are no hydrogen bonds between bases. All hydrogen bonds are between base and sugar. There is an intramolecular hydrogen bond between O-5′ and N-3 (N-4). This intramolecular interaction has been observed in purine nucleosides in the syn conformation, and it is thought to add to the stability of the molecule in its present conformation.[20] The exocyclic atom N-6 (N-7) donates its hydrogens to O-5′ and O-2′, whereas N-7 (N-1) accepts the hydrogen from O-2′ and N-1 (N-6) accepts a hydrogen from O-3′ is the only possible hydrogen bond acceptor that is not involved in the entire scheme. No significant "base stacking" is present in the molecule packing.

Acknowledgment. We wish to thank Professor M. Sundaralingam for making available the coordinates of formycin. This research was supported primarily from Grant No. CA12391 of the U. S. Public Health Service, National Institutes of Health, and in part by Grant No. C72-3710, Research Contract with the Division of Cancer Treatment, NIH.

Supplementary Material Available. Table I and a listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-62.

References

(1) R. K. Robins, L. B. Townsend, F. C. Cassidy, J. F. Gerster, A. F. Lewis, and R. L. Miller, *J. Heterocycl. Chem.*, **3**, 110 (1966).
(2) G. Koyama, K. Meada, J. Umezawa, and Y. Itake, *Tetrahedron Lett.*, 597 (1966).
(3) M. Hori, E. Ito, T. Takita, G. Koyama, and H. Umezawa, *J. Antibiot., Ser. A*, **17**, 96 (1964).
(4) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.
(5) T. Odaka, K. Takizawa, K. Yamaura, and T. Yamamoto, *Jap. J. Exp. Med.*, **39**, 327 (1969).
(6) D. C. Ward, A. Cerami, E. Reich, G. Acs, and L. Altewerger, *J. Biol. Chem.*, **244**, 3243 (1969).
(7) M. Ikehara, K. Murao, F. Harada, and S. Nishimura, *Biochem. Biophys. Acta*, **174**, 696 (1968).
(8) T. Sawa, Y. Fukagawa, U. Shimauchi, K. Ito, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot., Ser. A*, **18**, 259 (1965).
(9) T. Sawa, Y. Fukagawa, I. Homma, T. Takeuchi, and H. Umezawa, *ibid.*, **20**, 317 (1967).
(10) K. K. Ogilve, L. Slotin, and P. Rheault, *Biochem. Biophys. Res. Commun.*, **45**, 297 (1971).
(11) M. Sundaralingham, *Biochemistry*, in press.
(12) M-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Heterocycl. Chem.*, **10**, 427 (1973).
(13) P. Main, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(14) W. R. Busing, K. A. Martin, and H. A. Levy, Oak Ridge National Laboratory Report ORNL-TM-305, Oak Ridge, Tenn., 1962.
(15) D. T. Cromer and J. T. Waber, *Acta Chrystallogr.*, **18**, 104 (1965).
(16) R. F. Steward, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(17) C. K. Johnson, Oak Ridge National Laboratory Report ORNL-3794, Oak Ridge, Tenn., 1965.
(18) S. T. Rao and M. Sundaralingam, *J. Amer. Chem. Soc.*, **92**, 4963 (1970).
(19) M. Sundaralingam, *Biopolymers*, **7**, 821 (1969).
(20) D. C. Ward and T. Reich, *Proc. Nat. Acad. Sci. U. S.*, **61**, 1494 (1968).
(21) M. Sundaralingam, *Symp. Quant. Chem. Biochem., 5th*, 417 (1973).
(22) M-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Heterocycl. Chem.*, **10**, 431 (1973).
(23) R. A. Long, L. B. Townsend, D. W. Miles, H. Eyring, and R. K. Robins, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 25, 1971.

Antidepressant Agents. 1. Chemistry and Pharmacology of Amino-Substituted Spiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,1′-cycloalkanes]

B. Carnmalm, E. Jacupovic, L. Johansson, T. de Paulis, S. Rämsby, N. E. Stjernström,*,†

Department of Organic Chemistry

A. L. Renyi, S. B. Ross, and S. O. Ögren

Department of Pharmacology, Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.
Received June 4, 1973

A series of spiro compounds structurally related to the common tricyclic antidepressants has been tested as inhibitors of the neuronal reuptake of noradrenaline and 5-hydroxytryptamine. Also, some behavioral tests have been performed. Two of the substances, *N,N*-dimethylspiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (**11**) and *N,N*-dimethylspiro[5*H*-dibenzo[*a*,*d*]cycloheptene-5,1′-cyclohexan]-4′-amine (**18**), are very active in the NA-uptake inhibition assay. A discussion on structure–activity relationships is given.

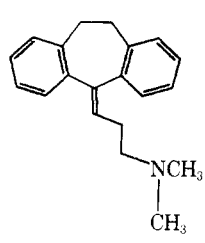
Tricyclic antidepressant agents show a variety of pharmacological properties, *i.e.*, inhibition of the presynaptic uptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT), prevention of the reserpine syndrome, anticholinergic effect, and cardiotoxic effect.[1] This lack of specificity may be explained by the multitude of possible conformations of these drug molecules. The tricyclic antidepressants consist of a condensed three-ring system connected to a three-carbon side chain which is terminated by a tertiary or a secondary amino group.[2] The side chain has a considerable degree of freedom due to rotation around the single bonds and the terminal amino group can therefore occupy a great number of positions in relation to the tricyclic skeleton.

In our search for selective antidepressants it was consequently considered to be of interest to study compounds where the terminal amino group is locked in a defined position. This was achieved by letting the side chain participate in a ring system of rigid structure.

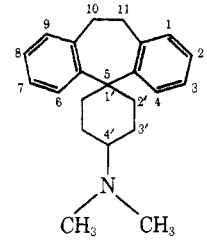
We have now synthesized a series of amino-substituted spiro[5*H*-dibenzo[*a*,*d*]cyclohexanes] and spiro[5*H*-dibenzo[*a*,*d*]cyclopentanes] in which the structural features of

†This paper is dedicated to my former professor, Alfred Burger.

amitriptyline (I) are preserved but the number of possible positions of the nitrogen atom is limited (*e.g.*, formula II).



I



II

Since there is evidence that the antidepressive action of the tricyclic agents is due to inhibition of the neuronal reuptake of noradrenaline (NA)[3,4] or 5-hydroxytryptamine (5-HT)[5,6] or both, the new compounds and a few reference drugs were examined for their inhibitory activity on the uptake of these amines in brain slices. We have also studied some of the behavioral effects of these compounds.

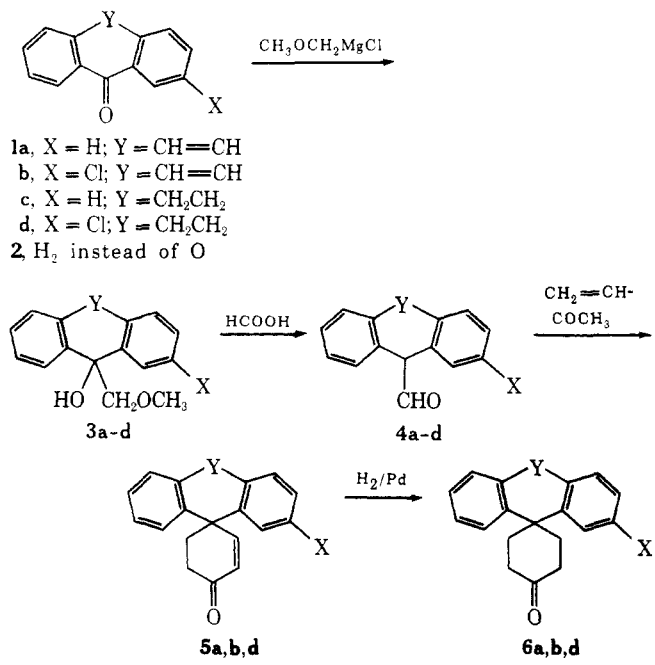
Chemistry. The crucial step in the preparation of spiro compounds is to assemble the structural unit around the quaternary carbon atom. When planning this work it seemed attractive to start with the ketones **1** or the hydrocarbons **2**.

