tion occurred and 2-(4-benzamidopiperidino)ethyl hydroxymethyl ketone crystallized out and was recrystallized from EtOH (3.2 g, mp 154.5°). The foregoing intermediate (3.0 g, 0.01 mol) in EtOH (10 ml) was added to a mixture of cupric acetate (5 g), 0.880 ammonia (40 ml), and 40% aqueous formaldehyde (3 ml) and heated at 100° for 1 hr. The Cu salt was collected, suspended in hot $H_2O$, and brought to pH 3. $H_2S$ was passed in until there was no further precipitation; then the mixture was filtered and the filtrate was evaporated. Trituration of the residue with EtOH gave the product dihydrochloride hydrate (2.37 g).

**1-[2-(2-Benzimidazolyl)ethyl]-4-benzamidopiperidine (17).** A mixture of 4-BAP (2.0 g, 0.0098 mol), ethyl 3-bromopropionate (1.30 g, 0.01 mol), and $K_2CO_3$ (2.0 g, 0.015 mol) in 2-PrOH (25 ml) was refluxed for 18 hr and filtered while hot and the filtrate allowed to cool whereupon 1-(2-ethoxycarbonylethyl)-4-benzamidopiperidine (1.93 g, mp 112–113°) crystallized. The foregoing intermediate (3.16 g, 0.01 mol) was added to *o*-phenylenediamine (1.08 g, 0.01 mol) in 4 *N* HCl (10 ml) and the solution was refluxed for 2 hr, cooled, and filtered. The solid was recrystallized from EtOH to give the product as a quarter-hydrate (0.58 g).

**1-[2-(3-Benz[*g*]indolyl)ethyl]-4-benzamidopiperidine (18).** 1-(4,4-Diethoxybutyl)-4-benzamidopiperidine[2] (3.48 g, 0.01 mol) was added portionwise to a solution of 1-naphthylhydrazine hydrochloride (1.95 g, 0.01 mol) in 25% aqueous acetic acid (15 ml) with stirring at 80°. Stirring and heating were continued for 2.5 hr; then the mixture was left for 3 days. Recrystallization of the precipitate from EtOH gave the product as a hydrochloride hemihydrate (1.28 g).

**1-(2-Hydroxyethyl)-4-benzamidopiperidine (20).** 4-BAP (20.4 g, 0.1 mol), 2-bromoethanol (15.0 g, 0.12 mol), and $K_2CO_3$ (27.6 g, 0.2 mol) were intimately mixed and suspended in methyl ethyl ketone (20 ml). The mixture was stirred at 100° for 2 hr and filtered hot and the residue washed well with hot MEK. Evaporation of the filtrate and recrystallization of the residue from EtOAc gave the product (15.5 g), mp 133° (hydrochloride mp 189°).

**1-(2-Chloroethyl)-4-benzamidopiperidine Hydrochloride (21).** $SOCl_2$ (2.3 g, 0.019 mol) and **20** (3.7 g, 0.015 mol) in benzene (20 ml) were stirred and refluxed 3 hr, then cooled, and filtered. Recrystallization from EtOH–$Et_2O$ gave the product hydrochloride (2.9 g), mp 239°.

**1-[2-[*N*-(*p*-Methoxybenzyl)-*N*-(2-pyridyl)amino]ethyl]-4-benzamidopiperidine (3).** 2-(*p*-Methoxybenzyl)aminopyridine (3.11 g, 0.0145 mol) was added to $LiNH_2$ [from Li (120 mg, 0.017 mol) and liquid $NH_3$] in benzene (170 ml). After refluxing 2 hr, **21** (5.29 g, 0.0155 mol) was added portionwise. The mixture was refluxed 6.5 hr, cooled, and filtered. Petroleum ether (bp 60–80°) was added to the filtrate to induce crystallization. Recrystallization from PhH–P (60) gave the product hemihydrate (3.20 g).

**1-[2-(Phenothiazin-10-yl)ethyl]-4-benzamidopiperidine (19).** A suspension of **21** (5.03 g, 0.015 mol) in xylene (30 ml) was added during 50 min to phenothiazine (3.75 g, 0.019 mol) and sodamide (0.87 g, 0.022 mol) in boiling xylene (90 ml). The mixture was refluxed 3 hr, cooled, and washed with $H_2O$. Evaporation of the dried xylene layer gave crude product (5.32 g) which was converted to the product hydrochloride quarter hydrate (2.51 g).

**Method F. 1-[2-Hydroxy-2-(2-pyrrolyl)ethyl]-4-benzamidopiperidine (5).** Compound 4 (3.4 g, 0.0105 mol) in THF (80 ml) was added to a stirred suspension of $LiAlH_4$ (1.9 g, 0.05 mol) in THF (100 ml). The suspension was refluxed 3 hr, followed by dropwise addition of $H_2O$ (5.5 ml), and the inorganic material was filtered off. Evaporation of the filtrate and recrystallization of the residue from EtOH gave the product (2.5 g).

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## References

(1) J. L. Archibald, *Chim. Ther.*, **3**, 397 (1968).
(2) J. L. Archibald, B. J. Alps, J. F. Cavalla, and J. L. Jackson, *J. Med. Chem.*, 14, 1054 (1971).
(3) B. J. Alps, J. L. Archibald, E. S. Johnson, and A. B. Wilson, *Cardiovascular Research*, Abstracts, 6th World Congress of Cardiology, 1970, p 62.
(4) B. J. Alps, E. T. Borrows, E. S. Johnson, M. W. Staniforth, and A. B. Wilson, *Cardiovasc. Res.*, **6**, 226 (1972).
(5) B. J. Alps, M. Hill, E. S. Johnson, and A. B. Wilson, *Brit. J. Pharmacol.*, **44**, 52 (1972).
(6) R. B. Royds, *Brit. J. Pharmacol.*, **44**, 379P (1972).
(7) C. T. Dollery, C. F. George, and P. J. Lewis, *Brit. J. Pharmacol.*, **46**, 542P (1972).
(8) A. J. Boakes, B. N. C. Prichard, and P. C. Teoh, *Brit. J. Pharmacol.*, 44, 378P (1972).
(9) T. Baum and A. T. Shropshire, *Amer. J. Physiol.*, **212**, 1020 (1967).
(10) O. Arunlakshana and H. O. Schild, *Brit. J. Pharmacol. Chemother.*, 14, 48 (1959).
(11) J. L. Archibald, *J. Heterocycl. Chem.*, 4, 335 (1967).

