A New Series of Tricyclic (Aryloximino)propanolamines Displaying Very High Selective β_2-Blocking Properties

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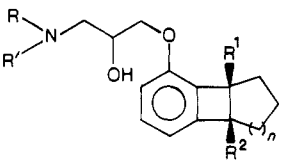
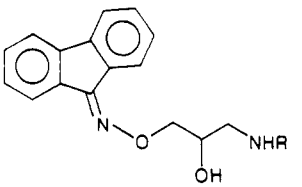
A new class of indanones **4** easily obtained by aryne type condensations, followed by transposition of the benzocyclobutanols **3** thus formed, were transformed into the corresponding oximinopropanolamines **7**. These compounds were studied for their potential β-blocking properties. It was found that **7** have generally low β_1-blocking properties. Their β_2-blocking action varies from low to very high. Interestingly one of them (**7b**) has the highest β_2 activity/β_1 activity (343) value known to date.

A few years ago, we reported the synthesis of a new series of (aryloxy)propanolamines **1** which displayed marked selective β_2-adrenoreceptor blocking activity.[1] A number of these compounds demonstrated excellent β_2-blocker selectivity. This was primarily attributed to the presence of the hydrophobic portion of these molecules containing the cyclobutene ring. However, altered selectivity was also observed upon variation of the presence and position of the hydroxyl group at the junction of the saturated ring. Studies by Leclerc, Schwartz, and colleagues[2] showed that the insertion of a C=N bond in the ethanolamine side chain of the molecule did not abolish β-adrenoreceptor action and, in some cases, lead to the production of selective β_2 antagonists[3] **2**. These findings could be the first step of interesting research concerning the syntheses of a new series of antiglaucoma agents with decreased cardiac side effects.[4]

We also found that the aryne type condensation of ketone enolates which provided the starting material for the subsequent (aryloxy)propanolamines (**1**) synthesis could be used as a simple access to the polycyclic indanones **4**.[5] The basic principle of these syntheses is given in Scheme I. On the basis of all these observations, it appeared that (aryloximino)propanolamines prepared from the oxime of **4** could have some β-blocking activity with potentially high β_2 selectivity. In the present publication, we report the synthesis and pharmacological properties of these new compounds. As predicted, some of the (aryloximino)-propanolamines are exceptionally selective β_2-blocking agents.



1: $R^1 = R^2 = H$; $R^1 = H$ and $R^2 = OH$; $R^1 = OH$ and $R^2 = H$



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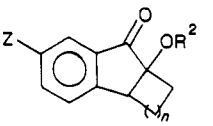
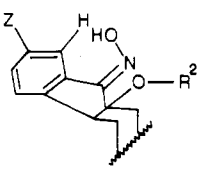


4: Z = H, F; R^2 = Me, H, or CH_2CH_2OH, n = 3, 4, 8



(*E*)-oxime **5**

Chemistry

Starting indanones **4** prepared in the present work have the general formula shown below. For Z = H, the alcohols **3** were obtained by the reaction as described in Scheme I.[6] When Z = F, the aryne type condensations were performed with *p*-FC_6H_4Br as the starting material with the complex base $NaNH_2$–*t*-BuONa[7] in THF (further details are given in the Experimental Section). When submitted to the action of HCl or H_2SO_4, **3** led to indanones **4** with R^2 = H. The preparation of **4** (R^2 = CH_3, CH_2CH_2OH) required the action of BF_3–Et_2O under dry conditions (see the Experimental Section). The cis or trans nature of the saturated ring junction of **4** was established elsewhere.[5]

Oximes **5** were obtained in good yields (see Table II) by the very general reaction of the corresponding ketone with NH_2OH, HCl in ethanol. The determination of *Z* or *E* stereochemistry of these oximes was established by NMR and X-ray studies. First, we compared the ^{13}C NMR spectra of oximes **5** and the corresponding ketones **4**. According to the studies by Garrigues and Maffrand,[8] we could expect a shielding effect of the two carbon C^α and $C^{\alpha'}$ passing from ketone to the corresponding oxime. Moreover, $\Delta\delta$ (corresponding to $\delta_{CX=NOH} - \delta_{CX=O}$) should be more negative for the carbon situated in the syn position with respect to the hydroxyl group. As we can see in Table I, $\Delta\delta$ for the $C^{\alpha'}$ carbon is always more negative than that for the C^α carbon, which means that all the molecules used

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(1) (1) Carré, M. C.; Youlassani, A.; Caubère, P.; Saint-Aubin-Floch, A.; Blanc, M.; Advenier, C. *J. Med. Chem.* **1984**, *27*, 792.
(2) Leclerc, G. *J. Med. Chem.* **1980**, *23*, 620.
(3) Bouzoubaa, M.; Leclerc, G.; Decker, N.; Schwartz, J.; Andermann, G. *J. Med. Chem.* **1984**, *27*, 1291.
(4) Nathanson, J. A. *Br. J. Pharmacol.* **1984**, *83*, 821.
(5) Carré, M. C.; Grégoire, B.; Geoffroy, P.; Caubère, P. *Tetrahedron* **1988**, *44*, 127.
(6) Grégoire, B.; Carré, M. C.; Caubère, P. *J. Org. Chem.* **1986**, *51*, 1419.
(7) Caubère, P. *Top. Curr. Chem.* **1978**, *73*, 50.
(8) Garrigues, B.; Maffrand, J. P. *Bull. Soc. Chim. Fr.* **1986**, *2*, 304.

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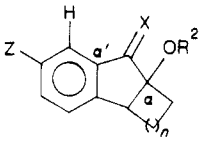
Table I



Z	R^2	n	X = O Cα	X = O Cα′	X = NOH Cα	X = NOH Cα′	$\Delta\delta_{C\alpha}$	$\Delta\delta_{C\alpha'}$
H	H	3	80.1	133.8	79.2	131.2	−0.9	−2.6
H	H	4	82.4	133.6	85.3	133.2	+2.9	−0.4
H	Me	3	84.5	134.3	84.0	131.2	−0.5	−3.1
H	Me	4	84.0	134.6	86.0	131.6	+2.0	−3.0
H	Me	8	88.8	133.9	86.7	131.5	−2.1	−2.4
F	Me	3	82.7	137.5[a]	80.2	125.9[a]	−2.5	−11.6
H	$(CH_2)_2OH$	3	84.8	134	84.2	131.3	−0.6	−2.7
H	$(CH_2)_2OH$	4	84.6	135.1	84.2	131.2	−0.4	−3.9

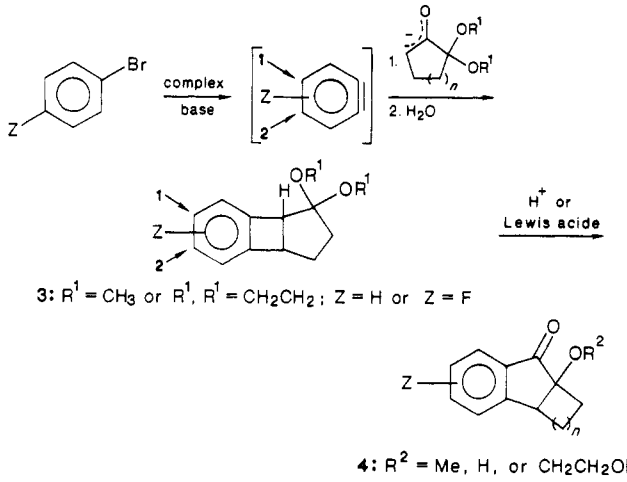
[a] Center value of the two signals of this carbon due to the fluorine coupling.

