deriv.), 100166-80-1; (±)-7 (isomer 1)·CH_3SO_3H, 100166-62-9; (±)-7 (isomer 2)·CH_3SO_3H, 100166-82-3; 8, 67287-36-9; (±)-9, 53631-49-5; (±)-10, 100166-64-1; (±)-11·CH_3SO_3H, 100166-66-3; (±)-12, 87863-72-7; (±)-13·HCl, 100166-67-4; (±)-14, 100166-68-5; (±)-15·HCl, 100166-69-6; (±)-16·HBr, 100166-70-9; (±)-17·CH_3SO_3H, 100166-72-1; (±)-18·HCl, 100166-73-2; (±)-19·HBr, 100166-74-3; (±)-20, 100166-75-4; (±)-21, 100166-76-5; (±)-22·CH_3SO_3H, 100166-78-7; 3-$H_3COC_6H_4CHO$, 591-31-1; $(CH_3)_3SI$, 2181-42-2; $BrCH_2CH{=}CH_2$, 106-95-6; $HC{\equiv}CCH_2Br$, 106-96-7; (*E*)-$H_3CCH{=}CHCH_2Cl$, 4894-61-5; (*E*)-$C_6H_5CH{=}CHCH_2Cl$, 21087-29-6; ethylene oxide, 75-21-8; cyclopropanecarboxylic acid chloride, 4023-34-1; (±)-glycidol, 61915-27-3.

Conformational Effects on the Activity of Drugs. 11.[1] Stereostructural Models for the Direct Activation of the α- and β-Adrenergic Receptor[2]

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Two kinds of cyclic analogues of norepinephrine (NE, **7**) and isoprenaline (ISO, **8**), in which the C(1)–C(2) side chain of these amino alcohols is incorporated in its preferred conformation in the ring of the 2-(3,4-dihydroxyphenyl)-morpholines **9** and **10** (2-DPMs) and in the ring of the 3-(3,4-dihydroxyphenyl)-3-piperidinols **11** and **12** (3-DPPs), respectively, were synthesized and assayed for their adrenergic activity on various isolated preparations. The 2-DPMs and the 3-DPPs showed an α- and β-agonist activity comparable to that of NE and ISO and to that of the *trans*-2-amino-5,6-dihydroxytetrahydronaphthalen-1-ols **13** and **14** (2-ADTNs), which represent another kind of semirigid analogue of NE and ISO. Through a comparison of the stereo structures of the compounds examined and of their pharmacological properties, it was possible to suggest a spatial situation in which the pharmacophoric groups of the adrenergic drugs examined (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) should interact at the receptor site. This spatial situation corresponds to the one found in the preferred conformation of NE and ISO. It was also possible to construct two theoretical three-dimensional molecular models that provide information about steric requirements for the direct activation of α- and β-adrenoceptors, respectively.

The molecular mechanism of the interaction that takes place at the adrenergic receptor has been the subject of extensive work. A number of studies have dealt with the problem of the pharmacophoric conformation and, in particular, with the question of whether the most stable conformation is the one that is "active" at the receptor site. Adrenergic drugs are flexible molecules, and the differences between the ground-state free energies of their conformers are too small to guarantee that no conformational changes take place during the initial process of binding with the receptor. Semirigid cyclic analogues of adrenergic drugs have proved to be a useful tool in studying the conformational aspects of the activity of these drugs at the molecular level, but, although they have yielded some interesting information, they have not made it possible to advance any definite suggestion as to the precise conformation acting at the receptor, because of a residual flexibility. Recently, some rigid analogues have appeared to make a contribution to the solution of this problem.[3,4] It may be pointed out, however, that the steric and electronic effects arising from the additional neighboring atoms necessary to make up the semirigid or rigid structure lead to primary modifications of the physical and chemical properties of the flexible parent compound. This in turn may cause a modification in the biological activity of the pharmacophoric groups in the new molecules compared with the activity elicited by the same groups in the original flexible molecule.[5,6]

Previous papers in this series[5,7-9] have discussed the synthesis and the pharmacological properties of the 1-aryl-2-aminoethanols **1** and **2** and of the corresponding cyclic analogues **3–6**. Compounds **3–6** represent two different ways in which the C(1)–C(2) side chain of the amino alcohols **1** and **2** can be locked in a semirigid system. In the morpholine derivatives (**3** and **4**), the C(1)–C(2) chain is incorporated in the ring through the alcoholic oxygen and the amine nitrogen, which are therefore a part of the ring. In the piperidine derivatives (**5** and **6**), the C(1) of the side chain is directly engaged in the formation of the ring, and consequently, the alcoholic OH remains free. Both morpholine and piperidine derivatives, either as free bases or as salts, preferentially exist[5,7-9] in the conformations shown in **3**, **4** and **5**, **6**, respectively, with the aryl group in the equatorial position. In both types of cyclic derivatives, the O–C(1)Ar–C(2)–N portion exists in the

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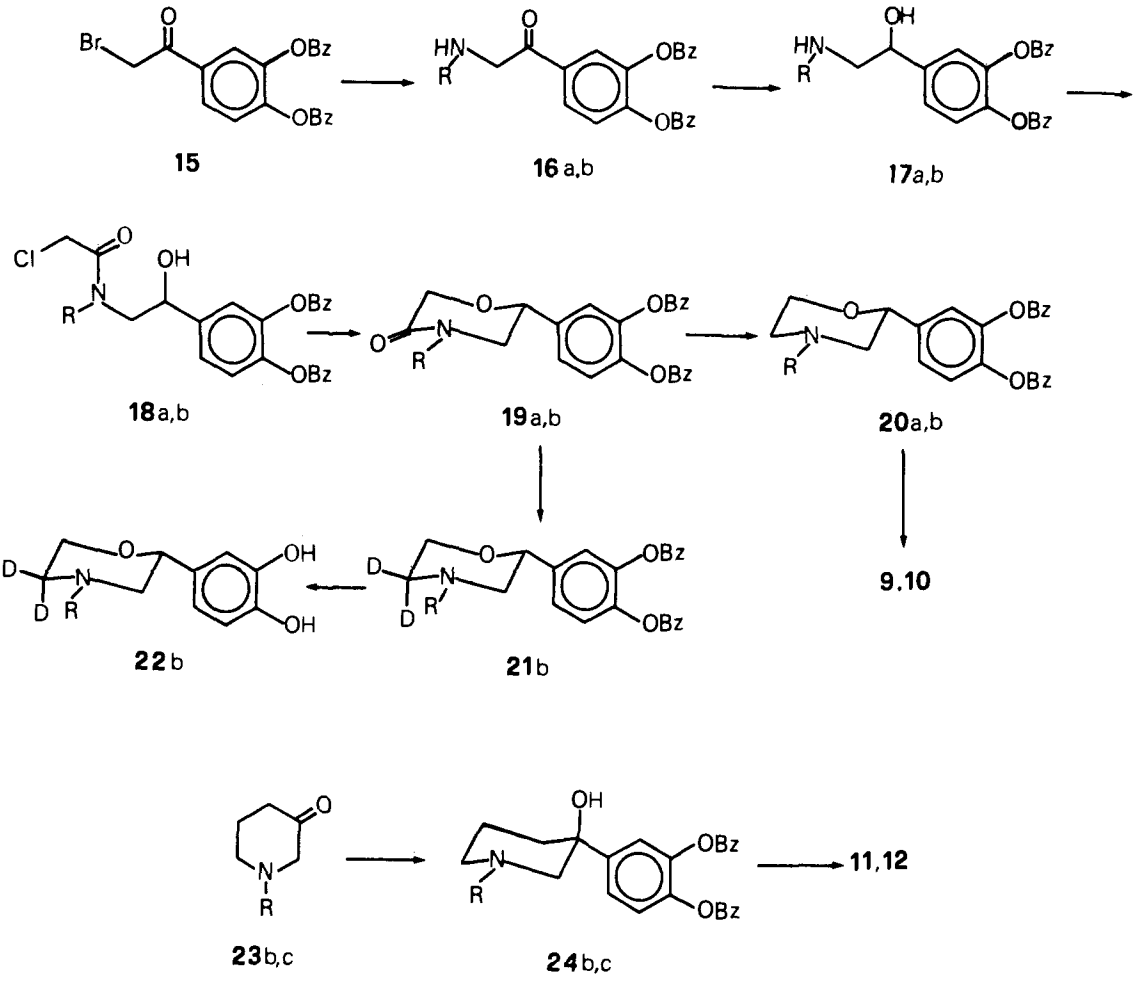
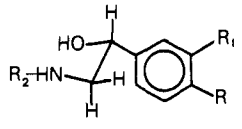
Scheme I

