left lever (L) was correct when LSD was administered. The conditions were reversed for the other group.

From the first discrimination session onward, an injection of either LSD or saline was given prior to the session. Discrimination training was carried out 7 days per week. Initially rats were shaped to press the left lever, which was programmed to deliver a food pellet for each lever press (FR1). Once the rats acquired the lever-pressing response, the number of responses required for the delivery of the pellet was gradually increased until a fixed ratio of 32 (FR32, one reinforcement for every 32 lever presses) was achieved. Initially, only responding on the left lever was reinforced, so half the rats received saline and the other half received LSD.

Once three consecutive days of training on the FR32 schedule with a criteria of 85% correct responding on the left lever had been achieved, responding on the left lever was made inconsequential and the right lever was activated for the second phase. At this time, the rats that originally received LSD, received saline, and the rats that originally received saline, now received LSD. Discrimination training was again carried on until the rats were responding on the drug-appropriate lever on a FR32 schedule of reinforcement.

The third and final phase of discrimination training involved administration of the first training drug (either LSD or SAL) for 3 consecutive daily sessions, followed by administration of the second training drug for 3 more daily sessions. Following this, the first drug was again administered for 3 consecutive days, followed by the second drug for 2 more days. Finally, the first training drug was administered for 2 days. If responding during this last phase of discrimination training fulfilled the criteria of 85% responding on the appropriate lever, the stimulus generalization test procedure was initiated. If not, the rats were kept on discrimination training until the criterion was achieved.

Stimulus Generalization. The drug discrimination training required 5–6 weeks. Those rats that also successfully met the criteria of 85% correct responses on the appropriate levers in the final phase were included in the stimulus generalization procedure. During this phase of the study, test sesions were run on Wednesdays and Saturdays, with training sessions conducted on Monday, Tuesday, Thursday, and Friday. All injections were given 30 min before the session. The animals received no

treatment on Sundays. In order to receive a test drug on Wednesday or Saturday, the animals were required to satisfy the 85% correct lever response criteria on both preceding training days. If the criterion was not satisfied, the testing session was used as a training session. The rates of responding for the LSD and saline training sessions were not significantly different.

During all phases of the experiment, the training sessions were of 15-min duration, and lever responses on both levers were recorded and the results were expressed as percent responding on the appropriate lever. On testing days, the session was terminated following 32 responses on either lever. No reinforcement was given. This was designated the lever selected by the rat in response to the drug cue. In all cases, responding on the incorrect lever had no programmed consequence.

Several preliminary experiments to determine appropriate dosages to use for new compounds were carried out; these data were discarded. Based on these initial experiments, dosages were selected for each test compound. The drug treatments in this study, including LSD, were randomized over the entire experimental period.

Data Analysis. An ED_{50} was calculated for LSD and for each test compound by the method of Litchfield and Wilcoxon.[16] This was defined as the dose at which responses were equally distributed on the drug and saline appropriate levers.

Registry No. 2, 89556-64-9; 2 (free base), 89556-70-7; 3, 89556-69-4; 3 (free base), 89556-71-8; 4, 150-78-7; 5, 79-30-1; 6, 89556-60-5; 7, 26172-15-6; 8, 35205-30-2; 9, 89556-61-6; 10, 89556-62-7; 11, 89556-63-8; 12, 1201-38-3; 13, 89556-65-0; 14, 72648-95-4; 15, 89556-66-1; 16, 13620-78-5; 17, 89556-67-2; 18, 89556-68-3; EtNO$_2$, 79-24-3; EtBr, 74-96-4.

(16) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* 1949, *96*, 99.

Synthesis of a Novel Series of (Aryloxy)propanolamines: New Selective β₂-Blocking Agents

Marie-Christiane Carré,[†] Alphonse Youlassani,[†] Paul Caubère,*,[†] Anne Saint-Aubin-Floch,[‡] Marie Blanc,[‡] and Charles Advenier[‡]

Laboratoire de Chimie Organique I, ERA CNRS 476, Université de Nancy I, B.P. 239, 54506 Vandoeuvre les Nancy Cédex, and Laboratoire de Pharmacologie, Faculté de Médecine Paris-Ouest, 75270 Paris Cedex 06, France. Received July 19, 1983

A new family of β-blocking drugs is described. The originality of the new molecules lies in their functionalized hydrophobic folded structure, the basic part of which contains a benzocyclobutene ring. Excellent β₂-blocker selectivity has been obtained with some of these compounds. Interestingly, this selectivity was not modified toward β₁-blocker activity by introduction of the usual β₁ inducer groups.

β-Adrenoceptor blocking drugs have proved to be the most important advance in the pharmacotherapy of serious and widespread cardiovascular diseases.[1] They also have much to offer as therapy for some other serious clinical disorders.[2] However, β-blockers are far from being devoid of toxic or adverse effects.[3] These properties explain the constant efforts made to find new selective drugs.

Motivations other than therapeutic ones also explain the number of works presently devoted to the development

of new β antagonists. Indeed, the different clinical events mentioned above are related to whether or not the drugs are selective for β₁ and β₂ adrenoceptors, as well as to whether or not they possess membrane-stabilizing qualities and/or intrinsic sympathomimetic activities. Knowledge of the behavior of the adrenergic system, as well as the

†Université de Nancy I.
‡Faculté de Medecine Paris-Ouest.

(1) Benaim, R.; Sevan, Cl.; Witchitz, S. *Cah. Med. (Villeurbanne, Fr.)* 1980, *5*(17), 1003–1014.
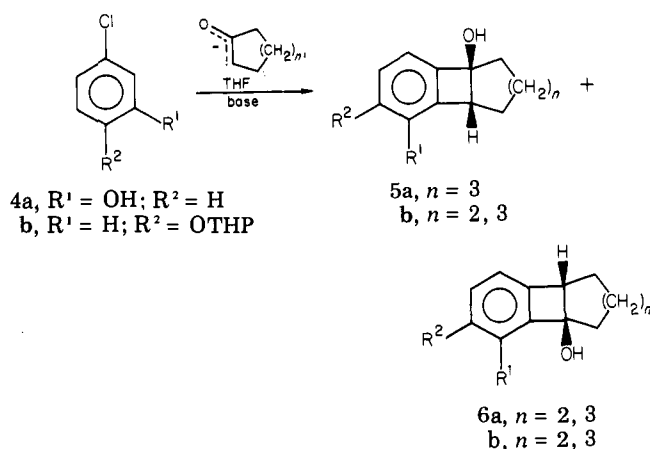(2) Frishman, W. H. *New. Engl. J. Med.* 1981, *305*, 500–506.
(3) Heikkila, J.; Jounela, A.; Katila, M.; Lusmanmäki, K.; Frick, M. H. *Ann. Clin. Res.* 1979, *11*, 267–289.

Scheme I

4a, R^1 = OH; R^2 = H
 b, R^1 = H; R^2 = OTHP

5a, n = 3
 b, n = 2, 3

6a, n = 2, 3
 b, n = 2, 3

Scheme II

7, 1-OH; n = 2, 3
8, 2-OH; n = 2, 3

1-substituted
9a, R = i-Pr; n = 2
 b, R = i-Pr; n = 3
 c, R = t-Bu; n = 3
 d, R = 3,4-(CH$_3$O)$_2$C$_6$H$_3$CH$_2$CH$_2$; n = 3
2-substituted
10a, R = i-Pr; n = 2
 b, R = t-Bu; n = 2
 c, R = i-Pr; n = 3
 d, R = t-Bu; n = 3

^{a} HCl-MeCOMe. ^{b} Ac$_2$O-pyridine. ^{c} H$_2$O (see Experimental Section). ^{d} H$_2$, Pd/C. ^{e} LiAlH$_4$-ether. 2-(ClCH$_2$)-c-OC$_2$H$_3$. ^{g} RNH$_2$.

determination of drug structure–activity correlations, necessitates having a spectrum of substrates as wide as possible to allow a good analysis of the pharmacological mechanisms. From the literature data,[4] it appears that while numerous β_1-blocking agents are presently known, only a few selective β_2 blockers are described.
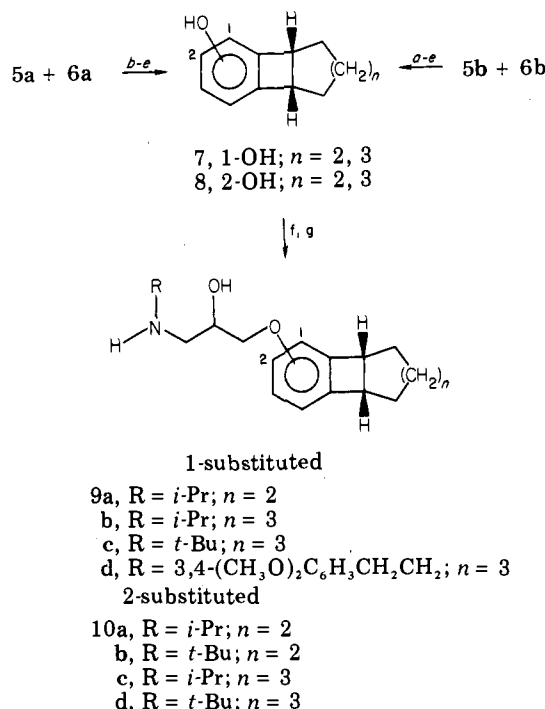
In regard to the chemical aspect of β-blockers, it appears that arylethanolamines and, above all, (aryloxy)-propanolamines are particularly efficient as β-blocking drugs. Most of the hundreds of publications devoted to (aryloxy)propanolamines are focused on modification of the amino part of the molecule and on introduction of usual substituting groups (halogen, OH, CON<, etc.) on the aromatic ring. Only a very few investigations are concerned with the contribution that could be introduced by the presence of a hydrophobic group placed outside of the aromatic plane and in the neighborhood of the oxy-propanolamine group.

