Synthesis and β-Adrenergic Blocking Activity of a Novel Class of Aromatic Oxime Ethers

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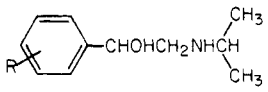
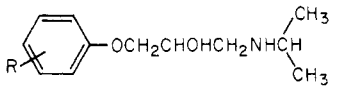
A new series of β-adrenergic blocking amines containing an oximino-propanolic chain linked to an aromatic nucleus was synthesized. Most of the derivatives are characterized by β_2-selectivity. The structure–activity relationships are discussed. One of the compounds, selected for further studies, was more active on the trachea than on the atria of guinea pig, 155 times in vitro and 26 times in vivo. In comparison, butoxamine's β_2-selectivity is 13 in vitro and only 2 in vivo. With a series of 30 acetophenone oxime derivatives, no quantitative structure–activity relationships could be detected.

Most adrenergic β-receptor blocking compounds conform to one of two basic structures, A or B. The recent β-blockers are variants of structure B. Potency or selectivity in these series was essentially sought by varying the nature of the aromatic substituents, the aromatic nucleus itself, or the nature of the terminal amine. In contrast, very few β-blockers have been described in which the side chain itself is modified. Among these, one can mention compounds C and D in which the ethereal oxygen of B is omitted[2] or compounds E and F in which the side chain of B is partially included in a benzofuran[3] or a benzodioxan ring;[4] one can also mention benzoazocine G.[5]



A



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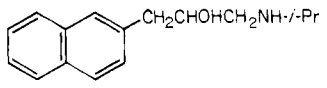
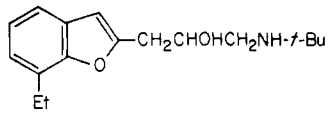
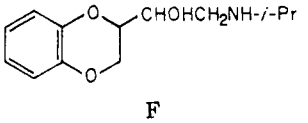


C

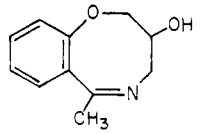
D



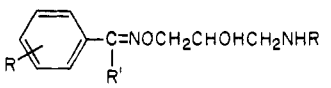
E



F



G

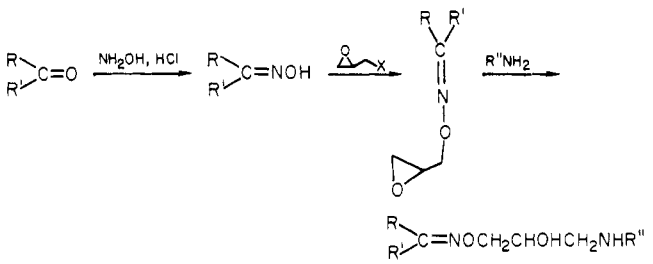


H

Previous work done in this laboratory on oxime derivatives[6] led us to examine another type of side-chain modification illustrated by the general formula H and characterized by the attachment of the 1-alkylamino-2-hydroxypropyl chain to the oxygen of an oxime function. Such compounds can be considered as aza vinylogues of B compounds.

This paper describes the synthesis and the structure–activity relationships in this new series of β-blockers and discusses the pharmacological results. In a preliminary report we have described the potent β-adrenergic blocking activity of (*tert*-butylamino-3-hydroxy-2-propyl)oximino-9-fluorene.[7] While our work was in progress Martani et al. reported on the β-adrenergic blocking activity of some derivatives of aromatic oxime ethers.[8]

Scheme I



Chemistry. The compounds were prepared as indicated in Scheme I and are listed in Tables I–IV.

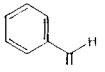
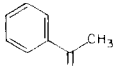
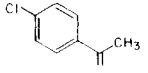
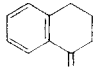
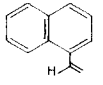
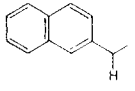
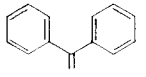
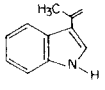
The oximes were usually prepared by refluxing, for 12 h, 2 equiv of hydroxylamine hydrochloride with the appropriate ketone in anhydrous pyridine (method A). For the compounds bearing an acetamido group (**31**, **33**, and **49**) this method led to a considerable amount of hydrolysis of the amide group; in these cases pyridine was replaced by a mixture of water and alcohol or preferably by water and Me_2SO (method B), reported to accelerate formation of oximes.[9]

The sodium salt of the oxime was allowed to react with epichlorohydrin in anhydrous DMF and the crude epoxide treated with an excess of the required amine in ethanol.

The recent report of Hoefle et al.[10] that certain amino substituents, e.g., the 3,4-dimethoxyphenethylamino group, enhance cardioselectivity in a series of 1-amino-3-(substituted phenoxy)-2-propanols induced us to examine the influence of such amines as well. Compounds **5**, **10**, **25**, and **26** were therefore synthesized. The unusual $CHCl_3$ solubility of the hydrochloride salts of these analogues enabled the separation of the end products from 3,4-dimethoxyphenethylamine or 1-methyl-3-phenylpropylamine which are otherwise difficult to eliminate.