Table II. Synthesis of Oximes **5**[a]

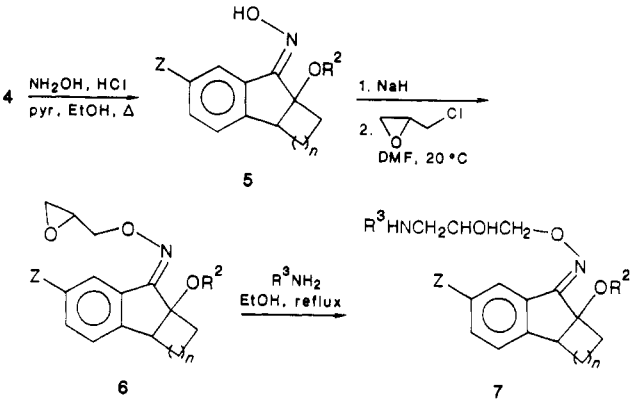
5	time, h	yield, %	formula
Z = H, n = 3; R^2 = H (cis H, OH) anti[b]	1	78	$C_{13}H_{15}O_2N$[c]
Z = H; n = 3; R^2 = H (cis H, OH) syn[b]		19	
Z = H; n = 4; R^2 = H	2	50	$C_{14}H_{17}O_2N$[d]
Z = H; n = 3; R^2 = Me (cis H, OMe)	1.2	91	$C_{14}H_{17}O_2N$[d]
Z = F; n = 3; R^2 = Me (cis H, OMe)	1	89	$C_{14}H_{16}O_2NF$[e]
Z = H; n = 4; R^2 = Me	1	82	$C_{15}H_{19}O_2N$[d]
Z = H; n = 8; R^2 = Me (cis H, OMe)	2	87	$C_{19}H_{27}O_2N$[d]
Z = H; n = 3; R^2 = CH_2CH_2OH (cis H, OCH_2CH_2OH)	0.75	66	$C_{15}H_{19}O_3N$[d]
Z = H; n = 4; R^2 = CH_2CH_2OH (trans H, OCH_2CH_2OH)	12	67	$C_{16}H_{21}O_3N$[d]

[a] Yields calculated from the corresponding indanone **4**. [b] Formation of the two oximes *Z* and *E*: 78% *E*, 19% *Z*. [c] Analyses C, H, N were within ±0.4% of the theoretical values. [d] Mass spectra recorded. [e] Analyses C, H, N were within ±0.4% of the theoretical values.

Scheme I



Scheme II



for the (aryloximino)propanolamines synthesis have *E* stereochemistry. ^1H NMR studies lend further support of *E* geometry, since for each oxime we found one of the aromatic hydrogens shifted downfield with respect to the others, as in the studies by Anastasia and colleagues.[9] This deshielding is explained by an anisotropic effect of the hydroximino oxygen atom. Finally, X-ray studies performed on oxime **5** (*n* = 3, R^2 = Me, Z = H) have confirmed this result.[10] So, all the starting oximes used for these syntheses are *E* isomers and have the formula as shown below.

Oximinopropanolamine derivatives of oximes **5** were prepared following the classic pathway summarized in Scheme II. Although, the transformation **5** → **6** appears obvious, it necessitated a large number of careful preliminary experiments. The key step was the formation of the oxime salt without destruction of **6**. So, different experimental conditions must be used when R_2 = CH_3 or R_2 = H (see the Experimental Section). As we can see in Table III, the overall yields of (aryloximino)propanolamines are good to excellent.

Pharmacological Results and Discussion

With the aim of determining the activity and selectivity of these compounds for β_1- or β_2-adrenoceptor subtypes, we carried out our studies with pharmacological models. Thus, isoproterenol-induced relaxation on guinea pig trachea was used for β_2 adrenoceptors, whereas isoproterenol-positive inotropic action on guinea pig isolated atria was used for β_1 adrenoceptors. Results are presented in Table III. These data show that some compounds, especially **7b**, **7g**, and **7d**, have selective antagonistic effects on β_2 adrenoceptors. The most interesting substance proved

(9) Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Perkins Trans. 1* **1986**, 2123.
(10) Jamart-Gregoire, B.; Caubere, P.; Ianelli, S.; Nardelli, M. To be published.

