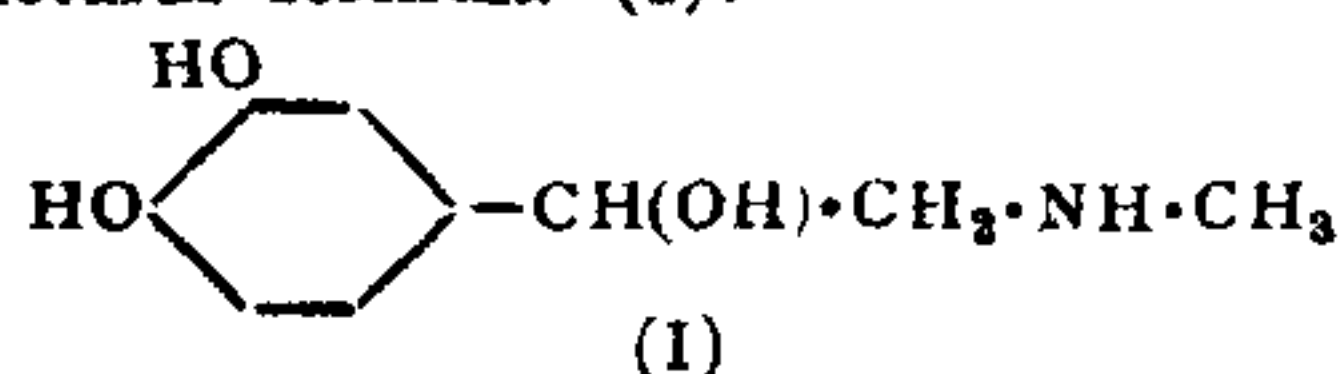


THE SYMPATHOMIMETIC GROUP OF DRUGS

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ONE of the earliest and possibly best known studies in correlating chemical structures and pharmacological behaviour was made with compounds that produce a rise in blood pressure. Interest in these compounds was aroused when Oliver and Schaefer¹ in 1894 and Scymonovicz² independently in 1895 found that extracts of the suprarenal glands, when injected intravenously in experimental animals, caused a swift and precipitate rise of blood pressure and produced all the changes which occur when the animals are preparing for battle, such as the quick pulse, the dilated pupil and the inhibition of the peaceful activities of the abdominal viscera. The subsequent analytical³ and synthetic^{4,5} experiments have proved conclusively that the active principle, responsible for this effect, viz., adrenaline, possesses the structural formula (I).



More recently, the discovery of its possible function as a transmitter of certain nervous impulses has played a fundamental part in the evolution of physiological and pharmacological concepts.

Before 1905 the existence of internal secretions of certain glands had been proved by circumstantial evidence, but nothing was known in regard to the chemical composition of the active principles responsible for their vital physiological activities. Apart from the demonstration of the comparatively simple composition of adrenaline, it was the first hormone to be synthesised and there is no doubt that this rapid success with the chemistry of adrenaline gave an impetus and encouragement to the successful chemical study of other hormones.

While the interest in adrenaline is usually associated with its presence and functions in the higher animals, it is found in structures other than the suprarenal glands. Abel and Macht,⁶ and many other workers have shown the presence of adrenaline or similar bodies in the venoms of different toads. Collip¹⁰ has demonstrated the presence of an adrenaline-like substance in the prostate gland of the bull.

While the fame of adrenaline was thus steadily rising, Abelous *et al.*¹¹ made the interesting observation that extracts of putrefied meat also contained a substance that produced a rise in blood pressure. Barger and Dale¹² identified the active ingredients as two definite compounds, isoamylamine and tyramine. Since both may be derived by putrefactive processes from the amino acids leucine and tyrosine respectively, they were led to investigate other bases of putrefactive origin and also substances structurally related to adrenaline and tyramine: their results¹³ first showed that an intimate relationship existed between the physiological