# Benzamidopiperidines. 3. Carbocyclic Derivatives Related to Indoramin

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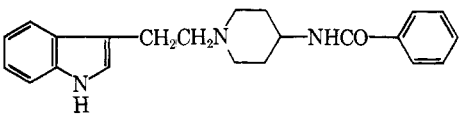
The synthesis of a series of 1-aralkyl derivatives of 4-benzamidopiperidine and related compounds is reported. Some of these compounds show greater activity than indoramin as hypotensive agents, antihistamines, and α-adrenoceptor antagonists.

In part 2[1] the investigation of compounds related to indoramin[2,3] was extended to cover a variety of derivatives in which the indole ring had been replaced by other heterocyclic systems. The present study deals with those compounds where the indole ring of indoramin has been replaced by a variety of aryl groups, and the length and nature of the chain linking these groups to the piperidine ring have been extensively modified. These compounds are listed (in Table II) in order of increasing chain length.

Hypotensive and antihypertensive activities have been determined for most members of the series (Table II), and selected compounds have also been investigated for α-adrenoceptor antagonism and antihistamine activity (Table III). More detailed pharmacological evaluations of




indoramin

some of these compounds have been carried out and will be reported elsewhere.

Structural modifications within the series have resulted in useful variations of the pharmacological profiles such that some of these compounds are more potent and selective than indoramin with respect to individual biological properties. The antihypertensive, antihistamine, and α-adrenoceptor blocking activities of indoramin have been

**Table I**

| Compd | $R_1$ | A | $R_2$ | X | Crystn solvent | Mp, °C | % yield | Method | Formula |
|---|---|---|---|---|---|---|---|---|---|
| | | | A. Pyridinium Salts $X^-$ $R_1AN^+$ $NHR_2$ | | | | | | |
| **1** | $C_6H_5$ | $CH_2$ | $COCH_3$ | Cl | DMF | 237–238 | 78 | A | $C_{14}H_{15}ClN_2O$ |
| **2** | $C_6H_5$ | $CH_2$ | $COC_6H_4$-*p*-$OCH_3$ | Cl | EtOH | >200 dec | 54 | A | $C_{20}H_{19}ClN_2O_2$ |
| **3** | $C_6H_5$ | $CH_2$ | $COC_6H_4$-*p*-$NO_2$ | Cl | EtOH | 210–215 | 24 | A | $C_{19}H_{16}ClN_3O_3$ |
| **4** | $C_6H_5$ | $CH_2CH_2$ | $COC_6H_5$ | Br | EtOH + $Et_2O$ | 200–203 | 49 | A | $C_{20}H_{19}BrN_2O$ |
| **5** | 3,4-$(CH_3O)_2C_6H_3$ | $CH_2CH_2$ | $COCH_3$ | I | EtOH | 201–202 | 49 | A | $C_{17}H_{21}IN_2O_3$ |
| **6** | $C_6H_5$ | $COCH_2$ | $COC_6H_5$ | Br | EtOH | 170–172 | 96 | A | $C_{20}H_{17}BrN_2O_2 \cdot 0.5C_2H_5OH$ |
| **7** | $C_6H_5$ | $OCH_2CH_2$ | $COC_6H_5$ | Br | EtOH | 176–180 | 43 | A | $C_{20}H_{19}BrN_2O_2$ |
| **8** | 2-$CH_3C_6H_4$ | $NHCOCH_2CH_2$ | H | Cl | EtOH | 219–220 | 78 | A | $C_{15}H_{18}ClN_3O$ |
| | | | B. 1,2,5,6-Tetrahydropyridines $R_1AN$ $NHR_2$ | | | | | | |
| **9** | $C_6H_5$ | $CH_2$ | $COC_6H_5$ | | EtOH | 214–215 | 14 | B | $C_{19}H_{20}N_2O \cdot (COOH)_2$ |
| **10** | $C_6H_5$ | $CH_2CH_2$ | $COC_6H_5$ | | MeOH–$H_2O$ | 115–117 | 90 | B | $C_{20}H_{22}N_2O$ |

confirmed in man,[4-7] and some of the compounds described herein may have further advantages in the treatment of cardiovascular disease and in conditions where potent and selective $\alpha$ blockers or antihistamines are likely to be useful.

**Chemistry.** The methods used to prepare the compounds described in this publication were in general similar to those previously reported.[1-3] Quaternary salts (Table IA) were obtained from the appropriately substituted 4-aminopyridines (method A). Two of these salts were reduced with $NaBH_4$ to give tetrahydropyridines (Table IB, method B), but as these showed only slight hypotensive activity, no further examples were prepared. Most of the pyridinium salts were reduced with Raney nickel to the corresponding piperidines (Table II, method C). The primary amine **96** was also obtained in this way, but other 4-aminopiperidines were obtained by hydrolysis of acetamido or benzamidopiperidines (method D). Acylation of these amines provided one route to the corresponding benzamidopiperidines (method E). Most of the compounds in Table II were prepared by alkylation of 4-benzamidopiperidine[3] (4-BAP) with an aralkyl halide, tosylate, epoxide, or alcohol (method F). Five different sets of conditions were used for these alkylations, the first three of which applied to halides or tosylates and were respectively $F_1$, DMF–$Et_3N$; $F_2$, 2-PrOH–$K_2CO_3$; and $F_3$, $K_2CO_3$ (no solvent). The latter conditions, where the two reactants were intimately mixed with powdered $K_2CO_3$ and heated on a steam bath, generally gave the highest yields. It was not essential to convert alcohols to halides or tosylates, since they could be condensed directly with 4-BAP in the presence of Raney nickel ($F_4$). Method $F_5$ involved alkylation of 4-BAP with an epoxide. Some examples were obtained by transformations carried out on substituents attached to ring $R_1$ (method G). These transformations were $G_1$, reduction of $-NO_2$; $G_2$, acylation of $NH_2$; $G_3$, demethylation of -OMe; and $G_4$, alkylation of -OH. Reductions involving the linking chain A (method H) consisted of $H_1$, reduction of C=O to CHOH; $H_2$, reduction of C=O to $CH_2$; and $H_3$, reductions of olefinic linkages. Compound **13** was prepared by a Mannich reaction (method I). In two examples, introduction of a Me substituent on the amide N was achieved by reduction of an *N*-carbethoxy group (method J). Compound **102** was obtained by reaction of the corresponding side-chain ester with aniline (method K). Finally, compound **87** was prepared by resolution of **86** (method L).

**Biological Results.** An evaluation of the hypotensive activities of compounds in Table II was carried out in dialurethane or sodium pentobarbital anesthetized normotensive rats, and diastolic blood pressure was measured directly by carotid artery manometry. Most of the compounds were also examined for antihypertensive activity in conscious renal hypertensive rats. Systolic blood pressure was measured by an indirect tail-cuff technique.[8] Results are listed in Table II. For comparison, indoramin was rated +++ in both of these tests. Antihistamine activity was determined for selected compounds using an isolated guinea-pig ileum preparation. The $pA_2$ values[9] are given in Table III. $\alpha$-Adrenoceptor antagonism was determined for selected compounds using an isolated guinea-pig aortic spiral preparation,[10] and the resulting $pA_2$ values are also listed in Table III. Standard drugs are included for comparison.

