additional 2 hr and then concentrated under vacuum. The residual oils were converted to solid salts.

Aroyloxyalkylpyrrolidines.—To a stirred mixture of 0.04 mole of 1-(hydroxyalkyl)-3-(*o*-methoxyphenoxy)pyrrolidine and 0.088 mole of anhydrous Na_2CO_3 in 75 ml of $CHCl_3$, 0.044 mole of an aroyl chloride was added dropwise. The mixture was then stirred for 4–21 hr depending on the aroyl halide used. The mixture was shaken with 50 ml of H_2O and the $CHCl_3$ layer was separated, dried (Na_2SO_4), and concentrated under vacuum. The residual oil was dissolved in Et_2O and an excess of ethereal HCl was added. The separated hydrochloride was dissolved in a basic solution, and the free amine was extracted into Et_2O. The ethereal extracts were dried and concentrated under vacuum. The residual oils were converted into solid salts.

Phenoxyalkylpyrrolidines.—A mixture of 0.063 mole of a phenoxyalkyl halide,[3-5] 0.06 mole of 3-(*o*-methoxyphenoxy)-pyrrolidine, and 0.126 mole of anhydrous K_2CO_3 in 125 ml of EtOH, *i*-PrOH, or PhMe was allowed to reflux for 4–36 hr depending on the phenoxyalkyl halide used. The mixture was filtered, and the filtrate was concentrated under vacuum. The oily residue was dissolved in C_6H_6 and the solution was extracted with 3 *N* HCl. The aqueous layer and oily hydrochloride were combined and made basic. The basic mixture was extracted with C_6H_6 and the collected extracts were dried, filtered, and concentrated. In some instances the oily residue was purified on a Florisil column using an Me_2CO–C_6H_6 gradient elution before making a salt. In all cases the free amine was finally characterized by conversion to a solid addition salt.

1-(*p*-Fluorophenyl)-4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-1-butanol.—A solution of 90.3 g (0.25 mole) of 4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone in 50 ml of MeOH was added to a stirred mixture of 37.84 g (1.0 mole) of $NaBH_4$ in 150 ml of MeOH at a rate so as to maintain a mild reflux. After the addition was complete the mixture was stirred for 20 hr. A large excess of H_2O was added, the mixture was stirred for an additional 1 hr and extracted with $CHCl_3$, and the extracts were dried and concentrated. Nmr, ir, and tlc indicated the expected product was pure.

***trans*-1-[4-(*p*-Fluorophenyl)-3-butenyl]-3-(*o*-methoxyphenoxy)pyrrolidine Maleate.**—A mixture of 20 g (0.056 mole) of 1-(*p*-fluorophenyl)-4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-1-butanol and 400 ml of 6 *N* HCl was allowed to reflux for 1 hr. After cooling and making basic, the solution was extracted with C_6H_6. The C_6H_6 extracts were dried and concentrated. The oily residue was purified by column chromatography (Florisil), eluting with C_6H_6 containing increasing amounts of Me_2CO. The free amine was converted to the maleate salt.

Acknowledgments.—The authors wish to express their appreciation to Marvel Daugherty, Donald L. Gilbert, Marilyn Houff, William E. King, and Dana M. Sakalas for pharmacological technical assistance.

Dibenz[*c*,*d*,*h*]azulenes. II. "Bridged" Amitriptyline Analogs[1]

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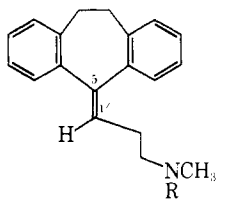
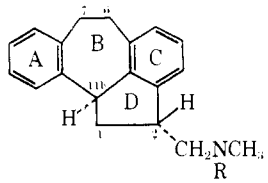
Tetracyclic (dibenz[*c*,*d*,*h*]azulene) analogs of amitriptyline and nortriptyline were synthesized and compared pharmacologically to the parent compounds. While in tests reflecting enhancement of central sympathetic activity (*e.g.*, reserpine reversal test) the compounds gave negative results, their peripheral autonomic profiles (with respect to potentiation of sympathomimetic activity) were very similar to those of the tricyclic analogs.

It is generally known that within the class of the so-called tricyclic drugs, several of the established ring systems (like the dibenzocycloheptylidene ring system in the antidepressant drugs amitriptyline and nortriptyline, **1**) are not planar but are skewed and bent;[2] therefore, a convex and a concave side may be distinguished with such ring systems. No one seems to have drawn attention, however, to an additional feature deducible from models: that the nitrogen atom in **1**, in all possible conformations of the seven-membered ring,[3] always stays above the convex side of the bent surface defined by the tricycle. Indeed, the length and rotational freedom of the side chain is such that the nitrogenous group cannot assume positions below (*i.e.*, on the concave side of) that surface.

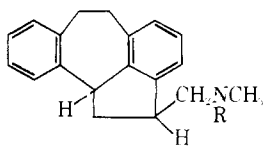
This recognition and the desirability to test its potential significance led us to construct molecules **2** and **3**. On one hand, as again studied on models, the geometry of the moiety formed by rings A, B, and C in these tetrahydrodibenzazulenes (although somewhat more "bent" and less "skewed") is reassuringly similar to that of the dibenzocycloheptylidene tricycle. On the other hand, the amitriptyline side chain is now linked to ring C to form a five-membered ring, extending the "side-chain rigidity," originally restricted to the two carbons, 5 and 1′ in **1**, by a further carbon atom. This



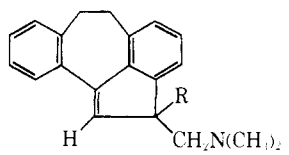
1a, R = H, nortriptyline
b, R = CH_3, amitriptyline



2a, R = H
b, R = CH_3



3a, R = H
b, R = CH_3



4a, R = H
b, R = CH_3

(1) Paper I: E. Galantay, H. Agahigian, and N. Paolella, *J. Amer. Chem. Soc.*, **88**, 3875 (1966).

