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Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene and Related Compounds. 6. Aminoalkyl Derivatives of the Aza Isosteres†,[1]

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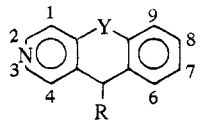
The synthesis, antianaphylactic and antihistaminic potency, and structure-activity relationships of a series of aminoalkyl derivatives of the aza isosteres of 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene are described. Compound 33, azatadine dimaleate, 6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine, conveniently designated as a member of the 4-aza-10,11-dihydrodibenzocycloheptene series, has shown very potent biological properties which have been confirmed in clinical trials in man.

Our studies of aminoalkyl derivatives of dibenzocycloheptenes[2,3] have included the synthesis and biological evaluation of the isosteric aza analogs, I.‡ The synthesis of



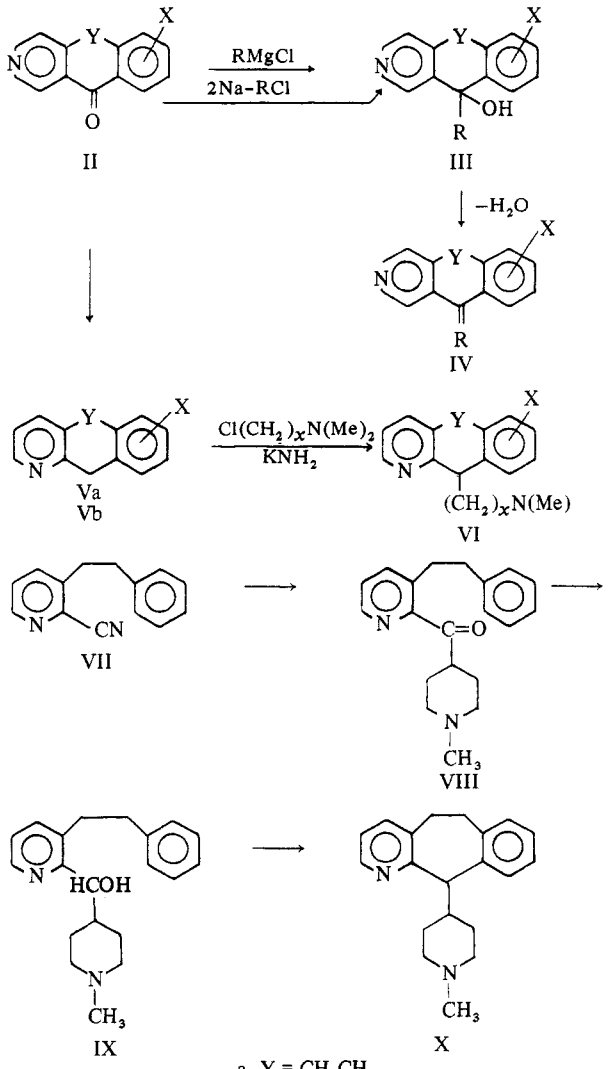
Ia, Y = CH_2CH_2
Ib, Y = CH=CH

R values given in Tables I, II, and III

these compounds is shown in Scheme I. Aza ketones II[4] were treated with a Grignard reagent to give the corresponding tertiary carbinols listed in Table I. In those cases wherein R is a dialkylaminoethyl or when the Grignard reagent would not form readily, the novel reductive alkylation procedure[5] gave good yields of III. The carbinols were subjected to the usual acid dehydrating conditions and gave the unsaturated compounds listed in Table II. In the 4-aza series, *i.e.*, those compounds wherein the pyridyl nitrogen is attached to a carbon atom which is α to the carbinol group, vigorous dehydrating conditions are required.[6] In these cases prolonged heating at 160-165° in the presence of excess PPA or the use of 85% H_2SO_4 is necessary to effect the dehydration. A number of the compounds listed in Table II were obtained as a mixture of the cis and trans isomers and no effort was made to separate the mixture for preliminary biological evaluation.§

Since it soon was apparent that maximum antianaphylactic and antihistaminic activity was found in the 4-aza series we concentrated our synthetic efforts in this area. The 4-aza ketones were converted to the 4-aza hydrocarbons V by a modified Wolff-Kischner reduction. Alkylation of V in the presence of KNH_2 with a variety of alkylaminoalkyl halides

Scheme I



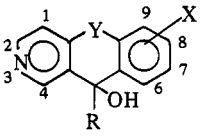
II, III, IV, Va, Vb, VI, VII, VIII, IX, X

a, Y = CH_2CH_2
b, Y = CH=CH

†Presented in part before the Division of Medicinal Chemistry Section of the 124th National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

‡For clarity throughout, we prefer to name these compounds as derivatives of azadibenzocycloheptenes and to standardize the number around the ring as shown in I. Thus, compound 33 (Table II) is named 4-aza-5-(1-methyl-4-piperidylidene)-10,11-dihydrodibenzo[*a,d*]cycloheptene. The Chemical Abstract name for this compound is 6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

§Compound 31 (Table II) showed some interesting CNS properties and was separated into the cis and trans isomers. A future communication from this laboratory will describe this work.

