# Role of the (Acyloxy)methyl Moiety in Eliciting the Adrenergic β-Blocking Activity of 3-(Acyloxy)propanolamines[1]

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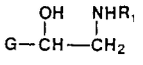
Some totally aliphatic 3-(acyloxy)propanolamines were synthesized with the aim of testing whether β-blocking activity could be obtained from this class of drugs, even in the absence of an aromatic group. The significant and, in most cases, competitive β-blocking activity shown by the compounds under examination, together with the results of a theoretical study in which their reactivity was compared with that of other adrenergic β-blocking drugs, seems to confirm a hypothesis previously advanced on the basis of knowledge about the action mechanism of adrenergic β-blocking drugs and of the results of structural studies. It was also possible to suggest some considerations about the role played by the (acyloxy)methyl portion of 3-(acyloxy)propanolamines in eliciting their adrenergic β-blocking activity.

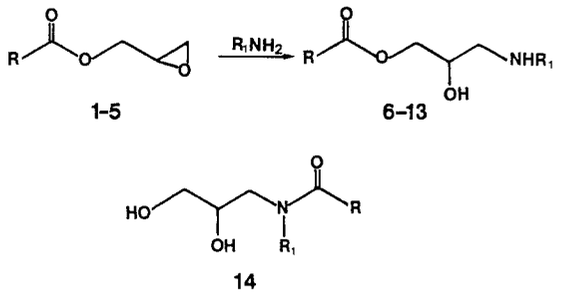
The difference between the two principal classes, A and B, of β-blocking adrenergic drugs lies in the presence of the $OCH_2$ group between the Ar portion and the ethanolamine chain in type B derivatives. The CH(OH)-$CH_2NHR_1$ moiety is associated with the drug's affinity for adrenergic receptors whereas its stimulating or blocking properties are determined by the nature of the aryl group.[2,3] To explain the similar pharmacological activity of the two classes of drugs, several hypotheses have been advanced[2,4-14] about the mechanism through which the $CH_2$-O-Ar portion of the class B agents can substitute for the single aromatic moiety (Ar) of the class A compounds in the drug-receptor interaction.



A, G = Ar
B, G = $ArOCH_2$; B', G = RRC=$NOCH_2$
C, G = $ArCOOCH_2$; C', G = $RCOOCH_2$

X-ray diffraction studies have shown[11] (see Figure 1) that the C(3)-O(2)-C(4)-C(5) atoms of a class B drug define a plane, and the spatial relationship between this plane and the ethanolamine side chain is the same as that observed between the aromatic ring and the ethanolamine side chain in class A drugs. On the basis of this observation, it was hypothesized[8] that the C(3)-O(2)C(4)-C(5) portion of class B adrenergic β-blocking drugs might in some way "simulate" the aromatic portion of class A drugs, and therefore be a "bioisoster"[15] of the Ar group. This hypothesis was later backed up[2,13,16] by quantum mechanical studies showing that the C(3)-O(2)-C(4)-C(5) portion of class B drugs and the aryl moiety of class A drugs possess a comparable "chemical reactivity". Further studies,[3,17-19] carried out on type B drugs, showed that a marked, competitive β-blocking activity could be obtained also from compounds lacking aromatic groups, such as the aliphatic oxime ether derivatives of class B'. Theoretical studies[3] showed that the chemical reactivity of these compounds appeared comparable to that of other β-blocking drugs of both class A and class B. In particular, the trend of the electrostatic molecular potential (EMP) generated by the C(3)-O(2)-N(2)-C(4) portion of these compounds agreed reasonably well with that generated by the aromatic ring of class A drugs and by the C(3)-O-(2)-C(4)-C(5) portion of class B drugs, in spite of the decidedly different molecular structure.

**Scheme I**




3-(Aroyloxy)propanolamines C, in which there is the insertion of a C=O group between the oxygen and the Ar

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(1) A preliminary account of this work was presented at the 3rd Noordwijkerhout Symposium of the Medicinal Chemistry Division of the Royal Netherlands Chemical Society, Noordwijkerhout, Sept 1985, Abstr, p 74.
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(16) Macchia, B.; Macchia F.; Martinelli, A. *Eur. J. Med. Chem.* **1983**, *18*, 85.
(17) Leclerc, G.; Bieth, N.; Schwartz, J. *J. Med. Chem.* **1980**, *23*, 620.
(18) Bouzoubaa, M.; Leclerc, G.; Decker, N.; Schwartz, J.; Andermann, G. *J. Med. Chem.* **1984**, *27*, 1291.
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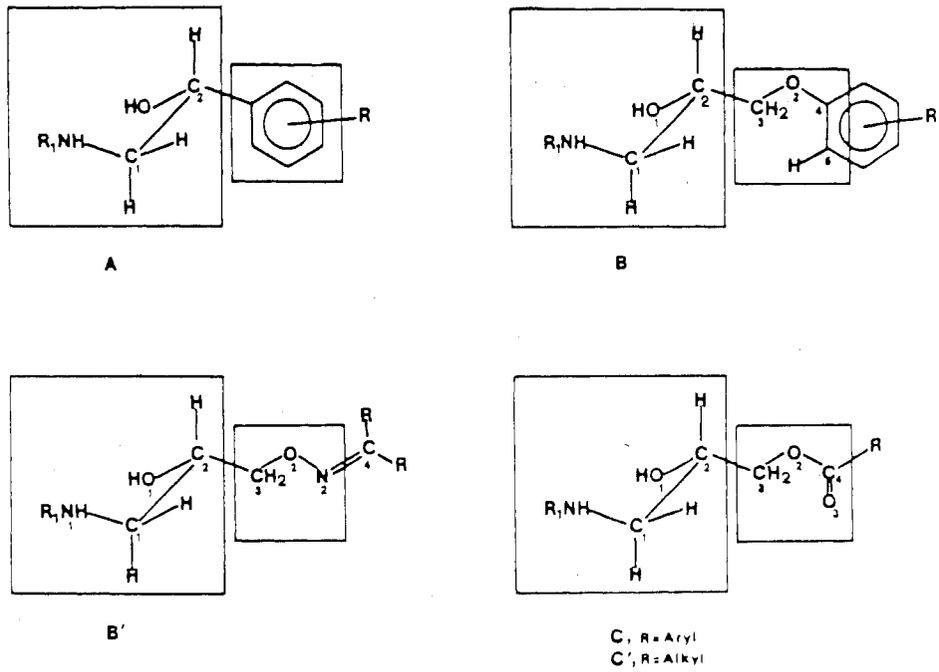
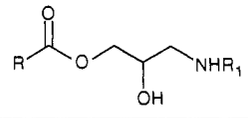