(2) K. Stach and W. Pöldinger, *Progr. Drug Res.*, **9**, 129 (1966).

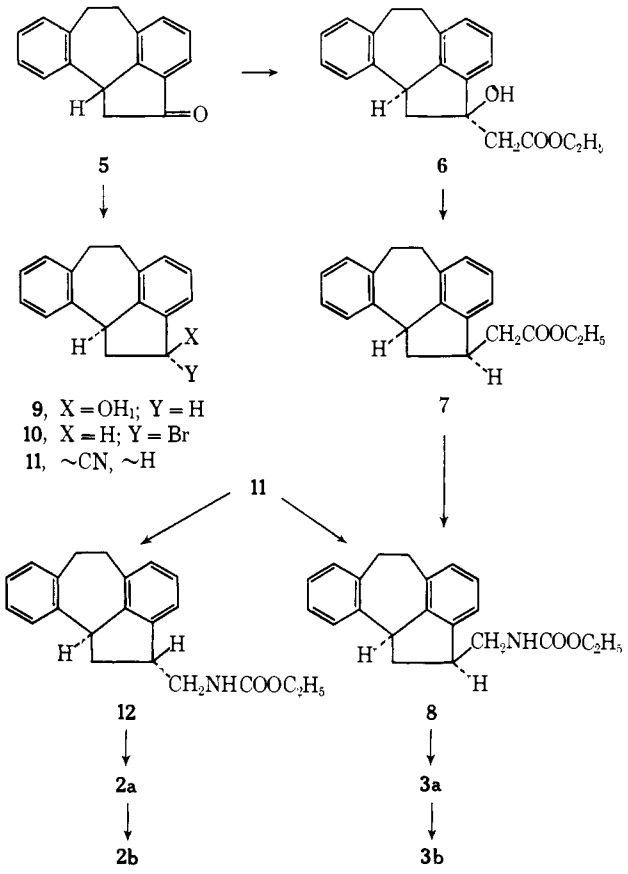
(3) For a discussion of the stereochemistry of dibenzocycloheptene derivatives see, *e.g.*, A. Ebnöther, E. Jucker, and A. Stoll, *Helv. Chim. Acta*, **48**, 1237 (1965).

carbon (number 2 in **2** or **3**) becomes asymmetrical and control of its configuration, relative to carbon 11b, leads in compounds **2a** and **2b** to an *exo* relationship similar to what we recognize with amitriptyline and, in **3a** and **3b**, to a novel *endo* relationship.[4]

It was reasonable to expect that biological evaluation of these compounds with clearly defined geometry *yet without the double bond* (corresponding to C-1′ and 5 in **1**) could also help to analyze the nature of a structure–activity phenomenon often encountered with tricyclic drugs, *i.e.*, the necessity of trigonal carbon or heteroatoms either in the "bridge" or at the site of the junction with the side chain, or both. In the case of **1** (or of their double-bond isomer protriptyline) the presence of the double bond is clearly a condition to antidepressant potency.[5-7] One might ask the question whether the double bond is necessary mostly because of its geometrical contributions (defining the geometry and rigidity both of the tricycle and of the side chain), or is it also because of its electronic properties (providing π electrons, establishing conjugation between the two aromatic nuclei). In our attempt to answer this question through the study of compounds **2** and **3**, we felt it desirable to include a compound of structure **4**, in which both "variables," *i.e.*, the five-membered ring and the double bond would be incorporated. As shown below, however, we were successful only in preparing a double-bond isomer of **4a**, *i.e.*, **19**.

Chemistry.—Reformatzky reaction of 1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulen-2-one (**5**)[1,8,9] with ethyl bromoacetate gave a single hydroxy ester **6**, to which we tentatively assign the relative configuration as shown on the basis of an assumed "*exo*" approach of the reagent (Scheme I). Dehydration of **6** led to a mixture of unsaturated esters which, on hydrogenation, gave almost quantitatively a single product which we formulate as **7**, *i.e.*, with the acetate side chain on the *endo* side of the molecule.[10] This ester was then

Scheme I



degraded, through a Curtius sequence involving the related hydrazide, azide, and isocyanate, to the *endo* urethan **8**, mp 115°. LAH reduction of **8** gave the desired *endo*-methylaminomethyl compound **3a**.

To prepare the *exo* isomer **2a**, the bromo compound **10** (obtained from **5** *via* the *endo* alcohol **9**[1,7]) was treated with NaCN in DMF. As expected, in the basic medium an epimeric (if not equilibrium) mixture of the two possible nitriles **11** was formed, along with elimination products. After treatment of this mixture with the LAH–$AlCl_3$ reagent, the basic fraction of the reaction product, containing now the epimeric aminomethyl compounds, was treated with ethyl chlorocarbonate. Fractional crystallization of the urethan product yielded, in addition to the *endo* urethan **8** described above, a new urethan of mp 146–149°, which, therefore, was the *exo* urethan **12**. Reduction of the latter, with LAH, gave the *exo*-monomethylaminomethyl compound **2a**. Finally the dimethylaminomethyl derivatives **2b** and **3b** were prepared by Leuckart methylation of **2a** and **3a**, respectively.