However, the literature gives some indications that such an approach to the design of new β-blockers could be of interest. For example, in FM 24 (**1**)[5] and penbutolol (**2**),[6]

1

2

3
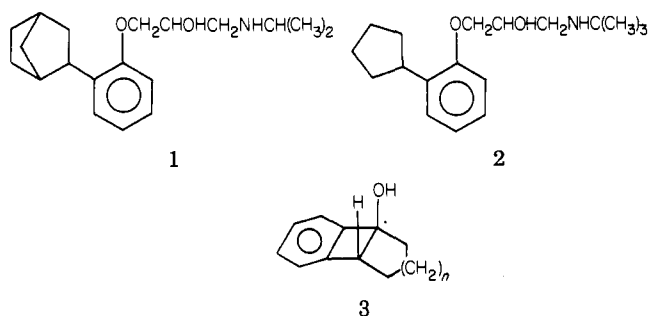
the hydrophobic ortho substitution seems to give some

special properties, such as a long-lasting action, to the molecules. Furthermore, for some years we have been developing the synthesis of new compounds (**3**), some of the derivatives of which have shown anticonvulsant properties.[7]

We thought that it could be of interest to use **3** as a basic structure for the preparation of new (aryloxy)propanol-amines and for studying the influence of the hydrophobic ring, situated outside of the plane of the aromatic ring, on their possible β-blocking activity. In this paper we describe the first results obtained in this way, which lead to new selective β_2-blocking agents.

Synthesis. The key intermediates for the synthesis of the new (aryloxy)propanolamines were the alcohols **5** and **6**, which were directly obtained as a mixture by cyclo-addition of an aryne to a ketone enolate[8] on the suitable aromatic halide (Scheme I). These reactions easily took place directly from m-chlorophenol. In contrast, good results were obtained from p-chlorophenol only if the hydroxyl group was protected. Finally, comparison of NaNH$_2$ with the complex base[9] NaNH$_2$-Bu^{t}ONa for the generation of the aryne showed that the complex base gave the best results.

The preparation of **9** and **10** (Scheme II) merits some comments. During the dehydration of alcohols **5** and **6**, reproducible formation of the unstable alkenic interme-diates was obtained only when the phenolic hydroxyl group was protected as an acetate. The nature of the dehydrating reagent must also be carefully chosen. Indeed, while classical p-toluenesulfonic acid led to good results with the acetates of **5b** (n = 3) and **6b** (n = 3), the other substrates

(4) (a) Levy, B. *J. Pharmacol. Exp. Ther.* **1966**, *151*, 413–422. (b) Levy, B.; Wilkenfeld, B. E. *Eur. J. Pharmacol.* **1969**, *5*, 227–234. (c) Imbs, J. L.; Miesch, F.; Schwartz, J.; Velly, J.; Leclerc, G.; Mann, A.; Wermuth, C. G. *Br. J. Pharmacol.* **1977**, *60*, 357–362. (d) Bilski, A.; Dorries, S.; Fitzgerard, J. D.; Jessup, R.; Tucker, H.; Wale, J. *Br. J. Pharmacol.* **1980**, *69*, 292P–293P. (e) Tattersfield, A. E.; Cragg, D. J. B. *Br. J. Clin. Pharmacol.*, in press. (f) Jung, O. L. *N. Engl. J. Med.* **1979**, *301*, 1005. (g) Nathanson, J. A. *Br. J. Pharmacol.* **1981**, *73*, 97–100.

(5) Le Fur, G.; Schmelck, P. H.; Geynet, P.; Hanoune, J.; Uzan, A. *Life Sci.* **1978**, *23*, 1841–1850. Hardy, J. C.; Villatte, G.; Gueremy, C. *Bull. Soc. Chim. Fr.* **1982**, 304–308 and references cited therein.

(6) Sakurai, Masao; Nagata, Katsuyoshi; Komine, Isamu; Inoue, Tsutomu; Fujimoto, Kazumi *Chem. Abstr.* **1982**, *96*, 115821*t*, 115822*u*.

(7) Carre, M. C.; Caubere, P.; Trockle, G.; Jacque, M. *Eur. J. Med. Chem.* **1977**, *12*, 577. Trockle, G.; Catau, G.; Barberi, C.; Jacque, M.; Carre, M. C.; Caubere, P. *Life Sci.* **1981**, *28*, 23.

(8) Ibrahim, M. Thèse 3e cycle, Université de Nancy, 1981, CDST Centre National de la Recherche Scientifique.

(9) Caubere, P. *Top. Curr. Chem.* **1978**, *73*, 50, and references cited therein.

Scheme III

11

12

13
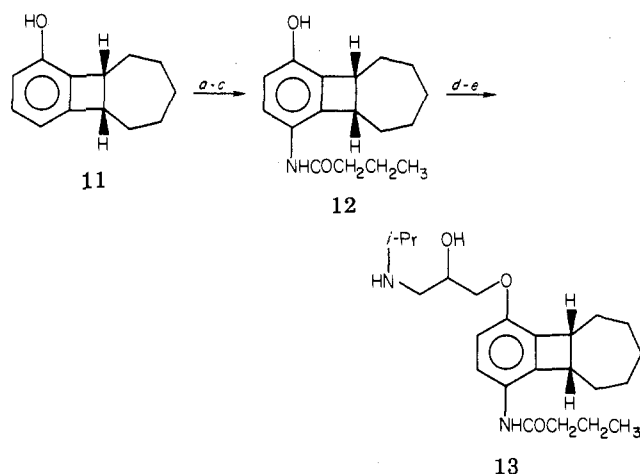
^{a} Fuming HNO_3, CH_2Cl_2. ^{b} H_2, Pd/C, AcOEt.
^{c} $(CH_3CH_2CH_2CO)_2O$-acetone. ^{d} 2-($ClCH_2$)-c-OC_2H_3.
^{e} i-$PrNH_2$.

Scheme IV

14a, R = t-Bu; n = 2
   b, R = i-Pr; n = 3
   c, R = t-Bu; n = 3
   d, R = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2$; n = 3

15a, R = i-Pr
   b, R = t-Bu
   c, R = 3,4-$(CH_3O)_2C_6H_3CH_2CH_2$

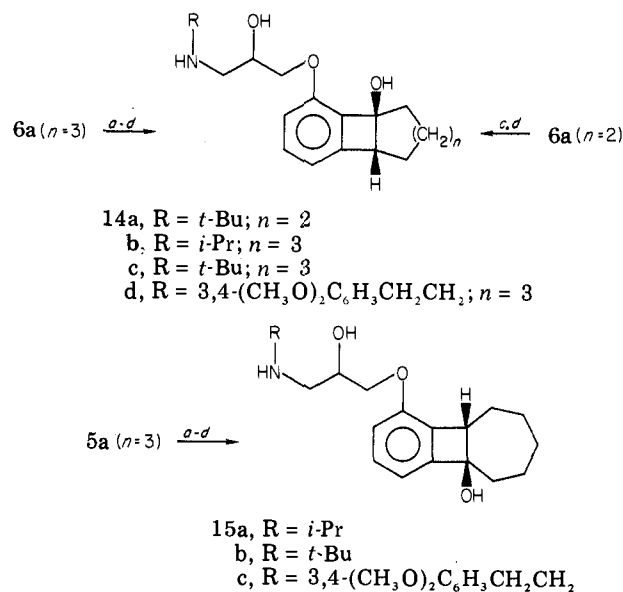^{a} Ac_2O-pyridine. ^{b} $LiAlH_4$-Et_2O. ^{c} 2-($ClCH_2$)-c-OC_2H_3. ^{d} RNH_2.

necessitated the use of $POCl_3$-pyridine or Burgess's salt.[10] After the double bond was hydrogenated and the protecting acetate was removed, the phenolic precursors were reacted with epichlorohydrin in an alkaline medium, and the resulting 1,2-epoxy-3-phenoxypropane was then aminated with the chosen amine.

