Stereochemical Considerations and the Antiinflammatory Activity of 6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and Related Derivatives†

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The antiinflammatory activity of a series of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and related derivatives was examined using the reverse passive Arthus reaction (RPAR). The antiinflammatory activity of these compounds was markedly influenced by the stereochemistry of the amino alcohol moiety. The threo diastereomer exhibited activity in the RPAR, while the erythro diastereomer was devoid of any significant antiinflammatory activity. The antiinflammatory activity of the amino alcohols was also significantly influenced by the position and nature of the aromatic substituent. Latentiation of the amino alcohol function resulted in analogues exhibiting antiinflammatory activity equivalent to their amino alcohol precursors. Masking the amino alcohol function as a more stable derivative led to analogues exhibiting an antiinflammatory profile unique to their structural class.

The relationship between the stereochemistry of phenethyl and phenethanolamines and their central nervous system pharmacology has been subject of considerable attention. The concept has been particularly attractive in determining the structural dimensions of receptors by describing the conformational requirements of associated agonists. A useful probe has been to examine the biological activity of conformationally restricted analogues.[1-5] The rigidity of these analogues strictly defines the stereochemistry by limiting the number of accessible conformations.

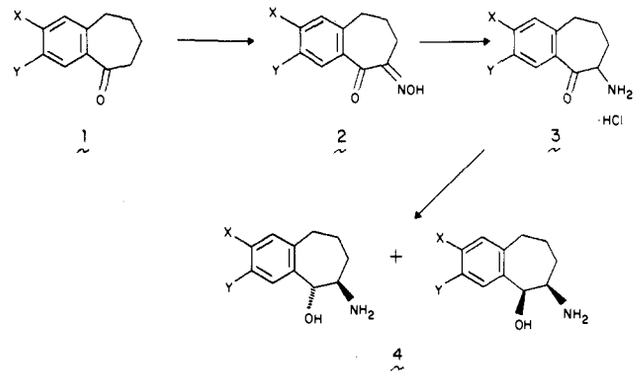
From systematic screening and chemical modifications, the antiinflammatory activity of a series of conformationally restricted 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and related derivatives was identified. The antiinflammatory activity was determined by the reverse passive Arthus reaction.[6] The purpose of this report is to describe our results concerning the stereochemistry of the amino alcohol moiety and its effect on the antiinflammatory activity. Investigation of the regiochemistry of the amino alcohol, substitutions in the "tetrahydrobenzocycloheptane" framework, the position and nature of the aromatic substituent, and derivatization of the amino alcohol established the relative importance of these parameters on the antiinflammatory activity.

Chemistry. Several 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols have been described previously.[7-13] The synthetic route (Scheme I) to 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols requires the availability of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1**). Most of the requisite substrates were either known compounds or could be obtained by using established methods (Table I).[14-19]

Acylation of 2- or 3-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1b** or **1h**) with dimethylthiocarbamoyl chloride gave the corresponding dimethylthiocarbamate. Thermal rearrangement of the thiocarbamate,[20] basic hydrolysis, and alkylation in situ afforded the 2- or 3-(alkylthio)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1d** or **1j,p,q**, respectively). Oxidation of the alkylthio analogues with 1 or 2 equiv of *m*-chloroperbenzoic acid gave the corresponding sulfoxide and sulfone derivatives.

3-Methoxy-4-(methylthio)benzaldehyde (**5**) was prepared from vanillin. Condensation of **5** with methyl crotonate, catalytic reduction of the dienoic acid, and polyphosphoric acid cyclization gave 2-methoxy-3-(methylthio)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1x**).

Scheme I. Synthesis of 6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols



Substitution of a methylene group with a sulfur atom in the "tetrahydrobenzocycloheptane" framework was accomplished with the preparation of 3,4-dihydro-2-benzothiepin-5(1*H*)-one (**6**).[21] Acid-catalyzed cyclization of

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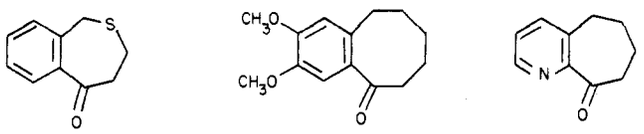

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6-(3,4-dimethoxyphenyl)hexanoic acid gave 2,3-dimethoxy-7,8,9,10-tetrahydro-6*H*-benzocycloocten-5-one (**7**),[22] the ring-expanded homologue of **1w**. Isosteric substitution of carbon with nitrogen in the "tetrahydrobenzocycloheptane" framework was accomplished with the synthesis of 5,6,7,8-tetrahydro-9*H*-cyclohepta[*b*]pyridin-9-one (**8**).[23]

Treatment of each of the ketones **1** and **6–8** with *n*-butyl or isoamyl nitrite, under anhydrous acidic or basic conditions, gave the corresponding oximido ketones **2**, 2-benzothiepin-4,5(1*H*,3*H*)-dione 4-oxime (**9**), 2,3-dimethoxy-7,8,9,10-tetrahydro-5,6-benzocyclooctenedione 6-oxime (**10**), and 6,7-dihydro-5*H*-cyclohept[*b*]pyridine-8,9-dione 8-oxime (**11**) (Table II), respectively.

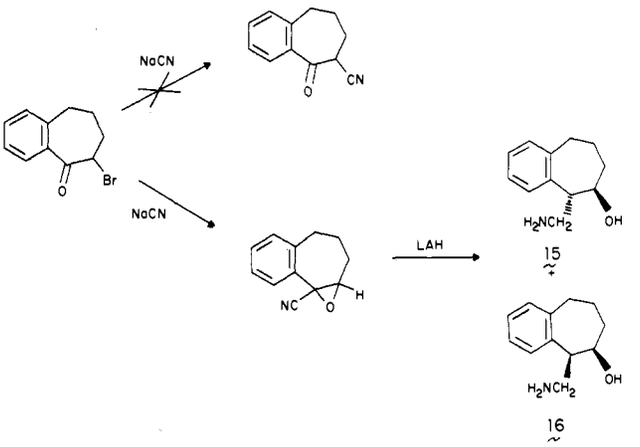
Catalytic hydrogenation of **2** and **10**, controlling the hydrogen stoichiometry, gave the α-amino ketones **3** and 6-amino-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5*H*-benzocycloocten-5-one hydrochloride. Sodium borohydride reduction of **3** produced diastereomeric mixtures of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**4**) (Table III). The threo and erythro diastereomers were separated by fractional crystallization. The composition and stereochemical assignment of the diastereomeric mixtures were accomplished by analysis of the C-5 methine proton coupling constant.[10] Sodium borohydride reduction of 6-amino-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5*H*-benzocycloocten-5-one hydrochloride gave only the *erythro*-6-amino-2,3-dimethoxy-5,6,7,8,9,10-hexahydro-5*H*-benzocycloocten-5-ol (**12**), determined by ^1H and ^{13}C NMR spectroscopy.

Diastereomeric mixtures of 4-amino-5-hydroxy-1,3,4,5-tetrahydro-2-benzothiepin (**13**) and 8-amino-9-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (**14**) were prepared by treatment of **9** and **11**, respectively, with acetic anhydride and reduction of the intermediate O-acetylated oximido ketones with borane in tetrahydrofuran.