**Figure 1.** Perspective views of 2-arylethanolamine (A), 3-(aryloxy)propanolamine (B), 3-(iminooxy)propanolamine (B'), 3-(aroyloxy)propanolamine (C), and 3-(acyloxy)propanolamine (C') derivatives.

**Table I.** Chemical Data



| compd | R | $R_1$ | crystn solvent[a] | mp, °C | yield,[b] % | formula[c] |
|---|---|---|---|---|---|---|
| 6·0.5$H_2C_2O_4$ | Et | *t*-Bu | A | 146–148 | 43 | $C_{11}H_{22}NO_5$ |
| 7·HCl | *i*-Pr | *i*-Pr | B | 97–99 | 46 | $C_{10}H_{22}ClNO_3$ |
| 8·HCl | *i*-Pr | *t*-Bu | B | 158–160 | 52 | $C_{11}H_{24}ClNO_3$ |
| 9·HCl | c-$C_6H_{11}$ | *i*-Pr | C | 108–110 | 41 | $C_{13}H_{26}ClNO_3$ |
| 10·HCl | c-$C_6H_{11}$ | *t*-Bu | C | 128–130 | 46 | $C_{14}H_{28}ClNO_3$ |
| 11·$H_2C_2O_4$ |  | *i*-Pr | A | 134–136 | 37 | $C_{14}H_{21}NO_7S$ |
| 12·HCl |  | *i*-Pr | A | 158–159 | 38 | $C_{11}H_{18}ClNO_3S$ |
| 13·HCl |  | *t*-Bu | C | 167–168 | 62 | $C_{12}H_{20}ClNO_3S$ |

[a] A, MeOH–$Et_2O$; B, *i*-PrOH–*i*-$Pr_2O$; C, EtOH–$Et_2O$. [b] No efforts were made to optimize yields. [c] All compounds were analyzed for C, H, N.

of B, have been found to constitute a new class of β-blocking adrenergic agents.[20,21] The X-ray crystallographic study of a drug of this class, 1-(isopropylamino)-3-[[3,4-(methylenedioxy)benzoyl]oxy]propan-2-ol (**15**), showed that the C(3)–O(2)–C(4)–O(3) fragment forms a highly planar ringlike structure (see Figure 1).[22] These results revealed the existence of a clear spatial relationship between the benzene ring of class A compounds, the C(3)–O(2)–C(4)–C(5) planar portion of class B compounds, and the C(3)–O(2)–C(4)–O(3) planar portion of class C compounds, suggesting that this moiety of C compounds could mimic the Ar group of compounds A, or the C(3)–O(2)–C(4)–C(5) portion of compounds B, in the drug–receptor interaction.[22]

Totally aliphatic compounds of class C (**6–10**, $R_2$ = alkyl, class C') were therefore synthesized in order to verify whether the C(3)–O(2)–C(4)–O(3) moiety could elicit a β-blocking activity in this class of drugs,[23] even when not linked to an aromatic group. In the course of the work three new compounds of class C (**11–13**), containing a thienyl group, were also prepared.

The EMP of model compounds of class C and C' drugs was calculated in order to study the electrostatic interaction energy of the (arylcarbonyl)methyl portion of class C drugs and the (alkylcarbonyl)methyl portion of class C' drugs and thus their chemical reactivity. The EMP maps were also compared with that of the model compounds of a representative class B β-adrenergic drug.

**Chemistry.** The (acyloxy)propanolamines **6–13** were prepared (see Scheme I) by means of the ring-opening

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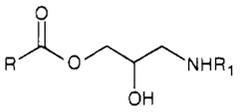
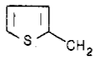
(23) In ref 21 the synthesis and β-blocking activity of one totally aliphatic derivative were also reported.