Table III. Pharmacological Data of (Aryloximino)propanolamines Compounds 7

compounds 7		R^3NH_2	time,	yield,[b]				guinea pig trachea (IT)		guinea pig atria (IA)		selectivity ratio
no.	substit	(equiv)	h	%	salt	mp, °C	formula	IC_{50},[g] M	act. vs. propranolol[h] (h)	IC_{50},[g] M	act. vs. propranolol[h]	IC_{50}(IA)/IC_{50}(IT)
7a	Z = H, *n* = 3, R^2 = Me, R^3 = *i*-Pr (cis H, OMe)	*i*-$PrNH_4$ (4)	4	33[c]	base	oil	$C_{20}H_{30}O_3N_2$[e]	$(3.0 \pm 0.8) \times 10^{-7}$	0.010	$(1.2 \pm 0.8) \times 10^{-6}$	0.009	4.0
7b	Z = H, *n* = 3, R^2 = Me, R^3 = *t*-Bu (cis H, OMe)	*t*-$BuNH_2$ (4)	10	33[c]	oxalate	142	$C_{21}H_{32}O_3N_2$[f]·HOOC–COOH·$0.5H_2O$	$(3.5 \pm 1.7) \times 10^{-8}$	0.086	$(1.2 \pm 0.6) \times 10^{-5}$	0.0009	33
7c	Z = H, *n* = 3, R^2 = Me, R^3 = HVA[a] (cis H, OMe)	HVA-NH_2[a] (4)	4	35[c]	base	oil	$C_{27}H_{36}O_5N_2$[e]	$>10^{-5}$	–	$>10^{-5}$	–	–
7d	Z = H, *n* = 4, R^2 = Me, R^3 = *i*-Pr (trans H, OMe)	*i*-$PrNH_2$ (4)	5	55[c]	oxalate	170	$C_{21}H_{32}O_3N_2$[f]·HOOC–COOH	$(3.5 \pm 2.1) \times 10^{-8}$	0.086	$(3.0 \pm 2.1) \times 10^{-6}$	0.004	85.7
7e	Z = H, *n* = 4, R^2 = Me, R^3 = *t*-Bu (trans H, OMe)	*t*-$BuNH_2$ (4)	5	50[c]	oxalate	194	$C_{22}H_{34}O_3N_2$[f]·HOOC–COOH·$1.5H_2O$	$(4.4 \pm 2.7) \times 10^{-7}$	0.007	$(1.6 \pm 1.2) \times 10^{-7}$	0.067	0.38
7f	Z = H, *n* = 4, R^2 = Me, R^3 = HVA[a] (trans H, OMe)	HVA-NH_2[a] (4)	2	36[c]	oxalate	150	$C_{28}H_{38}O_5N_2$[f]·HOOC–COOH·$2H_2O$	$>10^{-5}$	–	$(1.3 \pm 1.1) \times 10^{-5}$	0.0008	–
7g	Z = F, *n* = 3, R^2 = Me, R^3 = *i*-Pr (cis, H, OMe)	*i*-$PrNH_2$ (4)	4	47[c]	oxalate	115	$C_{20}H_{29}O_3NF$[f]·HOOC–COOH	$(7.9 \pm 3.4) \times 10^{-7}$	0.004	$(1.9 \pm 0.9) \times 10^{-5}$	–	24.1
7h	Z = F, *n* = 3, R^2 = Me, R^3 = *t*-Bu (cis H, OMe)	*t*-$BuNH_2$ (4)	6	60[c]	base	oil	$C_{21}H_{31}O_3N_2F$[e]	$(4.5 \pm 2.9) \times 10^{-7}$	0.007	$(8.3 \pm 0.9) \times 10^{-7}$	0.014	1.84
7i	Z = F, *n* = 3, R^2 = Me, R^3 = HVA[a] (cis H, OMe)	HVA-NH_2[a] (4)	5	54[c]	oxalate	114	$C_{27}H_{35}O_5N_2F$[f]·HOOC–COOH·H_2O	$>10^{-5}$	–	$>10^{-5}$	–	–
7j	Z = H, *n* = 8, R^2 = Me, R^3 = i-Pr (cis H, OMe)	*i*-$PrNH_2$ (4)	3	60[c]	oxalate	118	$C_{25}H_{40}O_3N_2$[f]·HOOC–COOH·$2.5H_2O$	$>10^{-5}$	–	$>10^{-5}$	–	–
7k	Z = H, *n* = 8, R^2 = Me, R^3 = HVA[a] (cis H, OMe)	HVA-NH_2[a] (4)	7	44[c]	oxalate	128	$C_{32}H_{46}O_5N_2$[f]·HOOC–COOH·$1.5H_2O$	$>10^{-5}$	–	$>10^{-5}$	–	–
7l	Z = H, *n* = 3, R^2 = H, R^3 = *i*-Pr (cis H, OH)	*i*-$PrNH_2$ (1.1)	5	33[d]	base	174	$C_{19}H_{28}O_3N_2$[e]	$>10^{-5}$	–	$>10^{-5}$	–	–
7m	Z = H, *n* = 3, R^2 = H, R^3 = *t*-Bu (cis H, OH)	*t*-$BuNH_2$ (1.1)	5	48[d]	HCl	118	$C_{20}H_{30}O_3N_2$[f]·HCl·$2H_2O$	$(3.1 \pm 2.6) \times 10^{-5}$	0.0001	$(2.8 \pm 1.8) \times 10^{-6}$	0.004	0.09
7n	Z = H, *n* = 3, R^2 = CH_2CH_2OH, R^3 = *i*-Pr (cis H, $O(CH_2)_2OH$)	*i*-$PrNH_2$ (1.1)	5	68[d]	base	oil	$C_{21}H_{32}O_4N_2$[e]	$>10^{-5}$	–	$>10^{-5}$	–	–
7o	Z = H, *n* = 3, R^2 = CH_2CH_2OH, R^3 = *t*-Bu (cis H, OCH_2CH_2OH)	*t*-$BuNH_2$ (1.1)	5	63[d]	base	133	$C_{22}H_{34}O_4N_2$[f]	$(3.1 \pm 2.7) \times 10^{-6}$	0.001	$(8.5 \pm 3.4) \times 10^{-7}$	0.013	0.28
7p	Z = H, *n* = 4, R^2 = H, R^3 = *i*-Pr (cis H, OH)	*i*-$PrNH_2$ (1.1)	5	68[d]	base	oil	$C_{20}H_{30}O_3N_2$[e]	$>10^{-5}$	–	$(8.9 \pm 3.2) \times 10^{-7}$	0.012	–
7q	Z = H, *n* = 4, R^2 = H, R^3 = *t*-Bu (cis H, OH)	*t*-$BuNH_2$ (1.1)	5	47[d]	base	oil	$C_{21}H_{32}O_3N_2$[e]	$(4.4 \pm 2.8) \times 10^{-7}$	0.007	$(3.4 \pm 2.1) \times 10^{-7}$	0.032	0.79
7r	Z = H, *n* = 4, R^2 = $(CH_2)_2OH$, R^3 = *i*-Pr (trans H, CH_2CH_2OH)	*i*-$PrNH_2$ (1.1)	14	51[d]	base	oil	$C_{22}H_{34}O_4N_2$[e]	$>10^{-5}$	–	$>10^{-5}$	–	–
7s	Z = H, *n* = 4, R^2 = $(CH_2)_2OH$), R^3 = *t*-Bu (trans H, CH_2CH_2OH)	*t*-$BuNH_2$ (1.1)	12	54[d]	base	oil	$C_{23}H_{36}O_4N_2$[f]·$0.5H_2O$	$(7.9 \pm 3.9) \times 10^{-6}$	0.0004	$>10^{-5}$	–	–

[a] HVA = CH_2CH_2-3,5-$(OMe)_2C_6H_3$. [b] Yields of isolated (aryloximino)propanolamines 7 with respect to indanone oximes 5. [c] Yields obtained with 4 equiv of NaH, $\overline{CH_2OCH(CH_2Cl)}$, and the appropriate amine. [d] Yields obtained with 1.1 equiv of NaH, $\overline{CH_2OCH(CH_2Cl)}$, and the appropriate amine. [e] Mass spectra are recorded. [f] Formula determined by analyses C, H, and N. Analyses were within ±0.4% of the theoretical values. [g] IC_{50} on isolated guinea pig trachea (IT) or atria (IA) is the molar concentration of the tested compound necessary to give 50% inhibition of the isoproterenol submaximal response. Values are the mean ±SEM of three experiments. [h] Activity vs propranonol is the ratio:IC_{50}(propranolol)/IC_{50}(compound tested). Propranolol IC_{50} were as follows: guinea pig trachea $(3.0 \pm 1.1) \times 10^{-9}$ M and guinea pig atria $(1.12 \pm 0.61) \times 10^{-8}$ M.

to be **7b**, which revealed on the isolated guinea pig trachea a lower potency than that of propranolol, but a very high selectivity for β_2 adrenoceptors. Its ratio β_2 activity/β_1 activity value is 343, which is the highest β_2 adrenergic blocking activity ever described. This ratio is 41 for butoxamine, 158 for IPS 339,[11] 22 for 1-[3-[(1,1-dimethylmethyl)amino]-2-hydroxypropoxy]-4b,6,7,8,9,9a-hexahydro-5*H*-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol,[1] or 123 for ICI 118,551.[12] Conversely, **7m** and, in a lesser way, **7o**, **7e**, and **7q** are rather β_1 selective but with low potency.