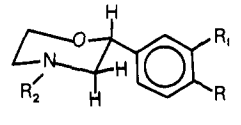


a, R= $CHPh_2$; b, R=$CHMe_2$; c, R=Bz

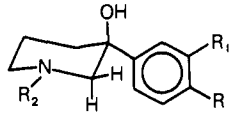
conformation that corresponds to the preferential one found[10] in the parent open-chain compounds 1 and 2.



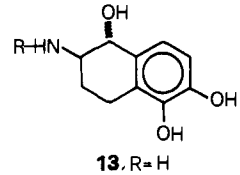
1, R=NO_2; R_1=H; R_2=H
2. R=NO_2; R_1=H; R_2=$CHMe_2$
7, R=R_1=OH; R_2=H
8, R=R_1=OH; R_2=$CHMe_2$



3. R=NO_2; R_1=H; R_2=H
4, R=NO_2; R_1=H; R_2=$CHMe_2$
9. R=R_1=OH; R_2=H
10. R=R_1=OH; R_2=$CHMe_2$



5, R=NO_2; R_1=H; R_2=H
6, R=NO_2; R_1=H; R_2=$CHMe_2$
11, R=R_1=OH; R_2=H
12, R=R_1=OH; R_2=$CHMe_2$



13. R=H
14. R=$CHMe_2$

Pharmacological studies carried out on isolated preparations of rat vas deferens[7-9] showed that the heterocyclic analogues **3–6** exhibit an α-adrenergic stimulating activity fairly similar to that of the parent amino alcohols **1** and **2**. On the basis of a comparison of the molecular frameworks of these compounds with their pharmacological properties, it was possible to suggest the stereostructural requirements for interaction at the α-adrenergic receptor.[9]

This hypothesis was based on pharmacological data obtained for the adrenergic drugs (**1** and **2**) and their cyclic analogues (**3**, **4** and **5**, **6**), which, because of the nature of the aryl group, possess a rather weak α-adrenergic activity. We therefore synthesized the 2-(3,4-dihydroxyphenyl)-morpholines (2-DPMs, **9** and **10**) and the 3-(3,4-dihydroxyphenyl)-3-piperidinols (3-DPPs, **11** and **12**) in order to compare their biological activity with that of the parent open-chain compounds norepinephrine (NE, **7**) and isoprenaline (ISO, **8**), which, as is well known, exhibit a marked activity on the adrenergic system.

The pharmacological properties of the catecholic derivatives **9–12** can also be compared with those previously reported[11] for *trans*-2-amino- and *trans*-2-(ispropylamino)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalen-1-ol (2-ADTNs, **13** and **14**), which represent another kind of conformationally semirigid analogues of the adrenergic catecholamines **7** and **8**. In the 2-ADTNs **13** and **14**, **7** and

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Table I. Adrenoceptor Agonistic Activities[a] of 2-DPMs and 3-DPPs on Various Isolated Preparations with Reference to NE (7) and ISO (8)

	α-adrenoceptor activity[a]				β-adrenoceptor activity[a]			
	isolated rat vas deferens		isolated rat tail artery		isolated guinea pig atria		isolated guinea pig tracheal strip	
compd	pD_2	ia[b]	pD_2	ia[b]	pD_2	ia[b]	pD_2	ia[b]
NE (7)	4.96 (±0.20)	1	6.16 (±0.33)	1	6.50 (±0.14)	1	6.04 (±0.12)	1
2-DPM (9)	4.75 (±0.25)	0.91	5.82 (±0.29)	0.92	5.31 (±0.30)[c]	0.91	4.76 (±0.20)[c]	0.70
3-DPP (11)	4.53 (±0.30)	0.95	4.01 (±0.37)	1	6.75 (±0.26)	1	4.20 (±0.37)[c]	0.77
2-ADTN (13)[d]					6.74 (±0.21)[e]	1[e]	7.49 (±0.05)[e]	1[e]
ISO (8)	3.50				8.35 (±0.10)	1	8.47 (±0.16)	1
2-DPM (10)					5.74 (±0.34)[c]	0.88	6.34 (±0.19)[c]	0.93
3-DPP (12)					8.14 (±0.28)	1	8.26 (±0.31)	1
2-ADTN (14)[d]					7.56 (±0.08)[e]	1[e]	8.41 (±0.09)[e]	1[e]

[a] The values represent the mean of six experiments for each drug ± standard error in parentheses. [b] Intrinsic activity, i.e., the ratio between the maximal response elicited by the compound under test and that elicited by the full agonist, namely, NE and ISO for α- and β-adrenoceptors, respectively. [c] $P < 0.001$, as judged by the Student's t test. [d] These compounds showed a practically negligible activity on the α-adrenoceptors of the isolated rabbit aortic strips ($pD_2 < 3.5$).[11] [e] From ref 11.

8 are cyclized, linking the C(2) of the side chain to a carbon atom of the aromatic moiety by means of an ethylene bridge; both the alcoholic and the amine groups thus remain free. The 2-ADTNs **13** and **14** preferentially exist[12] in the half-chair conformation with both the hydroxy and the amine groups in the pseudoequatorial position. Also in this case, the conformation of the O–C(1)Ar–C(2)–N portion corresponds to the preferential one of the amino alcohols **7** and **8**, except for small differences in the torsion angles due to the half-chair system.

Chemistry

2-DPMs **9**[13] and **10** were synthesized as shown in Scheme I, starting from ω-bromo-3,4-bis(benzyloxy)acetophenone (**15**).[14] Treatment of **15** with benzhydrylamine or isopropylamine gave the corresponding amino ketones **16**, which were reduced with $LiAlH_4$ to amino alcohols **17**. The reaction of **17** with $CH_2ClCOCl$ and Et_3N in anhydrous $CHCl_3$ gave the corresponding *N*-chloroacetyl derivatives **18**, which were converted into the morpholines **19**, by base-catalyzed (KOH) cyclization. Reduction of the cyclic amides **19** with B_2H_6 in anhydrous THF gave the morpholine derivatives **20**, which were catalytically hydrogenolyzed to **9** and **10**.

