= 2 Hz, *J'* = 9 Hz, 4-phenyl), 7.28 (d, 1, *J* = 4 Hz, 3-furyl), 6.98 (d, 1, *J* = 9 Hz, 3-phenyl), 6.61 (q, 1,4-furyl), 5.4 (m, 1, *H*COH), 3.96 (s, 3, OCH$_3$).

Methyl 5-(2-Bromoacetyl)-2-hydroxybenzoate (46). To a stirred solution of 19.42 g (0.1 mol) of methyl 5-acetyl-2-hydroxybenzoate (44) in 65 mL of CHCl$_3$ was added dropwise a solution of 16.0 g (0.1 mol) of Br$_2$ in 190 mL of CHCl$_3$. The solution was evaporated to dryness and the residue was recrystallized from EtOAc/heptane to give 22.1 g (81%) of 46, mp 89–90 °C.

Methyl 5-(2-Bromoacetyl)-2-methyoxybenzoate (47). A mixture of 66.1 g (0.341 mol) of 44, 7.26 g (0.511 mol) of MeI, and 47.0 g (0.341 mol) of K$_2$CO$_3$ in 400 mL of DMF was stirred at room temperature for 65 h. The mixture was poured on 1.5 L of 1 N HCl and extracted 6 times with Et$_2$O; the extract was washed with water, NaHCO$_3$ solution, and cold 1 N NaOH and dried over Na$_2$SO$_4$, and the solvent was evaporated to give 51.3 g (72%) of 45, mp 95–96 °C.

To a solution of 52.0 (0.25 mol) of 45 in 400 mL of CHCl$_3$ was added a solution of 40.0 g (0.25 mol) of Br$_2$ in 200 mL of CHCl$_3$ at such a rate that the reaction mixture decolorized (50 min after a 25-min initiation period). Solvent was evaporated and the residue was recrystallized from MeOH to give 54.1 g (75%) of 47, mp 149–153 °C. A second crop of 10.4 g was obtained from the mother liquor.

2-Bromo-1-[4-hydroxy-3-(1*H*-tetrazol-5-yl)phenyl]-ethanone (52). 5-(2-Hydroxyphenyl)-1*H*-tetrazole (53) was prepared from 2-hydroxybenzonitrile and hydrazoic acid in 86% yield by the procedure of Veldstra.[46] To a cooled (0 °C) suspension of 16.2 g (0.1 mol) of 53 in 300 mL of CH$_2$Cl$_2$ was added 39.9 g (0.3 mol) of AlCl$_3$ and, dropwise, 8.1 g (0.1 mol) of CH$_3$COCl. The mixture was refluxed for 3.5 h, cooled, and decomposed by the addition of 200 mL of 2 N HCl. The resulting precipitate was washed with 2 N HCl and water and recrystallized twice from *i*-PrOH/H$_2$O to give 8.0 g (39%) of [(4-hydroxy-3-1*H*-tetrazol-

5-yl)phenyl]ethanone (54), mp 260–261 °C dec; IR (KBr) 1680 cm^{-1}. Anal. (C$_9$H$_8$N$_4$O$_2$) C, H, N.

To a solution of 6.9 g (0.034 mol) of 54 in 800 mL of refluxing THF was added 15.2 g (0.068 mol) of cupric bromide in six portions over 2 h. About 600 mL of THF was removed by distillation, the cuprous bromide formed was removed by filtration, and the filtrate was concentrated and diluted with CHCl$_3$. The product 52 crystallized, 8.2 g (84%), and a sample was recrystallized from THF/CHCl$_3$: mp 177–178 °C dec; IR (KBr) 1670 cm^{-1}; NMR (Me$_2$SO) δ 4.93 (s, 2). Anal. (C$_9$H$_7$BrN$_4$O$_2$) C, H, N.

Compound **39** was prepared from **52** as described for **37**.

Methyl 5-(2-Bromoacetyl)-2-ethoxybenzoate (55). A mixture of 19.4 g (0.1 mol) of methyl 5-acetyl-2-hydroxybenzoate, 13.8 g (0.1 mol) of K$_2$CO$_3$, and 23.4 g (0.15 mol) C$_2$H$_5$I in 70 mL of dry DMF was stirred at room temperature for 45 h. The mixture was poured into ice–water and extracted with CH$_2$Cl$_2$. The extract was washed with H$_2$O, 2 N Na$_2$CO$_3$, and NaCl solution, dried (Na$_2$SO$_4$), and evaporated. The residue was crystallized from Et$_2$O/pentane to yield 16.8 g (76%) of methyl 5-acetyl-2-ethoxybenzoate (56), mp 47–50 °C.

To a solution of 14.4 g (0.065 mol) of 56 in 80 mL of CHCl$_3$ was added dropwise a solution of 10.4 g (0.065 mol) of Br$_2$ in 30 mL of CHCl$_3$. After an initiation period of 1.5 h and the addition of a few drops of HBr/AcOH, the addition was complete after 1 h. The solution was evaported to dryness and the residue was recrystallized from methanol/acetone to give 10.0 g (51%) of 55, mp 147–149 °C; IR (KBr) 1690, 1680 cm^{-1}; NMR (CDCl$_3$) δ 4.43 (s, 2, COCH$_2$Br). Anal. (C$_{12}$H$_{13}$BrO$_4$) C, H, Br.

Compound **43** was prepared from **55** as described for **37** and **22**. Compounds **40** and **41** were similarly prepared from methyl 5-(2-bromoacetyl)-2-methoxybenzoate (**47**).

(46) H. Veldstra, *Recl. Trav. Chim. Pays-Bas*, **77**, 1129 (1958).

Imine Analogues of Tricyclic Antidepressants[1a]

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Analogues of tricyclic antidepressants were synthesized in which the α-carbon of the side chain was replaced by nitrogen. The antidepressant activity of these imines, as measured by the reversal of the effects of tetrabenazine in mice, showed a structure–activity relationship similar to that of the carbon analogues. The most active imine (19) was six times as potent as amitriptyline. Some of the compounds differed from amitriptyline in that they produced stimulation in mice.

