# CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY OF CATECHOLAMINES

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Ever since 1910, the year in which the famous work of Barger and Dale[1] on the sympathicomimetic activity of a series of amines structurally related to adrenaline was published, the subject of the relationships between chemical structure and biological activity in the catecholamine field periodically comes up for discussion.

This persistent interest in the subject is, in itself, a significant pointer to its complexity, the main reason for which is based on the complexity of the kind of phenomena induced by the natural sympathicomimetic amines, adrenaline and noradrenaline.

Some of the effector cells responding to the adrenergic stimulus are stimulated, others inhibited; some responses may be inhibited by the classic adrenergic antagonists (ergotamine, dibenamine), while others, in contrast, are unaffected.

Cannon and Rosenblüth[2] suggested an explanation of this involved behaviour, postulating the existence of two different chemical mediators (Sympathin E and I).

The synthesis and study of *N*-alkyl derivatives of noradrenaline has revealed the possibility of potentiating some of the properties of this base and of reducing or abolishing others, and has thus permitted tackling the problem of the mechanism of action of catecholamines in different terms.

To Ahlquist[3] goes the merit of being the first to have suggested the hypothesis of the existence of two different adrenergic receptors ($\alpha$ and $\beta$) capable of reacting with the same mediator (adrenaline) but triggering opposite responses. According to Ahlquist's hypothesis, the $\alpha$ receptors would be involved in the majority of stimulant-type manifestations, while the $\beta$ receptors would take part in the majority of inhibiting-type manifestations.

The principle enunciated by Ahlquist, although apparently presenting some contradictions, which have been particularly emphasized and discussed by Lands[4] and Furchgott[5], must be considered valid and operative in the present state of knowledge.

Study of the structure–action relationships represents the most suitable means available in order to obtain information on the interactions between agonist and receptor, and is all the more effective when working with a homologous series.

The two natural sympathicomimetic catecholamines are both $\beta$-phenylethylamine derivatives. Chemically, they are characterized by the presence of a primary or secondary amine group, a secondary alcohol group and two phenol groups in positions 3 and 4, within the molecule.

These groups and the molecular configuration—the two molecules present a centre of asymmetry—govern all the interactions of said molecules with the receptor.

Our studies deal with the optical configuration, the basic function and the catechol group.

## THE CONFIGURATION OF CATECHOLAMINES

It is a well-known fact that the biological activity of the catecholamines depends on the configuration of these bases and this holds true for both α-type and β-type effects.

It is obvious that before the structure–action relationships can be discussed, the configuration must be known.

The configuration of the two natural catecholamines and also of the most significant synthetic catecholamines has been established in our laboratory.

In 1953 we found[6] that optically active mandelamides may be reduced to the corresponding amines, by means of lithium aluminium hydride, without appreciable racemization. It became possible, therefore, to determine the configuration of β-phenyl- β-hydroxyethylamine.

The same reaction also offered the possibility of deducing the configuration of various sympathicomimetic amines from that of suitably substituted mandelic acids.

The scheme given in *Figure 1* summarizes the transformations carried out in determining the configuration of adrenaline[7], noradrenaline[8] and isopropyl noradrenaline[9].

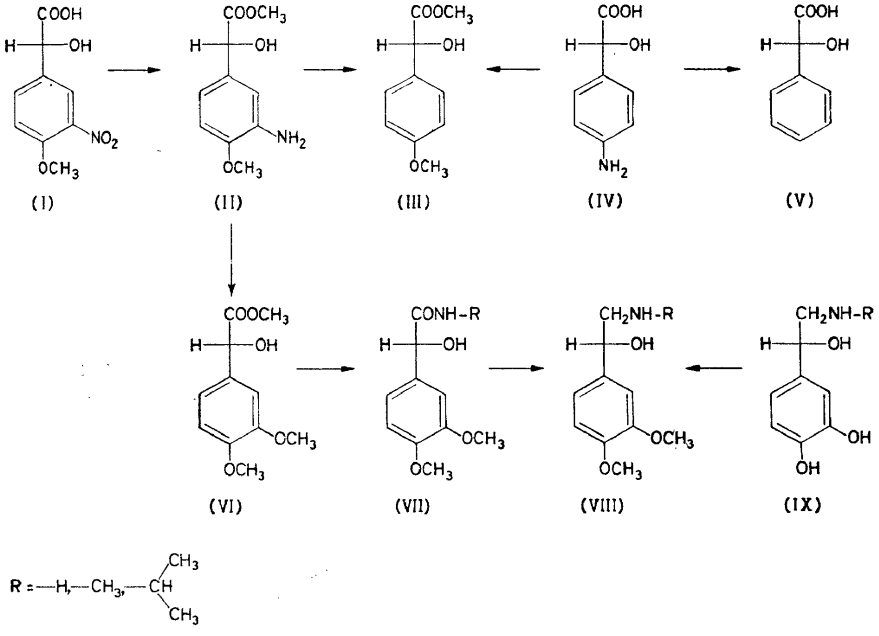



*Figure 1*

4-Methoxy-3-nitro-mandelic acid was chosen as the starting point. This acid was unknown and was prepared and then resolved into the optical antipodes. The relationship of the optically active acid (I) with 4-amino-mandelic acid (IV) was worked out through methyl 3-amino-4-methoxy-mandelate (II) and methyl 4-methoxymandelate (III); in turn, Fredga and Andersson had already correlated 4-aminomandelic acid with mandelic acid (V). On the basis of these transformations, the D configuration must be assigned to *laevorotatory* methyl 3-amino-4-methoxymandelate.