Table I. Compounds of Formula 

No.	Position of N	Y	X	R	Method	Yield, %	Mp or bp (mm), °C	Formula[a]
1	1	CH_2CH_2	H	$(CH_2)_3N(Me)_2$	A	55	106-109[b]	$C_{19}H_{24}N_2O$
2	1	CH_2CH_2	H	$C_6H_{12}N$[c]	A	49	172-174[d]	$C_{20}H_{24}N_2O$
3	1	CH=CH	H	$C_6H_{12}N$	B	60	212-214[e]	$C_{20}H_{22}N_2O$[f]
4	1	CH_2CH_2	H	$C_9H_{18}N$[g]	A	39	179-182[d]	$C_{23}H_{20}N_2O$[h]
5	2	CH_2CH_2	H	$(CH_2)_3N(Me)_2$	A	49	101-102[d]	$C_{19}H_{24}N_2O$
6	2	CH=CH	H	$(CH_2)_3N(Me)_2$	B	66	117-118[d]	$C_{19}H_{22}N_2O$
7	2	CH_2CH_2	H	$C_6H_{12}N$	A	52	201-202[e]	$C_{20}H_{24}N_2O$
8	3	CH_2CH_2	H	$(CH_2)_3N(Me)_2$	A	36	100-102[d]	$C_{19}H_{24}N_2O$
9	3	CH=CH	H	$(CH_2)_3N(Me)_2$	B	76	114-115[i]	$C_{19}H_{22}N_2O$
10	3	CH_2CH_2	H	$C_6H_{12}N$	A	35	201-202[e]	$C_{20}H_{24}N_2O \cdot H_2O$[j]
11	4	CH_2CH_2	H	$(CH_2)_2N(Me)_2$	C	65	66-68[i]	$C_{18}H_{22}N_2O$
12	4	CH_2CH_2	H	$C_6H_{12}N$	A	63	174-176[d]	$C_{20}H_{24}N_2O$
13	4	CH_2CH_2	H	$(CH_2)_3N(Me)_2$	A	73	174-176 (2)	$C_{19}H_{24}N_2O$[k]
14	4	CH=CH	H	$C_6H_{12}N$	B	36	172-174[d]	$C_{20}H_{22}N_2O$
15	4	CH=CH	H	$(CH_2)_3N(Me)_2$	B	66	199-202 (2)	$C_{19}H_{22}N_2O$
16	4	CH_2CH_2	H	$CH_2CH(Me)CH_2N(Me)_2$	A	78	173-175 (0.15)	$C_{20}H_{26}N_2O$
17	4	CH_2CH_2	7-Cl	$C_6H_{12}N$	A	43	168-170	$C_{20}H_{23}ClN_2O$
18	4	CH_2CH_2	8-Cl	$(CH_2)_3N(Me)_2$	A	69	200-203 (2)	$C_{19}H_{23}ClN_2O$[l]
19	4	CH_2CH_2	8-Cl	$C_6H_{12}N$	A	56	141-143[d]	$C_{20}H_{23}ClN_2O$
20	4	CH_2CH_2	6-Cl	$C_6H_{12}N$	A	35	121-123[d]	$C_{20}H_{23}ClN_2O$
21	4	CH_2CH_2	7-Br	$C_6H_{12}N$	A	41	172-174[d]	$C_{20}H_{23}BrN_2O$
22	4	CH_2CH_2	H	3-$C_7H_{14}N$[m]	C	78	93-95[i]	$C_{21}H_{26}N_2O$

[a] All compds were analyzed for C, H, N. [b] From Et_2O. [c] $C_6H_{12}N$ is 1-methyl-4-piperidyl. [d] From i-Pr_2O. [e] From MeCN. [f] Calcd C: 78.40; found C: 78.84. [g] $C_9H_{18}N$ is 4-dimethylaminocyclohexylmethyl. [h] Calcd H: 8.63; found H: 7.20. [i] From hexane. [j] Calcd H: 8.03; found H: 7.60. [k] Calcd C: 76.99; found C: 76.57. [l] Calcd C: 69.08; found C: 70.01. [m] 3-$C_7H_{14}N$ is 1-ethyl-3-piperidyl.