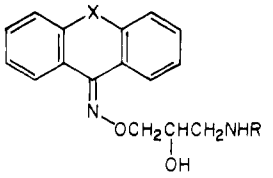
Structure–Activity Relationships. Compounds **1–63** listed in Tables I–IV were evaluated for their in vitro β-blocking activity on tracheal smooth muscle and right atrium from guinea pigs. Table I shows biological results obtained with compounds bearing a mono- or bicyclic aromatic system. Most of the compounds are characterized by bronchoselectivity (β_2/β_1 or T/A > 1). In this respect, tetralone oxime derivatives **8** and **9**, closely followed by the benzophenone oxime derivative **14**, are the most interesting. With the exception of compound **1** the change of

Table I. Physical Properties and β-Blocking Activities of Aromatic Oxime Ethers

		A=NOCH$_2$CHOHCH$_2$NHR					
					Apparent pA_2[c]		Broncho-selectivity,
Compd	A	R	Mp, °C[a]	Emp formula[b]	Atrium[d] (A)	Trachea (T)	T/A
1		*i*-Pr	163	$C_{13}H_{19}N_2O_2$·HCl	5.83 ± 0.12 (8)	6.89 ± 0.20 (7)	11.5
2		*t*-Bu	199	$C_{14}H_{21}N_2O_2$·HCl	6.26 ± 0.21 (5)	6.23 ± 0.09 (4)	0.9
3		*i*-Pr	129	$C_{14}H_{22}N_2O_2$·HCl	6.92 ± 0.45 (7)	7.54 ± 0.16 (4)	4.2
4		*t*-Bu	125	$C_{15}H_{23}N_2O_2$·HCl	6.70 ± 0.21 (5)	7.62 ± 0.13 (4)	8.3
5		-CH(CH$_3$)CH$_2$CH$_2$-C$_6$H$_5$	132[e]	$C_{21}H_{27}N_2O_2$·HCl	5.70 ± 0.14 (5)	5.98 ± 0.31 (9)	1.9
6		*i*-Pr	136	$C_{15}H_{22}N_2O_2$·HCl	6.45 ± 0.29 (7)	7.20 ± 0.46 (9)	5.7
7		*t*-Bu	204[f]	$C_{16}H_{24}N_2O_2$·HCl	6.57 ± 0.20 (7)	7.45 ± 0.25 (8)	8
8		*i*-Pr	110	$C_{16}H_{24}N_2O_2$·HCl	6.12 ± 0.13 (5)	7.90 ± 0.14 (6)	54
9		*t*-Bu	149	$C_{17}H_{26}N_2O_2$·maleate	7.06 ± 0.19 (7)	9.01 ± 0.31 (12)	89
10		-CH$_2$CH$_2$-C$_6$H$_3$-3,4-(OCH$_3$)$_2$	123	$C_{23}H_{27}N_2O_4$·HCl	6.45 ± 0.12 (6)	6.71 ± 0.37 (6)	1.8
11		*t*-Bu	115	$C_{18}H_{24}N_2O_2$·maleate	7.45 ± 0.22 (6)	7.38 ± 0.13 (6)	0.8
12		*i*-Pr	191	$C_{17}H_{22}N_2O_2$·HCl	5.0[g]	6.74 ± 0.20 (6)	
13		*i*-Pr	189	$C_{19}H_{24}N_2O_2$·HCl	6.89 ± 0.31 (6)	7.49 ± 0.19 (4)	4.0
14		*t*-Bu	153	$C_{20}H_{26}N_2O_2$·HCl	6.42 ± 0.26 (11)	7.96 ± 0.50 (8)	35
15		*t*-Bu	140[h]	$C_{17}H_{25}N_3O_2$·0.5citrate	7.69 ± 0.15 (10)	7.23 ± 0.48 (10)	0.3
16[i]		*t*-Bu	146[e]	$C_{14}H_{22}N_2O_2$·fumarate	7.19 ± 0.06 (6)	8.00 ± 0.21 (11)	6.6

[a] All compounds were recrystallized from 2-PrOH–Et_2O unless otherwise noted. [b] All compounds were prepared by method A + D, except compound **10** for which method A + C was used. [c] pA_2 values ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive chronotropic effect. [e] Recrystallized from EtOAc. [f] Recrystallized from 2-PrOH. [g] Noncompetitive antagonism pD'_2. [h] Citrate made in EtOAc and triturated with Et_2O. [i] The initial tropone was prepared according to P. Radlick, *J. Org. Chem.*, **29**, 960 (1964).