Condensation of **1** with, *e.g.*, malodinitrile, followed by addition of hydrogen cyanide was one obvious route, but it failed at the condensation stage.

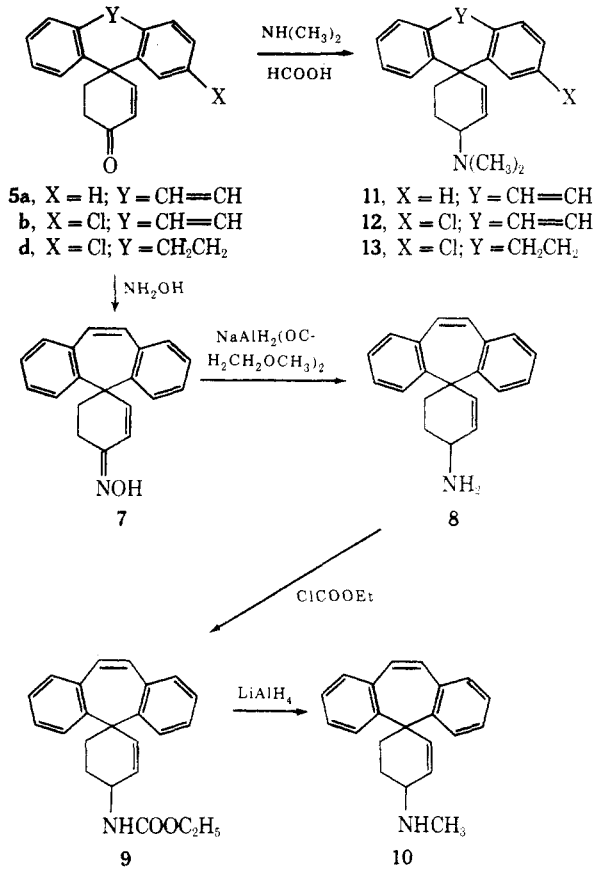
Cyanoethylation of **2**, in analogy with the preparation of a series of spiro[cyclohexane-1,9′-fluorene]-4-amino derivatives reported by Stauffer and Fancher,[7] was also unsuccessful.

A successful preparation of the spiro compounds was achieved by applying the Robinson annelation reaction to the aldehydes **4** in analogy with Zimmerman's preparation of diphenylcyclohexenone.[8] One of these aldehydes, **4a**, has been described previously in connection with rearrangements of limited preparative value.[9,10] We have found that a modification of the two-step procedure for converting ketones into carbaldehydes described by Normant and Crisan[11] is a convenient route to these starting materials (Scheme I). During the course of our work the preparation of **4c** by the same procedure has been reported by Bruderlein and Humber.[12] Salisbury has recently described the synthesis of **4a** by a different route.[13]

Scheme I



Scheme II



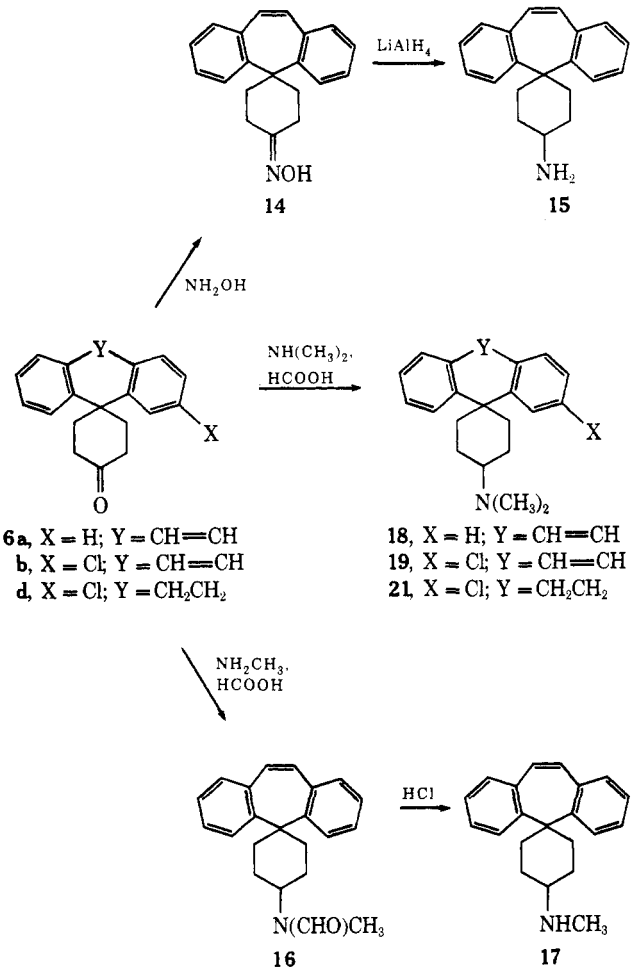
With the exception of **4c**, the aldehydes **4** underwent the annelation reaction and gave the unsaturated spiro ketones **5** in low to medium yields (Scheme I). All the reaction mixtures were rather complex and the failure with the aldehyde **4c** may be attributed to difficulties in isolating the product. Catalytic hydrogenation of the unsaturated ketones **5** gave the corresponding cyclohexanones **6**. Finally, the ketones **5** and **6** were converted to the amines **8**, **10–13** and **15**, **17–19**, **21** by using standard methods as shown in the Schemes II and III. The amine **20** was prepared from the amine **18** by catalytic hydrogenation.

The ketone **6a** was found to be a suitable starting material for the synthesis of amines with a five-membered ring. Bordwell, *et al.*,[14] have described the preparation of diphenylcyclopentanecarboxylic acid from bromodiphenylcyclohexanone using the Favorsky rearrangement. We arrived at the spirocarboxylic acid **23** by applying an analogous procedure (Scheme IV). Two types of amines were prepared from this acid: one with the amine function directly bound to the five-membered ring (**28–30**) and the other with a methylene group in between (**31** and **32**).

The primary amide **24** underwent the Hofmann rearrangement to give the methyl carbamate **27**, which was converted to the secondary amine **29**. Compound **28** was prepared from the carboxylic acid **23** using the Weinstock modification[15] of the Curtius rearrangement. The tertiary amine **30** was prepared from **28** by an Eschweiler-Clarke reaction.

Structure-Activity Relationships. The results and the

Scheme III



tive, being about equipotent to amitriptyline *in vitro*. *In vivo* both the spiroamines and most of the reference drugs showed no or very low activity.

Inhibition of the Uptake of NA. Many of the spiro compounds are as active NA-uptake inhibitors as the reference tricyclic antidepressants. The activity of the amines with a six-membered ring increases in the order of primary, secondary, tertiary **8, 10, 11** and **15, 17, 18.** For the compounds with a five-membered ring we found the secondary amines, **29** and **31,** to be the most potent.