Of the attempts to prepare compounds of the type **4**, a sequence starting with the dihydrodibenzoheptafulvene **13**[11] is worth mentioning (see Scheme II). While we were unable to effect its condensation with aminoacetaldehyde derivatives directly to **4a**, with

(4) In the Experimental Section, for the sake of shortness, we designate as α the substituents drawn with dotted lines, *i.e.*, the ones on the same (*exo*) side of the dibenzazulene skeleton as the hydorgen in 11b position. *endo* substituents are designated with β.

(5) J. Stewart, M.-P. Charest, and F. Herr, *J. Med. Chem.*, **6**, 338 (1963).

(6) F. Häfliger and V. Burckhardt in "Psychopharmacological Agents," Vol. 4-I, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 35.

(7) E. L. Engelhardt, M. E. Christy, C. D. Colton, M. B. Freedman, C. C. Boland, L. M. Halpern, V. G. Vernier, and C. A. Stone, *J. Med. Chem.*, **11**, 325, (1968).

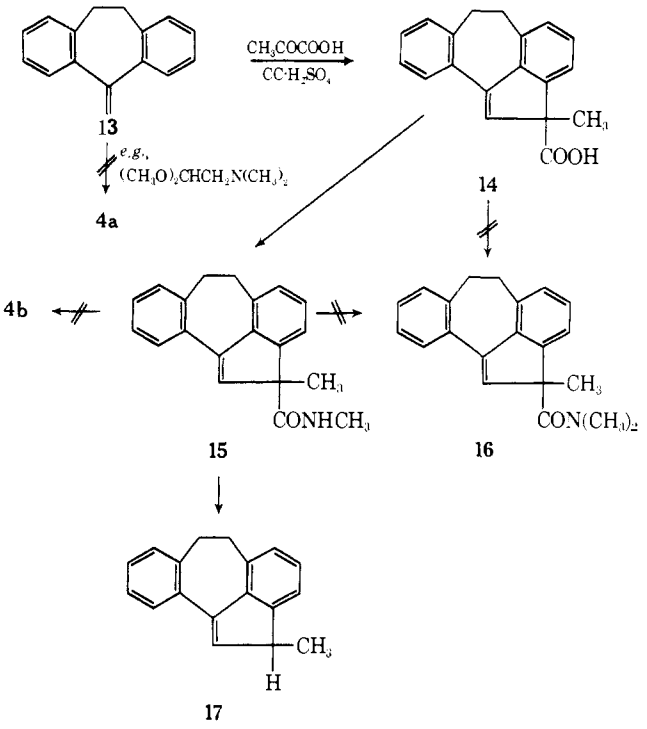
(8) C. van der Stelt, A. Hassjes, H. M. Terstege, and W. Th. Nauta, *Rec. Trav. Chim.*, **84**, 1466 (1965).

(9) C. Humber, M. A. Davis, R. A. Thomas, R. Otson, and J. R. Watson, *J. Heterocycl. Chem.*, **3**, 247 (1966).

(10) This assignment of relative configuration, crucial for the whole chemistry and, indeed, for the philosophy of the present work, is based on the recognition that approach of the catalyst surface, apparently highly selective for *one* side of the indane–indene (rings C–D) moiety, is likely to come from the "*exo*" rather than the "*endo*" side, where it would be hindered by a protruding (115–130° from plane C–D) benzene ring A. In agreement with this picture, most of the reactions involving attack of a bulky reagent at C-2 are highly stereospecific (formation of, *e.g.*, **6** or **9**). Support for this assignment may be derived from the study of the (100 Mc) nmr spectra of the diastereomeric pair of urethans **8** and **12**. While the analysis *via* determining the coupling constants between the protons on C-11b, C-1, and C-2, respectively, appears, at least in the absence of extensive deuterium work, as hopeless [for conditions in a simple indane system, see W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964)], the chemical shifts of the —$NHCOOCH_2CH_3$ protons in the spectra of **8** and **12** are different and allow interpretation. The Me triplet (J = 7 cps) and the CH_2 quartet in *exo*-**12** appear at δ 0.63 and 3.53 ppm, respectively, that is, at significantly higher fields than the corresponding resonances in *endo*-**8** (δ 0.72 and 3.65 ppm, respectively. These differences, considering that the Et group is separated from ring C by six linkages, among them two C–C and one C–N single bonds, must be attributed to long-range effects from the aromatic rings A and (predominantly) C. In the *exo* compound **12** the side chain (apart, of course, from the rigidities inherent in the NHCOO moiety) can essentially rotate freely, thus it also assumes conformations in which the Et group is within the "*shielding* cone" at the α face of ring C. The contribution of these conformations would cause the Me and CH^2 absorptions to appear at *higher* fields. The statistical probability of corresponding "shielding" conformations with the *endo* compound **8** (involving the β face of ring C) can be safely assumed to be smaller, due to steric hindrance from ring A; indeed, the probability of conformations with the Et group exposed to the *deshielding* effect of ring C (and here also to that of ring A) is much greater. Concluding, we can reasonably expect, and we find, that the Et group of the *exo* urethan **12** absorbs at a higher and the *endo* urethan **8** at a lower field.

(11) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951).

