TABLE IV

PHARMACOLOGICAL ACTIVITIES OF 1-AMINOACYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONE HYDROCHLORIDES

No.	Choleretic act., mg/kg[a,d]	Antifibrillatory act. mg/kg[b,d]	Antifibrillatory act. mg/l.[c,d]	LD_{50}, mg/kg ip	Other pharmacol act.
1	6.25	(48)	(10)	560[h]	
2	25	31	(10)	500[h]	
3	(130)	41		1300	*k*
4	45	(56)		450[h]	*l, m*
5	75	(190)		1500	*k*
6	30	(36)		300[h]	*l, m*
7	20	(25)		200[i]	*m*
8	35	44		350[j]	*m*
9	12.5	(31)		250[i]	
10	30	37		300	
11	18	(22)		180[i]	
12	15	10	0.81[f]	150[i]	
13	25	31		250	
14	(25)	12	1.8[f]	250[i]	
15	(8)	10	2.6[g]	80	
16	(15)	(5)[e]		150	
17	(25)	(31)		250	
18	(28)	10	6.2[g]	280[i]	
19	(20)	25		200[i]	
20	(30)	38		300[i]	
21	(25)	31		250[i]	
22	25	16	3.3[f]	250	
23	(20)	12		200[i]	
24	(20)	6	2.5[f]	200[i]	

[a] Dose which increased the bile flow to 50%. Maximum tested doses were $0.1LD_{50}$. Sodium dehydrocholate was active at 50 mg/kg. [b] Dose which prevented the cardiac arrhythmia in 50% of animals. Maximum tested doses were $0.12LD_{50}$. Procainamide was active at 50 mg/kg. [c] Concentration which reduced to 50% the heart sensitivity to the electric stimulation. Maximum tested doses were 10 mg/l. [d] Numbers in parentheses are maximum tested nonactive doses. [e] Higher doses were toxic. [f] Quinidine was active at 2.8 mg/l. [g] Quinidine was active at 6.1 mg/l. [h] Clonic convulsions. [i] Hypnosis. [j] Tonic convulsions. [k] Anticonvulsant activity. [l] Transient increase of arterial blood pressure and stimulant effect on respiration. [m] Inhibition of formalin edema of the paw.

the calculated amount of ethanolic HCl to a solution of the base in ether, benzene, acetone, or EtOH, or by dissolving the base in aqueous HCl and concentrating the solution until crystallization set in. Recrystallization from a suitable solvent (see Table III) may follow.

Pharmacological Methods. Animals.—NMRI albino mice (18–20 g) and Wistar albino rats (200–250 g) were used. For choleretic activity, 100-day-old Wistar albino female rats, 220–240 g, were used.

Acute Toxicity.—LD_{50} values were determined in mice intraperitoneally, and the mortality over 5 days was recorded. The animals were also observed for behavior and objective symptoms according to the Irwin[15] scheme.

Choleretic Activity.—Female rats, fasted for 14 hr and anesthetized with urethan, were used. The substances were injected into the duodenum. The bile flow was recorded 1 hr before and 1 hr after the administration of the compounds, by means of a graduated pipet connected to the cannulated choledochus.

Antifibrillatory Activity.—The compounds were given intravenously to rats anesthetized with pentobarbital sodium, and their ability to prevent cardiac arrhythmias induced by $CaCl_2$ was determined. Active compounds were then tested on rabbit heart by the method of Visentini.[16] The heart was stimulated with a frequency of 50/sec for 1 msec. The intensity which provoked the fibrillation was recorded before and after 20 min of perfusion with the testing compounds.

Other Tests.—All compounds were screened also for their antispasmodic activity *"in vitro"* following the methods described by Setnikar and Tirone,[17] and for their local anesthetic activity on the mouse tail according to Bianchi's method.[18] The analgetic activity was assayed in mice after oral administration, according to Bianchi and Franceschini.[19] Coronary vasodilatator activity on the isolated rabbit heart following the method of Setnikar, *et al.*,[20] was also determined.

Antimicrobial and antifungal activity, effects on blood pressure and on respiration, anticonvulsant activity, antitussive activity, and antiinflammatory activity were determined according to the methods previously described.[21]

(15) This scheme was discussed informally by S. Irwin at a Gordon Research Conference, New London, N. H., 1959.
(16) P. Visentini, *Arch. Ital. Sci. Farmacol.*, **4**, 16 (1954).
(17) I. Setnikar and P. Tirone, *Arzneimittel-Forsch.*, **16**, 1146 (1966).
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Synthesis and Antiinflammatory Activity of 4-(*p*-Biphenylyl)-3-hydroxybutyric Acid and Related Compounds

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4-(*p*-Biphenylyl)-3-hydroxybutyric acid and about 50 related compounds are reported. The title compound showed pronounced antiinflammatory activity.

Some years ago as part of a program for the investigation of compounds related to mephenesin (I, R = *o*-tolyloxy; R′ = OH) and chlorphenesin (I, R = *p*-chlorophenoxy; R′ = OH), the formally related 4-aryloxy-3-hydroxybutyric acids (I, R = *o*-tolyloxy or *p*-chlorophenoxy; R′ = CO_2H) were prepared for routine biological screening.

$$RCH_2CHOHCH_2R'$$
I

Subsequently the series was extended and the unexpected observation was made that 4-(*p*-biphenylyloxy)-3-hydroxybutyric acid showed significant antiinflammatory activity in the uv erythema and rat paw tests. A systematic study of this group of compounds was therefore made (see Table I), but a product worthy of clinical study did not emerge.

