomers can be formed) by fractional crystallization (see the Experimental Section).

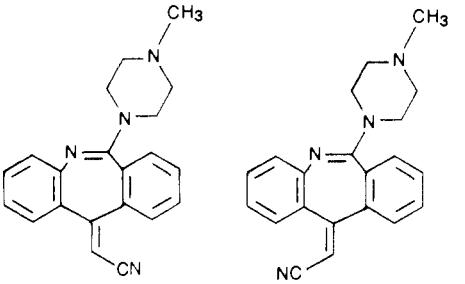
The introduction of the cyanomethylene group at the 11-position of the 11*H*-dibenz[*b*,*e*]azepine framework was effected via a Wittig–Horner reaction under mild reaction conditions.

The reaction of the morphanthridine-6,11(5*H*)-diones **9** with diethyl (cyanomethyl)phosphonate in the presence of sodium methylate in dimethylformamide gave the new [5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene]-acetonitrile derivatives **10** as 1:1 (*E*)/(*Z*) isomer mixtures in 95–98% yield. These were reacted with phosphorus oxychloride in the presence of a trace of *N*,*N*-dimethylaniline at 100–120 °C to yield the [6-chloro-11*H*-dibenz-[*b*,*e*]azepin-11-ylidene]acetonitriles **11**, which were converted to the desired title compounds **12–51** by nucleophilic substitution reactions with the appropriate alkylamines or alkylamino alcohols (HNu) in 45–92% yields.

Some compounds strongly absorb water or the solvents methanol and ethanol, and therefore they cannot be obtained entirely free of water and solvent.

Table I shows a selection of the synthesized and screened [11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitriles **12–51**.

The novel compounds **12–51** exist as (*E*),(*Z*) isomers.



The (*E*),(*Z*) isomers could be separated by fractional crystallization from suitable solvents (see the Experimental Section). The different chemical shifts of the cyanomethylene proton in the ^{1}H NMR spectra of the isomers (Δ = 0.04 ppm in $CDCl_3$) made it possible to differentiate between the geometric isomers, and the purity of these could be checked by thin-layer chromatography. In every case, the (*E*) isomer proved to be the nonpolar component. The structures for the individual geometric isomers were determined by X-ray structure analyses.

The (*E*),(*Z*) isomers are stable in the crystalline state; solutions of these isomers must be protected from light in order to avoid the small amount of isomerization that otherwise occurs.

Biology. The action profile of neuroleptics typically includes sedative, muscle-relaxing, antimonaminergic, and anticholinergic properties that may be more or less pronounced. In the case of clozapine, sedative and anticholinergic actions are particularly pronounced,[3] and screening of the new compounds was therefore initially directed at these properties.

The inhibition of the spontaneous motor activity in the mouse was determined as a measure of the quality of sedative action. To determine the anticholinergic action, the antagonistic effect of physostigmine was tested in mice.

From these data (Table I), it is evident that a basic piperazine ring attached to the 11*H*-dibenz[*b*,*e*]azepine framework at position 6 leads to the highest activity. The presence of the distal nitrogen with respect to the tricyclic ring system also seems essential, since compounds that are similarly substituted with a piperidine or morpholine ring (compounds **41–45**), where this nitrogen is absent, are less effective by more than a power of 10 in both sedative and anticholinergic activity, in agreement with findings for clozapine and similar tricyclic piperazine derivatives.[1,6,7]

(10) Clark, M. L.; Paredes, A.; Costiloe, J.; Wood, F. *J. Clin. Pharm.* **1977**, *17*, 529.
(11) Eichenberger, E. *Arzneim.-Forsch.* **1984**, *34*, 110. Fischer-Cornelssen, K. A. *Arzneim.-Forsch.* **1984**, *34*, 125.
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The methyl group is the most effective substituent on the nitrogen of the piperazine ring, since the introduction of an ethyl, hydroxyethyl, or oxazolidin-2-onylethyl group (compounds **18**, **19**, and **25**) as well as the replacement of the alkyl radical with hydrogen (compound **17**) results in a substantial loss of activity in some cases.[7] In the case of the *N*-oxides **20** and **21**, a similar result is found as in the literature:[6,7] the derivatives show less activity than their parent compounds, presumably since the *N*-oxide function will be converted to the corresponding tertiary amine by in vivo enzymatic reduction.

A very recent and surprising finding is the modification of the action spectrum of the geometric (*E*) and (*Z*) isomer pairs **12**, **14**, **18**, and **20**, where substantial differentiation in the sedative and anticholinergic actions is observed. In every case, the (*E*) isomer possesses the sedative activity, which is noticeably greater than that of the correpsonding (*Z*) isomer, this being so by a factor of >12 in the case of **12**, 32 in the case of **14**, >42 in the case of **18**, and 6.5 in the case of **20**. Each of the (*Z*) isomers possesses an anticholinergic activity that is greater than that of the (*E*) isomer by just as large a factor, the relevant factors being 3.7 for **12**, 8.2 for **14**, >3 for **18**, and 11 for **20**.

The ED values found for the isolated isomers are not an exact indication of the ED value of the mixture. Because of the biological scatter, the fact that the isomers and the mixture are investigated at different times, and possible interaction between the two isomers (synergistic effects), more or less substantial deviations from the calculated arithmetic value are to be expected for comparisons of this type.

The introduction of a second methyl group into the piperazine ring (compounds **23** and **24**) results in a decrease in activity, which is presumably due to steric interactions. Increasing the piperazine ring to homopiperazine (**27**) leads to a decrease in the sedative activity.

Compounds substituted by open-chain aminoalkylamines in the 6-position (**28–36**), where the conformational freedom of these chains is greater than that of the rigid piperazine ring, are less active. Only the (piperidin-1-ylethyl)amino derivative **33** shows a sedative activity similar to that of the methylpiperazine compound **12**. This confirms that a certain conformational state of the distal nitrogen atom is required for good activity.[6] The distance between the aromatic ring and the distal nitrogen appears to be critical with regard to the activity (see Discussion). Increasing the N_3–N_4–C_2 bridge in the basic side chain in the 6-position by one carbon atom (**32**, **37–39**) leads to a drastic reduction in the activity.

The (alkoxyalkyl)amino derivatives **46–51** are substantially less active, only the (oxymethylene)piperidine derivative **48** still possessing a good anticholinergic activity.

The introduction of a chlorine or methyl substituent into the 2-position of the aromatic ring (**15**, **13**) leads to a reduction in the activity, the sedative component being more affected that the anticholinergic activity. In contrast, corresponding substitution at the 3- or 8-position of the aromatic ring (**16**, **14**), in analogy to the higher neuroleptic action in the case of clozapine and related compounds,[1] results in a substantial increase in the sedative activity but an accompanying reduction in the anticholinergic component.

Further pharmacological actions for some of the most effective compounds in Table I are shown in Table II.

The sedative action of tricyclic neuroleptics is frequently due to, among other things, a central muscle-relaxing action. In conscious rabbits, the isomer mixtures show muscle-relaxing effects that are similar or, in the case of

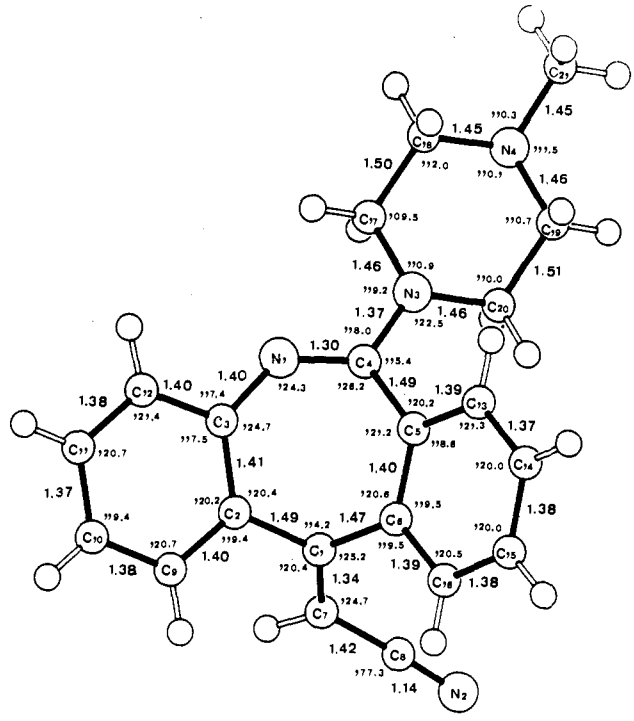


Figure 1. Structure of compound (*E*)-**12** (bond lengths in Å, standard deviations 0.003–0.004 Å; bond angles in deg, standard deviations 0.2–0.3°).

(*E*)-**14**, substantially superior to those of clozapine. As in the case of the sedative action, this action is associated with the (*E*) isomer (in the case of **14**, the ratio of the activities of the (*E*) and (*Z*) isomers is 18).