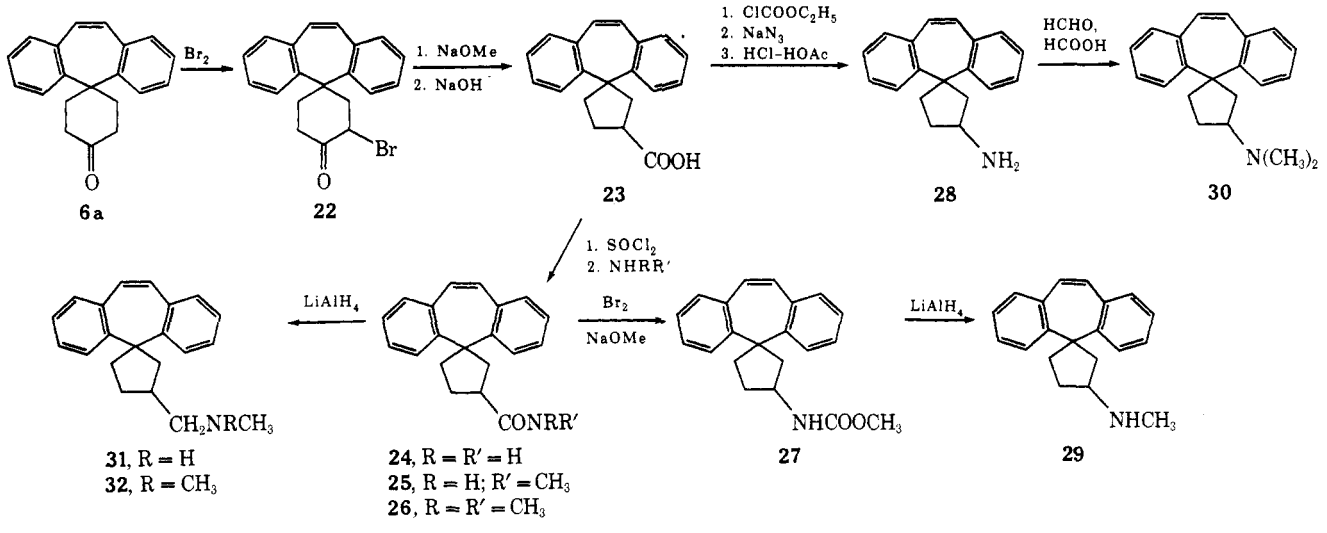
Among the tricyclic antidepressants the secondary amines are generally considered the most active. Thus Salama, *et al.*,[16] found that the secondary amines in the dihydrodibenzazepine and the dibenzocycloheptadiene series are more potent inhibitors in brain slices than the corresponding primary and tertiary derivatives. However, in the dibenzocycloheptatriene series they found all three derivatives to be equipotent. In agreement with these results, our findings that the tertiary amines are the most potent compounds indicate that the secondary amino group is not necessarily the optimal structure element.

The isolated effect of a chlorine atom can be seen by comparing the three pairs **11, 12** and **18, 19** and **20, 21.** Thus chlorine substitution in the 3 position reduces the potency of the tertiary amines.

The high potency of especially the tertiary amines **11** and **18,** as well as the observation in experiments with synaptosomes‡ showing that they are competitive inhibitors of the NA uptake, indicates that these compounds fit well into receptor sites directly coupled to the NA transfer mechanism.

Structural Requirements for NA-Uptake Inhibition. It has already been pointed out by Galantay, *et al.*, that the amino group of amitriptyline can occupy a considerable number of positions, all above the convex side of the surface defined by the tricyclic skeleton.[17] These positions may be described by a space, the coordinates of which are

Scheme IV



structures of the tested amines are summarized in Table I. The following discussion concerns mainly the *in vitro* data.

Inhibition of the Uptake of 5-HT. The spiro compounds inhibit the active transport of 5-HT *in vitro* in the same concentration range as some of the reference compounds, *e.g.*, protriptyline and nortriptyline, but they are much weaker inhibitors than chlorimipramine. Of the new compounds, **13,** which contains chlorine, is the most active, being about equipotent to amitriptyline *in vitro*. *In vivo* both the spiroamines and most of the reference drugs showed no or very low activity.

Inhibition of the Uptake of NA. Many of the spiro compounds are as active NA-uptake inhibitors as the reference tricyclic antidepressants. The activity of the amines with a six-membered ring increases in the order of primary, secondary, tertiary **8, 10, 11** and **15, 17, 18.** For the compounds with a five-membered ring we found the secondary amines, **29** and **31,** to be the most potent.

Among the tricyclic antidepressants the secondary amines are generally considered the most active. Thus Salama, *et al.*,[16] found that the secondary amines in the dihydrodibenzazepine and the dibenzocycloheptadiene series are more potent inhibitors in brain slices than the corresponding primary and tertiary derivatives. However, in the dibenzocycloheptatriene series they found all three derivatives to be equipotent. In agreement with these results, our findings that the tertiary amines are the most potent compounds indicate that the secondary amino group is not necessarily the optimal structure element.

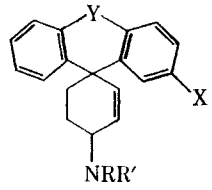
The isolated effect of a chlorine atom can be seen by comparing the three pairs **11, 12** and **18, 19** and **20, 21.** Thus chlorine substitution in the 3 position reduces the potency of the tertiary amines.

The high potency of especially the tertiary amines **11** and **18,** as well as the observation in experiments with synaptosomes‡ showing that they are competitive inhibitors of the NA uptake, indicates that these compounds fit well into receptor sites directly coupled to the NA transfer mechanism.

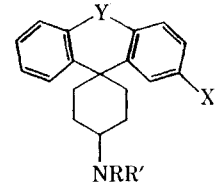
Structural Requirements for NA-Uptake Inhibition. It has already been pointed out by Galantay, *et al.*, that the amino group of amitriptyline can occupy a considerable number of positions, all above the convex side of the surface defined by the tricyclic skeleton.[17] These positions may be described by a space, the coordinates of which are defined by the mobility and bulk of the amino group. An examination of models reveals that this space is confined in the case of the six-membered ring compounds while the corresponding space of amitriptyline and other tricyclic agents is much wider and unrestricted. The two spaces overlap as illustrated in Figure 1 and this indicates that there is an optimal structural requirement for inhibition of NA uptake, which should have its counterpart in the

‡S. O. Ogren, unpublished results.

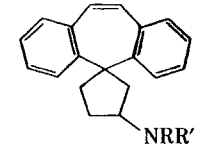
Table I



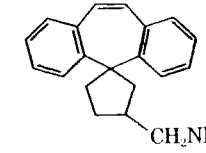
A



B



C



D

Compd no.		X	Y	R	R[1]	Inhibition of the uptake *In vitro*, ED_{50}, μM: NA	5-HT	*In vivo*, ED_{50}, mg/kg ip: NA	5-HT	Potentiation of: Dopa	5-HTP	Decrease in motor activity, ED_{50}, mg/kg	Mydriatic effect, PD_{200}, mg/kg iv	Toxicity, LD_{50}, mg/kg iv
8	A	H	CH=CH	H	H	13	18	>40	>40	1	0	25	>25	23
10	A	H	CH=CH	H	CH_3	2.2	15	10	>40	1.5	0	13	2	22
11	A	H	CH=CH	CH_3	CH_3	0.30	12	8	>40	2	0	27	<1	30
12	A	Cl	CH=CH	CH_3	CH_3	6.7	19	>40	>40	1	0	6	15	22
13	A	Cl	CH_2CH_2	CH_3	CH_3	>27	2.7	>40	>40	1	0	4	>40	>40
15	B	H	CH=CH	H	H	13	5.1	>40	>40	2	0	50	1.5	32
17	B	H	CH=CH	H	CH_3	3.5	18	>40	>40	1.5	0	35	3.5	60
18	B	H	CH=CH	CH_3	CH_3	0.9	12	5	>40	2	0	27	1	32
19	B	Cl	CH=CH	CH_3	CH_3	4.0	11	>40	>40	1	0	12	18	18
20	B	H	CH_2CH_2	CH_3	CH_3	2.9	8.8	40	>40	2	0	35	1.5	23
21	B	Cl	CH_2CH_2	CH_3	CH_3	4.0	13	>40	>40	1	0	14	15	27
28	C	H	CH=CH	H	H	23	5.0	>40	>40	2	0	55	17	35
29	C	H	CH=CH	H	CH_3	7.7	5.1	>40	>40	2	0	38	17	30
30	C	H	CH=CH	CH_3	CH_3	26	7.9	>40	>40	1.5	0	>50	0.3	30
31	D	H	CH=CH	H	CH_3	4.6	7.7	8	>40	2.5	0	25	3	30
32	D	H	CH=CH	CH_3	CH_3	28	14	>40	>40	1.5	0	>50	3.5	30
Protriptyline						2.0	13	10	>40	2	0	>50	<1	30
N-Methylprotriptyline						2.5	7.6	10	>40	2	0	40	2	27
Nortriptyline						0.33	6.7	20	>40	3	0	>50	13	17
Amitriptyline						4.8	2.6	7	36	2	0	28	2.5	16
Chlorimipramine						0.86	0.1	35	7	3	E	60	>25	30