It is again evident, as in the case of the heterocyclic derivatives,[1] that there is no consistent correlation between the results obtained with normotensive and hypertensive animals, but this lack of correlation might possibly reflect differences in methodology. The normotensive anesthe-

tized rats were dosed iv and blood pressure was measured directly at 15-min intervals while the hypertensive conscious rats were dosed orally and blood pressure was measured indirectly at 2 hr after dosing.

In general, hypotensive and antihypertensive activity tends to increase with increasing chain length, reaching optimal values when A is a 4-carbon unit. Examples where A is methylene (11–18) show only low or moderate hypotensive activities.

Compounds 11, 17, and 19 have been previously described,[11] but no pharmacological results were reported. Compounds 19–58 have in common a 2-carbon A chain and can be subdivided into three main categories. Firstly, where A is $CH_2CH_2$, optimum hypotensive activity occurs when $R_1$ is phenyl (19), 3,4-dichlorophenyl (31), 2-naphthyl (34), or cyclohexyl (20). The last example is of particular interest since it is the only compound where $R_1$ is alicyclic rather than aromatic, and it is the only example where A = $CH_2CH_2$ to show good activity in both hypotensive and antihypertensive tests. Other examples with an ethylidene chain to show good antihypertensive activity are 27 ($R_1$ = 2-aminophenyl) and 28 ($R_1$ = 3,4-dimethoxyphenyl). No consistent trend is apparent when A = $CH_2CH_2$ is replaced by A = $COCH_2$ or $CHOHCH_2$. Optimum hypotensive activity for these two chains occurs when $R_1$ = 3,4-dihydroxyphenyl (49) and 1,2,3,4-tetrahydro-6-naphthyl (54), respectively. Finally, good antihypertensive activity occurs in one branched chain example (52) where A = $CH_2CH(CH_3)$.

Considering next those examples where A is a three-atom chain (59–65), good activity in both hypotensive and antihypertensive tests is evident when A = $COCH_2CH_2$ and $R_1$ = phenyl (61). Good hypotensive activity also occurs when A = $CHOHCH_2CH_2$ and $R_1$ = benzodioxan-6-yl (63), whereas good antihypertensive activity results when A = $OCH_2CH_2$ and $R_1$ = phenyl (64).

The highest activities in the series as a whole are found among the four-atom chain compounds (66–100). Good hypotensive activity occurs in two out of three examples where A = $CH_2CH_2CH_2CH_2$ (67, $R_1$ = *p*-fluorophenyl, and 68, $R_1$ = tetrahydronaphthyl), in three out of six examples where A = $CHOHCH_2CH_2CH_2$ (87, $R_1$ = phenyl, *d* enantiomer; 89, $R_1$ = 2-naphthyl; and 90, $R_1$ = tetrahydronaphthyl), in one out of three examples where A = $OCH_2CH_2CH_2$ (94, $R_1$ = 1-naphthyl), and in one out of two examples where A = $:CHCH_2CH_2CH_2$ (100, $R_1$ = di-*p*-fluorophenyl). Within the subdivision A = $COCH_2CH_2CH_2$ (69–85), 75–78 and 85 show good hypotensive activity and 69, 70, 74, and 80 show excellent activity. Of these nine, only one (69, $R_1$ = phenyl) also shows good antihypertensive activity. Another compound where A = $COCH_2CH_2CH_2$ to show good antihypertensive activity (83, $R_2$ = cyclohexanecarbonyl) is only moderately hypotensive.

With respect to $\alpha$-adrenoceptor blocking and antihistamine activities, optimal $pA_2$ values of 8.4 and 9.6 occur when A = $COCH_2CH_2CH_2$ and $R_1$ = chlorophenyl or phenyl, respectively. There is no apparent correlation between $\alpha$-adrenoceptor antagonism and hypotensive or antihypertensive potency.

Optimal hypotensive as well as antihistamine activity in the series as a whole is shown by 1-(3-benzoylpropyl)-4-benzamidopiperidine (69). The corresponding 3-(*p*-chlorobenzoylpropyl) derivative 71 is the most potent $\alpha$-adrenoceptor antagonist in the series.

## Experimental Section

Melting points are uncorrected. Ir spectra supporting the assigned structures were obtained for all compounds. Nmr spectra of representative examples also confirm the structures. C, H, and N analyses were obtained for all compounds and were within ±0.4% of the theoretical values.

**Methods A–C.** The pyridinium salts and 1,2,5,6-tetrahydropyridines in Table I were prepared by standard procedures as described in part 1.[3] Raney nickel catalyzed reduction of the quaternary salts was also carried out as described in part 1.

**Method D. 1-(3-Benzoylpropyl)-4-aminopiperidine (81).** 1-(3-Benzoylpropyl)-4-benzamidopiperidine (69, 0.5 g) was suspended in 5 *N* HCl (10 ml) and refluxed for 6 hr. On cooling, crystals of benzoic acid separated out and were removed by filtration. The filtrate was basified ($K_2CO_3$) and the liberated oil extracted into $CHCl_3$ (2 × 50 ml). The bulked organic extracts were washed with $H_2O$, dried ($MgSO_4$), filtered, and evaporated to give a yellow oil which slowly crystallized (0.30 g, 94%). The crude base was dissolved in a little EtOH and acidified with EtOH–HCl. The resulting 1-(3-benzoylpropyl)-4-aminopiperidine dihydrochloride was filtered off, washed with a little cold EtOH, and dried to give colorless needles (0.38 g).

**Method E. 1-(3-Benzoylpropyl)-4-(3,4-methylenedioxybenzamido)piperidine (82).** Compound 81 (3.19 g, 0.01 mol) was stirred in a mixture of $CHCl_3$ (50 ml) and $H_2O$ (20 ml) in which was dissolved $K_2CO_3$ (8.28 g, 0.006 mol). 3,4-Methylenedioxybenzoyl chloride (1.84 g, 0.01 mol) in $CHCl_3$ (10 ml) was added dropwise over 10 min and stirring continued 6 hr. The organic phase was then separated, washed with $H_2O$, dried ($MgSO_4$), filtered, and evaporated to give a cream solid. This was dissolved in a minimum of EtOH–HCl and $Et_2O$ added to induce crystallization. Filtration afforded colorless needles of 82 hydrochloride three-quarter hydrate (3.88 g).