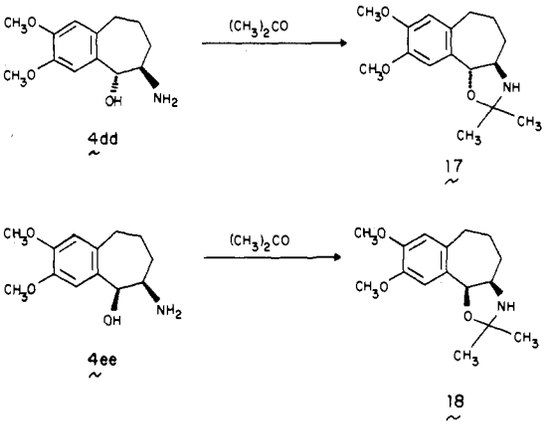
The regiochemistry of the amino alcohol moiety in the "tetrahydrobenzocycloheptane" framework was examined with the preparation of *trans*- and *cis*-5-(aminomethyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ols (**15** and **16**). In contrast to Tarbell,[24] treatment of 6-bromo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one with sodium cyanide gave 1a,2,3,4-tetrahydro-8b*H*-benzo[3,4]cyclohept[1,2-*b*]oxirene-8b-carbonitrile instead of 6-cyano-6,7,8,9-tetrahydro-5*H*-carbonitrile (Scheme II). Nucleophilic addition of cyanide to the carbonyl group and subsequent formation of the cyano epoxide, rather than direct displacement of the α-halogen atom, are consistent with the indirect observations of Kohler.[25] Lithium aluminum hydride reduction of the "cyano epoxide" gave a diastereomeric mixture of **15** and **16**.

The amino alcohol function in the tetrahydrobenzocycloheptane framework was derivatized by reaction with a ketone. Treatment of **4dd** and **4ee** with acetone gave *trans*- and *cis*-8,9-dimethoxy-2,2-dimethyl-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazoles (**17** and **18**), respectively (Scheme III).

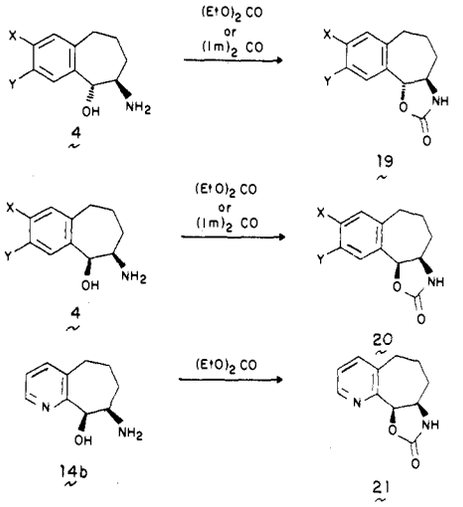
Scheme II. Synthesis of *trans*- and *cis*-5-(Aminomethyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ols



Scheme III. Synthesis of *trans*- and *cis*-8,9-Dimethoxy-2,2-dimethyl-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazoles



Scheme IV. Synthesis of *trans*- and *cis*-3,3a,4,5,6,10b-hexahydro-2*H*-benzocyclohept[1,2-*d*]oxazol-2-ones



Treatment of the threo and erythro diastereomers of **4** with diethyl carbonate or carbonyldiimidazole (Scheme IV) gave the corresponding *trans*- and *cis*-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazol-2-ones (**19** and **20**), respectively; treatment of the erythro diastereomer **14b** with diethyl carbonate gave **21** (Table IV).

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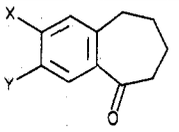
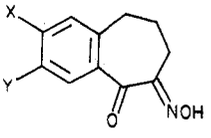
Table I. Intermediate 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-ones (1)



no.	X	Y	mp, °C	yield, %	formula	anal.	ref
1a	H	H					*a*
1b	HO	H					14
1c	CH_3O	H					15
1d	CH_3S	H	64-65 [b,d]	80			Ex [c]
1e	CH_3	H	oil [d]				Ex [c]
1f	Cl	H					16
1g	F	H					17
1h	H	OH					18
1i	H	CH_3O					14
1j	H	CH_3S	oil [d]				Ex [c]
1k	H	*i*-PrO					14
1l	H	*t*-$BuCO_2$	54-55 [b,d]	42			Ex [c]
1m	H	*t*-$BuCO_2CH_2O$	oil [d]				Ex [c]
1n	H	CH_3SO	oil [d]	82	$C_{12}H_{14}O_2S$	C, H, S	Ex [c]
1o	H	CH_3SO_2	67-68 [e]	89	$C_{12}H_{14}O_3S$	C, H, S	Ex [c]
1p	H	*i*-PrS	oil [d]				Ex [c]
1q	H	$PhCH_2S$	oil [d]				Ex [c]
1r	H	*i*-Pr	oil [d]				Ex [c]
1s	H	CH_3CONH					18
1t	H	Cl					16
1u	H	F					16
1v	H	NO_2					18
1w	CH_3O	CH_3O					19
1x	CH_3O	CH_3S	96-99	82	$C_{13}H_{16}O_2S$	C, H, S	Ex [c]
1y	CH_3O	CH_3SO	126-128	90	$C_{13}H_{16}O_3S$	C, H, S	Ex [c]

[a] Available from the Aldrich Chemical Co. [b] From petroleum ether. [c] Ex = experimental procedure described. [d] Isolated and used without further purification. [e] From dichloromethane-ether.

Table II. Intermediate 6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-5,6-dione 6-Oximes (2)



no.	X	Y	recrystn solvent	mp, °C	yield, %
2a	CH_3S	H	CH_3OH/Et_2O	176-178	86
2b	CH_3	H	CH_3OH/EtOAc	166-168	70
2c	Cl	H	CH_3OH/EtOAc	202-206	46
2d	F	H	CH_3OH/Et_2O	163-166	62
2e	H	CH_3S	CH_3OH/Et_2O	148-150	86
2f	H	*i*-PrO	CH_3OH/Et_2O	136-139	67
2g	H	*t*-$BuCO_2$	CH_3OH/Et_2O	140-143	57
2h	H	*t*-$BuCO_2$-	CH_3OH/Et_2O	94-96	65
2i	H	CH_3SO	CH_3OH/EtOAc	194-196	64
2j	H	CH_3SO_2	CH_3OH/EtOAc	215 dec	62
2k	H	*i*-PrS	CH_3OH/Et_2O	146-156	69
2l	H	$PhCH_2S$	CH_3OH/Et_2O	113-115	67
2m	H	*i*-Pr	CH_3OH/Et_2O	143-145	55
2n	H	CH_3CONH	CH_3OH/EtOAc	230-232 dec	77
2o	H	Cl	CH_3OH/Et_2O	181-183	69
2p	H	F	CH_3OH/Et_2O	152-154	52
2q	H	NO_2	CH_3OH/EtOAc	214-215	45
2r	CH_3O	CH_3S	CH_3OH/Et_2O	183-187	74
2s	CH_3O	CH_3SO	CH_3OH/Et_2O	206-208	68
9			CH_3OH/Et_2O	193-195	80
10			CH_3OH/Et_2O	117-120	60
11			CH_3OH/EtOAc	220-221 dec	56