The acids described in Table I were prepared starting from the aryloxychlorohydrins[1] (I, R = aryloxy; R′ = Cl) which were converted into the nitriles (I, R =

(1) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).

TABLE I

$ROCH_2CHOHCH_2R'$

No.	R	R'	Bp (mm) or mp, °C	Recrystn solvents[a]	Formula	Analyses	Uv erythema test[b]	Rat paw test[b]
1	*o*-Tolyl	CN	130 (0.2)		$C_{11}H_{13}NO_2$	C, H, N		
2		CO_2Et	123 (0.1)		$C_{13}H_{18}O_3$	C, H		
3		$CONH_2$	104–105	D + J	$C_{11}H_{15}NO_3$	C, H, N		
4		CO_2H	51–52	D + J	$C_{11}H_{14}O_4$	C, H		
5	*o*-Isobutylphenyl	CO_2Me	125 (0.1)		$C_{15}H_{22}O_3$	C, H		
6		CO_2H	82–83	F + J	$C_{14}H_{20}O_4$	C, H	0.1	0
7	*p*-Isobutylphenyl	CO_2Me	58–80	J	$C_{15}H_{22}O_3$	C, H		
8		CO_2H	76	F + J	$C_{14}H_{20}O_4$	C, H	0	0
9	*p*-*s*-Butylphenyl	CN	149 (0.1)		$C_{14}H_{18}NO_2$	C, H, N		
10		CO_2Me	47–48	H	$C_{15}H_{22}O_3$	C, H		
11		CO_2H	66–67	F + J	$C_{14}H_{20}O_4$	C, H	0	NT
12	*p*-*t*-Butylphenyl	CO_2Me	52–53	J	$C_{15}H_{22}O_4$	C, H	0.05	0
13		CO_2H	96–97	F + J	$C_{14}H_{20}O_4$	C, H	0.09	0
14	*p*-Chlorophenyl	CN	60–62	E + H	$C_{10}H_{10}ClNO_2$	C, H, Cl, N		
15		CO_2H	125–126	A	$C_{10}H_{11}ClO_4$	C, H, Cl		
16	*o*-Bromophenyl	CO_2H	80–82	D + J	$C_{10}H_{11}BrO_4$	C, H; Br[c]	0	NT
17	*o*-Methoxycarbonylphenyl	CN	170 (0.25)		$C_{12}H_{13}NO_4$	C, H, N		
18	*o*-Ethoxycarbonylphenyl	CO_2Et	164 (0.2)		$C_{15}H_{20}O_6$	C, H	0	0
19	*p*-Ethoxycarbonylphenyl	CN	200 (0.3)		$C_{13}H_{15}NO_4$	C, H, N		
20		CO_2Et	180 (0.25)		$C_{15}H_{20}O_6$	C, H	0	0
21	*p*-Carboxyphenyl	CN	172–174	D + J	$C_{11}H_{11}NO_4$	C, H, N		
22		CO_2H	216 dec	D	$C_{11}H_{12}O_6$	C, H	0	NT
23	*o*-Biphenylyl	Cl	152 (0.3)		$C_{15}H_{13}ClO_2$	C, H, Cl		
24		CN	182 (0.3)		$C_{16}H_{15}NO_2$	C, H, N		
25		$CONH_2$	139–141	B	$C_{16}H_{17}NO_3$	C, H, N	0	0
26		CO_2H	143–145	D + J	$C_{16}H_{16}O_4$	C, H	0.07	0
27	*p*-Biphenylyl	Cl	95–96	J	$C_{15}H_{13}ClO_2$	C, H, Cl		
28		CN	118–120	D + J	$C_{16}H_{15}NO_2$	C, H, N		
29		$CONH_2$	190–192	A + C	$C_{16}H_{17}NO_3$	C, H, N	0	0
30		CO_2Et	106–108	A + C	$C_{18}H_{20}O_4$	C, H	0.05	0.2
31		CO_2H	164–166	D	$C_{16}H_{16}O_4$	C, H	0.1	0.5
32	3-Chloro-*p*-biphenylyl	CO_2Et	190 (0.05)		$C_{18}H_{19}ClO_4$	C, H		
33		CO_2H	89–90	F	$C_{16}H_{15}ClO_4$	C, H, Cl	0.1	0
34	3-Bromo-*p*-Biphenylyl	Cl	188 (0.3)		$C_{15}H_{14}BrClO_2$	Br		
35		CN	80–83	D + J	$C_{16}H_{14}BrNO_2$	C, H, N; Br[d]		
36		CO_2Et	210 (0.2)		$C_{18}H_{19}BrO_4$	C, H; Br[e]		
37	3,5-Dichloro-*p*-biphenylyl	Cl	190 (0.3)		$C_{15}H_{12}Cl_2O_2$	Cl		
38		CO_2Et	97–99	J	$C_{18}H_{18}Cl_2O_4$	C, H, Cl		
39		CO_2H	111–113	E + J	$C_{16}H_{14}Cl_2O_4$	C, H, Cl	0	0.25
40	*p*-Benzylphenyl	Cl	176 (0.25)		$C_{16}H_{17}ClO_2$	C, H, Cl		
41		CN	65–67	J	$C_{17}H_{17}NO_2$	C, H, N		
42		CO_2Et	184 (0.2)		$C_{19}H_{22}O_4$	C, H	0	0
43		CO_2H	92–94	D	$C_{17}H_{18}O_4$	C, H	0.03	0
44	*p*-Benzoylphenyl	Cl	198 (0.15)		$C_{16}H_{15}ClO_3$			
45		CN	112–113	C	$C_{17}H_{15}NO_3$	C, H, N		
46		CO_2Et	80–82	C + J	$C_{19}H_{20}O_5$	C, H	0	NT
47		CO_2H	84–86	D + J	$C_{17}H_{16}O_5$	C, H	0	NT
48	1-Naphthyl	CN	88–90	D + J	$C_{14}H_{13}NO_2$	C, H, N		
49		CO_2Et	178 (0.25)		$C_{16}H_{18}O_3$	C, H		
50		CO_2H	100–102	D + J	$C_{14}H_{14}O_4$	C, H	0	0
51	2-Naphthyl	CN	142–143	D	$C_{14}H_{13}NO_2$	C, H, N		
52		CO_2H	134–135	D + J	$C_{14}H_{14}O_4$	C, H	0.05	0
53	Cyclohexyl	Cl	84 (0.5)		$C_9H_{17}ClO_2$	C, H, Cl		
54		CN	100 (0.1)		$C_{10}H_{17}NO_2$	C, H, N		
55		CO_2H	154 (0.6)		$C_{10}H_{18}O_4$	C, H		