Butyramide derivative 13 was obtained from 11 (prepared as described above) according to Scheme III. The nitration led to a mixture of ortho/para isomers (40:60), which were easily separated by silica gel column chromatography. The other steps are classical and merit no special comments (details are given in the Experimental Section).

Preparation of 14 and 15 (Scheme IV) necessitated the preparation of the corresponding pure alcohols 6a and 5a (n = 3), which could not be separated as such from the mixture obtained after the arynic condensation (Scheme I). However, the acetates obtained by selective acetylation of the phenolic function (vide supra) were easily separated by silica gel column chromatography. After separation, the alcohols were quantitatively recovered by $LiAlH_4$ reduction. They were selectively transformed into the corresponding phenoxypropanolamine as described above.

The nature of the ring junction of compounds 5 and 6 may be deduced from our previous work.[9,11] Indeed, the NMR spectra of benzocyclobutenols derived from cyclohexanone showed a triplet between 3.12 and 3.40 ppm for the benzylic proton. For those obtained from cycloheptanone, the benzylic proton appeared as a broad signal between 3.10 and 3.60 ppm. The assignment of the cis junction in both cases was confirmed by an X-ray diffraction study of p-bromobenzoates of the simplest alcohols, 3 (n = 2, 3).[12a,b] On the other hand, photocyclization of benzocyclodecenones[13] led to the formation of the cis and trans alcohols 3 (n = 4): the trans product showed a benzylic proton signal at a much lower field than the cis alcohol.

In the present study, all the signals for the benzylic protons of alcohols 5 and 6 (n = 2) appeared as triplets between 3.10 and 3.40 ppm, whereas those of 5 and 6 (n = 3) appeared as broad signals between 3.10 and 3.60 ppm; thus, it must be concluded that alcohols 5 and 6 exhibit a cis junction. Note that this is in agreement with the cis attack of ketone enolates on benzyne.[11a,14]

The stereochemistry of alcohol 11 was determined by X-ray diffraction.[15] Its spectral data were used to determine the stereochemistry of the phenolic precursors 7 and 8.

The (aryloxy)propanolamines were produced as mixtures of diastereoisomers. The diastereoisomeric pairs did not show separation by TLC, and therefore it was not possible to assay the relative compositions of these isomers mixtures. No conditions (chromatography or recrystallization) were found for effecting separation into individual diastereoisomers. Accordingly, these compounds were evaluated as mixtures for their β-blocking activity.

Pharmacological Results and Discussion

With the aim of determining the activity of these compounds for β_1- or β_2-adrenoceptor subtypes, we carried out our studies with pharmacological models to show receptor specificity, i.e., isoproterenol-induced hypotension (β_2 receptors) and tachycardia (β_1 receptors), in anesthetized guinea pigs, on the one hand, and against the relaxing effects of isoproterenol on acetylcholine-precontracted, guinea pig, isolated trachea, on the other hand. The results are presented in Table I. These data show that the compounds described herein are endowed with selective antagonistic effects on β_2 adrenoceptors. The most interesting substances prove to be 9b and 15a, which show strong activity against isoproterenol-induced hypotension, compared to propranolol, and have selective affinity for β_2 adrenoceptors, especially at the tracheal level.

In this latter model, only compounds 9b and 15a, like propranolol, exert competitive antagonism against isoproterenol-induced relaxation; thus, experiments performed under these conditions furnish the following data

(10) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(11) (a) Mourad, M. S. Thèse d'Etat, Université de Nancy, 1974, CNRS no. A.O. 9673. (b) Guillaumet, G. Thèse d'Etat, Université de Nancy, 1972, CNRS no. A.O. 7643.

(12) (a) Courtois, A.; Protas, J.; Guillaumet, G.; Caubere, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1973**, *276*, 407. (b) Courtois, A.; Protas, J.; Guillaumet, G.; Caubere, P. *Ibid.* **1973**, *276*, 1173.

(13) Carre, M. C.; Viriot-Villaume, M. L.; Caubere, P. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2542-2549.

(14) Caubere, P.; Guillaumet, G.; Mourad, M. S. *Tetrahedron* **1973**, *29*, 1857-1863.

(15) Courtois, A.; Pesme, V., to be published.

Table I. Physical and Pharmacological Properties of (Aryloxy)propanolamine Derivatives

compd	n	R	yield,[a] %	salt	mp, °C	formula[b]	in vivo experiments act.: $ED_{50} \pm SEM$, mg/kg DBP	HR	act. vs. propranolol[c] DBP	HR	selectivity ratio: $ED_{50}(HR)/ED_{50}$ (DBP)	in vitro experiments: isolated guinea pig trachea $EC_{50} \pm SEM$, M^d	act.[c] vs. propranolol
9a	2	i-Pr	68	oxalate	110	$C_{20}H_{29}O_6N \cdot 0.5H_2O^e$	0.11 ± 0.02	>3	1.00			(7.00 ± 1.21) × 10^{-8}	0.14
9b	3	i-Pr	72	oxalate	146	$C_{19}H_{29}O_2N$	0.056 ± 0.014	0.89 ± 0.06	1.96	0.46	15.90	(2.00 ± 0.41) × 10^{-9}	5.00
9c	3	t-Bu	46	oxalate	156	$C_{20}H_{31}O_2N$	0.26 ± 0.07	0.70 ± 0.11	0.42	0.57	2.70	(4.57 ± 0.88) × 10^{-8}	0.22
9d	3	2-[3,4-(MeO)₂Ph]Et	42	base	99	$C_{26}H_{35}O_4N$	3.00 ± 0.37	>10	0.03			(1.10 ± 0.40) × 10^{-6}	0.01
10a	2	i-Pr	78	oxalate	128	$C_{18}H_{27}O_2N$	5.30 ± 0.84	>10	0.02			(5.02 ± 1.02) × 10^{-7}	0.02
10b	2	t-Bu	80	oxalate	138-140	$C_{21}H_{31}O_6N^f$	1.58 ± 0.17	>3	0.06			(2.01 ± 0.56) × 10^{-7}	0.05
10c	3	i-Pr	81	oxalate	134	$C_{19}H_{29}O_2N$	8.91 ± 0.95	16.90 ± 0.98	0.01	0.02	1.80	(4.17 ± 0.63) × 10^{-7}	0.02
10d	3	t-Bu	87	oxalate	254	$C_{21}H_{32}O_4N \cdot 0.5H_2O^g$	>10	>10				(1.38 ± 0.27) × 10^{-6}	0.007
13			77	base	164	$C_{23}H_{36}O_3N$	0.30 ± 0.13	>3	0.37			(3.41 ± 0.55) × 10^{-7}	0.03
14a	2	t-Bu	55	tartrate	76-78	$C_{19}H_{29}O_3N$	4.80 ± 0.91	>10	0.02			(1.15 ± 0.25) × 10^{-7}	0.09
14b	3	i-Pr	85	base	oil	$C_{19}H_{29}O_3N$	1.20 ± 0.50	>3	0.09			(1.30 ± 0.27) × 10^{-7}	0.08
14c	3	t-Bu	80	tartrate	68	$C_{20}H_{31}O_3N^h$	0.53 ± 0.08	4.60 ± 0.53	0.20	0.08	8.70	(5.49 ± 0.73) × 10^{-9}	1.82
14d	3	2-[3,4-(MeO)₂Ph]Et	41	oxalate	128	$C_{27}H_{37}O_9N \cdot H_2O^i$	2.60 ± 0.80	>10	0.04			(7.01 ± 0.77) × 10^{-6}	0.01
15a	3	i-Pr	92	tartrate	64	$C_{19}H_{29}O_3N^j$	0.023 ± 0.009	0.51 ± 0.12	4.78	0.80	22.20	(1.30 ± 0.13) × 10^{-9}	7.77
15b	3	t-Bu	70	tartrate	70	$C_{20}H_{31}O_3N$	0.71 ± 0.31	0.96 ± 0.28	0.15	0.42	1.35	(1.26 ± 0.33) × 10^{-9}	8.01
15c	3	2-[3,4-(MeO)₂Ph]Et	51	oxalate	118	$C_{27}H_{37}O_9N \cdot 0.5H_2O^k$	0.25 ± 0.18	0.60 ± 0.14	0.44	0.68	2.40	(2.60 ± 0.61) × 10^{-7}	0.04
16				chlorhydrate	139		0.71 ± 0.26	>10				(5.50 ± 0.94) × 10^{-8}	0.18
propranolol							0.11 ± 0.01	0.41 ± 0.01			3.70	(1.01 ± 0.38) × 10^{-8}	