Since the introduction of amitriptyline for the treatment of depressive states, numerous analogues of this drug have been synthesized and some are being used clinically.[2]
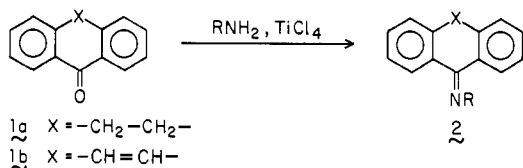
Although many tricyclic oxime ethers with a basic side chain have been described in the literature, there had been at the time this work was initiated no report of the syn-

(1) (a) Contribution no. 2529 from the Central Research & Development Department of E. I. du Pont de Nemours & Co. (b) Geomet Technologies Inc., Rockville, MD 20852.
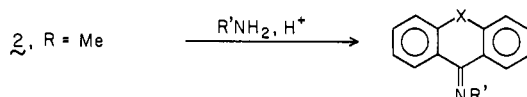
(2) N. Finch in "Antidepressants", S. Fielding and H. Lal, Eds., Futura Publishing Co., Mount Kisco, NY, 1975, and references cited there.
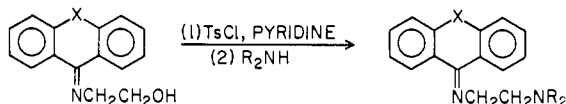
Scheme I

METHODS A AND B:

RNH$_2$, TiCl$_4$

1a X = $-$CH$_2$$-CH_2$$-$
1b X = $-$CH$=$CH$-$

2

METHOD C:

2, R = Me

R'NH$_2$, H$^+$

NR'

METHOD D:

(1)TsCl, PYRIDINE
(2) R$_2$NH

NCH$_2$CH$_2$OH

NCH$_2$CH$_2$NR$_2$

Scheme II

2PCl$_5$

1a

3

Cl Cl

3

RNH$_2$
25°C

NR

Scheme III

H$_2$NCH$_2$CH$_2$OH
170°C

1b

4

NCH$_2$CH$_2$OH

O   NR

5a R = H
5b R = Me

thesis and pharmacology of the corresponding imine analogues,[3] possibly because of the assumption that the inherent sensitivity of the imine function toward acids would make oral administration of such drugs impossible. This paper describes the preparation and pharmacology of 5*H*-dibenzo[*a,d*]cyclohepten-5-imines, the corresponding 10,11-dihydro derivatives, as well as imines derived from 1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cyclohepten-6-one, dibenz[*b,e*]oxepin-11(6*H*)-one, dibenzo[*b,e*]thiepin-11(6*H*)-one, 5,6-dihydromorphanthridin-11-one, 9-xanthenone, 9-thioxanthone, and 10,10-dimethyl-9-anthrone.[4] For comparison, we have also synthesized *N*-(aminoalkyl)benzophenone imines.

Synthesis. Heating a mixture of *N,N*-dimethylethylenediamine and 5*H*-dibenzo[*a,d*]cyclohepten-5-one (**1b**) or its 10,11-dihydro derivative (**1a**) to 180 °C for 24 h produces the desired imines **2b** and **2a** (R = CH$_2$CH$_2$NMe$_2$) in 70 and 20% yield, respectively. *p*-Toluenesulfonic acid accelerates this reaction; thus, after 18 h at 120 °C, the imines **2b** and **2a** (R = CH$_2$CH$_2$NMe$_2$) are formed in 38 and 10% yield. However, titanium tetrachloride, either in benzene (method A)[5] or, preferably, hexamethylphosphoramide (method B),[6] is a much better
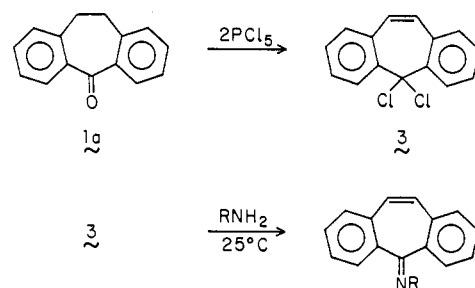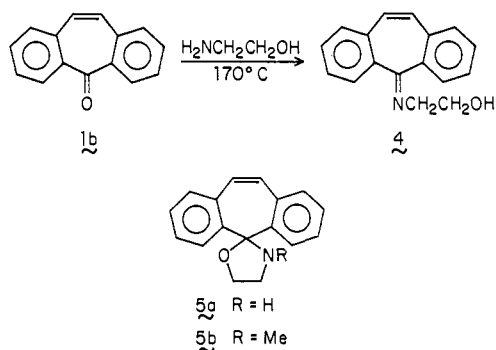
catalyst which permits the reaction to be carried out at room temperature or slightly above (Scheme I). Alternatively, the *N*-methylimine may be prepared first and then converted to the desired imine by acid-catalyzed amine exchange (method C, Scheme I). Finally, aminoalkylimines may be obtained by reaction of tosyloxalkylamines with ammonia or primary or secondary amines (method D, Scheme I). Ketones containing substituents in the aromatic rings or having nonsymmetric chains X give mixtures of syn and anti imines. Except for one case (see Experimental Section), these were not separated. The imines prepared by these methods are listed in Table I.

Imines derived from the ketone **1b** may also be prepared by the reaction of 5,5-dichloro-5*H*-dibenzo[*a,d*]cycloheptene (**3**) with primary amines (Scheme II). The dichloro compound **3** is obtained from **1b** by reaction with 1 mol of phosphorus pentachloride[7] or from the cheaper dihydro ketone **1a** using 2 mol of phosphorus pentachloride. Reaction of **1a** with 1 mol of the reagent produces an equimolar mixture of **3** and unreacted ketone.