Methyl 3-amino-4-methoxymandelate, which represents the key substance, as it may be correlated with mandelic acid on the one hand, and with the catecholamines on the other, was transformed through diazotization, substitution of the diazo group with hydroxyl, and methylation with diazomethane, into methyl 3,4-dimethoxymandelate (VI). From this ester were then prepared the amides (VII: R = H, $CH_3$, iso-$C_3H_7$) and they were reduced with lithium aluminium hydride, giving rise to the respective bases (VIII). The primary amine and the *N*-methyl base were isolated as *N*-acetyl- or *N*-carboethoxy-derivatives. The same compounds can be obtained starting from optically active catecholamines (IX), through methylation with diazomethane, or else by the action of the latter on the *N*-acetate, triacetate, or *N*-carboethoxy derivative of the base.

As a result of these transformations, the configuration of *laevorotatory* noradrenaline, adrenaline and isopropyl noradrenaline, clearly corresponds to that of D(-)mandelic acid. The configuration of the three laevorotatory catecholamines can, therefore, be indicated with the prefix D.

On the basis of the "sequence rule"[10], the three laevorotatory catecholamines are R forms. The steric correspondence between natural adrenaline and noradrenaline, is definitely established by these researches.

The above-mentioned methyl 4-methoxymandelate, has been linked[7] to methylaminomethyl-(4-hydroxyphenyl)-carbinol (Sympathol, Synephrine) through a similar series of transformations (*Figure 2*). It has thus been possible to assign the D configuration to *laevorotatory* methylaminomethyl-(4-hydroxyphenyl)-carbinol.

The configuration of methylaminomethyl-(3-hydroxyphenyl)-carbinol (Meta-Sympathol, Phenylephrine) was determined[11] through the transformations indicated in *Figure 3*, starting from the laevorotatory isomer. This compound was acetylated and methylated at the phenolic hydroxyl group; the ether was then nitrated in the 4- position. D(-)$O^3$,$O^4$-dimethyl-*N*-acetyl-adrenaline, that is, the same compound obtained starting from natural adrenaline, was reached through reduction of the nitro group to an amine, substitution of the amine group by a hydroxyl, and methylation of the resulting phenol with diazomethane. This permits the D configuration to be assigned to *laevorotatory* Phenylephrine.

*Tertiary butyl-noradrenaline* has not yet been split into its optical antipodes. We resolved this substance with (+) camphosulphonic acid[12]: the optical antipodes melt at 134–138° and show $[\alpha]_D^{20} = \pm 39{\cdot}0°$ ($c = 2$ per cent in N/2 HCl). The D configuration must be attributed to the *laevorotatory* base from a comparison of the rotatory dispersion curve of this substance with those of the preceding bases.