[a] Yield based on the phenolic precursor. [b] All compounds were analyzed for C, H and N as the free base unless otherwise noted. Analyses were within ±0.4% of the theoretical values unless otherwise indicated. [c] Activity vs. propranolol is the ratio of ED_{50} (propranolol)/ED_{50} (compound tested). [d] EC_{50} on isolated guinea pig trachea is the molar concentration of the compound tested that is required to give 50% inhibition of the isoproterenol response (1 × 10^{-6} M). [e] Oxalate hemihydrate. [f] Oxalate. H: calcd, 7.94; found, 8.55. [g] Hemioxalate hemihydrate. C: calcd, 67.90; found, 68.44. [h] C: calcd, 72.03; found, 70.45. N: calcd, 4.20; found, 3.63. [i] Oxalate monohydrate. [j] C: calcd, 71.44; found, 70.66. [k] Oxalate hemihydrate.

for compounds **9b**, **15a**, and propranolol, respectively: regression-line slopes (calculated according to ref 16): 0.85, 0.93, 0.92; pA_2 9.7, 9.9, 8.95. The in vivo activities of **9b** and **15a** seem to be higher than those of butoxamine and H 35/25. The β_2 selectivity appears to be higher compared to that of butoxamine,[4a] quite similar to that of H 35/25[4b] and IPS 339,[4c] and inferior to that of ICI 188581.[4d]

Finally, preliminary experiments performed in vivo with **15a** showed that the recovery time, from the hypotensive effects of isoproterenol, was 50 ± 7 min, after administration of 0.2 mg/kg of the compound, while it was 27 ± 5 min after administration of propranolol (1 mg/kg). This long-lasting action must be further studied.

Concerning the structure–activity relationships, the following main points emerge from Table I: (1) Reduction of the saturated ring sizes (**9b** vs. **9a**; **14c** vs. **14a**) decreases the activity of the products. (2) Interestingly, introduction of an hydroxyl group on one of the two benzylic positions unexpectedly modifies β-blocking activity. Thus, the activity was decreased if the OH group was introduced on the same side as the oxypropanolamine substituent (cf. **14b** vs. **9b**; **14c** vs. **9c**). On the contrary, if the OH group was in the opposite position, the activity was increased (cf. **15a** vs. **9b**; **15c** vs. **9d**) or at least preserved (cf. **15b** vs. **9c**). (3) It seems that no relation exists between the activity and the nature of the nitrogen substituent. In particular, introduction of a homoveratryl group (**9d**, **14d**, and **15c**) did not increase the cardioselectivity of the compounds studied here, as was previously reported.[17] (4) In the same way, it is well-known that introduction of an amide group para to the oxypropanolamine moiety increases the β_1-blocking selectivity.[18] No such effect has been observed with compound **13**. It is particularly striking to note that such an observation has been made recently[19] with naphthyl derivatives when cardioselectivity was found with the corresponding simple benzene ring. (5) Finally, introduction of the oxypropanolamine group in the 2-position (**10a–d**) considerably decreased the activity. Similar results were observed with the propranolol analogue **16**, which in our tests appears as 7 and 20 times less active on the diastolic blood pressure and heart rate responses, respectively, than propranolol itself.

OCH₂CHOHCH₂NH-*i*-Pr structure
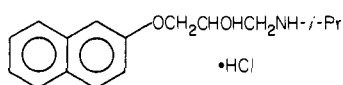
16

Conclusion

From the above study it must be concluded that a new family of β-blocking agents has been found and that some of them may be classified among the most selective β_2 blockers described. From current chemical studies it appears that in the near future we will easily be able to prepare derivatives of alcohols **3** bearing functional groups not only on the aromatic ring and on the benzylic positions but also on the saturated ring. The main interest of such molecules lies in their original hydrophobic folded framework, the lipophilic saturated size of which may be

modified. Thus, large dynamic conformational variations may be obtained, leading to a change in the lipophilic properties, as well as in the distances between the functional groups attached to the aromatic and the saturated parts of the molecules. The pharmacological consequences of such variations should be of interest and justify the intensive work we are presently developing in our laboratory.

Experimental Section

Melting points were obtained on a Kofler hot-stage apparatus. The IR spectra were taken on a Perkin-Elmer 257 spectrometer. UV spectra with a Beckman DK 2A spectrophotometer. ¹H NMR spectra were recorded on a Perkin-Elmer R 12 B instrument, ¹³C NMR spectra were obtained on a Bruker WP 80 spectrometer, with tetramethylsilane as internal standard. TLC was carried out with Merck silica gel G, and with ethyl acetate–hexane. Column chromatography was carried out with Merck silica gel (0.05–0.2 mm) with the solvents indicated.

Phenolic Precursors. (a) Arynic Condensations (Scheme I). 1,2,3,4,4a,8b-Hexahydrobiphenylene-4a,5-diol (6a, n = 2). A solution of *t*-BuOH (100 mmol) in THF (15 mL) was added dropwise to a suspension of NaNH₂ (450 mmol) in THF (75 mL). The mixture was then heated for 2 h at 40–45 °C. After the mixture was cooled, cyclohexanone (100 mmol) in THF (15 mL) was added dropwise at 25–30 °C, and the mixture was stirred at 35 °C for 2 h. After the mixture cooled to room temperature, the *m*-chlorophenol **4a** (50 mmol) in THF (15 mL) was added, and stirring was continued for 46 h. The mixture was poured onto ice and extracted with ether to remove unreacted excess of ketone. The aqueous basic layer was acidified with dilute HCl and extracted with ether. The organic layer was dried over MgSO₄ and evaporated, and the residue was chromatographed (EtOAc–petroleum ether, 10–40%) to give, successively, the unreacted *m*-chlorophenol **4a** (1.92 g, 30%), a ketonic compound of condensation, and then the alcohol **6a** (n = 2) (2.55 g, 25% yield): mp 142 °C (petroleum ether); IR (KBr) 3600–2500 (OH); UV (MeOH) λ_{max} 270 nm (log ϵ 2.97), 277 (2.95); ¹H NMR (Me₂CO-d_6) δ 0.90–2.20 (8 H, 2 m, 4 CH₂); 3.15–3.42 (1 H, pseudo-t, benzylic H), 4.62 (1 H, s, OH, exchanged with D₂O), 6.52–7.30 (3 H, m, Ar), 8.26 (1 H, br s, OH, exchanged with D₂O); ¹³C NMR (Me₂CO-d_6) of aromatic carbons, δ 151.81, 147.88, 134.43, 130.91, 115.22, 114.68; of aliphatic carbons, δ 78.45 (Ar COH), 53.19 (benzylic CH), 31.99, 23.99, 18.54, and 18.23 (cyclic CH₂). Anal. (C₁₂H₁₄O₂) C, H.

4b,6,7,8,9,9a-Hexahydro-5H-benzo[3,4]cyclobuta[1,2]-cycloheptene-1,4b- and -4,4b-diol (5a and 6a, n = 3). The enolate of cycloheptanone was prepared following the procedure described above in the synthesis of **6a** (n = 2). The *m*-chlorophenol **4a** (50 mmol) in THF (15 mL) was added, and stirring was continued for an additional 20 h at 45 °C. After cooling to room temperature, the mixture was poured onto ice and worked up as above. Chromatography of the residue on a silica gel column packed and eluted with EtOAc–petroleum ether mixtures (20–40%) gave a mixture of alcohols **5a** and **6a** (n = 3) (6.4 g, 63% yield).

6- and 7-[(Tetrahydro-2H-pyran-2-yl)oxy]-1,2,3,4,4a,8b-hexahydro-4a-biphenylenol (5b and 6b, n = 2). To the enolate of cyclohexanone, prepared as described above in the synthesis of **6a** and then cooled at 10 °C, was added 2-(p-chlorophenoxy)tetrahydropyran (**4b**; 50 mmol) in THF (15 mL). Stirring was continued for 24 h at this temperature. The reaction mixture was poured onto ice and extracted with ether. The organic layer was dried over MgSO₄ and evaporated. The residue was chromatographed on silica gel (EtOAc–petroleum ether, 5–30%) to give the following three fractions in order of elution: unreacted **4b** (5.4 g, 50%), a ketonic product of condensation, and a mixture of **5b** and **6b** (n = 2) (2.7 g, 20% yield): ¹H NMR (CCl₄) δ 0.91–2.22 (14 H, m, 7 CH₂), 2.61 (1 H, br s, OH, exchanged with D₂O), 3.17–3.44 (1 H, pseudo-t, benzylic H), 3.45–4.20 (2 H, m, CH₂), 5.22–5.49 (1 H, m, CH), 6.82–7.33 (3 H, m, Ar).