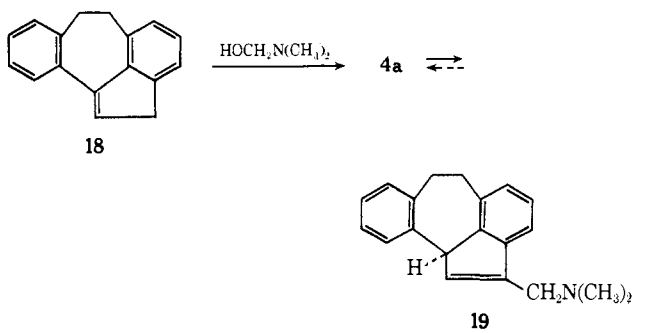
SCHEME II



pyruvic acid in concentrated H_2SO_4 we did obtain in quantitative yield the acid **14** which we hoped to convert through the monomethylamide **15**, into **4b**. Amide **15** was indeed obtained without difficulty (whereas, in perfect agreement with model considerations, it appeared to be impossible to prepare the seriously congested dimethylamide **16**). Reduction of **15** to **4b**, however, failed under all conditions tried. LAH, for example, even at 0°, reduced **15** to a hydrocarbon mixture, the main component of which appeared to have structure **17**. This was obviously the result of retro-Mannich (or retroaldol) type reaction, subsequent to the reduction of the amide group.

Using this experience "in reverse," we treated the known olefin **18** under Mannich conditions[12] (Scheme III). The basic product, obtained in fair yields,

SCHEME III



appeared (nmr) to be **19**, the isomerization[13] product of the initially formed **4**, R = H.

(12) We are not aware of any previously reported case, where an indene-type compound would have been utilized as the acid component in a Mannich-type reaction. See, *e.g.*, B. Reichert, "Die Mannich Reaction," Springer-Verlag, Berlin, 1959.

(13) Similar (base-catalyzed) isomerizations with substituted indenes have been observed: (a) A. M. Weidler, *Acta Chem. Scand.*, **17**, 2724 (1963); (b) S. J. Dykstra, J. M. Berdahl, K. N. Campbell, C. M. Combs, and D. G. Lankin, *J. Med. Chem.*, **10**, 418 (1967).

Biological Evaluation.—This work, as we outlined in the introduction, was based on the question whether the importance of certain structural features present in the amitriptyline molecule which relate to its "antidepressant" activity can be analyzed with the help of the novel dibenzazulene analogs. Among the biological testing procedures presently accepted as predictors of clinical antidepressant activity, the ability of a compound to reverse reserpine-induced hypothermia in mice or rats[14-16] is considered one of the criteria which determines the CNS stimulant aspect of the compound activity. Accordingly, the dibenzazulene compounds of this work were first tested in this procedure, using mice as the experimental animal

As shown in Table I, none of the novel model compounds gave, in comparison to the "standard antidepressants," significant activity in this test.

While this negative finding put the basic philosophy of the work in jeopardy, we undertook defining a "profile" of the various activities exerted in these substances on the CNS. Using the most readily available compound **3a**, we determined acute toxicity and studied behavior alterations in mice. In this regard, the tests utilized modifications of the methods described by Irwin.[17] The CNS depressant activity of the compounds was determined by testing the ability of substances to reinduce "sleep" in mice following recovery from anesthesia produced by intravenous administration of hexobarbital (70 mg/kg),[18] and by interacting the compounds with amphetamine using standard photocell activity cages for measuring motor activity.[19]

Because of the demonstrated, albeit gross, relationship between clinical antidepressant activity of substances such as amitriptyline or nortriptyline and their abilities to augment sympathomimetic activity in laboratory testing procedures,[20,21] studies were undertaken in chloralose–urethan-anesthetized cats to determine the effects of selected compounds on the pressor responses elicited by intravenous administration of norepinephrine and a ganglionic stimulant, dimethylphenylpiperazinium (DMPP). Additional analysis of sympathetic interaction was obtained by recording contractions of the nictitating membrane elicited by norepinephrine, DMPP, or superior cervical nerve (pre- and postganglionic) stimulation.[22]

A. Acute Toxicity and Effects on Behavior in Mice.—As indicated, only **3a** was submitted for toxicity and behavioral evaluation. This compound provided a profile and level of activity quite similar to those of

(14) B. M. Askew, *Life Sci.*, 2, 725 (1963).

(15) S. Garattini, A. Giacheti, A. Jori, L. Vieri, and L. Valzelli, *J. Pharm. Pharmacol.*, **14**, 509 (1962).

(16) S. Garattini and A. Jori in "Antidepressant Drugs," S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1967, pp 179–193.

(17) S. Irwin in "Animal & Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Inc., Chicago, Ill., 1964.

(18) C. F. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948).

(19) Activity Cages manufactured by Woodard Research Corp., Herndon, Pa.

(20) E. B. Sigg, L. Soffer, and L. Gyermek, *J. Pharmacol. Exptl. Therap.*, **142**, 13 (1963).

(21) C. A. Stone, ref 16, pp 158–163.

(22) The right superior cervical nerve (pre- and postganglionic) was isolated in chloralose–urethan-anesthetized cats. The nerve was ligated or cut preganglionically, with bipolar Pt electrodes placed distal to the ligature at pre- and postganglionic sites. Contractions of the nictitating membrane were recorded isometrically through a Grass Ft. 03 transducer with recordings made via a Grass Model 7 polygraph. With the nerve immersed in warm mineral oil, submaximal electrical stimuli were applied either pre- or postganglionically using a Grass S-4 stimulator (20/sec frequency, 2.5 msec, 0.3–3.0 V).