Reaction of ketone **1b** with 2-aminoethanol at 170 °C has been claimed[8] to give the amino ketal **5a**. We find that this product is actually the imine **4** on the basis of spectral evidence (Scheme III). The infrared spectrum of **4** (in KBr) shows the strong carbon–nitrogen double bond stretching band at 1625 cm^{-1}, characteristic of all imines reported in this paper. By contrast, the amino ketal **5b**, prepared from the dichloro derivative **3** and 2-(methylamino)ethanol, shows no bands in this region, since the 10,11 double bond is infrared inactive.

The imines described in this paper are remarkably stable toward acid-catalyzed hydrolysis. Thus, they may be purified by extraction into aqueous hydrochloric acid followed by treatment with base. An aqueous solution of the maleate of imine **2a** (R = CH$_2$CH$_2$NMe$_2$) undergoes hydrolysis to the extent of only 7% after 17 h at room temper-

(3) After the completion of most of the work described in this paper, reports appeared in the patent literature dealing with the same subject: P. Dostert and E. Kyburz, *Ger. Offen.*, 2 150 079 (1971); *Chem. Abstr.*, 77, 19451*j* (1972). Some of the compounds reported here have been synthesized and tested for antihistaminic, anticholinergic, and antiinflammatory activity: T. Bultsma, J. F. M. Meijer, F. I. Pauli, J. P. Ramaker, and W. T. Nauta, *Eur. J. Med. Chem. Chim. Ther.*, 12, 427 (1977); J. F. M. Meijer, T. Bultsma, J. Zaagsma, O. P. Zuiderveld, and W. T. Nauta, *ibid.*, 12, 437 (1977); J. F. M. Meijer, J. Zaagsma, and W. T. Nauta, *ibid.*, 12, 443 (1977). *N*-Alkyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-imines have been prepared as intermediates: D. Taub and R. D. Hoffsommer, Jr., U.S. Patent 3 780 106 (1973). For the synthesis of *N*-phenyl-5*H*-dibenzo[*a,d*]cyclohepten-5-imine, see J. J. Looker, *J. Org. Chem.*, 36, 1045 (1971). Derivatives of *N*-benzyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-imine have been described by J. A. Gautier, M. Miocque, C. Fauran, A. Lacour, G. Raynaud, and Y. Bailly, *Fr. Demande* 2 244 478 (1975); *Chem. Abstr.*, 83, 113935*r* (1975). For analogues in which the imine function is incorporated in a fourth ring, see A. J. Frey, E. E. Galantay, and H. Ott, U.S. Patent 3 296 252 (1967); S. C. Bell and S. J. Childress, U.S. Patent 3 417 101 (1968).

(4) Some of the subject matter is claimed in the following issued U.S. Patents: R. Uyeda, 3 901 945 (1975); E. Ciganek, 3 954 865 (1976).
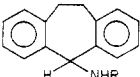
(5) I. Moretti and G. Torre, *Synthesis*, 141 (1970).

(6) **Caution:** hexamethylphosphoramide has been found to be a carcinogen in rats by inhalation [J. A. Zapp, Jr., *Science*, 190, 422 (1975)].

(7) J. J. Looker, *J. Org. Chem.*, 31, 3599 (1966).

(8) M. A. Davis, U.S. Patent 3 560 493 (1971).