Bearing in mind the biological activity of the optical antipodes of

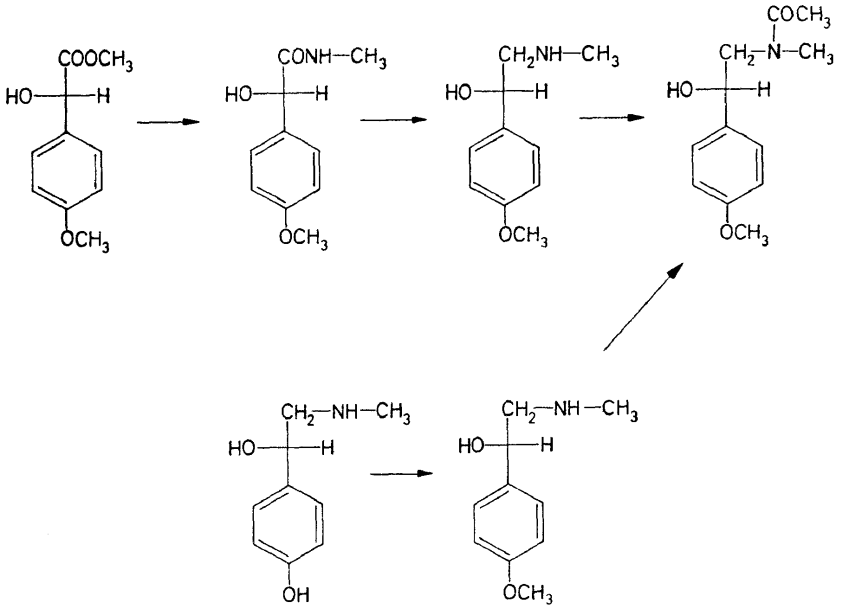


*Figure 2*

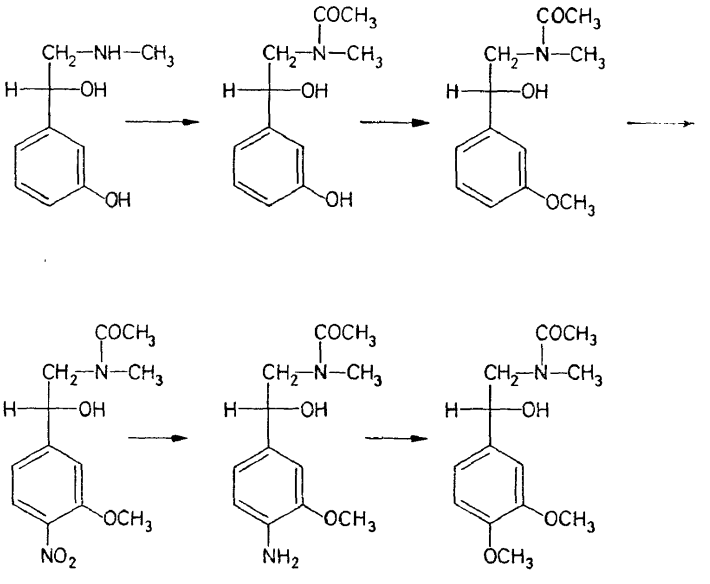


*Figure 3*

noradrenaline and *N*-alkyl-substituted catecholamines, we may state that both the $\alpha$ and $\beta$ effects are favoured by a D configuration.

## THE BASIC FUNCTION

The many studies dealing with the influence of *N*-alkylation on the activity of catecholamines[13–19] have demonstrated that the hypertensive effect is reduced on substituting a methyl group for a hydrogen atom (from noradrenaline to adrenaline), while a hypotensive effect accompanies the hypertensive one on increasing the mass of the alkyl group (ethyl-, n-propyl-noradrenaline), or else the said hypertensive effect is inverted, being turned into a distinct hypotensive one (isopropyl-noradrenaline, butyl-homologous).

The hypotensive effect is more pronounced in those compounds where the *N*-alkyl group has a branched chain (isopropyl, t-butyl).

Compounds capable of producing a hypotensive effect also reveal other activities, the main and most thoroughly studied being the broncholytic, tachycardia-producing and smooth-muscle-inhibiting effects (uterus and intestine) which, from the quantitative standpoint, parallel the hypotensive action.

The over-all conclusion to be drawn from these data in conformity with Ahlquist's theory, is that the nature of the alkyl group linked to the nitrogen directs the biological response towards either $\alpha$ or $\beta$ effect.

Noradrenaline is mainly an $\alpha$ receptor activator, while adrenaline is a pharmacodynamically more active substance, being capable of producing both $\alpha$ and $\beta$ effects. The $\beta$ activity sharply predominates in some of the higher homologues, such as *N*-isopropyl-noradrenaline. *N*-isopropyl-noradrenaline can even be considered a test substance for studying $\beta$-type activities.

A whole series of researches have been undertaken at our Institute on the basis of this assumption, with the aim of determining the position of some very important biological effects of natural catecholamines, which up to now have received slight attention from this aspect, within the classification proposed by Ahlquist.

One of these effects is the corticostimulating action ascribed to, and confirmed for adrenaline by Martha Vogt[20] and Long and Fry[21]. The results obtained from studying noradrenaline, adrenaline and isopropyl-noradrenaline have permitted placing this activity among the $\beta$ effects[22–24].

The metabolic activity was next examined. A comparative study of the metabolic activity of *N*-isopropyl-noradrenaline, noradrenaline and adrenaline[25], and research on antagonists of the metabolic effects[26] have revealed that the effect on muscular glycogenolysis—deduced from the hyper-lactico-acidemia effect— must be considered of $\beta$ type.

Classification of the metabolic activities of adrenaline among the $\beta$ effects becomes especially important with regard to the catalytic action of adrenaline itself on the transformation of adenosine-triphosphate (ATP) into adenosine-3′,5′-phosphate (cyclic AMP) stimulating the formation of active phosphorylase which, in turn, stimulates glycogenolysis[27].

It was decided, therefore, to study the course of the cortico-stimulating and metabolic activities in a wider series of noradrenaline *N*-alkyl derivatives.