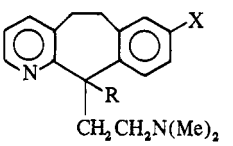
gave a series of compounds (Table III) wherein the exocyclic bond at position 5 in IV is reduced. To prepare the corresponding 5-(1-methyl-4-piperidyl) analog X, the secondary carbinol IX, obtained by $NaBH_4$ reduction of ketone VIII, was subjected to an internal cyclodehydration using PPA.

Biological Results and Structure-Activity Relationships. The compounds were screened for their antianaphylaxis and antihistamine activities in laboratory animals. Those compounds having a 1-methyl-4-piperidylidene group at position 5 showed high activity against fatal anaphylaxis in mice sensitized with horse serum and pertussis vaccine and later challenged with horse serum. Table IV lists the approximate protective dose (PD_{50}) of the more active compounds in this test. Compound **33**, azatadine dimaleate, the 4-aza-10,11-dihydro derivative, is the most potent compound in this series. Introduction of a double bond in the 10,11 position or substitution of a chlorine in the 7 or 8 position results in a slight loss of activity. In the 5-(1-methyl-4-piperidylidene) series of compounds moving the nitrogen around the ring has a pronounced effect on the potency. In this study the order of decreasing potency is the 4-aza > 2-aza > 1-aza > 3-aza. The carbinols of Table I and the dialkylaminoalkylidenes of Table II showed minimal protective action at much higher doses (2-10 mg/kg).

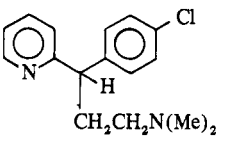
In the classical isolated guinea pig ileum *in vitro* antihistamine screen, compound **33** exhibited excellent activity having a relative potency of approximately 3.4 times the standard (Chlorpheniramine Maleate,# XId). In the guinea pig, compound **33** orally was able to protect against death induced by the intravenous injection of twice the lethal dose of histamine dihydrochloride (1.1 mg/kg) at a dose of 0.0091 mg/kg. In this assay, compound **33** was calculated to be 7.4 times more potent than the standard.

#Chlorpheniramine Maleate is a registered trademark of the Schering Corp.

5-Dialkylaminoalkyl derivatives of 4-azadihydrodibenzo[a,d]cycloheptenes (Table III) exhibited a low order of activity in the mouse anaphylaxis screen. However, they showed very potent classical antihistaminic activity both *in vitro* and *in vivo*. Compounds **53** and **60** maleate were approximately 3-3.5 times as potent as the standard in the guinea pig assays. This was not completely unexpected because of the structural similarity of compounds XIa,b with standard XId. The introduction of an additional alkyl substituent (XIc) at position 5 resulted in a marked drop in activity.



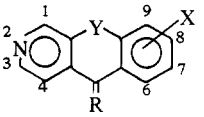
XIa, X = H; R = H
XIb, X = Cl; R = H
XIc, X = H; R = Et



XId

Having established the potent antianaphylactic and antihistamine potency of compound **33**, systematic modifications in the structure of this compound were made and the compounds were screened for antihistaminic activity *in vitro* using XId as the reference standard. The chemical properties of these compounds are incorporated into Table II. Maximum activity was found in those compounds having a 1-lower alkyl substituent on the 4-piperidylidene ring. Branching of the 1 substituent, *e.g.*, 1-isopropyl (**48**) or larger substituent, *e.g.*, 1-β-phenethyl (**49**), causes a considerable reduction in activity. Changing the basic tertiary amine nature at this position (**46**) or the formation of amides (**50, 51**) results in complete loss of activity at the screening dose of 160 μg/l.

The replacement of the 5-(1-methyl-4-piperidylidene) group by the 1-ethyl-3-piperidylidene group (**52**) results in