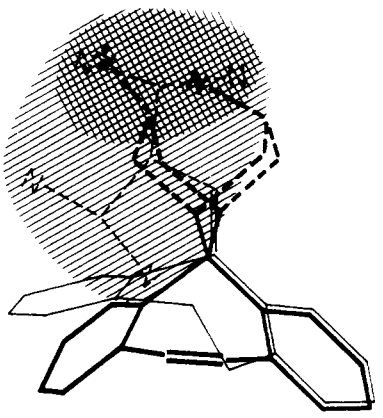


Figure 1. The "amine space" of *N,N*-dimethylspiro[5*H*-dibenzo-[*a,d*]cycloheptene-5,1'-cyclohexan]-4'-amine (**18**, heavy lines) on which the "amine space" of amitriptyline (fine lines) is superimposed. One aromatic ring and the carbon atom at the 5 position are common to the two molecules. For each structure some different conformations are depicted as dashed lines.

hypothetical receptor. However, this simplified discussion is only dealing with the stereochemistry of the terminal amino group. Other steric factors and electronic features are not taken into consideration. A similar overlap cannot be observed among the five-membered ring compounds **28–30**, which still possess a considerable activity. In this series the secondary amine **29** is the most active compound, indicating that other factors should be taken into account during further elucidations of the structure–activity relationship.

Potentiation of L-Dopa and 5-Hydroxytryptophan. The syndromes produced by L-dopa and 5-hydroxytryptophan (5-HTP) are potentiated by inhibitors of NA and 5-HT, respectively.[18] There is a rough correlation between inhibition of the uptake and the degree of potentiation of L-dopa and 5-HTP.

Other Pharmacological Effects. All new compounds decrease motor activity in mice. With the exception of the chlorine-containing compounds, this sedative property is in the same range as that found in the amitriptyline series.

Compounds **12, 13, 19,** and **21,** all with a chlorine atom bound to one of the benzene rings, have neuroleptic properties, *e.g.*, strong sedative effect and inhibition of the conditioned avoidance response and of the amphetamine induced hyperactivity, both at a dose of 5–10 mg/kg ip, about the same as for chlorpromazine.

The anticholinergic activity *in vivo* is generally strong, but substitution with a chlorine atom in the 3 position diminishes this activity considerably.

The compounds are all devoid of anticonvulsant properties at nontoxic doses. The intravenous toxicity is in the same range as that of the reference compounds.

Experimental Section

Pharmacology. The compounds were administered as salts intraperitoneally (ip) or intravenously (iv) to male albino mice (the NMRI strain) weighing 18–22 g.

Inhibition of the uptake of noradrenaline and of 5-hydroxytryptamine was examined both *in vitro* and *in vivo* according to the methods of Ross, *et al.*,[18] by recording simultaneously the uptake of [^{3}H]NA and of [^{14}C]-5-HT. In the *in vitro* method slices of mouse midbrain were preincubated for 5 min with solutions of the compound to be tested and then incubated for 5 min with a 1×10^{-7} *M* solution of [^{3}H]NA and [^{14}C]-5-HT. In the *in vivo* experiments the compound was injected ip 0.5 hr before the sacrifice of the mice and then brain slices were incubated as above with [^{3}H]NA and [^{14}C]-5-HT. Four determinations were performed for each concentration or dose. The values for 50% decrease of the active uptake (EC_{50}, ED_{50}) were found graphically. The active amine uptake was defined as that inhibited by a high concentration (3×10^{-5} *M*) of cocaine.

Potentiation of the effects induced by L-Dopa was tested in mice treated with pargyline, 40 mg/kg po, 16 hr prior to the test.[19] The test drug (10 mg/kg ip) was injected 1 hr prior to 100 mg/kg ip of L-Dopa. The strength of the L-Dopa syndrome was recorded on a scale from +1 to +3. L-Dopa alone causes slight piloerection, salivation, and irritability scored as +1. In the full syndrome, +3, these symptoms are more pronounced and, in addition, there is also jumping, squeaking, and fighting. Four groups, each consisting of three mice, were used. Desmethylimipramine, as standard, regularly gives +3 at the dose of 10 mg/kg ip.

The syndrome produced by potentiation of the effect of DL-5-hydroxytryptophan (5-HTP) consists of head twitching, tremor, and abduction of hind legs.[18] The test drug (25 mg/kg ip) was given to ten mice 1 hr before 5-HTP (90 mg/kg iv) and the presence (E) or the absence (0) of the syndrome was scored.

Motor activity was recorded for 10 min in a locomotion cage 1 hr after intraperitoneal injection. The animals were tested individually and the motor activity was compared with controls run simultaneously. Four doses with 12 animals per dose were used for the determination of the ED_{50}.

Peripheral parasympatholytic effect was tested in mice by observing the mydriatic effect after intravenous injection[20] (four doses with three animals per dose). PD_{200} refers to the dose which increases the pupil width by 200%.

Acute toxicity was tested by the intravenous route of administration. The animals were observed for 24 hr. The LD_{50} values were obtained graphically from dose–response curves based on four doses with three animals per dose.

The anticonvulsive effects were evaluated by the maximal electroshock test and the pentylenetetrazole test.[21]

Chemistry. Melting points were determined on a microscope hot stage (Leitz) and are uncorrected. Mass spectra were recorded at 70 eV on a LKB 9000 spectrometer. Nmr spectra were obtained in $CDCl_3$ solution on a Varian A-60A instrument operating at 37°. Chemical shifts are expressed as δ values (ppm) from tetramethylsilane. Analyses were performed by Dr A. Bernhardt, Mühlheim, Germany, and by Professor K. J. Karrman, Lund, Sweden, and are within ±0.4% of the calculated values if not otherwise stated. Thin-layer chromatography was performed on precoated Merck Silica Gel F_{254} plates.

Preparation of the Glycol Monoethers 3. 5-Methoxymethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (3a). Magnesium turnings (48.6 g, 2.0 mol) were covered with 100 ml of dry THF and reacted with 2.5 g of $HgCl_2$ under dry N_2 atmosphere. After 5 min 150 ml (2.0 mol) of freshly distilled CH_3OCH_2Cl in 150 ml of dry THF was added dropwise during 1 hr. As soon as the reaction had started the mixture was rapidly cooled to −5 to −10°, and this temperature was maintained throughout the rest of the addition. Stirring was continued for 1 hr; then 206 g (1.0 mol) of 5*H*-dibenzo[*a,d*]cyclohepten-5-one (**1a**)[22] in 1 l. of dry THF was added dropwise. One hour after the addition was completed the deep purple solution was allowed to slowly reach room temperature. The reaction mixture was poured into 1.5 l. of ice–water containing 200 g of NH_4Cl. An oil separated which on working up gave 226 g of light yellow crystals. Recrystallization from 800 ml of EtOH gave 203 g (81%) of the glycol ether **3a**: mp 86–87° (recrystallized twice from EtOH); nmr 8.0 (m, 2, 4,6-Ar H), 7.5 (m, 6, Ar H), 7.0 (s, 2, CH=CH), 3.9 (s, 1, OH), 3.7 (s, 2, CH_2OCH_3), and 3.0 (s, 3, OCH_3). *Anal.* ($C_{17}H_{16}O_2$) C, H, O.