2- and 3-[(Tetrahydro-2H-pyran-2-yl)oxy]-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (5b and 6b, n = 3). The cycloheptanone (100 mmol) in THF (20 mL) was added dropwise to a suspension of NaNH₂ (200 mmol) in THF

(16) Arunlashana, G.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48–58.

(17) Hoefle, M. L.; Hastings, S. G.; Meyer, R. F.; Corey, R. M.; Holmes, A.; Stratton, C. D. *J. Med. Chem.* **1975**, *18*, 149.

(18) Weiner, N. In "The Pharmacological Basis of Therapeutics", 6th ed.; Goodman, L. S.; Gilman, A., Eds.; Macmillan: New York, 1980; pp 176–210.

(19) Rzeszotarski, W. J.; Gibson, R. E.; Simms, D. A.; Jagoda, E. M.; Vaughan, J. N.; Eckelman, W. C. *J. Med. Chem.* **1983**, *26*, 644–648.

(50 mL) at 25-30 °C, and then the mixture stirred for 2 h at 35 °C. 2-(p-Chlorophenoxy)tetrahydropyran (4b; 50 mmol) in THF (20 mL) was added, and stirring was continued at 40 °C for 5 h. After cooling, the mixture was poured onto ice and worked up as described above in the synthesis of 5b and 6b (n = 2). Silica gel chromatography of the residue (EtOAc–petroleum ether, 5–20%) gave a mixture of 5b and 6b (n = 3) (10.05 g, 70% yield): IR (neat, NaCl) 3600–3200 (OH); ^{1}H NMR (CCl$_4$) δ 1.09–2.31 (16 H, m, 8 CH$_2$), 2.67 (1 H, br s, OH, exchanged with D$_2$O), 3.10–4.11 (3 H, 2 m, benzylic H and CH$_2$), 5.13–5.42 (1 H, m, CH), 6.69–7.17 (3 H, m, Ar).

(b) **Miscellaneous Reactions (Scheme II).** *cis*-**4b,5,6,7,8,8a-Hexahydro-1-biphenylenol (7, n = 2).** To the alcohol 6a (n = 2) (3.49 g, 18.37 mmol) dissolved in pyridine (30 mL) was added 3 mL of acetic anhydride. At the end of the reaction [45 min, followed by TLC (EtOAc–hexane, 15%)], the mixture was poured into water, acidified with dilute HCl, and extracted with ether. The ether layer was washed with a saturated solution of NaHCO$_3$, dried over MgSO$_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel, with ether–petroleum ether (10%) to elute 5-acetoxy-1,2,3,4,4a,8b-hexahydro-4a-biphenylenol (3.85 g, 90% yield): IR (neat, NaCl) 3600–3200 (OH), 1765–1745 (CO); UV (MeOH) λ$_{max}$ 255 nm (log ε 2.86), 263 (2.94), 271 (2.90); ^{1}H NMR (CCl$_4$) δ 0.82–2.36 (11 H, m, 4 CH$_2$, with s at 2.1, OCOCH$_3$), 3.11–3.42 (1 H, pseudo-t, benzylic H), 4.07–4.47 (1 H, m, OH, exchanged with D$_2$O), 6.62–7.38 (3 H, m, Ar). Anal. (C$_{14}$H$_{16}$O$_3$) C, H.

To the above alcohol acetate (3.85 g, 16.59 mmol) dissolved in pyridine (35 mL) and maintained at 0 °C was slowly added 3 mL of POCl$_3$ in pyridine (5 mL). The mixture was stirred at this temperature for 3 h and then poured cautiously into crushed ice and worked up as above. The residue was chromatographed (eluent ether–petroleum ether, 10%) to yield 4b,5,6,7-tetrahydro-1-biphenylenol acetate (1.57 g): IR (neat, NaCl) 1770 (CO); ^{1}H NMR (CCl$_4$) δ 1.02–2.47 (9 H, m, 3 CH$_2$ with s at 2.18, OCOCH$_3$), 3.36–3.82 (1 H, m, benzylic H), 5.55–5.89 (1 H, m, ethylenic H), 6.82–7.44 (3 H, m, Ar).

The unstable ethylenic compound (1.57 g) dissolved in ethyl acetate (15 mL) was rapidly hydrogenated over 10% palladium on charcoal (50 mg) at room temperature and atmospheric pressure. After filtration over Celite and evaporation of the solvent, the crude acetate in ether (20 mL) was reduced with 530 mg (13.95 mmol) of LiAlH$_4$ at ambient temperature. The reaction was quenched by the cautious addition of EtOAc. Ether and 5% HCl were added, the layers were separated, and the organic layer was dried (MgSO$_4$). Solvent removal gave 7 (n = 2) [1.07 g, 6.15 mmol, 33% yield based upon 6a (n = 2)]: mp 86 °C (benzene); IR (KBr) 3600–2700 (OH); UV (MeOH) λ$_{max}$ 271 nm (log ε 2.93), 277 (2.92); ^{1}H NMR (CCl$_4$) δ 1.23–2.11 (8 H, 2 m, 4 CH$_2$), 3.20–3.67 (2 H, m, benzylic H), 5.69–6.11 (1 H, m, OH, exchanged with D$_2$O), 6.38–7.20 (3 H, m, Ar). Anal. (C$_{12}$H$_{14}$O) C, H.

cis-**4b,6,7,8,9,9a-Hexahydro-5H-benzo[3,4]cyclobuta-[1,2]cyclohepten-1-ol (11).** To a mixture of the alcohols 5a and 6a (n = 3) (4.1 g, 20.1 mmol) in pyridine (30 mL) was added 4 mL of acetic anhydride. At the completion of the reaction [30 min; monitored by TLC (EtOAc–hexane, 15%)], the mixture was worked up as above to give the mixture of 1- and 4-acetoxy-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclo-hepten-4b-ol (5 g), which was used without further purification. To the mixture of alcohol acetates (5 g) dissolved in pyridine (50 mL) and maintained at 0 °C was slowly added (30 min) 3.5 mL of POCl$_3$ in pyridine (7 mL). After the completion [4 h, verified by TLC (EtOAc–hexane, 15%)], workup of the reaction as above gave 1- and 4-Acetoxy-6,7,8,9-tetrahydro-9aH-benzo[3,4]cyclo-buta[1,2]cycloheptene (3.5 g): IR (neat, NaCl) 1770 (CO); ^{1}H NMR (CCl$_4$) δ 1.05–2.42 (11 H, m, 4 CH$_2$ with s at 2.13, OCOCH$_3$), 3.51–3.93 (1 H, m, benzylic H), 5.64–6.13 (1 H, m, ethylenic H), 6.67–7.33 (3 H, m, Ar).

The crude alkenic products (3.5 g) were then rapidly hydrogenated in ethyl acetate (15 mL) over 10% palladium on charcoal (50 mg) at atmospheric temperature and pressure. After filtration and evaporation, the residue dissolved in ether (30 mL) was reduced with 1.14 g (30 mmol) of LiAlH$_4$ at ambient temperature and worked up in an analogous manner as described above for the preparation of 7 (n = 2) to give the alcohol 11, which was rapidly purified on a short column of chromatography (ether–

petroleum ether, 5%; 2.8 g, 14.9 mmol, 74% yield): mp 108 °C (EtOAc); IR (KBr) 3600–2200 (OH); UV (MeOH) λ$_{max}$ 263 nm (log ε 2.83, sh), 270 (2.87), 275 (2.81); ^{1}H NMR (CCl$_4$) δ 1.02–2.38 (10 H, m, 5 CH$_2$), 3.33–3.82 (2 H, m, benzylic H), 5.27 (1 H, br s, OH, exchanged with D$_2$O), 6.40–7.22 (3 H, m, Ar). Anal. (C$_{13}$H$_{16}$O) C, H.

cis-**4b,5,6,7,8,8a-Hexahydro-2-biphenylenol (8, n = 2).** To a mixture of the alcohols 5b and 6b (n = 2) (4.8 g, 17.5 mmol) in solution in acetone (50 mL) was added 3 drops of concentrated HCl. At the completion of the reaction (1 h, followed by TLC (EtOAc–hexane, 15%)], the mixture was poured into a 20% NaOH solution and extracted twice with ether to remove nonphenolic products. The alkaline aqueous solution was acidified with 20% HCl and then extracted with ether. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure to give 1,2,3,4,4a,8b-hexahydrobiphenylene-4a,6- and -4a,7-diol (2.66 g): IR (KBr) 3600–2200 (OH); ^{1}H NMR (Me$_2$CO-d$_6$) δ 0.96–2.17 (8 H, m, 4 CH$_2$), 3.11–3.38 (1 H, pseudo-t, benzylic H), 4.24–4.48 (1 H, m, OH, exchanged with D$_2$O), 6.62–7.12 (3 H, m, Ar), 7.97–8.21 (1 H, m, OH, exchanged with D$_2$O).