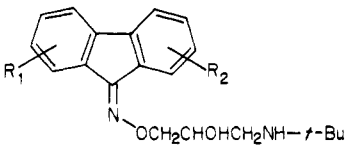
Table II. Physical Properties and β-Blocking Activities of Tricyclic Aromatic Oxime Ethers



Compd	X	R	Mp, °C[a]	Emp formula[b]	Apparent pA_2[c] Atrium[d] (A)	Apparent pA_2[c] Trachea (T)	Broncho-selectivity, T/A
17	CH_2CH_2	*i*-Pr	198	$C_{21}H_{26}N_2O_2 \cdot HCl$	4.70[e]	*f*	
18	CH_2CH_2	*t*-Bu	194	$C_{22}H_{28}N_2O_2 \cdot HCl$	4.40[e]	*f*	
19	CH=CH	*t*-Bu	230	$C_{22}H_{26}N_2O_2 \cdot HCl$	4.73[e]	*f*	
20	CH=CH	*i*-Pr	214	$C_{21}H_{24}N_2O_2 \cdot HCl$	4.65[e]	*f*	
21	Oxygen	*i*-Pr	157	$C_{19}H_{22}N_2O_2 \cdot HCl$	5.40[e]	5.97 ± 0.30 (4)	
22	Oxygen	*t*-Bu	208	$C_{20}H_{24}N_2O_2 \cdot HCl$	7.10 ± 0.45 (5)	6.81 ± 0.21 (6)	0.5
23	None	*i*-Pr	153	$C_{19}H_{22}N_2O_2 \cdot HCl$	7.39 ± 0.32 (8)	6.78 ± 0.09 (5)	0.2
24	None	*t*-Bu	160	$C_{20}H_{24}N_2O_2 \cdot HCl$	7.04 ± 0.24 (10)	9.23 ± 0.24 (25)	155
25	None	$-CH_2CH_2-C_6H_3$-3,4-$(OCH_3)_2$	162	$C_{26}H_{28}N_2O_4 \cdot HCl$	4.96[e]	5.64 ± 0.11 (11)	
26	None	$-CH(CH_3)CH_2CH_2-C_6H_5$	141[g]	$C_{26}H_{28}N_2O_2 \cdot HCl$	5.82 ± 0.15 (7)	6.43 ± 0.40 (9)	4.3

[a] All compounds were recrystallized from MeOH-2-PrOH unless otherwise noted. [b] All compounds were prepared by method A + D, except compounds **25** and **26** for which method A + C was used. [c] pA_2 values ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive chronotropic effect. [e] Noncompetitive antagonism pD'_2. [f] pA_2 values were not determined. [g] Recrystallized from EtOAc.

Table III. Physical Properties and β-Blocking Activities of Fluorene Oxime Ether Derivatives



Compd	R_1	R_2	Mp, °C[a]	Emp formula[b]	Apparent pA_2[c] Atrium[d] (A)	Apparent pA_2[c] Trachea (T)	Broncho-selectivity, T/A
27	H	2-NO_2[e]	247	$C_{20}H_{23}N_3O_4 \cdot HCl$	6.43 ± 0.24 (8)	6.84 ± 0.25 (10)	2.6
28	2-Br	7-Br[f]	>260	$C_{20}H_{22}Br_2N_2O_2 \cdot HCl$	5.46 ± 0.14 (8)	5.72 ± 0.13 (14)	1.8
29	H	2-Br[f]	190[g]	$C_{20}H_{23}BrN_2O_2 \cdot$ maleate	5.82 ± 0.10 (5)	6.50 ± 0.30 (10)	4.8
30	H	1-Br[h]	210	$C_{20}H_{23}BrN_2O_2 \cdot 0.5$fumarate	6.50 ± 0.19 (9)	6.16 ± 0.14 (12)	0.5
31	H	1-NHAc[i]	~110 dec[j]	$C_{22}H_{27}N_3O_3 \cdot$ tartrate	<5[k]	<4.7[k]	
32	H	2-Cl[l]	157[m]	$C_{20}H_{23}ClN_2O_2 \cdot HCl$	6.20 ± 0.05 (4)	6.65 ± 0.32 (10)	2.8
33	H	2-NHAc[i]	~160[n]	$C_{22}H_{27}N_3O_3 \cdot$ tartrate	7.35 ± 0.17 (6)	7.14 ± 0.63 (7)	0.6
34	H	2-NH_2	~150[o]	$C_{20}H_{25}N_3O_2 \cdot 2HCl \cdot H_2O$	6.90 ± 0.09 (7)	7.53 ± 0.44 (8)	4.3