**Table II.** Antagonistic Activity of 3-(Acyloxy)propanolamines on $\beta_1$- and $\beta_2$-Adrenoceptors



| | | | | isolated guinea pig atria[a] | | | isolated guinea pig trachea[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| compd | R | $R_1$ | type | $pA_2$ | $pA_{10}$ | $pA_2 - pA_{10}$ | $pA_2$ | $pA_{10}$ | $pA_2 - pA_{10}$ | selectivity[b] |
| **6** | Et | *t*-Bu | C′ | 4.55 ± 0.26 | 3.74 ± 0.12 | 0.81 ± 0.06 | 4.58 ± 0.30 | 3.79 ± 0.22 | 0.79 ± 0.09 | 1.05 |
| **7** | *i*-Pr | *i*-Pr | C′ | 4.57 ± 0.12 | 3.90 ± 0.18 | 0.67 ± 0.08 | 5.37 ± 0.24 | 4.52 ± 0.20 | 0.85 ± 0.05 | 6.27 |
| **8** | *i*-Pr | *t*-Bu | C′ | 4.94 ± 0.22 | 4.10 ± 0.16 | 0.84 ± 0.09 | 4.54 ± 0.17 | 3.94 ± 0.20 | 0.60 ± 0.08 | 0.39 |
| **9** | c-$C_6H_{11}$ | *i*-Pr | C′ | 4.91 ± 0.19 | 4.20 ± 0.25 | 0.71 ± 0.08 | 5.64 ± 0.18 | 4.62 ± 0.15 | 1.02 ± 0.08 | 5.43 |
| **10** | c-$C_6H_{11}$ | *t*-Bu | C′ | 5.10 ± 0.22 | 4.22 ± 0.20 | 0.88 ± 0.03 | 5.60 ± 0.26 | 4.71 ± 0.21 | 0.89 ± 0.05 | 3.14 |
| **11** |  | *i*-Pr | C, C′ | 4.96 ± 0.14 | 4.28 ± 0.21 | 0.70 ± 0.07 | 5.00 ± 0.30 | 4.35 ± 0.31 | 0.65 ± 0.06 | 1.10 |
| **12** |  | *i*-Pr | C | 5.80 ± 0.35 | 5.11 ± 0.19 | 0.69 ± 0.06 | 6.33 ± 0.14 | 5.54 ± 0.16 | 0.78 ± 0.05 | 3.40 |
| **13** |  | *t*-Bu | C | 6.34 ± 0.15 | 5.42 ± 0.10 | 0.92 ± 0.07 | 7.72 ± 0.17 | 6.82 ± 0.15 | 0.89 ± 0.08 | 24.2 |
| practolol | | | | 5.78 ± 0.11 | 4.98 ± 0.11 | 0.80 ± 0.06 | 4.50 ± 0.19 | 3.74 ± 0.18 | 0.76 ± 0.06 | 0.05 |
| butoxamine | | | | 4.35 ± 0.10 | 3.98 ± 0.07 | 0.37 ± 0.10 | 6.89 ± 0.30 | 5.96 ± 0.21 | 0.93 ± 0.06 | 346 |

[a] Each value represents the mean ± the respective SD of six experiments. Practolol and butoxamine have been taken as the reference antagonists. [b] Antilog of the difference between the tracheal and atrial $pA_2$ values for each antagonist.

reaction of the glycidyl esters **1–5** with an excess of *i*-$PrNH_2$ or *t*-$BuNH_2$ in *t*-BuOH. The pure esters **6–13** were isolated as hydrochlorides or oxalate salts from the crude reaction mixtures (Table I). Compounds **6–13** are stable in their protonated form. On the contrary their free bases partially rearranged to the corresponding amides **14** on standing at room temperature for a few days. This intramolecular rearrangement process has been previously reported[21] for a series of compounds closely related to ours. The rearranged compounds of type **14** were also obtained as byproducts from the reaction of the glycidyl esters **1–5** with amines.

The relative position of the acyloxy group ($RCO_2$) in **6–13** was inferred by IR study in the 6-$\mu$m range in a dilute solution of $CCl_4$. The very similar C=O stretching frequency for the amino esters **6–13** and for the corresponding glycidyl esters **1–5** (see the Experimental Section) indicates that in both types of compounds the ester group is bonded to the same methylenic carbon.[24] The position of the amino group in **6–13** was determined by analyzing the $^1H$ NMR spectra of both the free bases and the salts. The conversion of the basic nitrogen of **6–13** to the positively charged atom brought about a 0.5-ppm downfield shift[25] of the signals of the methylenic protons adjacent to the nitrogen, without significantly affecting the methine proton signals (see the Experimental Section).

As the salts of **6–13** were expected to be unstable in solution,[21] their chemical stability was investigated in the same conditions (type of solution, concentration, temperature, and duration) in which pharmacological tests were later to be carried out. The results (see the Experimental Section) showed that at the end of the maximum contact time used in the pharmacological tests, the hydrochlorides of **7–10, 12,** and **13** remained practically unchanged and that 70% and 78% of the oxalates of **6** and **11**, respectively, were still present.

**Pharmacology. Guinea Pig Atria.** All the 3-(acyloxy)propanolamines (**6–13**) were able to antagonize isoprenaline inotropic activity in a dose-related fashion. Log dose–response curve to isoprenaline was shifted to the right when each antagonist was added to the bath. $pA_2$, $pA_{10}$, and $pA_2 - pA_{10}$ values of the drugs examined are shown in Table II. Compounds **6–11** show $pA_2$ values all about 5, which are intermediate between those of practolol (5.78 ± 0.11) and butoxamine (4.35 ± 0.10). Compound **12** exhibits a $pA_2$ value (5.80 ± 0.35) practically identical with that of the reference $\beta_1$ antagonist, while the $pA_2$ value of **13** (6.34 ± 0.15) is higher, indicating a great affinity for $\beta_1$ adrenoceptors.

$pA_2 - pA_{10}$ differences indicate that the antagonistic activity of the compounds tested is in most cases competitive in nature. All the *tert*-butyl derivatives show a high degree of competitivity, comparable to that of practolol (0.80 ± 0.06); among them, compound **13** shows the highest $pA_2 - pA_{10}$ difference (0.92 ± 0.07), fairly similar to the theoretical value of 0.95.

The drugs tested did not show any stimulating effect on atrial $\beta_1$ adrenoceptors; no modification of the cardiac chronotropic activity was observed up to doses of $10^{-4}$ M.

**Guinea Pig Trachea.** All the (acyloxy)propanolamines (**6–13**) displayed blocking properties on $\beta_2$ tracheal adrenoceptors. The relative $pA_2$ values show various degrees of affinity for this receptor. Compounds **6–12** exhibit $pA_2$ values lower than that of butoxamine (6.89 ± 0.30) and among them **6** and **8** reveal the lowest affinity for $\beta_2$ adrenoceptors (5.58 ± 0.30 and 4.54 ± 0.17, respectively) similar to that of practolol (4.50 ± 0.19). Compound **13** exhibits a $pA_2$ value (7.72 ± 0.17) significantly higher than that of butoxamine.