Table II. Compounds of Formula 

No.	Position of N	Y	X	R	Method	Yield, %	Mp or bp (mm), °C	Formula[a]
23	1	CH_2CH_2	H	$CH(CH_2)_2N(Me)_2$	E	53	175–180 (1)	$C_{19}H_{22}N_2$[b]
23·maleate							154–156[c]	$C_{19}H_{22}N_2 \cdot C_4H_4O_4$
24	1	CH_2CH_2	H	$C_6H_{11}N$[d]	*e*		136–138[f]	$C_{20}H_{22}N_2$
24·HCl					E		180–185[g]	$C_{20}H_{22}N_2 \cdot 2HCl \cdot 2H_2O$
25	1	CH_2CH_2	H	$C_9H_{14}N$[h]	E		95–97[f]	$C_{23}H_{28}N_2$
25·2HCl							212–216[c]	$C_{23}H_{28}N_2 \cdot 2HCl \cdot H_2O$[i,j]
26	1	CH=CH	H	$C_6H_{11}N$	D	87	154–156[f]	$C_{20}H_{20}N_2$
27	2	CH_2CH_2	H	$CH(CH_2)_2N(Me)_2$	D	65	178–180 (0.5)	$C_{19}H_{22}N_2$
28	2	CH=CH	H	$CH(CH_2)_2N(Me)_2$	D	69	196–200 (1)	$C_{19}H_{20}N_2$
29	2	CH_2CH_2	H	$C_6H_{11}N$	D	83	125–126[k]	$C_{20}H_{22}N_2$
30	3	CH_2CH_2	H	$CH(CH_2)_2N(Me)_2$	D	70	173–175 (0.7)	$C_{19}H_{22}N_2$
31	3	CH=CH	H	$CH(CH_2)_2N(Me)_2$	D	69	172–174 (0.2)	$C_{19}H_{20}N_2$
32	3	CH_2CH_2	H	$C_6H_{11}N$	D	58	148–149[f]	$C_{20}H_{22}N_2$
33	4	CH_2CH_2	H	$C_6H_{11}N$	F	81	124–126[l]	$C_{20}H_{22}N_2$
33·dimaleate							152–154[m]	$C_{20}H_{22}N_2 \cdot 2C_4H_4O_4$
34	4	CH_2CH_2	H	$CH(CH_2)_2N(Me)_2$	F	40	163–165 (0.5)	$C_{19}H_{22}N_2$
35·dimaleate	4	CH=CH	H	$C_6H_{11}N$	G		144–148[m]	$C_{20}H_{20}N_2 \cdot 2C_4H_4O_4$
36	4	CH=CH	H	$CH(CH_2)_2N(Me)_2$	G	69	165–169 (1)	$C_{19}H_{20}N_2$
37	4	CH_2CH_2	H	$CHCH(CH_3)CH_2N(Me)_2$	G	87	140–144 (0.01)	$C_{20}H_{24}N_2$[n]
38	4	CH_2CH_2	7-Cl	$C_6H_{11}N$	G	86	135–137[k]	$C_{20}H_{21}ClN_2$
39	4	CH_2CH_2	8-Cl	$C_6H_{11}N$	G	63	117–118	$C_{20}H_{21}ClN_2$
40	4	CH_2CH_2	6-Cl	$C_6H_{11}N$	G	42	*o*	
41	4	CH_2CH_2	H	$CHCH_2N(Me)_2$	G	89	67–69[f]	$C_{18}H_{20}N_2$
41·maleate							156–158[p]	$C_{18}H_{20}N_2 \cdot C_4H_4O_4$
42	4	CH_2CH_2	7-Br	$C_6H_{11}N$	G	65	120–122[f]	$C_{20}H_{21}BrN_2$
43	4	CH_2CH_2	7-NO_2	$C_6H_{11}N$	*q*	45	174–175[l]	$C_{20}H_{21}N_3O_2$
44	4	CH_2CH_2	7-NH_2	$C_6H_{11}N$	*r*	74	153–155[l]	$C_{20}H_{23}N_3$
45	4	CH_2CH_2	H	$C_6H_8N_2$[s]		58	119–120[t]	$C_{20}H_{19}N_3$
46	4	CH_2CH_2	H	C_6H_9N[u]	*v*	84	123–126[w]	$C_{19}H_{20}N_2$
47	4	CH_2CH_2	H	$C_7H_{13}N$[x]	H	96	85–87[k]	$C_{21}H_{24}N_2$
47·maleate							170–173[y]	$C_{21}H_{24}N_2 \cdot C_4H_4O_4$
48	4	CH_2CH_2	H	$C_8H_{15}N$[z]	*aa*	33	140–142[g]	$C_{22}H_{26}N_2$
49	4	CH_2CH_2	H	$C_{13}H_{17}N$[bb]	H	37	119–120[k]	$C_{27}H_{28}N_2$
49·dimaleate							178–180[c]	$C_{27}H_{28}N_2 \cdot 2C_4H_4O_4$
50	4	CH_2CH_2	H	$C_{10}H_{18}N_2O$[cc]	*dd*	34	116–117[l]	$C_{24}H_{29}N_3O$
51	4	CH_2CH_2	H	$C_{10}H_{10}NO$[ee]	*ff*	89	168–170[t]	$C_{29}H_{29}N_3O$
52	4	CH_2CH_2	H	3-$C_7H_{13}N$[gg]	F	57	81–83[k]	$C_{21}H_{24}N_2$