3-Chloro-5-methoxymethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (3b) was prepared as described for compound **3a** but with methylal (formaldehyde dimethylacetal) instead of THF as solvent.[23] The starting ketone **1b**[24] had poor solubility in dry methylal and was added as a finely ground solid portionwise during 1 hr. The yield of **3b** was 82%, mp 92–93° (from EtOH). *Anal.* ($C_{17}H_{15}ClO_2$) C, H, Cl, O.

10,11-Dihydro-5-methoxymethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (3c). This compound was prepared from the ketone **1c** as described for compound **3a**: yield 84%; bp 142–145° (0.06 mm) [lit.[12] bp 143–144° (0.05 mm)]; $n^{25}D$ 1.5962.

3-Chloro-10,11-dihydro-5-methoxymethyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (3d) was prepared from **1d**[24] as described for compound **3a**. The desired product was obtained in 89% yield as a viscous oil: bp 186–187° (0.05 mm). Tlc (*i*-Pr_2O) revealed a minor amount of an impurity (R_f 0.5) together with the compound **3d** (R_f 0.6): nmr 7.9 (m, 2, Ar H), 7.1 (m, 5, Ar H), 3.9 (s, 2, CH_2OCH_3), 3.7 (s, 1, OH), 3.2 (s, 3, OCH_3). The glycol ether was used without further purification.

Preparation of the Aldehydes 4. 5*H*-Dibenzo[*a,d*]cyclohep-

tene-5-carboxaldehyde (4a). To 350 ml of HCOOH (98%) at 50°, 166 g (0.66 mol) of the glycol ether **3a** was rapidly added with stirring. When the temperature was raised to 60° the solution became clear (in 10 min) and then 10 ml of 0.1 *N* H_2SO_4 was added. After additional stirring for 5 min the solution was chilled to 30° and poured into a well-stirred mixture of ice-water (1.5 l.) and 200 ml of 2 *N* H_2SO_4. After 2 hr of stirring the precipitated aldehyde was collected. Recrystallization from 500 ml of Et_2O-*i*-Pr_2O (1:1) afforded 71 g (49%), mp 109.5–110.5° (lit.[13] mp 109–111°). The 2,4-dinitrophenylhydrazone had mp 215–217° (lit.[10] mp 221–223°).

3-Chloro-5*H*-dibenzo[*a,d*]cycloheptene-5-carboxaldehyde (4b) was prepared as described for compound **4a** from the glycol ether **3b** in 51% yield: mp 133–134° (from *i*-Pr_2O). *Anal.* ($C_{16}H_{11}ClO$) C, H, Cl, O.

10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-carboxaldehyde (4c) was prepared as described for compound **4a** except that the HCOOH solution was heated under reflux for 30 min: yield of **4c**, 54%; mp 75–77° (from Et_2O) (lit.[12] mp 76–77°). The 2,4-dinitrophenylhydrazone had mp 218–220° (from $CHCl_3$) [lit.[12] mp 217° (HOAc)]. *Anal.* ($C_{22}H_{18}N_4O_4$) C, H, N, O.

3-Chloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-carboxaldehyde (4d). The glycol ether **3d** (20.0 g, 0.07 mol) was added to 150 ml of 98% HCOOH and heated under reflux. After 5 min 10 ml of 2 *M* H_2SO_4 was added dropwise and the solution heated another 15 min. An oil separated on cooling to 0° and crystallized on standing. Washing with cold Et_2O and recrystallization from MeCN gave 14.6 g (83%) of the aldehyde: mp 144–146°; nmr 9.8 (s, 1, CHO), 6.9–7.3 (m, 7, Ar H), 4.5 (s, 1, 5-H), 2.9 (m, 4, 10,11-CH_2CH_2). *Anal.* ($C_{16}H_{13}ClO$) C, H, Cl.

Preparation of the Spiro Ketones 5. Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-one (5a). To 33 g (0.15 mol) of the aldehyde **4a** and 11 g (0.16 mol) of freshly distilled methyl vinyl ketone in 250 ml of dry THF, 10 ml of 10% ethanolic KOH was added during 1 hr at 10° under N_2 atmosphere. After 3 hr at ambient temperature 200 ml of water and 1 l. of Et_2O were added and the mixture was neutralized with 2 *M* HCl. Washing (H_2O), drying (Na_2SO_4), and evaporation gave 40.8 g of a product which did not crystallize. The crude product was shown by tlc (*i*-Pr_2O–hexane, 1:1) to consist of at least three components. The starting material had R_f 0.46 and the other two components had R_f 0.36 and 0.28. Chromatography on a column of silica gel (Merck 0.2–0.5 mm, 1 kg, diameter 5.6 cm, constructed in *i*-Pr_2O) with i-Pr_2O as eluent gave 18.6 g (44%) of the spiro ketone **5a**: R_f 0.28; mp 138–139° (from 500 ml of EtOH). For analyses the product was recrystallized twice from EtOH: mp 138.5–139.5°; mass spectrum 272 M^+ (100%), 230 (M − 42,[25] 27%). *Anal.* ($C_{20}H_{16}O$) C, H, O.

3-Chlorospiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-one (5b) was prepared from compound **4b** as described for compound **5a** and isolated by column chromatography on Al_2O_3 (Woelm neutral, activity II) with *i*-Pr_2O as eluent: yield 7.3 g (41%); mp 123–125° (from EtOH); mass spectrum 306 M^+ (67%), 271 (100%). *Anal.* ($C_{20}H_{15}ClO$) H, Cl, O; C: calcd, 78.30; found, 78.76.

3-Chloro-10,11-dihydrospiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4-one (5d). A solution of 5.15 g (0.020 mol) of the aldehyde **4d** and 1.68 g (0.024 mol) of freshly distilled methyl vinyl ketone in 10 ml of HMPT and 40 ml of dry THF was stirred under N_2 atmosphere. To this solution, 2.1 ml of 3 *M* ethanolic KOH was slowly added at room temperature. After 2 hr the temperature was raised to 40° and kept there for 16 hr. The mixture was cooled, neutralized with 2 *M* HCl, and extracted with C_6H_6. Tlc (C_6H_6) revealed four components of R_f 0.5 (unchanged aldehyde), 0.2 (blue spot with vanillin reagent), 0.1 (red spot), and 0.05 (brown spot). Column chromatography as described for compound **5a** with C_6H_6 instead of *i*-Pr_2O gave 2.0 g (31%) of the ketone **5d**: R_f 0.1; mp 113–114° (from EtOH); mass spectrum 308 M^+ (100%), 266 (M − 42,[25] 29%). *Anal.* ($C_{20}H_{17}ClO$) C, H, Cl, O.

Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohexan]-4′-one (6a). A solution of 17.0 g (0.062 mol) of **5a** in 200 ml of AcOH was hydrogenated over 3.0 g of 5% Pd/C at atmospheric pressure. When 1.4 l. (0.06 mol) of H_2 had been absorbed the catalyst was filtered off (Celite) from the warm solution. The filtrate was cooled giving crystals which were collected. Recrystallization from 400 ml of EtOH gave 12.3 g (72%) of the ketone **6a**, mp 164–165°. *Anal.* ($C_{20}H_{18}O$) C, H, O.

3-Chlorospiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohexan]-4′-one (6b) was prepared by the procedure described for compound **6a**: yield 1.5 g (78%); mp 132–134° (from *i*-PrOH); mass spectrum 308 M^+ (100%). *Anal.* ($C_{20}H_{17}ClO$) C, H, Cl, O.