Under our experimental conditions, propranolol is a competitive antagonist against both the isoproterenol-induced relaxation on the guinea pig trachea and the increase of inotropism of the guinea pig atria. The slope of the regression lines and pA_2 (calculated according to Arunlakshana and Schild[13]) are respectively 0.95, 0.86, 9.36, and 8.92. Conversely, **7b**, **7g**, and **7d** antagonist effects vs isoproterenol on the isolated guinea pig trachea and atria do not appear to be of the competitive type since slopes of the regression lines are respectively 0.56, 0.54, 0.74 and 0.38, 0.41, 0.3.

With regard to the structure–activity relationships, the following points emerge from Table III.

(1) The functionalization of the nitrogen atom of the lateral chain by a homoveratryl group (**7c**, **7i**, **7f**, **7k**) induces a loss of activity. The cardioselectivity of the compound was never increased as could be expected.[14]

(2) Similarly, increasing the size of the saturated ring to 11 carbons **7i**, **7k** instead of six or seven carbons in other compounds leads to a loss of activity.

(3) Replacement of a methoxy group with an hydroxy group (R^2 = Me → R^2 = H) strongly decreases the activity (**7l**, **7a**, **7m**, **7b**, **7p**, **7d**), with the exception of **7q**, **7e**. In a previous paper, we have also shown in another series of β-blocking drugs that introduction of an OH group on the same side as the oxypropanolamine substituent decreases the activity, but the activity was increased if the OH group was situated at the opposite side.[1]

(4) Introduction of a fluorine atom on the aromatic ring (**7g**, **7a**) slightly reduces the activity.

(5) No clear relationship appears to be predictive of β_2 selectivity.

Experimental Section

Melting points were obtained on a Kofler hot-stage apparatus. The IR spectra were taken on a Perkin-Elmer 257 and UV spectra with a Beckman DK 2A spectrophotometer. ^{1}H NMR were recorded at 60 MHz on a Perkin-Elmer R12B instrument or at 80 MHz on a Brucker AW 80. ^{13}C NMR spectra were obtained on a Brucker WP 80 spectrometer or on a Brucker AM 400 with Me_4Si as internal standard. Elemental analyses were performed by CNRS Laboratory (Vernaison) and by François M. (Strasbourg). Mass spectra were performed in the Mass Spectroscopy Laboratory of Nancy. Thin-layer chromatography was performed by using Kieselgel G (Merck) with an hexane–EtOAc mixture as eluent. The silica gels used for liquid-phase chromatography and flash chromatography were respectively Kieselgel 0.063 (0.2 mm) and Kieselgel 0.04 (0.063 mm). High-pressure liquid chromatography was carried out on a Waters PREP 500 chromatograph with a silica gel column. Analytical HPLC was performed in a Waters Model 6000 A instrument with a stainless stell column Merck Hibar RT 250-4 (Lichrosorb Si 60-5 μM). GLC analyses were carried out with a Girdel Model 300 instrument with a 15% SE-30 column (Chromosorb WDMCS).

2- and 3-Fluoro-5,6,7,8,9,9a-hexahydro-5,5-dimethoxy-4b*H*-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (3, Z = F^1, *n* = 4, R^1 = Me). To the enolate of 2,2-dimethoxycyclohexanone (50 mM) prepared in THF as previously described[5] was slowly added *p*-bromofluorobenzene (25 mM) in THF (20 mL) at room temperature. Stirring was continued for 1 h at this temperature. Upon completion, the reaction mixture was poured into ice and extracted with ether. The organic layer was dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was chromatographed by HPLC. This reaction led to two benzocyclobutenic compounds due to the formation of unsymmetric fluoroaryne. The less polar was **2-fluoro-5,6,7,8,9,9a-hexahydro-5,5-dimethoxy-4b*H*-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (3, *n* = 3, R^1 = CH_3, Z = F^2)** (1.89 g, 30% yield): IR (NaCl) 3200–3610 (OH), 1595–1615 cm^{-1} (substituted aromatic); UV (MeOH) λ (log ϵ) 279 (3.39), 273.5 (3.44), 266 (sh); ^{1}H NMR (CCl_4) δ 0.95–2.44 (m, 8 H, 4 × CH_2), 2.98–3.62 m, 8 H with 2 s at 3.19 and 3.36; C(OCH_3)$_2$, benzylic H, OH exchanged with D_2O), 6.74–7.41 (m, 3 H aromatics H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.6, 30.1, 32.7 (aliphatic C), 49.8, 50.0 (OCH_3 × 2), 57.2 (PhCH), 85.2 (COH), 103.5 [C(OMe)$_2$], [110.7 (d, J = 22 Hz), 116.3 (d, J = 23.2 Hz), 123.6 (d, J = 8.5 Hz), 142.1, 147.1 (d, J = 6.1 Hz), 162.4 (d, J = 244.1 Hz), aromatic C]. Anal. ($C_{15}H_{19}O_3F$) C, H, F. The most polar was **3-fluoro-5,6,7,8,9,9a-hexahydro-5,5-dimethoxy-4b*H*-benzo[3,4]cyclobuta[1,2]cyclohepten-4b-ol (3, *n* = 3, R^1 = CH_3, Z = F^1)** (1.58 g, 25% yield): IR (NaCl) 3160–3700 (OH), 1590–1610 cm^{-1} (substituted aromatic); ^{1}H NMR (CCl_4) δ 1.00–2.88 (m, 8 H (4 × CH_2)), 3.05–3.67 (m, 8 H, with 2 s at 3.22 and 3.38 (OCH_3 × 2; PhCH; OH exchanged with D_2O)), 6.62–7.32 (m, 3 H (aromatic H)); UV (MeOH) λ (log ϵ) 276.5 (3.33), 270.7 (3.39), 267.5 (sh); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.8, 29.9, 32.8 (4 × CH_2), 50.0 (OCH_3 × 2), 57.7 (PhCH), 85.0 (COH), 103.65 [C(OMe)$_2$] [109.7 (d, J = 22 Hz), 114.9 (d, J = 23.2 Hz), 125.1 (d, J = 8.6 Hz), 141.1, 148.5 (d, J = 7.3 Hz), 163.6 (d, J = 246.6 Hz) aromatic C]. Anal. ($C_{15}H_{19}O_3F$) C, H, F.