The monoamine-inhibiting actions typical of neuroleptics were tested on the model of apomorphine-induced stereotypy (antidopaminergic action) and the model of tryptamine-induced agitation (antiserotoninergic action). Compared with clozapine, the effective doses as shown in Table II are 2–5 times higher in the case of apomorphine antagonism and 1–10 times higher in the case of tryptamine antagonism. The (*E*) and (*Z*) isomers were not found to exhibit such great differences in their levels of activity in this case as in the case of the sedative and anticholinergic actions. The apomorphine-antagonistic activity of the (*Z*) form is found to be 4–5 times higher.

None of the substances given in Table II showed a cataleptic effect in doses up to 21.5 mg/kg.

Crystallography. Crystals of (*E*)-**12**, (*Z*)-**12**, and (*Z*)-**13** suitable for X-ray structure analyses were obtained by recrystallization from ethanol. Experimental details are summarized in Table III. The crystals of compound (*Z*)-**12** contain two independent molecules m1 and m2 in two slightly different conformations. A least-squares fit of all corresponding atoms (except hydrogens) of m1 and m2 give a root-mean-square deviation of 0.088 Å. Figures 1–3 show the molecules with bond lengths and angles and the atomic numbering scheme used in the X-ray structure analyses. This scheme is the same for all compounds. The numbering of atoms in m2 of (*Z*)-**12** is derived by adding 30 to the numbers in m1. H atoms are given the number of the C atoms to which they are attached plus an additional cipher.

Superposition of the molecules of the (*E*) and (*Z*) isomers of **12** (the least-squares fit of all atoms of the tricyclic structure gives a root-mean-square deviation of 0.042 Å) indicates that, with the exception of the cyanomethylene groups in the 11-position, their conformations are virtually identical (Figure 4).

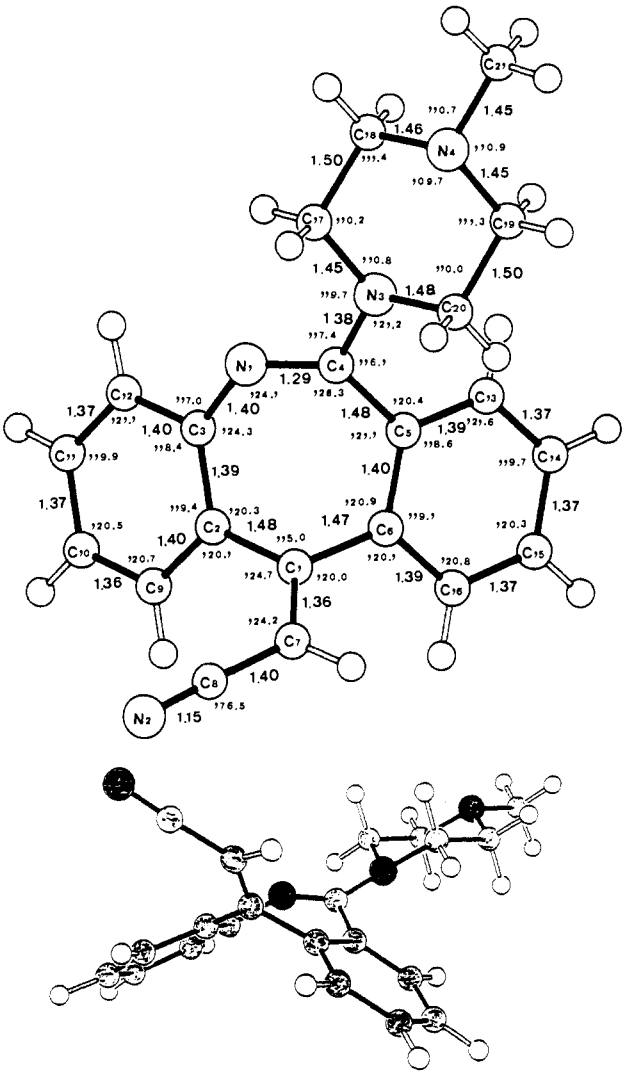


Figure 2. Structure and perspective view of compound (*Z*)-**12** m1 (averaged bond lengths (m1 and m2) in Å, standard deviations 0.004–0.010 Å; averaged bond angles in deg, standard deviations 0.3–0.7°).

The parameters of interest are the distances from the two nitrogen atoms N(3) and N(4) to the centers of the aromatic rings Ar(1) [C(2), C(3), C(9), C(10), C(11), C(12)] and Ar(2) [C(5), C(6), C(13), C(14), C(15), C(16)], the dimension of the molecules expressed by the distance N(2)···N(4), the interplanar angles between the best planes through the atoms of Ar(1) and Ar(2), and significant torsion angles (Table IV; see Discussion).

The methylpiperazino derivatives are of particular interest as they are very rigid molecules, apart from rotation about the exocyclic C(4)–N(3) bond (which is presumably restricted due to a partial double bonding) and small conformational changes in the piperazine ring. Hence, the compounds are very suitable for determining these geometrical parameters. All compounds have very similar conformations confirmed by the torsion angles and the interplanar angles between Ar(1) and Ar(2).

In order to study the effect of this C(4)–N(3) rotation on the distances N(4)···Ar(1) and N(4)···Ar(2), this rotation was carried out in 20° steps for molecule m1 of compound (*Z*)-**12**, using the program SHELXTL.[15] However, these

(15) Scheldrick, G. M. *SHELXTL*, An Integrated System for Solving, Refining and Displaying Structures from Diffractometer Data; University of Göttingen: Federal Republic of Germany, 1978.

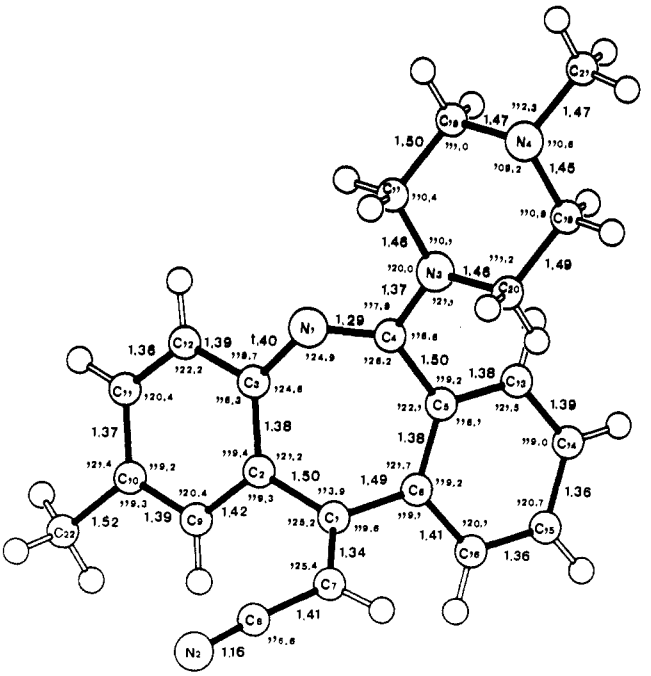


Figure 3. Structure of compound (*Z*)-**13** (bond lengths in Å, standard deviations 0.004–0.009 Å; bond angles in deg, standard deviations 0.2–0.6°).

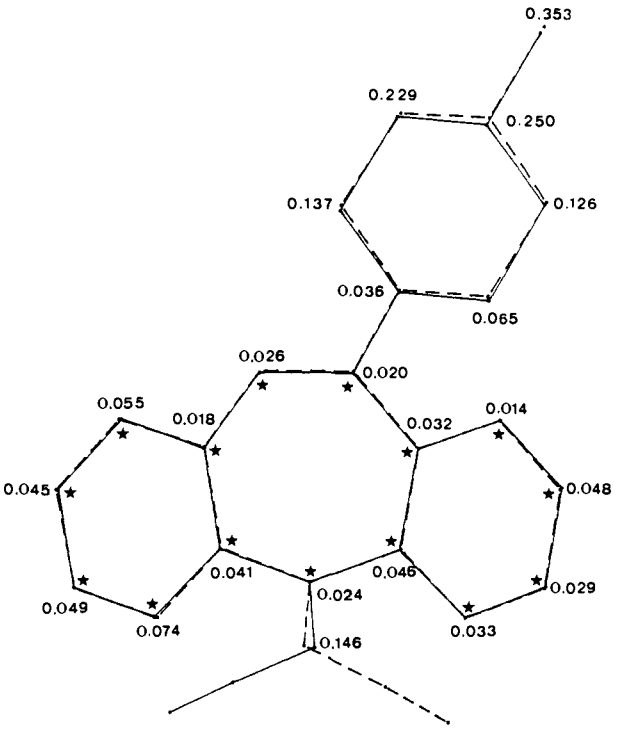


Figure 4. Comparison of the isomer structures of (*E*)-**12** and (*Z*)-**12** m1 with distances from corresponding atoms (in Å). Atoms marked by asterisks are those used for the least-squares fit.

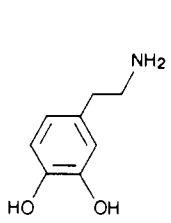
distances show very little dependence on the C(4)–N(3) rotation: the values vary only from 7.72 to 7.80 Å for N(4)–Ar(1) and from 6.01 to 6.11 Å for N(4)–Ar(2).