[a] All compounds were recrystallized from EtOH-MeOH unless otherwise noted. [b] All compounds were prepared by method A + D, except compounds **31** and **33** for which method B + D was used. [c] pA_2 values ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive chronotropic effect. [e] 2-Nitrofluorenone was prepared according to G. Schultz, *Justus Liebigs Ann. Chem.*, **203**, 103 (1880). [f] 2-Bromofluorenone and 2,7-dibromofluorenone were prepared according to J. Schmidt and K. Bauer, *Chem. Ber.*, **38**, 3764 (1905). [g] Recrystallized from CH_3CN-2-PrOH. [h] For the preparation of 1-bromofluorenone, see E. H. Huntress, K. Pfister, and K. H. T. Pfister, *J. Am. Chem. Soc.*, **64**, 2885 (1942). [i] 1-Acetamidofluorenone was prepared according to the procedure used by A. Eckert and E. Langecker, *J. Prakt. Chem.*, **118** (2), 263 (1928), for the preparation of 2-acetamidofluorenone. [j] Tartrate made in Me_2CO and washed with Et_2O. [k] Noncompetitive antagonism pD'_2. [l] Chloro-2-fluorenone prepared according to C. Courtot, *Ann. Chim.*, **14**, 5 (1930), was oxidized to chloro-2-fluorenone with $Na_2Cr_2O_7$ in AcOH. [m] Recrystallized from MeCN. [n] Recrystallized from 2-PrOH. [o] Hydrochloride made in EtOAc and washed with Et_2O.

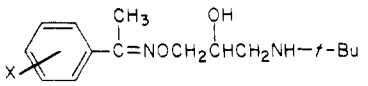
the amino substituent from isopropyl into *tert*-butyl enhances β_2-selectivity rather than β-adrenergic blocking potency. It should be noted that the gain in bronchoselectivity by this procedure is very pronounced with the benzophenone derivatives (cf. **13** and **14**).

Table II shows the influence of the nature of X upon the blocking activity of tricyclic derivatives. Compounds **17–20**, where X is a carbon chain, exhibit weak and noncompetitive antagonism on the atrium and no effect on the trachea. When X is a heteroatom, like oxygen (**21** and **22**), only a moderate activity and no selectivity is observed.

Among the compounds from which X is omitted, fluorene derivatives **23–26**, **24** is unique. Indeed it is 155 times more active in vitro on the trachea than on the atria of guinea pig. In vivo, its β_2-selectivity is still 23 for the dog and 26 for the guinea pig.[7] Again, the considerable influence of the *tert*-butyl group on the β_2-activity is noteworthy. On the contrary the isopropyl derivative **23** exhibits appreciable (five times) selectivity for the atrium. This β_1-selectivity of **23** does not increase by changing the isopropylamino group to a 3,4-dimethoxyphenethylamino (**25**) or a 1-methyl-3-phenylpropylamino (**26**) substituent; instead, the latter compounds show a dramatic decrease in cardiac β-adrenergic blocking potency. This observation agrees with the finding of Schwender et al.[11] who were also unable to achieve cardioselectivity by incorporating this group in a series of benzophenone and tetralone derivatives.

Table III shows the highly detrimental effect on the β-blocking activity of introducing substituents on the aromatic ring of **24**. All seven derivatives synthesized are less potent and less selective than **24** as far as β-blocking activity is concerned.

Table IV. Physical Properties and β-Blocking Activities of Acetophenone Oxime Ether Derivatives