[a] A, H_2O; B, MeOH; C, EtOH; D, EtOAc; E, Et_2O; F, C_6H_6; G, $C_6H_5CH_3$; H, petroleum ether (bp 40–60°); J, petroleum ether (bp 60–80°); K, ligroin; L, CCl_4. [b] Phenylbutazone (standard) = 1.0; NT = not tested. [c] Br: calcd, 29.05; found, 28.60. [d] Br: calcd, 24.1; found, 24.6. [e] Br: calcd, 21.1; found, 20.5.

aryloxy; R' = CN) by reaction with potassium cyanide in aqueous–alcoholic solution. Treatment of the latter with ethanolic HCl furnished the esters (I, R = aryloxy; R' = COOEt) which were hydrolyzed to the acids[2] (I, R = aryloxy; R' = CO_2H) in alkaline solution.

(2) A. N. Dey, *J. Chem. Soc.*, 1057 (1937); M. Julia and G. Tschernoff, *Bull. Soc. Chim. Fr.*, 474 (1954).

Interest was then turned to the preparation of related deoxy acids when it was found that 4-(*p*-biphenylyl)-3-hydroxybutyric acid (I, R = *p*-biphenylyl; R' = CO_2H) was a very potent antiinflammatory agent. As a consequence of this important finding, a series of about 30 related 4-aryl-3-hydroxybutyric acids were prepared for biological testing (Table II).

The acids in Table II were prepared similarly starting

from the arylchlorohydrins[3] (I, R = aryl; R′ = Cl).

The amides in Tables I and II were prepared by treatment of the appropriate nitriles with alkaline H_2O_2 in acetone.

Pharmacology.—The antiinflammatory activity of the compounds was assessed by determining their ability to delay the development of erythema in guinea pig skin induced by exposure to uv radiation[4] and to inhibit edema formation induced in the rat hind paw by subplantar injection of carrageenin.[5] Preliminary tests were carried out at a dose level of 200 mg/kg *po* using groups of five animals for each compound. The criteria by which compounds were selected for further examination were (a) "protection" of at least four animals in the uv erythema test, and (b) a mean inhibition of edema formation of at least 30% as compared with a control group in the rat paw test. Such compounds were compared directly with phenylbutazone at varying dose levels in order to determine relative potencies. The most potent compound, 4-(*p*-biphenylyl)-3-hydroxybutyric acid (**67**, Table II), was further examined for inhibition of granuloma formation induced in rats by subcutaneous implantation of cotton wool pellets,[6] reduction of the febrile response of rats to bacterial endotoxin,[7] and reduction of the frequency of "writhes" induced in mice by intraperitoneal injection of phenylquinone.[8] In these three tests the potency of the compound relative to phenylbutazone was 3.5, 2.5, and 5.6, respectively. The detailed pharmacological examination of this compound is the subject of a separate publication.[9]

Structure–Activity Relationships.—The activities of the compounds in the uv erythema and rat paw tests are included in Tables I and II. The highest order of activity is associated with the unsubstituted *p*-biphenylyl nucleus, and its replacement by *o*-biphenylyl (*cf.* **31** and **26**, Table I; **58** and **65**, Table II), *m*-biphenylyl (*cf.* **62** and **67**, Table II), α- or β-naphthyl (*cf.* **31** and **50** or **52**, Table I; **67** and **116** or **120**, Table II), or phenanthren-9-yl (*cf.* **67** and **123**, Table II) yielded compounds of lower activity.

Substitution of either ring of the *p*-biphenylyl nucleus by alkyl (*cf.* **67** and **103**, Table II), alkoxy (*cf.* **67** and **76**, Table II), or halogen (*cf.* **31** and **33** or **39**, Table I; **67** and **70** or **73**, Table II) gave less active compounds.

Replacement of the B ring in the *p*-biphenylyl compounds by alkyl (*cf.* **31** and **6**, **8**, **11**, or **13**, Table I; **65** and **5** or **17**, **67** and **6**, **51**, or **55**, Table II), alkoxy (*cf.* **66** and **9**, **67** and **10**, **14**, **30**, **35**, or **40**, Table II), halogen (*cf.* **31** and **16**, Table I; **67** and **22**, **44**, or **47**, **65** and **42**, **66** and **43**, Table II), trifluoromethyl (*cf.* **67** and **26**, Table II), benzyl (**30** and **42**, **31** and **43**, Table I), benzoyl (*cf.* **30** and **46**, **31** and **47**, Table I), phenoxy (*cf.* **65** and **79**, **67** and **80**, Table II), cyclopentyl or cyclohexyl (*cf.* **65** and **84** or **87**, Table II), and cyclopentenyl, cyclohexenyl, or cycloheptenyl (*cf.* **67** and **91**, **95**, or **99**, Table II) always yielded compounds of lower activity.