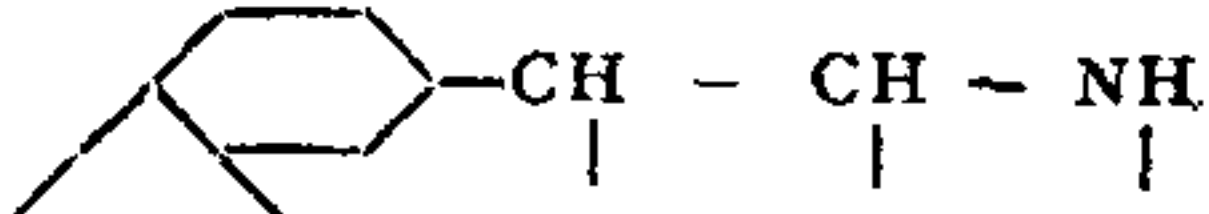
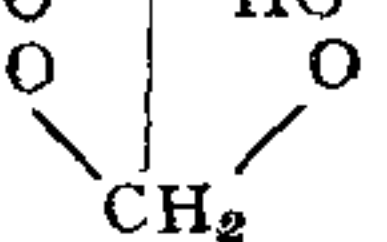
activity of compounds possessing structural similarity. Because all of the substances investigated caused a rise in blood pressure by constricting the muscular lining of the arterioles, Barger and Dale described them as "Sympathomimetic", a term which is now in the vocabulary of all physiologists and pharmacologists.

During the fourteen years following the work of Barger and Dale in 1910 nothing of particular interest developed; known compounds were more intensely investigated and occasionally new ones, without special merit, were introduced. Meanwhile, adrenaline was becoming more firmly established and was being more extensively used than any other compound in physiological and chemical investigations, thereby illustrating the important position occupied by adrenaline in therapeutics, diagnoses and physiological experiments and even as a chemical reagent. However, in 1923, Chen¹⁴ demonstrated that a decoction of the Chinese Ma Huang, a plant of the ephedra species, containing the active principle ephedrine, produced an action on blood pressure simulating that of adrenaline. Chen and Schmidt, the modern sponsors of ephedrine, have covered the history, chemistry and drug action of ephedrine in a monograph.¹⁵

Once the chemical structure of adrenaline has been elucidated it was natural that attempts should have been made to determine whether the molecule in its entirety was necessary for exerting the particular action of adrenaline. Much of the ground was covered by the pioneer work of Barger and Dale.¹³ The molecule of adrenaline is such as to have encouraged the ingenuity of organic chemists, who have prepared a series of over 200 substances containing most of the permutations and combinations of the peripheral groups, of which the following are better known:—

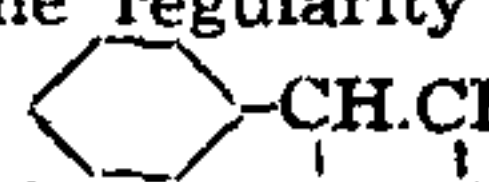
All these substances have pharmacological action like adrenaline in varying degrees. Some of them which have been adequately covered in medical texts and have formed the subject of some excellent reviews¹⁶ recently, have great advantages over adrenaline as therapeutic agents.