Table I

Compd	LD_{50},[a] mg/kg ip	Hexobarbital reinduction[b] RD_{50}, mg/kg ip	Amphetamine interaction[c] Dose, mg/kg ip	Amphetamine interaction[c] % of control	Reversal of reserpine hypothermia[d] ED_{50}, mg/kg ip
Nortriptyline (**1a**)	*e*	37.5	25.0	7 ↑	5.3
			50.0	44 ↓	
3a	62.5	12.5	12.5	50 ↓	>12.5
3b	*e*	20.2	20.4	50 ↓	>12.5
19	*e*	>50.0	9.8	50 ↓	>12.5
2a	*e*	12.5	23.7	50 ↓	>25.0
2b	*e*	*e*	*e*	*e*	>12.5
Amitriptyline (**1b**)	68.7	14.6	12.5	54 ↑	8.0
			50.0	70 ↓	
Imipramine	116.7	50.0	12.5	14 ↑	10.0
			50.0	8 ↓	
Desmethylimipramine	91.7	>50.0	12.5	93 ↑	6.0
			50.0	58 ↓	

[a] Modification of the General Activity and Acute Toxicity (GAAT) methods, as presented by S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Inc., Chicago, Ill., 1964; ten mice/dose. [b] Modified method of C. F. Winter, *J. Pharmacol. Exptl. Therap.*, **94**, 7 (1948), in which mice were administered the compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time; ten mice/dose. [c] Determined in mice using *dl*-amphetamine at 2.5 mg/kg ip and measuring activity in standard photocell activity cages, Woodard Research Corp., Herndon, Va.; ten mice/dose. [d] Modification of the method presented by P. S. J. Spencer, ref 16, pp 194–204. Reserpine was injected at 5.0 mg/kg ip followed 1 hr later by intraperitoneal administration of the test substance (ten animals/dose). Rectal temperatures were measured hourly for 2 hr previous to reserpine and for 5 hr following reserpine. ED_{50} is defined as that dose of the substance which reverses the hypothermia produced by reserpine by 50% at the 5-hr interval following reserpine. [e] Not tested.

amitriptyline and nortriptyline, with a moderate degree of toxicity accompanied by convulsive activity at lethal doses and, at sublethal doses, by moderate depression of spontaneous motility and reflexes (*e.g.*, ataxia, loss of traction, etc.).

B. CNS Depressant Profile.—As can be seen from Table I, all but two of the tested compounds (including standards) provided moderate to marked CNS depressant activity as defined by the hexobarbital reinduction test; the two exceptions, desmethylimipramine and **19** were inactive in this test at sublethal doses. With regard to amphetamine interaction, the test substances provided only antagonism of amphetamine-induced hypermotility in mice, whereas the standards produced potentiation at low doses and antagonism at high doses. The potentiation of amphetamine-induced hypermotility is interpreted as augmentation of central sympathomimetic (CNS stimulant) activity, whereas antagonism of amphetamine is seen as evidence of neuroleptic (CNS depressant) activity.

C. Autonomic Profile.—Table II presents data obtained in autonomic interaction studies in the anesthetized cat. As can be seen, all substances except **19** produced moderate to marked augmentation of the pressor response to norepinephrine and DMPP and appeared to "sensitize" the nictitating membrane to the two agonists.[23] Compound **19**, on the other hand, provided mild antagonism of the pressor response to norepinephrine with little or no effect on the DMPP response. The responsiveness of the nictitating membrane to the two agonists could not be measured following the high dose of **19** because of a sustained contraction of the membrane induced by the substance. This latter effect has, in our experience, been observed reproducibly only with two other substances, *d*-amphetamine and guanethidine (in certain experiments, nortriptyline has produced a moderate contraction of the nictitating membrane).

Regarding the effect of these compounds on contractions of the nictitating membrane elicited by electrical stimulation of the pre- and postganglionic superior cervical nerve, all compounds except amitriptyline and substance **19** facilitated contractions following preganglionic stimulation, whereas only desmethylimipramine (and possibly imipramine at the lower dose) and **2b** facilitated contractions elicited by postganglionic nerve stimulation. These apparently paradoxical results were completely unexpected and, thus far, no explanation can be provided. However, it is of interest that the most active substances with regard to facilitation of contractions elicited by preganglionic stimulation were nortriptyline and an *exo*-type of dibenzazulene analog, **2b**.

Summary and Conclusions

"Bridged" analogs of amitriptyline and nortriptyline, with a delicate structural and geometrical relationship to the parent compounds, were synthesized to provide models for a closer definition of the structural features essential for "antidepressant" activity. The new substances, possessing a dibenzazulene skeleton, were then subjected to selected specific biological testing procedures.

Due to the absence, with the dibenzazulenes, of significant activity in the "reserpine reversal" test (or, generally, in tests reflecting enhancement of central sympathetic activity), the questions raised in the introduction cannot be answered with confidence. It seems that the very creation of the models, *i.e.*, "tying" the amitriptyline side chain to one of the benzene rings, would abolish these activities irrespective of the relative configurations at the asymmetric centers thus created.[24]

On the other hand, the peripheral autonomic profiles of these bridged analogs, with respect to potentiation

(23) Compounds **2a** and **2b**, interestingly, only potentiated the response of the nictitating membrane to the ganglionic stimulant effects of DMPP.

(24) A critical dependence of the "reserpine reversal" on small structural variations was also observed in the phenylindene series; see ref 13b.

