Novel Tricyclic Systems. Oxazole, Thiazole, and Imidazole Analogs of the Amitriptyline Type

Eugene E. Galantay,*·†Ronald Simpson, George Corriveau, Max Denzer, Douglas C. Knorr, Robert J. Strohschein, Nicholas A. Paolella, Yasuyuki Uike,

Department of Chemical Research

John H. Gogerty, Eileen A. Ryan, and Louis C. Iorio

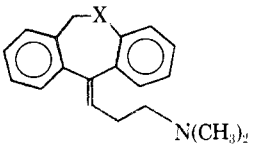
Department of Biological Research, Sandoz Pharmaceuticals, Sandoz-Wander Inc., Hanover, New Jersey 07936. *Received April 25, 1973*

The preparation of a series of novel tricyclic ketones—heterocyclic analogs of dibenzosuberone—is described. These compounds served as intermediates toward analogs of the amitriptyline type in which an oxazole, thiazole, or imidazole ring was substituted for one of the benzene moieties. The oxazole and thiazole analogs of amitriptyline were highly potent CNS depressant drugs. This CNS depressant spectrum could be shifted toward an antidepressant profile by side-chain modification. The imidazole analogs showed less CNS activity and the derivatives of the isomeric "curved" oxazole tricycle had insignificant CNS activity while producing profound alterations in the electrocardiograms of dogs.

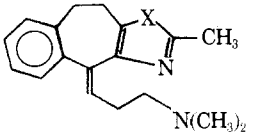
The tricyclic ring system of the antidepressant drug amitriptyline has inspired many endeavors toward molecular modification. It is well established now that even minor structural changes affecting the geometry or the electronic properties of this system bring about distinct shifts in the neuropharmacological spectrum.[1] One of the fruitful modifications was the introduction of a heteroatom (O, S, N) into the so-called "bridge," as exemplified by doxepin. Less explored, on the other hand, is the field in which a heterocyclic ring replaces one or both of the benzene moieties. Only two such systems have been thoroughly studied, featuring thiophene[2] and pyridine,[3] and these are heterocycles that are the "closest" to benzene in the repertoire of the medicinal chemist. Undoubtedly, the effort necessary to arrive at such systems by conventional synthesis is in part responsible for this situation.

Here we wish to report that the oxazole and thiazole analogs 1 and 2—in both cases the isomer with a *Z* (cis) geometry‡—are highly active CNS *depressant* agents and, furthermore, that some compounds featuring the ring system of 1 but a modified side chain exhibit a pharmacological spectrum that is related to those of the clinical *antidepressants*.

The preparation of these compounds, in fact a fairly extensive modification program, has become feasible through our discovery of a new reaction pathway for α-oximino ketones in general and for the α-oximinobenzosuberones (3) in particular.[4] With the help of this reaction,



amitriptyline, X = CH_2
doxepin, X = O

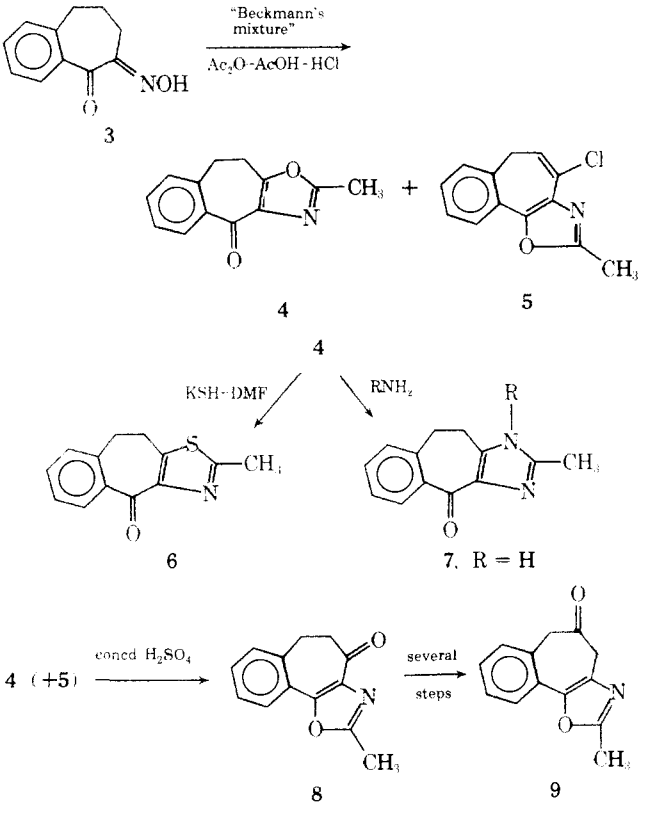


1, X = O
2, X = S

tricyclic oxazole ketones of type 4 can be obtained in one single chemical step (Scheme I). The latter, in turn, could be converted into the thiazole and imidazole analogs 6 and 7 or could be isomerized to the "curved" ketones 8 and 9. Thus, a whole set of novel tricyclic ketone intermediates was at our disposal to explore further the field of heterocyclic analogs of amitriptyline.

In the Chemistry section below, we describe these dibenzosuberone-like intermediates in some detail since some of them—and especially 27 (the alcohol correspond-

Scheme I



*Address correspondence to this author at Sandoz AG, 4002 Basle, Switzerland.

†Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 8-12, 1969.

‡For obvious reasons, we designate "cis" the isomer in which the nitrogenous ring and the nitrogenous side chain are in cis relation with respect to the exocyclic double bond. Unfortunately, the Ingold-Cahn-Prelog absolute nomenclature leads to the "*Z*"-"sec-trans" designation for the same isomer. The assignment of configuration can be based with reasonable confidence on nmr considerations. The signal (triplet, J = 7.0 Hz) for the olefinic proton in 1 (δ 5.74) and 2 (δ 5.83) appears in the same region as the corresponding signal of amitriptyline, (δ 5.86), indicating similar spatial relationships to a nearby benzene ring. As models indicate, the deformation of the seven-membered ring and, along with it, the angle between the plane of the benzene ring and that of the double bond increases as we pass from amitriptyline to 2 to 1. Gradual removal, therefore, of the vinyl proton from the deshielding zone of the benzene moiety may account for this trend in chemical shifts. In the trans isomers of 1 and 2 the olefinic proton gives rise to a lower field signal (δ 6.22 for compound 44, δ 6.38 for compound 45) reflecting the deshielding influence of the lone electron pair of the nitrogen in the heterocyclic ring, to which this proton is now strongly exposed. This assignment ties in with the difference in the "ease" of diprotonaton, as observed in the separation process. The isomers which we assume to be *E* (trans) on the basis of nmr considerations are also the ones which—because of lesser electrostatic interaction—are more easily diprotonated.

ing to ketone 4)—had interesting pharmacology *per se;* thus they produced, through mechanisms as yet undefined, significant reductions of body temperature in mice. An account of this part of the pharmacological work can be found in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.) Below in the Pharmacology section we wish to concentrate on compounds 1, 2, and others listed in Tables III–V.

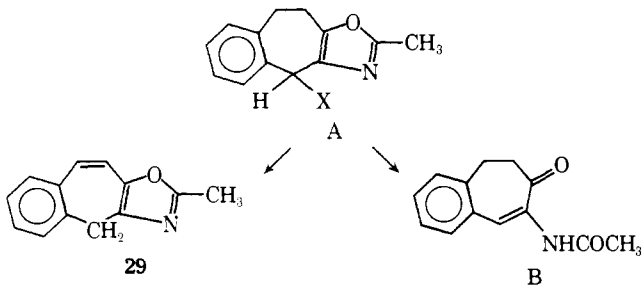
Chemistry. As mentioned above, basic to this development was the finding that when the oximinobenzosuberone (3) was allowed to react with "Beckmann's mixture" (Ac_2O, AcOH, HCl), only a little Beckman fragmentation was observed, and the main products were the oxazoles 4 and 5. The scope of this novel reaction, along with some mechanistic considerations, has been discussed in brief publications.[4,5] Details of this and other illustrative reactions of Scheme I are now given below in the Experimental Section. Table I summarizes information on the tricyclic ketones thus prepared.

The use of "homologous Beckmann's mixtures" (with, *e.g.*, propionyl, isobutyryl, or benzoyl residues) leads smoothly to the appropriately alkylated (or arylated) oxazoles of types 4 and 5. Formic or trifluoroacetic acid, which should yield the unsubstituted or the trifluoromethyl-substituted oxazoles, cannot be utilized, in harmony with the mechanistic considerations.[4]

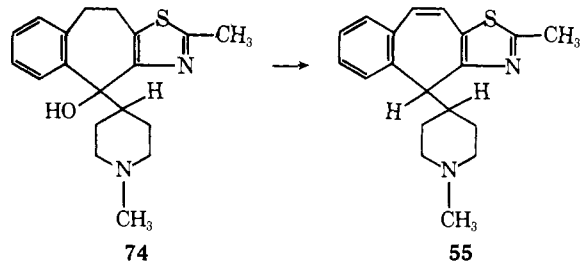
While the transformations 4 → 6 and 4 → 7 (an oxazole to thiazole or imidazole) are not completely unprecedented,[6] neither are they well-known preparative reactions; hence, we think it is appropriate to draw attention to the usefulness of 4-acyloxazoles as synthetic intermediates. The same could be said about the acid-catalyzed isomerization 4 → 8.[7]

Various simple derivatives were prepared from some of the ketones listed in Table I and these appear in Table II. Standard chemical methods were utilized; typical reaction conditions can be found in the Experimental Section. The interesting dual reactivity of system A,[5] shown on Scheme II, is worthy of mention. Where X represents chlorine, the 1,4 elimination product 29 can be obtained by treatment of the starting material with alcoholic KOH or, better, during simple vacuum distillation. Acid-catalyzed hydrolytic cleavage of the oxazole ring to give B occurs readily when X represents OH or NR_2.