**Method $F_1$. 1-[2-(1,2,3,4-Tetrahydro-6-naphthyl)-2-oxoethyl]-4-benzamidopiperidine (53).** A solution of 6-chloroacetyl-1,2,3,4-tetrahydronaphthalene (20.87 g, 0.10 mol), 4-benzamidopiperidine (20.40 g, 0.10 mol), and $Et_3N$ (11.1 g, 0.11 mol) in DMF (200 ml) was stirred for 3 days at room temperature. The resulting crystals were collected, washed ($H_2O$), dried, and dissolved in EtOH. Acidification with EtOH–HCl gave 53 hydrochloride (31.3 g).

**Method $F_2$. 1-[2-(*p*-Methoxyphenyl)ethyl]-4-benzamidopiperidine (21).** 2-(*p*-Methoxyphenyl)ethanol *p*-toluenesulfonate ester (1.53 g, 0.005 mol), 4-BAP (1.02 g, 0.005 mol), and anhydrous $K_2CO_3$ (1.10 g, 0.008 mol) were refluxed in 2-PrOH (50 ml) for 8 hr; then the hot mixture was filtered. The product which crystallized on cooling was recrystallized from EtOAc to give 21 (1.17 g).

**Method $F_3$. 1-(3-Benzoyl)propyl-4-benzamidopiperidine (69).** An intimate mixture of 4-BAP (4.08 g, 0.02 mol), $K_2CO_3$ (2.76 g, 0.02 mol), and 4-chlorobutyrophenone (3.64 g, 0.02 mol) was heated on a steam bath with stirring for 1 hr. The resulting solid was washed ($H_2O$), dried, and recrystallized from EtOH–HCl and $Et_2O$ to give 69 hydrochloride quarter-hydrate (3.89 g).

**Method $F_4$. 1-(2-Phenyl)ethyl-4-benzamidopiperidine (19).** 2-Phenylethanol (0.61 g, 0.005 mol), 4-BAP (1.02 g, 0.005 mol), and W7 Raney nickel (*ca.* 2 g) were stirred under reflux in xylene for 16 hr. Liberated $H_2O$ was separated by a Dean and Stark head. Filtration of the hot mixture allowed the product (0.85 g) to crystallize from the filtrate or cooling.

**Method $F_5$. 1-[1-(4-Acetamidophenoxy)-2-hydroxyprop-3-yl]-4-benzamidopiperidine (92).** A solution of 2,3-epoxy-1-(4-acetamidophenoxy)propane (5.18 g, 0.025 mol) and 4-BAP (6.13 g, 0.045 mol) in 2-PrOH (250 ml) was refluxed 24 hr, cooled, and filtered. The resulting solid was recrystallized from 2-PrOH to give 92 quarter-hydrate (7.41 g).

**Method $G_1$. 1-[2-(4-Aminophenyl)ethyl]-4-benzamidopiperidine (24).** Compound 23 (3.0 g) was hydrogenated in absolute EtOH (400 ml) at 3.25 kg/cm² and 20° for 3 hr in the presence of $PtO_2$ (300 mg). The catalyst was filtered off and the filtrate evaporated to give a foam which was crystallized from PhH–*n*-hexane to give 24 (2.3 g).

**Method $G_2$. 1-[2-(4-Acetamidophenyl)ethyl]-4-benzamidopiperidine (25).** Compound 24 (2.3 g) was heated under reflux for 2 hr in $Ac_2O$ (22 ml) and pyridine (100 ml). The solution was kept at 5° for 24 hr; then the crystalline product (1.5 g) was collected, washed ($Et_2O$), and dried.

**Method $G_3$. 1-[2-(3,4-Dihydroxyphenyl)ethyl]-4-benzamidopiperidine (29).** Compound 28 (12.2 g, 0.032 mol) in dry $CH_2Cl_2$ (400 ml) was added dropwise with stirring to $BBr_3$ (40 g, 0.16 mol) in dry $CH_2Cl_2$ (120 ml) at −50°. When the addition was complete, the solution was kept at room temperature for 48 hr; then $H_2O$ (100 ml) was added with stirring. The resulting precipitate was collected and crystallized from EtOH. Recrystallization