TABLE II

Compd	Dose, mg/kg iv	Effect on superior cervical nerve stim., % of control: Preganglionic	Postganglionic	Effect (% of control) on pressor response to: Norepinephrine	DMPP[a]
Nortriptyline (**1a**)	0.5	100 ↑	23 ↓	127 ↑ [e]	21 ↑ [a]
	1.5	100 ↑	70 ↓	81 ↑ [e]	33 ↑ [a]
3a	1.0	53 ↑	34 ↓	50 ↑ [b]	19 ↑ [b]
	3.0	50 ↑	48 ↓	95 ↑ [b]	24 ↑ [b]
3b	1.0	40 ↓	35 ↓	0	20 ↑ [d]
	3.0	55 ↓	35 ↓	38 ↑	80 ↑ [d]
19	1.0	28 ↓	6 ↓	10 ↓	2 ↓
	3.0	[c]	[c]	29 ↓	2 ↓
2a	[f]	[f]	[f]	[f]	[f]
	1.0	100 ↑	100 ↑	31 ↑	0 [d]
	3.0	100 ↑	100 ↑	48 ↑	0 [d]
Amitriptyline (**1b**)	1.0	22 ↓	20 ↓	3 ↑	[f]
	3.0	30 ↓	27 ↓	6 ↑	
Imipramine	1.0	31 ↑	26 ↑	82 ↑	[f]
	3.0	15 ↑	17 ↓	[f]	
Desmethylimipramine	1.0	14 ↑	28 ↑	54 ↑ [e]	9 ↑ [e]
	3.0	14 ↓	10 ↑	62 ↑ [e]	6 ↑ [e]

[a] Norepinephrine and DMPP pressor responses accompanied after nortriptyline by 20–40 mm contraction of the nictitating membrane. [b] Norepinephrine and DMPP pressor responses accompanied after II by 7–11-mm contraction of the nictitating membrane. [c] Compound **19** produced sustained contraction of the nictitating membrane at 3.0 mg/kg iv. [d] DMPP pressor response accompanied after VI by 5–17-mm contraction of the nictitating membrane. Norepinephrine had no effect on the membrane postdrug. [e] Norepinephrine and DMPP pressor responses accompanied after desmethylimipramine by 3–6-mm contraction of the nictitating membrane. [f] Not tested. [g] Dimethylphenylpiperazinium.

of sympathomimetic activity, were very similar to those of the tricyclic parent compounds. It is also interesting that the CNS depressant activity, as well as the antagonism of postganglionic superior cervical nerve stimulation as presented by amitriptyline and nortriptyline, is represented by these tetracyclic analogs. The "specific" potentiation of the nictitating membrane response to intravenous DMPP following the dimethyl derivatives of the present series appears to represent a significant difference from the standards and may be due to sensitization of superior cervical ganglion cells.

Experimental Section[4]

2β-Hydroxy-2α-ethoxycarbonylmethyl-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulene (6).—To a refluxing mixture containing 50.0 g (0.214 mole) of 1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]-azulen-2-one (**5**),[1,8,9] 31.28 g (0.479 g-atom) of activated Zn, and 1500 ml of PhH–PhMe (1:1), there was slowly added 80.0 g (0.479 mole) of ethyl bromoacetate. A crystal of I_2 was added whereupon the exothermic reaction started; refluxing was maintained without heating by regulating the rate of addition, which was then completed in 35 min. After 2 more hr of refluxing, the mixture was cooled in ice water and decomposed by the careful addition of saturated NH_4Cl. The organic layer yielded 73.9 g of slowly crystallizing oil, which was triturated with *i*-Pr_2O. The product 43.8 g (70.4%), could be then obtained by filtration, mp 101–104°. The analytical sample, obtained after two recrystallizations (Et_2O), formed prisms, mp 104–105°. *Anal.* ($C_{21}H_{22}O_3$) C, H, O, EtO.

2β-Ethoxycarbonylmethyl-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulene (7).—A mixture of 44.0 g (0.137 mole) of **6**, 1.72 g of *p*-toluenesulfonic acid, and 300 ml of PhMe was refluxed under a Dean–Stark water separator until (30 min) H_2O formation had ceased. The solution was cooled to room temperature, washed (10% $NaHCO_3$ solution H_2O), dried, and evaporated to 41.3 g of a dark brown oil, apparently a mixture of unsaturated esters: $\lambda\lambda_{max}^{EtOH}$ 235 mμ (ε 13,800), 240 (14,000), 265 (4700), 280 (4000), 293 (3500), 303 (2410). This mixture (38.0 g, 0.125 mole) was hydrogenated in EtOAc (150 ml) in the presence of 1.0 g of 10% Pd–C at room temperature and 3.5 kg/cm² of H_2. The theoretical amount of H_2 was taken up in 30 min. After filtration, the solution was evaporated to 38.0 g of crystalline material, mp 76–79°, after four recrystallizations (EtOH) mp 78–80°. *Anal.* ($C_{21}H_{22}O_2$) C, H, O, EtO.

2β-Hydrazinocarbonylmethyl-1,6,7,11b-tetrahydro-2H-dibenz-[*c,d,h*]azulene.—A mixture containing 30.8 g (0.101 mole) of **7**, 35.5 g of hydrazine, and 200 ml of *n*-PrOH was refluxed for 5 hr. Upon cooling, the product (25.2 g, mp 203–205°) crystallized. *Anal.* ($C_{19}H_{20}N_2O$) C, H, N, O.