The $pA_2 - pA_{10}$ differences of the compounds tested indicate that the antagonism is competitive except for **8** and **11**, whose values (0.60 ± 0.08 and 0.65 ± 0.06, respectively) are significantly different from that of butoxamine (0.93 ± 0.06).

No stimulant activity was detected for any of the drugs examined in this experimental preparation.

**Rat Vas Deferens.** None of the (acyloxy)propanolamines **6–13** displayed any stimulating or blocking properties on $\alpha$-adrenoceptors up to doses of $10^{-3}$ M.

## MO Calculations

In order to study the electrostatic molecular potential of type C and C′ $\beta$-adrenergic drugs, one compound of each type was selected: compound **15** of type C and compound

(24) Bellamy, L. J. *The Infra-red Spectra of Complex Molecules*; Chapman and Hall: London, 1975; p 205.
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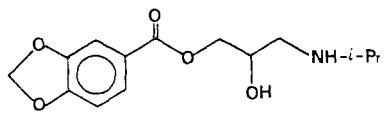
6 of type C'. The EMP was then calculated on two model compounds, 16 and 17, of these drugs; the model compounds differ from the drugs in that the $CH_2NHR$ portion of 15 and 6 is simply replaced by a hydrogen atom. This is a simplification that greatly reduces the computation time and its validity has been widely checked and discussed in previous studies on β-adrenergic drugs.[2,3,13,16]

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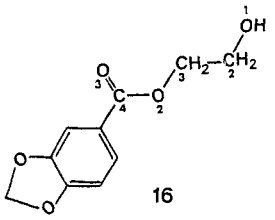


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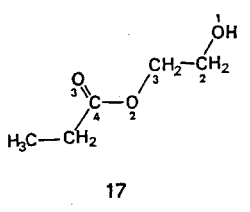


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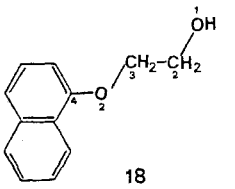
The molecular wave functions were computed at the "ab initio" SCF MOLCAO level, using a minimal STO-3G Gaussian basis set. The geometry of the model compound 16 was established on the basis of X-ray data found for 15,[22] except for the torsion angles O(2)–C(3)–C(2)–O(1) and C(3)–C(2)–O(1)–H, for which values of 180° and 160°, respectively, were selected, in accordance with the choice made in studying the EMP of other β-adrenergic drugs both of type A and B.[2] As regards compound 17, the same geometry was selected for the $COOCH_2CH_2OH$ portion as in the analogous portion of 16; the ethyl group was placed in the same plane as the carboxyl group, with the methyl carbon oriented "anti" with respect to the O(2).

Figure 2 shows the EMP maps of 16 and 17 in the plane defined by the C(4)–O(3)–O(2)–C(3)–C(2) atoms and in the plane parallel to it, on the same side as the alcoholic oxygen, at a distance of 1.7 Å, which approximately corresponds to the van der Waals radius.[2] The plane defined by the C(4)–O(3)–O(2)–C(3)–C(2) atoms also contains the 3,4-(methylenedioxy)phenyl portion in the case of 16 or the ethyl group in the case of 17 and will be referred to as the "molecular plane".

The maps of 16 and 17 are very similar in the regions corresponding to the common $COOCH_2CH_2OH$ portions, in both considered planes. There are three negative minima due to the oxygen atoms O(1), O(2), and O(3). The most negative value is generated by the O(3) atom: −54.9 and −56.7 kcal/mol in the molecular plane and −15.8 and −15.9 kcal/mol in the parallel plane for 16 and 17, respectively. The O(2) atom generates a minimum of −29.5 and −38.2 kcal/mol in the molecular plane and of −6.3 and −7.2 kcal/mol in the parallel plane for 16 and 17, respectively, thus exhibiting a less nucleophilic potency than an ethereal atom of type B β-adrenergic drugs (in the case of doberol, for example, the ethereal atom generates a minimum of −52.9 and −13.1 kcal/mol in the molecular plane and in the parallel plane, respectively).[2] The EMP of 16 and 17 differ in the region where the two molecules are structurally different. Compound 16 shows a negative region that extends over a large part of the aromatic ring, with two minima due to the ethereal oxygen atoms of the dioxolane group; by contrast, compound 17 reveals a wholly positive EMP in the corresponding region, generated by the ethyl group.

The EMPs of 16 and 17 were compared with that of the model compound 18 of propranolol, a representative β-blocking drug of type B. The EMP of 18 was calculated in the same manner as that of 16 and 17; the geometry of 18 was selected in accordance with the one used in previous

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works[2,3,13,16] for other type B β-adrenergic drugs; in this conformation, the aromatic group and the O(2)–C(3)–C(2) atoms define a plane (also in this case called the "molecular plane"), while the O(1)–C(2)–C(3)–O(2) atoms possess the same spatial relationship as the corresponding atoms of 16 and 17.