Compd	X	Mp, °C	Crystn solvent[a]	Emp formula[b]	Apparent pA_2[c] Atrium[d] (A)	Apparent pA_2[c] Trachea (T)	Broncho-selectivity, T/A
4	H	125	A	$C_{15}H_{23}N_2O_2 \cdot HCl$	6.70 ± 0.21 (5)	7.62 ± 0.13 (4)	8.3
35	4-Cl	135	B	$C_{15}H_{23}ClN_2O_2 \cdot HCl$	7.29 ± 0.22 (19)	6.61 ± 0.22 (7)	0.2
36	4-Me	123	C	$C_{16}H_{26}N_2O_2 \cdot$ maleate	7.84 ± 0.65 (5)	7.89 ± 0.16 (7)	1.1
37	4-OMe	142	B	$C_{16}H_{26}N_2O_3 \cdot HCl$	7.86 ± 0.19 (9)	8.74 ± 0.20 (10)	7.7
38	4-NO_2	220	D	$C_{15}H_{23}N_3O_4 \cdot HCl$	7.47 ± 0.11 (6)	7.54 ± 0.31 (9)	1.2
39	4-Br	106	B	$C_{15}H_{23}BrN_2O_2 \cdot$ maleate	7.59 ± 0.12 (5)	8.51 ± 0.42 (8)	8.5
40	4-NH_2	141	E	$C_{15}H_{25}N_3O_2 \cdot$ oxalate $\cdot$ 0.5H_2O	7.64 ± 0.08 (6)	7.11 ± 0.40 (6)	0.3
41	4-Et[e]	134	B	$C_{17}H_{28}N_2O_2 \cdot$ maleate	7.35 ± 0.41 (9)	6.75 ± 0.20 (8)	0.2
42	4-*i*-Pr[e]	135	B	$C_{18}H_{30}N_2O_2 \cdot$ maleate	5.82 ± 0.11 (7)	7.26 ± 0.29 (9)	28
43	4-CN[f]	221	D	$C_{16}H_{23}N_3O_2 \cdot 0.5$ oxalate	6.91 ± 0.05 (5)	6.99 ± 0.27 (5)	1.2
44	4-SOMe[g]	181	C	$C_{16}H_{26}N_2O_3S \cdot HCl$	6.53 ± 0.30 (6)	6.59 ± 0.28 (11)	1.1
45	4-SO_2Me[g]	202	C	$C_{16}H_{26}N_2O_4S \cdot HCl$	6.82 ± 0.07 (9)	6.01 ± 0.20 (12)	0.1
46	4-F	117	F	$C_{15}H_{23}FN_2O_2 \cdot HCl$	6.32 ± 0.12 (10)	7.30 ± 0.14 (8)	9.7
47	4-SMe[h]	152	C	$C_{16}H_{26}N_2O_2S \cdot HCl$	7.23 ± 0.24 (10)	6.92 ± 0.18 (11)	0.5
48	4-Ph[i]	177	C	$C_{21}H_{28}N_2O_2 \cdot HCl$	5.63 ± 0.07 (6)	6.05 ± 0.36 (10)	2.8
49	4-NHAc[j]	116	C	$C_{17}H_{27}N_3O_3 \cdot$ maleate	5.66 ± 0.18 (7)	6.30 ± 0.03 (6)	4.5
50	4-OH[g]	155	C	$C_{15}H_{24}N_2O_3 \cdot HNO_3$	7.64 ± 0.68 (6)	7.17 ± 0.14 (11)	0.3
51	4-O-*i*-Pr	151	C	$C_{18}H_{30}N_2O_3 \cdot$ maleate	6.42 ± 0.31 (9)	7.20 ± 0.16 (6)	6.2
52	4-NMe_2[k]	196	E	$C_{17}H_{29}N_3O_2 \cdot 0.5$ tartrate	6.44 ± 0.07 (5)	8.03 ± 0.39 (8)	39
53	4-SO_2NMe_2[g]	198	C	$C_{17}H_{29}N_3O_4S \cdot HCl$	5.62 ± 0.28 (6)	5.20 ± 0.30 (7)	0.4
54	2-Me	158	A	$C_{16}H_{26}N_2O_2 \cdot$ maleate	6.67 ± 0.14 (5)	7.90 ± 0.42 (7)	17
55	2-OH[h]	161	C	$C_{15}H_{24}N_2O_3 \cdot$ maleate	7.06 ± 0.43 (8)	8.13 ± 0.45 (6)	12
56	2-OMe	109	B	$C_{16}H_{26}N_2O_3 \cdot$ maleate	5.87 ± 0.09 (5)	6.82 ± 0.35 (6)	8.9
57	2-Cl	127	G	$C_{15}H_{23}ClN_2O_2 \cdot$ maleate	8.34 ± 0.26 (7)	7.86 ± 0.17 (7)	0.3
58	3-Me	118	G	$C_{16}H_{26}N_2O_2 \cdot$ maleate	8.11 ± 0.05 (6)	8.30 ± 0.47 (12)	1.5
59	2-*o*-Allyl[l]	112	H	$C_{18}H_{28}N_2O_3 \cdot$ maleate	5.96 ± 0.10 (6)	6.25 ± 0.53 (8)	1.9
60	2,4-Cl_2	199	H	$C_{15}H_{22}Cl_2N_2O_2 \cdot HCl$	6.56 ± 0.33 (5)	6.94 ± 0.43 (12)	2.4
61	2,4-$(OMe)_2$	147	H	$C_{17}H_{29}N_2O_4 \cdot HCl$	6.12 ± 0.36 (5)	6.84 ± 0.13 (5)	5.2
62	3,4-Cl_2	137	H	$C_{15}H_{22}Cl_2N_2O_2 \cdot$ maleate	6.75 ± 0.32 (9)	7.11 ± 0.62 (6)	2.3
63	3,4-$(OMe)_2$	133	H	$C_{17}H_{28}N_2O_4 \cdot$ maleate	6.19 ± 0.07 (6)	6.65 ± 0.22 (12)	2.9

[a] The abbreviations have the following meanings: A, 2-PrOH-Et_2O; B, EtOAc; C, MeCN; D, MeCN-MeOH; E, 2-PrOH-MeOH; F, EtOAc-Et_2O; G, EtOAc-MeOH; H, 2-PrOH. [b] All compounds were prepared by method A + D, except compound **49**, for which method B + D was used. [c] pA_2 values ± SD, with the number of experiments in parentheses. [d] Antagonism of the isoprenaline-induced positive chronotropic effect. [e] 4-Ethyl- and 4-isopropylacetophenone were prepared according to G. H. Mowry, B. R. Renoll, and R. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946). [f] See L. Friedmann and H. Schechter, *J. Org. Chem.*, **26**, 2522 (1961). [g] See Experimental Section. [h] For the preparation of 4-methylthioacetophenone, see F. Krollpfeiffer, H. Hartmann, and F. Schmidt, *Justus Liebigs Ann. Chem.*, **563**, 25 (1949). [i] *p*-Acetyldiphenyl was prepared according to L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941). [j] 4-Acetamidoacetophenone; see J. Klingel, *Chem. Ber.*, **18**, 2691 (1885). [k] A. W. Nineham, *J. Chem. Soc.*, 636 (1952). [l] *o*-Allyloxyacetophenone; see R. E. Nitz, W. Persch, and A. Schmidt, *Arzneim.-Forsch.*, 5, 357 (1955).