2β-Ethoxycarbonylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulene (8).—The above hydrazide (16.5 g) was dissolved with heating in 125 ml of AcOH. After rapid cooling, 125 ml of Et_2O was added and introduction of HCl was started. Soon, a fine suspension of the hydrazide hydrochloride was formed. BuONO was slowly added under vigorous stirring while the temperature was maintained at 5°. After 45 min, the mixture was concentrated *in vacuo* from a 5° bath to about one-third of its original volume and the crude azide was filtered off and washed with ice-cold H_2O. After careful drying, first azeotropically (PhH, 15 mm, 30°) then in desiccator over P_2O_5 in the cold, 15.3 g of the azide, mp 91–93°, was obtained: $\lambda\lambda_{max}^{Nujol}$ 2130, 1730 cm⁻¹, no N–H bands. This azide, 15.3 g (0.050 mole), was thermolyzed in refluxing C_6H_6 for 30 min, filtered from a small amount of undissolved solid, and evaporated to dryness. The crude **isocyanate** was an oil, $\lambda_{max}^{CHCl_3}$ 2250 cm⁻¹. It was taken up in 200 ml of absolute EtOH, refluxed for 15 min, then evaporated to 15.9 g of slowly crystallizing oil, mp 90–105°. Crystallization (MeOH) yielded the pure product, mp 112–115°. *Anal.* ($C_{21}H_{22}N_2O_2$) C, H, N, O.

2β-Methylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]-azulene (3a).—To a stirred mixture of 1.710 g of LAH in 75 ml of THF, there was added, at room temperature, a solution of 1.440 g (4.48 moles) of **8** in 75 ml of THF. After heating to reflux for 2.5 hr, 100 ml of saturated NH_4Cl was added dropwise, under cooling, and the separated THF layer, after filtration through Celite and drying (Na_2SO_4), was evaporated to yield 1.396 g of a light yellow gum. Dissolution in absolute Et_2O and introduction of HCl precipitated the HCl salt (1.2867 g), mp 220–225° dec after recrystallization from absolute EtOH. *Anal.* ($C_{19}H_{21}N \cdot HCl$) C, H, Cl, N.

2-Cyano-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulene (11). A mixture of 6.46 g of NaCN and 412 ml of DMF was refluxed shortly, then cooled to room temperature. 2-Bromo-1,6,7,11b-tetrahydro-2H-dibenz[*c,d,h*]azulene (**10**)[25] (9.0 g) was added portionwise. After 4 hr, the mixture was evaporated *in vacuo* and worked up with $CHCl_3$ to give 8.03 g of the crude product as an oil, which was used in the next step. One of the two diastereomers, however, was isolated in pure form also, by silica gel chromatography followed by crystallization from *i*-Pr_2O, mp 144–147°, λ_{max}^{KBr} 2220 cm⁻¹. *Anal.* ($C_{18}H_{17}N$) C, H, N.

[25] Mp 120–122°; prepared from the alcohol **9**[8,9] with HBr in C_6H_6 (0°).

2-Aminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[c,d,h]azulene.—To a suspension of 1.32 g of LAH in 50 ml of Et_2O, there was dropwise added, under cooling, a solution of 4.65 g of anhydrous $AlCl_3$ in 100 ml of Et_2O. Then, within 15 min, there was added a solution of 7.7 g of the crude cyanide (**11**) in 275 ml of Et_2O, and the resulting mixture was refluxed for 3 hr. After recooling, 150 ml of 50% NaOH was dropped in and the biphasic system was gently refluxed for 16 hr. The organic layer gave, on work-up, 7.78 g of a reddish gum, which was separated into a neutral (3.18 g) and a basic (4.38 g) fraction by distribution between C_6H_6 and 2 *N* HCl, followed by alkalinization and reextraction of the aqueous phase. The basic fraction was used, without purification, in the next step. However, in one instance, the basic fraction was also converted into a mixture of the crystalline HCl salts and, by recrystallization from *i*-PrOH, one of the two diastereomers was obtained in pure form, mp 275–277°. *Anal.* ($C_{18}H_{19}N \cdot HCl$) C, H, Cl, N.

2α-Ethoxycarbonylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[c,d,h]azulene (12).—A solution of 4.38 g of the crude basic fraction from the above example in 60 ml of ethylene dichloride was emulsified by the aid of a vibro mixer with 24.0 ml of 1 *N* NaOH and cooled to 0°. Ethyl chloroformate (2.28 ml) was then added. After 3 hr, the organic phase was separated, washed, dried, and evaporated to 6.02 g of a gum. Crystallization from 7 ml of hot MeOH gave, in the first crop, 2.99 g of a substance with mp 103–110°, essentially the previously described β isomer **8** (on one recrystallization from 7 ml of MeOH, it yielded 2.69 g of pure **8**, mp 112–115°).

From the mother liquor of the first crystallization, 0.73 g of the α isomer crystallized, mp (132)–136–141°; 0.31 g more of this material was obtained from the mother liquor. Recrystallization (MeOH) yielded the pure α isomer, mp 146–149°. *Anal.* ($C_{21}H_{23}NO_2$) N.

The nmr[10] and solid phase (KBr) ir spectra of the two diastereomeric urethans showed distinct differences, *e.g.*, the β isomer had its amide II band at slightly higher frequency (1550 cm^{-1}) than the α isomer (1535 cm^{-1}); the appearance of the 700–800-cm^{-1} region (C–H out-of-plane deformations: several sharp bands) is very different in the two compounds. A strong melting point depression between **8** and **12** could be observed. The mass spectra and solution ir spectra, on the other hand, were virtually identical.

2α-Methylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[c,d,h]-azulene (2a).—Reduction of **12** was carried out under the same conditions as that of the diastereomeric urethan **8**. The product was isolated as the HCl salt, mp 225° dec. *Anal.* ($C_{19}H_{21}N \cdot HCl$) Cl, N.

The solid-phase (KBr) ir spectrum exhibited small differences in the 700–800-cm^{-1} region relative to the spectrum of the diastereomeric **3a**.