Figure 3 shows the EMP trends of 16–18 in the plane parallel to the molecular plane at a distance of 1.7 Å on the same side as O(1). In this figure, the negative EMP areas are brought out by drawing several negative isopotential levels without drawing any positive ones. Compounds 15 and 6 present considerable structural differences compared with propranolol; however, the general EMP trends of the model compounds of these three drugs (16–18) show some significant analogies: (i) taking as reference points the minima corresponding to O(1) and O(2), which are in the same relative positions for all three compounds, it may be observed that the negative region generated by O(3) in the compounds 16 and 17 is in a position that is not very different from the negative minimum corresponding to the ring of the naphthalene nucleus bound to the ethereal oxygen of 18; (ii) the negative region corresponding to the 3,4-(methylenedioxy)phenyl group of compound 16 is in a position that corresponds to the region, likewise negative, that is generated by the other ring of the naphthalene nucleus; (iii) in all three compounds, a clear separation can be observed between the negative EMP region generated by O(1) and the other negative EMP regions. This last fact was found to be a characteristic of β-blocking drugs of both A and B types.[2,3,13,16]

Finally, it may be pointed out that the higher pharmacological activity of 15 ($pA_2 = 6.9 \pm 0.1$ on guinea pig atria)[20] compared with that of 6 (see Table II) could be explained in terms of a greater extension of negative EMP areas in the [3,4-(methylenedioxy)benzoyl]oxy region, in comparison with the corresponding propionyloxy region; at this point it is important to emphasize that regions spatially corresponding to those considered above, both in A and B type β-adrenergic drugs, generally show a negative EMP that has been related to the affinity of these drugs for the β-adrenergic receptor.[2,3,13]

## Discussion and Conclusions

All compounds tested (6–13) showed a significant, and in most cases, competitive β-blocking activity both on atrial $\beta_1$-receptors and on tracheal $\beta_2$-receptors.[26] The fact that this kind of activity is shown by the totally aliphatic compounds of class C' (6–10), demonstrates that, in agreement with what has been observed in the case of class B β-blocking drugs, the presence of an aromatic group

(26) Compounds 6–13, with the exception of 8, show a weak degree of bronchoselectivity, expressed in Table II as the T/A ratio, which is, however, not worthy of any remark. The activity exhibited by thienyl derivatives 11–13 is comparable to that reported[21] for structurally corresponding compounds of class C.

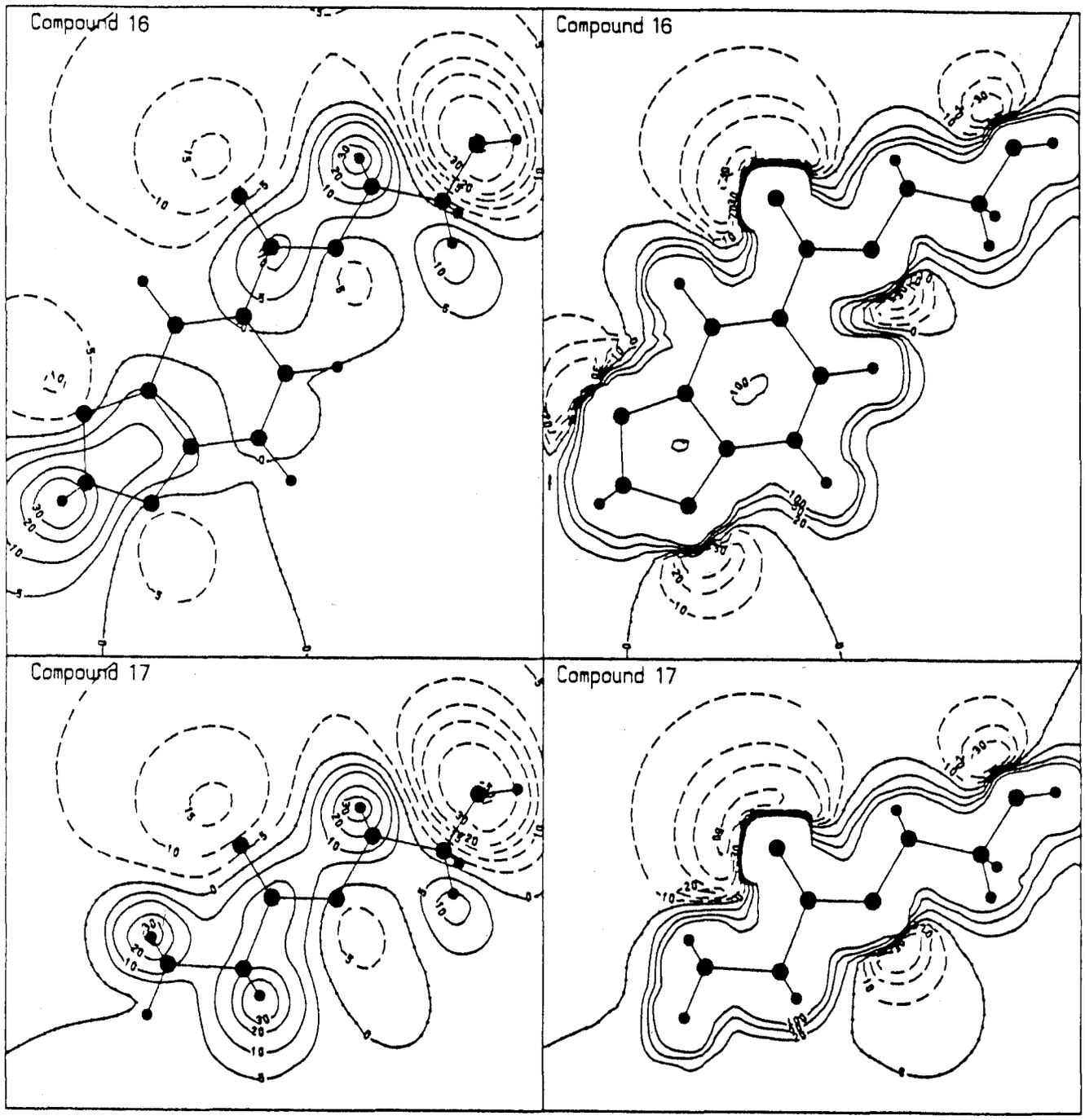



**Figure 2.** EMP contour maps of compounds **16** and **17**: on the left, in the plane parallel to the "molecular plane" at a distance of 1.7 Å and on the same side of O(1); on the right, in the "molecular plane". Dashed levels represent negative potential and full levels indicate positive potential. All values in kcal $mol^{-1}$.

linked to C(4) is not indispensable in class C drugs, in order to elicit the β-blocking activity. On the contrary, this fact would seem to support the hypothesis previously advanced on the basis of the results of structural studies[22] (see introduction), that the C(3)–O(2)–C(4)–O(3) portion of class C drugs could in some way take the place of the aromatic ring directly linked to the C(2) atom of class A drugs or the C(3)–O(2)–C(4)–C(5) moiety of class B drugs, in the interaction with the β-adrenergic receptor. The theoretical calculations carried out on model compounds of **6**, **15**, and propranolol have shown that the EMP trends account for the analogous chemical reactivity for the above-mentioned portions of the three classes of drugs.