**Table II.** 1,4-Disubstituted Piperidines $R_1AN$⟨⟩$—NR_2R_3$

| Compd | $R_1$ | A | $R_2$ | $R_3$ | Crystn solvent | Mp, °C | % yield | Method | Formula | Hypotensive act.[a] | Antihypertensive act.[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **11** | $C_6H_5$ | $CH_2$ | $COC_6H_5$ | H | EtOH–$Et_2O$ | 237 dec | 86 | E | $C_{19}H_{22}N_2O \cdot HCl$ | ++ | |
| **12** | 3,4-$OCH_2O$-$C_6H_3$ | $CH_2$ | $COC_6H_5$ | H | 2-PrOH | 179.5–180.5 | 78 | $F_2$ | $C_{20}H_{22}N_2O_3 \cdot 0.5H_2O$ | + | ++ |
| **13** | 2-OH-5-AcNH-$C_6H_3$ | $CH_2$ | $COC_6H_5$ | H | EtOH | 242 | 36 | I | $C_{21}H_{25}N_3O_3$ | ± | |
| **14** | $C_6H_5$ | $CH_2$ | $COC_6H_{11}$ | H | EtOAc | 158 dec | 72 | E | $C_{19}H_{28}N_2O$ | + | |
| **15** | $C_6H_5$ | $CH_2$ | *f* | H | 2-PrOH | 165 dec | 94 | E | $C_{20}H_{22}N_2O_3$ | + | |
| **16** | $C_6H_5$ | $CH_2$ | $COC_6H_4$-*m*-$OCH_3$ | H | 2-PrOH | 154 dec | 82 | E | $C_{20}H_{24}N_2O_2$ | ± | |
| **17** | $C_6H_5$ | $CH_2$ | $COC_6H_4$-*p*-$CH_3$ | H | 2-PrOH | 161 dec | 67 | E | $C_{20}H_{24}N_2O$ | ± | |
| **18** | $C_6H_5$ | $CH_2$ | $COCH_3$ | H | $H_2O$ | 139–140 | 83 | C | $C_{14}H_{20}N_2O$ | + | |
| **19** | $C_6H_5$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 166–168 | 81 | C, $F_4$ | $C_{20}H_{24}N_2O$ | +++ | |
| **20** | $C_6H_{11}$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 174–175 | 45 | $F_1$ | $C_{20}H_{30}N_2O$ | +++ | +++[g] |
| **21** | 4-$CH_3O$-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOAc | 178 | 69 | $F_2$ | $C_{21}H_{20}N_2O_2$ | ++ | ± |
| **22** | 4-Cl-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | 2-PrOH | 190–195 | 65 | $F_2$ | $C_{20}H_{23}ClN_2$ | ++ | ++ |
| **23** | 4-$NO_2$-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | PhH + P (40) | 209–216 | 99 | $F_2$ | $C_{20}H_{23}N_3O_3$ | + | ± |
| **24** | 4-$NH_2$-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | PhH + *n*-hexane | 193–195 | 85 | $G_1$ | $C_{20}H_{25}N_3O$ | ± | ± |
| **25** | 4-AcNH-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 270–275 | 56 | $G_2$ | $C_{22}H_{27}N_3O_2$ | ++ | ++ |
| **26** | 2-$NO_2$-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 236–241 | 11 | $F_2$ | $C_{20}H_{23}N_3O_3 \cdot HCl$ | ++ | ++[g] |
| **27** | 2-$NH_2$-$C_6H_4$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 264 | 57 | $G_1$ | $C_{20}H_{25}N_3O \cdot 2HCl$ | ++ | +++ |
| **28** | 3,4-$(CH_3O)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 194–195 | 82 | E | $C_{22}H_{28}N_2O_2$ | ± | +++ |
| **29** | 3,4-$(HO)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 265–267 | 24 | $G_3$ | $C_{20}H_{24}N_2O_3 \cdot HBr \cdot 0.5H_2O$ | ± | ±[g] |
| **30** | 3,4,5-$(CH_3O)_3$-$C_6H_2$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 193–194 | 33 | F | $C_{20}H_{30}N_2O_4 \cdot H_2O$ | ++ | +[g] |
| **31** | 3,4-$(Cl)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 286 | 39 | $F_3$ | $C_{20}H_{22}Cl_2N_2O \cdot HCl$ | +++ | + |
| **32** | 2,6-$(Cl)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 286 | 41 | $F_3$ | $C_{20}H_{22}Cl_2N_2O \cdot HCl$ | ± | ± |
| **33** | 1-Naphthyl | $CH_2CH_2$ | $COC_6H_5$ | H | PhH | 160–162 | 66 | $F_1$ | $C_{24}H_{26}N_2O$ | ± | |
| **34** | 2-Naphthyl | $CH_2CH_2$ | $COC_6H_5$ | H | 2-PrOH | 190–193 | 87 | $F_1$ | $C_{24}H_{26}N_2O$ | +++ | + |
| **35** | 1-Indenyl | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 148–149 | 17 | $F_2$ | $C_{23}H_{26}N_2O$ | ++ | |
| **36** | 3,4-$(CH_3)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 276 | 41 | $F_3$ | $C_{22}H_{28}N_2O \cdot HCl \cdot H_2O$ | ++ | + |
| **37** | 3,4-$(CH_3O)_2$-$C_6H_3$ | $CH_2CH_2$ | $COCH_3$ | H | EtOH + $H_2O$ | 152–154 | 65 | C | $C_{17}H_{24}N_2O_3$ | ± | |
| **38** | 3,4-$(CH_3O)_2$-$C_6H_3$ | $CH_2CH_2$ | H | H | EtOH | 260–263 | 60 | D | $C_{15}H_{24}N_2O_2 \cdot 2HCl$ | ± | |
| **39** | 3,4-$(HO)_2$-$C_6H_3$ | $CH_2CH_2$ | H | H | EtOH | 287–290 dec | 51 | $G_3$ | $C_{13}H_{20}N_2O_2 \cdot 2HCl$ | ± | ± |
| **40** | 3,4-$(CH_3O)_2$-$C_6H_3$ | $CH_2CH_2$ | $COC_6H_4$-*o*-Cl | H | EtOH + $Et_2O$ | 250–252 | 49 | E | $C_{22}H_{26}ClN_2O_3 \cdot HCl$ | + | |
| **41** | 3,4-$(CH_3O)_2$-$C_6H_3$ | $CH_2CH_2$ | *f* | H | EtOH + $Et_2O$ | 285–288 | 47 | E | $C_{23}H_{28}N_2O_5 \cdot HCl \cdot 2H_2O$ | ± | ± |
| **42** | 2-Naphthyl | $CH_2CH_2$ | H | H | EtOH | >300 dec | 68 | D | $C_{17}H_{22}N_2 \cdot 2HCl$ | ± | ± |
| **43** | 2-Naphthyl | $CH_2CH_2$ | $COC_6H_{11}$ | H | EtOH + $Et_2O$ | 232–233 | 70 | E | $C_{24}H_{32}N_2O \cdot HCl$ | ++ | ± |
| **44** | 2-Naphthyl | $CH_2CH_2$ | $CO_2C_2H_5$ | H | EtOH + $Et_2O$ | 240 | 40 | E | $C_{20}H_{26}N_2O_2 \cdot HCl$ | | |
| **45** | 2-Naphthyl | $CH_2CH_2$ | H | $CH_3$ | EtOH + $Et_2O$ | 281 | 52 | J | $C_{18}H_{24}N_2 \cdot 2HCl \cdot H_2O$ | | |
| **46** | 2-Naphthyl | $CH_2CH_2$ | $COC_6H_5$ | $CH_3$ | EtOH + $Et_2O$ | 283 | 84 | E | $C_{25}H_{28}N_2O \cdot HCl$ | ++ | ++ |
| **47** | $C_6H_5$ | $COCH_2$ | $COC_6H_5$ | H | 2-PrOH + $H_2O$ | 168 | 49 | $F_2$ | $C_{20}H_{22}N_2O_2$ | ++ | ± |
| **48** | $C_6H_5$ | $CHOHCH_2$ | $COC_6H_5$ | H | MeOH + $H_2O$ | 178–180 | 51 | $H_1$ | $C_{20}H_{24}N_2O_2$ | ++ | ++[g] |
| **49** | 3,4-$(HO)_2$-$C_6H_3$ | $COCH_2$ | $COC_6H_5$ | H | 2-PrOH | 220 dec | 52 | $F_2$ | $C_{20}H_{22}N_2O_4 \cdot 0.25H_2O$ | +++ | + |
| **50** | 3,4-$(Cl)_2$-$C_6H_3$ | $COCH_2$ | $COC_6H_5$ | H | EtOH–$Et_2O$ | 226 | 34 | $F_1$ | $C_{20}H_{20}Cl_2N_2O_2 \cdot HCl$ | ± | |
| **51** | 3,4-$(Cl)_2$-$C_6H_3$ | $CHOHCH_2$ | $COC_6H_5$ | H | EtOH–$Et_2O$ | 270 | 75 | $H_1$ | $C_{20}H_{22}Cl_2N_2O_2 \cdot HCl$ | ± | ± |
| **52** | $C_6H_5$ | $CH_2CH(CH_3)$ | $COC_6H_5$ | H | EtOH | 238 dec | 30 | $F_2$ | $C_{21}H_{26}N_2O \cdot HCl \cdot 0.5H_2O$ | ++ | +++ |
| **53** | 1,2,3,4-H-6-naphthyl | $COCH_2$ | $COC_6H_5$ | H | EtOH | 270 dec | 76 | $F_1$ | $C_{24}H_{28}N_2O_2 \cdot HCl$ | ++ | ± |
| **54** | 1,2,3,4-H-6-naphthyl | $CHOHCH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 253 dec | 71 | $H_1$ | $C_{21}H_{30}N_2O_2 \cdot HCl$ | +++ | ± |
| **55** | 4-HO-$C_6H_4$ | $COCH(CH_3)$ | $COC_6H_5$ | H | EtOH + EtOAc | 224 dec | 60 | $F_3$ | $C_{21}H_{24}N_2O \cdot HCl \cdot 0.5H_2O$ | ± | ± |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **56** | 4-HO-$C_6H_4$ | $CHOHCH(CH_3)$ | $COC_6H_5$ | H | EtOH | >130 dec | 27 | $H_1$ | $C_{21}H_{26}N_2O_3 \cdot HCl \cdot 0.75H_2O$ | + | ± |
| **57** | *c* | $COCH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 153 dec | 24 | $F_2$ | $C_{30}H_{40}N_2O_2$ | ++ | |