Discussion. There is a considerable amount of evidence to support the concept that the antipsychotic activity, as well as the extrapyramidal side effects (EPS), of neuroleptic drugs are correlated with their ability to block dopamine receptors in the brain.[8,16] It is now believed that

(16) Horn, A. S.; Post, M. L.; Kennard, O. *J. Pharm. Pharmacol.* **1975**, *27*, 553.

the EPS are probably caused by blockage of the dopamine receptors in the striatum, whereas the antipsychotic activity is produced by blocking dopamine receptors in the mesolimbic area of the brain.[17] Moreover, it has been observed that neuroleptics that possess anticholinergic properties (like clozapine) produce a reduced incidence of EPS in clinical trials.[3]

In the published crystal structures of dopamine (**52**) and the rigid dopamine agonist apomorphine (**53**), the distance



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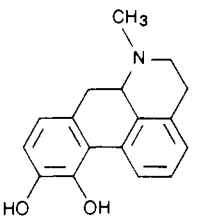

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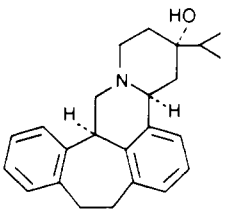

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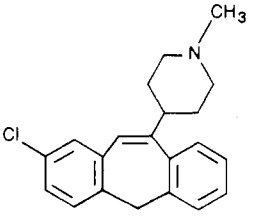
of the nitrogen atom from the center of the catechol ring is 5.10 Å.[16,18] This distance is in very good agreement with the corresponding N···Ar distance of 4.90 Å in the potent neuroleptic (+)-dexclamol (**54**), which has a very rigid molecule (use of the biologically relevant conformer B[19]), and with the proximal piperazine nitrogen–distal aromatic ring distances N(3)···Ar(1) in the reference substances clozapine (**6**)[20] (4.97 Å), loxapine (**3**)[20] (4.99 Å), and our rigid compounds (Table IV).

The rigidity and geometrical similarity of our compounds and the reference compounds clozapine (**6**)[20] and loxapine (**3**)[20] are indicated by the torsion angles and the interplanar angles of the phenyl rings. These values are nearly the same besides some small differences caused by the different bridge atoms C, N, and O at position 1 [torsion angles implicating the bonds X(1)–C(2) and X(1)–C(6)]. These differences of the seven-membered rings are also indicated by the torsion angles involving the bonds C(4)–N(3). In all cases the atoms N(1), C(4), N(3), and C(17) are nearly coplanar (torsion angles near zero), whereas C(20) is out of this plane. Because we find very similar Ar···N distances in all rigid structures, these should correspond very closely to the distances occurring at the receptor.

Olson et al.[21] proposed a hypothetical model of the dopamine receptor on the basis of a comparison of the molecular similarities of the B conformer of (+)-dexclamol with those of other neuroleptic drugs.

In this model, the proximal piperazine nitrogen N(3) forms a polar bond with COO^- (one of the three postulated binding sites).

However, our structure–activity results and those of others[1,6] reveal that even more important for the neuroleptic activity is the presence of the distal piperazine nitrogen, which is absent in the dopamine and apomorphine molecules (cf. compounds **12** and **14**). For example, for compound **55** (no roximal nitrogen), Smith et al.[9] (cf. ref 7) found good activity in studies on the binding affinity at nonmuscarinic clozapine sites in rat forebrain, which is supposed to reflect the antipsychotic potential.



55

The fact that ring opening of the piperazine ring causes a drastic loss of activity (cf. compounds **12** and **28**) suggests that a certain orientation of the distal N(4) lone electron pair is required for neuroleptic activity. These important distances N(4)···Ar(1) and N(4)···Ar(2) (Table IV) in our compounds (7.74–7.75 and 6.06–6.09 Å, respectively) agree very well with the corresponding crystal structure parameters of clozapine (**6**) (7.72 and 5.97 Å)[20] and loxapine (**3**) (7.73 and 6.19 Å, respectively).[20] This means that, for the distal N(4) atom in tricyclic neuroleptics of this type, it is necessary to postulate an additional, fifth polar binding site at the receptor itself or at an adjacent polar structure (e.g., $\equiv N_4^+H\cdots{}^-OOC-$).[21]

The N(4)···Ar(2) distance of about 6.00 Å is in good agreement with the corresponding parameters for the typical and nontypical anticholinergics and hence makes the anticholinergic action of the neuroleptics of the clozapine type plausible.[8,22]

A new discovery is the interesting separation of the action spectrum for the (*E*) and (*Z*) isomers with regard to the rigid cyanomethylene group in the 11-position, this indicating an interaction with different receptors for the specific levels of action. This surprising effect of the changing activity profile is a new one for neuroleptics; only in the case of the thioxanthenes and the dibenzoxepin pinoxepin are the (*Z*) isomers known to be more active than the virtually inactive (*E*) isomers.[23]

In the compounds described, the pharmacophoric cyanomethylene group that not only causes separation of the action profile but generally results in an increase in activity (comparison of the pharmacological properties of compound **12** with those of perlapine **5**) is rigid; hence, the geometrical parameters (e.g., the distances N(2)···N(4) from the nitrile nitrogen to the distal piperazine nitrogen atom in Table IV) indicate the goodness of fit in the corresponding receptors. Further work aimed at answering these interesting questions is in progress.

Experimental Section

The following instruments were used to determine the physical properties of the compounds: ^1H NMR, Bruker WP 80, WP 200, WH 270, WM 360, Nicolet QE 300 (internal standard tetramethylsilane); ^{13}C NMR, Bruker WH 270, WM 360; IR, Bruker IFS 85 (KBr disks). Melting points (uncorrected) were determined

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(20) Petcher, T. J.; Weber, H. P. *J. Chem. Soc., Perkin Trans.* **1976**, *2*, 1415. Fillers, J. P.; Hawkinson, S. W. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1982**, *B38*, 1750.

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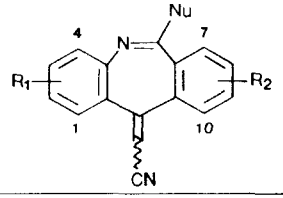
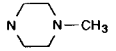
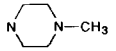
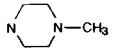
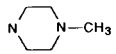
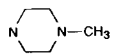
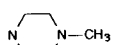
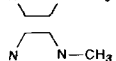
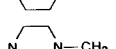
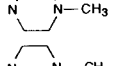
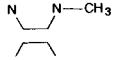
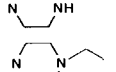
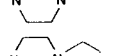
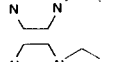
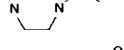
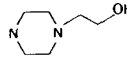
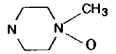
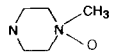
(23) Moller-Nielsen, J.; Pedersen, V.; Nymark, M.; Franck, K. F.; Boeck, V.; Fjallan, B.; Christensen, A. V. *Acta Pharmac. Tox.* **1973**, *33*, 353. Miller, R. J.; Horn, S. A.; Iversen, L. L. *Mol. Pharmac.* **1974**, *10*, 759. Schmutz, J.; Picard, C. W. In *Psychotropic Agents*, Part I; Hoffmeister, F., Stille, G., Eds.; 1980; p 9.

Table I. [6-(Alkylamino)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitriles **12–45** and [6-(Aminoalkoxy)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitriles **46–51**: Chemical Data and Sedative and Anticholinergic Activity



						sedative act. in mice		anticholinergic act. in mice	
no.	Nu	R_1	R_2	formula[a]	mp, °C	ED_{50}, mg/kg po	rel act.[b]	ED_{50}, mg/kg po	rel act.[b]
12		H	H	$C_{21}H_{20}N_4 \cdot 0.2H_2O$	148–150	2.78 (1.76/4.39)[c]	1.71	6.26 (4.25/9.23)[c]	2.25
(*E*)-**12**		H	H	$C_{21}H_{20}N_4$	210–212	1.98 (1.06/3.67)	2.39	17.4 (10.93/27.75)	0.81
(*Z*)-**12**		H	H	$C_{21}H_{20}N_4$	182–184	>21.5[d]	<0.2	4.7 (3.38/6.53)	3.00
13		2-CH_3	H	$C_{22}H_{22}N_4 \cdot 0.25H_2O$	162–164	3.35 (2.67/4.21)	1.41	2.74 (1.84/4.05)	5.15
14		3-CH_3	H	$C_{22}H_{22}N_4$	192–200	0.80 (0.56/1.14)	5.90	31.2 (22.9/42.6)	0.45
(*E*)-**14**		3-CH_3	H	$C_{22}H_{22}N_4$	224	1.06 (0.89/1.26)	4.47	~100	~0.14
(*Z*)-**14**		3-CH_3	H	$C_{22}H_{22}N_4$	193–195	33.6 (27.3/41.8)	0.14	12.3 (9.67/15.7)	1.15
15		2-Cl	H	$C_{21}H_{19}ClN_4 \cdot 0.33H_2O$	157–162	25.6	0.19	16.1	0.88
16		(3)-Cl	(8)-Cl[e]	$C_{21}H_{19}ClN_4 \cdot 0.15CH_3OH$	95–98	~1.0	~4.74	>10	<1.4
17		H	H	$C_{20}H_{18}N_4 \cdot 1.5H_2O$[f]	208–211	30.6 (23.2/40.3)	0.15	21.3 (15.3/29.6)	0.66
18		H	H	$C_{22}H_{22}N_4$	86–90	3.34 (2.76/4.06)	1.42	7.80 (6.02/10.1)	1.81
(*E*)-**18**		H	H	$C_{22}H_{22}N_4$	138–140	2.79 (2.18/3.56)	1.70	>21.5	<0.66
(*Z*)-**18**		H	H	$C_{22}H_{22}N_4$	181–183	>100	<0.04	5.60 (3.17/9.65)	2.52
19		H	H	$C_{22}H_{22}N_4O \cdot 0.33H_2O$	111–113	14.6 (10.5/20.5)	0.32	~68.1	~0.21
20		H	H	$C_{21}H_{20}N_4O \cdot 2H_2O$	141–148	14.3 (6.27/32.4)	0.33	15.88 (12.3/20.9)	0.89
(*E*)-**20**		H	H	$C_{21}H_{20}N_4O \cdot 1.3H_2O$	241	17.6 (12.2/25)	0.26	~100	~0.14
(*Z*)-**20**		H	H	$C_{21}H_{20}N_4O \cdot 1.9H_2O$	169	~100	~0.04	~8.75	~1.61