Alteration of the side chain had a marked effect on antiinflammatory activity and the aryloxy compounds in Table I were much less active than their aryl analogs in Table II (*cf.* **8**, **13**, **31**, and **52**, Table I, and **51**, **55**, **67**, and **120**, Table II, respectively).

The free acids were more active than their esters (*cf.* **12** and **13**, **30** and **31**, **42** and **43**, Table I; **65** and **67**, Table II) or amides (*cf.* **25** and **26**, **29** and **31**, Table I; **66** and **67**, Table II).

Experimental Section

Melting points are uncorrected. The experiments described illustrate the general method of preparation of compounds listed in the tables. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-*o*-Biphenylyloxy-2-hydroxypropyl Chloride.—A solution of *o*-hydroxybiphenyl (85.1 g) in 2,3-epoxypropyl chloride (185 g) containing pyridine (0.5 ml) as catalyst was heated at 95° for 18 hr when excess 2,3-epoxypropyl chloride was distilled at reduced pressure. The residual viscous liquid was dissolved in $CHCl_3$ (300 ml) and the solution was shaken carefully with concentrated HCl (100 ml). The $CHCl_3$ layer was washed acid free and the solvent was boiled off; the residual oil was distilled to yield the product, 114.5 g, bp 152° (0.3 mm), which solidified slowly on standing. *Anal.* ($C_{15}H_{15}ClO_2$) C, H, Cl.

1-*o*-Biphenylyloxy-2,3-epoxypropane.—A solution of the foregoing chlorohydrin (94 g) in MeOH (400 ml) was treated with a solution of 85% KOH (26.2 g) in MeOH (200 ml) at 25°. After 30 min the mixture was neutralized (AcOH) and diluted (H_2O) and the product (48.8 g) was isolated with $CHCl_3$. It had bp 120° (0.1 mm). *Anal.* ($C_{15}H_{14}O_2$) C, H.

1-*p*-Biphenylyloxy-2,3-epoxypropane, obtained in 66% yield, had mp 90–92° (from MeOH). *Anal.* ($C_{15}H_{14}O_2$) C, H.

4-*p*-Biphenylyloxy-3-hydroxybutyronitrile.—A solution of 3-*p*-biphenylyloxy-2-hydroxypropyl chloride (52.4 g) in MeOH (500 ml) was treated with a solution of 96% KCN (16.0 g) in the minimum of H_2O. The mixture was refluxed for 4 hr, concentrated, diluted with H_2O, and neutralized (AcOH) and the product was isolated with $CHCl_3$. It (38.0 g) had mp 118–120° [from EtOAc–petroleum ether (bp 60–80°)].

Ethyl 4-*p*-Biphenylyloxy-3-hydroxybutyrate.—A solution of the foregoing nitrile (25.3 g) in EtOH (250 ml) was saturated with HCl gas and allowed to stand for 1 hr when it was refluxed for 4 hr, cooled, and resaturated with HCl gas; the heating was continued for 6 hr. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic extract was washed (H_2O), concentrated, and diluted with petroleum ether (bp 60–80°) to yield the ester (24.3 g) which was purified by crystallization from EtOH–H_2O and had mp 106–108°.

4-*p*-Biphenylyloxy-3-hydroxybutyramide.—A stirred solution of 4-*p*-biphenylyloxy-3-hydroxybutyronitrile (25.3 g) in acetone (300 ml) was treated with NaOH (16 g) in H_2O (50 ml); 30% H_2O_2 (100 ml) was then added during 15 min with intermittent cooling to control the exothermic reaction. The mixture was then refluxed for 1 hr, concentrated to remove most of the acetone, diluted (H_2O, 400 ml), and neutralized with dilute HCl. The product (14.4 g) had mp 190–192° (from 75% EtOH).

4-*p*-Biphenylyloxy-3-hydroxybutyric Acid. (**a**) A suspension of the foregoing amide (3 g) in H_2O (100 ml) and EtOH (20 ml) containing NaOH (5 g) was heated under reflux for 90 min. The solution was acidified with dilute HCl to yield the product, mp 163–166° (from MeOH).

(**b**) Ethyl 4-*p*-biphenylyloxy-3-hydroxybutyrate (30 g) was heated with a solution of NaOH (8 g) in H_2O (500 ml) for 1 hr, sufficient EtOH being added at first to give a clear solution. The solution was acidified with dilute HCl to yield the product, mp 163–166° as above.