With these results in mind, it seemed worthwhile to develop a very homogeneous series of derivatives to see if we could establish any quantitative correlations[12] between structure and biological activities. Since this was not easy with fluorenone derivatives, which were not generally available commercially, or which were difficult to come by, we chose the acetophenone series. Thirty derivatives of acetophenone oximes having various aromatic substituents and bearing a *tert*-butylamino group were therefore synthesized (Table IV). The relationships of the tracheal (β_2) activities, the cardiac (β_1) activities, and the β_2/β_1 ratio with the physicochemical parameters of the oxime derivatives were examined with the multiparametric approach of Hansch and others.[13,14] From the data of Table IV (**53** and **59** being excluded because substituent parameters are not available), we were unable to correlate significantly the biological response β_1, β_2, or β_2/β_1 (T/A ratio) with the physicochemical parameters π, π^2, σ, the field constant F,[15] the resonance constant R,[15] the molar refraction,[16] the Taft steric factor,[17] and the parachor.[18] This contrasts with the observations of Basil et al.[19] on a series of 1-(2-acyl-4-acetylaminophenoxy)-3-isopropylaminopropan-2-ols where good correlations between vascular and cardiac β-adrenergic blocking activities and E_s and π values of the alkyl groups carried by the acyl and acylamino functions were obtained. Their results were consistent with the vascular receptor being associated with a more lipophilic environment than the cardiac receptor. It has also been recently proposed by Germer[20] on the basis of CNDO/2 calculation that the selectivity in β-adrenoreceptor blocking agents could be related to their geometry. A similar explanation has been put forward by Hieble and Ellis[21] to explain the higher potency of *o*-methylpropranolol when compared to propranolol. In the former compound the side chain could be rotated out of the plane of the aromatic ring due to steric repulsion between the side chain and ortho substituent. This explanation does not fit with the results contained in Table IV, since compound **52** bearing a 4-dimethylamino group is the most potent β_2-blocker of the series (pA_2 ~8.03, bronchoselectivity = 39), while the more potent β_1 and slightly β_1-selective compound **57** bears a chlorine atom in the 2 position of the aromatic nucleus (pA_2 = 8.34, bronchoselectivity = 0.33).

On a large-scale screening **24** did raise the blood pressure of spontaneously hypertensive rats (SHR) and did not prevent the occurrence of hypertension in young SHR rats. β_2-Selective adrenergic blockers could have a hypertensive action in human beings.

Experimental Section

Melting points were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12 A spectrometer using Me_4Si in a capillary as an external reference. The spectral data were consistent with the assigned structures. Sometimes the intermediate oxime derivatives gave rise to *E* and *Z* isomers but in all cases the final product moved as a single spot on TLC indicating that we are probably dealing with pure isomers of unknown configuration. All compounds were analyzed for C, H, and N and gave results within ±0.4% of the the theoretical values.

Most of the initial ketones are comercially available. Those which are not were prepared according to references appended to the tables or as described in the Experimental Section.

Pharmacological Tests of β-Adrenergic Blocking Activity. An in vitro guinea pig model was applied to determine the β_1- and β_2-adrenergic blocking activity. The antagonism of isoprenaline-induced positive chronotropism was measured on isolated spontaneously beating right atria according to Horii.[22] The preparations were suspended in a Krebs–Henseleit solution at 32 °C and aerated with a mixture of 95% O_2 and 5% CO_2. Contractions were recorded isometrically. The diastolic tension was set at 0.5 g. The preincubation time of the antagonists amounted to 30 min before the next cumulative dose–response curve with isoprenaline was performed. Ascorbic acid, 10^{-4} g/mL, was present during each curve.

β_2-Adrenergic blocking activity was estimated by the method described by Levy and Wilkenfield,[23] slightly modified. Two equal segments of the trachea were placed in a Krebs–Henseleit solution at 37 °C gassed with 5% CO_2 in O_2. Contractions were recorded isotonically with a preload of 2.5 g. The bath fluid contained ascorbic acid (10^{-4} g/mL) and phentolamine (10^{-7} g/mL). Fifteen minutes before the cumulative additions of isoprenaline, 10^{-7} g/mL of carbachol was given in order to increase muscle tone. The preincubation time of the antagonists was 60 min.

β-Adrenergic blocking activity was expressed in terms of pA_2 values (logarithm of the reciprocal concentration of antagonist which necessitates doubling the concentration of agonist in order to keep the effect constant) as determined according to Schild. A plot of log $(x - 1) = f(\text{colog } A)$ gives straight lines of slope 1 for competitive antagonists.