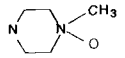
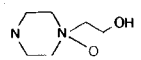
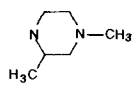
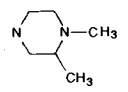
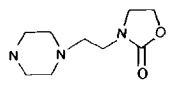
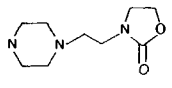
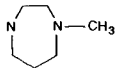
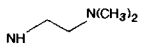
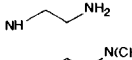
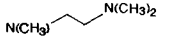
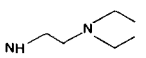
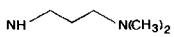
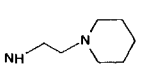
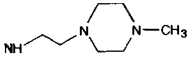
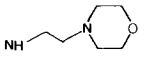
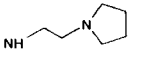
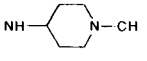
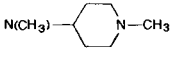
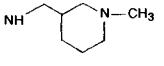
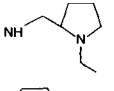
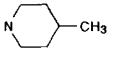
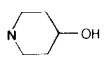
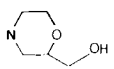
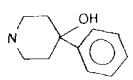
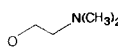
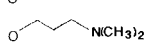
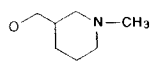
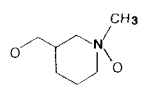
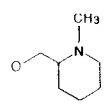
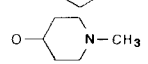
21		3-CH_3	H	$C_{22}H_{22}N_4O \cdot 2.25H_2O$	162[g]	2.66 (1.85/3.83)	1.78	31.0 (20.5/46.9)	0.45
22		H	H	$C_{22}H_{22}N_4O_2 \cdot 1.5H_2O$	144–146	10.3 (7.32/14.4)	0.46	39.0 (24.3/62.7)	0.36
23		H	H	$C_{22}H_{22}N_4 \cdot 0.75H_2O$	112–115	~21.5	~0.22	~21.5	~0.66
24		H	H	$C_{22}H_{22}N_4 \cdot 0.95H_2O$	93–96	8.08 (10.5/6.2)	0.59	7.68 (3.86/15.6)	1.84
25		H	H	$C_{25}H_{25}N_5O_2 \cdot 0.25H_2O$	102–105	39.4 (45.7/33.9)	0.12	51.0 (30/90)	0.28
26		3-CH_3	H	$C_{26}H_{27}N_5O_2$	106–108	9.56 (14.1/6.5)	0.50	>46.4	<0.30
27		H	H	$C_{22}H_{22}N_4 \cdot 0.5H_2O$	73–80	>21.5	<0.22	5.49 (4.1/7.41)	2.57
28		H	H	$C_{20}H_{20}N_4 \cdot 0.2CH_3OH$	76–79	15.5 (12.8/18.9)	0.31	>100	<0.14
29		H	H	$C_{18}H_{16}N_4 \cdot 0.75CH_3OH$	86–90	>100	<0.04	>100	<0.14
30		H	H	$C_{21}H_{22}N_4 \cdot 0.75H_2O$	65–67	~14.7	0.32	~31.6	~0.45
31		H	H	$C_{22}H_{24}N_4 \cdot H_2O$[h]	84–90	5.72 (4.49/7.31)	0.83	>100	<0.14
32		H	H	$C_{21}H_{22}N_4 \cdot 0.5EtOH$	70–72	>46.4	<0.1	>46.4	<0.30
33		H	H	$C_{23}H_{24}N_4 \cdot 0.5H_2O$	83–85	1.61 (1.32/1.95)	2.94	>10.0	<1.41
34		H	H	$C_{23}H_{25}N_5 \cdot 0.75H_2O$	89–92	27.7 (21.3/36.1)	0.17	>100	<0.14
35		H	H	$C_{22}H_{22}N_4O \cdot 0.25H_2O$	89–91	8.12 (6.36/10.4)	0.58	>100	<0.14
36		H	H	$C_{22}H_{22}N_4 \cdot 0.25H_2O$	84–88	4.96 (3.68/6.68)	0.96	>100	<0.14
37		H	H	$C_{22}H_{22}N_4 \cdot 0.5H_2O$	132–134	>100	<0.04	~68.1	~0.21
38		H	H	$C_{23}H_{24}N_4 \cdot 0.33H_2O$	105–107	13.4 (11.1/16.1)	0.35	~31.6	~0.45
39		H	H	$C_{23}H_{24}N_4 \cdot H_2O$	110–114	>100	<0.04	~46.4	~0.30
40		H	H	$C_{23}H_{24}N_4 \cdot 0.2EtOH$	75–79	17.2 (13.9/21.3)	0.28	>100	<0.14
41		H	H	$C_{22}H_{21}N_3 \cdot 0.1EtOH$	145–148	~68.1	~0.07	>46.4	<0.30

Table I (Continued)

no.	Nu	R_1	R_2	formula[a]	mp, °C	sedative act. in mice: ED_{50}, mg/kg po	sedative act. in mice: rel act.[b]	anticholinergic act. in mice: ED_{50}, mg/kg po	anticholinergic act. in mice: rel act.[b]
42		H	H	$C_{20}H_{17}N_3O$	181–185	>100	<0.04	>100	<0.14
43		H	H	$C_{21}H_{19}N_3O \cdot 1.25H_2O$[j]	105–108	>46.4	<0.1	>100	<0.14
44		H	H	$C_{21}H_{19}N_3O_2 \cdot 0.7H_2O$	172–177	>46.4	<0.1	~46.4	~0.30
45		H	H	$C_{27}H_{23}N_3O \cdot 0.5H_2O$	145–148	>46.4	<0.1	>100	<0.14
46		H	H	$C_{20}H_{19}N_3O \cdot 0.5H_2O$[j]	51–53	34.8 (28.9/41.8)	0.14	24.9 (17.3/36)	0.57
47		H	H	$C_{21}H_{21}N_3O \cdot H_2O$	54–56	>100	<0.04	24.0 (19.2/30)	0.59
48		H	H	$C_{23}H_{23}N_3O \cdot H_2O$	93–95	>46.4	<0.1	5.92 (4.5/7.74)	2.38
49		H	H	$C_{23}H_{23}N_3O_2 \cdot 2.5H_2O$	105–108	>100	<0.04	>100	<0.14
50		H	H	$C_{23}H_{23}N_3O \cdot 0.25H_2O$	67–70	43.6 (36.1/52.6)	0.11	~68.1	~0.21
51		H	H	$C_{22}H_{21}N_3O \cdot 0.25H_2O$	80–85	>21.5	<0.22	>21.5	<0.66
	clozapine					4.74 (3.8/5.91)	1.00	14.1 (11.5/17.4)	1.00

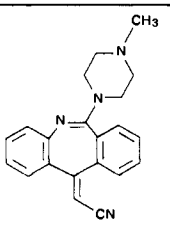
[a] The compounds gave satisfactory (±0.4%) elemental analyses for C, H, N, and Cl. [b] Relative activity, based on clozapine. [c] 95% confidence limit. [d] > = EC_{50} not reached. [e] Isomer mixture (1:1) of 3-Cl and 8-Cl derivatives. [f] H: calcd, 6.20; found, 5.7. [g] Decomposition. [h] N: calcd, 15.46; found, 14.9. [i] H: calcd, 6.16; found, 5.5. [j] H: calcd, 6.18; found, 5.7.