Table I. Physical and Analytical Data for the Imines

no.	X	Y	R	method of prepn[a]	yield, %	mp or bp,[b] °C	formula	anal.
6	$(CH_2)_2$	H	$(CH_2)_2NH_2$	C	70	157-158[c]	$C_{21}H_{22}N_2O_4$	C, H, N
7	$(CH_2)_2$	H	$(CH_2)_2NHMe$	C	68	156-157[c]	$C_{22}H_{24}N_2O_4$	C, H, N
8	$(CH_2)_2$	H	$(CH_2)_2NHEt$	C	91	130-150 (0.3)	$C_{19}H_{22}N_2$	NMR
9	$(CH_2)_2$	H	$(CH_2)_2NMe_2$	C	94	139-141[c]	$C_{23}H_{26}N_2O_4$	C, H, N
10	$(CH_2)_2$	Cl	$(CH_2)_2NMe_2$[d]	C	85	140-160 (0.1)	$C_{19}H_{21}ClN_2$	C, H, N
11	$(CH_2)_2$	H	$(CH_2)_2NEt_2$	B	71	160-170 (0.5)	$C_{21}H_{26}N_2$	C, H, N
12	$(CH_2)_2$	H	$(CH_2)_3NMe_2$	C	97	140-160 (0.5)	$C_{20}H_{24}N_2$	C, H, N
13	$(CH_2)_2$	H	$(CH_2)_2\text{-}c\text{-}N(CH_2CH_2)_2O$	C	87	160-180 (0.5)	$C_{21}H_{24}N_2O$	C, H, N
14	CH=CH	H	$(CH_2)_2NMe_2$	C	90	140-160 (0.5)	$C_{19}H_{20}N_2$	C, H, N
15	CH=CH	H	$(CH_2)_3NMe_2$	C	86	160-175 (0.1)	$C_{20}H_{22}N_2$	C, H, N
16	$c\text{-}CHCH_2CH$	H	$(CH_2)_2NH_2$	D	f	160 (0.1)	$C_{18}H_{18}N_2$	C, H, N
17	$c\text{-}CHCH_2CH$	H	$(CH_2)_2NHMe$	B	68	162-163[c]	$C_{23}H_{24}N_2O_4$	C, H, N
18	$c\text{-}CHCH_2CH$	H	$(CH_2)_2NHEt$	B	80	170 (0.2)	$C_{20}H_{22}N_2$	C, H, N
19	$c\text{-}CHCH_2CH$	H	$(CH_2)_2NMe_2$	B	60	153-154[c]	$C_{24}H_{26}N_2O_4$	C, H, N
20	$c\text{-}CHCH_2CH$	Cl	$(CH_2)_2NMe_2$[d]	B	53	160 (0.1)	$C_{20}H_{21}ClN_2$	C, H, N
21	$c\text{-}CHCH_2CH$	H	$(CH_2)_2NEt_2$	B	86	170 (0.1)	$C_{22}H_{26}N_2$	C, H, N
22	$c\text{-}CHCH_2CH$	H	$(CH_2)_3NMe_2$	B	61	170 (0.1)	$C_{21}H_{24}N_2$	C, H, N
23	$c\text{-}CHCH_2CH$	H	$(CH_2)_2\text{-}c\text{-}N(CH_2CH_2)_2$	B	52	190 (0.1)	$C_{22}H_{24}N_2$	C, H, N
24	$c\text{-}CHCH_2CH$	H	$(CH_2)_2\text{-}c\text{-}NC_5H_{10}$	B	57	200 (0.2)	$C_{23}H_{26}N_2$	C, H, N
25	$c\text{-}CHCH_2CH$	H	$(CH_2)_2\text{-}c\text{-}N(CH_2CH_2)_2O$	B	50	200 (0.1)	$C_{22}H_{24}N_2O$	C, H, N
26	$c\text{-}CHCH(Cl)CH$[e]	H	$(CH_2)_2NMe_2$	B	65	160[c]	$C_{24}H_{25}ClN_2O_4$	C, H, N
27	$c\text{-}CHC(Cl_2)CH$	H	$(CH_2)_2NMe_2$	B	43	160 (0.1)	$C_{20}H_{20}Cl_2N_2$	C, H, N
28	$c\text{-}CHC(F_2)CH$	H	$(CH_2)_2NMe_2$	B	50	80-81	$C_{20}H_{20}F_2N_2$	C, H, N
29	CH_2O	H	$(CH_2)_2NMe_2$[d]	C	88	150 (0.1)	$C_{18}H_{20}N_2O$	C, H, N
30	CH_2O	H	$(CH_2)_3NMe_2$[d]	C	91	170-180 (0.2)	$C_{19}H_{22}N_2O$	C, H, N
31	CH_2NH	H	$(CH_2)_2NMe_2$[d]	B	50	180 (0.1)	$C_{18}H_{21}N_3$	C, H, N
32	CH_2NMe	H	$(CH_2)_2NMe_2$[d]	B	64	115 (0.03)	$C_{19}H_{23}N_3$	C, H, N
33	CH_2NMe	H	$(CH_2)_3NMe_2$[d]	B	70	130 (0.5)	$C_{20}H_{23}N_3$	C, H, N
34	CH_2NCOMe	H	$(CH_2)_2NMe_2$[d]	B	30	144-145	$C_{20}H_{23}N_3O$	C, H, N
35	CH_2S	H	$(CH_2)_2NMe_2$[d]	B	60	100 (0.05)	$C_{18}H_{20}N_2S$	C, H, N
36	CH_2S	H	$(CH_2)_3NMe_2$[d]	B	59	120 (0.3)	$C_{19}H_{22}N_2S$	C, H, N
37	CH_2SO_2	H	$(CH_2)_2NMe_2$[d]	B	65	150 (0.1)	$C_{18}H_{20}N_2O_2S$	C, H, N
38	CH_2SO_2	H	$(CH_2)_3NMe_2$[d]	B	38	170 (0.2)	$C_{19}H_{22}N_2O_2S$	NMR
39	O	H	$(CH_2)_2NMe_2$	B	43	125 (0.5)	$C_{17}H_{18}N_2O$	C, H, N
40	O	H	$(CH_2)_3NMe_2$	B	50	190 (0.5)	$C_{18}H_{20}N_2O$	C, H, N
41	S	H	$(CH_2)_2NMe_2$	B	36	130 (0.01)	$C_{17}H_{18}N_2S$	C, H, N
42	S	H	$(CH_2)_3NMe_2$	B	43	130 (0.5)	$C_{18}H_{20}N_2S$	C, H, N
43	CMe_2	H	$(CH_2)_2NMe_2$	B	69	175 (1)	$C_{20}H_{24}N_2$	C, H, N
44			$(CH_2)_2NMe_2$[g]					
45			$(CH_2)_3NMe_2$[g]					
46	$Ph_2C=N(CH_2)_2NMe_2$			A	94	120-130 (0.1)	$C_{17}H_{20}N_2$	C, H, N
47	$Ph_2C=N(CH_2)_3NMe_2$			A	94	144-145 (0.1)	$C_{18}H_{22}N_2$	C, H, N

[a] Method A, directly from ketone and primary amine in benzene with $TiCl_4$ as catalyst; method B, directly from ketone and primary amine in hexamethylphosphoramide with $TiCl_4$ as catalyst; method C, by amine exchange from N-methylimine and primary amine; method D, from the hydroxyalkylimine via the tosylate and reaction of the latter with ammonia. [b] All liquids were short-path distilled; temperature listed is that of the bath; pressures are in μm; temperatures without pressures are melting points. [c] Maleate salt. [d] Mixture of syn and anti isomers. [e] Single isomer of unknown stereochemistry. [f] See Experimental Section. [g] See ref 12.

ature. Even in boiling water, 70% of the maleate remains unhydrolyzed after 15 min. By contrast, the corresponding benzophenone derivative ($Ph_2C=NCH_2CH_2NMe_2$) is hydrolyzed almost instantaneously by cold dilute acid.

Results and Discussion

The potential antidepressant effect of the imines was determined by the reversal of tetrabenazine-induced ptosis and decreased exploratory activity in mice. The method is described under Experimental Section. The results are listed in Table II, which also contains some relevant parameters of the mouse general pharmacology screen.

The most potent compound in the 10,11-dihydrodibenzo[a,d]cyclohepten-5-imine series was the amitriptyline analogue 9. It showed anti-TBZ (antitetrabenazine) ac-

tivity, as well as pupil dilation, motor incoordination, and electroshock protection in the same dose range as amitriptyline.

Replacing the methyl by ethyl groups in 7 and 9 (compounds 8 and 11) reduced or abolished anti-TBZ activity but increased toxicity. All anti-TBZ activity was lost by incorporation of the terminal nitrogen into a heterocyclic ring (compound 13). Increasing the chain length by one carbon (compound 12) reduced anti-TBZ activity. The anti-TBZ activity of the unsaturated analogue 14 was about that of 9, but unlike the latter, it caused excitement at low doses.