To the above phenolic compounds (2.66 g) dissolved in pyridine (25 mL) was added 2.5 mL of acetic anhydride. After 30 min at ambient temperature, the usual workup led to a residue, which was washed with petroleum ether to give a solid mixture of 6- and 7-acetoxy-1,2,3,4,4a,8b-hexahydro-4a-biphenylenol (2.7 g): IR (KBr) 3700–2200 (OH), 1755 (CO); ^{1}H NMR (CCl$_4$) δ 0.87–2.47 (11 H, m, 4 CH$_2$ with s at 2.14, OCOCH$_3$), 3.02–3.33 (1 H, pseudo-t, benzylic H), 3.73 (1 H, br s, OH, exchanged with D$_2$O), 6.67–7.27 (3 H, m, Ar).

Following Burgess's method,[10] we added, dropwise, the mixture of alcohol acetates (2.7 g, 11.64 mmol) dissolved in 25 mL of benzene to a solution of Burgess's salt [(carboxysulfamoyl)tri-ethylammonium hydroxide inner salt methyl ester] (3.3 g, 13.87 mmol) in 50 mL of benzene at ambient temperature under an atmosphere of dry nitrogen. After the addition was complete (30 min), the temperature was raised to 50 °C and maintained for 1 h. Water (10 mL) was added, the benzene layer was separated, dried over MgSO$_4$, and evaporated, and the residue was chro-matographed (EtOAc–petroleum ether, 10%) to give a mixture of 4b,5,6,7-tetrahydro-2- and -3-biphenylenol acetate (1.37 g): IR (neat, NaCl) 1765 (CO); ^{1}H NMR (CCl$_4$) δ 1.02–2.42 (9 H, m, 3 CH$_2$, with s at 2.12, -OCOCH$_3$), 3.24–3.62 (1 H, m, benzylic H), 5.49–5.82 (1 H, m, ethylenic H), 6.56–7.17 (3 H, m, Ar).

Catalytic hydrogenation of the above unstable mixture of al-kenes (1.37 g) in ethyl acetate (15 mL) over 10% palladium on charcoal (50 mg) at atmospheric pressure and temperature was carried out until 1 molar equiv of hydrogen had been absorbed. *cis*-4b,5,6,7,8,8a-Hexahydro-2-biphenylenol acetate was obtained quantitatively: ^{1}H NMR (CCl$_4$) δ 1.09–2.34 (11 H, m, 4 CH$_2$ with s at 2.13, OCOCH$_3$), 3.26–3.67 (2 H, m, benzylic H), 6.61–7.06 (3 H, m, Ar).

The above acetate dissolved in ether (20 mL) was reduced with 450 mg (11.84 mmol) of LiAlH$_4$ at ambient temperature and worked up in a manner similar to that described above for the preparation of 7 (n = 2) to yield the alcohol 8 (n = 2) (1.03 g, 5.92 mmol, 34% yield): mp 88 °C (EtOAc); IR (KBr) 3500–2300 (OH), UV (MeOH) λ$_{max}$ 284 nm (log ε 3.59); ^{1}H NMR (CCl$_4$) δ 1.02–2.11 (8 H, 2 m, 4 CH$_2$), 3.20–3.60 (2 H, m, benzylic H), 5.33–5.71 (1 H, m, exchanged with D$_2$O), 6.38–6.91 (3 H, m, Ar). Anal. (C$_{12}$H$_{14}$O) C, H.

cis-**4b,6,7,8,9,9a-Hexahydro-5H-benzo[3,4]cyclobuta-[1,2]cyclohepten-2-ol (8, n = 3).** To a mixture of the alcohols 5b and 6b (n = 3) (6.4 g, 22.2 mmol) in solution in acetone (60 mL) was added 3 drops of concentrated HCl. After 24 h at ambient temperature, the mixture was worked up as above to give, after evaporation the mixture of 4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-2,4b- and -3,4b-diols (3.85 g): IR (KBr) 3600–3200 (OH); ^{1}H NMR (Me$_2$CO-d$_6$) δ 1.1–2.3 (10 H, m, 5 CH$_2$), 3.1–3.6 (1 H, m, benzylic H), 4.2–4.4 (1 H, m, OH, exchanged with D$_2$O), 6.6–7.2 (3 H, m, Ar), 7.9 (1 H, br s, OH, exchanged with D$_2$O).

To the above mixture of phenols (3.85 g) dissolved in pyridine (40 mL) was added 4 mL of acetic anhydride. After 30 min at ambient temperature, the reaction was complete. The mixture was poured into water, acidified with dilute HCl, and extracted with ether. The organic layer was washed with a saturated solution

of NaHCO$_3$, dried over MgSO$_4$, and evaporated under reduced pressure to give a mixture of 2- and 3-acetoxy-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (4.1 g): IR (neat, NaCl) 3650–3100 (OH), 1765–1740 (CO); ^{1}H NMR (CCl$_4$) δ 0.91–2.43 (11 H, m, 4 CH$_2$ with s at 2.11, OCOCH$_3$), 3.09–3.53 (1 H, m, benzylic H), 4.38 (1 H, br s, OH, exchanged with D$_2$O), 6.69–7.38 (3 H, m, Ar).

The above mixture of alcohol acetates dissolved in 40 mL of benzene, in the presence of catalytic p-toluenesulfonic acid, was refluxed for 30 min in a Dean–Stark apparatus. After cooling, the mixture was diluted with ether, washed with a saturated solution of NaHCO$_3$, and dried over MgSO$_4$. The solvent was evaporated, and the residue was chromatographed (ether–petroleum ether, 10%) to give a mixture of 2- and 3-acetoxy-6,7,8,9-tetrahydro-9aH-benzo[3,4]cyclobuta[1,2]cycloheptene (3.1 g): IR (neat, NaCl) 1755–1745 (CO); ^{1}H NMR (CCl$_4$) δ 1.02–2.51 (11 H, m, 4 CH$_2$, with s at 2.16, OCOCH$_3$), 3.44–3.89 (1 H, m, benzylic H), 5.78–6.16 (1 H, pseudo-t, ethylenic H), 6.62–7.36 (3 H, m, Ar).

The above ethylenic mixture (3.1 g) in ethyl acetate (15 mL) was rapidly hydrogenated over 10% palladium on charcoal (50 mg) at atmospheric temperature and pressure. Filtration and evaporation of the solvent gave cis-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-2-ol acetate (3.1 g): IR (neat, NaCl) 1755–1740 (sh) (CO); UV (MeOH) λ_{max} 270 nm (log ϵ 3.45), 276 (3.40); ^{1}H NMR (CCl$_4$) δ 1.04–2.33 (13 H, m, 5 CH$_2$, with s at 2.15, OCOCH$_3$), 3.35–3.78 (2 H, m, benzylic H), 6.72–7.12 (3 H, m, Ar).

The above acetate (3.1 g) dissolved in ether (30 mL) was reduced with 1 g (26.31 mmol) of LiAlH$_4$ at ambient temperature. After 15 min, the reaction was complete, and the mixture was worked up in a manner analogous to the one described above for the preparation of 7 (n = 2) to give the alcohol 8 (n = 3) (2.4 g, 12.77 mmol, 57% yield): mp 84–86 °C (EtOAc); IR (KBr) 3600–2300 (OH); UV (MeOH) λ_{max} 286 nm (log ϵ 3.48); ^{1}H NMR (CCl$_4$) δ 1.02–2.22 (10 H, m, 5 CH$_2$), 3.23–3.68 (2 H, m, benzylic H), 6.31–6.93 (4 H, m, Ar and OH, exchanged with D$_2$O). Anal. (C$_{13}$H$_{16}$O) C, H.

cis-4-Butyramido-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-1-ol (12) (Scheme III). A solution of 0.7 mL of fuming HNO$_3$ in CH$_2$Cl$_2$ (5 mL) was slowly added (15 min) at –5 °C to 2.3 g (12.12 mmol) of the alcohol 11 dissolved in CH$_2$Cl$_2$ (35 mL). At the end of the addition, the mixture was poured into crushed ice. The organic layer was washed with water, dried over MgSO$_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel (EtOAc–petroleum ether, 15%) to give, successively, cis-2-nitro-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-1-ol (0.75 g, 26% yield) [mp 94–96 °C (EtOAc); IR (KBr) 3600–3000 (OH), 1515 (NO$_2$); UV (MeOH) λ_{max} 297 nm (log ϵ 3.90); ^{1}H NMR (CCl$_4$) δ 1.03–2.51 (10 H, m, 5 CH$_2$), 3.30–3.88 (2 H, m, benzylic H), 6.61 (1 H, d, J = 8 Hz, Ar), 7.94 (1 H, d, J = 8 Hz, Ar), 10.46 (1 H, s, OH, exchanged with D$_2$O)] and cis-4-nitro-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-1-ol (1.10 g, 39% yield): mp 103 °C (EtOAc); IR (KBr) 3560–3000 (OH), 1500 (NO$_2$); UV (MeOH) λ_{max} 315 nm (log ϵ 4.14), 233 (3.65); ^{1}H NMR (Me$_2$CO-d_6) δ 1.02–2.60 (10 H, m, 5 CH$_2$), 3.44–4.06 (2 H, m, benzylic H), 6.78 (1 H, d, J = 9.33 Hz, Ar), 7.84 (1 H, d, J = 9.33 Hz, Ar), 9.11–9.68 (1 H, m, OH, exchanged with D$_2$O). Anal. (C$_{13}$H$_{15}$O$_3$N) C, H, N.