The [5,5-$^2H_2$]morpholine derivative **22b** was obtained by reducing the morpholinone **19b** with $LiAlD_4$, followed by catalytic hydrogenolysis of the bis(benzyloxy) derivative **21b**.

The synthetic route to 3-DPPs **11** and **12** is outlined in Scheme I. Treatment of the 3-piperidones **23**[9] with [3,4-bis(benzyloxy)phenyl]magnesium bromide[15] yielded the piperidinols **24**. Catalytic hydrogenolysis of **24** afforded **11** and **12**. All the catecholic derivatives (**9–12** and **22b**) were isolated as hydrochlorides because of their instability as free bases.

The preferred conformation of the hydrochlorides of the 2-DPMs (**9**·HCl and **10**·HCl) was determined by means of the vicinal coupling constants of the proton α to the aryl group; these values were obtained for **9**·HCl through its NMR spectrum but for **10**·HCl through the spectrum of the hydrochloride of its [5,5-$^2H_2$] analogue (**22b**·HCl). This choice was made due to the complexity of the spectrum of **10**·HCl (overlap of the signals of the protons linked to

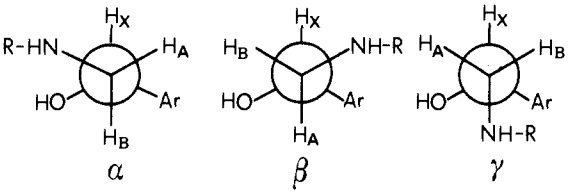

Figure 1. Newmann projections of the three classical staggered rotamers of the 1-aryl-2-aminoethanol derivatives **7** and **8**.

the carbon in the α position with respect to the nitrogen. The values of these constants indicate a marked conformational preference for the conformer with the aryl group in the equatorial position, in accordance with previous results obtained with other 2-arylmorpholines.[5,7,8] The preferred conformation of 3-piperidinols **11** and **12** can be assumed on the basis of the one previously determined[9] for **5** and **6**, which preferentially exist in the chair conformation with the bulkiest aryl group in the more favorable equatorial position.[16]

The percentages of rotamers α, β, and γ (Figure 1) of NE·HCl (**7**·HCl) and ISO·HCl (**8**·HCl) were recalculated[1,10] from the values[17] of J_{AX} and J_{BX} of their ABX system, by using "pure" J_{gauche} and J_{trans} obtained by correcting[1,10] the J_{AX} and the J_{BX} of the ABX system of **9**·HCl and **22b**·HCl. The rotameric population values thus obtained (**7**·HCl, α = 72%, β = 11%, γ = 17%; **8**·HCl, α = 82%, β = 15%, γ = 3%) do not differ very much from those previously calculated[17] using reference values of J_{gauche} and J_{trans} obtained with morpholine derivatives, which cannot be considered to be closely related to **7** and **8**.

Pharmacology

α-Adrenoceptor Activity. The 2-DPMs and the 3-DPPs were tested for their direct α-adrenergic activity on isolated rat vas deferens and on perfused isolated rat tail artery. The activities of NE and ISO on isolated rat vas deferens were found to be in agreement with previous reports.[18,19]

Furthermore the α-adrenergic activity of NE and ISO was tested on perfused rat tail artery. NE increased the

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(16) The instability of the free bases of **11** and **12** unfortunately does not make it possible to infer their preferred conformation by means of an IR study in the 3-μm range in a dilute solution, which would have made it possible to observe the presence or the absence of an intramolecular OH···N bond.
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perfusion pressure dose-dependently, in agreement with the literature.[20] ISO did not produce any measurable change in the resistance of the vascular bed on the whole perfused rat tail in doses up to 1×10^{-5} M.[21]

Rat Vas Deferens. The results obtained with the compounds under examination are shown in Table I. The 2-DPM **9** and the 3-DPP **11** elicited a dose-related smooth muscle contraction. This stimulating effect was due to an action upon α-adrenoceptors since it was antagonized by the α-adrenoceptor antagonist phentolamine (1×10^{-5} M). This effect seemed, moreover, to be produced by a direct mechanism because the biological tests were performed in tissues from rats that had been pretreated with reserpine to deplete the sympathetic terminals of endogenous NE. The dose–response curves of **9** and **11** were parallel to the one obtained with NE. The affinities of the drugs for α-adrenoceptors, expressed as pD_2 values, were not statistically different from that of NE ($P > 0.05$) calculated in the same experimental conditions. Also the intrinsic activities of **9** and **11** were quite similar to that of NE. The *N*-isopropyl-substituted 2-DPM **10** and 3-DPP **12** did not show any activity on α-adrenoceptors up to doses of 1×10^{-3} M. ISO showed a weak α-stimulating activity, but its affinity for α-adrenoceptors was lower than 3.5 and the dose–response curve was quite different from that of NE.

Perfused Rat Tail Artery. The 2-DPM **9** and the 3-DPP **11** showed a direct α-adrenergic stimulating activity comparable to that of NE as regards intrinsic activity (Table I). It was clear that the drugs acted on α-adrenoceptors through a direct mechanism since the activity was antagonized by phentolamine (1×10^{-5} M). The activity was clearly direct and not mediated by NE release since the pharmacological tests were carried out on tissues from animals pretreated 24 h before with reserpine. The 2-DPM **10** and the 3-DPP **12**, as well as ISO, were devoid of any α-adrenergic stimulating activity at doses up to 1×10^{-3} M.

The results obtained for the 2-DPM **9**, both on isolated rat vas deferens and on perfused rat tail artery, are substantially in agreement with others previously obtained[13] with different pharmacological models.

β-Adrenoceptor Activity. The β-adrenoceptor activity of the 2-DPMs and the 3-DPPs was tested on isolated guinea pig atrial and tracheal preparations obtained from animals pretreated with reserpine (to exclude an indirect mechanism of receptor activation). The activities of NE and ISO on the same tissues were also reinvestigated and found to be in agreement with previous reports.[11,22-24]

Guinea Pig Atria. All the 2-DPMs and the 3-DPPs displayed a stimulating and dose-related activity on β_1-adrenoceptors (Table I). The atrial responses were in fact completely abolished by the β-adrenoceptor antagonist propranolol (1×10^{-5} M).

As expected, ISO affinity for β_1-adrenoceptors was the highest observed. The affinity of the 3-DPP **12** was not statistically different from that of ISO; the affinity of the other ISO analogue, the 2-DPM **10**, was still comparable to that of ISO itself, even though significantly lower. The cyclic analogues of NE, the 2-DPM **9** and the 3-DPP **11**, as well as NE itself, showed pD_2 values significantly lower than that of ISO; also in this case, the piperidine analogue, the 3-DPP **11**, showed an affinity very similar to that of the open-chain compound (NE), while the affinity of the morpholine analogue, the 2-DPM **9**, was significantly lower.

The trend of the intrinsic activity was similar to that of the affinity, while for the 3-DPPs the intrinsic activity was identical with that of NE and ISO; for the 2-DPMs it was slightly different.

Guinea Pig Tracheal Strip. The activity of the 2-DPMs and the 3-DPPs on β_2-adrenoceptors was tested on this isolated tissue; all the compounds displayed a β_2-stimulating dose-related activity (Table I).