Replacing the ethylene bridge (X) by a cyclopropane ring increased anti-TBZ potency; this also was seen in the aminoalkylidenedibenzocyclopropacycloheptenes.[9] Com-

Table II. Effects of Imines in Mice (Oral ED_{50}, mg/kg)

| compd | TBZ antagonism | | mouse general pharmacology screen | | | | |
	ptosis[a]	exploratory loss[a]	pupil dilation	excitement	ataxia	EST protection	24-h mortality
amitriptyline	1.4 (1.1–1.8)	3.5 (2.7–4.6)	23	>324	14	43	190
imipramine	0.9 (0.5–1.6)	2.2 (1.7–3.0)	198	>324	62	209	305
doxepin	5.9 (4.2–8.3)	27	56	>324	23	62	232
6	18 (11–29)	56 (121–146)	200	>324	100	200	200
7[c]	<5	8.5 (2.6–28)	60	>324	36	>324	200
8	>125	>125	20	>324	20	60	36
9	1.9 (1.3–2.7)	9 (4.7–17)	20	>324	20	36	100
10	4.9	11.2 (8.1–15.4)	36	>324	20	60	100
11	>125	36	36	>324	20	200	60
12	24 (10–57)	34 (22–53)	20	>324	60	>324	36
13	>125	>125	100	>324[b]	200[b]	300[b]	300[b]
14	2.5 (2.0–3.1)	6.4 (4.2–9.7)	4	7	4	>324	36
15	9.5 (5.8–15.6)	>125	7[b]	36[b]	20[b]	>324[b]	60[b]
16	0.7 (0.5–0.9)	1.5 (1.1–2.1)	100	>324	60	100	200
17[c]	0.6 (0.3–1.2)	2.6 (1.2–5.5)	60	>324	36	300	300
18	1.1 (0.7–1.9)	8.4 (6.0–12.0)	36	>324	36	>324	200
19	0.25 (0.17–0.37)	0.7 (0.4–1.1)	20	60	20	>324	>324
20	3.7 (2.7–5.1)	11.2 (7.9–16)	12	60	20	200	200
21	1.4 (0.8–2.6)	6.9 (4.1–12)	36	>324	36	100	200
22	1.7 (0.9–3.3)	>81	12	>324	12	>324	200
23	>125	>125	7	>324	60	200	300
24	34 (22–53)	>125	>324	>324	12	>324	200
25	79 (37–170)	>125	>324	>324	200	>324	>324
26[c]	>125	>125	200	>324	200	>324	>324
27	>125	>125	>324	>324	200	>324	>324
28	3.7 (2.2–6.2)	12.5 (9.2–17)	200	>324	60	200	>324
29	6.0 (3.0–12.0)	33	20	>324	36	60	200
30	99 (48–203)	>125	20[b]	>324[b]	20[b]	>324[b]	200[b]
31	12 (7–22)	20 (12–32)	36	>324	36	>324	300
32	11 (6–21)	22 (16–31)	60	>324	60	200	60
33	56 (26–122)	96 (39–238)	100	>324	200	>324	20
34	>125	>125	200	>324	100	>324	>324
35	47 (30–73)	27 (20–36)	20	>324	20	>324	60
36	>81	81	60	>324	60	>324	60
37	40 (27–60)	>125	36	200	200	>324	>324
38	>125	>125	20	>324	200	>324	20
39	>125	73 (34–158)	>324	60	60	>324	300
40	>125	>125	>324	>324	60	>324	300
41	11 (6–20)	22 (8–58)	36	>324	60	>324	300
42	96 (84–110)	125	60	60	60	>324	200
43	>125	>125	>324	>324	36	>324	200
44	>125	>125	20	>324	20	60	200
45	>125	>125	60[b]	>324[b]	60[b]	>324[b]	200[b]
46	>81[b]	>81[b]	>324[b]	>324[b]	36[b]	>200[b]	>324[b]
47	>125	>125	>324	>324	60	>324	200

[a] Confidence limits (in parentheses) determined according to J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99 (1949). [b] Given intraperitoneally. [c] Maleate.

pound 19 was six times as potent as amitriptyline, and like amitriptyline it caused mydriasis. Unlike amitriptyline or imipramine, 19 caused central nervous system stimulation at high doses. The demethyl analogue 17 was three times as potent as amitriptyline in the anti-TBZ test but one-third as potent for dilation of mouse pupils, which suggests it may be less anticholinergic. As in the previously discussed series, all modifications, such as changing nitrogen substituents or chain length, decreased or abolished anti-TBZ activity. Two fluorine substituents on the cyclopropane ring caused some loss of anti-TBZ potency; one or two chlorines abolished this activity completely.

Imines in which one carbon atom of the ethylene chain X is replaced by a hetero atom or where chain X is a single atom had much reduced or no anti-TBZ activity. Compound 29, the imine analogue of doxepin, had a profile similar to that of doxepin. Saturation of the imine double bond abolished anti-TBZ activity (compounds 44 and 45). The imines 46 and 47 derived from benzophenone were also inactive.

Structure–activity relationships of the imines reported in this paper are very similar to those of their carbon analogues. Substitution of the α-carbon of the side chain by nitrogen thus has little effect on the activity of tricyclic antidepressants.

It has been reported elsewhere[10] that *N*-(cyclopropylmethyl)-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-imine (2, X = CH_2CH_2; R = cyclopropylmethyl) is a potent selective inhibitor of dopamine uptake in vitro.

Experimental Section

Melting points are uncorrected. Proton nuclear magnetic resonance spectra were recorded in deuteriochloroform on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Ketones 1 were purchased or prepared by methods described in the literature.