2β-Dimethylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz-[c,d,h]azulene (3b).—To a mixture of 1.31 g of 90% HCO_2H and 0.92 ml of 37% HCHO, there was added 567 mg of 2β-methylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz[c,d,h]azulene (freshly prepared from its HCl salt) and heated at 85–90° for 2.5 hr. After cooling 0.44 ml of 11 *N* HCl was added and the mixture was evaporated to dryness. The free base was liberated as usual and the HCl salt was prepared in Et_2O, mp 145° dec. *Anal.* ($C_{20}H_{23}N \cdot HCl$) Cl N.

2α-Dimethylaminomethyl-1,6,7,11b-tetrahydro-2H-dibenz-[c,d,h]azulene (2b).—Prepared analogously to **3b**, from **3a**, the HCl salt had mp 110° dec. *Anal.* ($C_{20}H_{23}N \cdot HCl$) Cl, N.

2-Carboxy-2-methyl-6,7-dihydro-2H-dibenz[c,d,h]azulene (14).—Pyruvic acid (18.2 g, 0.207 mole) was added over 10 min to 198 ml of concentrated H_2SO_4 at 0–3°. Portionwise, over 20 min, 20.0 g of 5-methyl-5-hydroxy-9,10-dihydro-5H-dibenzo[a,d]cycloheptene[11] (mp 140–143°) was added to the stirred solution, while the temperature was allowed to rise to 14°. After 48 hr at room temperature, the red, viscous mixture was poured onto ice (400 g) and the colorless product was collected by filtration: 24.5 g, mp 123–126°; after recrystallization from Et_2O–petroleum ether (bp 30–60°) (1:1), mp 125–128°; nmr, singlet at δ 1.66 ppm (three protons), singlet at 3.04 (four protons), singlet at 6.70 (one proton), multiplet centered at 7.18 (six protons), multiplet centered at 7.70 (one proton), singlet, exchangeable, at 11.3 (one proton). *Anal.* ($C_{19}H_{16}O_2$) C, H, O.

2-Methoxycarbonyl-2-methyl-6,7-dihydro-2H-dibenz[c,d,h]-azulene.—A mixture of 20.0 g of **14**, 1.0 g of *p*-toluenesulfonic acid, and 600 ml of MeOH was refluxed for 6 hr, then evaporated to dryness, taken up in C_6H_6, and washed with 10% $NaHCO_3$ solution. The dried C_6H_6 phase was evaporated to give 22.4 g of the oily ester which was used without purification in the next step.

2-Methylaminocarbonyl-2-methyl-6,7-dihydro-2H-dibenz-[c,d,h]azulene (15).—The above ester (11.2 g), 25 ml of liquid $MeNH_2$, and 30 ml of C_6H_6 were heated, in a closed vessel, at 60° for 15 hr. The evaporated reaction mixture was treated with Et_2O (50 ml), whereupon 7.4 g of the product, mp 177–180°, crystallized. *Anal.* ($C_{20}H_{19}NO$) C, H, O.

LAH Reduction of 15.—To a refluxing mixture of 396 mg of LAH in 30 ml of Et_2O, there was added, by the Soxhlet method, 392 mg of **15**. The reaction was followed by tlc which indicated the formation of only two nonpolar products. These were isolated, after standard work-up of the reaction mixture, by preparative tlc on a silica plate with heptane: product A, 142 mg, and product B, 80 mg. Product A was further purified by microdistillation at 80° (0.001 mm). *Anal.* ($C_{18}H_{16}$) C, H.

That product A had indeed the structure of **2-methyl-6,7-dihydro-2H-dibenz[c,d,h]azulene (17)** was proved by its nmr spectrum: doublet (J = 7.5 cps) at δ 1.34 ppm (three protons), singlet at 3.07 (four protons), multiplet at around 3.52 (one proton), doublet (J = 2.5 cps) at 6.71 (one proton), multiplet between 6.97 and 7.34 (six protons), and multiplet at 7.7 (one proton); $\lambda\lambda_{max}^{EtOH}$ 244 mμ (δ 21,200), 250 sh (20,600), 288 (4700), 296 (4560), 306 (4140).

2-Dimethylaminomethyl-6,7-dihydro-11bH-dibenz[c,d,h]azulene (19).—To a solution of 1.916 g of 6,7-dihydro-2H-dibenz-[c,d,h]azulene (**18**)[9] in 5 ml of AcOH at 95°, there was added 0.02 ml of 11 *N* HCl then, dropwise over 30 min, 5 ml of Me_2NCH_2OH ($n^{20}D$ 1.4072). This mixture was then poured on 200 g of ice-cold 2 *N* HCl and the unreacted starting material, along with some neutral side products (total 841 mg), was removed by PhH extraction. The pH of the aqueous phase was now adjusted to 9.0 (Na_2CO_3) and the basic Mannich reaction product was extracted ($CHCl_3$). Evaporation of the dried $CHCl_3$ gave the oily base (1.1490 g) from which, by passing HCl in its Et_2O solution, the solid hydrochloride was prepared, mp 150° dec. *Anal.* ($C_{20}H_{21}N \cdot HCl$) Cl, N. Nmr of the free base showed a singlet at δ 2.24 ppm (six protons), broad singlet at 3.05 (four protons), doublet (J = 6 cps) at 3.60 (one proton), broad singlet at 3.66 (two protons), doublet (J = 6 cps) at 7.03 (one proton), and multiplet between 7.05 and 7.50 (seven protons); $\lambda\lambda_{max}^{EtOH}$ 243 mμ (δ 17,300), 274 (9300); shoulders at 237, 249, 283, 295 and 305 mμ.

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