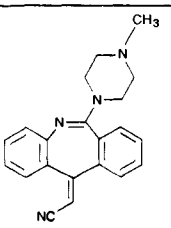
Table II. [6-(Alkylamino)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitriles: Muscle-Relaxing Activity, Apomorphine Antagonism, Antitryptamine Action, and Toxicity

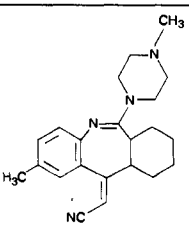
no.	muscle-relaxing act. in rabbits: ED_{50}, mg/kg iv	muscle-relaxing act. in rabbits: rel act.	apomorphine antag in rats: ED_{50}, mg/kg po	apomorphine antag in rats: rel act.	antitryptamine act. in rats: ED_{50},[a] mg/kg ip	antitryptamine act. in rats: rel act.
12	0.059 (0.043/0.078)[b]	0.47	22	0.37	30 (13/68)[b]	0.17
(*E*)-12	0.046 (0.02/0.076)	0.61	46	0.17	79 (43/160)	0.06
(*Z*)-12	~1.0	~0.03	12	0.67	32 (16/69)	0.16
13	~0.1	~0.28	42	0.19	~21	~0.23
14	0.028 (0.01/0.15)	1.0	35	0.23	6.0 (3.5/10)	0.83
(*E*)-14	0.014 (0.001/0.029)	2.0	85	0.09	10 (4.3/24)	0.50
(*Z*)-14	0.25	0.11	19	0.42	51 (25/120)	0.10
18	~0.32	~0.09	43	0.19	6.6 (2.9/12)	0.76
(*Z*)-18	>0.46	<0.06	22	0.37	>100	<0.05
clozapine	0.028 (0.019/0.41)		8	1.00	5.0 (1.4/8.9)	1.00

[a] Activity after 30 min. [b] 95% confidence limit.

Table III. Summary of Crystal Data and of Experimental Details for the X-ray Structure Analyses of Compounds 12 and 13


(*E*)-12


(*Z*)-12


(*Z*)-13

	$C_{21}H_{20}N_4$	$C_{21}H_{20}N_4 \cdot 0.5C_2H_5OH$	$C_{22}H_{22}N_4 \cdot 0.5C_2H_5OH$
M_r	328.4	328.4	342.4
space gp	$P2_12_12_1$	$P2/c$	$C2/c$
a, Å	9.036 (2)	18.773 (5)	30.188 (17)
b, Å	9.207 (2)	9.026 (3)	9.077 (6)
c, Å	20.960 (6)	26.989 (6)	18.785 (12)
β, deg		123.16 (2)	128.55 (5)
V, Å^3	1743.75	3820.15	4025.59
Z	4	8	8
d_{calcd}, g·cm^{-1}	1.251	1.222	1.206
μ(Cu Kα), cm^{-1}	5.61	5.61	5.49
cryst, size, mm	0.33 × 0.30 × 0.15	0.20 × 0.25 × 0.30	0.35 × 0.35 × 0.15
no. of unique reflcns	1346	4285	2437
no. of reflcns used for refinement	1287	2954	2048
no. of parameters refined	244	487	257
final R	0.0345	0.0719	0.0805
final R_w	0.0363	0.0730	0.0907

Table IV. Distances from N(3) and N(4) to Centers of Phenyl Rings Ar(1) and Ar(2), N(2)···N(4) Distances, Interplanar Angles between Ar(1) and Ar(2), and Torsions Angles[a] in Compounds (*E*)-12, (*Z*)-12, (*Z*)-13,[a] Loxapine (3) and Clozapine (6)

	(*E*)-12	(*Z*)-12 m1	(*Z*)-12 m2	(*Z*)-13	3	6
			Distances, Å			
N(3)···Ar(1)	5.016	5.000	5.005	5.000	4.997	4.974
N(3)···Ar(2)	3.687	3.710	3.686	3.674	3.746	3.682
N(4)···Ar(1)	7.749	7.737	7.747	7.740	7.731	7.716
N(4)···Ar(2)	6.067	6.094	6.066	6.062	6.188	5.973
N(2)···N(4)	8.270	9.118	9.340	9.440		
			Interplanar Angles, deg			
Ar(1)/Ar(2)	116.2	116.9	116.3	119.0	114.0	115.0
			Torsion Angles, deg			
C(6)-X(1)-C(2)-C(9)	119.8	120.0	118.4	120.6	113.1	112.9
C(6)-X(1)-C(2)-C(3)	−57.7	−54.7	−54.8	−55.6	−68.3	−66.4
C(2)-X(1)-C(6)C(16)	−117.1	−119.4	−120.4	−123.4	−109.5	−117.2
C(2)-X(1)-C(6)-C(5)	56.5	56.8	56.7	54.8	70.1	63.5
C(3)-N(1)-C(4)-C(5)	2.9	3.2	0.9	−1.1	3.9	−2.2
C(3)-N(1)-C(4)-N(3)	176.2	176.6	173.8	173.3	178.8	171.8
N(1)-C(4)-N(3)-C(17)	−2.7	0.5	−3.5	−4.0	4.2	−8.9
N(1)-C(4)-N(3)-C(20)	144.6	144.9	142.6	140.5	154.1	151.3
C(5)-C(4)-N(3)-C(17)	171.3	174.6	170.2	171.0	179.5	165.8
C(5)-C(4)-N(3)-C(20)	−41.4	−41.0	−43.7	−44.5	−30.7	−34.1
C(7)-C(1)-C(2)-C(3)	128.3	131.5	131.3	130.4		
C(7)-C(1)-C(2)-C(9)	−54.2	−53.8	−55.5	−53.4		
C(7)-C(1)-C(6)-C(5)	−129.8	−129.1	−129.2	−130.7		
C(7)-C(1)-C(6)-C(16)	56.5	54.7	53.8	51.0		
C(2)-C(1)-C(7)-C(8)	176.9	−7.5	−4.6	−3.4		
C(6)-C(1)-C(7)-C(8)	3.6	179.0	−178.2	−177.1		

[a] Standard deviations: distances for (*E*)-12, 0.03–0.04, for (*Z*)-12 and (*Z*)-13, 0.06–0.08 Å: angles for (*E*)-12, 0.2–0.5, for (*Z*)-12 and (*Z*)-13, 0.3–0.9°.

on a Büchi melting point apparatus.

(*E*),(*Z*)-[6-(4-Methyl-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (12). Phosphorus oxychloride (280 mL) and 3.5 mL of *N*,*N*-dimethylaniline were added to 40.0 g (162 mmol) of (*E*),(*Z*)-(5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile (10), and the mixture was refluxed for 4 h under nitrogen. The excess phosphorus oxychloride and dimethylaniline were then completely distilled off under reduced pressure from an oil pump, the residue was partitioned between methylene chloride and water, the aqueous phase was extracted twice more with methylene chloride, and the combined organic phases were thoroughly washed with dilute HCl and with water, dried, and evaporated, giving 41.6 g (97%) of (*E*),(*Z*)-(6-chloro-11*H*-dibenz[*b*,*e*]azepin-11-ylidene)acetonitrile (11), which was sufficiently pure for further reaction.

This crude product was dissolved in 230 mL of toluene with heating, and after filtration, the solution was heated to reflux. *N*-Methylpiperazine (28.8 g, 288 mmol, 32 mL) was added dropwise in the course of 15 min with stirring, and the mixture was stirred for 3–5 h at the reflux temperature. After the reaction mixture was cooled in an ice bath, the yellowish crude product 12 separated out slowly. This was filtered off, dried in an oven under reduced pressure, and recrystallized from ethanol in the presence of active charcoal, giving *49.0 g (92%) of 12, mp 148–150 °C.*

To separate the (*E*) and (*Z*) isomers, the isomer mixture 12 was digested in about 180 mL of boiling methanol, and the insoluble material was filtered off while the solution was hot. This gave 6.8 g of a yellow soild which, on the evidence of the thin-layer chromatogram (silica gel, 85:15 toluene/methanol as the mobile

phase), consisted in the main of the nonpolar (*E*) isomer. The filtrate was concentrated, and the residue was taken up in a small amount of boiling methylene chloride, just sufficient to dissolve all the material. On cooling, 6.5 g of a yellow product crystallized out; this was filtered off rapidly and washed with a very small amount of ice-cold methylene chloride. Thin-layer chromatography indicated a very high concentration of the polar (*Z*) isomer.

When these two successive operations were repeated several times, about 15–17-g fractions of each of the highly enriched isomers were obtained, and these were then recrystallized once or twice more from ethanol.

The pure (*E*) isomer was obtained in the form of yellow rectangular flakes of mp 210–212 °C and the pure (*Z*) isomer in the form of sharp yellow needles of mp 182–184 °C.

The appropriate structure was assigned to the individual geometric isomers by X-ray structural analysis.

(*E*)-**12**: IR 2220 (C≡N), 1576, 1555, 1404, 764 (arom) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3, NCH_3), 2.39–2.65 (m, 4, piperazine H), 3.37–3.65 (m, 4, piperazine H), 5.60 (s, 1, CHCN), 6.98–7.65 (m, 8, arom H); ^{13}C NMR ($CDCl_3$) δ 46.05, 47.33, 47.33, 54.85, 54.85, 97.31 (12-C), 116.64 (13-C), 123.36 (4-C), 126.01 (10-C), 126.19 (2-C), 126.71 (6a-C), 126.87 (1-C), 128.82 (3-C), 129.19 (7-C), 130.16 (8-C), 131.33 (9-C), 131.86 (11a-C), 139.78 (10a-C), 144.10 (4a-C), 158.73 (6-C), 162.21 (11-C).