Also in this case, ISO affinity for the β_2-adrenoceptors was the highest observed. Among the cyclic analogues of ISO, the 3-DPP **12** exhibited an affinity for β_2-adrenoceptors practically equal to that of the parent open-chain compounds, while the 2-DPM **10** exhibited an affinity significantly lower. Both the cyclic analogues of NE, the 2-DPM **9** and the 3-DPP **11**, showed an affinity significantly lower than that of NE itself.

Also in this preparation the trend of the intrinsic activity was similar to that of the affinity, while for the 3-DPP **12** the intrinsic activity was the same as for ISO; for the 2-DPM **10** and for the two cylic analogues of NE (**9** and **11**), the intrinsic activity was quite different from that of their parent open-chain compounds.

The results obtained for the 2-DPM **9** are in accordance with others previously obtained with isolated frog heart,[13] another pharmacological preparation used for the study of β_2-adrenoceptors.[25]

The trend of the affinity and of the intrinsic activity of all the compounds under examination was somewhat similar in both guinea pig atria and tracheal strip, with the only exception of the 3-DPP **11**, which exhibited a markedly different affinity and intrinsic activity in the two pharmacological preparations. As expected, pD_2 values calculated for NE and for its analogues were lower than those of ISO and of its analogues.

The 2-DPMs **9** and **10** showed a decrease both in affinity and intrinsic activity compared with the parent open-chain compounds (NE and ISO), both on β_1- and β_2-adrenoceptors. The 3-DPPs **11** and **12** showed an activity of the same intensity as the corresponding open-chain compound on the cardiac β_1-adrenoceptors; on the tracheal β_2-adrenoceptors, on the contrary, only the 3-DPP **12** showed the same activity as ISO, while the 3-DPP **11** showed an activity considerably lower than that of NE and comparable to that of 2-DPM **9**.

Discussion

α-Adrenoceptor Activity. The N-unsubstituted 2-DPM (**9**) and 3-DPP (**11**) show in the rat vas deferens affinities and intrinsic activities that are similar to those of NE (**7**) (Table I). These compounds (**9** and **11**) demonstrate a direct α-stimulant activity also on the rat tail artery, similar to that of NE (**7**); the affinity of the piperidine derivative **11** is, however, inferior to that of **7** and **9**. The difference in the behavior of the piperidine derivative **11** in the two isolated preparations is difficult to explain. It might be possible however that the additional atoms necessary to build up the piperidine ring may cause a quantitatively different biological response depending on differences between the two kinds of tissues; these differences might reside, for instance, in the receptor morphology and/or in the receptor phospholipidic envi-

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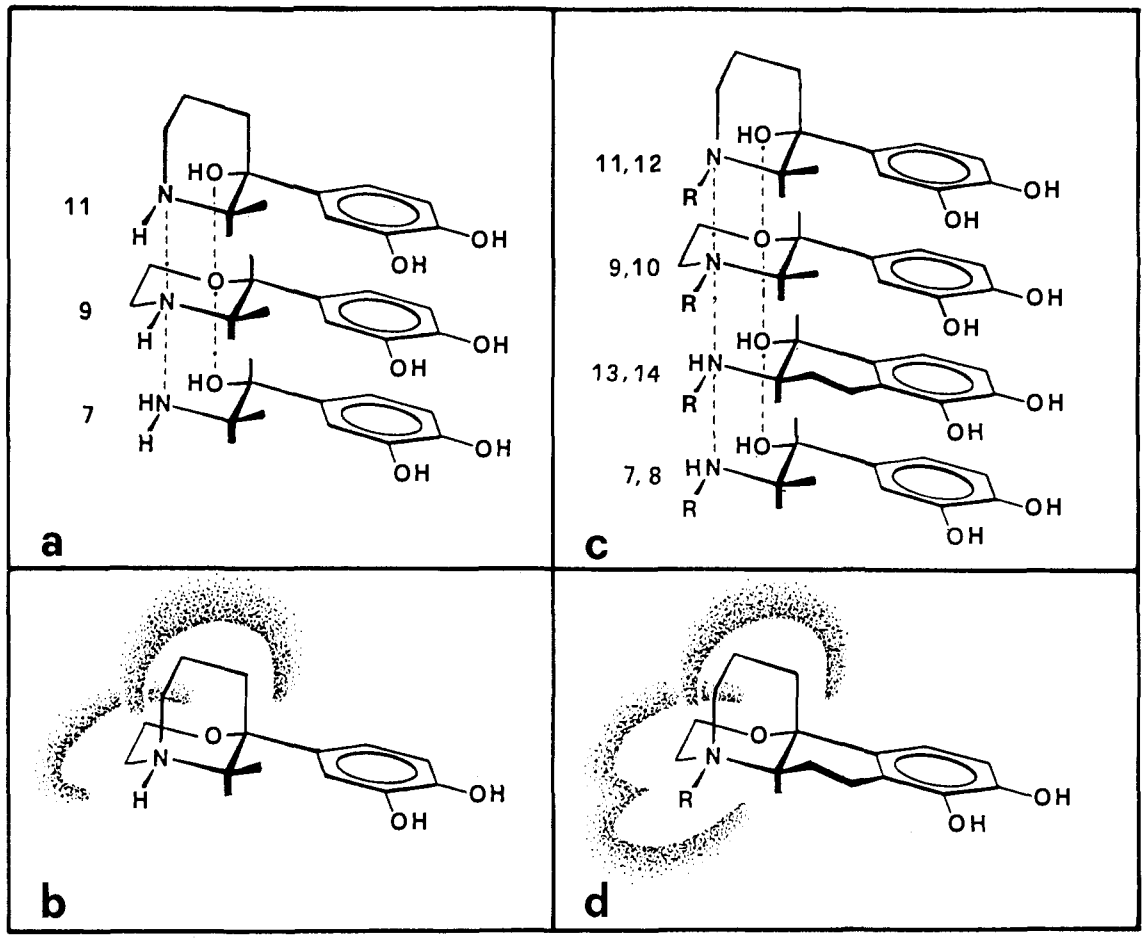

Figure 2. Molecular models (b and d) arising from the superimposition of the pharmacophoric groups (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) of the drugs **7**, **9**, and **11** (a) and of the drugs **7**–**14** (c) in the conformations in which they should react respectively with the α- and the β-receptors.

ronment. *N*-Isopropyl-substituted derivatives (**10** and **12**) are unable to bring about any effect on the α-adrenoceptor. This result was to be expected, as the 2-DPM **10** and the 3-DPP **12** are analogues of the ISO (**8**), which, as is well known, lacks α-sympathomimetic properties. The fact that the activity of the 2-DPM **9**, which lacks the proton of the hydroxyl group present in the side chain of the parent compound (NE, **7**) varies only very slightly from the activity of NE itself seems to confirm that this proton does not play a decisive role in the activation of the α-receptor.[7,26,27]

The data obtained from compounds **7**, **9**, and **11** indicate that the cyclization of NE (**7**) to its corresponding morpholine (**9**) and piperidine (**11**) derivatives leads to compounds showing an α-adrenergic receptor activity of the same type as that of the original parent compound. These results are in complete agreement with those previously obtained in analogous studies[7-9] (see introduction).