[a] All compds were analyzed for C, H, N. [b] Calcd N: 10.06; found N: 10.69. [c] From *i*-PrOH–Et_2O. [d] $C_6H_{11}N$ is 1-methyl-4-piperidylidene. [e] Liberated from the 2HCl salt with NH_4OH. [f] From petroleum ether (bp 30–90°). [g] From *i*-PrOH. [h] $C_9H_{14}N$ is 4-dimethylaminocyclohexylmethylidene. [i] Calcd C: 65.39; found C: 63.97. [j] Calcd Cl: 16.75; found 16.89. [k] From hexane. [l] From *i*-Pr_2O. [m] From MeOH–*i*-PrOAc. [n] Calcd C: 82.14; found C: 82.67; Calcd H: 8.27; found H: 9.05. [o] Isolated as the dipicrate, mp 230–234°. *Anal.* ($C_{20}H_{21}ClN_2 \cdot 2C_6H_3N_3O_7$) C, H, N. [p] From EtOAc. [q] From compd **33** by nitration using KNO_3 in H_2SO_4. [r] From compd **34** by $SnCl_2$–HCl reduction. [s] $C_6H_8N_2$ is 1-cyano-4-piperidylidene prepared from compd **33** using CNBr in C_6H_6. [t] From C_6H_6–petroleum ether. [u] C_6H_9N is 4-piperidylidene. [v] Hydrolysis of compd **45** using HCl–H_2O–HOAc. [w] From cyclohexane. [x] $C_7H_{13}N$ is 1-ethyl-4-piperidylidene. [y] From EtOAc–Et_2O. [z] $C_8H_{15}N$ is 1-isopropyl-4-piperidylidene. [aa] Prepared from compd **46** by alkylation with *i*-Pr I and K(*tert*-OBu) in C_6H_6. [bb] $C_{13}H_{17}N$ is 1-phenethyl-4-piperidylidene. [cc] $C_{10}H_{18}N_2O$ is 1-(*N*-diethylcarbamyl)piperidylidene. [dd] From compd **46** and diethylcarbamoyl chloride in C_6H_6. [ee] $C_{10}H_{10}NO$ is *trans*-phenylcyclopropylcarbamoyl. [ff] From compd **46** and *trans*-phenylcyclopropyl isocyanate in anhyd C_6H_6. [gg] 3-$C_7H_{13}N$ is 1-ethyl-3-piperidylidene.

a compound equipotent with the standard.

The pronounced biological activity of compound **33** in laboratory animals has been substantiated by preliminary clinical studies in man.[7-12]

Experimental Section**

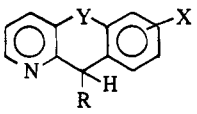
Carbinols of Table I. Method A. The Grignard reagent was prepared in Et_2O or THF from freshly distd 3-dimethylaminopropyl chloride (23 g, 0.19 mole) and 4.6 g of Mg metal using I_2 as an initiator. With stirring and cooling in an ice bath, a soln of the ketone in Et_2O or THF was added dropwise and the mixt was refluxed with stirring for 6 hr and NH_4Cl soln (10%) was added. The organic layer was sepd and the aqueous layer was extd with $CHCl_3$. The combined organic layers were evapd to dryness on the steam bath and the residue was triturated with petroleum ether (bp 60–90°). If the crude product contained a small amount of starting ketone (ir 5.9–6.1 μ) or if the product would not cryst readily it was absorbed on a column of alumina (40 g/g) and eluted with C_6H_6–$CHCl_3$.

Method B. To 2.4 g of Mg and 20 ml of THF (dried over CaH_2) was added 12.1 g (0.1 mole) of 3-dimethylaminopropyl chloride in an equal vol of THF. A cryst of I_2 and ethylene dibromide (0.5 ml) was added. The mixt was heated on steam bath until the Mg had gone into soln (1–1.5 hr). With cooling, a suspension of the dehydro ketone (0.04 mole) in 200 ml of THF was added quickly and the mixture was stirred for 15 min in an ice bath. NH_4Cl soln was added, the layers were sepd, extd 3 times with $CHCl_3$, and washed with H_2O, the solvent was removed, and the product isolated as in method A.

Method C. Reductive Alkylation. Na metal (5.1 g, 0.2 g-atom + 10%) was dissolved in about 300 ml of anhyd liquid NH_3. With stirring, a soln of ketone (0.1 mole) in 100 ml of THF was added slowly and stirring was continued for 20 min. A soln of 0.1 mole of the aminoalkyl halide in 70 ml of THF was added and the reaction stirred for an additional 4 hr. Solid NH_4Cl (20 g) was added and the mixt was decompd by the addn of H_2O. The product was extd with $CHCl_3$, concd, and recrystd.