The most significant compounds were examined in both the racemic and optically active form. An already well-recognized activity—the bronchodilating effect—was systematically re-studied in order to obtain a term of comparison with the data in the literature. The data obtained are summarized in *Table 1* which gives the relative activities obtained on the basis of

*Table 1*

| *Compound* | *Bronchodilator action* | | | | *Corticostimulating effect* | *Lactic acid-stimulating effect* |
|---|---|---|---|---|---|---|
| | Konzett 1940 | Marsh 1948 | Moed 1955 | | | |
| D (−) Arterenol | | 2 | 1 | 12·5 | <20 | <2 |
| D (−) *N*-methyl-art. | 5 | 20 | 25 | 50 | 100 | 5–10 |
| DL *N*-ethyl-art. | 15 | 25 | 15 | 25–50 | 50 | 20–50 |
| D (−) *N*-isopropyl-art. | | | | 100 | 100 | 100 |
| DL *N*-isopropyl-art. | 50 | 50 | 50 | 50 | 50 | 50 |
| D (−) *N*-t-butyl-art. | | | | | | 200 |
| DL *N*-t-butyl-art. | | 100 | 75 | 50–100 | 50 | 100 |
| DL *N*-s-butyl-art. | | 25 | | 50 | <10 | 20–50 |
| DL *N*-n-butyl-art. | 5 | | | 25 | <10 | 5–12·5 |
| DL *N*-isobutyl-art. | 0·5 | | | <6 | <5 | ⩽1 |

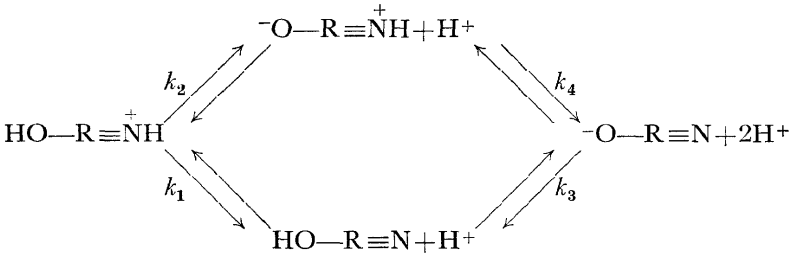
the proportions of the doses necessary for comparable effects. It is clearly manifest that, whatever the type of activity considered, the compounds under study can always be arranged in a series of decreasing activity, starting with t-butyl-noradrenaline and ending with isobutyl-noradrenaline. The results obtained confirm that the activities studied—the corticostimulating and metabolic actions—are of the $\beta$ type.

By facilitating the classification of the $\beta$-active substances according to their degrees of activity, they allow more precise comparisons of structure–action relationships to be made.

On examining the influence of the structure of the alkyl group it is necessary to remember that the shape and size of the alkyl group refer automatically to the number and position of the methyl groups within the radical. The influence of these groups is exerted through the positive inductive effect (+I) and also as a steric factor determining, on the one hand, the possibility of access of the molecule to the critical bond distance with the receptor and, on the other, the setting up of internal tension forces at the moment of interaction with the receptor itself. At this point we thought that a systematic study of the dissociation equilibria, which are affected by all the above-mentioned structural factors, would be extremely interesting. Only few data are available in the literature[28, 29]; moreover, there is also a surprising tendency to misinterpret the experimental values.

The work of G. P. Lewis[30], who determined the ionizations of a series of sympathicomimetic amines, and distinguished the possibility of multiple ionization, is formally correct. However, this author does not mention the various equilibria to which the constants measured should be referred. In the catecholamines studied, and referring to the pH range tested, two non-symmetrical functions dissociate: $\equiv\overset{+}{N}H$ and $-OH$ (this last function is a phenolic hydroxyl of the catechol grouping). It is thus possible to write out

the following dissociation scheme, where the $k$ values refer to the single microscopic equilibria:




The general relationship

$$k_1 k_3 = k_2 k_4$$

exists between the microscopic constants $k_1$, $k_2$, $k_3$ and $k_4$. It can be demonstrated[31] that these four constants may be determined through three distinct potentiometric measurements aimed at determining two macroscopic equilibrium constants of the system under consideration and one relating to the corresponding 3,4-dimethylethers. The $pk_1$, $pk_2$, $pk_3$, $pk_4$ values are reported in *Table 2.*

*Table 2.* $pk_1$, $pk_2$, $pk_3$ and $pk_4$ values of the catecholamines

| *Compound* | $pk_1$ | $pk_2$ | $pk_3$ | $pk_4$ |
|---|---|---|---|---|
| Arterenol | 9·18 | 8·92 | 9·39 | 9·64 |
| *N*-Methyl-arterenol | 9·51 | 8·88 | 9·38 | 10·00 |
| *N*-Ethyl-arterenol | 9·61 | 8·94 | 9·44 | 10·11 |
| *N*-Isopropyl-arterenol | 9·58 | 8·91 | 9·44 | 10·11 |
| *N*-n-Butyl-arterenol | 9·56 | 8·94 | 9·46 | 10·08 |
| *N*-s-Butyl-arterenol | 9·48 | 8·90 | 9·45 | 10·03 |
| *N*-Isobutyl-arterenol | 9·28 | 8·89 | 9·43 | 9·82 |
| *N*-t-Butyl-arterenol | 9·73 | 8·88 | 9·46 | 10·31 |
| *N,N*-Dimethyl-arterenol | | 8·88 | | |
| *N,N*-Dimethyl-arterenol-methyl-bromide | | 8·89 | | |

Now let us consider the course of the $pk_1$ or $pk_4$ values in relation to the alkyl radicals linked to the nitrogen. $pk_1$ depends mainly on: (*a*) the sum of the inductive effects exerted by the radicals linked to the nitrogen; (*b*) possible tensions linked to steric hindrance of the radicals themselves; (*c*) solvation phenomena or, more generally, solute–solvent interactions; (*d*) possible internal hydrogen bonding in the molecule.