It is not possible a priori to establish the conformation through which the 2-DPM (**9**) and the 3-DPP (**11**), as well as NE (**7**), interact with the receptor site. However, the similar α-adrenergic activity of **7**, **9**, and **11** indicates that these compounds act at the same receptor site. This means that their groups that are assumed to be active[28] (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) must be situated in a strictly similar spatial relationship, complementary to that of the corresponding receptor active centers. Therefore both the open-chain compound NE (**7**) and its cyclic analogues (2-DPM **9** and 3-DPP **11**) should interact with the receptor in conformations that respond to this requirement. This condition is satisfied only when compounds **7**, **9**, and **11** are in the conformations shown in Figure 2a. Incidentally it may be observed that, for each compound, the conformation shown corresponds to the preferential one.

Superimposing the above-mentioned pharmacophoric groups of the three drugs **7**, **9**, and **11** in the conformations in which, as discussed above, they should react with the receptor (see Figure 2a), the molecular model shown in Figure 2b is obtained.[29]

In this three-dimensional model the fundamental frame of NE (**7**) is contained both in the morpholine ring of the 2-DPM **9** and in the piperidine ring of the 3-DPP **11**. This molecular model, resulting from the combination of active drugs, should in theory be pharmacologically active itself.

In this model (Figure 2b) there are some steric hindrances that arise from the additional atoms present in turn in the individual cyclic analogues. These regions of bulk should not therefore hinder a hypothetical "fit" of the "pharmacologically active" model with the receptor. They should, instead, indicate areas through which interactions of pharmacophoric groups with corresponding receptor active sites are not possible. These interactions should,

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(27) Gray, A. P.; Reit, E.; Ackerly, J. A.; Hava, M. *J. Med. Chem.* **1973**, *16*, 1023.
(28) Petrongolo, C.; Tomasi, J.; Macchia, B.; Macchia, F. *J. Med. Chem.* **1974**, *17*, 501 and references therein cited.
(29) This model is practically rigid. Apart from the free rotation of the aromatic ring, the only conformational liberties allowed depend on hypothetical chair $\rightleftharpoons$ boat conversions for both the morpholine and piperidine rings.

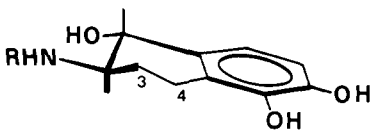

Figure 3. Perspective view of the molecular structure of tetrahydronaphthalene derivatives 13 and 14 in their preferred conformation. The heavy line indicates the molecular portion that 13 and 14 have in common with the three-dimensional model shown in Figure 2b.

therefore, take place from other directions that are sterically less hindered.

It is interesting to compare the above-mentioned results with those obtained for the 2-ADTNs **13** and **14**. These compounds have been reported[11] to exhibit an α-adrenomimetic activity that is practically negligible when compared with that of NE (see Table I). The relative spatial arrangement of the pharmacologically active groups in the 2-ADTNs **13** and **14** in their preferred conformation (see Figure 3) closely corresponds to the "pharmacophoric" spatial arrangement found in the model shown in Figure 2b. In **13** and **14**, therefore, the active centers are in a spatial arrangement that should make positive drug–receptor interaction possible.

As in the case of **10** and **12**, the inactivity of the *N*-isopropyl derivative **14** is not surprising if we think that this compound is an analogue of ISO (**8**). The loss of α-adrenergic stimulating activity observed by passing from NE (**7**) to its 2-ADTN analogue (**13**) may be attributed to the steric hindrance created by the C_3–C_4 ethylenic bridge in the latter. The CH_2CH_2 group of **13** represents a region of molecular bulk that is not present in the other molecules that are active at the α-adrenoceptor and that may interfere with the receptor topology, preventing the interaction of **13** with the receptor site. An alternative hypothesis is that the aryl group is constrained in this molecule by the tetrahydronaphthalene system into conformations different from the one that allows the formation of the active drug–receptor complex; the limited freedom of movement of the aromatic moiety might moreover modify the reactivity of the other biologically active groups of the molecule. The high steric requirement necessary to elicit α-adrenergic activity[30] as well as the importance of the rotameric state of the catecholic ring in the drug–receptor interaction[4] has been previouly pointed out.

β-Adrenoceptor Activity. The pharmacological results (Table I) indicate that both the 2-DPMs **9** and **10** and the 3-DPPs **11** and **12** were effective in directly stimulating the β_1-adrenergic receptors of isolated guinea pig atria and the β_2-adrenergic receptors of isolated guinea pig tracheal strips. In accordance with the variation of the pharmacological activity expected from the N-substitution of the adrenergic drugs, the β-activity of the *N*-isopropyl-substituted compounds (**8**, **10**, and **12**) is markedly higher than that of the corresponding N-unsubstituted compounds (**7**, **9**, and **11**).

The semirigid analogues of NE (**9** and **11**) as well as those of ISO (**10** and **12**) present a pharmacological activity qualitatively comparable to that of their respective open-chain parent compounds (NE and ISO), even though some differences between the values of the pD_2 and of the intrinsic activity of the single compounds may be observed. The decrease in activity observed in the 2-DPMs (**9** and **10**), which lack the proton of the hydroxyl group present in the side chain of the parent compounds (NE, **7** and ISO, **8**) could be attributed to a negative effect of the substitution of this proton[5,31] on the interaction with the β-receptor. It seems, therefore, that cyclization of NE (**7**) and ISO (**8**) into their corresponding morpholine and piperidine derivatives does not modify the type of their β-adrenergic receptor activity.

Unlike what has been done with results obtained from α-receptors, it is impossible to compare these results directly with those obtained in our former analogous works (see introduction) because the compounds previously examined (**1–6**) did not possess any stimulating activity on the β-adrenergic receptor. During our previous studies, however, it had been observed that the semirigid derivatives **3–6** maintained a certain degree of the β-blocking activity present in the open-chain parent compounds, only on some tissues and not in a dose-related way.

In this case, however, it is possible to compare the pharmacological activity of 2-DPMs (**9**, **10**) and 3-DPPs (**11**, **12**) with that previously reported[11] for 2-ADTNs (**13**, **14**). It may be observed that the β-adrenergic activity of the N-unsubstituted 2-ADTN (**13**) resembles that of NE and the other semirigid N-unsubstituted analogues (**9**, **11**) in the same way as the activity of *N*-isopropyl-substituted 2-ADTN (**14**) resembles that of ISO and the other semirigid *N*-isopropyl-substituted analogues (**10**, **12**).

As pointed out above in the discussion about the α-adrenoceptor activity, the maintenance by the morpholine (**9**, **10**), piperidine (**11**, **12**), and tetrahydronaphthalene (**13**, **14**) cyclic analogues of the β-adrenoceptor stimulating activity characteristic of the corresponding open-chain compounds (**7**, **8**) requires that the three pharmacophoric groups of compounds **7–14** assume an equivalent "pharmacophoric" spatial position complementary to that of the β-adrenergic receptor active sites when interacting at the receptor. This requirement is satisfied only when compounds **7–14** are in the conformations shown in Figure 2c. Also, in this case, it may be pointed out that these conformations correspond to the preferred ones.