We have checked by Student's *t* test that the slopes were not significantly different from 1.[24] When this was not true the antagonism was expressed using pD'_2. β_2-Selectivity (T/A ratio) is expressed as the antilog of the difference of the pA_2 between isolated trachea and isolated atria.

Preparation of the Oximes. Procedure A. A solution of the appropriate ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) in dry pyridine (500 mL) was refluxed under stirring for 12 h. The mixture was then poured into excess water. In general, the oxime precipitated. It was collected by filtration and recrystallized. When the oximes were oily, they were extracted with EtOAc, washed several times with dilute HCl and finally with water, dried over $MgSO_4$, and evaporated to dryness.

Procedure B. This procedure was applied for the synthesis of acetamido-substituted fluorene oximes. 2-Acetamidofluorenone (9.6 g, 40 mmol) was dissolved in Me_2SO (190 mL). A solution of hydroxylamine hydrochloride (3.1 g, 44 mmol) in water (10 mL) was added and the reaction mixture stirred at 80 °C for 30 min. The solution was poured into 500 mL of water. The precipitate was filtered off, washed with water, and dried to give 7.7 g of crude oxime (*E* and *Z* isomers in approximate 1:1 ratio were shown with TLC using EtOAc as eluent). 1-Acetamidofluorene oxime was similarly prepared and purified from the remaining ketone with silica column chromatography (solvent $CHCl_3$). $CHCl_3$–EtOAc (95:5) eluted the oxime (30% yield) as a mixture of isomers. 4-Acetamidoacetophenone oxime was purified by recrystallization from MeCN. The oximes were then converted to the ether derivatives **31**, **33**, and **49** according to general procedure D described for the synthesis of **24**.

Preparation of the Oxime Ether Derivatives 5, 10, 25, and 26. Procedure C. The following method applied for **25** is typical. A mixture of (epoxy-2-propyl)oximino-9-fluorene (12.5 g, 50 mmol) and 3,4-dimethoxyphenethylamine (9.05 g, 50 mmol) in absolute ethanol (25 mL) was refluxed for 3 h. EtOH was removed and the resulting gum taken up in $CHCl_3$ and washed with 1 N HCl (2 × 250 mL), 1 N NaOH (250 mL), and water (250 mL). Evaporation of $CHCl_3$ yielded the base of **25** which was purified through its oxalate (recrystallized, with loss, in DMF). Due to the insolubility of the oxalate in water, the base of **25** was liberated by prolongated treatment with concentrated NaOH: yield, 4.5 g; mp 94 °C. The base was dissolved in a mixture of EtOAc (20 mL)–*i*-PrOH (10 mL) and bubbled with HCl gas to give the hydrochloride. Two successive recrystallizations in a mixture of MeOH–*i*-PrOH (2:8) yielded 3.5 g of **25** (mp 161 °C).

5, **10**, and **26** were purified by column chromatography using SiO_2 (250 g) and graded mixtures of hexane–EtOAc–$NHEt_2$.

General Preparation of the Oxime Ether Derivatives. Procedure D. This procedure is illustrated by the synthesis of (*tert*-butylamino-3-hydroxy-2-propyl)oximino-9-fluorene hydrochloride (**24**).

A solution of sodium methoxide was prepared from 1.18 g (50 g-atoms) of sodium and 150 mL of methanol. 9-Oximinofluorene (10 g, 51 mmol) was added to this solution over a period of 5 min. The mixture was refluxed for 1 h. The methanol was then thoroughly removed in vacuo and the dry residue taken up in 80 mL of anhydrous DMF. This solution was then added dropwise to a solution of 4.75 g (50 mmol) of epichlorohydrin in 20 mL of anhydrous DMF and stirred for 1 h, during which a precipitation of NaCl was formed. The mixture was poured into 500 mL of water and extracted three times with 100 mL of $CHCl_3$. The $CHCl_3$ phase was washed twice with water to remove most of the DMF and dried over $MgSO_4$, and the solvent was evaporated.

For characterization, 1 g of the crude oil was chromatographed on silica (Merck) with a mixture of hexane–EtOAc (8:2). Recrystallization from hexane gave 300 mg of slightly yellow crystals of the epoxide: mp 60 °C; ^1H NMR ($CDCl_3$) 2.65 and 2.97 (m, 2 H), 3.29 and 3.54 (m, 1 H), 4.19 and 4.77 (m, 2 H), 7.20 and 7.84 (m, 7 ArH), 8.30 (m, 1 ArH); mass spectrum *m/e* 237 (M^+). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

The above crude epoxide was dissolved in 20 mL of benzene containing 14 g of *tert*-butylamine and treated for 12 h at 90 °C in an autoclave. After cooling, the solvents were removed at a reduced pressure, and the oily residue, taken up in *i*-PrOH, was treated with oxalic acid in Me_2CO. The oxalate was then converted to the hydrochloride of **24**: 6.3 g (34%); mp 160 °C (*i*-PrOH–MeOH); ^1H NMR ($CDCl_3$) 1.06 (s, $3CH_3$), 2.42 (m, 2 H, exchangeable with D_2O), 2.72–2.95 (m, $-CH_2NHCH<$), and 4.12–4.50 (m, $-OCH_2CHOH-$), 7.35 and 7.82 (m, 7 ArH), 8.23 and 8.37 (m, 1 ArH). Anal. ($C_{20}H_{24}N_2O_2$·HCl) C, H, N.