The p-nitrophenol compound (1.5 g, 6.44 mmol) in ethyl acetate (15 mL) was hydrogenated over 10% palladium on charcoal at atmospheric temperature and pressure for 4 h to give cis-4-amino-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]-cyclohepten-1-ol (1.3 g, 99% yield): mp 167 °C (EtOAc); IR (KBr) 3600–2300 (OH, NH$_2$); UV (MeOH) λ_{max} 292 nm (log ϵ 3.75); ^{1}H NMR (Me$_2$CO-d_6) δ 0.93–2.50 (10 H, m, 5 CH$_2$), 3.17–3.82 (2 H, m, benzylic H), 4.75–5.35 (2 H, m, NH$_2$, exchanged with D$_2$O), 6.29 (1 H, d, J = 8 Hz, Ar), 6.33 (1 H, s, OH, exchanged with D$_2$O), 6.57 (1 H, d, J = 8 Hz, Ar).

A mixture of 1.2 g (5.91 mmol) of the above p-aminophenol compound and 1.2 mL of butyric anhydride in acetone (30 mL) was refluxed for 1 h. After removal of the solvent, the solid was washed with ether. Compound 12 weighed 1.5 g (5.49 mmol, 93% yield): mp 186 °C (EtOAc); IR (KBr) 3600–2700 (OH, NH), 1650–1535 (CO); UV (MeOH) λ_{max} 249 nm (log ϵ 4.17); ^{1}H NMR

(Me$_2$CO-d_6) δ 0.74–2.44 (17 H, m, 7 CH$_2$ with t at 0.92, J = 6.66 Hz CH$_3$), 3.29–3.82 (2 H, m, benzylic H), 6.51 (1 H, d, J = 8.67 Hz, Ar), 7.13 (1 H, d, J = 8.67 Hz, Ar), 7.87 (1 H, s, OH, exchanged with D$_2$O), 8.33–8.78 (1 H, m, NH, exchanged with D$_2$O). Anal. (C$_{17}$H$_{23}$O$_2$N) C, H, N.

4b,6,7,8,9,9a-Hexahydro-5H-benzo[3,4]cyclobuta[1,2]-cycloheptene-1,4b- and -4,4b-diol (5a and 6a, n = 3). To the isomeric mixture of alcohols 5a and 6a (6.4 g, 31.37 mmol) in pyridine (60 mL) was added 6 mL of acetic anhydride. At the completion of the reaction [30 min, monitored by TLC (EtOAc–hexane, 20%)], the mixture was poured into water, acidified with diluted HCl, and extracted with ether. The ether layer was washed with a saturated solution of NaHCO$_3$, dried over MgSO$_4$, and evaporated under reduced pressure. The crude mixture was chromatographed (EtOAc–petroleum ether, 5–20%) to afford, successively, 1-acetoxy-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]-cyclobuta[1,2]cyclohepten-4b-ol (4.8 g, 19.51 mmol, 62% yield) [IR (neat, NaCl) 3700–3100 (OH), 1765–1745 (CO); UV (MeOH) λ_{max} 258 nm (log ϵ 2.82, sh), 264 (2.91), 271 (2.85); ^{1}H NMR (CCl$_4$) δ 0.97–2.36 (13 H, m, 5 CH$_2$, with s at 2.17, OCOCH$_3$), 3.17–3.53 (1 H, m, benzylic H), 3.78 (1 H, br s, OH, exchanged with D$_2$O), 6.56–7.36 (3 H, m, Ar)] and 4-acetoxy-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (1.56 g, 6.34 mmol, 20% yield) [IR (neat, NaCl) 3600–3100 (OH), 1765–1745 (CO); UV (MeOH) λ_{max} 256 nm (log ϵ 2.76, sh), 263 (2.83), 270 (2.79); ^{1}H NMR (CCl$_4$) δ 0.98–2.24 (13 H, m, 5 CH$_2$, with s at 2.11, OCOCH$_3$), 3.03–3.46 (1 H, m, benzylic H), 3.71 (1 H, br s, OH, exchanged with D$_2$O), 6.63–7.36 (3 H, m, Ar).

The first acetate (3.5 g, 14.23 mmol) in ether (30 mL) was reduced with 1 g (26.31 mmol) of LiAlH$_4$ at ambient temperature to afford 6a (2.87 g, 14.07 mmol, 99% yield): mp 156 °C (benzene); IR (KBr) 3600–2500 (OH); UV (MeOH) λ_{max} 270 nm (log ϵ 2.97), 277 (2.95); ^{1}H NMR (Me$_2$CO-d_6) δ 1.09–2.49 (10 H, m, 5 CH$_2$), 3.09–3.64 (1 H, m, benzylic H), 4.30–4.60 (1 H, m, exchanged with D$_2$O), 6.51–7.33 (3 H, m, Ar), 8.03–8.23 (1 H, m, OH, exchanged with D$_2$O); ^{13}C NMR (Me$_2$CO-d_6), for aromatic carbons, δ 150.60, 147.27, 133.10, 130.55, 114.98, 114.32; for aliphatic carbons, δ 83.12 (ArCOH), 59.07 (benzylic CH), 36.29, 32.35, 30.65, 27.56, 24.29 (cyclic CH$_2$). Anal. (C$_{13}$H$_{16}$O$_2$) C, H.

The second acetate (1.05 g, 4.27 mmol) in ether (20 mL) was reduced with 300 mg (7.89 mmol) of LiAlH$_4$ at ambient temperature to afford 5a (0.8 g, 3.92 mmol, 92% yield); mp 178 °C (benzene); IR (KBr) 3660–2500 (OH); UV (MeOH) λ_{max} 270 nm (log ϵ 2.99), 277 (2.95); ^{1}H NMR (Me$_2$CO-d_6) δ 1.07–2.47 (10 H, m, 5 CH$_2$); 3.22–3.63 (1 H, m, benzylic H), 4.17–4.57 (1 H, m, OH, exchanged with D$_2$O), 6.52–7.27 (3 H, m, Ar), 7.82–8.27 (1 H, m, OH, exchanged with D$_2$O); ^{13}C NMR (Me$_2$CO-d_6), for aromatic carbons, δ 153.27, 153.03, 130.00, 129.52, 116.07, 112.80; for aliphatic carbons, δ 83.18 (ArCOH), 58.94 (benzylic CH), 37.18, 32.83, 30.77, 27.87, 24.90 (cyclic C). Anal. (C$_{13}$H$_{16}$O$_2$) C, H.

General Procedure for the Synthesis of (Aryloxy)-propanolamines (Table I). 1-[3-[(1,1-Dimethylethyl)-amino]-2-hydroxypropoxy]-4b,6,7,8,9,9a-hexahydro-5H-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (15b). To a mixture of 2 g (9.8 mmol) of the alcohol 5a (n = 3) and 1.2 mL of epichlorohydrin in 25 mL of acetone was added, over 15 min, a solution of 0.392 g (9.8 mmol) of NaOH in 4 mL of H$_2$O. The mixture was stirred at reflux under N$_2$ for 3 h (reaction was monitored by TLC (EtOAc–hexane, 20%)]. The reaction mixture was evaporated in vacuo, and the residue was partitioned between H$_2$O and CHCl$_3$. The aqueous layer was extracted with CHCl$_3$, dried (MgSO$_4$), and evaporated in vacuo to give an oil, which was used without further purifications.

Epoxide Opening. A solution of the above epoxide and 2.8 mL (2.5 equiv) of tert-butylamine in 20 mL of EtOH was refluxed for 3.5 h under N$_2$ [evolution of the reaction was followed by TLC (EtOAc–hexane, 15%)]. The solvent was removed in vacuo, and the residue was partitioned between ether and H$_2$O; the aqueous layer was acidified by cold diluted hydrochloric acid and extracted twice with ether. The cooled aqueous layer made alkaline with aqueous NaOH, extracted with ether, and dried over MgSO$_4$. Evaporation of the solvent gave an oil, which was purified by column chromatography (slight pressure), with MeOH as eluent, to give 15b (2.27 g, 6.81 mmol, 70% yield). The results reported in Table I were obtained under the same experimental conditions from the appropriate alcohol.