3-Bromo-4-*n*-butoxybiphenyl.—A solution of 3-bromo-4-hydroxybiphenyl (107.4 g) in EtOH (500 ml) containing 90% KOH (27.3 g) was treated with *n*-BuBr (69 g) and the mixture was heated under reflux for 5 hr. It was then cooled and diluted with H_2O and the resultant oil was isolated with $CHCl_3$. It had

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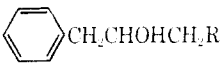
TABLE II



No.	Substituent at position 2	3	4	5	R	Bp (mm) or mp, °C	Recrystn solvents[a]	Formula	Analyses	Uv erythema test[b]	Rat paw test[b]
1	H	H	H	H	Cl	68 (0.05)		$C_9H_{11}ClO$	C, H, Cl		
2					CN	114 (0.3)		$C_{10}H_{11}NO$	C, H, N		
3					COOEt	92 (0.2)		$C_{12}H_{16}O_3$	C, H		
4					$CONH_2$	121–123	D	$C_{10}H_{13}NO_2$	C, H, N		
5	Me	H	H	H	COOEt	102 (0.2)		$C_{13}H_{18}O_3$	C, H	0	0
6					CO_2H	87–89	F	$C_{11}H_{14}O_3$	C, H	0	0
7	MeO	H	H	H	CN	158 (1.0)		$C_{11}H_{13}NO_2$	C, H, N		
8					COOEt	152 (1.2)		$C_{13}H_{18}O_4$	C, H		
9					$CONH_2$	111–113	A	$C_{11}H_{15}NO_3$	C, H, O	0	0
10					CO_2H	98–99	F + J	$C_{11}H_{14}O_4$	C, H	0	0
11	EtO	H	H	H	CN	69–70	F + J	$C_{12}H_{15}NO_2$	C, H, N		
12					COOEt	148 (0.9)		$C_{14}H_{20}O_4$	C, H		
13					$CONH_2$	87–88	F + J	$C_{12}H_{17}NO_3$	C, H, N		
14					CO_2H	62–64	F + J	$C_{12}H_{16}O_4$	C, H	0	0
15	H	Me	H	H	Cl	94 (0.7)		$C_{10}H_{13}ClO$	C, H		
16					CN	129 (0.5)		$C_{11}H_{13}NO$	C, H, N		
17					COOEt	102–104 (0.2)		$C_{13}H_{18}O_3$	C, H	0	0
18					CO_2H	86–88	F	$C_{11}H_{14}O_3$	C, H		
19	H	Cl	H	H	Cl	112–114 (0.1)		$C_9H_{10}Cl_2O$	C, H, Cl		
20					CN	146–148 (0.2)		$C_{10}H_{10}ClNO$	C, H, Cl, N		
21					COOEt	129–132 (0.3)		$C_{12}H_{15}ClO_3$	C, H, Cl		
22					CO_2H	86–88	F + J	$C_{10}H_{11}ClO_3$	C, H, Cl	0	0
23	H	CF_3	H	H	Cl	80 (0.1)		$C_{10}H_{10}ClF_3O$	C, H, Cl		
24					CN	130 (0.2)		$C_{11}H_{10}F_3NO$	C, H, F, N		
25					COOEt	120–124 (1.0)		$C_{13}H_{15}F_3O_3$	C, H		
26					CO_2H	89–91	F + J	$C_{11}H_{11}F_3O_3$	C, H, F	0	0
27	H	H	MeO	H	Cl	108–110 (0.1)		$C_{10}H_{13}ClO_2$	C, H, Cl		
28					CN	59–60	F + J	$C_{11}H_{13}NO_2$	C, H, N		
29					COOEt	139 (0.1)		$C_{13}H_{18}O_4$	H; C[c]		
30					CO_2H	92–94	F + J	$C_{11}H_{14}O_4$	C, H	0	0
31	H	H	EtO	H	Cl	112–114 (0.1)		$C_{11}H_{15}ClO_2$	C, H, Cl		
32					CN	138–140 (0.05)		$C_{12}H_{15}NO_2$	N		
33					COOEt	136 (0.1)		$C_{14}H_{20}O_4$	CH		
34					$CONH_2$	138–139	A	$C_{12}H_{17}NO_3$	N		
35					CO_2H	94–96	F	$C_{12}H_{16}O_4$	H; C[d]	0.09	0.05
36	H	H	BuO	H	Cl	116 (0.05)		$C_{13}H_{19}ClO_2$	Cl		
37					CN	156 (0.03)		$C_{14}H_{19}NO_2$	C, H, N		
38					COOEt	146 (0.03)		$C_{16}H_{24}O_4$	C, H		
39					$CONH_2$	130	A	$C_{14}H_{21}NO_3$	C, H, N		
40					CO_2H	80–82	F + J	$C_{14}H_{20}O_4$	C, H	0	0
41	H	H	Cl	H	CN	155 (0.8)		$C_{10}H_{10}ClNO$	C, H, Cl, N		
42					COOEt	112 (0.2)		$C_{12}H_{15}ClO_3$	C, H	0	0
43					$CONH_2$	134–136	D	$C_{10}H_{12}ClNO_2$	C, H, Cl, N	0	0
44					CO_2H	113–115	F	$C_{10}H_{11}ClO_3$	C, H, Cl	0	0
45	H	H	Br	H	Cl	138 (0.6)		$C_9H_{10}BrClO$	C, H, Br		
46					COOEt	170 (0.2)		$C_{12}H_{15}BrO_3$	C, H, Br		
47					CO_2H	126–128	F	$C_{10}H_{11}BrO_3$	C, H, Br	0	NT
48	H	H	Isobutyl	H	Cl	112–114 (0.1)		$C_{13}H_{19}ClO$	C, H, Cl		
49					CN	142–144 (0.25)		$C_{14}H_{19}NO$	C, H, N		
50					COOEt	142–146 (0.2)		$C_{16}H_{24}O_3$	C, H		
51					CO_2H	85–87	F + J	$C_{14}H_{20}O_3$	C, H	0.17	0.14
52	H	H	*t*-Butyl	H	Cl	106 (0.1)		$C_{13}H_{19}ClO$	C, H, Cl		
53					CN	140 (0.2)		$C_{14}H_{19}NO$	C, H, N		
54					COOEt	130–132 (0.2)		$C_{16}H_{24}O_3$	C, H		
55					CO_2H	101–103	F + J	$C_{14}H_{20}O_3$	C, H	0.07	0.25
56	Ph	H	H	H	Cl	54–56	J	$C_{15}H_{15}ClO$	C, H, Cl		
57					CN	155 (0.1)		$C_{16}H_{15}NO$	N		
58					COOEt	150 (0.1)		$C_{18}H_{20}O_3$	C, H	0	0
59	H	Ph	H	H	Cl	170 (0.4)		$C_{15}H_{13}ClO$	C, H, Cl		
60					CN	190 (0.2)		$C_{16}H_{13}NO$	N		
61					COOEt	190 (0.2)		$C_{18}H_{20}O_3$	C, H		
62					CO_2H	116–118	F	$C_{16}H_{16}O_3$	C, H	0.5	0.3
63	H	H	Ph	H	Cl	110–111	K	$C_{15}H_{15}ClO$	C, H, Cl		
64					CN	101–102	L	$C_{16}H_{15}NO$	C, H, N	2.0	0.13
65					COOEt	184 (0.1)		$C_{18}H_{20}O_3$	C, H	2.3	+
66					$CONH_2$	184–186	B	$C_{16}H_{17}NO_2$	C, H, N	4.6	2.5