Superimposition of the pharmacophoric groups of the biologically active drugs examined (**7–14**) in the conformations in which they should react with the receptor (see Figure 2c) allowed us to obtain a three-dimensional molecular model (Figure 2d), pharmacologically active in theory. The considerations made above in the discussion about α-adrenoceptor activity can also be applied to this model. Besides, in this case, the utilization of 2-ADTNs (**13**, **14**) in the construction of the three-dimensional molecular model limits the conformational freedom of the aromatic moiety.[32] This fact makes it possible to individualize a limited rotameric range within which the aryl can move when interacting with β-adrenergic receptors.

Conclusions

The present work shows that the adrenergic stimulating activity of NE and ISO persists in their corresponding morpholine (2-DPMs) and piperidine (3-DPPs) semirigid analogues, even if some quantitative differences were observed. The results obtained confirm previous data obtained with *p*-nitrophenyl-substituted compounds, offering a useful comparison with data obtained by other authors with tetrahydronaphthalene derivatives (2-ADTNs).

Through a comparison of the stereo structures of the compounds examined and of their pharmacological prop-

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(31) Biel, J. H.; Lum, B. K. B. *Progr. Drug Res.* **1966**, *10*, 46.

(32) The aromatic ring may only assume the two conformations deriving from equilibrium between the two half-chair conformations of the nonaromatic ring of the 2-ADTNs.

erties, it was possible to suggest a spatial situation in which the pharmacophoric groups of the adrenergic drugs examined (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) should interact at the receptor site. This spatial situation corresponds to the one found in the preferred conformation of NE and ISO.

It was also possible to construct two theoretical three-dimensional molecular models that provide information about steric requirements for the direct activation of α- and β-adrenoceptors, respectively.

Experimental Section

All compounds were routinely checked for their structure by IR and ^{1}H NMR spectroscopy. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra for comparison between compounds were taken with a Perkin-Elmer Infracord Model 137 instrument as Nujol mulls in the case of solid substances or as liquid film in the case of liquids. ^{1}H NMR spectra were obtained on a ~10% $CDCl_3$ [for the free bases (Me_4Si)] and D_2O or Me_2SO-d_6 [for the HCl salts ($Me_3SiCD_2CD_2COONa$)] solutions with a Varian EM 3-60 A spectrometer. ^{1}H NMR spectra for the conformational study were also measured on a Varian CFT-20 spectrometer operating at 80 MHz. The spectral parameters of **9**·HCl were obtained by making use of double-resonance techniques. The J_{AX} and J_{BX} values, obtained by the analysis of the ABX system of the protons $CHCH_2$ of the morpholine ring of **9**·HCl and **22b**·HCl, were refined by means of an iterative LEQUOR program.[33] Evaporations were made in vacuo (rotating evaporator). Magnesium sulfate was always used as the drying agent. Petroleum ether refers to the fraction boiling at 60–80 °C. Elemental analyses were performed by our analytical laboratory and agreed with theoretical values to within ±0.4%.

3,4-Bis(benzyloxy)-ω-bromoacetophenone (15). A stirred suspension of 3,4-bis(benzyloxy)acetophenone[14] (5.0 g, 0.015 mol) in MeOH (50 mL) was cooled at 0 °C and treated dropwise with a solution of Br_2 (2.4 g, 0.015 mol) in MeOH (5 mL). After the addition was complete, the reaction mixture was refluxed for 2 h, concentrated, and cooled at 0 °C. The solid was filtered and crystallized from absolute EtOH–CH_2Cl_2 to yield pure **15** (2.5 g, 40%): mp 89–90 °C (lit.[14] mp 92–93 °C).

1-[3,4-Bis(benzyloxy)phenyl]-2-(benzhydrylamino)ethanol (17a·HCl). A solution of **15** (2.0 g, 4.8 mmol) in a 1:1 mixture of anhydrous benzene–EtOH (10 mL) was added, dropwise, at room temperature to a solution of benzhydrylamine (3.6 g, 0.02 mol) in the same solvent mixture (4 mL). The resulting solution was stirred at room temperature for 30 min and at 50 °C for 5 min. After evaporation of the solution, the crude residue was triturated with anhydrous Et_2O (50 mL) and filtered, and the Et_2O solution of the crude **3,4-bis(benzyloxy)-ω-(benzhydrylamino)acetophenone (16a)** was added dropwise to a suspension of $LiAlH_4$ (1.5 g, 0.039 mol) in anhydrous Et_2O (20 mL). The mixture was refluxed for 4 h, cooled, and treated in succession with H_2O (10 mL), 10% aqueous NaOH (10 mL), and H_2O (10 mL). The treatment of the washed (H_2O) organic layer with 10% aqueous HCl gave a solid precipitate (1.3 g), which was filtered, washed (Et_2O), and crystallized from EtOH–Et_2O to yield **17a**·HCl (1.0 g, 38% calculated on **15**): mp 169–170 °C. Anal. ($C_{35}H_{34}ClNO_3$) C, H, N.

Compound **17a**·HCl (0.9 g) was converted to the free base by treating an aqueous solution of the salt with solid KOH and extracting the free base with Et_2O. The ether layer was washed with H_2O, dried, filtered, and evaporated to give **17a** (0.15 g) as a solid, which was crystallized from benzene–hexane (0.7 g): mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 4.64 (dd, 1, J = 4.0 and 7.3 Hz, CHO), 4.83 (s, 1, $CHPh_2$), 5.10 (s, 4, CH_2Ph). Anal. ($C_{35}H_{33}NO_3$) C, H, N.

3,4-Bis(benzyloxy)-ω-(isopropylamino)acetophenone Hydrobromide (16b·HBr). A solution of **15** (3.0 g, 7.3 mmol) in a 1:1 mixture of anhydrous benzene–EtOH (10 mL) was treated, as described above for the preparation of **16a**, with a solution of isopropylamine (1.3 g, 0.022 mol) in the same solvent mixture (5 mL). Evaporation of the solvent mixture gave a semisolid residue, which was triturated with Et_2O and filtered. The organic solvent was treated with 48% aqueous HBr, cooled at 0 °C, and filtered to give a solid (4.0 g), which was crystallized from EtOH to yield **16b**·HBr (1.5 g, 44%): mp 183–184 °C; IR 1660 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6) δ 4.85 (br, 2, $COCH_2$), 5.42 and 5.47 (2 s, 4, CH_2Ph). Anal. ($C_{25}H_{28}BrNO_3$) C, H, N.

1-[3,4-Bis(benzyloxy)phenyl]-2-(isopropylamino)ethanol (17b). To a stirred suspension of $LiAlH_4$ (1.5 g, 0.039 mol) in anhydrous Et_2O (70 mL) was added in portions **16b**·HBr (4.5 g, 0.009 mol). After the addition was complete, the reaction mixture was refluxed for 4 h, cooled, and treated in succession with H_2O (5 mL), 10% aqueous NaOH (5 mL), and H_2O (5 mL). The ether layer was dried and evaporated to give a solid, which on crystallization from i-Pr_2O yielded pure **17b** (1.5 g, 40%): mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ 4.70 (dd, 1, J = 4.3 and 8.9 Hz, CHO), 5.30 (s, 4, CH_2Ph). Anal. ($C_{25}H_{29}NO_3$) C, H, N.