| **58** | *c* | $CHOHCH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 253 dec | 78 | $H_1$ | $C_{30}H_{42}N_2O_2 \cdot HCl \cdot H_2O$ | + (+) | ++ |
| **59** | $C_6H_5$ | $CH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 237 | 33 | $F_3$ | $C_{21}H_{26}N_2O \cdot HCl \cdot 0.25H_2O$ | ++ | |
| **60** | 2-Indenyl | $CH_2CH_2CH_2$ | $COC_6H_5$ | H | 2-PrOH | 157–159 | 74 | $F_3$ | $C_{24}H_{28}N_2O$ | ++ | +++ |
| **61** | $C_6H_5$ | $COCH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 194 | 80 | $F_3$ | $C_{21}H_{24}N_2O_2 \cdot HCl$ | +++ | +++ |
| **62** | 3,4-$O(CH_2)_2O$-$C_6H_3$ | $COCH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 198 | 65 | $F_3$ | $C_{23}H_{26}N_2O_4 \cdot HCl \cdot 0.25H_2O$ | + | |
| **63** | 3,4-$O(CH_2)_2O$-$C_6H_3$ | $CHOHCH_2CH_2$ | $COC_6H_5$ | H | MeOH + EtOAc + $Et_2O$ | 193–197 | 45 | $H_1$ | $C_{23}H_{28}N_2O_4 \cdot HCl$ | +++ | + |
| **64** | $C_6H_5$ | $OCH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 207 | 73 | $F_3$ | $C_{20}H_{24}N_2O_2 \cdot HCl$ | ++ | +++ |
| **65** | 2-$CH_3O$-$C_6H_4$ | $OCH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 193 | 77 | $F_3$ | $C_{21}H_{26}N_2O_3 \cdot HCl$ | ++ | ± |
| **66** | $C_6H_5$ | $CH_2CH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 241 | 75 | $F_3$ | $C_{22}H_{28}N_2O \cdot HCl \cdot 0.25H_2O$ | ++ | + |
| **67** | 4-F-$C_6H_4$ | $CH_2CH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 228 | 16 | $H_2$ | $C_{22}H_{27}FN_2O \cdot HCl \cdot 0.5H_2O$ | +++ | +[i] |
| **68** | 1,2,3,4-H-6-naphthyl | $CH_2CH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 250 | 15 | $H_2$ | $C_{26}H_{34}N_2O \cdot HCl \cdot 0.25H_2O$ | +++ | + |
| **69** | $C_6H_5$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 241 | 84 | $F_3$ | $C_{22}H_{26}N_2O_2 \cdot HCl \cdot 0.25H_2O$ | ++++ | +++ |
| **70** | 4-F-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 258 | 26 | $F_1$, $F_3$ | $C_{22}H_{25}FN_2O_2 \cdot HCl$ | ++++ | ++[h] |
| **71** | 4-Cl-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 242–243 | 46 | $F_3$ | $C_{22}H_{25}ClN_2O_2 \cdot HCl$ | ++ | + |
| **72** | 4-Br-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 268 | 72 | $F_3$ | $C_{22}H_{25}BrN_2O_2 \cdot HCl$ | + | ± |
| **73** | 4-$CH_3O$-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 225 | 47 | $F_3$ | $C_{23}H_{23}N_3O_3 \cdot HCl \cdot H_2O$ | ++ | ++ |
| **74** | 4-$(CH_3)_3C$-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 268 | 53 | $F_3$ | $C_{26}H_{34}N_2O_2 \cdot HCl$ | ++++ | ± |
| **75** | 2,4-$(CH_3)_2$-$C_6H_3$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 215 | 43 | $F_3$ | $C_{24}H_{30}N_2O_2 \cdot HCl$ | +++ | ± |
| **76** | 2,5-$(CH_3)_2$-$C_6H_3$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 190 | 42 | $F_3$ | $C_{24}H_{30}N_2O_2 \cdot HCl$ | +++ | ± |
| **77** | 2-Naphthyl | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 251 | 39 | $F_3$ | $C_{26}H_{28}N_2O_2 \cdot HCl \cdot 0.75H_2O$ | +++ | + |
| **78** | 1,2,3,4-H-6-naphthyl | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 221 | 38 | $F_3$ | $C_{26}H_{32}N_2O_2 \cdot HCl \cdot H_2O$ | +++ | ± |
| **79** | 4-HO-$C_6H_4$ | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | 2-PrOH + EtOH | 276 | 43 | $F_1$ | $C_{22}H_{26}N_2O_3 \cdot HCl$ | + | + |
| **80** | *d* | $COCH_2CH_2CH_2$ | $COC_6H_5$ | H | MeOH + EtOAc | 207 | 11 | $G_4$ | $C_{28}H_{39}N_3O_4 \cdot 2HCl \cdot H_2O$ | ++++ | + |
| **81** | $C_6H_5$ | $COCH_2CH_2CH_2$ | H | H | EtOH | 276 | 91 | D | $C_{15}H_{22}N_2O \cdot 2HCl$ | ± | ± |
| **82** | $C_6H_5$ | $COCH_2CH_2CH_2$ | *f* | H | EtOH + $Et_2O$ | 236 | 88 | E | $C_{23}H_{26}N_2O_4 \cdot HCl \cdot 0.75H_2O$ | ++ | ± |
| **83** | $C_6H_5$ | $COCH_2CH_2CH_2$ | $COC_6H_{11}$ | H | MeOH + $Et_2O$ | 231 | 57 | E | $C_{22}H_{32}N_2O_2 \cdot HCl \cdot 0.5H_2O$ | ++ | +++ |
| **84** | $C_6H_5$ | $COCH_2CH_2CH_2$ | $COC_6H_4$-*p*-Cl | H | EtOH | 261 | 81 | E | $C_{22}H_{25}ClN_2O_2 \cdot HCl$ | ++ | + |
| **85** | $C_6H_5$ | $COCH_2CH_2CH_2$ | $CO_2C_2H_5$ | H | EtOH + $Et_2O$ | 221 | 39 | E | $C_{18}H_{26}N_2O_3 \cdot HCl \cdot 0.25H_2O$ | +++ | |
| **86** | $C_6H_5$ | $CHOHCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 221 | 56 | $H_1$ | $C_{22}H_{28}N_2O_2 \cdot HCl$ | ++ | ++ |
| **87** | $C_6H_5$[e] | $CHOHCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 238 | | L | $C_{22}H_{28}N_2O_2 \cdot HCl$ | +++ | |
| **88** | 4-F-$C_6H_4$ | $CHOHCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 241 dec | 49 | $H_1$ | $C_{22}H_{27}FN_2O_2 \cdot HCl$ | ++ | ++ |
| **89** | 2-Naphthyl | $CHOHCH_2CH_2CH_2$ | $COC_6H_5$ | H | MeOH + EtOAc | 241 | 54 | $H_1$ | $C_{26}H_{30}N_2O_2 \cdot HCl \cdot 0.5H_2O$ | +++ | + |
| **90** | 1,2,3,4-H-6-naphthyl | $CHOHCH_2CH_2CH_2$ | $COC_6H_5$ | H | MeOH + EtOAc | 239 | 84 | $H_1$ | $C_{26}H_{34}N_2O_2 \cdot HCl \cdot 0.25H_2O$ | +++ | ± |
| **91** | $C_6H_5$ | $CHOHCH_2CH_2CH_2$ | H | $CH_3$ | EtOH | 196 | 50 | J | $C_{16}H_{26}N_2O \cdot 2HCl$ | | |
| **92** | 4-AcNH-$C_6H_4$ | $OCH_2CHOHCH_2$ | $COC_6H_5$ | H | 2-PrOH | 226–228 | 54 | $F_5$ | $C_{23}H_{29}N_3O_4 \cdot 0.25H_2O$ | ± | |
| **93** | 1-Naphthyl | $OCH_2CHOHCH_2$ | $COC_6H_5$ | H | EtOH + $H_2O$ | 139–141 | 84 | $F_3$ | $C_{25}H_{25}N_2O_3$ | ++ | ± |
| **94** | 1-Naphthyl | $OCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 228 dec | 53 | $F_1$ | $C_{25}H_{28}N_2O_3 \cdot HCl$ | +++ | + |
| **95** | 2-$CH_3$-$C_6H_4$ | $NHCOCH_2CH_2$ | $COC_6H_5$ | H | 2-PrOH | 195–197 | 65 | $F_2$ | $C_{22}H_{27}N_3O_2$ | ± | |
| **96** | 2-$CH_3$-$C_6H_4$ | $NHCOCH_2CH_2$ | H | H | 2-PrOH | 208–210 | 67 | C | $C_{15}H_{23}N_3O \cdot 2HCl \cdot H_2O$ | ± | |
| **97** | $(C_6H_5)_2$ | $:C:CHCH_2CH_2$ | $COC_6H_5$ | H | EtOH | 220–230 dec | 38 | $F_3$ | $C_{28}H_{30}N_2O \cdot HCl \cdot 0.25H_2O$ | ++ | + |
| **98** | $(4\text{-F-}C_5H_4)_2$ | $:C:CHCH_2CH_2$ | $COC_6H_5$ | H | EtOH | 273 | 28 | $F_3$ | $C_{28}H_{28}F_2N_2O \cdot HCl \cdot 0.5H_2O$ | + | |
| **99** | $(C_6H_5)_2$ | $:CHCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH | 269 | 62 | $H_3$ | $C_{28}H_{32}N_2O \cdot HCl$ | ++ | + |
| **100** | $(4\text{-F-}C_6H_4)_2$ | $:CHCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 257 | 31 | $H_3$ | $C_{28}H_{30}F_2N_2O \cdot HCl$ | +++ | + |
| **101** | $C_6H_5$ | $COCH_2CH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + EtOAc | 230 | 47 | $F_3$ | $C_{23}H_{28}N_2O_2 \cdot HCl$ | ++ | ++ |
| **102** | $C_6H_5$ | $NHCOCH_2CH_2CH_2$ | $COC_6H_5$ | H | EtOH + $Et_2O$ | 203 | 67 | K | $C_{22}H_{27}N_3O_2 \cdot HCl \cdot 0.5H_2O$ | ++ | |