TABLE II (*Continued*)

No.	Substituent at position 2	3	4	5	R	Bp (mm) or mp, °C	Recrystn solvents[a]	Formula	Analyses	Uv erythema test[b]	Rat paw test[b]
67					CO_2H	151–152	D	$C_{16}H_{16}O_3$	C, H	7.0	2.5
68	H	H	*o*-Chlorophenyl	H	Cl	150 (0.02)		$C_{15}H_{15}Cl_2O$	Cl		
69					CN	190 (0.05)		$C_{16}H_{14}ClNO$	C, H, Cl, N		
70					CO_2H	100–102	F + J	$C_{16}H_{15}ClO_3$	C, H, Cl	2.0	1.0
71	H	H	*p*-Chlorophenyl	H	CN	90–92	F + J	$C_{16}H_{14}ClNO$	C, H, Cl, N		
72					COOEt	72–74	D + J	$C_{18}H_{19}ClO_3$	C, H; Cl[e]		
73					CO_2H	157–159	G	$C_{16}H_{15}ClO_3$	C, H, Cl	0.67	2.0
74	H	H	*p*-Methoxyphenyl	H	Cl	85–88	D + J	$C_{16}H_{17}ClO_2$	C, H		
75					CN	132–136	F + J	$C_{17}H_{17}NO_2$	N		
76					CO_2H	176–178	F	$C_{17}H_{18}O_4$	C, H	0.14	0.4
77	H	H	PhO	H	Cl	144 (0.1)		$C_{15}H_{15}ClO_2$	Cl		
78					CN	160 (0.1)		$C_{15}H_{15}NO_2$	C, H, N		
79					COOEt	171–174 (0.1)		$C_{18}H_{20}O_4$	C, H	0	1.0
80					CO_2H	83–85	F + J	$C_{16}H_{16}O_4$	C, H	0	1.0
81	H	H	$PhCH_2$	H	COOMe	165 (0.1)		$C_{18}H_{20}O_3$	C, H	0	0
82	H	H	Cyclopentyl	H	Cl	120–122 (0.05)		$C_{14}H_{19}ClO$			
83					CN	150 (0.1)		$C_{15}H_{19}NO$	C, H, N		
84					COOEt	145–147 (0.1)		$C_{17}H_{24}O_3$	C, H	0	0
85	H	H	Cyclohexyl	H	Cl	130–132 (0.1)		$C_{15}H_{21}ClO$	C, H, Cl		
86					CN	155 (0.1)		$C_{16}H_{21}NO$	C, H, N		
87					COOEt	150 (0.1)		$C_{18}H_{26}O_3$	C, H	0	0
88	H	H	Cyclopent-1-enyl	H	Cl	100–101	K	$C_{14}H_{17}ClO$	C, H, Cl		
89					CN	77–78	F + J	$C_{15}H_{17}NO$	C, H, N		
90					COOEt	165–169 (0.15)		$C_{17}H_{22}O_3$	C, H		
91					CO_2H	153–156	A + B	$C_{15}H_{18}O_3$	C, H	0.13	0.5
92	H	H	Cyclohex-1-enyl	H	Cl	103–104	K	$C_{15}H_{19}ClO$	C, H, Cl		
93					CN	104–105	F + J	$C_{16}H_{19}NO$	C, H, N		
94					COOEt	170 (0.1)		$C_{18}H_{24}O_3$	C, H		
95					CO_2H	148–150	G	$C_{16}H_{20}O_3$	C, H	0.07	1.0
96	H	H	Cyclohept-1-enyl	H	Cl	150 (0.1)		$C_{16}H_{21}ClO$	C, H, Cl		
97					CN	180–184 (0.1)		$C_{17}H_{21}NO$	C, H, N		
98					COOEt	171–174 (0.1)		$C_{19}H_{26}O_3$			
99					CO_2H	100–101	F + J	$C_{17}H_{22}O_3$	C, H	0.07	0.67
100	Me	H	Ph	H	Cl	164 (0.05)		$C_{16}H_{17}ClO$	C, H; Cl[f]		
101					CN	176 (0.03)		$C_{17}H_{17}NO$	H, N; C[g]		
102					COOEt	194 (0.02)		$C_{19}H_{22}O_3$	C, H		
103					CO_2H	154–156	G	$C_{17}H_{18}O_3$	C, H	0.13	0.5
104	H	Cl	Ph	H	Cl	160 (0.02)		$C_{15}H_{15}Cl_2O$	Cl		
105					CN	190 (0.05)		$C_{16}H_{14}ClNO$	Cl, N		
106	MeO	H	H	Ph	Cl	165 (0.05)		$C_{16}H_{17}ClO_2$	C, H, Cl		
107					CN	72–75	E + J	$C_{17}H_{17}NO_2$			
108					COOEt	178 (0.15)		$C_{19}H_{22}O_4$	C, H		
109					CO_2H	121–123	F	$C_{17}H_{18}O_4$	C, H	0	0
110	BuO	H	H	Ph	Cl	78–79	J	$C_{19}H_{23}ClO_2$	C, H, Cl		
111					CN	176–180 (0.1)		$C_{20}H_{23}NO_2$			
112					COOEt	182–186 (0.1)		$C_{22}H_{28}O_4$			
113					CO_2H	124–125	F + J	$C_{20}H_{24}O_4$	C, H	0.08	NT
114	1-Naphthyl				CN	68–69	F + J	$C_{14}H_{13}NO$	C, H, N		
115					COOEt	150 (0.25)		$C_{16}H_{18}O_3$	C, H		
116					CO_2H	110–111	F	$C_{14}H_{14}O_3$	C, H	0	0
117	2-Naphthyl				Cl	140 (0.05)		$C_{13}H_{13}ClO$	C, H, Cl		
118					CN	174 (0.05)		$C_{14}H_{13}NO$	C, H, N		
119					COOEt	158 (0.25)		$C_{16}H_{18}O_3$	C, H		
120					CO_2H	126–128	F	$C_{14}H_{14}O_3$	C, H	0.06	0.3
121	Phenanthren-(9)-yl				Cl	114–116	F + J	$C_{17}H_{15}ClO$	C, H, Cl		
122					CN	119–121	F + J	$C_{18}H_{15}NO$	C, H, N		
123					CO_2H	160–162	A + C	$C_{15}H_{16}O_3$	C, H	0	0