(*Z*)-**12**: IR 2215 (C≡N), 1602 (C=N), 1583, 1404, 771 (arom) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3, NCH_3), 2.38–2.65 (m, 4, piperazine H), 3.37–3.62 (m, 4, piperazine H), 5.56 (s, 1, CHCN), 7.00–7.60 (m, 8, arom H); ^{13}C NMR ($CDCl_3$) δ 46.08, 47.45, 47.45, 54.92, 54.92, 97.17 (12-C), 116.60 (13-C), 123.47 (4-C), 126.08 (1-C), 126.34 (2-C), 126.60 (6a-C), 127.13 (10-C), 128.90 (3-C), 129.06 (7-C), 129.78 (11a-C), 130.26 (8-C), 131.39 (9-C), 141.88 (10a-C), 144.37 (4a-C), 158.51 (6-C), 161.91 (11-C).

(*E*),(*Z*)-(5,6-Dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile (10). Diethyl (cyanomethyl)phosphonate (35.4 g, 200 mmol) and 35.0 g (200 mmol) of a 30% solution of sodium methylate in 100 mL of dimethylformamide were slowly added dropwise, at the same time, to 30.0 g (135 mmol) of morphanthridine-6,11(5*H*)-dione (**9**; R_1, R_2 = H) dissolved in 300 mL of dimethylformamide and stirred under nitrogen. An increase in the depth of color and a rise in temperature indicated that the Wittig reaction had started. After the mixture was stirred for a further 4 h at room temperature, the reaction product was poured into ice water and the solid precipitate was filtered off. The crude product was thoroughly washed with water, dried, and recrystallized from ethanol: yield 32.5 g (98%) of **10** in the form of colorless crystals; mp 221–223 °C.

(*E*),(*Z*)-[2-Methyl-6-(4-methyl-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (13). The compound was prepared similarly to **12**, and 55% of yellow crystals of mp 162–164 °C was obtained.

To separate the (*E*) and (*Z*) isomers, the isomer mixture was subjected to fractional recrystallization from ethanol. The first fraction obtained (silica gel TLC plate, 85:15 toluene/methanol) had a high concentration of the polar isomer, which was again recrystallized from ethanol. This compound (mp 183 °C) was identified as the (*Z*) isomer by X-ray structural analysis. The starting material used was 2-methylmorphanthridine-6,11-(5*H*)-dione (**9**; R_1 = 2-CH_3, R_2 = H) of mp 198–202 °C, which was obtained as the Schmidt ring-enlargment product of 2-methylanthraquinone [prepared by the method of Werner et al.[14] (this paper incorrectly describes this isomer as the 8-CH_3 derivative!)], from which the more readily toluene-soluble fraction was isolated by fractional crystallization from toluene and enriched by recrystallization from 1:2 dioxane/ethanol. Wittig–Horner carbonyl olefination gave (*E*),(*Z*)-(2-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]-azepin-6-on-11-ylidene)acetonitrile, mp 228–230 °C.

(*E*),(*Z*)-[3-Methyl-6-(4-methyl-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (14). The compound was prepared similarly to **13**, and 79% of yellow crystals of melting point 192–200 °C was obtained.

To separate the (*E*) and (*Z*) isomers, the isomer mixture was subjected to fractional recrystallization from methanol. The first fraction obtained (silica gel TLC plate, 85:15 toluene/methanol) had a high concentration of the nonpolar isomer, which was again recrystallized from methanol. X-ray structural analysis identified this compound (mp 224 °C) as the (*E*) isomer of **14**. The corresponding polar (*Z*) isomer was best obtained by fractionally crystallizing the residue from th mother liquor, obtained above, from cyclohexane; the pure (*Z*)-**14** melted at 193–195 °C.

The starting material used was 3-methylmorphanthridine-6,11(5*H*)-dione (**9**; R_1 = 3-CH_3, R_2 = H) of mp 259–263 °C, which was obtained as the more sparingly toluene-soluble fraction from the Schmidt ring-enlargement reaction of 2-methylanthraquinone (see **13**) and recrystallized from dimethylformamide. Wittig–Horner carbonyl olefination gave (*E*),(*Z*)-(3-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, mp 233–235 °C.

(*E*),(*Z*)-[2-Chloro-6-(4-methyl-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile Hemihydrate (15). The compound was prepared similarly to **12**, and 62% of yellow crystals of melting point 157–162 °C was obtained.

The starting material was 2-chloromorphanthridine-6,11-(5*H*)-dione (**9**; R_1 = 2-Cl, R_2 = H).[24] Wittig–Horner carbonyl olefination gave (*E*),(*Z*)-(2-chloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]-azepin-6-on-11-ylidene)acetonitrile, mp 270 °C.

(*E*),(*Z*)-[3(8)-Chloro-6-(4-methyl-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (16). The monochloromorphanthridine-6,11(5*H*)-dione isomer mixture, which contained three different chlorinated isomers, and was employed as the starting material, was obtained by ring enlargement of 2-chloroanthraquinone using the method of Werner et al.[14] This material proved impossible to separate by fractional crystallization, contrary to the statement in the literature (fractions with similar melting points were obtained, but on the evidence of the 270-MHz ^1H NMR spectrum these fractions were each mixtures of two or three isomers). Hence, the further reactions were carried out with the isomer mixture, and a separation was only performed on the product obtained in the last stage.

Carbonyl olefination gave an (*E*),(*Z*)-(monochloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile isomer mixture (89%) of melting point 148–151 °C. The end product (74%), consisting of eight isomers (as indicated by thin-layer chromatography on silica gel, using 85:15 toluene/methanol; doubling due to cis/trans isomerism) and having a melting point of 95–99 °C, was recrystallized from ethanol and then was subjected to column chromatography (silica gel, 95:5 methylene chloride/methanol) to concentrate the individual fractions. This allowed isolation and characterization of the (*E*),(*Z*) mixtures of the 2- and 9-chloro-substituted end products, obtained by different methods,[12] and that constituted the polar and less polar components, respectively. The remaining compound **16** was obtained in an enriched form as further fractions and recrystallized from ethanol to give yellow crystals, mp 95–98 °C.

General Procedure for the Preparation of the Compounds 17–19, 23–24, and 27–51. These compounds were prepared by introducing the various nucleophilic alkylamino or aminoalkoxy substituents into the 6-position of (*E*),(*Z*)-[6-chloro-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (**11**). Compound **11** was mixed with 2–5 equiv of the alkylamine or aminoalkanol (HNu), and the mixture was heated at 110 °C under nitrogen from 3 to 5 h. Where the nucleophilic agent HNu was volatile, the residue was then taken up in ice water and repeatedly extracted with methylene chloride; where the nucleophilic agent was not volatile, the entire reaction mixture was taken up in ice water and extracted repeatedly with methylene chloride. The combined methylene chloride phases were then washed with water, dried, and concentrated. The crude product that remained was either recrystallized from ethanol in the presence of active charcoal or (especially where alkylamines of relatively high molecular weight were present) was purified by column chromatography over silica gel, using 95:5 methylene chloride/methanol. Yields varied from 45 to 92%.

Separation of (*E*)- and (*Z*)-18. To separate the (*E*) and (*Z*) isomers of **18**, the isomer mixture was subjected to fractional recrystallization from methanol. The less soluble fraction, which crystallized out first, was the (*Z*) isomer (the polar component on a silica gel TLC plate, using 85:15 toluene/methanol as the mobile phase). Recrystallization from ethanol gave the pure (*Z*) isomer of melting point 181–183 °C.

(24) Hardtmann, G. E.; Ott, H. *J. Org. Chem.* **1969**, *34*, 2244.

Column chromatography over silica gel, using 95:5 methylene chloride/methanol, gave the less polar (*E*) isomer in a purified form, mp 138–140 °C.

(*E*),(*Z*)-[6-(4-Methyl-4-oxy-1-piperazinyl)-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile Dihydrate (20). Compound **12** (6.0 g, 18.2 mmol) was dissolved in 100 mL of hot ethanol, and 1.5 mL of 30% hydrogen peroxide was added. The mixture was refluxed for 5 h, and the excess hydrogen peroxide was then destroyed by dropping a small sheet of platinum into the reaction mixture and refluxing for a further 2 h. The reaction mixture was then filtered, the filtrate was evaporated, and the resulting *N*-oxide was purified by column chromatography over silica gel, using 95:5 methylene chloride/methanol as the mobile phase. A 2.5-g portion (80%) of **20** was obtained as yellow crystals of mp 141–148 °C.

To separate the (*E*) and (*Z*) isomers, the isomer mixture was subjected to fractional recrystallization from a small amount of methylene chloride. The first fraction isolated had a high concentration of the nonpolar isomer (according to a thin-layer chromatogram on silica gel, using 85:15 toluene/methanol) and was recrystallized from a small amount of ethanol. By analogy to the (*E*),(*Z*) isomer analyses described above, this isomer (mp 241 °C) was assumed to belong to the (*E*) series. The corresponding polar (*Z*) isomer (mp 169 °C) was obtained by subjecting the residue from the mother liquor, obtained above, to column chromatography over silica gel, using 95:5 methylene chloride/methanol as the mobile phase.