The $pk_1$ value of the individual members of the series arises from the different parts played by the above-mentioned factors.

For quantitative estimation of the inductive effects of radicals linked to nitrogen, we can utilize the polar constants $\sigma$ defined by Taft[32] and then used by Hall[33] for purposes similar to ours. To the radical

$$[(HO)_2C_6H_3—\underset{\displaystyle OH}{\underset{|}{CH}}CH_2—]$$

an unknown polar constant $c$ can be assigned, the same for all terms of the series. The values reported by Taft[32] can be used for the remaining substituents. They are given in *Table 3.*

*Table 3.* Values of the inductive effects according to Taft[32]

| *Substituents* | $-\sigma$ |
|---|---|
| —H | −0·490 |
| —$CH_3$ | 0 |
| —$C_2H_5$ | +0·100 |
| —$C_3H_7$ (iso-) | +0·200 |
| —$C_4H_9$(n-) | +0·130 |
| —$C_4H_9$ (iso-) | +0·125 |
| —$C_4H_9$ (s-) | +0·210 |
| —$C_4H_9$ (t-) | +0·320 |

If the values of $pk_1$ are plotted against those of $-\sum\sigma$ (total polar constant, proportional to the global inductive effect of the nitrogen substituents), an interesting fact is observed. Amines with unbranched substituents (R = $CH_3$, $C_2H_5$ and n-$C_4H_9$) fall approximately along the same straight line, while amines with branched substituents (R = iso-$C_4H_9$, s-$C_4H_9$, iso-$C_3H_8$ and t-$C_4H_9$) fall on a second straight line differing from the first (*Figure 4*). Very likely, between the two groups of compounds, there is a

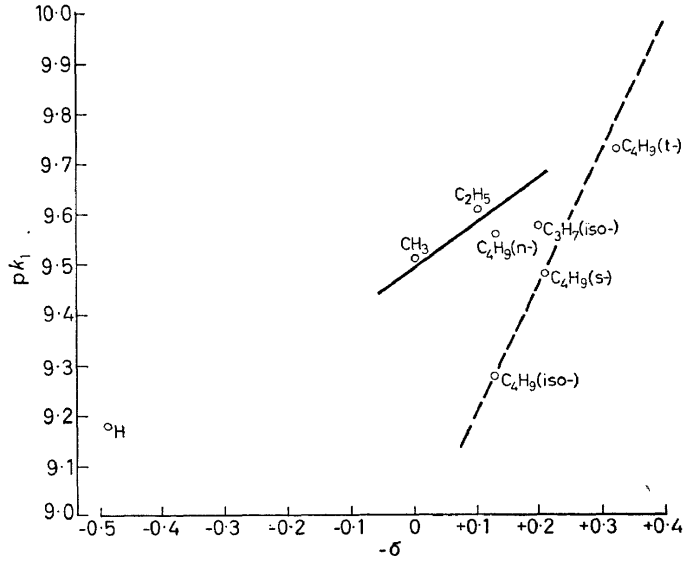



*Figure 4*

decisive intervention of diversification factors (for instance, steric factors, those relative to hydration, *etc.*), such as to allow a classification of the amines considered into two distinct groups differing from each other in their physico-chemical properties.

Regarding the other factors which influence the $pk_1$ values, it should be recalled that these compounds can from internal hydrogen bonds such as, for instance, that in which the positive nitrogen $\equiv\overset{+}{N}$—H acts as a hydrogen donor and the oxygen of the hydroxyl group as an acceptor (*Figure 5*). The

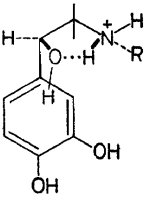



*Figure 5*

stability of similar 5-atom rings has already been demonstrated in the dialkylaminoethanols[34] and dialkylglycines[35]. In the present case it is to be expected that, all other factors being equal, the tendency to form hydrogen bonds will decrease with an increase of the +I inductive effect due to the *N*-alkyl group.