Pharmacology. β_1-Adrenergic and β_2-adrenergic blocking activities were determined in vivo in anesthetized guinea pigs. Anesthesia was induced with urethane (1.25 g/kg ip). Blood pressure was recorded from a carotid artery, and the pulse pressure was used to determine the heart rate. Three consecutive doses of isoproterenol (10 μg/kg iv) were injected, and the control mean decrease in diastolic blood pressure and mean increase in heart rate were calculated. Antagonists were then administered by four cumulative intravenous injections. Isoproterenol was injected 10 min after each dose of antagonist. The next dose of antagonist was injected 10 min after blood pressure and heart rate responses to isoproterenol came back to base line. Experiments were performed on groups of at least four animals.

In vitro experiments were realized on isolated guinea pig trachea.[20] Tracheal spirals were equilibrated under an initial tension of 1.50 g in Tyrode solution at 37 °C, gassed with O_2 plus CO_2 (95:5). The resting tension was between 0.4 and 0.6 g. The effects of isoproterenol (3×10^{-8} to 3×10^{-6}M) were tested on contraction induced by acetylcholine (Ach; 3×10^{-6} M). Antagonists were added to the bath 15 min before Ach, and isoproterenol (3×10^{-8} to 3×10^{-5} M) was added again after the maximal contraction had been developed. Experiments were performed on groups of at least four preparations. Four points were used to establish EC_{50}s.

Registry No. 4a, 108-43-0; 4b, 20443-90-7; 5a, 89638-60-8; 5a (1-acetate), 89638-70-0; 5b (n = 2), 89638-62-0; 5b (n = 2, diol), 89638-75-5; 5b (n = 2, 7-acetate), 89638-77-7; 5b (n = 3), 89638-64-2; 5b (n = 3, diol), 89638-83-5; 5b (n = 3, 2-acetate), 89638-85-7; 6a (n = 2), 89638-59-5; 6a (n = 2, 5-acetate), 89638-67-5; 6a (n = 3), 89638-61-9; 6a (n = 3, 4-acetate), 89638-71-1; 6b (n = 2), 89638-63-1; 6b (n = 2, diol), 89638-76-6; 6b (n = 2, 6-acetate), 89638-78-8; 6b (n = 3), 89638-65-3; 6b (n = 3, diol), 89638-84-6; 6b (n = 3, 3-acetate), 89638-86-8; 7 (n = 2), 89638-66-4; 8 (n = 2), 89638-74-4; 8 (n = 2, acetate), 89638-81-3; 8 (n = 3), 89638-82-4; 8 (n = 3, acetate), 89638-89-1; 9 (n = 2, epoxide, isomer 1), 89638-95-9; 9 (n = 2, epoxide, isomer 2), 89639-28-1; 9 (n = 3, epoxide, isomer 1), 89639-30-5; 9 (n = 3, epoxide, isomer 2), 89707-93-7; 9a (isomer 1), 89638-99-3; 9a (isomer 2), 89639-19-0; 9a oxalate (isomer 1), 89639-12-3; 9a oxalate (isomer 2), 89639-24-7; 9b (isomer 1), 89639-00-9; 9b (isomer 2), 89707-80-2; 9b oxalate (isomer 1), 89707-74-4; 9b oxalate (isomer 2), 89771-29-9; 9c (isomer 1), 89639-01-0; 9c (isomer 2), 89707-81-3; 9c oxalate (isomer 1), 89707-75-5; 9c oxalate (isomer 2), 89771-30-2; 9d (isomer 1), 89639-02-1; 9d (isomer 2), 89707-82-4; 10 (n = 2, epoxide, isomer 1), 89638-96-0; 10 (n = 2, epoxide, isomer 2), 89639-29-2; 10 (n = 3, epoxide, isomer 1), 89638-97-1; 10 (n = 3, epoxide, isomer 2), 89707-92-6; 10a (isomer 1), 89639-03-2; 10a (isomer 2), 89639-20-3; 10a oxalate (isomer 1), 89639-13-4; 10a oxalate (isomer 2), 89639-25-8; 10b (isomer 1), 89639-04-3; 10b (isomer 2), 89639-21-4; 10b oxalate (isomer 1), 89639-14-5; 10b oxalate (isomer 2), 89639-26-9; 10c (isomer 1), 89639-05-4; 10c (isomer 2), 89707-83-5; 10c oxalate (isomer 1), 89708-56-5; 10c oxalate (isomer 2), 89771-31-3; 10d (isomer 1), 89639-06-5; 10d (isomer 2), 89707-84-6; 10d 1/2oxalate (isomer 1), 89707-76-6; 10d·1/2oxalate (isomer 2), 89771-32-4; 11, 89638-69-7; 11 (2-nitro derivative), 89638-94-8; 11 (4-nitro-derivative), 89638-91-5; 11 (4-amino derivative), 89638-92-6; 12, 89638-90-4; 13 (isomer 1), 89708-55-4; 13 (isomer 2), 89639-22-5; 13 (epoxide, isomer 1), 89638-98-2; 13 (epoxide, isomer 2), 89707-94-8; 14 (n = 2, epoxide, isomer 1), 89639-32-7; 14 (n = 2, epoxide, isomer 2), 89639-33-8; 14 (n = 3, epoxide, isomer 1), 89639-31-6; 14 (n = 3, epoxide, isomer 2), 89707-95-9; 14a (isomer 1), 89639-07-6; 14 (isomer 2), 89639-23-6; 14a tartrate (isomer 1), 89655-83-4; 14a tartrate (isomer 2), 89639-27-0; 14b (isomer 1), 89639-08-7; 14b (isomer 2), 89707-85-7; 14c (isomer 1), 89639-15-6; 14c (isomer 2), 89707-86-8; 14c tartrate (isomer 1), 89639-16-7; 14c tartrate (isomer 2), 89771-33-5; 14d (isomer 1), 89639-09-8; 14d (isomer 2), 89707-87-9; 14d oxalate (isomer 1), 89707-77-7; 14d oxalate (isomer 2), 89771-34-6; 15 (epoxide, isomer 1), 89638-93-7; 15 (epoxide, isomer 2), 89707-91-5; 15a (isomer 1), 89639-10-1; 15a (isomer 2), 89707-88-0; 15a tartrate (isomer 1), 89707-78-8; 15a tartrate (isomer 2), 89771-35-7; 15b (isomer 1), 89639-11-2; 15b (isomer 2), 89707-89-1; 15b tartrate (isomer 1), 89707-79-9; 15b tartrate (isomer 2), 89771-36-8; 15c (isomer 1), 89639-17-8; 15c (isomer 2), 89707-90-4; 15c oxalate (isomer 1), 89639-18-9; 15c oxalate (isomer 2), 89771-37-9; 16, 2007-72-9; 16·HCl, 56354-24-6; i-PrNH$_2$, 75-31-0; t-BuNH$_2$, 75-64-9; 3,4-(CH$_3$O)$_2$C$_6$H$_3$CH$_2$CH$_2$NH$_2$, 120-20-7; (CH$_3$CH$_2$CH$_2$CO)$_2$O, 106-31-0; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; 4b,5,6,7-tetrahydro-1-phenylenol acetate, 89638-68-6; 1-acetoxy-6,7,8,9-tetrahydro-9aH-benzo[3,4]cyclobuta[1,2]cycloheptene, 89638-72-2; 4-acetoxy-6,7,8,9-tetrahydro-9aH-benzo[3,4]cyclobuta[1,2]cycloheptene, 89638-73-3; 4b,5,6,7-tetrahydro-2-biphenylenol acetate, 89638-79-9; 4b,5,6,7-tetrahydro-3-biphenylenol acetate, 89638-80-2; 2-acetoxy-6,7,8,9-tetrahydro-9aH-benzo-[3,4]cyclobuta[1,2]cycloheptene, 89638-87-9; 3-acetoxy-6,7,8,9-tetrahydro-9aH-benzo[3,4]cyclobuta[1,2]cycloheptene, 89638-88-0; epichlorohydrin, 106-89-8.

Supplementary Material Available: Full IR, UV, and ^{1}H and ^{13}C NMR for all prepared (aryloxy)propanolamines (3 pages). Ordering information is given on any current masthead page.

(20) Advenier, A.; Bidet, D.; Floch-Saint-Aubin, A.; Renier, A. *Br. J. Pharmacol.* **1982**, *77*, 39–44.