Advantageously, both isomers were prepared directly by oxidizing, respectively, (*E*)-**12** and (*Z*)-**12** by the method described above; no cis/trans isomerization occurred during the oxidation.

(*E*),(*Z*)-[6-[4-[2-(2-Oxo-3-oxazolidinyl)ethyl]-1-piperazinyl]-11*H*-dibenz[*b*,*e*]azepin-11-ylidene]acetonitrile (25). Finely powdered potassium carbonate (15.4 g, 104 mmol), 1.04 g (6.3 mmol) of finely powdered potassium iodide, and 19.7 g (131 mmol) of 3-(2-chloroethyl)oxazolidin-2-one were added to 17.2 g (55 mmol) of (*E*),(*Z*)-[6-(1-piperazinyl)-11*H*-dibenz[*b*,*e*]-azepin-11-ylidene]acetonitrile (**17**) in 200 mL of toluene, and the thoroughly stirred mixture was refluxed for 20–30 h. After it had been cooled, the mixture was poured onto ice water, the organic phase was separated, and the aqueous phase was extracted repeatedly with toluene. The combined organic phases were washed with dilute sodium chloride solution, dried, and concentrated to give 17 g of crude product, which was still contaminated with unconverted starting material. Purification was carried out by column chromatography (silica gel, 95:5 methylene chloride/methanol), and 6.2 g (26%) of **25** of melting point 102–105 °C was isolated.

Pharmacological Experiments. Sedative Effect. The substances were administered orally to four or eight groups of three female NMRI mice. The orientation hypermotility induced by a new environment was determined photoelectrically, 30 min after the administration of the substances, for a period of 30 min. The ED_{50} was taken as the dose that reduced the orientation hypermotility by 50%, compared to control animals treated with placebo.

Anticholinergic Effect. A lethal dose (0.825 mg/kg) of physostigmine was administered subcutaneously to groups of 10 female NMRI mice. The test substances were administered orally 30 min before administering the physostigmine. The ED_{50} was the dose of substance that protected 50% of the animals against death from physostigmine.

Muscle-Relaxing Action. The measurement was based on quantifying the tonic extensor reflex on the rabbit gastrocnemius.[25] The rabbit was fixed on a special apparatus that permits bending the paw at the talocalcanean joint in a defined and reproducible manner. As a result of this bending, a tonic extensor reflex was triggered in the thigh muscle. The electrical activity of the muscle during contraction was registered and the individual pulses were counted. The extension (duration 5 s) was repeated at intervals of 1 min. After a constant number of pulses had been reached (constituting the control value), the test substance was administered intravenously. The number of pulses after administration was related to the previous value. For each dose investigated, four to six animals were used. The ED_{50} was the dose that reduced the muscle activity to half, on the basis of the initial value.

Apomorphine Antagonistic Effect. Mandibular movements were triggered in groups of four to six female Sprague–Dawley rats by subcutaneous administration of 1.5 mg of apomorphine/kg and were recorded by means of implanted electrodes (mandibulogram as described by Kubacki).[26] The test substances were administered orally 90 min prior to apomorphine. The ED_{50} was the dose that reduced the number of jaw movements by 50% compared to placebo-treated control animals.

Antitryptamine Action. Tryptamine hydrochloride (16 mg/kg administered intravenously) regularly causes the following symptoms in rats: clonic front paw movements, back arching and retropulsion, as well as jaw movements.[27] The test substances were administered intraperitoneally 30 min before the tryptamine. The criterion for whether a compound had an effect was whether the front paw movements remained absent over a period of observation of 5 min after the injection of tryptamine. The mean inhibitory dose (ED_{50}) was determined, by means of Probit analysis, as the dose that prevented the symptom in half the animals.

Cataleptogenic Effect. Female Sprague–Dawley rats (body weight 150–200 g) were given the substances intraperitoneally. n/dose = 10. At 60, 120, and 240 min after administration the animals were checked for the presence of catalepsy. The force paws of the animal were put on a horizontal rod (8 cm above ground). The animal was regarded as cataleptic, if it maintained this position for at least 15 s.

In the tests described the ED_{50} values (with 95% confidence limits) were determined by means of Probit or linear regression analysis. Where this was not possible, the ED values were estimated graphically.

Crystallography. All intensity data were measured on a Syntex $P2_1$ diffractometer using Cu Kα radiation with graphite monochromator (λ = 1.541 78 Å) at 295 K. Data: ($\sin\theta/\lambda_{max}$ = 0.547 for (*E*)-**12** and (*Z*)-**13** and 0.511 Å^{-1} for (*Z*)-**12**); $\theta/2\theta$ data collection; scan width 3.2° for (*E*)-**12** and (*Z*)-**12** and 3.6° in θ for (*Z*)-**13**; measuring time 4–30° min^{-1} for (*E*)-**12** and 2–30° min^{-1} for (*Z*)-**12** and *Z*-(**13**), the profiles of the differential scans being fitted for (*E*)-**12** with a program from Clegg[28] and for (*Z*)-**12** and (*Z*)-**13** with an algorithm due to Lehman and Larson[29] and with a program developed by Schwarzenbach;[30] lattice parameters measured with 25 reflections up to 21° for (*E*)-**12**, 14° for (*Z*)-**12**, and 15° for (*Z*)-**13** in θ using Cu radiation: range of hkl, $+h,+k,+l$ for (*E*)-**12**, $+h,+k,\pm l$ for (*Z*)-**12** and (*Z*)-**13**: one standard reflection for each measurement (2, 1, 2 for (*E*)-**12**, 2, 0, −2 for (*Z*)-**12**, and 4, 2, −3 for (*Z*)-**13**) monitored every 26 reflections with intensity variations of 1.9% for (*E*)-**12**, 3.1% for (*Z*)-**12**, and 1.6% for (*Z*)-**13**; corrections for Lorentz and polarization but not for absorption applied; for (*E*)-**12** 1346 reflections measured and unique, 59 unobserved (criterion $4\sigma(F)$, for (*Z*)-**12** 4437 reflections measured, 4285 unique [R_{int} = 0.015: $R_{int} = (\sum(N\sum[w(F(\text{mean}) - F)^2])/\sum((N-1)\sum[wF^2]))^{1/2}$ where the inner summations are over the N equivalent reflections averaged to give F(mean) and the outer summations are over all unique observed reflections with weights w], 1331 unobserved (criterion $4\sigma(F)$ and −2, 0, 2, −2, 1, 2, and 0, 1, 3), and for (*Z*)-**13** 2487 reflections measured, 2437 unique (R_{int} = 0.001), 389 unobserved (criterion $4\sigma(F)$ and −1, 1, 2). Weissenberg photographs clearly indicated for (*E*)-**12** the orthorhombic space group $P2_12_12_1$ (for hOO $h = 2n + 1$, for OkO $k = 2n + 1$ and for OOl $l = 2n + 1$ were absent), for (*Z*)-**12** the monoclinic space group $P2/c$ (for hOl $l = 2n + 1$ were absent), and for (*Z*)-**13** the monoclinic space group $C2/c$ (for hkl $h + k = 2n + 1$ and hOl $h, l = 2n + 1$ were absent). We could exclude $P2_1/c$ for (*Z*)-**12** because $F/\sigma(F)$ is 393.5 for 010, 9.3 for 030, 5.8

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for 050, 3.4 for 070, and 2.2 for 090.

The structures were solved by direct methods and refined by a block-cascade least-squares method using the program SHELXTL[15] on a Data General ECLIPSE S200 mini computer.

In structures (*Z*)-**12** and (*Z*)-**13** we found disordered solvent molecules of ethanol. Since all these ethanol molecules have their middle carbon atom on a crystallographic 2-fold axis, this atom has half-occupancy. As a consequence, the methyl carbon and the hydroxyl oxygen, related to this 2-fold axis, are not individually assignable and hence all atoms were treated as carbons. In (*Z*)-**12** there are two independant ethanol molecules [molecule 1, C(1E), CO(1E); molecule 2, C(2E), CO(2E)] and in (*Z*)-**13** one single ethanol (C(E) and CO(E)) of this type.