1-[3,4-Bis(benzyloxy)phenyl]-2-[(chloroacetyl)amino]-ethanol Derivatives 18. To a solution of Et_3N (1.72 g, 0.017 mol) in anhydrous $CHCl_3$ (20 mL) was added the corresponding amino alcohol **17** (0.006 mol). The mixture was cooled at 0 °C and treated with stirring, dropwise, with $ClCH_2COCl$ (1.48 g, 0.013 mol). After completion of the addition, the ice bath was removed and the mixture stirred at room temperature for 4 h. The layers were separated, and the organic phase was washed with dilute aqueous HCl and $NaHCO_3$, filtered, and evaporated to give a residue, which was fully characterized only in the case of **18a**. **18a** (52%): mp 139–140 °C (EtOH); IR 1640 cm^{-1} (C=O). Anal. ($C_{37}H_{34}ClNO_4$) C, H, N. **18b** (84%, calculated on the crude oily residue): IR 1620 cm^{-1} (C=O).

2-[3,4-Bis(benzyloxy)phenyl]morpholin-5-one Derivatives 19. To a solution of the N-chloroacetyl derivative **18a** or **18b** (0.004 mol) in EtOH (60 mL) was added in portions a solution of KOH (0.84 g, 0.015 mol) in EtOH (20 mL). The resulting mixture was stirred at room temperature for 30 h, then diluted with H_2O, and extracted with CH_2Cl_2. Evaporation of the washed (H_2O) and filtered organic extracts yielded a residue essentially consisting of the corresponding morpholinone derivative **19a** or **19b**, respectively, which was fully characterized only in the case of **19a**. **19a** (58%): mp 111–114 °C (benzene–petroleum ether); IR 1631 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.5 (s, 2, $COCH_2$), 4.75 (dd, 1, J = 5.3 and 8.2 Hz, CHO), and 5.07 (s, 4, CH_2Ph). Anal. ($C_{37}H_{33}NO_4$) C, H, N. **19b** (97%, calculated on the crude oily residue): IR 1620 cm^{-1} (C=O).

2-[3,4-Bis(benzyloxy)phenyl]morpholine Derivatives 20. A stirred solution of $NaBH_4$ (42.3 mmol) in anhydrous THF (90 mL) was cooled at 0 °C and treated, under external cooling, dropwise with a solution of BF_3·Et_2O (57.0 mmol) and then with a solution of morpholine (**19a** or **19b**) (7.0 mmol) in anhydrous THF (90 mL). After completion of the addition, the reaction mixture was stirred at room temperature for 10 min, refluxed for 1.5 h, cooled, treated with H_2O (15 mL) and 10% aqueous HCl (40 mL), and stirred for 20 min. After evaporation of THF, the aqueous solution was washed (CH_2Cl_2), basified with solid KOH, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was filtered and evaporated to give a residue consisting of **20a** or **20b**, respectively, which was crystallized from the appropriate solvent. **20a** (35%): mp 140–141 °C (AcOEt–EtOH); ^{1}H NMR ($CDCl_3$) δ 4.27 (s, 1, $CHPh_2$), 4.51 (dd, 1, J = 2.5 and 10.0 Hz, CHO), and 5.08 (s, 4, CH_2Ph). Anal. ($C_{37}H_{35}NO_3$) C, H, N. **20b** (34%): mp 84–85 °C (i-Pr_2O); ^{1}H NMR ($CDCl_3$) δ 4.45 (dd, 1, J = 3.0 and 10.0 Hz, CHO), 5.13 (s, 4, CH_2Ph). Anal. ($C_{27}H_{31}NO_3$) C, H, N.

2-(3,4-Dihydroxyphenyl)morpholine Hydrochloride (9·HCl). A solution of **20a** (0.5 g, 0.9 mmol) in a 1:1 anhydrous CH_2Cl_2–EtOH mixture (10 mL) was shaken under hydrogen at room temperature and atmospheric pressure in the presence of 10% Pd on charcoal (0.2 g). When the absorption stopped, the catalyst was filtered off and the solution was concentrated and then acidified to pH 5 with Et_2O·HCl. The solution, cooled at −20 °C, gave a solid, which was collected by filtration and then recrystallized from MeOH–Et_2O to yield **9**·HCl (0.078 g, 37%): mp 208–209 °C dec (lit.[10] mp 221 °C dec); ^{1}H NMR (D_2O) δ 3.00 (dd, 1, J_{BA} = −13.2 Hz, J_{BX} = 11.4 Hz, H_B), 3.31 (dd, 1, J_{AB} = −13.2 Hz, J_{AX} = 2.4 Hz, H_A), 4.65 (dd, 1, J_{AX} = 2.4 Hz, J_{XB} = 11.4 Hz, H_X).

(33) Diehl, P.; Kellerhals, H.; Niederberger, W. *J. Magn. Reson.* **1971**, *4*, 352.

2-(3,4-Dihydroxyphenyl)-4-isopropylmorpholine Hydrochloride (10·HCl). A solution of **20b** (0.3 g, 0.7 mmol) in an anhydrous CH_2Cl_2–EtOH mixture (6 mL) was hydrogenated as described above for the preparation of **9**·HCl in the presence of 10% Pd on charcoal (0.15 g). Following removal of the catalyst by filtration, the solution was concentrated, acidified with Et_2O·HCl to pH 5, and cooled at −20 °C. The precipitate (0.13 g) was collected by filtration and crystallized from EtOH–Et_2O to yield pure **10**·HCl (0.09 g, 45%): mp 181–182 °C. Anal. ($C_{13}H_{20}ClNO_3$) C, H, N.

2-[3,4-Bis(benzyloxy)phenyl]-4-isopropyl-5,5-dideuteriomorpholine (21b). To a stirred suspension of $LiAlD_4$ (0.88 g, 21 mmol) in anhydrous Et_2O (15 mL) was added dropwise, with stirring, a solution of **19b** (1.0 g, 2.3 mmol) in anhydrous Et_2O (65 mL). After the addition was complete, the reaction mixture was refluxed for 8 h, cooled, and treated in succession with H_2O (4 mL), 10% aqueous NaOH (4 mL), and H_2O (4 mL). The ether layer was dried and evaporated to yield a solid residue (0.5 g), which was crystallized from *i*-Pr_2O to give **21b** (0.38 g, 39%): mp 70–72 °C. Anal. ($C_{27}H_{29}D_2NO_3$) C, H + D, N.

2-(3,4-Dihydroxyphenyl)-4-isopropyl-5,5-dideuteriomorpholine Hydrochloride (22b·HCl). A solution of **21b** (0.34 g, 0.81 mmol) in a 1:2 anhydrous CH_2Cl_2–EtOH mixture (6 mL) was hydrogenated as described above for the preparation of **9**·HCl, in the presence of 10% Pd on charcoal (0.18 g) to yield **22**·HCl (0.09 g, 40%): mp 171–172 °C (EtOH–Et_2O); ^1H NMR (D_2O) δ 2.90 (dd, 1, J_{BA} = −12.4 Hz, J_{BX} = 11.2 Hz, H_B), 3.32 (dd, 1, J_{AB} = −12.4 Hz, J_{AX} = 1.7 Hz, H_A), 4.83 (dd, 1, J_{XA} = 1.7 Hz, J_{XB} = 11.2 Hz, H_X). Anal. ($C_{13}H_{18}D_2ClNO_3$) C, H + D, N.