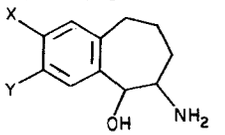
Although the relative composition of the diastereomeric mixture in each case could be determined by integration of the C-5 methine proton signals, stereochemical assignment by analysis of the C-5 proton coupling constants was not possible. In the oxazoles and oxazol-2-ones, the C-5 methine coupling constant for each diastereomer of the mixture was fortuitously equivalent. Assignment of the different C-5 methine proton signals to the trans and cis stereoisomers was accomplished by preparing each diastereomeric derivative from its respective *threo*- or *erythro*-**4** precursors: *trans*-8,9-dimethoxy-2,2-dimethyl-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]-oxazole (**17**), δ_{H_5} 4.5 (J = 9 Hz), and the cis isomer (**18**), δ_{H_5} 5.1 (J = 9 Hz); *trans*-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazol-2-one (**19b**), δ_{H_5} 5.2 (J = 10 Hz), and the cis isomer (**20a**), δ_{H_5} 5.7 (J = 10 Hz).

Results and Discussion

Comparison between the antiinflammatory activity of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**4a**) (Table III) and phenethanolamine **22** (21% inhibition at 50 mg/kg, po) demonstrates the significant effect on the biological activity of rigidly defining the stereochemistry of the amino alcohol by conformational restriction. The antiinflammatory activity of **4b** and **4c** determined at a single dose (Table III) also suggests that the pharmacological activity resides predominantly in the threo diastereomer and not in the erythro diastereomer. Examination of the antiinflammatory activity determined for other substituted *threo*- and *erythro*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol diastereomers (Table III) further supports this observation. Consistent with the activities observed in the single-dose assay, the potency of the threo diastereomer is also greater than the potency of the erythro diastereomer when compared relative to indomethacin.

The importance of the regiochemistry between the amino and hydroxyl functions in analogues of **4** on the antiinflammatory activity was examined with the preparation of *trans*- and *cis*-5-(aminomethyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ols (**15** and **16**). Isomerization and the

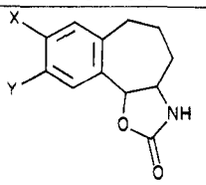
Table III. Substituted 6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (4)



no.	X	Y	composition threo/erythro	recrystn solvent	mp, °C	mol formula	anal.	inhibitory response, %, at 50 mg/kg, po	rel potency[a]
4a	H	H	60:40	$EtOH/Et_2O$	250-255	$C_{11}H_{15}NO\cdot HCl$	C, H, N	93	
4b	H	H	threo	$EtOH/Et_2O$	258-260	$C_{11}H_{15}NO\cdot HCl$	C, H, N	98	0.15 (0.10-0.23)
4c	H	H	erythro	$EtOH/Et_2O$	285-286	$C_{11}H_{15}NO\cdot HCl$	C, H, N	11	0.02 (0.003-0.05)
4d	CH_3O	H	threo	CH_3OH/Et_2O	133-135	$C_{12}H_{17}NO_2$	C, H, N	80	0.10 (0.07-0.14)
4e	CH_3S	H	threo	CH_2Cl_2/Et_2O	148-150	$C_{12}H_{17}NOS$	C, H, N, S	84	0.04 (0.02-0.06)
4f	CH_3	H	threo	$(i\text{-Pr})_2O$	127-130	$C_{12}H_{17}NO$	C, H, N	93	0.05 (0.02-0.09)
4g	Cl	H	threo	$(i\text{-Pr})_2O$	155-163	$C_{11}H_{14}ClNO$	C, H, N, Cl	94	0.08 (0.04-0.14)
4h	F	H	threo	$EtOH/Et_2O$	252-253	$C_{11}H_{14}FNO\cdot HCl$	C, H, N, Cl, F	100	0.18 (0.05-0.42)
4i	H	CH_3O	80:20	CH_2Cl_2/Et_2O	101-103	$C_{12}H_{17}NO_2$	C, H, N	98	0.75 (0.38-1.57)
4j	H	CH_3O	erythro	CH_2Cl_2/Et_2O	134-136	$C_{12}H_{17}NO_2$	C, H, N	13	0.02 (0.004-0.05)
4k	H	CH_3S	threo	CH_2Cl_2/Et_2O	113-115	$C_{12}H_{17}NOS$	C, H, N, S	90	0.56 (0.30-1.42)
4l	H	CH_3S	15:85	CH_2Cl_2/Et_2O	102-108	$C_{12}H_{17}NOS$	C, H, N, S	11	0.02 (0.001-0.08)
4m	H	*i*-PrO	70:30	Et_2O/pet. ether	69-76	$C_{14}H_{21}NO_2$	C, H, N	77	0.18 (0.07-0.41)
4n	H	*i*-PrO	erythro	Et_2O/pet. ether	124-126	$C_{14}H_{21}NO_2$	C, H, N	4	
4o	H	*t*-$BuCO_2$	threo	Et_2O/pet. ether	131-134	$C_{16}H_{23}NO_3$	C, H, N	34	
4p	H	*t*-$BuCO_2$	erythro	$EtOAc/Et_2O$	149-151	$C_{16}H_{23}NO_3$	C, H, N	11	
4q	H	*t*-$BuCO_2CH_2O$	threo	Et_2O/pet. ether	85-90	$C_{17}H_{25}NO_4$	C, H, N	16	
4r	H	*t*-$BuCO_2CH_2O$	erythro	Et_2O/pet. ether	95-98	$C_{17}H_{25}NO_4$	C, H, N	3	
4s	H	CH_3SO	50:50	CH_2Cl_2/EtOAc	138-153	$C_{12}H_{17}NO_2S$	C, H, N, S	7	
4t	H	CH_3SO_2	threo	CH_3OH/EtOAc	261-263	$C_{12}H_{17}NO_3S$	C, H, N, S	5	
4u	H	*i*-PrS	threo	Et_2O	110-113	$C_{14}H_{21}NOS$	C, H, N, S	39	
4v	H	$PhCH_2S$	threo	CH_2Cl_2/Et_2O	118-120	$C_{18}H_{21}NOS$	C, H, N, S	99	
4w	H	$PhCH_2S$	erythro	CH_2Cl_2/pet. ether	95-97	$C_{18}H_{21}NOS$	C, H, N, S	31	
4x	H	*i*-Pr	threo	CH_2Cl_2/Et_2O	148-150	$C_{14}H_{21}NO$	C, H, N	100	0.12 (0.07-0.23)
4y	H	CH_3CONH	threo	$CHCl_3/Et_2OAc$	160-162	$C_{13}H_{18}N_2O_2$	C, H, N	18	
4z	H	Cl	threo	CH_2Cl_2/EtOAc	160-162	$C_{11}H_{14}ClNO$	C, H, N	94	0.34 (0.20-0.57)
4aa	H	Cl	35:65	CH_2Cl_2/Et_2O	103-105	$C_{11}H_{14}ClNO$	C, H, N	44	
4bb	H	F	threo	CH_2Cl_2/Et_2O	156-158	$C_{11}H_{14}FNO$	C, H, N	96	0.15 (0.05-0.32)
4cc	H	NO_2	threo	CH_3OH/Et_2O	252-253	$C_{11}H_{14}N_2O_3\cdot HCl\cdot H_2O$	C, H, N, Cl	100	0.25 (0.20-0.43)
4dd	CH_3O	CH_3O	threo	$CH_3OH/(i\text{-Pr})_2O$	200-201	$C_{13}H_{19}NO_3\cdot HCl$	C, H, N	93	0.20 (0.12-0.35)
4ee	CH_3O	CH_3O	erythro	$CH_3OH/(i\text{-Pr})_2O$	236-238	$C_{13}H_{19}NO_3\cdot HCl$	C, H, N	13	0.03 (0.01-0.05)
4ff	CH_3O	CH_3S	threo	$(i\text{-Pr})_2O$	126-134	$C_{13}H_{19}NO_2S$	C, H, N, S	81	0.05 (0.01-0.14)
4gg	CH_3O	CH_3S	erythro	EtOAc	163-170	$C_{13}H_{19}NO_2S$	C, H, N, S	29	
4hh	CH_3O	CH_3SO	threo	CH_3CN	164-170	$C_{13}H_{19}NO_3S$	C, H, N, S	8	
4ii	CH_3O	CH_3SO	erythro	CH_3CN	156-158	$C_{13}H_{19}NO_3S$	C, H, N, S	0	
12			erythro	$EtOH/Et_2O$	211-215	$C_{14}H_{21}NO_3\cdot HCl$	C, H, N	0	
13			4:60	$EtOH/Et_2O$	210-218	$C_{10}H_{13}NOS\cdot HCl$	C, H, N, S	2	
14a			threo	$CH_3OH/(CH_3)_2CO$	238 dec	$C_{10}H_{14}N_2O_2\cdot HCl\cdot H_2O$	C, H, N, Cl	36	
14b			erythro	$EtOAc/Et_2O$	107-109	$C_{10}H_{14}N_2O$	C, H, N	28	
15					111-112.5	$C_{12}H_{17}NO$	C, H, N	0	
16					109-111	$C_{12}H_{17}NO$	C, H, N	8	