Scheme II



From the dehydration reaction of the carbinol 74 in addition to the expected 1,2-elimination product, about 50% of 55 was obtained, apparently the result of a stepwise or concerted 1,4 elimination followed by prototropy. This reaction, observed neither with the oxazole or imidazole analogs nor with the thiazole systems featuring unbranched side chains, could in principle also proceed through a transannular hydride migration step, similarly to a case demonstrated in the dibenzocycloheptene series.[8]



In the preparation of the "final" compounds listed in Tables III–V, the attachment of standard side chains to the above-described tricyclic intermediates could be achieved by methods well developed for the amitriptyline series.[9,10]

Of the "linear" tricyclic ketones listed in Table I, 4, 6, 10–15, and 20 were found to react smoothly with the usual amine-substituted Grignard reagents to form the corresponding 1,2-addition products (tertiary carbinols). In the case of the imidazole ketone 7, prior trimethylsilylation at the secondary nitrogen was necessary. Dehydration of these carbinols to the amitriptyline (or cyproheptadine) analogs could be again achieved by known methods.[9,10] In the dehydration reaction (where theoretically possible), a cis–trans mixture of the expected olefins was formed. In the oxazole and thiazole series, the olefin separation could be achieved with surprising ease, *i.e.*, by extracting a hydrochloric acid (pH 1) solution of the isomers with chloroform, when the hydrochloride of the pharmacologically interesting *Z* (cis) isomer[11] dissolved in the organic phase, leaving the less interesting *E* (trans) isomer, presumably diprotonated, in the aqueous phase.‡

The "curved" ketones 8 and 9, presumably because they enolize in basic conditions, failed to react satisfactorily with Grignard reagents. The nonenolizable, troponoid ketone 24, obtained from 8 by DDQ dehydrogenation, does react, however, and the results of this complex reaction are shown on Scheme III. Ketones 8 and 9 were then converted into a series of aminoalkyl ethers and diamines (Table V), an effort triggered by the Japanese work on the quasi-isosteric dibenzo[*a*,*c*]cycloheptene system.[12]

Scheme III

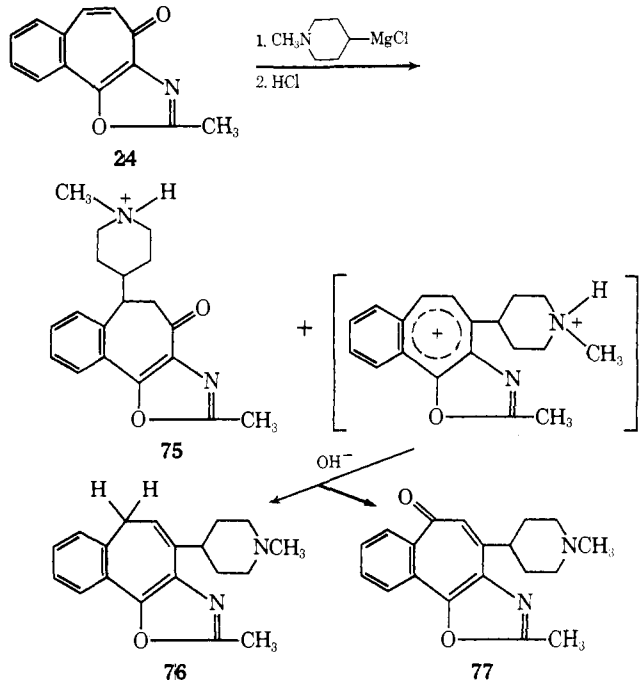
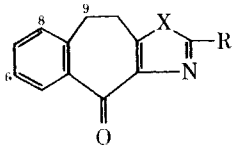
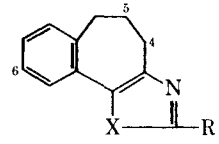


Table I. Tricyclic Ketones



I

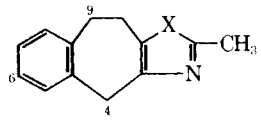


II, 4-keto
III, 5-keto

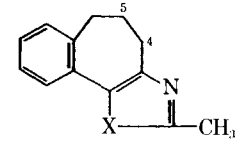
Compd	Type	X	R	Other substitution	Mp, °C	Formula[a]	Method[b]	Yield, %	Recrystn solvent
4	I	O	CH_3		178–179	$C_{13}H_{11}NO_2$	A[c]	37	EtOAc
10	I	O	C_2H_5		122–123	$C_{14}H_{13}NO_2$	A	36	EtOAc
11	I	O	i-C_3H_7		73–76	$C_{15}H_{15}NO_2$	A	32	EtOAC–hexane
12	I	O	C_6H_5		158–160	$C_{18}H_{13}NO_2$	A[c]	34	$CHCl_3$–CH_3OH
13	I	O	CH_3	9-Phenyl	190–192	$C_{19}H_{15}NO_2$	A	48	Benzene
14	I	O	CH_3	6-Chloro	198–199	$C_{13}H_{10}ClNO_2$	A	60	Benzene
15	I	O	CH_3	8-Chloro	125–126	$C_{13}H_{10}ClNO_2$	A	62	EtOAc
16	I	O	CH_3	6-Nitro	215–216	$C_{13}H_{10}N_2O_4$	A	58	EtOAc
17	I	O	CH_3	6-Acetamido	244–246	$C_{15}H_{14}N_2O_3$	*d*	82	EtOAc–hexane
18	I	O	CH_3	6-Dimethylamino	150–153	$C_{15}H_{16}N_2O_2$	*e*	78	EtOAc–hexane
19	I	O	CH_3	Δ^9-Dehydro	178–181	$C_{13}H_9NO_2$	*c*	>5	Sublim at 140° (0.01 mm)
6	I	S	CH_3		138–141	$C_{13}H_{11}NOS$	B[c]	95	Et_2O
7	I	NH	CH_3		203–204	$C_{13}H_{12}N_2O$	C[c]	43	EtOAc
20	I	NCH_3	CH_3		134–135	$C_{14}H_{14}N_2O$	C[c]	87	EtOAc–hexane
21	I	$NCH_2C_6H_5$	CH_3		142–144	$C_{20}H_{18}N_2O$	C	62	EtOAc–hexane
22	I	$NCH_2CH_2N(CH_3)_2$	CH_3		135–136	$C_{17}H_{21}N_3O$	C	56	EtOAc–hexane
23	I	$N(CH_2)_3N(CH_3)_2$	CH_3		93–95	$C_{18}H_{23}N_3O$	C[c]	62	EtOAc–hexane
8	II	O	CH_3		112–113	$C_{18}H_{11}NO_2$	D[c]	84[f]	Et_2O
24	II	O	CH_3	Δ^5-Dehydro	195–196	$C_{13}H_9NO_2$	*c*	65	EtOH
25	II	O	CH_3	9-Nitro	197–199	$C_{13}H_{10}N_2O_4$	D	69[f]	Benzene
9	III	O	CH_3		117–118	$C_{13}H_{11}NO_2$	*c*	58	Et_2O

[a]All compounds were analyzed for C, H, and N; in addition 14 and 15 for Cl and 6 for S. Analytical values were within ±0.4% of the calculated values, with one exception; **20**: calcd for C, 74.3; found, 74.8. [b]Methods that, in the framework of the present paper, can be regarded as general procedures are described in the Experimental Section under the corresponding capital letters. [c]Preparation of the compound described in the Experimental Section. [d]Prepared from 16 by hydrogenation (Pd/C 10%, 25°, 4 atm, 24 hr) in 20 vol of AcOH containing 15 mol of Ac_2O. [e]From 16 by hydrogenation (Raney nickel, 25°, 4 atm, 18 hr) in a mixture of 25 vol of MeOH and 1 vol of 38% aqueous CH_2O solution. [f]Yield based on type 3 starting material.

Table II. Simple Derivatives



IV

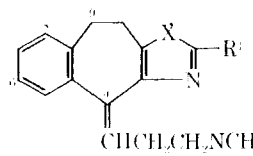


V

Compd	Type	X	Other substitutions	Salt form	Mp or bp (mm), °C	Formula[a]	Method[b]	Yield, %	Recrystn solvent
26	IV	O			57–59	$C_{13}H_{13}NO$	*c*	32	Et_2O
27	IV	O	4-OH		134–135	$C_{13}H_{13}NO_2$	E[c]	98	*i*-PrOH
28	IV	O	4-OH		141–142	$C_{13}H_{13}NOS$	E	98	EtOH–Et_2O
29	IV	O	Δ^9-Dehydro		130–135 (0.1)	$C_{13}H_{11}NO$	*c*	68	
5	V	O	Δ^4-Dehydro, 4-Cl		83–89	$C_{13}H_{10}ClNO$	A[c]	45	Et_2O
30	V	O	Δ^4-Dehydro, 4-Cl, 6-NO_2		146–148	$C_{13}H_9ClN_2O_3$	A	29	EtOAc–hexane
31	V	O			196–199	$C_{13}H_{13}NO$	*d*	78	*i*-PrOH
32	V	O	4-OH		114–115	$C_{13}H_{13}NO_2$	E	96	Et_2O–cyclohexane
33	V	O	Δ^4-Dehydro		115 (0.04)	$C_{13}H_{11}NO$	*c*	73	
34	V	O	4-NH_2	Maleate	178–179	$C_{17}H_{18}N_2O_5$	*c*	96	EtOH–Et_2O
35	V	O	4-NHCHO		152	$C_{14}H_{14}N_2O_2$	*c*	54	EtOAc–hexane
36	V	O	4-$NHCH_3$	Hydrochloride, H_2O	207 dec	$C_{14}H_{19}ClN_2O_2$	*c*	67	EtOH–Et_2O
37	V	O	4-$N(CH_3)_2$	Maleate	178–179	$C_{19}H_{22}N_2O_5$	*c*	76	EtOH–Et_2O
38	V	O	4-$N(CH_2CH_2OH)_2$	Hydrochloride	195–198	$C_{17}H_{23}ClN_2O_3$	*c*	63	EtOH–Et_2O
39	V	O	5-NH_2	Maleate	138–139	$C_{17}H_{18}N_2O_5$	*c*	32	*i*-PrOH–Et_2O
40	V	O	5-$NHCH_3$	Hemifumarate	120 dec	$C_{16}H_{18}N_2O_3$	*c*	81	*i*-PrOH–Et_2O
41	V	O	5-$N(CH_2CH{=}{=}CH_2)_2$		Oil	$C_{19}H_{22}N_2O$	*e*	67	
42	V	O	5-$N(CH_2CH_2OH)_2$	Hydrochloride	114–116	$C_{17}H_{23}ClN_2O_3$	*f*	80	*i*-PrOH–Et_2O
43	V	O	4,5-$(OH)_2$		168–169	$C_{13}H_{13}NO_4$	*g*	63	AcOEt