N-Methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-imine (2, X = CH_2CH_2; R = Me). General Method A. A solution of 52.5 g (0.27 mol) of titanium tetrachloride in 300 mL of anhydrous benzene was added slowly, under nitrogen, to a stirred, cooled (ice bath) mixture of 100 g (0.48 mol) of 10,11-

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(10) W. F. Herblin, *Neurochem. Res.*, 2, 111 (1977).

dihydro-5*H*-dibenzo[*a*,*d*]hepten-5-one, 103 g (3.4 mol) of methylamine, and 1200 mL of anhydrous benzene. After stirring at room temperature for 12 days, the mixture was cooled, treated with concentrated aqueous sodium bicarbonate solution, and filtered through Celite. The layers of the filtrate were separated, and the benzene layer was dried with magnesium sulfate. Removal of the solvent and crystallization of the residue from 200 mL of hexane gave 95.6 g (88% yield) of the title compound, mp 89–90 °C. An analytical sample (hexane) also had mp 89–90 °C: NMR τ 2.3–3.2 (m, 8, aromatic H), 6.8–7.2 (m, 4, H-10, H-11), 6.7 (s, 3, Me); UV λ_{max} (cyclohexane) 275 nm (sh, ϵ 1420), 243 (11700). Anal. ($C_{16}H_{15}N$) C, H, N.

N-Methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (2, X = CH=CH; R = Me). (a) **From 5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one.** Using procedure A described above, a mixture of 100 g (0.48 mol) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 98 g (3.2 mol of methylamine, and 1000 mL of benzene was treated with 53 g (0.28 mol) of titanium tetrachloride. The mixture was worked up after stirring at room temperature for 6 days. Short-path distillation of the crude product at 120 °C bath temperature and 0.1 μm pressure gave 101.2 g (95% yield) of N-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine as a viscous oil that solidified slowly on standing. A sample crystallized from cyclohexane had mp 76–78 °C: NMR τ 2.3–2.9 (m, 8, aromatic H), 3.2 (s, 2, H-10 and H-11), 6.7 (s, 3, Me); UV λ_{max} (cyclohexane) 290 nm (ϵ 12900), 226 (31700); IR (KBr) 1625 cm^{-1} (vs), among others. Anal. ($C_{16}H_{13}N$) C, H, N.

(b) **From 5,5-Dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene (3).** A mixture of 10.14 g (0.049 mol) of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 20.13 g (0.098 mol) of phosphorus pentachloride, and 50 mL of phosphorus oxychloride was heated under reflux for 3 h. The excess phosphorus oxychloride was removed under vacuum, the residue was dissolved in 200 mL of toluene, the solvent was removed under vacuum, and the residue was kept at 40 °C under 0.5 mm vacuum for 30 min to give 13.3 g of essentially pure 3, identical by infrared and NMR spectroscopy with the product prepared by the method of Looker.[7]

A solution of 8 g (0.26 mol) of methylamine in 40 mL of tetrahydrofuran was added to a solution of 2.85 g (0.011 mol) of 3 in 10 mL of tetrahydrofuran. The mixture was stirred at room temperature overnight and filtered. Benzene was added to the filtrate, which was then washed with 10% aqueous sodium hydroxide solution and concentrated sodium chloride solution and dried. Removal of the solvent gave 2.85 g of a viscous oil, which was essentially pure N-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine as shown by infrared and NMR spectroscopy.

N-Methyldibenzo[*b*,*e*]thiepin-11(6*H*)-imine (2, X = CH$_2$S; R = Me). General Method B. A solution of 17 g (0.09 mol) of titanium tetrachloride in 50 mL of anhydrous benzene was added slowly, under nitrogen, to a stirred, cooled (ice bath) mixture of 29 g (0.13 mol) of dibenzo[*b*,*e*]thiepin-11(6*H*)-one, 40 g (1.3 mol) of methylamine, and 130 mL of hexamethylphosphoramide (Caution: see ref 6). After stirring at room temperature for 6 days, the mixture was poured into a cooled mixture of ether and sodium hydroxide solution and then filtered through Celite. The ether layer was washed with water and was then extracted several times with cold 5% hydrochloric acid. The extracts were washed with ether and then treated with excess cold aqueous sodium hydroxide solution. Extraction with ether and short-path distillation of the residue obtained on removal of the solvent from the dried extracts gave 26 g (83%) of N-methyldibenzo[*b*,*e*]thiepin-11(6*H*)-imine, as a mixture of syn and anti isomers: bp 126 °C (7 μm); NMR τ 2.1–3.2 (m, 8, aromatic H), 5.3–6.0 (m, 1, H-6), 6.4–6.9 (m + 2 s, 4, H-6 and Me). Anal. ($C_{15}H_{13}NS$) C, H, N, S.

N-[2-(Dimethylamino)ethyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (9). General Method C. A mixture of 15.3 g (0.069 mol) of N-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine, 100 mL of N,N-dimethylethylenediamine, and 1.5 g of p-toluenesulfonic acid hydrate was heated to 112 °C bath temperature for 64 h. Ether was added to the cooled mixture, and the solution was washed with aqueous potassium hydroxide solution and concentrated sodium chloride solution and dried. Removal of the solvent and short-path distillation of the residue at 120–140 °C bath temperature and 0.1 μm pressure gave 17.66 g (94% yield) of 9 as a viscous oil: NMR τ 2.3–2.6 (m, 1, aromatic

H), 2.8–3.3 (m, 7, aromatic H), 6.3–6.7 (t, J = 7 Hz, 2, CH$_2$N=), 6.8–7.2 (m, 4, C-10 and C-11), 7.3–7.6 (t, J = 7 Hz, 2, CH$_2$NR$_2$), 7.9 (s, 6 Me); UV λ_{max} (cyclohexane) 275 nm (sh, ϵ 1900), 243 (11700). Anal. ($C_{19}H_{22}N_2$) C, H, N.