[a] Relative potency of indomethacin = 1.0, $p = 0.05$.

Table IV. *trans*- and *cis*-3,3a,4,5,6,10b-Hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazol-2-ones (19 and 20)



no.	X	Y	composition trans/cis	mp, °C	mol formula	anal.	inhibitory response, %, at 50 mg/kg, po	rel potency[b]
19a	H	H	55:45	140-180	$C_{12}H_{13}NO_2$	C, H, N	77	
19b	H	H	trans	190-194[a]	$C_{12}H_{13}NO_2$	C, H, N	24	
19c	CH_3O	H	trans	212-214[a]	$C_{13}H_{15}NO_3$	C, H, N	0	
19d	CH_3	H	trans	202-204[a]	$C_{13}H_{15}NO_2$	C, H, N	28	
19e	Cl	H	trans	204-206[a]	$C_{12}H_{12}ClNO_2$	C, H, N, Cl	9	
19f	F	H	trans	165-167[a]	$C_{12}H_{12}FNO_2$	C, H, N, F	39	
19g	H	CH_3O	trans	217-219[a]	$C_{13}H_{15}NO_3$	C, H, N	20	
19h	H	*i*-Pr	trans	168-170[a]	$C_{15}H_{19}NO_2$	C, H, N	7	
19i	H	Cl	trans	224-225[a]	$C_{12}H_{12}ClNO_2$	C, H, N, Cl	9	
19j	H	F	trans	231-233[a]	$C_{12}H_{12}FNO_2$	C, H, N, F	19	
20a	H	H	cis	138-140[a]	$C_{12}H_{13}NO_2$	C, H, N	92	0.06 (0.03-0.10)
20b	CH_3O	H	cis	202-204[a]	$C_{13}H_{15}NO_3$	C, H, N	0	
20c	CH_3	H	cis	171-173[a]	$C_{13}H_{15}NO_2$	C, H, N	28	
20d	Cl	H	cis	175-178[a]	$C_{12}H_{12}ClNO_2$	C, H, N, Cl	18	
20e	F	H	cis	155-158[a]	$C_{12}H_{12}FNO_2$	C, H, N, F	96	0.04 (0.01-0.11)
20f	H	CH_3O	cis	181-183[a]	$C_{13}H_{15}NO_3$	C, H, N	24	
20g	H	*i*-Pr	cis	180-182[a]	$C_{15}H_{19}NO_2$	C, H, N	37	
20h	H	Cl	cis	190-192[a]	$C_{12}H_{12}ClNO_2$	C, H, N, Cl	29	
20i	H	F	cis	145-147[a]	$C_{12}H_{12}FNO_2$	C, H, N, F	78	0.03 (0.004-0.10)
21			cis	180-182	$C_{11}H_{12}N_2O_2$	C, H, N	82	0.30 (0.20-0.70)

[a] Recrystallization form chloroform-ether. [b] Relative potency of indomethacin = 1, $p = 0.05$.

lack of the *vicinal* relationship between the amino and hydroxyl functions, regardless of the stereochemistry of the diastereomer, resulted in the loss of antiinflammatory activity: **15** (0% inhibition) and **16** (8% inhibition) at 50 mg/kg, po.

Modification of the tetrahydrobenzocycloheptane framework by ring expansion, substitution of a methylene group with a sulfur atom, and isosteric substitution of carbon with nitrogen produced inactive analogues: **12** (0% inhibition), **13** (2% inhibition as a threo/erythro 40:60 diastereomeric mixture), 14a (36% inhibition), and **14b** (28% inhibition) at 50 mg/kg, po, respectively.

The most significant parameters affecting the antiinflammatory activity of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**4**) were the position and nature of the aromatic substituent.

Although relatively few substituents were examined, comparison of the antiinflammatory activity of 2-substituted analogues of **4** (Table III) suggests that the potency of the nucleus may be insensitive to the nature of the 2-substituent; i.e., the potencies of the 2-*H* compound and its 2-substituted analogues are all equivalent statistically.

On the other hand, as shown in Table III, introduction into **4** of either an electron-donating or an electron-withdrawing 3-substituent produces analogues that are more potent than the unsubstituted compound.

The 3-methoxy (**4i**) and the 3-methylthio (**4k**) isosteres are equipotent and exhibit a potency approaching that of the standard, indomethacin. Oxidation of the sulfur atom of the 3-substituent results in the loss of antiinflammatory activity.

The steric bulk of the 3-substituent appears to be important in determining the antiinflammatory activity of the analogue. The potency of the 3-isopropoxy analogue (**4m**) is lower than the potency of the 3-methoxy analogue (**4i**), while the 3-fluoro analogue (**4bb**) and the unsubstituted analogue exhibit equivalent potencies.

In the 2,3-disubstituted analogues of **4**, replacement of the 3-methoxy group with a 3-methylthio results in an analogue (**4ff**) that is less potent than the corresponding 2,3-dimethoxy derivative (**4dd**) (Table III). Oxidation of the 3-methylthio substituent eradicates antiinflammatory activity.