[a]Cumulative iv doses producing a fall in diastolic blood pressure of 30 mm or more, sustained for at least 15 min: 0.8 mg/kg, ++++; 1.6 or 3.2 mg/kg, +++; 6.4 or 12.8 mg/kg, ++; 25.6 mg/kg, +. Falls of <30 mm, ±. [b]Falls in systolic blood pressure 2 hr after an oral dose of 40 mg/kg: >50 mm, +++; 50–30 mm, ++; 30–15 mm, +; <15 mm, ±. [c]$R_1$ = 5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl. [d]$R_1$ = 4-(2-hydroxy-*N*-isopropylaminopropoxy)phenyl. [e]*d* enantiomer. [f]$R_2$ = 3,4-methylenedioxybenzoyl. [g]Oral dose of 75 mg/kg. [h]Oral dose of 10 mg/kg. [i]Oral dose of 2.5 mg/kg.

**Table III**

| Compd | α blockade $pA_2$ | Antihistamine $pA_2$ | Compd | α blockade $pA_2$ | Antihistamine $pA_2$ |
|---|---|---|---|---|---|
| **19** | | 7.1 | **74** | 6.6 | |
| **31** | 7.35 | 8.4 | **75** | 7.2 | 8.0 |
| **34** | 7.4 | 7.6 | **76** | 7.5 | 7.7 |
| **47** | 5.8 | | **78** | 6.9 | |
| **48** | 6.6 | | **79** | 7.0 | 8.9 |
| **59** | 7.1 | 8.6 | **80** | 8.1 | |
| **60** | 7.4 | | **82** | 6.4 | |
| **61** | 6.6 | | **83** | 6.9 | |
| **63** | 6.6 | | **88** | 6.6 | 6.5 |
| **64** | 5.9 | | **90** | 6.05 | 7.0 |
| **66** | 6.95 | 7.4 | **92** | | 7.0 |
| **67** | 6.4 | 7.5 | **100** | 5.9 | |
| **68** | 6.6 | | Phentolamine | 7.6 | 5.5 |
| **69** | 7.7 | 9.6 | Thymoxamine | 6.9 | 6.7 |
| **70** | 7.5 | 8.6 | Chloropheniramine | <6.9 | 8.9 |
| **71** | 8.4 | 7.7 | Indoramin | 7.4 | 8.2 |
| **72** | 6.9 | | | | |

from EtOH-$Et_2O$ gave **29** hydrobromide hemihydrate (6.0 g).