***cis*-9a-Hydroxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one [4, *n* = 3, R^2 = H, Z = H (cis H, OH)].** To a solution of 10% HCl (20 mL) was added alcohol **3** (*n* = 3, R^1 = Me, Z = H) (2 mmol) in MeOH (20 mL). The reaction was instantaneous (monitored by TLC), and the mixture was poured into water and extracted with ethyl ether. The organic layer was then washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. A rapid filtration on column chromatography gave compound **4** (*n* = 3, R^2 = H, Z = H) (323 mg, 80% yield): IR (KBr) 3570 (OH), 1730 cm^{-1} (C=O); UV λ (log ϵ) 293 (3.51), 246 (4.13); ^{1}H NMR ($CDCl_3$) δ 1.00–2.40 (8 H, 2 m, 4 × CH_2), 3.17 (1 H, OH exchanged with D_2O), 3.30 (1 H, pseudo t, benzylic H), 7.18–7.89 (4 H, m, ArH), ^{13}C NMR ($CDCl_3$) δ 208.30 (C=O), 153.54, 135.41, 133.83, 127.29, 124.92, 124.25 (aromatic C), 80.10 (COH), 44.60 (benzylic C), 32.70, 23.60, 20.30 (4 × CH_2); mp 144 °C (petroleum ether). Anal. ($C_{13}H_{14}O_2$) C, H.

***cis*-2,3,4,5,5a,10a-Hexahydro-10a-hydroxycyclohept[*a*]-inden-10(1*H*)-one [4, *n* = 4, R^2 = H, Z = H (cis H, OH)].** To alcohol **3** (*n* = 4, R^1, R^1 = $-CH_2CH_2-$, Z = H) (6 mmol) in acetone (20 mL) were added 10 drops of 12 N HCl and 5 mL of H_2O. After stirring at room temperature for 72 h, the mixture was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated in vacuo. The product was purified by liquid chromatography (985 mg, 76% yield): IR (KBr) 3600–3200 (OH), 1710 cm^{-1} (C=O); UV λ (log ϵ) 294 (3.45), 248.5 (4.15); ^{1}H NMR (CCl_4) δ 0.82–2.80 (10 H, m, 5 × CH_2), 2.96–3.62 (2 H, m, OH exchanged with D_2O, benzylic H), 7.16–7.98 (4 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 208.64 (C=O), 156.66, 135.88, 133.58, 127.77, 125.52, 124.43 (aromatic C), 82.39 (COH), 51.74 (benzylic C), 34.96, 31.87, 31.26, 26.72, 22.78 (5 × CH_2); MS ($C_{14}H_{16}O_2$), *m/e* 216 (M^+).

***trans*-2,3,4,5,5a,10a-Hexahydro-10a-methoxycyclohept-[*a*]inden-10(1*H*)-one [4, *n* = 4, R^2 = Me, Z = H (trans H, OMe)].** To a stirred solution of alcohol **3** (*n* = 4, R^1 = Me, Z = H) (2 mmol) in dry MeCN (10 mL) was added Me_3SiCl (5 mmol). The reaction was instantaneous (monitored by TLC). After addition of powdered $NaHCO_3$ until neutrality, the solution was filtered off and the solvent evaporated under vacuum. Keto ether **4** (*n* = 4, R^2 = Me, Z = H) was purified by liquid chromatography (285 mg, 62% yield); IR (NaCl) 1720 cm^{-1} (C=O); UV (MeOH) λ (log ϵ) 294 (3.33), 249 (3.98); ^{1}H NMR (CCl_4) δ 0.78–2.78 (10

(11) Imbes, J. L.; Miesch, F.; Schwartz, J.; Velly, J.; Leclerc, G.; Mann, A.; Wermuth, C. G.; Br. J. Pharmacol. 1977, 60, 357.
(12) Poilski, A.; Dorries, S.; Fitzgerald, J. D.; Sessup, R.; Tucker, H.; Wale, J. *Br. J. Pharmacol.* **1980**, *69*, 292P.
(13) Arunlakshana, G.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
(14) Hoeffe, M. L.; Hastings, S. G.; Meyer, R. F.; Corey, R. M.; Holmes, A.; Stratton, C. D. *J. Med. Chem.* **1975**, *18*, 149.

H, m, 5 × CH_2), 3.00–3.42 (4 H, m, benzylic H with s at 3.13, OMe), 7.10–7.83 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 202.35 (C=O), 155.66, 135.03, 134.6, 127.31, 124.28, 124.20 (aromatic C), 82.75 (COMe), 50.77 (OCH_3), 48.95 (benzylic C), 27.70, 26.91, 25.81, 24.34 (5 × CH_2); MS ($C_{19}H_{18}O_2$), *m/e* 230 (M^+).

***cis*-9a-Methoxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one [4, *n* = 3, R^2 = Me, Z = H (cis H, OMe)].** This compound was prepared by the same method as for **4** (*n* = 3, R^2 = Me, Z = H) starting from **3** [*n* = 3, Z = H, R^1 = CH_3 (cis H, OH)]. After completion and the usual work-up procedure, the residue was purified on chromatography column (263 mg, 61% yield): IR (NaCl) 1710 cm^{-1} (C=O); UV (MeOH) λ (log ε) 295 (3.40), 248 (4.22); ^1H NMR (CCl_4) δ 0.97–2.29 (8 H, m, 4 × CH_2), 3.11–3.57 (4 H, m, benzylic H with s at 3.22, OCH_3), 7.12–7.82 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 205.47 (C=O), 154.64, 135.11, 134.33, 127.55, 124.52, 124.23 (aromatic C), 84.51 (COMe), 52.06 (OCH_3), 40.36 (benzylic C), 29.63, 25.43, 21.02, 20.48 (4 × CH_2); mp 90 °C (petroleum ether). Anal. ($C_{14}H_{16}O_2$) C, H.

***cis*-7-Fluoro-9a-methoxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one [4, *n* = 3, R^2 = Me, Z = F (cis H, OMe)].** This compound was prepared by the same method as for **4** (*n* = 3, R^2 = CH_3, Z = H) starting from **3** [*n* = 3, R^1 = Me, Z = F (cis H, OH)] (281 mg, 60% yield): IR (NaCl) 1725 cm^{-1} (C=O); UV (MeOH) λ (log ε) 301.5 (3.61), 244.5 (4.11); ^1H NMR (CCl_4) δ 0.89–2.40 (m, 8 H, 4 × CH_2), 3.07–3.60 (m, 4 H with s at 3.24, OCH_3, PhCH), 6.95–7.69 (m, 3 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 208.51 (C=O), 162.08 (*J* = 246 Hz), 144.2 (d, *J* = 7 Hz), 137.55, 124.78 (*J* = 8.6 Hz), 121.19 (*J* = 23 Hz), 111.05 (*J* = 22 Hz), (aromatic C), 82.66 (COMe), 50.78, 48.69 (benzylic C, OCH_3), 25.57, 23.72, 21.28, 20.30 (4 × CH_2). Anal. ($C_{14}H_{15}O_2F$) C, H, F.