3-[3,4-Bis(benzyloxy)phenyl]-3-piperidinol Derivative (24). To a stirred solution of [3,4-bis(benzyloxy)phenyl]magnesium bromide,[15] prepared from Mg (1.55 g, 0.063 mol) and 3,4-bis(benzyloxy)phenyl bromide (10.7 g, 0.029 mmol), in anhydrous THF (30 mL), was added dropwise a solution of 3-piperidone[9] (**23b** or **23c**) (0.026 mmol) in anhydrous Et_2O (15 mL). The reaction mixture was stirred at room temperature overnight, hydrolyzed with cold 25% aqueous NH_4Cl (100 mL), and extracted with Et_2O. The combined extracts were washed (H_2O) and extracted with 5% aqueous HCl. The extracts were washed with Et_2O, basified with solid KOH, and extracted with Et_2O. Evaporation of the washed (H_2O) and dried Et_2O extracts gave a residue consisting of the 3-piperidinol derivative (**24b** or **24c**), which was fully characterized as free base only in the case of **24c**. **24c** (35%): mp 86–87 °C (MeOH). Anal. ($C_{38}H_{37}NO_3$) C, H, N. **24b** (50% calculated on the crude oily residue). The HCl salt of **24b** had mp 159–161 °C (EtOH–Et_2O). Anal. ($C_{28}H_{34}ClNO_3$) C, H, N.

3-(3,4-Dihydroxyphenyl)-3-piperidinol Hydrochloride Derivatives (11·HCl and 12·HCl). A solution of the 3-piperidinol (**24b** or **24c**) (1.5 mmol) in EtOH (15 mL) was stirred under hydrogen at 50 °C at atmospheric pressure in the presence of 10% Pd on charcoal (0.06 g). After 5 h the catalyst was removed by filtration. The solution was neutralized with Et_2O·HCl and evaporated to give a crude residue consisting of the expected hydrochloride of the catecholic derivative (**12** or **11**, respectively), which was crystallized from the appropriate solvent. **11**·HCl (35%): mp 192.5–194.5 °C (EtOH–Et_2O). Anal. ($C_{11}H_{16}ClNO_3$) C, H, N. **12**·HCl (60%): mp 60–80 °C (*i*-PrOH–Et_2O). Anal. ($C_{14}H_{22}ClNO_3$) C, H, N.

Pharmacological Methods. Isolated Rat Vas Deferens. α-Receptor activity was evaluated on the isolated vas deferens obtained from male Sprague–Dawley rats, average weight 250 g, sacrificed by a blow on the head. The organs, carefully dissected and separated from the surrounding tissues, were suspended in a 10-mL organ bath containing Tyrode solution maintained at 37 °C and aerated with 95% O_2–5% CO_2 throughout all the experiments. The organs were subjected to a tension of 1 g and allowed to stabilize for 30 min. The responses of the organs were recorded isotonically by a Microdinamometer Basile Model 70–50 with a force displacement transducer.

Perfused Rat Tail Artery. Ventral tail arteries were obtained from male rats [OFA-ICO: SD (IOPS Caw)], average weight 250 g; after isolation, the distal portion (2–3 cm) was incannulated by means of an Olsen needle, placed in a 10-mL organ bath containing Krebs–Hukovic solution aerated with a mixture of 95% O_2–5% CO_2, and thermoregulated at 37 °C. The arteries were perfused with the same solution by means of a peristaltic pump (Desaga) at a constant flow of 3 mL/min. Perfusion pressure variations were recorded on a Palmer Kymograph by means of a Hg manometer.

Isolated Guinea Pig Atria. The action of the compounds under test on β_1-receptors was determined by using isolated atria of male guinea pigs, average weight 300 g. The organs were suspended in Tyrode solution with a resting tension of 0.5 g, maintained at 32 °C and gassed with 95% O_2–5% CO_2. The equilibration period was 30 min. The responses of the atria to the drugs were recorded isometrically by a Microdinamometer Basile Model 70-50 by a force displacement transducer.

Isolated Guinea Pig Tracheal Strip. Relaxation of tracheal strip preparations obtained from male guinea pigs, average weight 300 g, was used to evaluate the effects of the tested drugs on β_2-receptors. The perfusion fluid was Krebs–Henseleit solution containing ascorbic acid (0.1 mg/mL) and phentolamine (0.1 μg/mL), which was thermoregulated at 37 °C and gassed with 95% O_2–5% CO_2. A tension of 0.5 g was applied to each strip and the tissue was allowed to stabilize 30 min before starting the experiments. A constant level of tone was maintained by adding carbachol to the bath at a concentration of 0.1 μg/mL. Changes in muscle tone were recorded isotonically by a Microdinamometer Basile Model 70-50 with a force displacement transducer. The agonists were allowed to act until the maximal response was achieved, and dose–response curves were obtained by using a single-dose technique.

Affinity of the agonists for the receptors were expressed as pD_2, that is, the negative log of ED_{50} values. ED_{50} represents molar contraction producing 50% of the maximum response calculated according to Ariens and Van Rossum.[34] Intrinsic activity was calculated as the ratio between the maximal response elicited by the compound under study and that elicited by the full agonist,[35] namely, NE and ISO for α- and β-receptors, respectively. To prevent the effect due to catecholamine release from presynaptical nerve terminals the animals were pretreated with reserpine (1 mg/kg ip 24 h before the experiment). The following drugs were used as salts: **7** (*l*-norepinephrine) as bitartrate, **8** (*l*-isoprenaline), carbachol, phentolamine, propranolol, and the cyclic analogues **9–12**, as hydrochlorides. Reserpine was used as a free base solution (Serpasil).

Statistical Analysis. Parallelism of the dose–effect curves for the reference agonists and the tested compounds was also evaluated by comparing the *b* values (slope of the log–dose effect curve) for the standard and for the tested compounds by means of Student's *t* test for paired data. Mean values are quoted together with the standard error (SE). Comparisons have been made by using Student's *t* test.

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Registry No. **9**, 54826-84-5; **9**·HCl, 13062-59-4; **10**, 100112-62-7; **10**·HCl, 100112-54-7; **11**, 100112-61-6; **11**·HCl, 100112-59-2; **12**, 100112-63-8; **12**·HCl, 100112-60-5; **15**, 27628-05-3; **16a**, 100112-45-6; **16b**·HBr, 100112-46-7; **17a**, 100112-44-5; **17a**·HCl, 100112-43-4; **17b**, 100112-47-8; **18a**, 100112-48-9; **18b**, 100112-49-0; **19a**, 100112-50-3; **19b**, 100112-51-4; **20a**, 100112-52-5; **20b**, 100112-53-6; **21b**, 100112-55-8; **22b**·HCl, 100112-56-9; **23b**, 77799-73-6; **23c**, 40114-49-6; **24b**, 100112-57-0; **24b**·HCl, 100112-58-1; **24c**, 61832-59-5; 3,4-bis(benzyloxy)acetophenone, 27628-06-4; 3,4-bis(benzyloxy)phenyl bromide, 16047-57-7; benzhydrylamine, 91-00-9; isopropylamine, 75-31-0; $ClCH_2COCl$, 79-04-9.

(34) Ariëns, E. J.; Van Rossum, J. M. *Arch Int. Pharmacodyn. Ther.* **1957**, *110*, 275.
(35) Ariëns, E. J. *Arch. Int. Pharmacodyn. Ther.* **1954**, *99*, 32.