To a warm solution of 3.88 g (0.014 mol) of the free base 9 in 10 mL of acetonitrile was added 1.65 g (0.014 mol) of maleic acid, and the clear solution was seeded with a crystal of the salt and allowed to stand at room temperature overnight. There was obtained 3.55 g (64% yield) of the 1:1 maleate of 9 in the form of colorless crystals, mp 139–141 °C. An analytical sample (MeCN) had mp 139.5–141 °C: NMR τ 4.5 (br, 2, HN$^+$), 2.2–3.1 (m, 8, aromatic H), 3.9 (s, 2, CH=CH), 6.0–7.5 (m + s, 14, H-10 and H-11, =NCH$_2$CH$_2$N, Me). Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

N-(Cyclopropylmethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (2, X = CH$_2$CH$_2$; R = CH$_2$C$_3$H$_5$). In a Carius tube was placed 4.52 g (0.02 mol) of N-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine, 9.2 g (0.13 mol) of cyclopropylmethylamine, and 0.46 g (0.004 mol) of p-toluenesulfonic acid hydrate, and the tube was sealed under vacuum and heated to 120 °C for 60 h. The cooled tube was opened, the cyclopropylmethylamine was removed under vacuum, and the residue was dissolved in ether. The solution was washed with aqueous sodium hydroxide solution and dried. The solvent was removed and the residue was combined with the recovered cyclopropylmethylamine and 0.43 g of p-toluenesulfonic acid hydrate. The mixture was transferred to a Carius tube which was then sealed under vacuum and heated to 120 °C for 30 h. The mixture was worked up as described above, and the crude product was crystallized from hexane to give 3.47 g (65%) of the title compound, mp 98–99 °C. An analytical sample (hexane) had mp 99–100 °C: NMR τ 2.1–3.0 (m, 8, aromatic H), 6.1–7.5 (m, 6, =NCH$_2$, H-10 and H-11), 8.3–9.0 (m, 1, cyclopropane), 9.1–10.0 (m, 4, cyclopropane). Anal. ($C_{19}H_{19}N$) C, H, N.

3-Chloro-N-[2-(dimethylamino)ethyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine (10). 3-Chloro-N-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-imine, mp 84–114 °C, was obtained in 58% yield from 3-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one by method A as described for the preparation of 2: NMR τ 2.3–3.3 (m, 7, aromatic H), 6.6–7.4 (m, 4, H-10 and H-11), 6.7 (s, 3, Me; however, the melting point indicates the presence of both syn and anti isomers). Anal. ($C_{16}H_{14}ClN$) C, H, N.

Using method C, the above N-methylimine was converted to 10 in 85% yield: bp 140–160 °C (bath temperature) (0.1 μm); NMR τ 2.3–3.2 (m, 7, aromatic H), 6.2–7.5 (m, 8, C-10 and C-11, CH$_2$CH$_2$), 7.8 (2 s, 6, NMe$_2$ ratio ca. 3:2). Anal. ($C_{19}H_{21}ClN_2$) C, H, N.

On standing at room temperature for 40 days, the isomer ratio changed from 3:2 to 4:1 and the product partially crystallized. Crystallization from hexane gave the pure major isomer. Stereochemical assignments have not been made.

N-(2-Aminoethyl)-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine (16). General Method D. N-(2-Hydroxyethyl)-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine. Using method B the 2-hydroxyethylimine was prepared in 79% yield: mp 123–124 °C (cyclohexane); NMR τ 2.5–3.2 (m, 8, aromatic H), 6.1–6.6 (m, 5, one H exchangeable with D$_2$O, CH$_2$CH$_2$OH), 7.7 (t, J = 7 Hz, 2, cyclopropane), 8.1–8.7 (m, 2, cyclopropane). Anal. ($C_{18}H_{17}NO$) C, H, N.

N-[2-(Tosyloxy)ethyl]-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine. To a solution of 20.3 g (0.076 mol) of N-(2-hydroxyethyl)-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-imine, 23.4 mL (0.16 mol) of triethylamine, and 141 mL of dry tetrahydrofuran at –5 °C was added dropwise, over a period of an hour, a solution of 16.2 g (0.085 mol) of p-toluenesulfonyl chloride in 70 mL of dry THF. The mixture was allowed to attain 25 °C, then stirred under nitrogen for 24 h, and then poured onto excess ice-water. The precipitate was filtered, thoroughly washed with water, and then dissolved in methylene chloride. The organic solution was, in turn, washed with 10% sodium hydroxide solution and saturated brine and dried, and the solvent was removed to give 29.4 g of a white solid. Recrystallization from ethanol gave 17.2 g (54%) of the tosylate: mp 150 °C; NMR τ 2.1–3.1 (m, 12, aromatic H), 5.6 (t, 2, CH$_2$O), 6.2 (t, 2, CH$_2$N), 7.3–7.8 (m + s, 5, cyclopropane + Me), 8.1–8.9

(m, 2, cyclopropane). Anal. ($C_{25}H_{23}NO_3S$) C, H, N.

N-(2-Aminoethyl)-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-imine (16). A solution of 4.8 g (0.0125 mol) of N-[2-(toxyloxy)ethyl]-1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cyclohepten-6-imine, 20 mL of dry hexamethylphosphoramide,[6] and 25 mL of ammonia was sealed in a Carius tube and kept at 25 °C for 5 days. The solution was poured into 150 mL of water and twice extracted with 75 mL of ether. The organic layer was twice extracted with 50 mL of cold 10% hydrochloric acid. The aqueous solution was washed with 75 mL of ether and then made basic by the addition to a cold solution of sodium hydroxide. The oil was extracted with ether and dried over potassium carbonate, and the solvent was evaporated. The residue was flash distilled at 170 °C (bath) (0.1 μm) to give 2.5 g (83% yield) of 16: NMR τ 2.4–3.1 (m, 8, aromatic H), 6.1–6.7 (m, 2, =NCH₂), 6.8–7.3 (m, 2, CH₂N), 7.4–7.8 (m, 2, cyclopropane), 8.1–8.7 [m + s, 4; the s (2 H) is exchangeable with D₂O; NH₂ and cyclopropane]. Anal. ($C_{18}H_{18}N_2$) C, H, N.