Comparison between the antiinflammatory activity of the oxazole diastereomers, *trans*-**17** and *cis*-**18**, demonstrates that the biological activity resides in the trans diastereomer: **17** (77% inhibition) and **18** (0% inhibition) at 50 mg/kg, po. The similarity between the single-dose antiinflammatory activity of **17** and **18** when compared to their respective precursor, **4b** and **4c**, suggests that these analogues may be exerting their antiinflammatory activity as prodrugs.[26] Support for this hypothesis was obtained by examining the in vitro hydrolysis of the *trans*- and *cis*-oxazole diastereomers. In 0.1 N hydrochloric acid at ambient temperature, the *trans*- and *cis*-oxazoles gave the corresponding *threo*- and *erythro*-**4** diastereomers without epimerization[27] at C-5; $t_{1/2} = 0.25$ h.

Unlike the oxazoles, the *trans*-**19b** and *cis*-**20a** oxazol-2-one derivatives were hydrolytically stable at ambient temperature, although hydrolysis of the corresponding **4** precursors occurred at elevated temperatures, without epimerization. The stability of the oxazol-2-ones toward hydrolysis suggests that the activity of these analogues could be intrinsic rather than via conversion by a nonenzymatic process to the amino alcohols **4**.

Comparison of the antiinflammatory activity of the oxazol-2-ones (Table IV) supports this hypothesis. In contrast to the oxazoles, the antiinflammatory activity of the oxazol-2-ones resides in the cis diastereomer, which is derived from the biologically inactive *erythro*-**4** precursor.

(26) DeNeale, R. J. *Diss. Abstr. Int. B.* **1973**, *34*, 2119; *Chem. Abstr.* **1974**, *80*, 95105.
(27) Bodor, N.; Yuan, S. S. *J. Pharm. Sci.* **1976**, *65*, 929.

The presence of 2- and/or 3-aromatic substituents in the oxazol-2-one reduces the antiinflammatory activity relative to the unsubstituted analogue regardless of the electronic nature of the substituent. Only the 2-fluoro (**20e**) or 3-fluoro (**20i**) substituted oxazol-2-one exhibited antiinflammatory activity comparable to that of the unsubstituted analogue. Interestingly, isosteric substitution of carbon with nitrogen resulted in **21**, which has an antiinflammatory potency five times **20a**.

In summary, the antiinflammatory activity of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and related derivatives in the reverse passive Arthus model has been shown to be markedly affected by the stereochemistry of the amino and hydroxyl functions in the analogue. The antiinflammatory activity of the amino alcohols **4** was also significantly influenced by the identity of the 3-substituent. Latentiation of the amino alcohol function resulted in analogues exhibiting antiinflammatory activity equivalent to their amino alcohol precursors. Masking the amino alcohol function as a more stable derivative led to analogues exhibiting an antiinflammatory profile unique to their structural class.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian CFT-20 spectrometer, IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were performed by the Physical Analytical Services Department of the Schering-Plough Corpn.

3-Methoxy-4-(methylthio)benzaldehyde (5). To 23 g (0.41 mol) of potassium hydroxide dissolved in 400 mL of water was added, with stirring, 60.8 g (0.4 mol) of vanillin. The solution was cooled in an ice–salt bath, and 50.4 g (0.41 mol) of *N,N*-dimethylthiocarbamoyl chloride in 250 mL of tetrahydrofuran was added dropwise with stirring. After stirring in the cold for 0.5 h, the mixture was extracted with chloroform, and the extracts were dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give a yellow solid. Recrystallization from benzene–hexane gave 3-methoxy-4-[(dimethylthiocarbamoyl)oxy]benzaldehyde: yield 67.0 g (0.29 mol, 70%); mp 109–112 °C. Anal. ($C_{11}H_{13}NO_3S$) C, H, N, S.

3-Methoxy-4-[(dimethylthiocarbamoyl)oxy]benzaldehyde (100 g, 0.42 mol) in 1 L of diphenyl ether was heated under reflux for 1 h in a nitrogen atmosphere. After the solution was heated for 1 h, approximately 800 mL of diphenyl ether was removed by distillation under reduced pressure. Then, 200 mL of the distillate, while hot, was added cautiously to 3 L of hexanes. On cooling, the solid was isolated by filtration. Recrystallization from ethyl acetate gave 3-methoxy-4-[(dimethylcarbamoyl)thio]benzaldehyde: yield 79.9 g (0.33 mol, 80%); mp 106–109 °C. Anal. ($C_{11}H_{13}NO_3S$), C, H, N, S.

To 23.5 g (0.42 mol) of potassium hydroxide dissolved in 20 mL of water and 360 mL of absolute ethanol in a nitrogen atmosphere was added 95.6 g (0.4 mol) of 3-methoxy-4-[(dimethylcarbamoyl)thio]benzaldehyde. The solution was heated under reflux for 12 h and then cooled to 0 °C, and 59.6 g (0.42 mol) of methyl iodide was added dropwise. The mixture was stirred for 3 h, 100 mL of water was added, and the ethanol was removed under reduced pressure. The aqueous layer was extracted with chloroform and dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give a brown oil: yield 66.0 g. Chromatography on silica gel, eluting with chloroform, gave **5**: yield 34.3 g (0.19 mol, 53%); bp 135–145 °C (0.06 mm); mp 41–43 °C. Anal. ($C_9H_{10}O_2S$), C, H, S.

Preparation of 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-ones (1). 2-(Methylthio)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1d). To 7 g (0.1 mol) of potassium hydroxide dissolved in 300 mL of water was added, with stirring, 16.3 g (0.09 mol) of **1b**. The solution was cooled in an ice–salt bath, and 11.6 g (0.09 mol) of dimethylthiocarbamoyl chloride in 150 mL of tetrahydrofuran was added dropwise with stirring. After stirring in the cold for 0.5 h, the mixture was extracted with chloroform, and the extracts were dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give a yellow solid. Recrystallization from benzene gave 2-[(dimethylthiocarbamoyl)oxy]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one [yield 17.5 g (0.065 mol, 72%); mp 81–85 °C], which was used without further purification.

2-[(Dimethylthiocarbamoyl)oxy]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (17.5 g, 0.065 mol) in 100 mL of diphenyl ether was heated under reflux for 1 h in a nitrogen atmosphere. After the solution was heated for 1 h, approximately 80 mL of diphenyl ether was removed by distillation under reduced pressure. Then, 20 mL of the distillate, while hot, was added cautiously to 500 mL of hexanes. When the solution cooled, the solid was isolated by filtration. The 2-[(dimethylcarbamoyl)thio]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one obtained, 14.2 g (0.06 mol, 87%), was used without further purification.

To 3.8 g (0.07 mol) of potassium hydroxide dissolved in 10 mL of water and 100 mL of absolute ethanol in a nitrogen atmosphere was added 14.2 g (0.06 mol) of 2-[(dimethylcarbamoyl)thio]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one. The solution was heated under reflux for 12 h and then cooled to 0 °C, and 10.3 g (0.07 mol) of methyl iodide was added dropwise. The mixture was stirred for 3 h, 50 mL of water was added, and the ethanol was removed under reduced pressure. The aqueous layer was extracted with chloroform and dried ($MgSO_4$).