***cis*-9a-[(2-Hydroxyethyl)oxy]-1,2,3,4,4a,9a-hexahydrofluoren-9-one [4, *n* = 3, Z = H, R^2 = CH_2CH_2OH (cis H, OCH_2CH_2OH)].** To a stirred solution of alcohol **3** (*n* = 3, R^1, R^1 = $-CH_2CH_2-$, Z = H) (2 mmol) in CH_2Cl_2 (10 mL) maintained at 0–5 °C was slowly added BF_3–OEt_2 (2.2 mmol) diluted in CH_2Cl_2 (5 mL). At the end of the addition, the mixture was allowed to warm to room temperature. At the completion (monitored by TLC), a saturated solution of $NaHCO_3$ (20 mL) was added and the stirring maintained for 10 min. After extraction with CH_2Cl_2, drying over $MgSO_4$, and removal of the solvents in vacuo, the products were purified by liquid chromatography (383 mg, 78% yield): IR (NaCl) 3680–3100 (OH), 1710 cm^{-1} (C=O); UV (MeOH) λ (log ε) 295 (3.32), 249 (3.94); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.20–2.09 (8 H, m, 4 × CH_2), 2.37–2.80 (1 H, m, OH exchanged with D_2O), 3.46–3.51 (1 H, pt, benzylic H), 3.51–3.58 and 3.65–3.76 (1 H and 3 H, 2 m, $COCH_2CH_2OH$), 7.36–7.78 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 206.81 (C=O), 153.72, 135.34, 127.69, 124.47, 124.46 (aromatic C), 84.82 ($COCH_2CH_2OH$), 66.33, 62.05 (OCH_2CH_2OH), 40.51 (benzylic C), 30.46, 24.61, 20.83, 20.48 (4 × CH_2); MS ($C_{15}H_{18}O_3$), *m/e* 246 (M^+).

***trans*-10a-[(2-Hydroxyethyl)oxy]-2,3,4,5,5a,10a-hexahydrocyclohept[*a*]inden-10(1*H*)-one [4, *n* = 4, R^2 = CH_2CH_2OH, Z = H (trans H, OCH_2CH_2OH)].** This compound was prepared by the same method as for **4** [*n* = 3, R^2 = CH_2CH_2OH, Z = H (cis H, OCH_2CH_2OH)] starting from **3** (*n* = 4, R^1, R^1 = $-CH_2CH_2-$, Z = H). After completion and the usual work-up procedure, the residue was purified on chromatography column (312 mg, 60% yield): IR (NaCl) 3700–3110 (OH), 1710 cm^{-1} (C=O); UV (MeOH) λ (log ε) 296.5 (3.33), 250 (4.10); ^1H NMR (400 MHz) ($CDCl_3$) δ 1.11–2.58 (11 H, m, 5 × CH_2 and OH exchanged with D_2O), 3.32–3.39 (1 H, dd, J_1 = 6 Hz, J_2 = 12 Hz, benzylic H), 3.44–3.51 and 3.53–3.65 (1 H and 3 H, 2 m, $COCH_2CH_2OH$), 7.24–7.89 (4 H, m, aromatic H); ^{13}C NMR ($CDCl_3$) δ 202.80 (C=O), 156.28, 135.87, 135.20, 127.84, 125.16, 124.49 (aromatic C), 84.67 ($COCH_2CH_2OH$), 64.49, 62.55 (OCH_2CH_2OH), 48.19 (benzylic C), 28.78, 27.11, 25.77, 24.43 (5 × CH_2). Anal. ($C_{16}H_{20}O_3$) C, H.

***cis*-14a-Methoxy-1,2,3,4,5,6,7,8,9a,14a-decahydrocyclohendec[*a*]inden-14-one [4, *n* = 8, R^2 = Me, Z = H (cis H, OMe)]. Preparation in Two Steps.** By the same procedure described for the preparation of compound **4** [*n* = 4, R^2 = H, Z = H (cis H, OH)], starting from alcohol **3** [*n* = 8, R^1, R^1 = $-CH_2CH_2-$, Z = H (trans H, OH)], compounds **4** [*n* = 8, R^1 = H, Z = H (cis and trans)] were obtained.

4 [*n* = 8, R^2 = H, Z = H (cis H, OH)] (636 mg, 39% yield): IR (KBr) 3580–3110 (OH), 1710 cm^{-1} (C=O); UV (MeOH) λ (log ε) 294 (3.42), 247.5 (4.01); ^1H NMR (CCl_4) δ 0.82–2.13 (18 H, m, 9 × CH_2), 2.73 (1 H, pseudo t, OH exchanged with D_2O), 3.02–3.31 (1 H, s, benzylic H), 7.15–7.85 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 208.64 (C=O), 155.06, 135.61, 133.04, 127.75, 125.15, 124.34 (aromatic C), 84.73 (COH), 50.64 (benzylic C), 33.77, 27.33, 26.98, 26.40, 25.04, 24.71, 21.43, 20.70, 18.89 (9 × CH2); mp 110 °C (petroleum ether); MS ($C_{18}H_{24}O_2$), *m/e* 272 (M^+).

4 [*n* = 8, R^2 = H, Z = H (trans H, OH)] (846 mg, 52% yield); IR (KBr) 3560–3160 (OH), 1695 cm^{-1} (C=O); UV (MeOH) γ (log ε) 296 (3.67), 249 (4.24), ^1H NMR (CCl_4) δ 0.89–2.62 (18 H, m, 9 × CH_2), 2.91 (1 H, pseudo s, OH exchanged with D_2O), 3.42–3.82 (1 H, m, benzylic H), 7.15–8.04 (4 H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 209.61 (C=O), 158.34, 136.00, 133.01, 127.78, 126.10, 124.67 (aromatic C), 80.62 (C-OH), 45.13 (benzylic C), 36.16, 30.26, 27.87, 27.35, 26.98, 25.48, 24.21, 22.66, 20.71 (9 × CH_2). Anal. ($C_{18}H_{24}O_2$) C, H. Hydroxyindanone **4** [*n* = 8, R^1 = H, Z = H (cis H, OH)] (4 mmol) was dissolved in CH_2Cl_2 (10 mL) with CH_3I (8 mmol, 2 equiv); 0.5 equiv of *n*-$Bu_4N^+Br^-$ and 50% aqueous NaOH were added, and the mixture was vigourously stirred at room temperature for 24 h. The two phases were decanted, and the aqueous layer was extracted twice with CH_2Cl_2. After drying over $MgSO_4$ and evaporation of the solvent in vacuo, keto ether **4** [*n* = 8, R^2 = Me, Z = H (cis H, OMe)] was rapidly isolated by chromatography on a short column (915 mg, 80% yield).