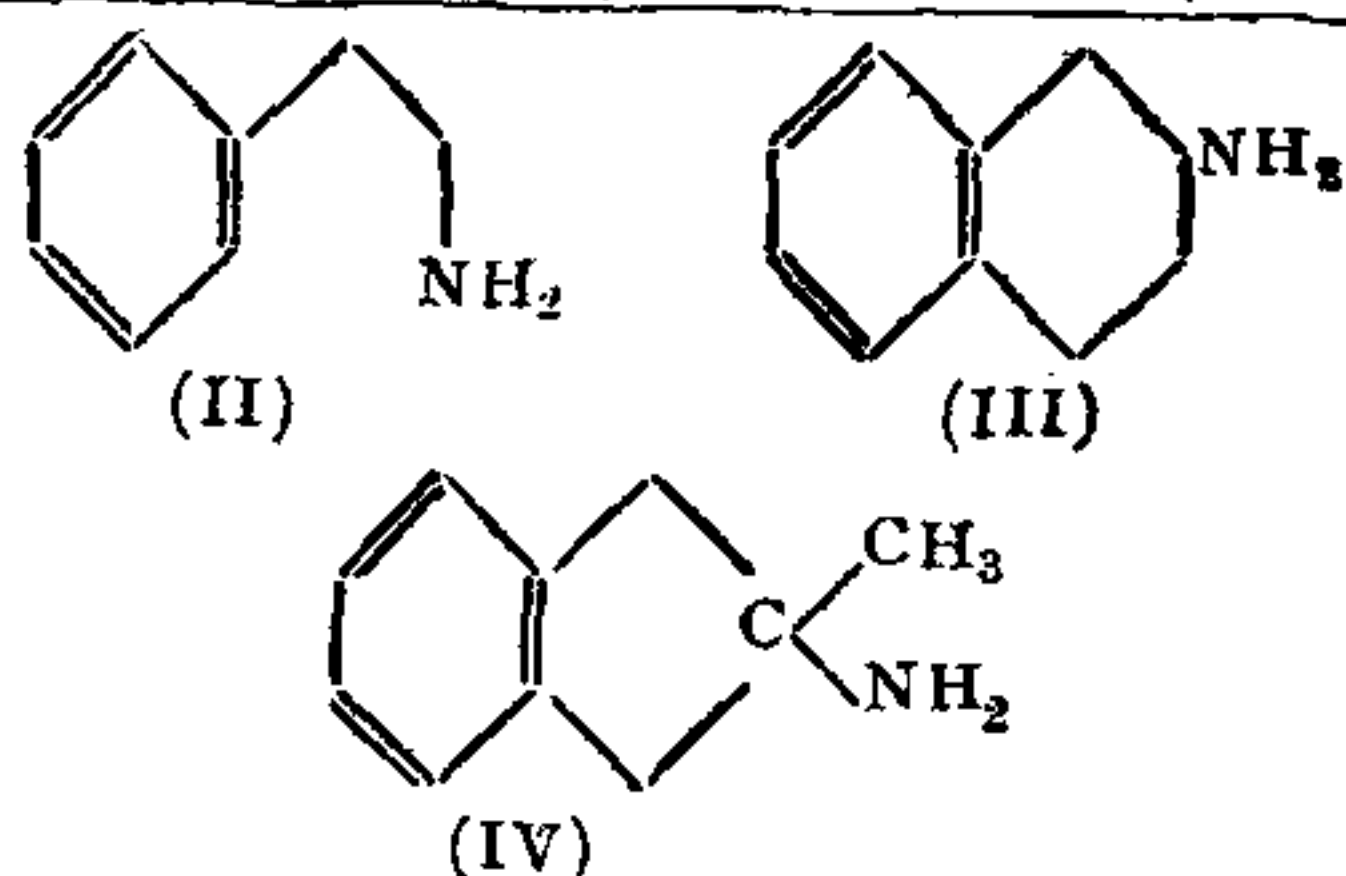
An examination of the group reveals an interesting relationship between chemical structure and pharmacological action. With an ethylamine side chain, the result of adding hydroxyl groups to the benzene ring is to increase the intensity but diminish the duration of pressor action. It can also be seen from the table that the addition of a single hydroxyl group, especially if it be in the *m*-position, increases the intensity but diminishes the duration of action. It is interesting to note that the stability of the compound is diminished if the hydroxyl groups are attached to the benzene ring; this explains why adrenaline solutions cannot be sterilised by boiling, whereas for example, those of neosynephrine (No. 4) can. It will be noticed that the first eight compounds have a methylene, $\text{—CH}_2\text{—}$, group in the α -position to the amino group in the side chains. In the remaining compounds, one of the hydrogen atoms of this group is replaced by a methyl radical, which has the effect of prolonging the duration of the pressor effect, although

No.	Name						Pressor Activity (Adrenaline = 1)	Pressor Duration (Adrenaline = 1 a)
1	β -Phenyl Ethylamine	H	H	H	H	H	1/200-1/80	3-4
2	Tyramine	HO	H	H	H	H	1/100-1/20	2
3	Synephrin	HO	H	H	H	CH ₃	1/50	10
4	Neosynephrin	H	H	HO	H	CH ₃	1/25	5
5	Sympatol	HO	H	HO	H	CH ₃	1/100-1/25	4
6	Epinephrine	HO	HO	H	H	CH ₃	1/12	2
7	Arterenol	HO	HO	HO	H	H	3/2	2
8	Adrenaline	HO	HO	HO	H	CH ₃	1	1
9	Benzedrine	H	H	H	CH ₃	H	1/300-1/100	5-10
10	Propadrine	H	H	HO	CH ₃	H	1/300-1/60	7
11	Ephedrine	H	H	HO	CH ₃	CH ₃	1/300-1/100	7
12	Veritol	HO	H	H	CH ₃	CH ₃	1/30	10
13	Corbasil	HO	HO	HO	CH ₃	H	1/4	2
14	Methylenedioxy, β -phenyl isopropylamine			H	CH ₃	H	1/400	10