[a]All compounds were analyzed for C, H, and N; in addition, **30** was also analyzed for Cl. Analytical values were within ±0.4% of the calculated values, the exceptions being **31** (C: calcd, 78.4; found, 78.9), **36** (C: calcd, 59.6; found, 58.9), and **41** (C: calcd 77.5; found, 77.0). [b]Methods that, in the framework of the present paper, can be regarded as general procedures are described in the Experimental Section under the corresponding capital letters. [c]Preparation of the compound described in the Experimental Section. [d]From **33** by hydrogenation (Pd/C 5%, EtOH, 4 atm, 25°). [e]From **39**, 6 mol of $CH_2{=}CHCH_2Br$ in CH_3OH, Na_2CO_3, reflux 6 hr. [f]From **39**, analogously to **38**. [g]See the preparation of **9** (Experimental Section).

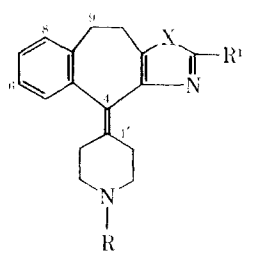
Table III. Derivatives of the Amitriptyline Type



Compd	X	R^1	R	Other structural features[a]	Salt form[a]	Mp or bp (mm), °C	Formula[b]	Method[c]	Yield, %	Recrystn solvent[a]
1	O	CH_3	CH_3	*Z* (cis)	HCl	207 dec	$C_{18}H_{23}ClN_2O$	F	32	$MeOH-CH_2Cl_2$
2	S	CH_3	CH_3	*Z* (cis)	HCl	225 dec	$C_{18}H_{23}ClN_2S$	F[d]	36	$MeOH-CH_2Cl_2$
44	O	CH_3	CH_3	*E* (trans)	HCl	243–245	$C_{18}H_{23}ClN_2O$	F	37	$EtOH-Et_2O$
45	S	CH_3	CH_3	*E* (trans)	HCl	150 dec	$C_{18}H_{23}ClN_2S$	F[d]	40	$EtOH-Et_2O$
46	O	CH_3	H	Cis–trans	Free base	185 (0.01)	$C_{17}H_{20}N_2O$	*e*	51	
47	S	CH_3	H	Cis–trans	Free base	190 (0.01)	$C_{17}H_{20}N_2S$	*e*	59	
48	NCH_3	CH_3	CH_3	Cis–trans	Free base	170 (0.01)	$C_{19}H_{25}N_3$	F	80	
49	O	C_2H_5	CH_3	Cis–trans	Free base	185 (0.01)	$C_{19}H_{26}N_2O$	F	82	
50	O	CH_3	CH_3	Cis–trans, 6-chloro	Free base	195 (0.01)	$C_{19}H_{21}ClN_2O$	F	86	
51	O	CH_3	CH_3	Cis–trans, 8-chloro	Free base	200 (0.01)	$C_{18}H_{21}ClN_2O$	F	73	
52	O	CH_3	CH_3	Cis–trans, 9-phenyl	Free base	230 (0.01)	$C_{24}H_{26}N_2O$	F	59	
53	O	CH_3	CH_3	4(1′)-Dihydro	HCl	191 dec	$C_{18}H_{25}N_2OCl$	*f*	68	$MeOH-Et_2O$
54	S	CH_3	CH_3	Δ^9-Dehydro, 4(1′)-dehydro, 1′-vinyl	Free base	190 (0.01)	$C_{20}H_{24}N_2S$	*d*	25	

[a]Compounds marked cis–trans were obtained and characterized as oily mixtures of the cis and trans free bases. Purification was effected by short-path distillation at the bath temperature and pressure as recorded. As deducible from nmr spectra, the cis–trans ratio in these samples was within 1.0:(1.0 ± 0.2). For testing, they were dissolved in the calculated volume of 0.5 *M* CH_3SO_3H solution. It is clear that *biological results obtained on cis–trans mixtures can serve for orientation only*. That such data, however, can indeed be used with confidence within reasonable limits was indicated by a comparison of data obtained on the cis trans mixtures 1/44 and 2/45 with those on pure 1 and 2, respectively. On the level of testing applied in this work, the differences observed were merely quantitative in nature and close to what one would deduce from an assumed additivity relationship. [b]Compounds were analyzed for C, H, and N; in addition, 1, 2, 44, and 45 for Cl also. An exception was 53 that was analyzed for Cl only. [c]Methods that, in the framework of the present paper, can be regarded as general procedures are described in the Experimental Section under the corresponding capital letters. [d]Preparation of the compound is described in the Experimental Section. [e]Analogously to 58 (Table IV), from the parent cis trans, R = CH_3 compound. [f]From 1, H_2–Pd/C 5%, 60 atm, 80°, 18 hr.

Table IV. Derivatives of the Cyproheptadine Type

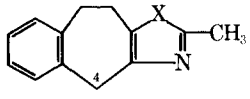


Compd	X	R^1	R	Other structural features	Salt form[a]	Mp or bp (mm), °C[a]	Formula[b]	Method[c]	Yield, %	Recrystn solvent

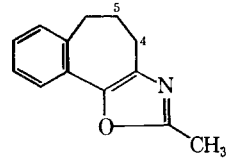
55	S	CH_3	CH_3	Δ^9-Dehydro, 4(1′)-dihydro	Fumarate	138–139	$C_{23}H_{26}N_2O_4S$	G[d]	62	MeOH–Et_2O
56	O	CH_3	CH_3		Free base	108–109	$C_{19}H_{22}N_2O$	G[d]	74	Cyclohexane
57	S	CH_3	CH_3		Free base	220 (0.01)	$C_{19}H_{22}N_2S$	G[d]	10	
58	O	CH_3	H		Methanesulfonate	145–150	$C_{19}H_{24}N_2O_4S$	*d*	47	MeOH–Et_2O
59	O	CH_3	$(CH_2)_2OH$		Free base	220 (0.02)	$C_{20}H_{24}N_2O_2$	*e*	83	
60	O	CH_3	$(CH_2)_2OCOCH_3$		Free base	200 (0.01)	$C_{22}H_{26}N_2O_3$	*f*	92	
61	O	CH_3	CH_3	6-Chloro	Fumarate	220–220	$C_{23}H_{25}ClN_2O_5$	G	81	*i*-PrOH
62	NH	CH_3	CH_3		Fumarate	229–230	$C_{23}H_{27}N_3O_4$	G[g]	63	MeOH–Et_2O
63	NCH_3	CH_3	CH_3		Difumarate	251–252	$C_{28}H_{33}N_3O_8$	G	69	MeOH–Et_2O

[a]Some of the compounds were characterized as free bases after purification by short-path distillation at the bath temperature and pressure recorded. [b]All compounds were analyzed for C, H, and N; values were within ±0.4% of the calculated figures. [c]Methods that, in the framework of the present paper, can be regarded as general procedures are described in the Experimental Section under the corresponding capital letters. [d]Preparation of the compound is described in the Experimental Section. [e]Analogously to **38**. [f]From **59**, Ac_2O, 25°, 18 hr. [g]Before the Grignard reaction as under G, the starting material **7** had to be trimethylsilylated (Me_3SiCl, pyridine in EtOAc-Et_2O, 25°, 18 hr).

Table V. Miscellaneous Derivatives



A



B

Compd	Type	X	Substitution	Salt form[a]	Mp or bp (mm), °C[a]	Formula[b]	Method[c]	Yield, %	Recrystn solvent
64	A	O	4-c-$N(CH_2CH_2)_2NCH_3$	Free base	113–115	$C_{18}H_{23}N_3O$	H[d]	95	Et_2O
65	A	S	4-c-$N(CH_2CH_2)_2NCH_3$	Free base	154–156	$C_{18}H_{23}N_3S$	H	81	Et_2O
66	A	O	4-$N(CH_3)(CH_2)_2NHCH_3$	Fumarate	191–192 dec	$C_{21}H_{27}N_3O_5$	H	61	CH_3OH–Et_2O
67	A	O	4-$NH(CH_2)_2N(CH_3)_2$	Fumarate	150–153 dec	$C_{21}H_{27}N_3O_5$	H	46	CH_3OH–Et_2O
68	A	O	4-c-$N(CH_2CH_2)_2NCH_3$, 1′-dimethyl	Difumarate	155–158	$C_{28}H_{35}N_3O_9$	H	92	CH_3OH–Et_2O
69	B	O	4-c-$N(CH_2CH_2)_2NCH_3$	Dihydrochloride, $2H_2O$	239–241	$C_{18}H_{29}Cl_2N_3O_3$	H	56	CH_3OH–Et_2O
70	B	O	5-c-$N(CH_2CH_2)_2NCH_3$	Dimaleate	170–171	$C_{26}H_{31}N_3O_9$	H[d]	68	CH_3OH–Et_2O
71	B	O	4-$O(CH_2)_2N(CH_3)_2$	Free base	140–145 (0.03)	$C_{17}H_{22}N_2O_2$	*d*	66	
72	B	O	4-$O(CH_2)_2N(C_2H_5)_2$	Free base	165–167 (0.03)	$C_{19}H_{26}N_2O_2$	*e*	61	
73	B	O	4-$O(CH_2)_3N(CH_3)_2$	Free base	270–278 (0.03)	$C_{18}H_{24}N_2O_2$	*e*	70	

[a]Some of the compounds were characterized as free bases after purification by short-path distillation at the bath temperature and pressure recorded. For testing, they have been dissolved in the calculated volume of 0.5 *M* methanesulfonic acid solution. [b]All compounds have been analyzed for C, H, and N; results were within ±0.4% of the calculated figures. [c]Methods that can be regarded, within the framework of the present paper, as general procedures are described in the Experimental Section under the corresponding capital letters. [d]Preparation of the compound is described in the Experimental Section. [e]Analogously to **71**.