Following filtration, the chloroform was removed under reduced pressure to give a yellow oil. Chromatography on silica gel, eluting with chloroform, gave **1d** as a colorless oil, which crystallized from petroleum ether: yield 9.0 g (0.05 mol, 80%); mp 64–65 °C.

The 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones, **1j,p,q** (Table I), were prepared by the procedure described above and used without further purification.

2-Methoxy-3-(methylthio)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1x). Compound **5** was used to prepare **1x** by the method described by Galantay.[7]

The 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones, **1e,l,r** (Table I), were prepared by the procedure described above and used without further purification.

3-[(Pivaloyloxy)methoxy]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1m). To a solution of 9.9 g (0.66 mol) of chloromethyl pivalate in 200 mL of acetone was added 9.9 g (0.66 mol) of sodium iodide. The mixture was stirred at ambient temperature for 3 h, and the sodium chloride precipitate was removed by filtration. The filtrate was added dropwise with stirring to 10.5 g (0.06 mol) of 3-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1h**) dissolved in 150 mL of water containing 3.9 g (0.06 mol) of potassium hydroxide at 0 °C. The mixture was stirred for 16 h and poured into 500 mL of ether. The ether layer was washed with water and dried ($MgSO_4$). Following filtration, the ether was removed under reduced pressure to give an oil. Chromatography on silica gel, eluting with dichloromethane, gave 8.0 g (0.028 mol, 42%) of **1m** as an oil: ^1H NMR ($CDCl_3$) δ 7.5 (d, 1 H), 7.15 (m, 2 H), 5.8 (s, 2 H), 2.95 (t, 2 H), 1.8 (m, 4 H).

3-(Methylsulfinyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1n). To a solution of 3.6 g (0.017 mol) of **1j** in 250 mL of dichloromethane at −10 °C was added 2.9 g (0.017 mol) of *m*-chloroperbenzoic acid in portions. The reaction mixture was stirred at −10 to 0 °C for 0.5 h, and 300 mL of dilute ammonium hydroxide was added. The dichloromethane extracts were combined and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a yellow oil: yield 4.1 g. Chromatography on silica gel, eluting with ethyl acetate/dichloromethane/methanol (20:80:1 v/v), gave 3.2 g (0.14 mol, 82%) of **1n** as an oil: ^1H NMR ($CDCl_3$) δ 7.8 (s, 1 H), 7.7 (d, 1 H), 7.3 (d, 1 H), 2.95 (m, 4 H), 2.72 (s, 3 H), 1.8 (m, 4 H). Anal. ($C_{12}H_{14}O_2S$), C, H, S.

3-(Methylsulfonyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1o). Following the procedure for the preparation of **1n**, but using 2 equiv of *m*-chloroperbenzoic acid, **1o** was obtained.

2-Methoxy-3-(methylsulfinyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1y). Following the procedure for **1n**, there was obtained **1y**.

General Procedure for the Preparation of the Oximido Ketones (2). The appropriate ketone (0.01 mol) was dissolved

in 500 mL of anhydrous ether or in 500 mL of a mixture of anhydrous ether containing enough tetrahydrofuran to dissolve the ketone. Ethereal hydrogen chloride (1.25 mol/equiv) was added, and the solution was cooled to −15 °C. With stirring, *n*-butyl or isoamyl nitrite (0.011 mol) was added dropwise, and the mixture was stirred for 3–5 h at 0 °C. After the mixture was left standing at −5 °C for 16 h, the volatiles were removed under reduced pressure to give a viscous oil. Addition of anhydrous ether precipitated the oximido ketone (**2**). The solid was isolated by filtration and recrystallized from either methanol/ethyl acetate or methanol/ether.

The oximido ketones described in Table II were prepared by the procedure described above and used without further purification.

General Procedure for the Preparation of 6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (4). Method A. The appropriate oximido ketone (0.03 mol) was dissolved in 150 mol of methanol containing ethanolic hydrogen chloride (1.1 mol/equiv). To the solution was added 1.5 g of palladium on carbon (10%), and the mixture was shaken until 2 mol/equiv of hydrogen was absorbed. The catalyst was removed by filtration and washed with methanol. The solvents were removed under reduced pressure, and the addition of acetone or anhydrous ether precipitated the intermediate α-amino ketone hydrochloride (**3**). The solid was isolated by filtration and used without purification.

The intermediate α-amino ketone hydrochloride (0.02 mol) was dissolved in 125 mL of methanol and cooled to 0 °C. With stirring, sodium borohydride (4.3 g, 0.12 mol) was added in *eight* portions over 1 h. After stirring for 1 h at 0 °C, the mixture was poured into ice and extracted with dichloromethane. The extracts were combined and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to afford a diastereomeric mixture of amino alcohols (**4**).

The diastereomers were separated by fractional crystallization.

Method B. A solution of 2-benzothiepin-4,5(1*H*,3*H*)-dione 4-oxime (**9**; 2.07 g, 0.01 mol) in 40 mL of acetic anhydride was heated for 1 h on a steam bath. After the solution was left standing at ambient temperature overnight, the acetic anhydride was removed in vacuo. The remaining solid was triturated with petroleum ether and isolated by filtration. Recrystallization from methanol gave 2-benzothiepin-4,5(1*H*,3*H*)-dione 4-*O*-acetyloxime (2.2 g, 0.009 mol, 90%), mp 133–135 °C. Anal. ($C_{12}H_{11}NO_3S$), C, H, N, S.

2-Benzothiepin-4,5(1*H*,3*H*)-dione 4-*O*-acetyloxime (5.25 g, 0.02 mol) was dissolved in 150 mL of anhydrous tetrahydrofuran and cooled to 0 °C. To this solution was added, with stirring, 90 mL of 1 M borane in tetrahydrofuran. After the addition was complete, the solution was decomposed by the addition of methanol, and the solvents were removed under reduced pressure. The residue remaining was dissolved in 400 mL of 6 N hydrochloric acid and stirred at ambient temperature overnight. The acidic solution was basified by the addition of anhydrous potassium carbonate and extracted with ether. The ethereal extracts were combined and dried ($MgSO_4$). Following filtration, the ether was removed under reduced pressure to give an oil. The oil was dissolved in 25 mL of acetone and diluted with 250 mL of ether. Treatment of this solution at 0 °C with ethereal hydrogen chloride gave a precipitate. The solid was isolated by filtration and dried in vacuo to give **13**: yield 2.2 g (0.009 mol, 47%); mp 210–218 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.4 (br s, 3 H, exchangeable), 7.6–7.0 (m, 4 H), 6.2 (br s, 1 H, exchangeable), 4.95 (m, 1 H), 3.8 (br s, 1 H), 3.4–2.8 (m, 4 H). Anal. ($C_{10}H_{13}NOS$·HCl), C, H, N, S, Cl.

The amino alcohols **4cc**, **14a**, and **14b** were prepared by method B. Compound **12** and the remaining amino alcohols described in Table II were prepared by method A.