***cis*-9a-Hydroxy-1,2,3,4,4a,9b-hexahydrofluoren-9-one Oxime [5, *n* = 3, R^2 = H, Z = H (cis H, OH)]. General Procedure.** A mixture of compound **4** [*n* = 3, R^2 = H, Z = H (cis H, OH)] (20 mmol), NH_2OH, HCl (40 mmol), and pyridine (10 mL), in EtOH (30 mL) was refluxed during the time indicated in Table II. The reaction mixture was then poured into water and extracted with Et_2O. The organic layer washed twice with a 10% HCl solution to remove pyridine and dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was chromatographed on flash chromatography with a mixture EtOAc–petroleum ether as eluent. Crude oxime **5** [*n* = 3, R^1 = H, Z = H (cis H, OH)] was obtained as a white powder: yields of indanone oxime **5** are given in Table II; IR ($CHCl_3$) 3660–3000 (OH), 1665 cm^{-1} (C=N); UV (MeOH) γ (log ε) 249.5 (4.25), 287 (3.77), 295 (3.69), ^1H NMR (CCl_4) δ 0.60–2.06 (m, 8 H, 4 × CH_2), 2.48 (s, 1 H, OH exchanged with D_2O), 2.80 (pt, 1 H, PhCH), 6.77–7.28 and 7.84–8.15 (2 m, 3 H and 1 H, aromatic H), 10.04 (s, 1 H, OH exchanged with D_2O); ^{13}C NMR ($CDCl_3$) δ 161.4 (C=N), 149.8, 132.2, 131.2, 130.2, 127.4, 124.5 (aromatic C), 79.2 (COH), 49.9 (PhCH), 34.8, 30.0, 29.8, 22.6 (4 × CH_2); mp 125 °C (petroleum ether). Anal. ($C_{13}H_{15}O_2N·0.5H_2O$) C, H, N.

***o*-[2-Hydroxy-3-(*tert*-butylamino)propyl]-*cis*-9a-hydroxy-1,2,3,4,4a,9b-hexahydrofluoren-9-one Oxime (7m).** After washing of NaH (5.5 mmol) three times with DMF (3 × 10 mL) under nitrogen atmosphere and addition of DMF (10 mL), ketone oxime **5** (*n* = 3, R^2 = H, Z = H) (5 mmol) in DMF (10 mL) was added dropwise. The solution was stirred magnetically for 2 h. This solution was then added dropwise to a solution of epichlorhydrin (5.5 mmol) in DMF (10 mL) and the mixture was stirred 2 h. The mixture was poured into ice water and extracted twice with Et_2O. The organic layer was dried over $MgSO_4$ and filtered off, solvents were evaporated, and the remaining DMF was removed by distillation (20 mmHg). The oily residue was dissolved in dry EtOH (20 mL) containing *t*-$BuNH_2$ (5.5 mmol) and the mixture was refluxed for 5 h. The solvents were removed in vacuo, the oily residue was dissolved in dilute HCl (10%) and extracted with Et_2O. The aqueous layer was made alkaline with NaOH (20%) and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and the solvent evaporated. Purification was performed under medium-pressure chromatography column with MeOH as solvent: IR (KBr) 3660–3220 cm^{-1} (OH, NH); UV (MeOH) γ (log ε) 254 (4.06), 265 (4.03), 286 (3.83), 2.99 (3.66); ^1H NMR δ ($CDCl_3$) 0.9–3.6 (m, 30 H with s at 2.8, OMe, 9 × CH_2, PhCH, $CH_2NHCH_2CH_2$, OH and NH exchanged with D_2O), 3.8 (s, 6 H, 2 × $PhOCH_3$), 3.9–4.4 (m, 3 H, $CHOCH_2$), 6.5–6.9 and 7.0–7.5 and 7.9–8.4 (3 m, 4 H, aromatic H); ^{13}C NMR (CD_3OD) δ 21.8, 23.7, 24.5, 25.2, 25.5, 26.1, 27.0, 30.0, 30.9 (9 × CH_2), 48.2, 48.6, 49.7, 49.8 (PhCH, $PhCH_2$, CH_2NHCH_2), 54.8 (2 × PhOMe), 64.8 ($COCH_3$), 75.4 (OCH_2), 86.0 (COMe), 111.1, 111.5, 120.1, 122.6, 125.9, 128.1, 128.4, 130.6, 130.7, 147.4 148.5, 150.8 (aromatic C), 157.1 (C=N), 163.7 (COOH); mp 128 °C (EtOAc–petroleum ether). The analysis was made on the oxalate salt. Anal.

($C_{21}H_{32}O_3N_2$·HOOC–COOH·1.5H_2O) C, H, N.

Pharmacology. β_1- and β_2-adrenergic blocking activities were determined in vitro on the isolated guinea pig atria and trachea.

Isolated Guinea Pig Atria. Guinea pigs of either sex, weighing from 250 to 350 g, were stunned by a blow on the head, and their hearts were quickly removed. The left atrium was dissected free and mounted in a muscle chamber containing 25 mL of Krebs solution gassed with O_2 plus CO_2 (95:5). The resting muscle tension applied to all preparations was adjusted to 0.5 g throughout the course of each experimental study. All experiments were performed at 37 °C. Concentration–response curves to isoproterenol-positive inotropic action were determined before and after increasing cumulative doses of drugs. Thus, after control responses to five cumulative concentrations of isoproterenol (10^{-9} to 10^{-7} M; exposure time, 2–3 min) had been obtained, increased concentrations of our new compounds or propranolol (exposure time, 15 min) were added to the bath, and dose–response curves to isoproterenol were determined again. Experiments were performed on groups of at least three preparations. The β-blocking effect of drugs was calculated from the concentration–response curves to isoprenaline (inotropism increase induced) and expressed as IC_{50}, i.e. the drug concentration inhibiting 50% of the response to the isoprenaline concentration giving 90–100% of the maximal effect.

Isolated Guinea Pig Trachea. Trachea spirals cut were equilibrated under an initial tension of 1.50 g in Krebs solution at 37 °C, gassed with O_2 plus CO_2 (95:5). The resting tension was between 0.4 and 1.0 g. The effects of isoproterenol (3×10^{-8} to 3×10^{-6} M) were tested against 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 contraction induced by ACh were developed. Experiments were performed on groups of at least three preparations. IC_{50} were assessed as described above.