**Method $G_4$. 1-[3-[4-[2-Hydroxy-3-(*N*-isopropylamino)propoxy]benzoyl]propyl]-4-benzamidopiperidine (80).** Compound **79** (12.06 g, 0.03 mol), 1-chloro-3-isopropylaminopropan-2-ol (4.55 g, 0.03 mol), 10 *N* NaOH (9 ml, 0.09 mol), and EtOH (150 ml) were refluxed for 2 days. The mixture was filtered hot and the filtrate was evaporated to dryness. The resulting foam was heated with 2 *N* NaOH solution (150 ml) on a steam bath for 10 min; then the mixture was allowed to stand overnight and the resulting solid was collected, washed ($H_2O$), and dried. The base was dissolved in MeOH and made just acid with HCl, and EtOAc was added to induce crystallization of **80** dihydrochloride monohydrate (1.85 g).

**Method $H_1$. 1-[2-(3,4-Dichlorophenyl)-2-hydroxyethyl]-4-benzamidopiperidine (51).** $NaBH_4$ (15.0 g, 0.395 mol) in 0.2 *N* NaOH solution (200 ml) was added during 30 min to a stirred solution of compound **50** (6.45 g, 0.015 mol) in MeOH (260 ml). Stirring was continued for 3 days; then the mixture was refluxed for 2 hr. Filtration of the hot mixture gave 4.83 g of **51** base which was crystallized from EtOH-HCl and $Et_2O$ to give **51** hydrochloride (4.86 g).

**Method $H_2$. 1-[4-(4-Fluorophenyl)butyl]-4-benzamidopiperidine (67).** Hydrazine hydrate (80%, 60 ml, 1.0 mol) was added to compound **70** (11.08 g, 0.03 mol, free base) in ethylene glycol (125 ml) and the solution was heated under reflux for 1 hr. KOH (6.0 g, 0.11 mol) was added and excess $H_2O$ and $NH_2NH_2$ were distilled off until the internal temperature reached 185°. Refluxing was continued at this temperature for 30 min; then the hot solution was poured into cold $H_2O$ (500 ml). The resulting precipitate was collected and twice recrystallized from EtOH-HCl and $Et_2O$ to give **67** hydrochloride hemihydrate (1.85 g).

**Method $H_3$. 1-(4,4-Diphenylbutyl)-4-benzamidopiperidine (99).** Compound **97** (4.1 g) in MeOH (250 ml) containing 10% Pd/C (500 mg) was hydrogenated at 3.25 kg/cm² and 50° for 24 hr. The catalyst was filtered off and the residue after evaporation of the filtrate was crystallized from EtOH-HCl to give **99** hydrochloride (2.8 g).

**Method I. 1-(5-Acetamido-2-hydroxybenzyl)-4-benzamidopiperidine (13).** 4-Acetamidophenol (1.51 g, 0.01 mol) and 39.4% aqueous formaldehyde (1.25 ml, 0.017 mol) were dissolved in 50% aqueous EtOH, and 4-BAP (2.04 g, 0.01 mol) was added. The resulting solution was heated under reflux for 30 min and then left overnight at room temperature. The solid was collected and purified by suspending in boiling EtOH and filtering to give **13** (1.32 g).

**Method J. 4-Methylamino-1-(2-naphth-2-ylethyl)piperidine (45).** Compound **44** (6.5 g, 0.02 mol, free base) was dissolved in 1,2-dimethoxyethane (DME, 200 ml) and added during 60 min to a stirred suspension of $LiAlH_4$ (4 g, 0.1 mol) in DME (100 ml). After refluxing for 4 hr, the reaction mixture was cooled and water (12 ml) was added cautiously. The inorganic precipitate was filtered off and washed well (DME), and the filtrate and washings were evaporated to give the base which was converted to **45** dihydrochloride hydrate (3.7 g).

**Method K. *N*-Phenyl-4-(4-benzamidopiperid-1-yl)butyramide (102).** 4-Benzamido-1-(3-methoxycarbonyl)propylpiperidine (5.0 g, prepared from 4-BAP by method $F_3$) was refluxed in freshly redistilled aniline (25 ml) under $N_2$ for 18 hr. Filtration of the cooled mixture afforded the free base which was recrystallized from EtOH-HCl and $Et_2O$ to give **102** hydrochloride hemihydrate (4.5 g).

**Method L. (+)-1-(4-Phenyl-4-hydroxybutyl)-4-benzamidopiperidine (87).** Compound **86** was resolved using (−)-di-*O*,*O*-*p*-toluoyltartaric acid, and the *d* enantiomer ($[\alpha]^{20}D$ +15.3°) was converted to the hydrochloride.

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## References

(1) J. L. Archibald and G. A. Benke, *J. Med. Chem.*, **17**, 736 (1974).
(2) J. L. Archibald, *Chim. Ther.*, **3**, 397 (1968).
(3) J. L. Archibald, B. J. Alps, J. F. Cavalla, and J. L. Jackson, *J. Med. Chem.*, **14**, 1054 (1971).
(4) R. B. Royds, *Brit. J. Pharmacol.*, 44, 379P (1972).
(5) C. T. Dollery, C. F. George, and P. J. Lewis, *Brit. J. Pharmacol.*, 46, 542P (1972).
(6) A. J. Boakes, B. N. C. Prichard, and P. C. Teoh, *Brit. J. Pharmacol.*, 44, 378P (1972).
(7) D. J. Coltart, J. D. F. Lockhart, R. B. Royds, and P. Turner, *Brit. J. Pharmacol.*, **43**, 467P (1971).
(8) T. Baum and A. T. Shropshire, *Amer. J. Physiol.*, **212**, 1020 (1967).
(9) O. Arunlakshana and H. O. Schild, *Brit. J. Pharmacol. Chemother.*, **14**, 48 (1959).
(10) B. J. Alps, M. Hill, E. S. Johnson, and A. B. Wilson, *Brit. J. Pharmacol.*, 44, 52 (1972).
(11) N. J. Harper and C. F. Chignell, *J. Med. Chem.*, 7, 729 (1964).