Finally, another fact of marked interest must be emphasized. Using *Table 2* it is possible to calculate the percentage of the various forms of catecholamines present at different pH values. The results of the calculations made for adrenaline are given in *Figure 6*. It is clearly seen that at physiological pH

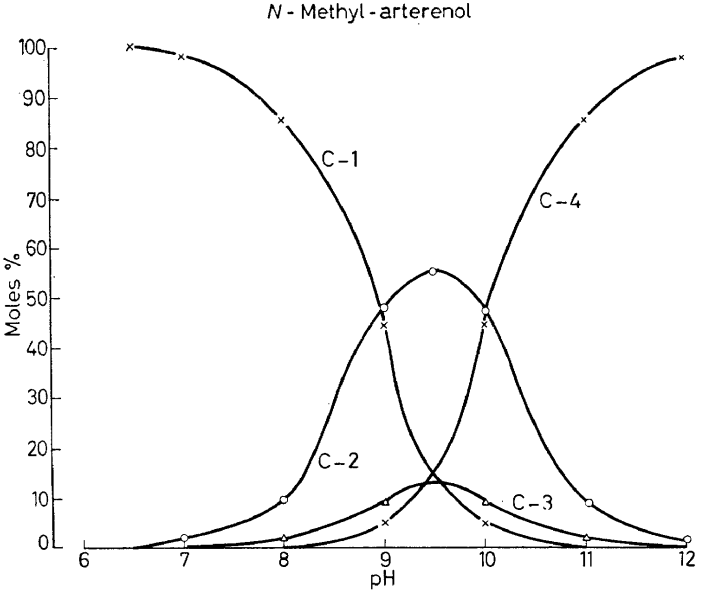
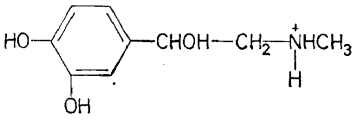



*Figure 6*

values, adrenaline exists mainly in the form:



and that the concentrations of the other structures are small.

Now let us examine the course of the biological properties of the catecholamines in the light of these facts. Noradrenaline shows a distinct predominance of $\alpha$ effects and, as regards the latter, is the most active of the group. Adrenaline and ethyl noradrenaline are capable of reacting with both $\alpha$ and $\beta$ receptors. The $\alpha$ activity is greatly reduced in the higher homologues, while the $\beta$ activity increases passing from the isobutyl–n-butyl pair to the s-butyl–isopropyl pair, reaching a maximum in t-butyl noradrenaline.

Since these bases are to a large extent protonated at physiological pH values, two types of interaction with a suitable substrate can, in general, be foreseen: ionic interaction with an anionic site, and hydrogen bonding with a suitable atom, at the expense of the proton attached to the nitrogen. It is important to note that the formation of one of the two types of bond does not exclude the formation of the other, and, therefore, that the action of the second type of bond may possibly be superimposed on that of the first. A study of models shows that for all members of the series examined, including the butyl isomers, there is at least one direction along which reaction is possible (*Figures 7* and *8*).

Of all the bases considered, noradrenaline is in an exceptionally favourable position as regards the possibility of hydrogen bonding. This is due, not merely to differences in the intensity of the inductive effects on the nitrogen atom, but also to the multiplicity of effective collision directions, to the smaller dimensions of the ammonium group which, permitting a closer position of the proton to the binding atom, further facilitates the formation of a strong hydrogen bond, and, finally, to the possibility that a single noradrenaline ion has of forming the greatest number of hydrogen bonds. These factors are weakened in the secondary homologous bases, in a manner which depends on the nature of R. The butyl isomers and the isopropyl compound, in which the steric factors are analogous, clearly show the influence of the inductive effect. The biological activity follows closely the course of the inductive effect in this family. Adrenaline and ethyl noradrenaline, which are closest to noradrenaline from the steric aspect, form a transition family between this base and the higher homologues, and this holds true for the biological properties also. In fact, they are found to be capable of reacting with both $\alpha$ and $\beta$ receptors. Confirmation of the previously discussed relationships is supplied by the behaviour of *N,N*-dimethyl noradrenaline[36] and of the related quaternary ammonium salt[37].

Progressive alkylation of the nitrogen, starting from noradrenaline, leads to progressive reduction of the number of linking protons and to a limitation of the directions of possible reaction. *N,N*-dimethyl-noradrenaline retains, in fact, the activity of adrenaline, but at a markedly lower level. The $\beta$-(3,4-dihydroxyphenyl)-$\beta$-hydroxyethyl-trimethylammonium ion which has