3-Chloro-10,11-dihydrospiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohexan]-4′-one (6d) was prepared as described for compound **6a**: yield 1.7 g (72%); mp 129–131° (from *i*-PrOH); mass spectrum 310 M^+ (59%), 253 (100%). *Anal.* ($C_{20}H_{19}ClO$) H, Cl, O; C: calcd, 77.28; found, 77.83.

Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-one Oxime (7). A mixture of 10 g (0.037 mol) of the ketone **5a** and 10 g (0.144 mol) of NH_2OH·HCl, 50 ml of dry pyridine, and 50 ml of absolute EtOH was heated under reflux for 45 min. The solvent was evaporated and the residue was crystallized from EtOH–water (4:1) and then from absolute EtOH, affording 10.0 g (83%) of the oxime, mp 88–89°. The analysis and nmr revealed 1 mol of EtOH of crystallization. *Anal.* ($C_{20}H_{17}NO \cdot C_2H_5OH$) C, H, N, O.

Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (8). A solution of 6.5 g (0.022 mol) of the oxime **7** in 250 ml of dry C_6H_6 was added with stirring to 40 g of a 70% solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ in C_6H_6. After heating under reflux for 4 hr saturated Na_2SO_4 was added and the precipitate was filtered off. Ethereal HCl was added to the filtrate and the precipitate was treated with 2 *M* NaOH and extracted with Et_2O. Drying (Na_2SO_4) and evaporation gave 4.6 g (88%) of the amine as an oil. Recrystallization of the maleate from 80 ml of *i*-PrOH afforded 2.3 g (26%), mp 188–194°. *Anal.* ($C_{24}H_{23}NO_4$) C, H, N, O.

***N*-Ethoxycarbonylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (9).** ClCOOEt (2.2 g, 0.020 mol) was added dropwise during 10 min with stirring to a cooled mixture of 3.2 g (0.012 mol) of the primary amine **8** and 10 ml of 2 *M* NaOH in 20 ml of $CHCl_3$. After stirring for a further 10 min the $CHCl_3$ layer was washed (H_2O), separated, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue which was triturated with *i*-Pr_2O giving 3.2 g (78%) of compound **9**, mp 155–156°. *Anal.* ($C_{23}H_{23}NO_2$) C, H, N, O.

***N*-Methylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (10).** To a solution of 0.75 g (0.0022 mol) of the urethane **9** in 50 ml of Et_2O, 0.25 g (0.0066 mol) of $LiAlH_4$ was added and the mixture was heated under reflux for 5 hr. The excess hydride was destroyed by adding 5 ml of saturated Na_2SO_4. The hydrochloride of **10** was crystallized from EtOH–water (1:1) to give 0.5 g (72%), mp 260° dec. *Anal.* ($C_{21}H_{22}ClN$) C, H, Cl, N.

***N,N*-Dimethylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (11).** To 10 ml (0.15 mol) of dry $NHMe_2$, 2.0 g (0.030 mol) of HCOOH (98%) was added with caution at −15°. A solution of 5.0 g (0.0167 mol) of spiro ketone **5a** in 12.5 ml of DMF was added. The mixture was heated for 5 hr in a bath of 150°. After dilution with H_2O, working up *via* extractions gave the amine **11** as an oil which was purified through its picrate, mp 196–203° (from EtOH–Me_2CO, 1:2). The free base (3.4 g, 62%) was obtained: mp 67–70° (from hexane); mp (for the hydrochloride) 185–187°. *Anal.* ($C_{22}H_{23}N$) C, H, N.

3-Chloro-*N,N*-dimethylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (12). Treatment of 1.40 g (4.6 mmol) of **5b** with dimethylammonium formate in DMF at 160° for 5 hr and work up gave 1.5 g of crude product. The amine **12** was isolated by chromatography on a column of basic alumina (Woelm 160 g, activity II) constructed in C_6H_6. The amine was eluted with a C_6H_6–*i*-Pr_2O gradient to give 1.20 g (77%). The hydrochloride had mp 232–235° (from EtOH–Et_2O): mass spectrum 335 M^+ (40%), 97 (100%). *Anal.* ($C_{22}H_{23}Cl_2N$) C, H, Cl, N.

3-Chloro-10,11-dihydro-*N,N*-dimethylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohex-2′-en]-4′-amine (13). Treatment of 1.0 g (3.2 mmol) of **5d** with dimethylammonium formate in DMF as described for the preparation of **12** gave 820 mg (69%) of the hydrochloride: mp 245–246° (from EtOH–Et_2O); mass spectrum 337 M^+ (13%), 97 (100%). *Anal.* ($C_{22}H_{25}Cl_2N$) C, H, Cl, N.

Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohexan]-4′-one Oxime (14). A solution of 4 g (0.014 mol) of the ketone **6a** and 4 g (0.058 mol) of NH_2OH·HCl in 40 ml of pyridine was heated under reflux for 2 hr. The mixture was poured into 400 ml of water. The crystalline precipitate was collected and washed with H_2O. Recrystallization from MeCN gave 3.1 g (73%), mp 181–183°. *Anal.* ($C_{20}H_{19}NO$) H, N, O; C: calcd, 83.01; found, 83.52.

Spiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1′-cyclohexan]-4′-amine (15). A mixture of 3.0 g (0.01 mol) of oxime **14** and 1.5 g (0.04 mol) of $LiAlH_4$ in 300 ml of Et_2O was heated under reflux for 4 hr. The excess of hydride was destroyed by adding 10 ml of saturated Na_2SO_4. The precipitate was filtered off and from the filtrate the amine **15** was isolated as an oil. It was converted to its maleate yielding 2 g (47%): mp 199–200° (from H_2O); mass spectrum 375 M^+ (86%), 87 (M − 178, 100%). *Anal.* ($C_{24}H_{25}NO_4$) C, H, N, O.

N-Formyl-N-methylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (16). Methylammonium formate (prepared from 4 ml of anhydrous NH_2Me and 0.8 ml of 98% HCOOH) and a suspension of 2 g (0.007 mol) of spiro ketone **6a** in 5 ml of *N*-methylformamide were heated for 5 hr at 150°. The reaction mixture was diluted with C_6H_6 and then working up gave 1.86 g of the desired amide. Crystallization from 15 ml of MeOH yielded 1.2 g (52%): mp 191–194°; nmr 8.0 ppm (s, 1, CHO). *Anal.* ($C_{22}H_{23}NO$) C, H, N, O.

N-Methylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (17). A mixture of 1.5 g (0.005 mol) of the formyl compound **16** and 5 ml of concentrated HCl in 25 ml of DMSO was heated at 100° for 3 hr. Evaporation gave a residue which was dissolved in 25 ml of water, washed with C_6H_6, and then made alkaline giving 1.2 g of an oil. The malate was prepared from 0.8 g of the oil. Recrystallization from EtOH gave 0.56 g (48%), mp 184–186°. The free base **17** had mp 86.5–88°. *Anal.* ($C_{25}H_{29}NO_5$) C, H, N, O.

N,N-Dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (18). A solution of 3.40 g (0.012 mol) of **6a** in 7.7 g of DMF was added to dimethylammonium formate [from 4.2 g (0.093 mol) of $NHMe_2$, see preparation of **11**] and the mixture heated in a bath at 200° for 5 hr. After cooling 100 ml of water was added and then extractive working up gave 3.2 g (85%) of the amine **18**. An analytical sample recrystallized twice from Et_2O had mp 104–105°: mass spectrum 303 M^+ (25%), 84 (100%). The hydrochloride had mp 180–185°. *Anal.* ($C_{22}H_{25}N$) C, H, N.

3-Chloro-N,N-dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (19). Treatment of 1.75 g (5.7 mmol) of the ketone **6b** with dimethylammonium formate in DMF as described for the preparation of **18** gave 1.70 g (80%) of the hydrochloride: mp 186–190° (from EtOH–Et_2O); mass spectrum 337 M^+ (16%), 84 (100%). *Anal.* ($C_{22}H_{25}Cl_2N$) C, H, Cl, N.