General Dehydration Procedure. Method D. A soln of the carbinol (0.03 mole), 10 ml of concd H_2SO_4, and 150 ml of Ac_2O

**Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated only by the empirical formula, elemental analyses were within 0.4% of the theoretical values. Microanalyses and spectral data were obtained by the Physical and Analytical Department of the Schering Corp. Spectral data (uv, ir, and nmr) were in agreement with the theoretical values.

Table III. Compounds of Formula 

No.	Y	X	R[a]	Yield, %	Mp or bp (mm), °C	Formula
53	CH_2CH_2	H	$(CH_2)_2N(Me)_2$	83	86–88[b]	$C_{18}H_{22}N_2$
54·maleate	CH=CH	H	$(CH_2)_2N(Me)_2$	65	141–142[c]	$C_{18}H_{20}N_2 \cdot C_4H_4O_4$
55·maleate	CH_2CH_2	H	$(CH_2)_2$N⟨ ⟩	73	139–141[d]	$C_{20}H_{24}N_2 \cdot C_4H_4O_4$
56·maleate	CH_2CH_2	H	$(CH_2)_2$N⟨ ⟩	87	173–174[c]	$C_{21}H_{26}N_2 \cdot C_4H_4O_4$
57·maleate	CH_2CH_2	H	$(CH_2)_2$N⟨ O ⟩	61	148–150[d]	$C_{20}H_{24}N_2O \cdot C_4H_4O_4$
58	CH_2CH_2	H	$(CH_2)_2N(Me)_2$	98	156–158 (2)	$C_{19}H_{24}N_2$
59·dimaleate	CH_2CH_2	H	$(CH_2)_3$N⟨ N–CH_3 ⟩	47	188–191[d]	$C_{22}H_{29}N_2 \cdot 2C_4H_4O_4$
60·maleate	CH_2CH_2	8-Cl	$(CH_2)_2N(Me)_2$	58	113–115[e]	$C_{18}H_{21}ClN_2 \cdot C_4H_4O_4$
61	CH_2CH_2	H	⟨ N–CH_3[f] ⟩	87	111–113[g]	$C_{20}H_{24}N_2$

[a]Unless otherwise noted all compounds were prepared by method I and were analyzed for C, H, and N. [b]Sample was sublimed at 110° (1 mm) and recrystd from hexane. [c]EtOAc–*i*-Pr_2O. [d]From EtOH–Et_2O. [e]From EtOAc. [f]See Experimental Section for preparation. [g]From *i*-Pr_2O.

Table IV

Compound[a]	Antianaphylaxis approx PD_{50}, mg/kg	Antihistamine *in vitro* ED_{50}, μg/l.
24	0.3	2.3
26	0.4	13.4
29	0.073	0.72
32	0.8	4.3
33	0.014	0.72
35	0.025	1.6
38	0.064	2.2
39	0.030	2.0
Cyproheptadine[b]	0.083	1.0
Chlorpheniramine Maleate	2.3	2.4

[a]Compound numbers refer to compounds in Table II. [b]See ref 13.

was warmed on the steam bath for 1 hr. The mixt was poured onto ice H_2O, basified (NH_4OH), extd with $CHCl_3$, and washed with H_2O, the solv removed, and the residue processed as in Table II.

Method E. The carbinol (0.03 mole), 80 ml of HOAc, and 25 ml of HCl were refluxed for 8 hr and concd *in vacuo* on the steam bath. The residue was poured into ice water and processed as in method D.

Method F. The tertiary carbinol was heated with stirring for 15 hr at 165–170° with 50 times its weight of PPA. After cooling the mixt was poured into ice, basified (NaOH), and extd ($CHCl_3$). The exts were washed, the solv was distd, and the residue was recrystd.

Method G. The carbinol (10 g) dissolved in 50 ml of 85% H_2SO_4 and allowed to stand for 2 hr at or below room temperature. The mixt was poured onto ice, basified (NaOH), extd (Et_2O), and washed, and the solv removed.

Method H. A soln of 2.7 g (0.01 mole) of amine (Table II, **46**) and 0.01 mole of aldehyde was reduced in a Parr hydrogenator using 5% Pd/C (1 g) at 4.22 kg/cm². The reaction was complete in 1.5 hr, the catalyst was removed, and the filtrate was concd to a residue, triturated with hexane, and recrystd.