[a] See footnote *a* in Table I. [b] Phenylbutazone (standard) = 1.0; NT = not tested; + = active at 200 mg/kg *po*. [c] C: calcd, 65.5; found, 66.1. [d] C: calcd, 64.8; found, 64.3. [e] Cl: calcd, 11.15; found, 11.6. [f] Cl: calcd, 13.5; found, 13.0. [g] C: calcd, 81.2; found, 80.7.

bp 143–150° (0.1 mm), yield 93.4 g, mp 45–47° (from MeOH). *Anal.* ($C_{16}H_{17}BrO$) C, H, Br.

(a) **4-(Cyclopent-1-enyl)bromobenzene.**—To a stirred solution of *p*-BrC_6H_4MgBr prepared from *p*-dibromobenzene (141 g) and Mg (14.4 g) in Et_2O (850 ml) was added during 1 hr a solution of cyclopentanone (50.5 g) in Et_2O (350 ml). The mixture was stirred for 3 hr and then decomposed by the careful addition of a concentrated aqueous solution of NH_4Cl (140 g). The ether layer was washed (H_2O) and dried (Na_2SO_4) and the ether was evaporated to yield an oil which was distilled at reduced pressure giving the crude carbinol (72 g), bp 120–140° (0.1 mm). This was dissolved in AcOH (400 ml) containing Ac_2O (35 ml) and the mixture was heated under reflux for 3 hr. The excess AcOH was distilled off at reduced pressure, the residue was diluted with H_2O, and the residual oil was isolated with $CHCl_3$ giving the product (44.8 g), mp 91–93° (from EtOH). *Anal.* ($C_{11}H_{11}Br$) C, H, Br.

(b) **1-Chloro-3-[*p*-(cyclopent-1-enyl)phenyl]propan-2-ol.**—To

a Grignard solution prepared from Mg (4.7 g) and 4-(cyclopent-1-enyl)bromobenzene (38 g) in a mixture of Et_2O (235 ml) and THF (95 ml), a solution of 2,3-epoxypropyl chloride (31.5 g) in Et_2O (40 ml) was added during 30 min with stirring at room temperature. After stirring for a further 30 min the mixture was decomposed by the addition of 5 *N* HCl. The ether layer was separated, washed (H_2O), and dried (Na_2SO_4) and the ether was distilled. The residual oil was distilled to yield a fraction (18.5 g), bp 120–155° (0.1 mm), which solidified and had mp 100–101° (from ligroin).

(c) **1-Cyano-3-[*p*-(cyclopent-1-enyl)phenyl]propan-2-ol.**—A solution of the foregoing chlorohydrin (14.8 g) in EtOH (150 ml) was treated with a solution of 96% KCN (5.1 g) in H_2O (11 ml) and the mixture was heated under reflux for 90 min. It was then cooled and diluted with iced H_2O and the product was isolated with $CHCl_3$. It (12 g) had mp 77–78° [from C_6H_6–petroleum ether (bp 60–80°)].

(d) **Ethyl 4-[*p*-(cyclopent-1-enyl)phenyl]-3-hydroxybutyrate** was obtained when a solution of the foregoing nitrile (7.5 g) in EtOH (75 ml) and H_2O (2 ml) was saturated with HCl gas and then heated under reflux for 12 hr. The ester (4.4 g) isolated with $CHCl_3$ had bp 165–169° (0.15 mm).