***trans*- and *cis*-5-(Aminomethyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ols (15 and 16).** 6-Bromo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[24] (12 g, 0.05 mol) was dissolved in 70 mL of ethanol and heated to boiling. Sodium cyanide (3.7 g, 0.076 mol) dissolved in 50 mL of water was added, and the solution was heated under reflux for 1 h. The volatiles were removed under reduced pressure, and the residue obtained was dissolved in 500 mL of ether. The ethereal solution was washed with water (4 × 150 mL) and dried ($MgSO_4$). Following filtration, the ether was removed under reduced pressure to give an oil: yield 8 g. Chromatography on silica gel, eluting with 40% chloroform in hexanes gave 1a,2,3,4-tetrahydro-8b*H*-benzo[3,4]cyclohept-[1,2-*b*]oxirene-8b-carbonitrile: yield 5.5 g (0.03 mol, 60%); oil; n^{27}_D 1.5458 (lit.[24] n^{23}_D 1.5466); IR (neat 2120, 1230, 910, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.8–6.9 (m, 4 H), 3.7 (q, 1 H), 3.3–0.8 (6 H); mass spectrum (70 eV), *m/e* (relative intensity) 185 (51), 156 (100). Anal. ($C_{12}H_{11}NO$), C, H, N.

To a suspension of of lithium aluminum hydride (4.6 g, 0.122 mol) in 200 mL of anhydrous ether at 0 °C was added dropwise with stirring 4.5 g (0.024 mol) of 1a,2,3,4-tetrahydro-8b*H*-benzo[3,4]cyclohept[1,2-*b*]oxirene-8b-carbonitrile. The reaction mixture was stirred at ambient temperature for 1 h, and the excess lithium aluminum hydride was decomposed by successive additions of water (4.6 mL), 15% sodium hydroxide (4.6 mL), and water (13.8 mL). The solids were removed by filtration; the filtrate was washed with brine (100 mL) and dried ($MgSO_4$). Following filtration, the ether was removed under reduced pressure to give an oil: yield 3.2 g. Chromatography on silica gel, eluting with 5% methanol in chloroform, gave **15** and **16**. **15**: yield 1.6 g (0.008 mol, 33%); mp 111–112.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 4 H), 3.95 (t, J = 9 Hz, 1 H), 3.4–3.0 (m, 3 H), 2.7 (m, 2 H), 2.5–1.3 (m, 7 H); mass spectrum (70 eV), *m/e* (relative intensity) 174 (15), 144 (76), 130 (32), 129 (100, 115 (21), 91 (13). Anal. ($C_{12}H_{17}NO$), C, H, N. **16**: yield 1.2 g (0.006 mol, 25%); mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 4 H), 4.62 (dd, J = 5 and 12 Hz, 1 H), 2.8 (m, 3 H), 2.6–1.8 (m, 5 H), 1.8–1.3 (m, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 188 (100), 170 (52), 143 (32), 129 (29), 115, 91 (20). Anal. ($C_{12}H_{17}NO$), C, H, N. Mixture melting point of **15** and **16** 89–93 °C.

***trans*-8,9-Dimethoxy-2,2-dimethyl-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazole (17).** To 120 mL of acetone was added **4dd** (1.5 g, 0.006 mol) and calcium carbide (0.5 g, 0.008 mol). The mixture was heated under reflux overnight and allowed to cool to room temperature. Following filtration, the filtrate was concentrated under reduced pressure to give an oil. Addition of hexanes gave a precipitate, which was isolated by filtration. Recrystallization from acetone gave **17**: yield 1.4 g (0.005 mol, 83%); mp 152–153 °C; ^{1}H NMR ($CDCl_3$) δ_{H_5} 4.5 (J = 9 Hz). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

***cis*-8,9-Dimethoxy-2,2-dimethyl-3,3a,4,5,6,10b-hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazole (18).** Following the procedure for the preparation of **17**, treatment of **4ee** with acetone gave **18**: bp 140 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ_{H_5} 5.1 (J = 9 Hz). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

***trans*-3,3a,4,5,6,10b-Hexahydro-2*H*-benzo[3,4]cyclohept-[1,2-*d*]oxazol-2-one (19b).** A mixture of **4b** (1.4 g, 0.01 mol), diethyl carbonate (10 mL), and sodium methoxide (0.1 g) was heated at 110 °C, collecting the ethanol as it was formed. After 6 h, the remaining diethyl carbonate was removed in vacuo. The residue was dissolved in chloroform, and the chloroform solution was washed with 50 mL of 5% hydrochloric acid and 50 mL of water. The chloroform solution was dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Trituration with isopropyl ether gave **19b**: yield 1.6 g (0.008 mol, 80%); mp 190–194 °C; ^{1}H NMR ($CDCl_3$) δ_{H_5} 5.2 (J = 10 Hz). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

***cis*-3,3a,4,5,6,10b-Hexahydro-2*H*-benzo[3,4]cyclohept[1,2-*d*]oxazol-2-one (20a).** Treatment of **4c** (1.4 g, 0.01 mol) with carbonyldiimidazole (1.8 g, 0.011 mol) in tetrahydrofuran heated under reflux gave **20a**: yield 1.7 g (0.0084 mol, 84%); mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ_{H_5} 5.7 (J = 10 Hz). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

The oxazol-2-ones described in Table IV were prepared by the procedures described above.

Hydrolysis of 17. To 100 mL of 0.1 N hydrochloric acid was added 2.8 g (0.01 mol) of **17**, and the solution was allowed to stand at ambient temperature overnight. Approximately 0.25 h after mixing, an aliquot of the solution was analyzed by ^{1}H NMR; one-half of **17** decomposed to **4dd**. After 24 h, the solution was neutralized with potassium carbonate and extracted with dichloromethane. The dichloromethane extracts were combined and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give **4dd**: yield 2.1 g (0.009 mol, 90%); mp 159–161 °C; ^{1}H NMR ($CDCl_3$) δ_{H_5} 4.8 (J = 9 Hz). No evidence of epimerization to **4ee** was observed.

Hydrolysis of 18 under the same conditions gave **4ee**: ^{1}H NMR ($CDCl_3$) δ_{H_5} 4.1 (J = 1 Hz). No evidence of epimerization to **4dd** was observed.

Hydrolysis of Compound 20a. To 40 mL of 50% ethanol containing 0.17 g (0.003 mol) of potassium hydroxide was added 0.5 g (0.0025 mol) of **20a**. The mixture was heated under reflux for 24 h, and after cooling, the volatiles were removed in vacuo. The residue was dissolved in dichloromethane, and the dichloromethane solution was washed with water. The dichloromethane solution was dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give **4ee**: yield 0.45 g (0.0025 mol, 100%); mp 125–129 °C; ^{1}H NMR ($CDCl_3$) δ_{H_5} 4.9 (J = 1 Hz). No evidence of epimerization to **4dd** was observed.

Biological Testing Method. In order to determine the antiinflammatory activity by the reverse passive Arthus response, male Wistar/Lewis inbred albino rats weighing 180–200 g were used. The rats were housed three animals per cage and fasted 24 h prior to and during the study. Water was allowed ad libitum.

All reagents and drugs were prepared prior to the study. Crystallized and lyophilized bovine serum albumin (BSA) was solubilized in cold, sterile, pyrogen-free saline, 10 mg/mL. Lyophylized antibovine serum albumin (anti-BSA), the IgG fraction, was suspended or solubilized in an aqueous solution of methylcellulose (MC) with a homogenizer prior to administration.