Method I. KNH_2 was prepared from 2.2 g of K metal (10% excess) and 200 ml of liquid NH_3 using a $Fe(NO_3)_3$ catalyst. To this soln was added, with stirring during 15 min, 10 g of the azahydrocarbon in 30 ml of Et_2O, followed in 15 min by the aminoalkyl halide (5% excess) in 15 ml of Et_2O; stirring was continued overnight. Water was added, the mixt was extd (Et_2O) and washed, and the solv was removed. If the residue would not crystallize directly or was nondistillable it was dissolved in EtOAc and added to a refluxing soln of maleic acid in EtOAc with stirring. On cooling the maleate salt crystd out.

4-Aza-10,11-dihydrodibenz[*a,d*]cycloheptene (Va). To a soln of 50 g of the 4-aza ketone in 400 ml of triethylene glycol was added hydrazine hydrate (50 g) and KOH (68 g) and the mixt was heated under reflux at 140–145° for 4–5 hr. The mixt was distd until the internal temp reached 200° and was so maintained for 3–5 hr. After cooling, the mixt was poured into ice water and extd (Et_2O), washed 3 times with ice H_2O, dried, and distd; bp 139–146° (1.2 mm); yield 40 g (85%). On cooling the distillate crystd and was recrystd from hexane; mp 48–49°. *Anal.* ($C_{14}H_{13}N$) C, H, N.

4-Azadibenz[*a,d*]cycloheptene (Vb). This compd was obtained in 95% yield by a similar procedure; bp 167–169° (5 mm). *Anal.* ($C_{14}H_{11}N$) C, H, N.

4-Aza-8-chloro-10,11-dihydrodibenz[*a,d*]cycloheptene. This compound was obtained from the 8-chloro ketone in 78% yield; mp 95–97° from hexane. *Anal.* ($C_{14}H_{12}NCl$) C, H, N.

2-(3-β-Phenethyl)pyridyl 1-Methyl-4-piperidyl Ketone (VIII). To a Grignard reagent prepared from 1-methyl-4-chloropiperidine (16 g, 0.12 mole) and Mg (2.9 g) in THF (60 ml), 3-phenethylpicolinonitrile[4] (20.8 g, 0.1 mole) in THF (100 ml) was added dropwise with stirring and the mixt was heated on a steam bath overnight. The solv was removed *in vacuo* and concd HCl (200 ml) was added with cooling. The soln was stirred for 6 hr at room temperature and then refluxed for 4 hr. After cooling, the mixt was extd (Et_2O) and the aqueous soln was basified (NH_4OH), extd ($CHCl_3$), washed (H_2O), and distd; bp 195–210° (2 mm); yield 16.7 g (55%). *Anal.* ($C_{20}H_{24}N_2O$) C, H, N.

2-(3-Phenethyl)pyridyl(1-methyl-4-piperidyl)carbinol (IX). To ketone VIII (10.9 g, 0.035 mole) in MeOH (140 ml) was added in several portions 1.7 g of $NaBH_4$ (0.045 mole). After 1 hr the MeOH was removed on the steam bath and the residue was dissolved in H_2O, extd ($CHCl_3$), washed, and distd; bp 190–195° (1 mm); yield 9.3 g (86%). *Anal.* ($C_{20}H_{26}N_2O$) C, H, N.

6,11-Dihydro-11-(1-methyl-4-piperidyl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (X). Carbinol IX (3.4 g, 0.01 mole) and 150 g of PPA were heated at 160–170° for 13 hr and poured into ice water, basified (NaOH), and extd (Et_2O). The residue, after removal of the solv, was recryst from *i*-Pr_2O; mp 111–112°.

5-Hydroxy-5-ethyl-4-aza-10,11-dihydrodibenz[*a,d*]cycloheptene (XIe). This compd was prepared by method C using EtI in THF in 87% yield; bp 183–188° (1 mm); mp 36–38° (from petroleum ether). *Anal.* ($C_{16}H_{17}NO$) C, H, N.

5-Ethyl-4-aza-10,11-dihydrodibenz[*a,d*]cycloheptene (XIf). The above compd (12.5 g, 0.052 mole) was added to a satd soln of HI in 60 ml of HOAc and warmed on the steam bath for 1 hr. The mixt was poured into ice H_2O, basified (NaOH), extd ($CHCl_3$), washed (satd $Na_2S_2O_7$ soln), concd, and distd, bp 153–157° (1 mm); yield, 9.1 g (77.5%). *Anal.* ($C_{16}H_{17}N$) C, H, N.

5-Ethyl-5-dimethylaminoethyl-4-aza-10,11-dihydrodibenz[*a,d*]cycloheptene (XIc). This compd was prepared by the alkylation of XIf using method I; yield, 59%; bp 171–176° (1 mm). *Anal.*

($C_{20}H_{26}N_2$) C, H, N. The maleate salt, mp 127–130°, was recrystd from *i*-PrOH–Et_2O. *Anal.* ($C_{20}H_{26}N_2 \cdot C_4H_4O_4$) C, H, N.