Table VI. Pharmacology§,[k]

Compd	LD_{50},[a] mg/kg ip	LRR_{50},[b] mg/kg	Docility$_{50}$,[b] mg/kg ip	Ataxia$_{50}$,[b] mg/kg ip	Hypothermic effect,[c] mg/kg ip	Rotarod, ND_{50},[d] mg/kg ip	Hexobarbital reinduction, RD_{50},[e] mg/kg ip	Amphet antag,[f] mg/kg ip	Tremorine (T)–oxotramorine (O) antag,[g] ED_{50}, mg/kg ip	Reserpine antag,[h] ED_{50}, mg/kg ip	Dopa potentiation,[i] mg/kg ip	Norepinephrine potentiation,[j] mg/kg ip
					Standards							
Amitriptyline	68.7	33.0	68.7	25.8	−0.2, 50.0	20.2	14.6	≥54, 12 ≤70, 50	>25.0 (O)	8.0	NT[d]	++, 3.0
Imipramine	116.7	100.0	93.4	58.3	−0.1, 50.0	14.1	50.0	≥14, 12 ≤8, 50	>25.0 (O)	10.0	NT	++, 3.0
Desipramine	91.7	NT	NT	NT	NT	NT	>50.0	≥93, 12 ≤58, 50	NT	6.0	NT	NT
Chlorpromazine	131.9	131.9	12.1	0.8	−1.0, 5.0	0.6	1.1	2.0	>5.0	>6.4	NT	NT
					Amitriptyline Analogs (Table III)							
1 (*Z*)-*cis*-oxazole	37.5	37.7	37.5	12.5	−0.8, 20.0	>10.6	9.2	5.0	17.2 (T)	>25.0	NA, 25.0	++, 1.0
2 (*Z*)-*cis*-thiazole	46.8	46.8	23.4	5.9	−0.4, 20.0	8.0	16.7	5.0	9.2 (T)	>15.0*	NA, 15.0	++, 10.0
44 (*E*)-*trans*-oxazole	37.5	NT	NT	37.5	NT	>18.7	>18.7	>18.7	>18.7 (O)	>25.0	NT	NT
45 (*E*)-*trans*-thiazole	43.8	NT	NT	41.6	NT	17.0	25.0	>12.0	>25.0 (O)	>25.0	NA, 15.0	NT
46 oxazole with nor chain	23.4	23.4	23.4	7.8	−2.2, 10.0	17.0	>20.0	>5.0	>20.0 (T)	>25.0	NA, 15.0	++, 10.0
47 thiazole with nor chain	75.0	75.0	NT	37.5	−1.1, 25.0	22.0	>50.0	>25.0	10.1 (T)	+, 25.0	NT	NT
48 imidazole	150.0	150.0	150.0	100.0	+0.8, 50.0	>50.0	>100.0	>25.0	>50.0 (T)	>15.0*	NA, 15.0	++, 10.0
49 oxazole with nuclear ethyl	37.5	37.5	25.0	<6.3	+0.4, 12.5	6.3	18.9	9.0	NT	>25.0	+, 25.0	NT
					Cyproheptadine Analogs (Table IV)							
56 oxazole	51.0	51.0	51.0	6.3	−2.8, 20.0	9.3	27.5	12.0	3.2 (O) 0.6 (T)	25.0	+25.0	NA, 1.0
55 thiazole	58.8	NT	NT	NT	−1.3, 25.0	30.5	>50.0	50.0	2.3 (T)	>25.0	NT	NT
59 oxazole with hydroxyethyl chain	150.0	NT	NT	50.0	−2.3, 25.0	6.4	45.8	25.0	9.3 (O)	NT	NA, 25.0	NT
60 oxazole with acetoxyethyl chain	175.0	NT	NT	50.0	−1.6, 25.0	9.0	37.5	25.0	18.8 (O)	+, 15.0	NA, 25.0	NT
61 oxazole with nuclear chloro	150.0	NT	NT	50.0	−2.9, 20.0	>10.0	>40.0	>20.0	>20.0 (T)	>25.0	NT	NA, 25.0
62 imidazole	300.0	200.0	NT	200.0	−6.4, 100.0	78.6	>25.0	100.0	>25.0 (O)	>25.0	NT	NT
63 imidazole with nuclear *N*-methyl	300.0	>200.0	>200.0	>200.0	−1.5, 100.0	>100.0	>25.0	>100.0	>25.0 (O)	>25.0	NT	NT

				Miscellaneous (Table V)						
64 oxazole with *N*-methylpiperazine	75.0	75.0	75.0	63.0	~0.1, 37.5	8.5	>37.5	≥65, 2.5 ≤12, 40.0	4.0 (O)	+, 25.0*	NT	++, 10.0

[c]Determined by the method of L. J. Reed and M. Muench, *Amer. J. Hyg.*, **27**, 493 (1938); five animals per dose. [b]Analysis of behavior using modification of the method of Irwin.[13] LRR ≈ loss of righting reflex. [c]Average change in body temperature of five mice determined by taking rectal temperature before and 1 hr after the indicated dose. [d]Rotarod method of Dunham and Miya;[14] five animals per dose. ND ≈ neurological deficit. [e]Modified method of Winter;[15] groups of five mice were administered compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time. [f]Determined in mice using standard photocell activity cages manufactured by Woodward Research Corp., Herndon, Va.: dose of *dl*-amphetamine, 2.5 mg/kg ip; five mice per group. [g]Modifications of the methods of Everett, *et al.*,[16] for tremorine and/or George, *et al.*,[17] for oxotremorine; five mice per group. In each of these tests, prevention of tremors was considered evidence of central anticholinergic activity. ED_{50} is defined as the dose that prevented tremors in 50% of mice. [h]Modification of the method of Spencer[18] except where designated with an asterisk, in which case the method was a modification of that described by Sulser, *et al.*[19] In each test, groups of five mice were administered reserpine at 5 mg/kg ip followed 1 hr later by the test drug administered intraperitoneally on the contralateral side. In the first mentioned test, rectal temperatures were taken before and 5 hr after reserpine; the ED_{50} is defined as that dose of test drug which prevented by 50% the hypothermic response measured the 5th hr after reserpine. In the second test, the ability of the test drugs to prevent the cataleptic-like position induced by reserpine was evaluated; the ED_{50} is that dose that prevented this response in 50% of the mice. [i]Modification of the method of Everett and Wiegard;[20] *dl*-Dopa (Dopa), administered at 50 mg/kg iv to groups of five mice that were pretreated with pargyline, caused stimulation characterized by spontaneous increased activity, exophthalmus, piloerection, and aggressiveness. Potentiation of these effects was graded on an arbitrary scale: + ≈ weak; ++ ≈ moderate; +++ ≈ marked potentiation. [j]Potentiation of norepinephrine-induced pressor effects in anesthetized dogs. Potentiation was scored on an arbitrary scale: + ≈ 15–100%; ++ ≈ >100% increase. [k] NA ≈ not active. NT ≈ not tested.

The structural assignments throughout this work fulfill the requirement that all chemical and spectral observations fit into a reasonable and self-consistent picture. The most significant spectral data for the key tricyclic ketones and for compounds **75–77** are recorded in the Experimental Section and thus the structural arguments can be easily reconstructed.

Biological Evaluation. Although, as mentioned above, some of the simpler "intermediary" tricyclic compounds (Tables I and II) also exhibited interesting pharmacological properties (see supplementary material), here we wish to concentrate on the derivatives listed in Tables III–V, *i.e.*, on the compounds offering a relevant comparison to the standard tricyclic drugs amitriptyline, imipramine, desmethylimipramine, and chlorpromazine. Our data obtained with these standards and with the most relevant new derivatives§ are compiled in Table VI (see also Table VII). We have employed a battery of tests in mice commonly used to define major tranquillizer and/or antidepressant profile.

Acute toxicity of each compound is expressed as the LD_{50} (lethal dose in 50% of animals) calculated from mortality of mice receiving the drugs intraperitoneally at log-spaced doses. Behavioral effects were evaluated by a modification of the observational techniques described by Irwin.[13] Effects on body temperature were obtained by comparing rectal temperatures obtained immediately before and 1 hr after the test drug was administered intraperitoneally.

CNS depressant activity was defined by the ability of the compounds to cause neurological deficit as measured using the rotarod test,[14] to reinduce anesthesia in mice recovering from hexobarbital-induced anesthesia,[15] and to antagonize amphetamine-induced hypermotility in mice as measured in activity cages.& Central anticholinergic effects were evaluated by testing for antagonism of tremorine-induced[16] or oxotremorine-induced[17] tremors in mice. The ability of compounds to augment central sympathomimetic activity was defined by antagonism of reserpine-induced hypothermia[18] or behavioral depression[19] and potentiation of aggressive behavior induced in mice by *dl*-dihydroxyphenylalanine (Dopa).[20] In addition, possible augmentation of peripheral sympathomimetic effects was evaluated by the ability of the compounds to potentiate norepinephrine-induced pressor effects in anesthetized dogs.