the intensity of the latter is slightly diminished. It has recently been shown that adrenaline is readily destroyed in the body by an oxidase, which attacks the side chain and thereby inactivates it pharmacologically.¹⁷ At the same time it was shown that this oxidase attacks phenyl ethylamine, tyramine, sympatol and epinephrine (Nos. 1, 2, 5, 6), but not benzedrine, ephedrine or corbasil (Nos. 9, 11, 13), which have a methyl group in the α -position. This explains why the last named compounds have more prolonged effect in the body and perhaps why, unlike adrenaline, they are active when orally administered.

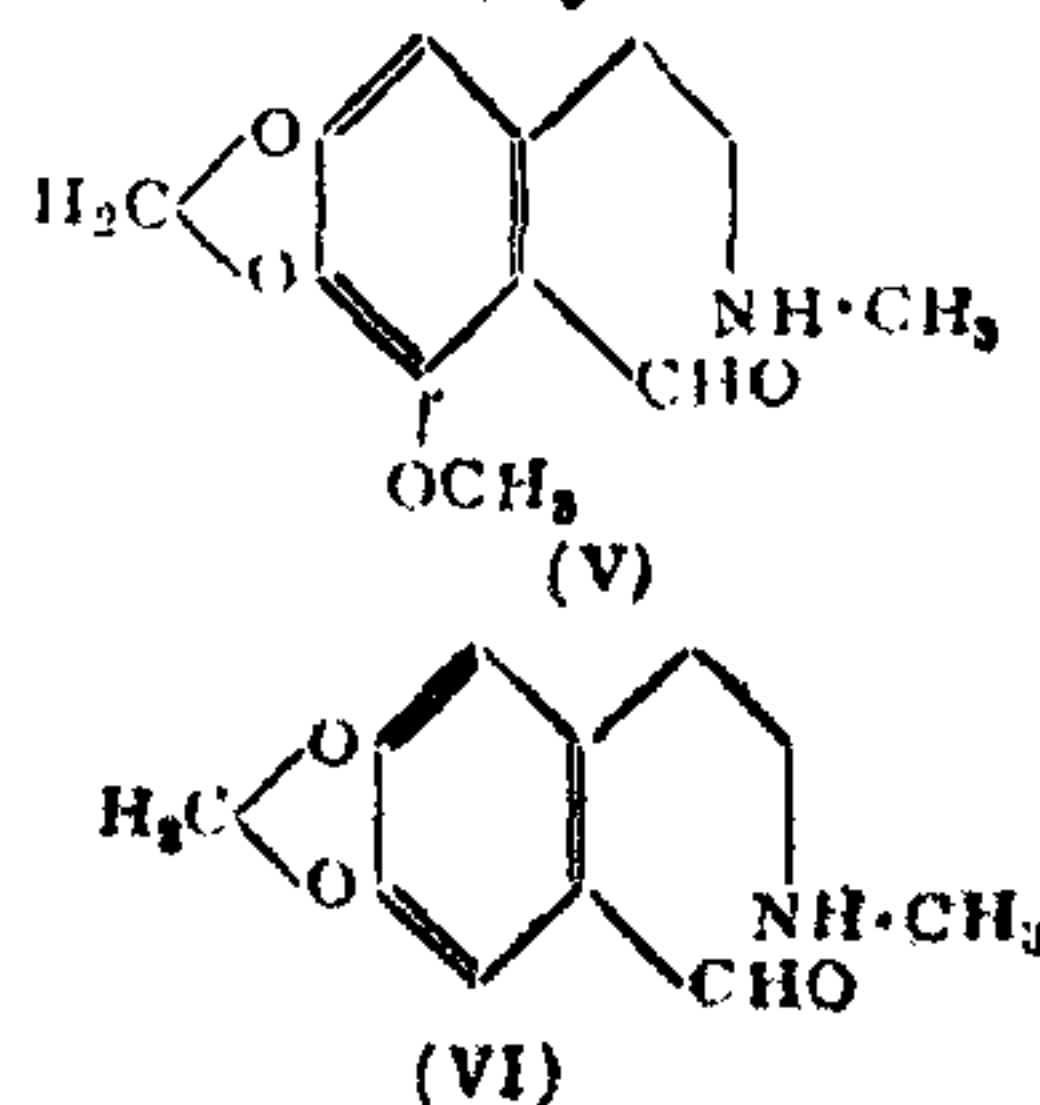
Adrenaline has practically no action on the central nervous system, but ephedrine and especially benzedrine have a marked stimulant action. Increased stimulation of the central nervous system is caused by compounds in which the benzene ring is not substituted, e.g., benzedrine, propadrine and ephedrine (Nos. 9, 10, 11) and in compounds containing an isopropyl side chain, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{NH}_2$. The stimulant action is enhanced by introducing a methylenedioxy group, $-\text{OCH}_2\text{O}-$, into the benzene ring (No. 14), or replacing this by a cyclohexanyl nucleus. Such compounds which have recently been prepared cause marked acceleration of respiration and increase of motor excitement.