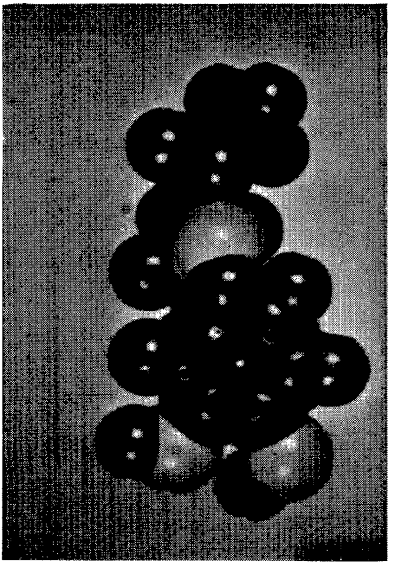


*Figure 7*

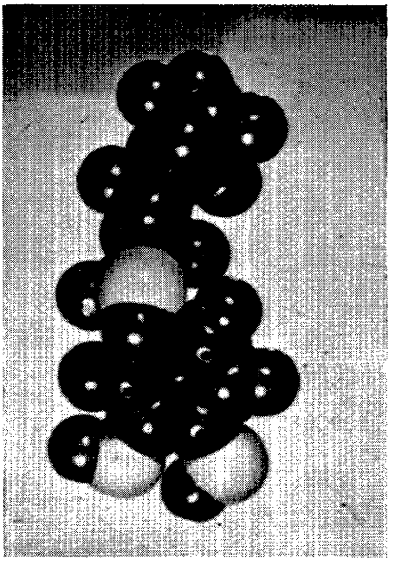


*Figure 8*

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no proton but a completely screened nitrogen, is practically free from adrenergic effects.

Thanks to the present research, the type and intensity of the boilogical activity of catecholamines can for the first time be correlated with some structural properties of these substances.

## CATECHOLIC GROUP

The importance of the catecholic group has been ascertained in a large number of studies mainly dealing with adrenaline and noradrenaline. Thus, it has been ascertained that displacement or abolition of even one of the two phenolic hydroxyls in the molecule causes a more-or-less marked loss of activity. It is also known that the most important hydroxyl from the activity standpoint appears to be the one in the *meta* position. In fact, Phenylephrine is approximately ten times more active on the blood pressure than Synephrine. $O^3$-Methylation represents the main "*in vivo*" inactivation mechanism of adrenaline and of noradrenaline[38].

Considering the profound changes which take place in the biological reactivity of catecholamines on *N*-alkyl-substitution, we considered it advisable to carry out a systematic study of the importance of the catechol group in a homologous series. Thus, the $O^3$-methylethers, $O^4$-methylethers and the $O^3,O^4$-dimethylethers of all the eight bases previously considered were prepared and studied. Twenty-four substances were involved, of which only ten were previously known. The $O^3,O^4$-dimethylethers were prepared either by methylation of the phenolic bases with diazomethane, or else by condensation of veratrol with a suitable alkylamino-acetonitrile and reduction of the amino-ketone obtained, according to Moed *et al.* (*Figure 9*)[39].

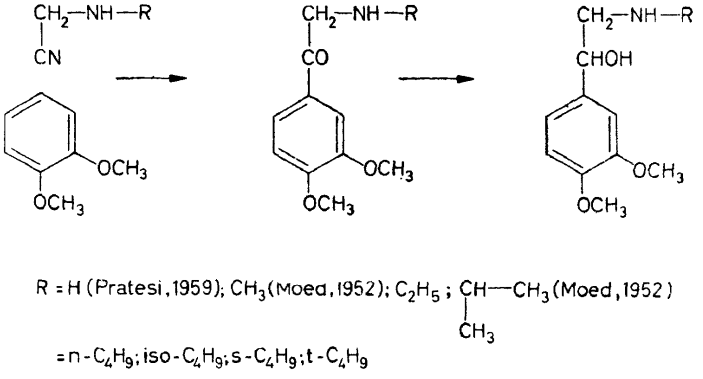
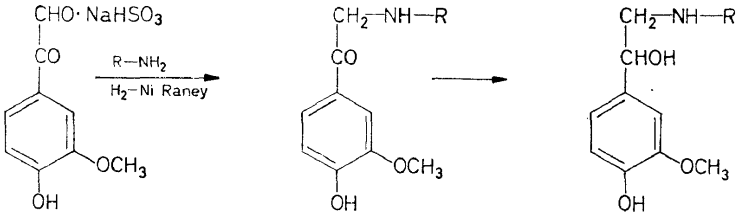



*Figure 9*

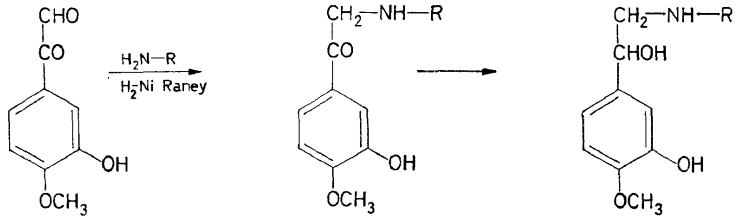
The majority of the $O^3$-methylethers were prepared according to the method of Fodor *et al.*[40], starting from 3-methoxy-4-hydroxyphenylglyoxal bisulphite, by condensation with the suitable amine and reduction of the aminoketones (*Figure 10*). The $O^4$-methylethers were the least known. The majority of these were prepared by condensation of 3-hydroxy-4-methoxyphenylglyoxal with the appropriate amine and successive hydrogenation (*Figure 10*). The

first member of the series was conveniently prepared by condensation of ω-bromo-3-hydroxy-4-methoxy-acetophenone with urotropin, decomposition of the urotropin salt to the aminoketone with acids, and reduction of the aminoketone.