Structure–Activity Relationships. The answer to the central question of this work—how the biological profiles of the novel hetero analogs relate to that of the parent amitriptyline—seems to some extent fit a generalization occasionally spelled out in the literature (*e.g.*, see ref 21): "... Hetero analogs ... frequently possess neuroleptic ... rather than thymoleptic properties." Thus **1**, the *Z* (cis) oxazole analog, produces marked CNS depression (sleep reinduction in the hexobarbital test—amphetamine antagonism), marked central anticholinergic activity (blockade or tremorine-induced tremors), and moderate potentiation (in dogs) of the norepinephrine-induced pressor effects. This neuroleptic profile was also shown by the thiazole **2**, a difference being that **1** but not **2** elicited clonic convulsions at toxic doses. The imidazole analog **48** was less active.

§Table VI contains, for the sake of clarity, data only on the more relevant ones of the compounds listed in Tables III-V. Testing results on compounds **50–54**, **57**, **58**, and **65–68** are summarized in Table VII. Compounds **52**, **57**, and **65** were not extensively tested because of poor availability at the time when the work was carried out.

&Woodard Research Corp., Herndon, Va.

Table VII. Pharmacology[k]

Compd	LD_{50},[a] mg/kg ip	LRR_{50},[b] mg/kg	Docility$_{50}$,[b] mg/kg ip	Ataxia$_{50}$,[b] mg/kg ip	Hypothermic effect,[c] mg/kg ip	Rotarod, ND_{50},[d] mg/kg ip	Hexabarbital reinduction, RD_{50},[e] mg/kg ip	Amphet antag,[f] mg/kg ip	Tremorine (T)–oxotremorine (O) antag,[g] ED_{50}, mg/kg ip	Reserpine antag,[h] ED_{50}, mg/kg ip	Dopa potentiation,[i] mg/kg ip	Norepinephrine potentiation,[j] mg/kg ip
50	68.8	68.8	NT	12.5	−0.1, 20.0	>20.0	>20.0	>50.0	>40.0 (T)	>25.0	NT	NT
51	75.0	75.0	NT	12.5	−0.6, 20.0	>20.0	>40.0	>20.0	>40.0 (T)	>25.0	NT	NT
53	45.8	>25.0	>25.0	>25.0	NT	>25.0	>25.0	NT	>25.0 (O)	>25.0	NT	NT
54	75.0	75.0	75.0	54.5	−0.1, 20.0	27.1	>37.0	>25	9.4 (O)	>25.0	NT	NT
58	75.0	NT	NT	NT	−0.1, 50.0	39.7	50.0	25.0	5.0 (T)	25.0	NT, 25.0	NT
66	>102.4	NT	NT	NT	NT	53.3	>102.4	+22, 50.0	>50.0 (O)	>25.0	NT	NT
67	162.5	150.0	150.0	133.3	NT	86.0	74.8	+13, 37.5	>25.0 (O)	>25.0	NT	NT
68	162.5	>100.0	>100.0	75.0	−0.2, 50.0	38.2	>50.0	12.0	>25.0 (O)	>25.0	NT	NT

a–kSee footnotes, Table VI.

That these activities clearly resided with the *Z* (cis) rather than the *E* (trans) isomers represents an interesting addition to a set of similar observations with tricyclic systems. In all previous cases where the configuration was established, the aminopropylidene side chain of the biologically more interesting isomer was oriented *away* from the "unsubstituted" benzene moiety and *toward* what was also a benzene ring** but substituted in such a fashion that the symmetry of its π-electron system was heavily perturbed. Apparently, an oxazole or thiazole can assume, with respect to fitting to the receptor(s), the role of these substituted benzene rings.

Some other structure–activity observations from the amitriptyline series[9] also appear to have their "equivalents" with these oxazole and thiazole analogs. An example is the necessity of at least one (nonaromatic) double bond in, or attached to, the seven-membered ring for any significant CNS activity. Thus, the intermediary carbinols leading to **1** and **2** (not presented in tables) and the dihydro product of **1** (**53**)§ are essentially inactive. The effect of N-demethylation of the amitriptyline side chain is mirrored by the analogous changes on **1** and **2**; compounds **46** and **47** have weaker CNS depressant activity, but the central anticholinergic activity was maintained and short-acting reserpine-antagonistic effects appeared. These changes of pharmacological profile are similar to that observed when one compares imipramine and desipramine.

The phenomenon of cis–trans isomerism does not, of course, present itself with the symmetrical *N*-methylpiperidylidene side chain, best known from cyproheptadine, a clinically useful antipruritic drug. While the latter is essentially devoid of CNS activities, it is known that the same side chain, when attached to other tricyclic systems, can give rise to (in part even clinically proven) CNS effects. A well-known example is BC 105.[2] The *N*-methylpiperidylidene derivatives of our oxazole and thiazole systems retained the CNS depressant activities observed with **1** or **2**, but their central anticholinergic activity—see, *e.g.*, **56**—was markedly increased. Also, potentiation of Dopa-induced central stimulation appeared, in absence of a stimulation of the norepinephrine-induced effects. With this side chain, the imidazole analogs (**62** and **63**) retained significant, albeit weaker CNS depressent activity (while the central anticholinergic and Dopa-potentiating effects were lost).

A shift toward the "antidepressant profile" took place, when, in the oxazole system, the *N*-methyl group of the piperidylidene side chain was replaced by a β-hydroxyethyl or β-acetoxyethyl residue (**59** and **60**), a standard modification in the tricyclic field. Thus, a loss in CNS depressant and anticholinergic potency on one hand, the appearance (with **60**) of a blockade of reserpine-induced behaviorial effects on the other hand, could be observed.

One of the most interesting compounds of this work (**64**) resulted through the replacement of the *N*-methylpiperidylidene side chain of **56** by the quasi-isosteric *N*-methylpiperazine moiety. In addition to the (somewhat weaker) CNS depressant and anticholinergic activities, it exhibited short-acting reserpine antagonistic effects. The ring-opened analogs of the *N*-methylpiperazine **64**, *i.e.*, **66** and **67**, were inactive.

As shown above, the chemical method utilized in this work allows also for the easy preparation of systems with substituents more bulky than methyl on the heterocyclic moiety. Our exploration of this aspect was restricted to the ethyl homolog of **1** (*i.e.*, **49**) and to the isopropyl ho-

**See, however, ref 2.

molog of 64 (*i.e.*, 68). The switch of methyl to ethyl (compound 49) left the pharmacological profile of 1 basically unaltered except that, at 25 mg/kg, Dopa potentiation became observable. Drastic pharmacological consequences were brought about by the change methyl → isopropyl, 64 → 68; the antidepressant profile of 64 disappeared,§ only to be replaced by questionable muscle-relaxing activity accompanied by unfavorable cardiovascular effects.

The introduction of a chlorine substituent on the benzene moiety was also counterproductive (structures 50, 51,§ and 61). Based on the above discussion about the relative potencies of cis-trans isomers in tricyclic systems, these compounds could be compared to an amitriptyline derivative having a chlorine substituent on each of the two benzene moieties. Like the latter, they had substantially reduced CNS and anticholinergic activities.

The pharmacology of the derivatives obtained from the "curved" systems 8 and 9 is not detailed here. From the CNS standpoint at least, they were much less interesting than the compounds with the "linear" ring system. Many of them (69–73) were eliminated at an early stage of the investigation because they had insignificant CNS activity and caused profound EKG changes in dogs.

Summary and Conclusions

The compounds tested provide a progression of pharmacological profiles ranging from those that are primarily sedatives to those that are antidepressants. The most active compound with respect to sedation, 2, is a good candidate for spinal reflex studies in cats and for being tested for its effects on sleep patterns in cats implanted with cortical and subcortical electrodes. At the other end of this spectrum are compounds like 64 and 56 which have less CNS depressant activity but do have central anticholinergic activity and CNS stimulant activity, as indicated by reversal of reserpine-induced hypothermia or potentiation of Dopa-induced CNS stimulation. This "mixed" activity shown by these latter compounds is similar to that observed with the "standard" antidepressants.

Importantly, 64 (although not 56) resembled these standards also in providing amphetamine potentiation at low doses, amphetamine antagonism at high doses, and a marked potentiation of the norepinephrine-induced pressor effects at 10 mg/kg ip.

Because of these interesting profiles and activity levels, it appears that certain substances, *e.g.*, 64, warrant further investigation as clinical antidepressants.

Experimental Section††

Starting Materials. α-Oximinobenzosuberone (3). Benzosuberone (1 kg, 6.1 mol) was dissolved in 20 l. of anhydrous etheral HCl (370 g) solution; then at 15–20°, 650 g (6.3 mol) of *n*-butyl nitrite was added over 50 min. At 5°, 4 l. of petroleum ether was added, whereupon 851 g of 3, mp 136–137°, crystallized. An additional 150 g (a total of 85%) was obtained through extraction of the mother liquor with 2 *N* NaOH and reacidification. *Anal.* ($C_{11}H_{11}NO_2$) C, H, N. The following compounds were similarly obtained from 1-chloro-,‡‡ 3-chloro-,‡‡ 3-nitro-,[22] and 9-phenylbenzosuberones.[23] **1-Chloro-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one** (92%): mp 174–175° (EtOAc-Et_2O). *Anal.* ($C_{11}H_{10}ClNO_2$) C, H, Cl, N. **3-Chloro-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one** (88%): mp 184–186° (EtOAc-Et_2O). *Anal.* ($C_{11}H_{10}ClNO_2$) C, H, Cl, N. **3-Nitro-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one** (81%): mp 207–208° (benzene-Et_2O). *Anal.* ($C_{11}H_{10}N_2O_4$) C, H, N. **9-Phenyl-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one** (71%): mp 176–177° (Et_2O). *Anal.* ($C_{17}H_{15}NO_2$) C, H, N.