10,11-Dihydro-N,N-dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (20). A mixture of 1.7 g (5 mmol) of the amine hydrochloride **18**, 0.8 g of 5% Pd/C in 150 ml of EtOH, and 1 ml of 2 *M* HCl was stirred under hydrogen at 50 kg/cm² and 60° for 2 hr. Filtration and evaporation gave 1.1 g of crystals which was recrystallized from 40 ml of *i*-PrOH giving 0.7 g (42%) of the amine **20** as its hydrochloride: mp 243–245°; mass spectrum 305 M^+ (17%), 84 (M − 219, 39%), 71 (100%); nmr 6.9–7.4 (m, 8, Ar H), 3.4 (s, 4, 10,11-CH_2CH_2), 3.1 (m, 1, 4'-CH), 2.2 [s, 6, $N(CH_3)_2$], and 1.2–2.4 (m, 8, cyclohexane-CH_2). *Anal.* ($C_{22}H_{28}ClN$) H, N, Cl; C: calcd, 77.28; found, 76.81.

3-Chloro-10,11-dihydro-N,N-dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (21). Treatment of 2.0 g (6.5 mmol) of **6d** with dimethylammonium formate in DMF as described for the preparation of **18** afforded 1.1 g (45%) of the hydrochloride of **21**: mp 270–273° (from *i*-PrOH); mass spectrum 339 M^+ (10%), 71 (100%). *Anal.* ($C_{22}H_{27}Cl_2N$) C, H, Cl, N.

Preparation of Five-Membered Spiro Compounds. 3'-Bromospiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-one (22). To a solution of 10.0 g (0.036 mol) of the ketone **6a** in 100 ml of $CHCl_3$, 5.8 g (0.036 mol) of Br_2 was added dropwise during 0.5 hr at 0°. Then 100 ml of water was added and working up gave a residue which was triturated with 200 ml of Et_2O affording 7.7 g (60%) of the bromo ketone, mp 140–142°. *Anal.* ($C_{20}H_{17}BrO$) C, H, Br, O.

Spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carboxylic Acid (23). The bromo ketone **22** (4.6 g, 0.013 mol) was added portionwise to a stirred solution of NaOMe [prepared from 0.7 g (0.03 mol) of Na in 50 ml of MeOH] at 0°. Stirring at 20° for 5 hr and evaporation gave methyl spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carboxylate which was treated with 80 ml of 0.2 *M* NaOH for 2 hr at 60°. Acidification gave 3.7 g (97%) of the acid **23**: mp 110–111° (from hexane); nmr 10.0 (s, 1, COOH), 7.0 (s, 2, CH=CH), 3.2 (m, 1, 3'-CH). *Anal.* ($C_{20}H_{18}O_2$) C, H, O.

Methyl Spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carbamate (27). Treatment of 11.3 g (0.039 mol) of the acid **23** with 60 ml of $SOCl_2$ for 2 hr at reflux temperature and evaporation of the excess $SOCl_2$ gave crude spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carbonyl chloride. Gaseous NH_3 was bubbled through 150 ml of a mixture of Et_2O–C_6H_6 (1:1). The crude chloride dissolved in 200 ml of Et_2O was added dropwise. The NH_3 inlet was continued for another 2 hr. H_2O was added and working up the mixture gave crystals upon trituration with boiling toluene. Spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carboxamide (**24**, 7.4 g, 65%) was collected: mp 181–183°; nmr 5.9 (b, 2, $CONH_2$).

This amide (6.5 g, 0.023 mol) was added portionwise to NaOMe [prepared from 1.05 g (0.095 mol) of Na in 150 ml of MeOH] followed by 3.6 g (0.023 mol) of Br_2 at 0°. The solution was slowly heated to 50° for 10 min. The excess MeOH was evaporated and H_2O was added. Extraction with $CHCl_3$ and working up gave 5.8 g (81%) of compound **27**, mp 65–67° (from Et_2O). *Anal.* ($C_{21}H_{21}NO_2$) C, H, N.

Spiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentan]-3'-amine (28). To 11 g (0.030 mol) of the acid **23** in 6 mol of H_2O and 30 ml of Me_2CO, 4.6 g (0.045 mol) of Et_3N in 50 ml of Me_2CO was added at 5°. ClCOOEt (5.4 g, 0.049 mol) in 20 ml of Me_2CO was slowly added and the mixture stirred for 2 hr at 10°. NaN_3 (3.7 g, 0.057 mol) in 15 ml of H_2O was added at 0°; the mixture was stirred for another 2 hr at 10°, poured into 500 ml of cold H_2O, and extracted with Et_2O. The residue after evaporation was dissolved in 100 ml of 70% AcOH and heated at 100° for 2 hr. Concentrated HCl (100 ml) was added and the heating continued for 15 hr. Working up with distillation gave 3.0 g (26%) of the desired amine, bp 180° (0.1 mm). The hydrochloride had mp 145–147° (from MeCN). *Anal.* ($C_{19}H_{20}ClN$) C, H, Cl, N.

N-Methylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentan]-3'-amine (29). To 0.50 g (0.0016 mol) of **27** dissolved in 20 ml of anhydrous Et_2O, 0.15 g (0.0039 mol) of $LiAlH_4$ was added in portions with stirring. The mixture was heated under reflux for 2 hr. The excess of hydride was destroyed by adding 2 ml of saturated Na_2SO_4 and the mixture filtered with the aid of Hyflo. From the filtrate 0.3 g of **29** was isolated as an oil. The maleate had mp 172–175° (from *i*-PrOH). *Anal.* ($C_{24}H_{25}NO_4$) C, H, N, O.

N,N-Dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentan]-3'-amine (30). The hydrochloride of **28** (0.88 g, 0.003 mol) was mixed with 1.0 g (0.012 mol) of 37% formalin, 0.2 g (0.003 mol) of sodium formate, and 0.7 g (0.015 mol) of HCOOH and heated on a bath at 120° for 3.5 hr. Then 50 ml of 2 *M* NaOH was added and working up yielded 0.6 g of the amine **30** as an oil. The oxalate was prepared from 0.2 g of oxalic acid in 50 ml of *i*-PrOH and recrystallized from 75 ml of MeCN giving 0.60 g (52%), mp 214–215°. *Anal.* ($C_{23}H_{25}NO_4$) C, H, N, O.

N-Methylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-methylamine (31). To a solution of 1.9 g (0.060 mol) of $MeNH_2$ in 100 ml of C_6H_6, the chloride of the acid **23** [from 3.6 g (0.012 mol) of **23**, see preparation of **27**] in 30 ml of C_6H_6 was added and the mixture stirred for 3 hr at 20°. Filtration and washing the filtrate with H_2O and working up gave an oily residue. This was triturated with Et_2O and dried to yield 2.4 g (64%) of *N*-methylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-carboxamide (**25**), mp 195–197°. Addition of 2.3 g (0.0076 mol) of **25** dissolved in 30 ml of THF to 0.75 g (0.020 mol) of $LiAlH_4$ in 40 ml of THF and boiling for 3 hr gave 1.2 g (55%) of **31**, mp 76–80° (from Et_2O–hexane, 1:1). The hydrochloride had mp 226–228°. *Anal.* ($C_{21}H_{24}ClN$) C, H, Cl, N.

N,N-Dimethylspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclopentane]-3'-methylamine (32). This compound was prepared as described for **31** from 0.9 g (0.003 mol) of the carboxylic acid **23** and dimethylamine. Reduction of the dimethylamide **26** with 0.4 g of $LiAlH_4$ in Et_2O afforded the amine **32** which was converted into its hydrochloride (0.6 g, 44%): mp 118–120° (from methyl isobutyl ketone); mass spectrum 303 M^+ (6%), 58 (100%). The oxalate was prepared as an analytical sample, mp 209–212° (from *i*-PrOH). *Anal.* ($C_{24}H_{27}NO_4$) C, H, N, O.