H atoms initially put in at calculated positions were constrained to give C–H = 0.96 Å, H–C–H = 109.5°, rigid CH_3 groups, riding CH_2, and CH groups with equal C–C–H angles. For C, N, and O atoms anisotropic thermal parameters were refined. For (*E*)-**12** we refined an isotropic temperature factor for the hydrogens of each CH, CH_2, and CH_3 groups; for (*Z*)-**12** and (*Z*)-**13** a common isotropic temperature factor for all H atoms was refined. In all cases the function minimized was $\sum w(|F_o| - |F_c|)^2$ where the weights w are calculated on the basis of counting statistics with a term g included for random error $w = (\sigma^2(F) + gF^2)^{-1}$ (g: for (*E*)-**12**, 0.00018; for (*Z*)-**12**, 0.0011; for (*Z*)-**13**, 0.001). The extinctions were corrected with an empirical extinction parameter x, where F_c becomes $F_c' = F_c/[1 + 0.002F_c^2/\sin(2\theta)]^{1/4}$ (x: for (*E*)-**12**, 86 (10) × 10^{-4}; for (*Z*)-**12**, 11 (3) × 10^{-4}; for (*Z*)-**13**, 11 (4) × 10^{-4}. Convergences were achieved and a weighting scheme was applied to obtain a flat variance in terms of sin θ and the magnitude of F_o. Scattering factors were taken from ref 31. Ratio of maximum least-squares shift to error in final refinement cycles: for (*E*)-**12** and (*Z*)-**13**, 0.03; for (*Z*)-**12**, 0.2. Maximum height in final difference Fourier synthesis: for (*E*)-**12**, 0.14 (1.18 Å apart from N(4)); for (*Z*)-**12**, 0.57 (1.17 Å apart from C(1E)); for (*Z*)-**13**, 0.81 e·Å^{-3} (0.52 Å apart from C(E)).

Registry No. **9** (R_1 = R_2 = H), 1143-50-6; **9** (R_1 = 2-CH_3, R_2 = H), 77047-17-7; **9** (R_1 = 3-CH_3, R_2 = H), 1218-70-8; **9** (R_1 = 2-Cl, R_2 = H), 786-87-8; **9** (R_1 = 3-Cl, R_2 = H), 62633-51-6; **9** (R_1 = H, R_2 = 8-Cl), 1147-14-4; (*E*)-**10**, 77042-88-7; (*Z*)-**10**, 77042-87-6; (*E*)-**11**, 77042-86-5; (*Z*)-**11**, 77042-85-4; (*E*)-**12**, 77046-86-7; (*Z*)-**12**, 77041-54-4; (*E*)-**13**, 77046-90-3; (*Z*)-**13**, 77046-89-0; (*E*)-**14**, 77046-88-9; (*Z*)-**14**, 77046-87-8; (*E*)-**15**, 77041-70-4; (*Z*)-**15**, 77041-69-1; (*E*)-**16** (3-chloro isomer), 77074-72-7; (*Z*)-**16** (3-chloro isomer), 77074-71-6; (*E*)-**16** (8-chloro isomer), 77041-72-6; (*Z*)-**16** (8-chloro isomer), 77041-71-5; (*E*)-**17**, 77042-09-2; (*Z*)-**17**, 77042-08-1; (*E*)-**18**, 77042-11-6; (*Z*)-**18**, 77042-10-5; (*E*)-**19**, 77042-07-0; (*Z*)-**19**, 77042-06-9; (*E*)-**20**, 77042-77-4; (*Z*)-**20**, 77042-76-3; (*E*)-**21**, 77042-82-1; (*Z*)-**21**, 77042-81-0; (*E*)-**22**, 77042-79-6; (*Z*)-**22**, 77042-78-5; (*E*)-**23**, 103002-93-3; (*Z*)-**23**, 103002-97-7; (*E*)-**24**, 103002-94-4; (*Z*)-**24**, 103002-98-8; (*E*)-**25**, 83889-04-7; (*Z*)-**25**, 83889-03-6; (*E*)-**26**, 83889-15-0; (*Z*)-**26**, 83889-14-9; (*E*)-**27**, 77042-69-4; (*Z*)-**27**, 77042-68-3; (*E*)-**28**, 77042-15-0; (*Z*)-**28**, 77042-14-9; (*E*)-**29**, 77042-17-2; (*Z*)-**29**, 77042-16-1; (*E*)-**30**, 77042-67-2; (*Z*)-**30**, 77042-66-1; (*E*)-**31**, 77042-49-0; (*Z*)-**31**, 77042-48-9; (*E*)-**32**, 77042-38-7; (*Z*)-**32**, 77042-37-6; (*E*)-**33**, 77042-24-1; (*Z*)-**33**, 77042-23-0; (*E*)-**34**, 77042-61-6; (*Z*)-**34**, 77042-60-5; (*E*)-**35**, 77042-20-7; (*Z*)-**35**, 77046-91-4; (*E*)-**36**, 77042-55-8; (*Z*)-**36**, 77042-54-7; (*E*)-**37**, 77042-32-1; (*Z*)-**37**, 77042-31-0; (*E*)-**38**, 77042-40-1; (*Z*)-**38**, 77042-39-8; (*E*)-**39**, 77042-75-2; (*Z*)-**39**, 77042-74-1; (*E*)-**40**, 77042-59-2; (*Z*)-**40**, 77042-58-1; (*E*)-**41**, 77042-34-3; (*Z*)-**41**, 77042-33-2; (*E*)-**42**, 77042-30-9; (*Z*)-**42**, 77042-29-6; (*E*)-**43**, 77042-36-5; (*Z*)-**43**, 77042-35-4; (*E*)-**44**, 103002-95-5; (*Z*)-**44**, 103002-99-9; (*E*)-**45**, 103002-96-6; (*Z*)-**45**, 103003-00-5; (*E*)-**46**, 77042-42-3; (*Z*)-**46**, 77042-41-2; (*E*)-**47**, 77042-44-5; (*Z*)-**47**, 77042-43-4; (*E*)-**48**, 77042-71-8; (*Z*)-**48**, 77042-70-7; (*E*)-**49**, 77042-84-3; (*Z*)-**49**, 77042-83-2; (*E*)-**50**, 77042-73-0; (*Z*)-**50**, 77042-72-9; (*E*)-**51**, 77046-92-5; (*Z*)-**51**, 77042-47-8; *N*-methylpiperazine, 109-01-3; diethyl(cyanomethyl)phosphonate, 2537-48-6; 2-methylanthraquinone, 84-54-8; (*E*)-(2-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77047-19-9; (*Z*)-(2-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77047-18-8; (*E*)-(3-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77047-14-4;, 77047-14-4; (*Z*)-(3-methyl-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)-acetonitrile, 77047-13-3; (*E*)-(2-chloro-5,6-dihydro-11*H*-dibenz-[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77047-05-3; (*Z*)-(2-chloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)-acetonitrile, 77047-04-2; 3-(2-chloroethyl)oxazolidin-2-one, 2508-01-2; piperazine, 110-85-0; 2-chloroanthraquinone, 131-09-9; (*E*)-(3-chloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77043-19-7; (*Z*)-(3-chloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77043-18-6; (*E*)-(8-chloro-5,6-dihydro-11*H*-dibenz[*b*,*e*]azepin-6-on-11-ylidene)-acetonitrile, 77043-21-1; (*Z*)-(8-chloro-5,6-dihydro-11*H*-dibenz-[*b*,*e*]azepin-6-on-11-ylidene)acetonitrile, 77043-20-0; 1-ethylpiperazine, 5308-25-8; 2-(1-piperazinyl)ethanol, 103-76-4; 1,3-dimethylpiperazine, 22317-01-7; 1,2-dimethylpiperazine, 25057-77-6; 1-methylhexahydro-1,4-diazepine, 4318-37-0; *N*,*N*-dimethylethylenediamine, 108-00-9; ethylenediamine, 107-15-3; trimethylethylenediamine, 142-25-6; *N*,*N*-dimethylethylenediamine, 108-00-9; *N*,*N*-dimethylpropylenediamine, 109-55-7; 1-(2-aminoethyl)piperidine, 27578-60-5; 1-(2-aminoethyl)-4-methylpiperidine, 934-98-5; 4-(2-aminoethyl)morpholine, 2038-03-1; 1-(2-aminoethyl)pyrrolidine, 7154-73-6; 4-amino-1-methylpiperidine, 41838-46-4; 4-(methylamino)-1-methylpiperidine, 73579-08-5; 3-(aminomethyl)-1-methylpiperidine, 14613-37-7; 2-(aminomethyl)-1-ethylpyrrolidine, 26116-12-1; 4-methylpiperidine, 626-58-4; morpholine, 110-91-8; 4-piperidinol, 5382-16-1; 2-(hydroxymethyl)morpholine, 103003-01-6; 4-phenyl-4-piperidinol, 40807-61-2; 2-(dimethylamino)ethanol, 108-01-0; 3-(dimethylamino)propanol, 3179-63-3; 3-(hydroxymethyl)-1-methylpiperidine, 7583-53-1; 3-(hydroxymethyl)-1-methyl-1-oxopiperidine, 103003-02-7; 2-(hydroxymethyl)-1-methylpiperidine, 20845-34-5; 1-methyl-4-piperidinol, 106-52-5.

Supplementary Material Available: Tables V–XXII listing final coordinates, thermal parameters, bond lengths, bond angles, and torsion angles with standard deviations for (*E*)-**12**, (*Z*)-**12**, and (*Z*)-**13** and Table XXIII showing distance variations of N(4)–Ar(1) and N(4)–Ar(2) as a function of rotations around bond C(4)–N(3) for (*Z*)-**12** m1 (15 pages). Ordering information is given on any current masthead page.

(31) International Tables for X-ray Crystallography Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 99 and 149.