(e) **4-[*p*-(Cyclopent-1-enyl)phenyl]-3-hydroxybutyric Acid.**—A solution of the foregoing ester (2.2 g) in 50% EtOH–H_2O (25 ml) containing NaOH (0.4 g) was heated under reflux for 1 hr. It was then cooled slightly and poured with stirring into excess warm, dilute HCl. The mixture was cooled and the acid was collected. It (1.7 g) had mp 153–156° (from MeOH–H_2O).

4-(Cylohept-1-enyl)bromobenzene, prepared as described for 4-(cyclopent-1-enyl)bromobenzene, using cycloheptanone in place of cyclopentanone, had mp 51–53° (from MeOH). *Anal.* ($C_{13}H_{15}Br$) C, H, Br.

N-(β-Hydroxyethyl)-4-(*p*-biphenylyl)-3-hydroxybutyramide.—A mixture of ethyl 4-(*p*-biphenylyl)-3-hydroxybutyrate (10 g) and ethanolamine (10 ml) was heated on the steam bath for 2 hr when it was cooled and stirred with dilute HCl. The amide (8 g) had mp 130–131° (from EtOH). *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

N-(β-Hydroxyethyl)-4-(*p*-biphenylyloxy)-3-hydroxybutyramide had mp 181–183° (from EtOH). *Anal.* ($C_{18}H_{21}NO_4$) C, H, N.

N-(β-Hydroxyethyl)-3-hydroxy-4-(2-naphthyloxy)butyramide had mp 161–163° (from EtOH). *Anal.* ($C_{16}H_{19}NO_4$) C, H, N.

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Potential Antihypertensive Agents. II.[1] Unsymmetrically 1,4-Disubstituted Piperazines. I

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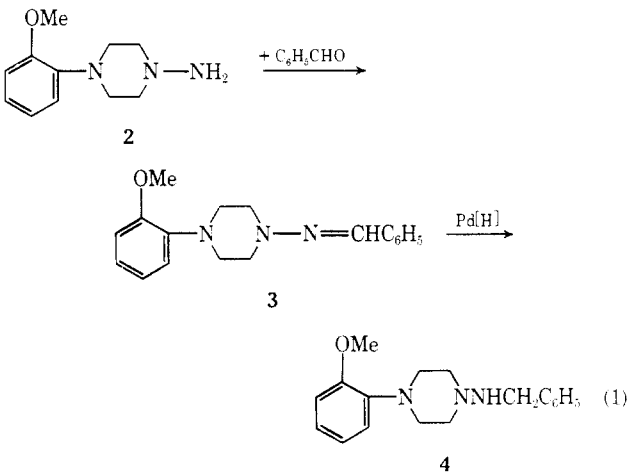
Several unsymmetrically 1,4-disubstituted piperazines have been prepared by reducing 1-acyl-4-substituted piperazines, the latter having been obtained by the acylation of 1-alkyl- or 1-arylpiperazines. Alkylation of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) gives 1-amino-1-alkyl-4-(*o*-methoxyphenyl)piperazinium halide (**5–8, 12**). Some of the 4-substituted derivatives of 1-phenyl- or 1-(*o*-methoxyphenyl)piperazines show appreciable antihypertensive activities, but the 1-methyl-4-substituted piperazines cause no significant fall in blood pressure.

In continuation of our studies of compounds having antihypertensive properties, we have prepared and tested a large number of unsymmetrically 1,4-disubstituted piperazines.

Chemistry.—The unknown 1-phenyl-4-aminopiperazine (**1**) was prepared by refluxing bis-β-chloroethyl aniline with hydrazine in ethanol. Preparation of 1-(*o*-methoxyphenyl)-4-aminopiperazine (**2**) was similarly achieved. These compounds could also be prepared by nitrosating the corresponding 1-substituted piperazine with sodium nitrite and hydrochloric acid and reducing the 4-nitrosopiperazine derivative with zinc dust in acetic acid.

Reaction of **2** with aromatic aldehydes resulted in the formation of the corresponding Schiff bases, *e.g.*, **3** (eq 1). Hydrogenation of **3** in the presence of 10% Pd–C gave **4**. Attempted reduction of **3** ($NaBH_4$ or $LiAlH_4$), or hydrogenation in the presence of PtO_2, failed to give **4**.

The reaction of **2** with benzyl chloride or benzyl iodide resulted in substitution on the 1-nitrogen atom to yield **5** and **6** (eq 2). Compound **7** (and **8**) was similarly obtained. Proof for the assignment of the structure of **5** (and **6**) was found in the reaction of benzylhydrazine and bis(β-chloroethyl)-*o*-anisidine (**9**) which yielded the hydrochloride **10** and could be converted to **5** by treatment with $NaHCO_3$ (eq 2).



(1)

Hydrogenolysis of **5** (eq 3) in the presence of PtO_2 gave 1-benzyl-4-(*o*-methoxyphenyl)piperazine (**11**) and ammonia. On the other hand, hydrogenolysis in the presence of 10% Pd–C gave 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) and toluene.

Substitution on the N-1 position of 1-amino-4-(*o*-methoxyphenyl)piperazine (**2**) may be explained by the assumption that N-1 has the highest nucleophilic activity of the three nitrogen atoms in the molecule. The amino group in compound **2** can be visualized as a

(1) F. Fried, R. N. Prasad, and A. P. Gaunce, *J. Med. Chem.*, **10**, 279 (1967), may be considered as paper I.