Acknowledgment. We wish to thank Dr. Brian Pring for reading the manuscript.

References

(1) F. Th. von Brücke and O. Hornykiewicz in "Pharmakologie der Psychopharmaka," Springer-Verlag, Berlin and Heidelberg, 1966, pp 95–98.
(2) K. Stach and W. Pöldinger, *Progr. Drug Res.*, **9**, 148 (1966).
(3) J. Glowinsky and J. Axelrod, *Nature (London)*, **204**, 1318 (1964).
(4) S. B. Ross and A. L. Renyi, *Eur. J. Pharmacol.*, **2**, 181 (1967).
(5) A. Carlson, H. Corrodi, K. Fuxe, and T. Hökfelt, *ibid.*, **5**, 357 (1969).
(6) S. B. Ross and A. L. Renyi, *ibid.*, **7**, 270 (1969).
(7) D. A. Stauffer and O. E. Fancher, *J. Org. Chem.*, **25**, 935 (1960).
(8) H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *J. Amer. Chem. Soc.*, **90**, 4892, 4901 (1968).
(9) M. P. Cava, R. Pohlke, B. W. Erickson, J. C. Rose, and G. Fraenkel, *Tetrahedron*, **18**, 1005 (1962).
(10) S. J. Cristol and R. K. Bly, *J. Amer. Chem. Soc.*, **82**, 6155

(1960).
(11) H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959).
(12) F. T. Bruderlein and L. G. Humber, German Patent 2,106,165 (1971).
(13) L. Salisbury, *J. Org. Chem.*, **37**, 4075 (1972).
(14) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).
(15) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
(16) A. I. Salama, J. R. Insalaco, and R. A. Maxwell, *J. Pharmacol. Exp. Ther.*, **178**, 474 (1971).
(17) E. Galantay, C. Hoffman, N. Paolella, J. Gogerty, L. Iorio, G. Leslie, and J. H. Trapold, *J. Med. Chem.*, **12**, 444 (1969).
(18) S. B. Ross, A. L. Renyi, and S. O. Ögren, *Eur. J. Pharmacol.*, **17**, 107 (1972).
(19) G. M. Everett in "Antidepressant Drugs," S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1967, pp 164–167.
(20) R. A. Turner "Screening Methods in Pharmacology," Academic Press, New York, N. Y., 1965, p 174.
(21) E. Soaje-Echagüe and R. K. S. Lim, *J. Pharmacol. Exp. Ther.*, **138**, 224 (1962).
(22) H. L. Slates and N. L. Wendler, *J. Med. Chem.*, **8**, 886 (1965).
(23) E. Taeger, E. Kahlert, and H. Walter, *J. Prakt. Chem.*, **28**, 13 (1965).
(24) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).
(25) H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Mass Spectrometry of Organic Compounds," Holden Day, San Francisco, Calif., 1967, p 151.

Aminoalkyldibenzo[*a*,*e*]cyclopropa[*c*]cycloheptene Derivatives. A Series of Potent Antidepressants

W. E. Coyne*,† and J. W. Cusic

G. D. Searle and Company, Chicago, Illinois. *Received June 11, 1973*

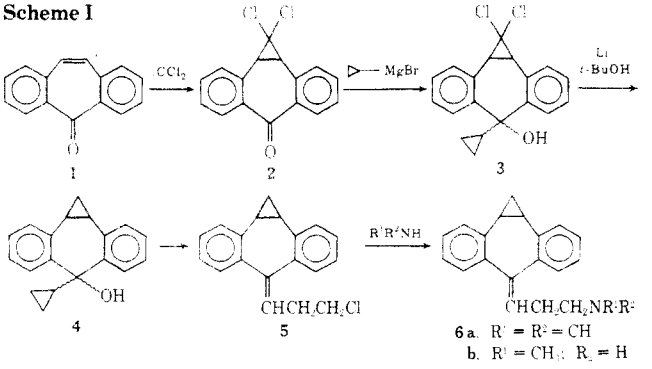
A new series of antidepressants, aminoalkyldibenzo[*a*,*e*]cyclopropa[*c*]cycloheptenes, has been synthesized and evaluated. One member of the series, **6b**, represents one of the most potent antidepressants reported to date.

The need for new antidepressants has existed since it became apparent with clinical experience that imipramine and amitryptyline lacked a quick onset of action and also possessed troublesome side effects. We felt that molecular modification in this area could lead to compounds with greater potency and minimal peripheral activity, properties that should lead to improvements over existing therapy. For example, anticholinergic activity has been related to a sedative component in known antidepressants, a limiting side effect in many instances.[1]

Most of the currently available antidepressants are based on a tricyclic nucleus in which the two aromatic rings are forced out of plane by the central connecting links. One modification which has not been reported is the fusion of a cyclopropyl ring to the dibenzocycloheptene system as in **6** to give a more rigid system. Although this was expected to change the chemical and pharmacological properties of this molecule, a surprising magnitude of difference was recognized early in the failure of this system to react similarly to the tricyclics. For example, tertiary alcohols formed from Grignard reactions on the ketone intermediates **2** and **8** were very resistant to dehydration, probably due to the ring strain existing in the tetracyclic system. Other chemical conversions similarly required forcing conditions. After this work was underway, the key cyclopropyl ketone intermediate **8** was reported,[2] although the synthetic sequence was not as useful as the sequence already discovered in our laboratory and reported here.[3]

Chemistry. The major route used to prepare the 5-aminoalkylidene compounds is outlined in Scheme I. Introduction of the cyclopropane ring was most efficiently accomplished by reaction of dichlorocarbene (generated from sodium methoxide and ethyl trichloroacetate) with dibenzo[*a*,*d*]-5*H*-cyclohepten-5-one **1** at 0–5° in benzene. Some of the other routes examined included Zn/Cu–CH_2I_2, CH_2N_2, and Et_2Zn–CH_2I_2 on either the free or protected ketones. The dichlorocarbene reaction gave the best results. The dichlorocyclopropane product **2** proved to be a key intermediate for subsequent conversions to the desired materials. It was stable to strong acid conditions and reacted smoothly with Grignard reagents to give good yields of aminoalkyl- or alkylcarbinols. No interaction of the Grignards with the cyclopropyl halogens was observed. Reaction of **2** with cyclopropylmagnesium bromide gave the cyclopropylcarbinol **3** which was dechlorinated with Li–*t*-BuOH to give a high yield of **4**. A variety of reducing reagents and conditions was tried for dechlorination [*e.g.*, $(n\text{-Bu})_3SnH$, $Zn(H^+)$, H_2/catalyst]; all were less desirable than the procedure reported here. Rearrangement of the cyclopropylcarbinol **4** in HCl–HOAc gave the chloropropylidene intermediate **5**. Under these conditions the fused cyclopropyl ring remained intact. Amination of the chloropropylidene **5** with a variety of amines gave the final products **6**.

Scheme I



6a. $R^1 = R^2 = CH$
b. $R^1 = CH_3$; $R^2 = H$

Alternate routes to these compounds as well as to the dichloro analogs are described in Scheme II. Preparation of the parent ketone **8** of this series was best accomplished by Li–*t*-BuOH reduction of the alcohol **7** followed by reoxidation. Ketone **8** reacted smoothly with Grignard reagents to give the alcohols **9**. A number of attempts to dehydrate **9** were unsuccessful, either leading to no reac-

† This paper is dedicated to my former professor and advisor, Dr. Alfred Burger.

* Address correspondence to this author at Riker Research Laboratories, 3M Center, St. Paul, Minnesota 55101.