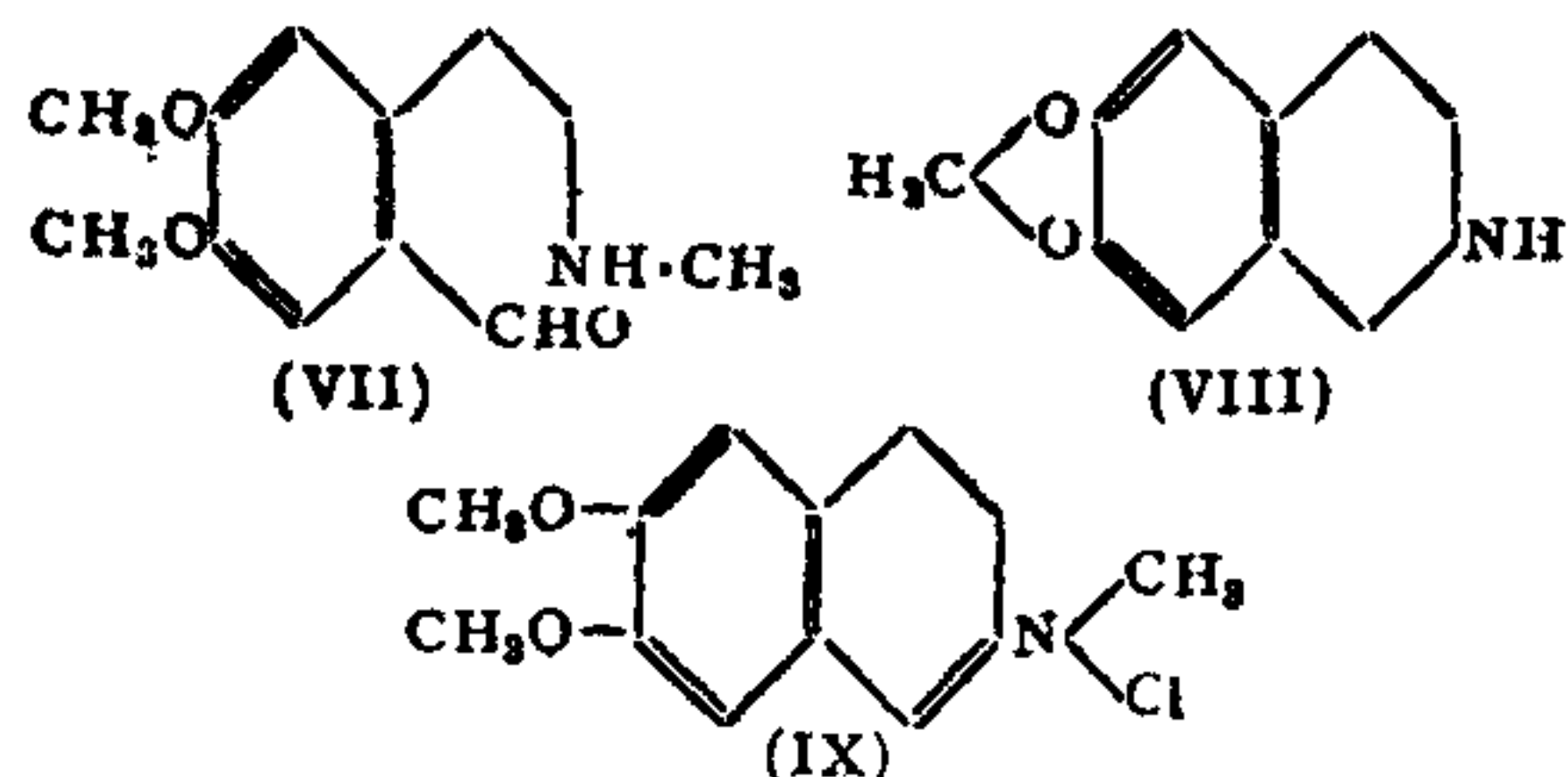
In examining the general pharmacological activities of this group of bases, one cannot fail to be struck by the regularity with which the atom-pattern,  occurs in their molecular architectures. However, sympathomimetic activity is not exclusively restricted to the β -phenyl-ethylamine derivatives. Fourneau,¹⁸ among others, has drawn attention to the way in which this type of aralkyl structure is usually accompanied, in even nonbenzenoid substances, with characteristic sympathomimetic activity. Thus, this activity which is observable in β -phenyl-ethylamine¹³ (II) is more strongly pronounced in *ac*-tetrahydro- β -naphthylamine^{19,20} (III) and intense in methylamino-hydrindene²¹ (IV).