General Methods. A. Oxazoles of Types 4 and 5. 2-Methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazol-4-one (4). AcCl (645 ml, 11 mol) was added dropwise (60 min) to a solution of 397 g (2.1 mol) of 3 in 4.2 l. of AcOH and 440 ml of Ac_2O at 85°. After 60 min at 85°, the mixture was poured on ice–NaOH and extracted with $CHCl_3$ to yield 469 g of thick oil from which (400 ml of AcOEt) 166 g (37%) of 4, mp 178–179°, crystallized: λ_{max} ($CHCl_3$) 6.06 μ; $\lambda\lambda_{max}$ (EtOH) 253 mμ (ε 8880), 281 (9280); nmr ($CDCl_3$) 3 H at δ 2.45 (s), 4 H at δ 3.14 (m, "quasi-s"), 3 H + 1 H at δ 7–8 (m). *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

The oil obtained on evaporation of the mother liquor was distilled [bp 130° (0.01 mm)] and the distillate crystallized from ether to yield 220 g (45%) of **2-methyl-4-chloro-6*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (5)**, mp 88–89°. *Anal.* ($C_{13}H_{10}ClNO$) C, H, Cl, N.

2-Phenyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazol-4-one (12). To a molten mixture of 100 g of PhCOOH, 50 g (0.36 mol) of PhCOCl, and 50 g of $(PhCO)_2O$, at 80–85°, there was added 15 g (0.08 mol) of 3. After 30 min, the mixture was stirred into iced 6 *N* NaOH (450 ml). On extraction with benzene and recrystallization of the solid residue from $CHCl_3$–CH_3OH, 9.35 g (34%) of 12, mp 158–160°, was obtained. *Anal.* ($C_{18}H_{13}NO_2$) C, H, N.

B. Transformation of Oxazole → Thiazole. 2-Methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]thiazol-4-one (6). A suspension of 30.0 g (0.27 mol) of KO-*t*-Bu in 300 ml of dry DMF was saturated at 5° with H_2S; 15 g (0.07 mol) of 4 was added and the mixture was stirred at 25° for 30 min and poured on ice. The pH was adjusted to 4 by the addition of concentrated HCl and the product was extracted with benzene. Crystallization from ether gave 15.3 g (95%) of 6: mp 138–141°; λ_{max} (KBr) 6.10 μ; $\lambda\lambda_{max}$ (EtOH) 253 mμ (ε 9030), 287 (9560); nmr ($CDCl_3$) 3 H at δ 2.55 (s), 4 H at δ 3.17 ("s"), 3 H + 1 H at δ 7–8 (m). *Anal.* ($C_{13}H_{11}NOS$) C, H, N, S.

C. Transformation of Oxazole → Imidazole. 2,3-Dimethyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]imidazol-4-one (20). A mixture of 20 g (0.094 mol) of 4 and 250 ml of liquid methylamine, enclosed in an autoclave, was rocked at 115° for 2 hr. The residue obtained on evaporation of the amine was chromatographed on silica gel ($CHCl_3$) to yield 18.5 g (87%) of 20: mp 134–135° (EtOAc-hexane); λ_{max} (KBr) (HCl salt) 6.12 μ; $\lambda\lambda_{max}$ (EtOH) (base) 275 mμ (ε 9350), 291 (7500); $\lambda\lambda_{max}$ (EtOH) (HCl salt) 221 mμ (ε 7960), 284 (16,300); nmr ($CDCl_3$) 3 H at δ 2.34 (s), 4 H at δ 2.94 (m), 3 H at δ 3.41 (s), 3 H + 1 H at δ 7–8 (m). *Anal.* ($C_{14}H_{14}N_2O$) C, H, N. The analogous transformation with liquid ammonia, yielding 43% of 7, required 15 hr.

1-(3-Dimethylaminopropyl)-2-methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]imidazol-4-one (23). A mixture of 21.3 g (0.1 mol) of 4 and 80 g (0.78 mol) of 3-dimethylaminopropylamine was refluxed for 2 hr and then stored at 5° for 18 hr whereupon 18.5 g (62%) of 23 crystallized. Recrystallization from AcOEt–hexane gave mp 93.5–95°. *Anal.* ($C_{18}H_{23}N_3O$) C, H, N.

D. Isomerization of Oxazole Ketones and Hydrolysis of Types 5. 2-Methyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazol-4-one (8). The crude mixture of 4 and 5 (120 g) obtained as shown above was dissolved in 250 ml of concentrated H_2SO_4. After 18 hr at room temperature, the evolution of HCl ceased and the mixture was poured on ice. On neutralization (NaOH) 97.1 g of 8 (84% based on 3) precipitated. Recrystallization from Et_2O gave mp 105–106°: λ_{max} ($CHCl_3$) λ 5.97 μ; $\lambda\lambda_{max}$ (EtOH) 226 mμ (ε 15,400), 298 (15,400); nmr ($CDCl_3$) 3 H at δ 2.55 (s), 4 H at δ 2.91 (m), 3 H + 1 H at 7.2–8 (m). *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

E. Borohydride Reduction of Ketones. 4-Hydroxy-2-methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazole (27). To a solution of 21.3 g (0.1 mol) of 4 in 210 ml of CH_2Cl_2–EtOH (1:4), chilled to 5°, there was added 2.9 g (0.06 mol) of $NaBH_4$. After stirring for 5 hr at 5°, 210 ml of 1 *N* NaOH was carefully added and the mixture worked up with CH_2Cl_2. Crystallization from 150 ml of *i*-PrOH yielded 21.0 g (98%) of 27, mp 134–135°. *Anal.* ($C_{13}H_{13}NO_2$) C, H, N.

F. Attachment of the Amitriptyline Side Chain. (*Z*)-2-Methyl-4-(3′-dimethylaminopropylidene)-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]thiazole (2). To a Grignard mixture[9] pre-

††Melting points were determined using a Thomas-Hoover melting point apparatus and were recorded uncorrected. Spectral (ir, uv, 60-MHz nmr, and mass) data were accumulated on each new compound; where particularly significant (key tricyclic ketones, compounds 75–77), their most relevant features are recorded. Symbols of elements refer to microanalyses with results within ±0.4% of the calculated values.

‡‡The chlorobenzosuberones were obtained through direct chlorination, in $C_2H_2Cl_4$, of a performed benzosuberone-$AlCl_3$ complex, followed by fractional distillation [E. Galantay, U. S. Patent 3,408,360 (Oct 29, 1968)]. The 3-chlorobenzosuberone thus obtained was identical with a sample obtained through an unequivocal route [high-dilution cyclization ($AlCl_3$–CS_2) of 5-*p*-chlorophenylvaleroyl chloride].

pared from 147 g (6 g-atoms) of Mg and 750 g (6.2 mol) of dimethylaminopropyl chloride in 6.3 l. of THF there was spoonwise added, at 0–10°, 558 g (2.62 mol) of 4 (20 min). After another 20 min at 10° 1.5 l. of concentrated aqueous NH_4Cl solution was added. The THF supernatant was evaporated and redissolved in AcOEt (5 l.) previously used for the washing of the residual Mg salts. Extraction of this AcOEt solution with 3 *M* aqueous AcOH, basification (ice-NaOH) of the acid extracts, and reextraction with CH_2Cl_2 yielded 780 g of the crude carbinol intermediate, which in turn was treated in EtOH (6.5 l.) with HCl gas (10 l./hr, 4 hr, 25°). Evaporation of the EtOH and the usual work-up [50% KOH-ice, ether extraction, and distillation, bp 207–210° (0.025 mm)] yielded 614 g (83%) of the cis–trans mixture of products. To obtain pure the mixture was distributed between 6 l. of $CHCl_3$ and 10 l. of 1 *N* HCl, and the separated aqueous phase was exhaustively extracted with $CHCl_3$. The crystalline residue obtained on evaporation of the combined $CHCl_3$ layers gave, on washing with CH_2Cl_2–MeOH, 310 g (36%) of the hydrochloride, mp 193–214°. *Anal.* ($C_{18}H_{23}ClN_2S$) C, H, N, Cl.

To obtain the *E* (trans) isomer of **2**, *i.e.*, **45**, the above acid aqueous phase was made strongly alkaline (500 g of Na_2CO_3 and 100 ml of 40% NaOH solution) and extracted with benzene. The oily residue obtained on evaporation of the benzene layers was distilled (180° bath temperature, 0.01 mm) and the thus purified free base (315 g) converted (*i*-PrOH–Et_2O–HCl) into **45** · HCl. After three recrystallizations from EtOH–Et_2O, 344 g (40%), mp 150° dec, was obtained. *Anal.* ($C_{18}H_{23}ClN_2S$) C, H, N, Cl.

G. **Attachment of the Cyproheptadine Side Chain. 2-Methyl-4-(1′-methyl-4′-piperidylidene)-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazole (56).** To a Grignard mixture, prepared[10] from 24 g (1 g-atom) of Mg, 133.5 g (1 mol) of 4-chloro-1-methylpiperidine, and 540 ml of THF, there was portionwise added, at 0–5°, 105.5 g (0.495 mol) of **4**. After 4 hr, the mixture was allowed to reach room temperature (18 hr), recooled, and decomposed with concentrated NH_4Cl solution. The THF layer was decanted, the salt phase was extracted several times with benzene, and the unified organic layers were washed with water, dried, and evaporated. On crystallization of the residue from EtOAc–Et_2O, the crude carbinol was obtained (140 g, mp 73–79°). It was dissolved in 310 ml of AcOH; the solution was saturated with HCl gas and, after addition of 90 ml of Ac_2O, heated at 100° for 30 min. After recooling, the mixture was poured on water, rendered strongly alkaline, and extracted with benzene. The crude **56** was purified by short-path distillation [bp 180–190° (0.01 mm)] and crystallized from cyclohexane: 107.8 g; 74%; mp 107–109°. *Anal.* ($C_{19}H_{22}N_2O$) C, H, N.