The β-blocking potency of the class C′ drugs **6**–**10** (Table II) is in general lower than that shown by class C drugs (see ref 20, 21 and compounds **12** and **13** in Table II). The higher pharmacological activity of **15** (a class C drug) in comparison with that of **6** (a class C′ drug) has been discussed in the MO Calculations section, in the light of the differences which have been found between the EMP trends on their (acyloxy)methyl moieties; on the basis of these considerations, it may be suggested that the aryl of class C drugs could play a part in modulating the affinity of the (acyloxy)methyl portion for the receptor. Similarly to what happens for the aromatic ring of class B drugs,[2,3,8,13,16] that of class C drugs would not have therefore the role of directly substituting the Ar directly linked to the C(2) in class A drugs, but it would seem rather to take part in a different way in the drug–receptor interaction. The different role of the aromatic moiety in class A and B drugs in the interaction with the receptor site had been hypothesized[2,3,16,19] or demonstrated[14,27] on several occa-

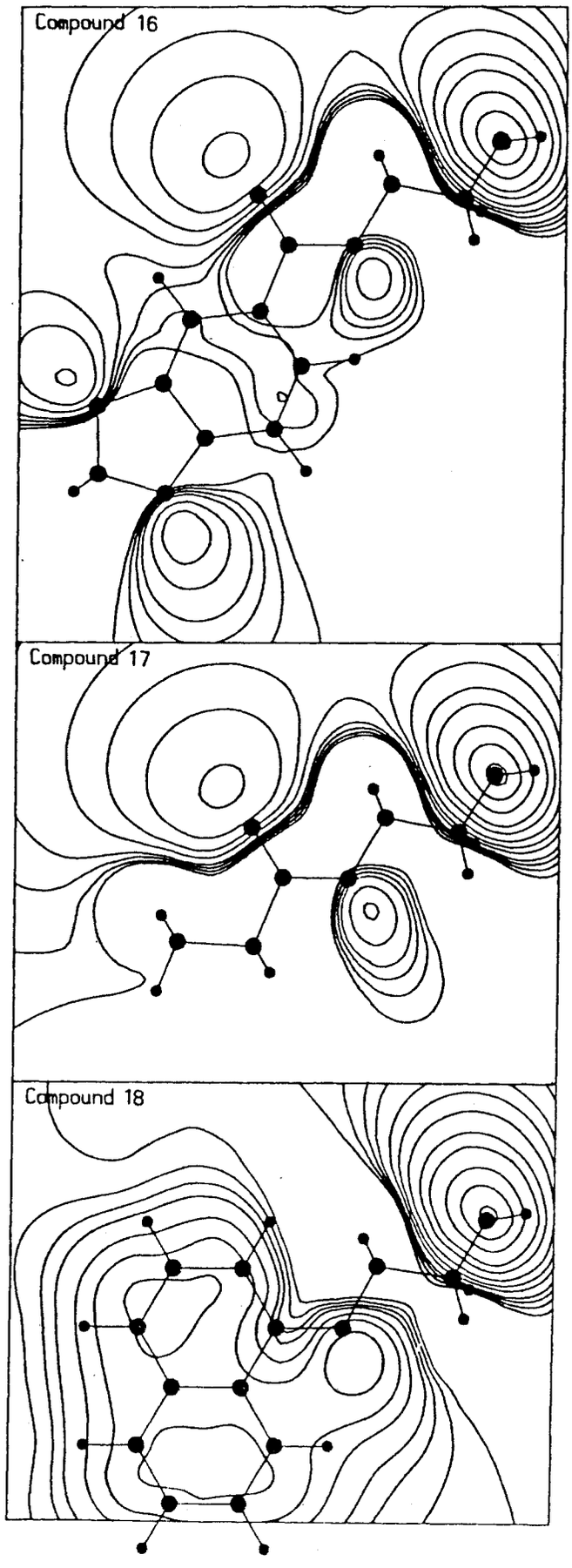
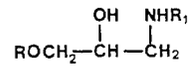



**Figure 3.** EMP contour maps of compounds **16–18** in the plane parallel to the "molecular plane" at a distance of 1.7 Å and on the same side of O(1). Only negative EMP levels are indicated.

sions. A recent structure–activity relationship study[21] carried out on a large number of class C drugs suggested on the other hand a different function for the aromatic portion of class B and class C drugs.

It is worthwhile mentioning that some completely aliphatic ether derivatives of type D exhibit β-blocking activity; these compounds are to a certain extent related to



D

C′, but the substituent linked to the $OCH_2CH(OH)CH_2NHR_1$ chain completely lacks any π system.[17,28] The activity of these compounds is of the same order as that of the C′ compounds. As has already been pointed out,[3] type D compounds offer an extremely simplified model of β-blocking adrenergic drugs. The fact that D compounds reveal a certain activity might lead one to suppose that the presence of the $OCH_2CH(OH)CH_2NHR_1$ group is sufficient for the eliciting the β-blocking properties of drugs with an (aryloxy)propanolamine structure (type B). These considerations will have to receive due attention in future studies in the field of β-adrenergic drugs dealing with subjects that go beyond the main goal of the present work, which is simply that of comparing the activity of drugs with an (acyloxy)propanolamine structure.

## Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra for comparisons of compounds were taken on paraffin oil mulls or as liquid film on a Perkin-Elmer Model 1310 instrument and those for the determination of C=O stretching bands frequency with a Perkin-Elmer Model 257 double-beam grating spectrophotometer using NaCl cell of 1-mm optical length in dried $CCl_4$. $^1H$ NMR spectra were obtained in ca. 10% $CDCl_3$ [for the free bases or neutral compounds ($Me_4Si$)] and $D_2O$ [for the salts ($Me_3SiCD_2CD_2COONa$)] solutions with a Varian EM360 A spectrometer. High-performance liquid chromatography was carried out on a Waters 6000A liquid chromatograph fitted with a Waters $C_{18}$ μBondapack column, using 6:4 mixture of MeCN–sodium phosphate buffer (pH 6.6) as the mobile phase. The sodium salts of the carboxylic acids for the synthesis of the glycidyl esters **1–5** were prepared by the usual methods. Analytical TLC were carried out on 0.25-mm layer silica gel plates (Merck $F_{254}$) containing a fluorescent indicator; spots were detected under UV light (254 nm) (in the case of **11–13**) or by spraying with 0.2 M $K_2Cr_2O_7$ in 40% aqueous sulfuric acid followed by gentle heating (in the case of **6–10**). Magnesium sulfate was always used as the drying agent. Evaporations were made in vacuo (rotating evaporator). Elemental analyses were performed by our analytical laboratory and agreed with theoretical values to within ±0.4%.

**General Procedure for the Synthesis of the Glycidyl Esters 1–5.** To a stirred suspension of the sodium salt of the appropriate acid (0.063 mol) in epichlorohydrin (8.9 g, 0.094 mol) and toluene (50 mL) at reflux was added benzyltrimethylammonium chloride (1.2 g, 6.4 mmol). The resulting suspension was refluxed for 45 min, cooled at room temperature, washed ($H_2O$, aqueous $NaHCO_3$, and $H_2O$), filtered, and evaporated to dryness to yield the crude epoxide (**1–5**) as an oil, which was distilled. [**1** (R = Et) (57%): bp 63–65 °C (0.3 mm); $n^{20}_D$ 1.6634; IR 1742 $cm^{-1}$ (C=O). Anal. ($C_6H_{10}O_3$) C, H. **2** (R = *i*-Pr) (56%); bp 69–71 °C (0.1 mm); $n^{20}_D$ 1.4252; IR 1738 $cm^{-1}$ C=O). Anal. ($C_7H_{12}O_3$) C, H. **3** (R = c-$C_6H_{11}$) (60%): bp 82–84 °C (0.2 mm); $n^{20}_D$ 1.4646;

(27) In ref 14, probably owing to a slip or a misprint, it was wrongly reported that ref 16 would corroborate a different and contrasting hypothesis.

(28) Type D (alkyloxy)propanolamines may be considered either as analogues of type C′ compounds where there is no carbonyl group between the oxygen and the alkyl moiety or as completely aliphatic analogues of type B drugs.

IR 1735 $cm^{-1}$ (C=O). Anal. ($C_{10}H_{16}O_3$) C, H. **4** (R = c-SCH=CHCH=C($CH_2$)), (40%); bp 115–117 °C (0.1 mm); $n^{20}_D$ 1.5291; IR 1745 $cm^{-1}$ (C=O). Anal. ($C_9H_{10}O_3S$) C, H. **5** (R = c-SCH=CHCH=C-) (70%); bp 112–114 °C (0.3 mm); $n^{20}_D$ 1.5458; IR 1717 $cm^{-1}$ (C=O). Anal. ($C_8H_8O_3S$) C, H.]

**General Procedure for the Preparation of the (Acyloxy)propanolamines 6–13.** A stirred solution of the epoxide (**1–5**) (3.9 mmol) and isopropylamine or *tert*-butylamine (4.7 mmol) in *tert*-butyl alcohol (4.0 mL) was heated at 50 °C for 4 h. After cooling, the crude mixture was evaporated to dryness and the oily residue was taken up in 10% aqueous HCl. The aqueous suspension was washed with $Et_2O$, alkalinized with solid $K_2CO_3$, and extracted with $CHCl_3$. Evaporation of the $Et_2O$ washings yielded a neutral fraction containing also type **14** compounds (IR, TLC) (see below). The washed ($H_2O$) and filtered $CHCl_3$ solution was evaporated, and the residue was dissolved in $Et_2O$ and treated with a small excess of $Et_2O$·HCl (or oxalic acid in 7:3 $Et_2O$–MeOH in the case of **6** and **11**) to yield a solid salt of **6–13**, which was crystallized from the proper solvent. The $^1H$ NMR spectra of these salts exhibit some complex signal systems whose middle points range from 3.07 to 3.27 ppm for the $CH_2NHR_1$ and from 4.07 to 4.28 ppm for the CHOH protons. For other physical and microanalytical data see Table I.

The salts of **6–13** were converted to the free bases by treating an aqueous ice-cooled solution of the salt with solid $Na_2CO_3$ and extracting the free bases with $CHCl_3$. Evaporation at room temperature of the filtered organic layer yielded pure **6–13** as an oil. [Middle points of the $^1H$ NMR signals: $\delta$ 2.55–2.71 (2 H, $CH_2NHR_1$) and 3.73–3.93 (1 H, CHOH). **6**: IR 1737 $cm^{-1}$ (C=O). Anal. ($C_{10}H_{21}NO_3$) C, H, N. **7**: IR 1736 $cm^{-1}$ (C=O). Anal. ($C_{10}H_{21}NO_3$) C, H, N. **8**: IR 1734 $cm^{-1}$ (C=O). Anal. ($C_{11}H_{23}NO_3$) C, H, N. **9**: IR 1731 $cm^{-1}$ (C=O). Anal. ($C_{13}H_{25}NO_3$) C, H, N. **10**: IR 1732 $cm^{-1}$ (C=O). Anal. ($C_{14}H_{27}NO_3$) C, H, N. **11**: IR 1741 $cm^{-1}$ (C=O). Anal. ($C_{12}H_{19}NO_3S$) C, H, N. **12**: IR 1713 $cm^{-1}$ (C=O). Anal. ($C_{11}H_{17}NO_3S$) C, H, N. **13**: IR 1714 $cm^{-1}$ (C=O). Anal. ($C_{12}H_{19}NO_3S$) C, H, N.]