R = H (Fodor, 1951); $CH_3$ (Külz, 1939); $C_2H_5$ (Külz, 1939); $CH(CH_3)_2$ (Fodor, 1955);

= n-$C_4H_9$ (Külz, 1939); iso-$C_4H_9$; s-$C_4H_9$; t-$C_4H_9$




R = H (Fodor, 1951); $CH_3$ (Külz, 1939); $C_2H_5$; $CH(CH_3)_2$;

= n-$C_4H_9$; iso-$C_4H_9$; s-$C_4H_9$; t-$C_4H_9$

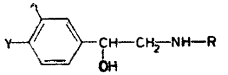
*Figure 10*

Only the β-type activities were explored. The corticostimulant, calorigenic and bronchodilating actions were studied. All the compounds were examined in racemic form. All were found to be practically inactive at a dose 100 times greater than the active dose of (—)-isopropyl noradrenaline. We therefore decided to compare the effects of *O*-methylation with those of replacement of the hydroxyl group with hydrogen, in the case of adrenaline and isopropyl noradrenaline, taken as examples of α and β reactive catecholamines, respectively.

The action on the arterial pressure and on the lactico-acidaemia were studied, using racemates. The results are summarized in *Table 4*. Leaving aside the activities relative to the optical antipodes, it is observed that disappearance of the catechol group through replacement of an OH with H or $OCH_3$ leads to a drop in both the α and β activities. It may therefore be concluded, as a first approximation, that the integrity of the catechol system is necessary for the full appearance of both types of activity. The greater importance of the hydroxyl in the *meta* position is observed also for

$\beta$ effects. On examining more thoroughly the activity relationships, it is noticed that replacement of an OH with an $OCH_3$ group generally produces a more dramatic fall of activity than replacement with H. This fact might be interpreted as due to a bond of the OH group with respect to the methoxyl in the *ortho* position. Measurement of the dipole moment[41] and infra-red light absorption properties of guaiacol[42] lend support to this point of view. In fact, such measurements show that in this monomethylether the phenolic OH is linked in a *cis-trans* structure. Other interpretations might be based on the steric hindrance due to the methoxy-group in the *ortho* position to the hydroxy group.

*Table 4*

|  | | R = $CH_3$ | R = iso-$C_3H_7$ |
|---|---|---|---|
| X | Y | *Pressor activity* | *Lactic acid-stimulating effect* |
| —OH | —OH | 100 | 100 |
| —OH | —H | 15 | 4 |
| —OH | —$OCH_3$ | 0·1 | 0·1 |
| —H | —OH | 1 | 0·4 |
| —$OCH_3$ | —OH | 1 | <0·1 |

The values of the microscopic ionization constants $k_2$ and $k_3$, relative to the true dissociation equilibria of the phenolic hydroxyls, were found to be remarkably constant, not only in the whole series of catecholamines examined, but also in the tertiary amine and in the quaternary ammonium derivative (see *Table 2*). They are, therefore, largely independent of *N*-alkylation.

These results confirm that the type of biological effect ($\alpha$ or $\beta$) is determined by the cationic head, and that the catechol group functions in both cases as a group anchoring the molecule to the receptor. At present, we can only speculate on the chemical forces involved in this latter reaction; the formation of hydrogen bonds, or of complexes with metallic ions, might be considered. New data are necessary to throw light on this aspect of the problem.

## CONCLUSIONS

In the present research, by utilizing a homologous series and an isomeric series of compounds, we have correlated the type and intensity of the biological response of catecholamines to some structural characteristics of these bases.

First of all, the optical configuration of the most significant catecholamines has been established, ascertaining that, so far as they are concerned, both the $\alpha$ effects and the $\beta$ effects are favoured by the D configuration.

It has been possible to show that the trend towards one or other type of

activity is linked to special structural characteristics of the cationic head, which determine the possibility of interaction with the $\alpha$ or with the $\beta$ receptor.

The catechol group is associated with $\alpha$ activity just as much as with $\beta$ activity.

These conclusions are far removed from the viewpoints according to which the action on the $\alpha$-receptors is linked, in particular to an interaction of the amino group with the $\alpha$-receptor, while the action on the $\beta$-receptors is associated with an interaction of the catechol group with the $\beta$-receptor[19, 43].

Recent studies[44] on biophysical modifications produced by adrenaline show that this amine has a dual action. One is a direct action on the membrane, while the other action affects the membrane only indirectly, the primary action being metabolic[44]. The sympathicomimetic effects of catecholamines can be considered as the resultant of these two types of actions which can often be opposed to one another and consequently govern, in relation to the predominance of one or of the other, the type of final effect.

At this stage, on the basis of the different reactivities of the cationic head in the various catecholamines a comparative study of the biophysical and biochemical modifications induced by a range of amines such as that examined, appears to be of great interest.

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