2-Methyl-4-(1′-methyl-4′-piperidyl)-4*H*-benzo[5,6]cyclohepta[1,2-*d*]thiazole (55) and 2-Methyl-4-(1′-methyl-4′-piperidylidene)-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]thiazole (57). The thiazolo ketone **6** (113 g, 0.493 mol) was treated as described for **4** in the example (**56**) above. On distillation [bp 200–220° (0.01 mm)] an oily mixture of **55** and **57** was obtained (123 g, 90.3%). For separation, it was redissolved in 300 ml of $CHCl_3$ and stirred with 8 l. of 1 *N* HCl. The $CHCl_3$ phase was separated and the aqueous phase exhaustively extracted with $CHCl_3$. The unified $CHCl_3$ layers were washed with 1 *N* NaOH and water, dried, and evaporated to give 99.5 g of **55** (free base) that was further purified by conversion into the fumarate salt (35.8 g of fumaric acid in 4 l. of Et_2O) and recrystallization (CH_3OH–Et_2O) of the latter: 134.5 g; 62%; mp 138–139°. *Anal.* ($C_{23}H_{26}N_2O_4S$) C, H, N. The isomeric **57** was obtained from the aqueous phase after the above $CHCl_3$ extraction, by rendering it strongly alkaline and extracting with benzene. On silica column chromatography followed by short-path distillation [bp 220° (0.01 mm)], 15.9 g or 10% was obtained. *Anal.* ($C_{19}H_{22}N_2S$) C, H, N.

H. **Attachment of the *N*-Methylpiperazine Side Chain. 2-Methyl-4-(4-methyl-1-piperazinyl)-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazole (64).** A mixture of 245 g (1.14 mol) of **27**, 136 g (1.16 mol) of $SOCl_2$, and 2.3 l. of toluene was kept for 18 hr at 0°. After distilling off 300 ml of toluene (15 mm, 30°), the crude product was treated at 0° with 655 g (6.55 mol) of *N*-methylpiperazine (90 min). After 18 hr at 25°, 1.25 l. of 1 *N* NaOH was added and the biphasic mixture was concentrated to 2 l. The basic product (320 g, 95%) was then obtained *via* conventional work-up and distillation: bp 173–175° (0.01 mm); mp (ether) 116–119°. *Anal.* ($C_{18}H_{23}N_3O$) C, H, N.

2-Methyl-5-(4-methyl-1-piperazinyl)-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (70). A solution of 3.5 g (0.0164 mol) of **9**, 9.6 g (0.96 mol) of *N*-methylpiperazine, and 12.5 g (0.715 mol) of *p*-toluenesulfonic acid in 50 ml of xylene was refluxed for 3 hr under a Dean-Stark trap. The enamine intermediate obtained on the usual work-up was refluxed for 15 hr with 10 g of $NaBH_4$, 20 ml of 2 *N* NaOH, and 50 ml of MeOH. After concentration the mixture was treated with 100 ml of 1 *N* HCl and the basic product, after washing with CH_2Cl_2, was liberated and extracted to give 3.5 g of an oil which was characterized as a dimaleate, mp 170–171.5° (5.91 g, 68%). *Anal.* ($C_{18}H_{29}Cl_2N_3O_2$) C, H, N.

Miscellaneous Reactions. 2-Methyl-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazol-5-one (9). Dropwise, 27 ml of 30% H_2O_2 was added to a stirred (10°) solution of **33** (26.9 g, 0.136 mol) in HCOOH (54 ml) over 30 min. After 45 hr at 25°, the mixture was diluted (400 ml of H_2O) and kept at 60° for 2 hr. On concentration of the mixture *in vacuo*, the intermediary **43** crystallized (20 g, 63%) and was recrystallized from AcOEt: mp 168–169°. Of the latter, 9 g was dissolved in 60 ml of concentrated H_2SO_4. After 90 min at 25° the solution was added to 150 ml of iced H_2O and this solution was treated with 355 ml of 6 *N* NaOH while the temperature was kept below 10°. Ether extraction gave **9**, which was recrystallized from ether at −19°: mp 117–118°; 4.8 g; 58%. *Anal.* ($C_{13}H_{11}NO_2$) C, H, N.

2-Methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazole (26). A solution of 2.15 g (0.01 mol) of **27** in 50 ml EtOH–AcOH (4:1) was hydrogenated at 3 atm in the presence of 80 mg of Pd/C 10% catalyst until the H_2 uptake stopped. The mixture was filtered and the filtrate evaporated to dryness; the residue was subjected to short-path distillation at 145° bath temperature (0.01 mm). The solidified distillate was recrystallized from Et_2O to give 1.60 g (82%) of **26**, mp 57–58°. *Anal.* ($C_{13}H_{13}NO$) C, H, N.

2-Methyl-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazole (29). To 30 ml of $SOCl_2$, there was added, under stirring, 4.30 g (0.02 mol) of **27** while the temperature was kept around 10° by cooling. After 2 hr, the $SOCl_2$ was stripped off *in vacuo* and the crude chloro intermediate thus obtained was subjected to thermolysis under the conditions of a short-path distillation at 150–170° bath temperature (0.01 mm). The partially solidified distillate (consisting of **29** and of **29** · HCl) was dissolved in Et_2O and washed with 1 *N* NaOH and water. The residue obtained on evaporation of the Et_2O was redistilled at 130–135° (0.1 mm) to give **29** as a colorless oil: 2.68 g; 68%. *Anal.* ($C_{13}H_{11}NO$) C, H, N.

2-Methyl-6*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (33). To a solution of 21.5 g of **32** (0.1 mol) in 120 ml of DMSO there was added 2 ml of concentrated H_2SO_4 and the mixture heated to 180° for 4 hr. After cooling, dilution with water, and neutralization of the acid, **33** was obtained by extraction ($CHCl_3$) and distillation [short path, 115° bath temperature (0.04 mm)]: 15.35 g (78%) of colorless oil. *Anal.* ($C_{13}H_{11}NO$) C, H, N.

2-Methyl-4-formamido-5,6-dihydro-4*H*-benzo[3,4]cyclohepta-[1,2-*d*]oxazole (35). A mixture of 21.3 g (0.1 mol) of **8** and 180 ml of Ingersoll reagent[24] was heated (165–185°) for 4 hr, then cooled back, and diluted with water (500 ml). Extraction with $CHCl_3$ and two crystallizations from EtOAc–hexane gave 13 g (54%) of **35**, mp 152–152.5°. *Anal.* ($C_{14}H_{14}N_2O_2$) C, H, N.

2-Methyl-4-amino-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (34). Compound **35** (6.0 g, 0.025 mol) was refluxed 3 hr with 150 ml of 10 *N* HCl. The mixture was evaporated to dryness, the residue redissolved in water, and the solution made alkaline (pH 12, NaOH). **34** was extracted (EtOAc) and then converted to its maleate salt by the dropwise addition of its EtOH (20 ml) solution to an Et_2O (150 ml) solution of maleic acid (2.9 g, 0.025 mol). Recrystallization from EtOH–Et_2O gave 7.88 g or 96%: mp 178–179°. *Anal.* ($C_{17}H_{18}N_2O_5$) C, H, N.

2-Methyl-4-methylamino-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (36). To a solution of 3.0 g (0.0125 mol) of **35** in 50 ml of dry THF there was added 40 ml of 1 *M* B_2H_6–THF solution and the mixture was refluxed for 4 hr. After cooling, 20 ml of 40% KOH solution was added; the THF layer was diluted with Et_2O, washed with water, and dried. Introduction of HCl gas led to the precipitation of **36** · HCl (hydrate) which was recrystallized from EtOH–Et_2O: 2.35 g; 67%; mp 207° dec. *Anal.* ($C_{14}H_{19}ClN_2O_2$) C, H, Cl, N.

2-Methyl-4-dimethylamino-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (37). A mixture of 2.14 g (0.01 mol) of **34**, 25 ml of HCOOH, and 0.5 ml of 37% CH_2O was heated (100°) for 3 hr and then evaporated *in vacuo*. The residue was dissolved in water, and the solution at pH 12 was extracted (Et_2O). The dried Et_2O layer was dropwise added to a solution of 1.16 g (0.01 mol) of maleic acid in Et_2O, whereupon **37** · maleate precipitated. Recrystallization from EtOH–Et_2O gave 2.70 g or 76%; mp 178–179°. *Anal.* ($C_{19}H_{22}N_2O_5$) C, H, N.

2-Methyl-4-bis(2′-hydroxyethylamino)-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (38). Into a solution of 4.28 g

(0.02 mol) of **34**, at 0°, ethylene oxide was introduced until the weight gain reached 1.88 g. Then the mixture was autoclaved at 100° for 3.5 hr. After cooling and evaporation to dryness, the product was chromatographed ($CHCl_3$–CH_3OH) on a silica gel column and converted (Et_2O–HCl) into **38** · HCl. Recrystallization from EtOH–Et_2O gave 4.25 g (63%). *Anal.* ($C_{17}H_{23}ClN_2O_3$) C, H, Cl, N.