Synthesis of Compounds 50 and 56. To the sodium salt of *p*(*o*)-hydroxyacetophenone in dry DMF 1 equiv of benzyl chloride was added dropwise. After stirring for 1 h at 80 °C, the solution was poured into water and extracted three times with EtOAc. Washing with 10% NaOH removed unreacted hydroxyacetophenone. The organic phase was washed with water until neutral, dried over $MgSO_4$, and evaporated to give 95% benzyloxyacetophenone, which was reacted with hydroxylamine hydrochloride as described in procedure A. Finally the protective group was removed at the last stage by hydrogenolysis with Pd/C (10%) at atmospheric pressure and gave good yields of **50** and **56**.

Initial Substituted Acetophenones for 44, 45, and 53. 4-Methylsulfinylacetophenone. 4-Nitroperbenzoic acid (18.3 g, 0.1 mol) was carefully added portionwise to 4-methylthioacetophenone (16.6 g, 0.1 mol) in $CHCl_3$ (100 mL). After the exothermic reaction had subsided, 10% aqueous Na_2CO_3 was added. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The analytical sample was recrystallized from benzene–cyclohexane: 15.1 g (83%); mp 110 °C. Anal. ($C_9H_{10}O_2S$) C, H, N.

4-Methylsulfonylacetophenone. To a stirred solution of 4-methylthioacetophenone (0.4 g, 2.4 mmol) in AcOH (1 mL) at 40 °C was added a solution of $KMnO_4$ (0.52 g) in water (12 mL). The temperature rose to 60–70 °C. Water (8 mL) was added, and the solution was cooled to room temperature. A saturated Na_2SO_3 solution was added to remove excess $KMnO_4$. After cooling, the solid was collected and recrystallized from EtOH: mp 127 °C (lit.[25] 128 °C).

4-Dimethylsulfamylacetophenone. 4-Acetylphenylsulfonyl chloride prepared by diazotization of 4-aminoacetophenone in

SO_2 according to ref 26 was carefully added to a well-stirred, ice-cooled 40% aqueous solution of $NHMe_2$. The *N,N*-dimethylsulfonamide, which precipitated immediately, was recrystallized twice from water: mp 103 °C (lit.[27] 102–103 °C).

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Notes

Prostaglandins and Congeners. 16.[1] Synthesis and Bronchodilator Activity of *dl*-11-Deoxy-3-thiaprostaglandins

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The interesting bronchodilator activity of certain *dl*-11-deoxy-3-thiaprostaglandins and their preparation by the conjugate addition of appropriately substituted (*E*)-1-alkenyllithio cuprate reagents to requisite cyclopentenones are described.

A recent report[2] from these laboratories described the preparation of several *dl*-11-deoxyprostaglandins which could be presumed to be resistant to fatty acid oxidation, a major route of prostaglandin metabolic inactivation.[3] One of the compounds reported, *dl*-11-deoxy-3-thiaprostaglandin E_1 (**10**), was found to be a potent bronchodilator in the guinea pig bronchodilator assays[4] (Table I) showing an extended duration of effect.

In order to further develop this interesting observation, we have prepared a series of *dl*-11-deoxy-3-thiaprostaglandins wherein the α chain (C_1–C_7) has been abbreviated or homologated by one carbon. Also prepared were several congeners in which the β chain was altered by the introduction of alkyl substituents[1,5] at C_{15} or C_{16}, features that would make these compounds ineffective substrates for 15-hydroxyprostaglandin dehydrogenase,[6] the primary agent of prostaglandin metabolism.[3]

Chemistry. Our approach to the synthesis of the *dl*-11-deoxy-3-thiaprostaglandins[7] relies on the facile lithio cuprate conjugate addition of fully elaborated alkenyl β-chain precursors to requisite cyclopentenones by the procedure of Sih and co-workers.[8] Sequential treatment of vinyl iodides **1**,[2] **2**,[1] and **3**[1] with *tert*-butyllithium and copper(I) pentyne ($CuC{:}CC_3H_7$)[9] in hexamethylphosphorous triamide[9b] afforded the lithium cuprate reagents **4**–**6**. The conjugate addition of cuprates **5** and **6** to cyclopentenone **8**,[10] followed by acidic removal of the trimethylsilyl (Me_3Si) protecting group of the conjugate adducts, dry column chromatography, and alkaline hydrolysis, furnished *dl*-11-deoxy-15ξ-methyl-3-thiaprostaglandin E_1 (**12**)[11] and *dl*-11-deoxy-16,16-dimethyl-3-thiaprostaglandin E_1 (**13**) and its C_{15} epimer **14**.[7] The