One hour prior to sensitization with BSA, groups of animals (minimum six per group) were given drug in MC by gavage according to body weight (1.0 mL/100 g). Controls were given MC alone, and a drug standard, indomethacin, was usually included in each assay. Drugs were prepared so as to provide a dose for a 200-g animal, which was equivalent to the milligram per kilogram dose for the experiment. Each rat received an oral dose in a volume of approximately 2.0 mL. One hour after dosing, the animals were lightly anesthetized with ether and "sensitized" by injection into the penile vein with 0.2 mL of PFS containing 1 mg of BSA. One hour later, the animals were "challenged" in the right hind paw with subplantar injections of 0.2 mL of PFS containing 0.1 mg of anti-BSA. Immediately after the subplantar injections, the right hand paw was immersed (to the lateral maleolus) into the mercury well of a plethysmograph. The volume of mercury displaced was converted to weight and recorded. This value was considered to be the control reading for the animal. Paw volumes were also recorded with a plethysmograph during the development of the inflammation at 2 h postchallenge.

Results were expressed by the change in paw volume from the control reading for each animal to that recorded 2 h postchallenge. All drug-treated groups were compared to the MC control for significant differences by using analysis of variance (Duncan and Dunnetts). Differences from control in drug-treated groups were expressed as percent inhibition.

In order to determine the dose required to inhibit the inflammatory response by 50% (EC_{50}), a minimum of three and a maximum of five points were included in the assay. The ED_{50} and the relative potency to a drug standard, indomethacin, were determined by linear regression analysis.

The antiinflammatory activity of the 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and related derivatives determined by the reverse passive Arthus reaction is described in Tables III and IV.

Registry No. **1a**, 826-73-3; **1a** (6-bromo derivative), 19844-70-3; **1b**, 3470-51-7; **1b** (dimethyl thiocarbamate), 87452-02-6; **1c**, 6500-65-8; **1d**, 87451-88-5; **1e**, 87451-93-2; **1f**, 24127-36-4; **1g**, 1479-20-5; 1h, 5454-03-5; **1i**, 6500-62-5; **1j**, 87451-89-6; **1k**, 87452-00-4; 1l, 87451-94-3; **1m**, 87451-96-5; **1n**, 87451-97-6; **1o**, 87451-98-7; **1p**, 87451-90-9; **1q**, 87451-91-0; **1r**, 87451-95-4; **1s**, 87452-01-5; **1t**, 21413-77-4; **1u**, 24484-21-7; **1v**, 7507-93-9; **1w**, 951-99-5; **1x**, 87451-92-1; **1y**, 87451-99-8; **2a**, 87452-04-8; **2b**, 87452-05-9; **2c**, 87452-06-0; **2d**, 87452-07-1; **2e**, 87452-08-2; **2f**, 87452-09-3; **2g**, 87452-10-6; **2h**, 87452-11-7; **2i**, 87452-12-8; **2j**, 87452-13-9; **2k**, 87452-14-0; **2l**, 87452-15-1; **2m**, 87452-16-2; **2n**, 87452-17-3; **2o**, 21413-81-0; **2p**, 87452-18-4; **2q**, 53924-95-1; **2r**, 87452-19-5; **2s**, 87452-20-8; *threo*-**4b**, 23445-21-8; *threo*-**4b**·HCl, 23445-22-9; *erythro*-**4c**, 23445-16-1; *erythro*-**4c**·HCl, 23445-17-2; *threo*-**4d**, 23983-57-5; *threo*-**4e**, 87452-23-1; *threo*-**4f**, 87452-24-2; *threo*-**4g**, 87452-25-3; *threo*-**4h**, 87452-71-9; *threo*-**4h**·HCl, 87452-26-4; *threo*-**4i**, 58330-71-5; *erythro*-**4j**, 58330-27-1; *threo*-**4k**, 87452-27-5; *erythro*-**4l**, 87452-28-6; *threo*-**4m**, 87452-29-7; *erythro*-**4n**, 87452-30-0; *threo*-**4o**, 87452-31-1; *erythro*-**4p**, 87452-32-2; *threo*-**4q**, 87452-33-3; *erythro*-**4r**, 87452-34-4; *threo*-**4s**, 87452-35-5; *erythro*-**4s**, 87452-36-6; *threo*-**4t**, 87452-37-7; *threo*-**4u**, 87452-38-8; *threo*-**4v**, 87452-39-9; *erythro*-**4w**, 87452-40-2; *threo*-**4x**, 87452-41-3; *threo*-**4y**, 87452-42-4; *threo*-**4z**, 87452-43-5; *erythro*-**4aa**, 87452-44-6; *threo*-**4bb**, 87452-45-7; *threo*-**4cc**, 87452-72-0; *threo*-**4cc**·HCl, 87452-46-8; *threo*-**4dd**, 23979-44-4; *threo*-**4dd**·HCl, 25573-36-8; *erythro*-**4ee**, 23983-55-3; *erythro*-**4ee**·HCl, 23983-56-4; *threo*-**4ff**, 87452-47-9; *erythro*-**4gg**, 87452-48-0; *threo*-**4hh**, 87452-49-1; *erythro*-**4ii**, 87452-50-4; **5**, 68885-46-1; **6**, 25606-97-7; **7**, 87451-76-1; **8**, 41043-13-4; **9**, 87451-77-2; **9** (acetate), 87452-21-9; **10**, 87451-78-3; 11, 87451-79-4; *erythro*-**12**, 87452-73-1; *erythro*-**12**·HCl, 87451-80-7; *threo*-**13**, 87452-74-2; *erythro*-**13**, 87452-76-4; *threo*-**13**·HCl, 87451-81-8; *erythro*-**13**·HCl, 87451-82-9; **14a**, 87452-75-3; **14a**·HCl, 87452-51-5; **14b**, 87452-52-6; **15**, 87451-83-0; **16**, 87451-84-1; **17**, 87451-85-2; **18**, 87451-86-3; **19b**, 87452-53-7; **19c**, 87452-55-9; **19d**, 87452-57-1; **19e**, 87452-59-3; **19f**, 87452-61-7; **19g**, 87452-63-9; **19h**, 87452-65-1; **19i**, 87452-67-3; **19j**, 87452-69-5; **20a**, 87452-54-8; **20b**, 87452-56-0; **20c**, 87452-58-2; **20d**, 87452-60-6; **20e**, 87452-62-8; **20f**, 87452-64-0; **20g**, 87452-66-2; **20h**, 87452-68-4; **20i**, 87452-70-8; **21**, 87451-87-4; $(EtO)_2CO$, 105-58-8; $(im)_2CO$, 530-62-1; vanillin, 121-33-5; *N,N*-dimethylthiocarbamoyl chloride, 16420-13-6; 3-methoxy-4-[(dimethylthiocarbamoyl)oxy]benzaldehyde, 71140-25-5; 3-methoxy-4-[(dimethylcarbamoyl)thio]benzaldehyde, 71125-95-6; 2-[(dimethylcarbamoyl)thio]-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one, 87452-03-7; chloromethyl pivalate, 18997-19-8; 1a,2,3,4-tetrahydro-8b*H*-benzo[3,4]cyclohept[1,2-*b*]-oxirene-8b-carbonitrile, 87452-22-0.