2-Methyl-5-amino-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (39). A solution of 2.13 g (0.01 mol) of **9** in 80 ml of EtOH was saturated at 0° with NH_3 and then shaken with 1.3 g of Raney nickel in a H_2 atmosphere of 4 atm (Parr apparatus) for 18 hr, at 25°. On usual work-up, conversion to the maleate salt, and recrystallization from *i*-PrOH–Et_2O, 2.70 g (82%) of **39** · maleate was obtained: mp 138–139°. *Anal.* ($C_{17}H_{19}N_2O_5$) C, H, N.

2-Methyl-5-methylamino-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (40). A mixture of 2.02 g (0.0095 mol) of **9**, 10 ml of liquid CH_3NH_2, 25 ml of EtOH, and 2.0 g of CH_3NH_2 – HCl was heated in a sealed tube for 1 hr at 100°. The concentrated residue was dissolved in 50 ml of dry THF and treated at 25° with 18 ml of 1 *M* B_2H_6–THF solution. After 90 min the λ_{max} 238 mμ absorption of the enamine intermediate disappeared; 10 ml of 6 *N* HCl was then added and the mixture was refluxed for 30 min. The THF was evaporated and the acid solution was washed with CH_2Cl_2. The pH was then adjusted to 13 and this solution was extracted with CH_2Cl_2 to yield the free base of **40** (1.73 g) or 81% which was characterized as the hemifumarate: mp 120° dec (*i*-PrOH–Et_2O). *Anal.* ($C_{16}H_{18}N_2O_3$) C, H, N.

2-Methyl-4-(3′-dimethylaminopropyl)-4-vinyl-4*H*-benzo[5,6]cyclohepta[1,2-*d*]thiazole (54). A solution of 6.2 g (0.02 mol) of **55** (free base) and 3.00 g (0.0211 mol) of CH_3I in 80 ml of acetone was allowed to stand at 5° for 18 hr and then evaporated to dryness. The solid residue was washed several times with Et_2O, dissolved in 150 ml of CH_3OH, and vibrated for 2 hr with AgOH, freshly prepared from 8.50 g (0.05 mol) of $AgNO_3$. The filtered solution was evaporated and the residual oil thermolyzed [200° (0.05 mm)] under the conditions of a short-path distillation. The distillate was chromatographed on silica and the main fraction redistilled [190° (0.01 mm)] to give 1.62 g (25%) of **54**. *Anal.* ($C_{20}H_{24}N_2S$) C, H, N.

2-Methyl-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazol-4-one (24). A mixture of 25 g (0.117 mol) of **8** and of 27.9 g (0.123 mol) of dichlorodicyano-*p*-benzoquinone in 300 ml of pure dioxane was kept at 98° for 3 hr. After cooling, the hydroquinone formed was filtered, the dioxane was stripped off, and the residue was redissolved in benzene and washed successively with $Na_2S_2O_4$ and Na_2CO_3 solutions and finally water. The residue obtained from the benzene solution was crystallized from EtOH: 16.1 g (62%); mp 196–199°; λ_{max} ($CHCl_3$) 6.15 μ; $\lambda\lambda_{max}$ (EtOH) 238 mμ (ε 18,500), 246 (19,400), 270 (52,200); nmr ($CDCl_3$) 3 H at δ 2.67 (s), 1 H at δ 6.90 (d, *J* = 13 Hz), 1 H at δ 7.49 (d, *J* = 13 Hz). *Anal.* ($C_{13}H_9NO_2$) C, H, N.

2-Methyl-4-(2′-dimethylaminoethoxy)-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (71). A mixture of 10 g (0.0465 mol) of **32**, 1.23 g of NaH, 7.2 g of dimethylaminoethyl chloride, and 60 ml of toluene was refluxed for 16 hr. Following the usual work-up and distillation [140–145° (0.03 mm)] 7.25 g (66%) of oil was obtained. *Anal.* ($C_{17}H_{22}N_2O_2$) C, H, N.

2-Methyl-6-(1′-methyl-4′-piperidyl)-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazol-4-one (75), 2-Methyl-4-(1′-methyl-4′-piperidyl)-6*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazole (76), and 2-Methyl-4-(1′-methyl-4′-piperidyl)-6*H*-benzo[3,4]cyclohepta[1,2-*d*]oxazol-6-one (77). A Grignard mixture was prepared as under G from 2.4 g (0.1 g-atom) of Mg and 13.35 g (0.1 mol) of 4-chloro-1-methylpiperidine. At 0°, 10.5 g (0.05 mol) of the troponoid **24** was portionwise added, and then the mixture was allowed to stand for 18 hr at 25°. After the work-up as under G with NH_4Cl, the crude base mixture was added to 300 ml of 5 *N* HCl whereupon a deep red solution was obtained. Exhaustive extraction with $CHCl_3$ and evaporation of the dried $CHCl_3$ layers yielded after trituration with Et_2O the crude HCl salt of **75** of which the free base was liberated and purified by vacuum distillation: 2.1 g (13.6%); mp 226–227°; λ_{max} ($CHCl_3$) 5.97 μ; $\lambda\lambda_{max}$ (EtOH) 228 mμ (ε 18,000), 305 (13,820); nmr ($CDCl_3$) 3 H at δ 2.62 (s), 3 H at δ 2.88 (s), nothing else resolved. *Anal.* C, H, O; N: calcd, 9.0; found, 10.0; *m/e* calcd 310, found 310.

The pH of the red aqueous solution was brought to 13 through the addition of 5 *N* NaOH–ice, whereupon the red color disappeared. The base mixture obtained on $CHCl_3$ extraction was chromatographed on a column of silica, benzene with increasing percentage of EtOAc being used as the eluent. Three pure fractions were (in that order) eluted: **76** (3.7 g, 25%), an additional amount (0.8 g, 5.2%) of **75**, and 5.5 g (35.7%) of **77**.

76 [distilled at 180° (0.02 mm)]: mp 60–63°; λ_{max} ($CHCl_3$) 6.25 μ; $\lambda\lambda_{max}$ (EtOH) 228 mμ (ε 15,680), 275 (7050), 295 (7650); nmr ($CDCl_3$) 3 H at δ 2.30 (s), 3 H at δ 2.57 (s), 1 H at δ 5.55 ("t," *J* = 7 Hz). *Anal.* ($C_{19}H_{22}N_2O$) C, H, N; *m/e* calcd 293, found 293.

77 [distilled at 220° (0.02 mm)]: mp 144–148°; λ_{max} ($CHCl_3$) 6.15 μ; $\lambda\lambda_{max}$ (EtOH) 239 mμ (ε 29,600), 252 (26,300), 325 (6975), 358 (6000); nmr ($CDCl_3$) 3 H at δ 2.34 (s), 3 H at δ 2.63 (s), 1 H at δ 6.90 (s). *Anal.* ($C_{19}H_{20}N_2O_2$) C, N; H: calcd, 6.5; found, 7.1; *m/e* calcd 308, found 308.

Supplementary Material Available. A compilation of pharmacological screening results obtained with the compounds of Tables I and II 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, 24× 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 $4.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-1316.

References

(1) K. Stach and W. Pöldinger, *Progr. Drug Res.*, **9**, 129 (1966).
(2) J. M. Bastian, A. Ebnöther, E. Jucker, E. Rissi, and A. P. Stoll, *Helv. Chim. Acta*, **54**, 277 (1971), and references cited therein.
(3) F. J. Villani, *et al.*, *J. Med. Chem.*, **15**, 750 (1972), and references cited therein.
(4) E. Galantay, C. Hoffman, and N. Paolella, *Chem. Commun.*, 274 (1970).
(5) E. Galantay and W. R. J. Simpson, *Chem. Commun.*, 754 (1970).
(6) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1950, p 214.
(7) J. W. Conforth, ref 6, p 334.
(8) D. E. Horning and J. M. Muchowski, *Can. J. Chem.*, **46**, 3665 (1968).
(9) E. L. Engelhardt, M. E. Christy, C. D. Colton, M. B. Freedman, C. C. Boland, L. H. Halpern, V. G. Vernier, and C. A. Stone, *J. Med. Chem.*, **11**, 325 (1968).
(10) E. L. Engelhardt, H. C. Zell, W. S. Saari, M. E. Christy, C. D. Colton, C. A. Stone, J. M. Stavorsky, H. C. Wenger, and C. T. Ludden, *J. Med. Chem.*, **8**, 829 (1965).
(11) C. Kaiser, R. J. Warren, and C. L. Zrke, *J. Med. Chem.*, **17**, 131 (1974).
(12) K. Kotera, M. Motomura, S. Miyakazi, T. Okada, Y. Hamada, R. Kido, K. Hirose, M. Eigyo, H. Jyoyama, and H. Sata, *Shionogi Kenkyusho Nempo*, **17**, 88 (1967).
(13) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Seigler, Ed., Year Book Medical Publishers, Chicago, Ill., 1964, pp 36–54.
(14) N. W. Dunham and T. S. Miya, *J. Pharm. Sci.*, **46**, 208 (1957).
(15) C. F. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 (1948).
(16) G. M. Everett, L. E. Bloucus, and J. M. Sheppard, *Science*, **124**, 79 (1956).
(17) R. George, W. L. Haslett, and D. J. Jenden, *Life Sci.*, **8**, 361 (1962).
(18) P. S. J. Spencer in "Antidepressant Drugs," S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1967, pp 194–204.
(19) F. Sulser, J. Watts, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **96**, 279 (1962).
(20) G. M. Everett and R. G. Wiegard in "Pharmacological Analysis of Central Nervous Action," Vol. 8, First International Pharmacology Meeting, Pergamon, Elmsford, N. Y., 1962, p 85.
(21) M. A. Davis, *Annu. Rep. Med. Chem.*, **1967**, 14 (1968).
(22) P. A. S. Smith and W. L. Berry, *J. Org. Chem.*, **26**, 27 (1961).
(23) L. H. Klemm and G. M. Bower, *J. Org. Chem.*, **23**, 344 (1958).
(24) A. W. Ingersoll, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 503.