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Registry No. **3** [n = 3, R^1 = CH_3, Z = 2-F(cis-H, OH)], 118017-57-5; **3** (n = 3, R^1 = CH_3, Z = 3-F), 118017-58-6; **3** [n = 3, R^1 = Me, Z = H(cis-H, OH)], 100703-72-8; **3** (n = 4, R^1,R^1 = CH_2CH_2, Z = H), 89874-29-3; **3** (n = 4, R^1 = Me, Z = H), 116822-93-6; **3** (n = 3, R^1,R^1 = CH_2CH_2, Z = H), 89874-28-2; **3** (n = 8, R^1,R^1 = CH_2CH_2, Z = H(trans-H,OH)], 100837-45-4; **4** [n = 3, R^2 = H, Z = H (cis-H,OH)], 116823-15-5; **4** [n = 4, R^2 = H, Z = H (cis-H,OH)], 116823-17-7; **4** [n = 4, R^2 = Me, Z = H (trans-H,OMe)], 116823-07-5; **4** [n = 3, R^2 = Me, Z = H(cis-H,-OMe)], 116823-05-3; **4** [n = 3, R^2 = Me, Z = F(cis-H,OMe)], 118017-59-7; **4** [n = 3, Z = H, R^2 = CH_2CH_2OH(cis-H,-OCH_2CH_2OH)], 116823-09-7; **4** [n = 4, R^2 = CH_2CH_2OH, Z = H(trans-H,OCH_2CH_2OH)], 116823-10-0; **4** [n = 8, R^2 = Me, Z = H (cis-H,OMe)], 116823-21-3; **4** [n = 8, R^2 = H, Z = H (cis-H,OH)], 116908-29-3; **4** [n = 8, R^2 = H, Z = H (trans-H,OH], 116823-20-2; **5** [Z = H, n = 3, R^2 = H (cis-H,OH) syn], 118017-60-0; **5** [Z = H, n = 3, R^2 = H (cis-H,OH) anti], 118017-61-1; **5** (Z = H, n = 4, R^2 = H), 118017-62-2; **5** (Z = H, n = 4, R^2 = Me), 118017-63-3; **5** [Z = H, n = 3, R^2 = Me (cis-H,OMe)], 118017-64-4; **5** [Z = F, n = 3, R^2 = Me(cis-H,OMe)], 118017-65-5; **5** [Z = H, n = 3, R^2 = CH_2CH_2OH (cis-H, OCH_2CH_2OH)], 118017-66-6; **5** [Z = H, n = 4, R^2 = CH_2CH_2OH (trans-H,OCH_2CH_2OH)], 118017-67-7; **5** [Z = H, n = 8, R^2 = Me (cis-H,OMe)], 118017-68-8; **7a**, 118017-69-9; **7b**, 118017-70-2; **7b**·oxalate, 118017-71-3; **7c**, 118017-72-4; **7d**, 118017-73-5; **7d**·oxalate, 118017-74-6; **7e**, 118017-75-7; **7e**·oxalate, 118017-76-8; **7f**, 118017-77-9; **7f**·oxalate, 118017-78-0; **7g**, 118017-79-1; **7g**·oxalate, 118017-80-4; **7h**, 118017-81-5; **7i**, 118017-82-6; **7i**·oxalate, 118070-30-7; **7j**, 118017-83-7; **7j**·oxalate, 118017-84-8; **7k**, 118017-85-9; **7k**·oxalate, 118017-86-0; **7l**, 118017-87-1; **7m**, 118017-88-2; **7m**·HCl, 118017-89-3; **7n**, 118017-90-6; **7o**, 118017-91-7; **7p**, 118017-92-8; **7q**, 118017-93-9; **7r**, 118017-94-0; **7s**, 118017-95-1; *i*-$PrNH_2$, 75-31-0; *t*-$BuNH_2$, 75-64-9; $HUANH_2$, 3213-28-3; 2,2-dimethoxy-1-hydroxycyclohexene, 118017-96-2; *p*-bromofluorobenzene, 460-00-4; epichlorhydrin, 106-89-8.

Supplementary Material Available: Full IR, UV, ^1H NMR and ^{13}C NMR for all prepared oximes **5** and all prepared (aryloximino)propanolamines (6 pages). Ordering information is given on any current masthead page.

Selective Thyromimetics. Cardiac-Sparing Thyroid Hormone Analogues Containing 3′-Arylmethyl Substituents

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Introduction of specific arylmethyl groups at the 3′-position of the thyroid hormone 3,3′,5-triiodo-L-thyronine (T_3), and its known hormonally active derivatives, gives liver-selective, cardiac-sparing thyromimetics, with potential utility as plasma cholesterol lowering agents. Selectivity-conferring 3′-substituents include substituted benzyl, e.g. *p*-hydroxybenzyl, and heterocyclic methyl, e.g. 2-oxo-1,2-dihydropyrid-5-ylmethyl and 6-oxo-1,6-dihydropyridazin-3-ylmethyl. Correlations between in vivo and in vitro receptor binding affinities show that liver/heart selectivity does not depend on receptor recognition but on penetration or access to receptors in vivo. QSAR studies of the binding data of a series of 20 3′-arylmethyl T_3 analogues show that electronegative groups at the para position increase both receptor binding and selectivity in vivo. However, increasing 3′-arylmethyl hydrophobicity increases receptor binding but reduces selectivity. Substitution at ortho and meta positions reduces both binding and selectivity. Replacement of the 3,5-iodo groups by halogen or methyl maintains selectivity, with 3,5-dibromo analogues in particular having increased potency combined with oral bioavailability. Diphenyl thioether derivatives also have improved potency but are less orally active. At the 1-position, the D enantiomer retains selectivity, but removal of the α-amino group to give a propionic acid results in loss of selective thyromimetic activity.

It is well known that hypothyroidism is accompanied by high levels of circulating cholesterol in low-density lipoprotein (LDL) and increased risk of atherosclerosis, while in hyperthyroidism LDL cholesterol levels are decreased.[1] Lipoprotein abnormalities in hypothyroid subjects are corrected by administration of thyroid hormones.[2] Although the natural hormones T_3 and T_4 (Figure 1) are potent hypocholesterolemics,[3] they cannot be used thera-

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(1) e.g. (a) O'Hara, P. D.; Porte, D., Jr.; Williams, R. H. *Metabolism* **1966**, *15*, 123. (b) Nikkila, E. A.; Kekki, M. *J. Clin. Invest.* **1972**, *51*, 2103. (c) Kutty, M. K.; Bryant, D. G.; Farid, N. R. *J. Clin. End. Metab.* **1978**, *46*, 55. (d) Katz-Feigenbaum, D.; Braun, L.; Wolinsky, H. *Circ. Res.* **1981**, *49*, 733.

(2) Aviram, M.; Luboschitzky, R.; Brook, J. G. *Clin. Biochem.* **1982**, *15*, 62.

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