The salts of **6–13** are stable. On the contrary, the free bases are quite unstable and their keeping for some days at room temperature lead to the amides of type **14** (IR, TLC), of which only **14** (R = c-SCH=CHCH=C($CH_2$), $R_1$ = *i*-Pr) was fully characterized: IR 1625 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 1.17 (d, 6, $J$ = 6.8 Hz, $CHMe_2$), 3.97 (s, 2, $CH_2COO$), and 4.19 (m, 1, $J$ = 6.8 Hz, $CHMe_2$). Anal. ($C_{12}H_{19}NO_3S$) C, H, N.

**Stability Study of the Salts of 6–13 in Tyrode Solution at 37 °C.** Aqueous 0.25 M solution of the salt of each ester (**7–10**, **12**, and **13**, as hydrochloride; **6** and **11** as oxalate) (0.1 mL) was added to Tyrode solution (see Pharmacological Methods section) (4.9 mL) at 37 °C and then left at the same temperature for 15 min. The test solutions were analyzed by high-performance liquid chromatography (HPLC). The percentages of the salts of **6–13** remaining after 15 min were 100% (for **7**, **8**, **12**, and **13**) and 70%, 97%, 95%, and 78% (for **6**, **9**, **10**, and **11**, respectively).

**Pharmacological Methods. Isolated Guinea Pig Atria.** The atria, removed from adult male guinea pigs weighing 300–350 g, were employed according to the method previously described.[3]

**Isolated Guinea Pig Trachea.** Trachea were dissected from adult guinea pigs weighing 300–350 g, by sealing both ends and placed in a 10-mL organ bath containing Tyrode saline solution[29] gassed with 95% $O_2$–5% $CO_2$ and maintained at a constant temperature of 37 °C. Smooth circular muscle activity was evaluated by measuring the variation in the internal pressure through a Bentley pressure transducer connected with a Basile Model 7050 microdynamometer. The tissue was allowed to stabilize for 45 min before the experiment was started.

**Isolated Rat Vas Deferens.** Vasa deferentia were obtained from adult albino rats (Sprague–Dawley) weighing 200–250 g and employed as previously described.[30]

In all preparations, agonists were allowed to act until maximal response was achieved. A dose–effect curve to the agonists isoprenaline or norepinephrine (for the $\beta$- and $\alpha$-receptors, respectively) was obtained by the method of single doses; antagonistic activity of the compounds was evaluated by assaying the percent inhibition of the maximal response to the agonist in the presence of increasing concentrations of the antagonist.

Aqueous solutions of agonists and antagonists (0.2 mL) were added to the bath containing Tyrode solution (9.8 mL). Solutions of the tested compounds (**6–13**) were prepared at the moment of the experiment, and the contact period for each dose of the antagonist was 15 min.

$pA_2$ and $pA_{10}$ (i.e., the negative logarithms of the molar concentrations of the antagonist that reduce the agonist activity by 50% and 90%, respectively) were calculated according to the method of Arunlakshana and Schild.[31] $pA_2$ was taken as the index of affinity of the antagonist for the receptor; the value of $pA_2 - pA_{10}$ was chosen to assess the competitive nature of this interaction, following the method described by Gaddum.[32] Practolol and butoxamine were taken as reference antagonists for $\beta_1$- and $\beta_2$-adrenoceptors, respectively.

The following drugs were used: isoprenaline, practolol, butoxamine, and **7–10**, **12**, **13** as hydrochlorides, and **6** and **11** as oxalates.

**Acknowledgment.** This work was supported by a grant from the Progetto Finalizzato del Consiglio Nazionale delle Ricerche, Roma, Chimica Fine e Secondaria.

**Registry No.** **1**, 37111-25-4; **1**·Na (acid), 137-40-6; **2**, 3669-66-7; **2**·Na (acid), 996-30-5; **3**, 24553-05-7; **3**·Na (acid), 136-01-6; **4**, 106420-52-4; **4**·Na (acid), 61341-42-2; **5**, 106420-53-5; **5**·Na (acid), 25112-68-9; **6**, 106420-54-6; **6**·1/2oxalate, 106420-61-5; **7**, 106420-55-7; **7**·HCl, 106420-62-6; **8**, 106420-56-8; **8**·HCl, 106420-63-7; **9**, 106420-57-9; **9**·HCl, 106420-64-8; **10**, 106420-58-0; **10**·HCl, 106420-65-9; **11**, 106420-59-1; **11**·oxalate, 106420-66-0; **12**, 106420-60-4; **12**·HCl, 106420-67-1; **13**, 96920-57-9; **13**·HCl, 106420-68-2; **14**, 106434-46-2; **15**, 90531-36-5; **16**, 89012-56-6; **17**, 24567-27-9; **18**, 711-82-0; *i*-$PrNH_2$, 75-31-0; *t*-$BuNH_2$, 75-64-9; epichlorohydrin, 106-89-8.

(29) The composition of this solution was (mM) 136.8, NaCl; 2.95, KCl; 1.80, $CaCl_2$; 1.05, $MgCl_2.6H_2O$; 0.41, $NaH_2PO_4$; 11.9, $NaHCO_3$; and 5.5, glucose.
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