N-(2-Hydroxyethyl)-5H-dibenzo[a,d]cyclohepten-5-imine (4). Using method C, 4 was obtained in 53% yield: mp 117–119 °C after crystallization from benzene (lit.[8] mp 113–114 °C); NMR τ 1.8–3.0 (m, 10, aromatic + H-10 and H-11), 5.7–7.6 (m, 5, CH₂CH₂OH). This compound was indentical, by infrared and NMR spectroscopy, with the product obtained according to ref 8. Anal. ($C_{17}H_{15}NO$) C, H, N.

2'-Methylspiro[5H-dibenzo[a,d]cycloheptene-5,2'-oxazolidine] (5b). A mixture of 5.00 g (0.019 mol) of 5,5-dichlorodibenzo[a,d]cycloheptene (3) and 40 mL of 2-(methylamino)ethanol was heated to 50 °C for a short period and then stirred at room temperature overnight. Ether and water were added, and the crude product obtained from the ether layer was crystallized from cyclohexane to give 1.94 g (38%) of 5b, mp 110.5–111.5 °C. An analytical sample had mp 111–112 °C: NMR τ 2.0–2.3 (m, 2, aromatic H), 2.5–2.8 (m, 6, aromatic H), 2.9 (s, 2, H-10 and H-11), 6.0 (t, J = 6.5 Hz, 2, CH₂O), 7.3 (t, J = 6.5 Hz, 2, CH₂N), 8.2 (s, 3, Me). Anal. ($C_{18}H_{17}NO$) C, H, N.

Pharmacology. Antitetrabenazine (TBZ) Test. This test was used to detect potential antidepressant activity. Groups of 10 Carworth CF₁S female mice, 18–21 g each, were fasted 1.5 h and were intubated with test compounds at oral doses of 0, 5, 25, and 125 mg/kg or 0, 1, 3, 9, 27, and 81 mg/kg in 0.20 mL of 1% Methocel. The mice were challenged 30 min later with tetrabenazine (as the methanesulfonate), 32 mg/kg intraperitoneally (dissolved in 0.20 mL of 0.05 M KCl at pH 2.0). One hour after the test was administered (30 min after tetrabenazine), the mice were examined for signs of exploratory activity and ptosis (eyelid closure). Antagonism of exploratory loss was recorded when a mouse, lifted by the tail from a group of 10 in a testing box and placed on a stainless-steel testing box lid (12.5 × 2 in. with 0.33 in. mesh), either turned its head horizontally 30° in both directions or moved to the edge of the screen within 10 s after being placed on the screen. Antagonism of ptosis was recorded when exactly 2 s after placing the mouse facing the observer lid closure was less than 50% in both eyes.

General Pharmacology Screen. Female white mice, 16–20 g each, were fasted 17–24 h and then dosed orally with test drug or standard drug at 0, 4, 12, 36, 108 or 324 mg/kg. Mice were observed at 0.5, 2, 5, and 24 h after drug administration for the number of survivors and for signs of ataxia, pupillary dilation, excitement, and protection from electroshock.

Ataxia. The mouse or rat was placed upright on the bench top facing away from the observer. Motor incoordination manifested by abnormal gait or lack of precision during purposive movements constituted ataxia. Mice which did not walk or run spontaneously were prodded gently.

Pupillary Diameter. The mouse was held by the tail and neck nape with one hand while its head was steadied by gently holding its muzzle with the other hand. Pupillary diameter was measured with a dissecting microscope (B and L) (20× magnification) with an eyepiece fitted with a 10-mm micrometer disk divided into 0.1-mm divisions. The head of the mouse was placed about 8 cm below the microscope objective. A Nichloas microscope lamp (B and L) was focused on the eye of the mouse and pupillary diameter was determined rapidly (2–5 s).

Electroshock Convulsions. At 2 and 5 h after dosing, each mouse was held by the tail and neck nape and was positioned with the corneas of the eye touching saline-saturated corneal wick electrodes. A supramaximal (about 50 mA) alternating current (from a Model B Medcraft ECT unit, set for 70 V) was passed for 0.2 s through the corneal electrodes. A decrease of the typical maximal convulsive seizure produced by this stimulus (i.e., absence of the hindlimb extensor component) constituted electroshock protection.

Excitement and Irritability. Increased spontaneous motor activity, running and jumping, prior to handling was recorded as excitement.

An ED₅₀, the calculated dose at which 50% of the test animals would have responded, was calculated by the method of Thompson[11] for each of the described parameters for the test compounds and the standard drugs.

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(12) J. Bernstein and K. Lossee, U.S. Patent 3052721 (1962); A. M. Monro, R. M. Quinton, and T. I. Wrigley, *J. Med. Chem.*, **6**, 255 (1963).

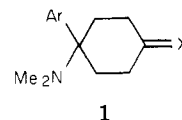# 4-Aryl-4-aminocyclohexanones and Their Derivatives, a Novel Class of Analgesics. 3. m-Hydroxyphenyl Derivatives

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Derivatives of 4-aryl-4-(dimethylamino)cyclohexan-1-ones substituted by m-hydroxy groups were obtained by using as a key reaction the displacement of cyanide from the α-aminonitrile of 1,4-cyclohexanedione ketal, with the THP ether of m-hydroxyphenylmagnesium bromide. A number of the products show narcotic antagonist activity. Amino alcohols obtained on reaction of the free ketones with phenethyl Grignard reagents are potent analgetics, though devoid of antagonist activity. Systematic variation of the substituent on nitrogen revealed nonclassical structure–activity relationships; the dimethylamino group gives the most potent antagonist.

We have reported earlier on the synthesis and opioid analgesic activity of derivatives of 4-aryl-4-aminocyclohexanone (1).[2,3] The nature of the synthesis used in the earlier work made it awkward to carry a phenol through the scheme. Since it is well known that a m-hydroxy group has a profound influence on molecules with analgesic activity, we sought a relatively short route to these analogues.

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(1) Adria Laboratories, Columbus, Ohio.
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