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Synthesis of Fatty Acids with Smooth Muscle Stimulant Activity. 3. Acetylenic Analogs of 12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic Acid[1]

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12-Hydroxyheptadeca-*trans*-8,*trans*-10-dienoic acid and analogs in which one or both double bonds are replaced by triple bonds have been prepared by methods which give products essentially free from cis isomers. These acids have been tested for smooth muscle stimulant activity and found to be approximately as active as ricinelaidic acid.

The prostaglandins are alicyclic hydroxy fatty acids with a very wide range of pharmacological actions (for a recent summary see ref 2) including luteolytic activity, of potential use in the control of conception, and uterine muscle stimulant activity, usable for therapeutic abortion. They may also have related physiological functions, particularly in the normal induction of labor. Simpler analogs with these activities, or with antagonistic actions, would therefore be of great interest.

$$C_6H_{13}CH(OH)CH_2CH{=}CH(CH_2)_7CO_2H$$
1

The simple fatty acids which have stimulant effects on smooth muscle fall into three classes. Unsaturated acids may become peroxidized and then act like other, nonacidic, peroxides.[3] Particular polyunsaturated acids may be metabolized to prostaglandins.[4] Some hydroxy unsaturated acids, for example, ricinoleic acid (**1**, cis isomer), which cannot act as prostaglandin precursors, have however an independent stimulant action[5] and can be distinguished from peroxides by correct choice of muscle preparation. The positions of functional groups in these acids were considered and compared with those in prostaglandins. It was consequently proposed in paper 1 of this series[6] that smooth muscle stimulant activity may occur in fatty acids possessing a hydroxyl group at position 12 and unsaturation or structural rigidity between positions 8 and 11. Of the monounsaturated acids then examined, 12-hydroxyheptadec-*trans*-10-enoic acid was found to be the most active. Synthesis of diunsaturated analogs was therefore undertaken.

Introduction of a triple bond at position 8 gives 12-hydroxyheptadec-*trans*-10-en-8-ynoic acid (**5**, X = CO_2H). The hydroxy-*trans*-enyne system occurs in helenynolic acid[7] (9-hydroxyoctadec-*trans*-10-en-12-ynoic acid) but in reverse order. It can be obtained,[8,9] among other products, by base-catalyzed cleavage of a methylene-interrupted epoxyacetylenic acid.

$$C_5H_{11}\overset{trans}{CH{=}CHCHO} \longrightarrow C_5H_{11}\overset{trans}{CH{=}CHCH(OH)C{\equiv}CH} \longrightarrow$$
2 **3**

$$C_5H_{11}CH(OR)\overset{trans}{CH{=}CHC{\equiv}CH} \longrightarrow C_5H_{11}CH(OH)\overset{trans}{CH{=}CHC{\equiv}C(CH_2)_6X}$$
4 **5**

In our approach oct-*trans*-2-enal[10] (**2**) was converted to dec-*trans*-4-en-1-yn-3-ol (**3**) which was rearranged[11] to dec-3-en-1-yn-5-ol (cis:trans ratio 1:3). Pure trans alcohol (**4**, R = H) was elaborated *via* the nitrile (**5**, X = CN) to the desired acid (**5**, X = CO_2H). The corresponding cis nitrile gave on hydrolysis and esterification also some methyl 8-(5′-pentylfur-2′-yl)octanoate, homologous with the furanoid acid obtained[12] from a seed oil. Preparation of this acid and of acids with cis double bonds will be reported elsewhere.

The isomeric 12-hydroxyheptadec-*trans*-8-en-10-ynoic acid (**11**, X = CO_2H) incorporates a hydroxy-yne-*trans*-ene sequence found naturally only in reverse order, in ximenynolic acid[13] (9-hydroxyoctadec-*trans*-12-en-10-ynoic acid) which has been synthesized[14] *via* acylation of a silver acetylide.

$$Cl(CH_2)_6CHO \qquad Cl(CH_2)_6CH(OH)CH_2C{\equiv}CH$$
6 **7**

$$PhOCH_2C{\equiv}CH \longrightarrow PhOCH_2C{\equiv}C(CH_2)_7Cl \longrightarrow$$
8 **9**

$$HC{\equiv}C\overset{trans}{CH{=}CH(CH_2)_6Cl} \longrightarrow C_5H_{11}CH(OH)C{\equiv}C\overset{trans}{CH{=}CH(CH_2)_6X}$$
10 **11**

Synthesis was initially attempted *via* the chloroynol (**7**) but elimination of the hydroxyl group, either as such or as