The activity of tetrahydro- β -naphthylamine has been attributed to its being a derivative of β -phenyl ethylamine (II) in addition to its resemblance to γ -phenyl propylamine and cyclohexenylamine.¹⁹ The high activity of methylamino-hydrindene (IV) has been explained on the basis of its being doubly a β -phenyl-ethylamine. Curiously enough, this activity, unlike that of phenyl-ethylamine, is not enhanced by the entry of a hydroxyl group into the aromatic ring.

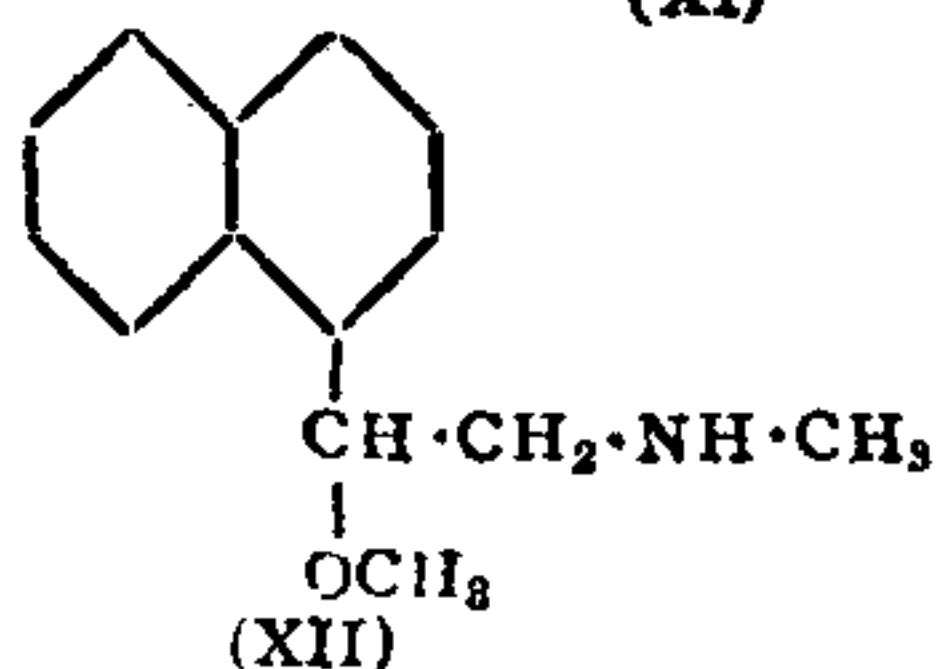
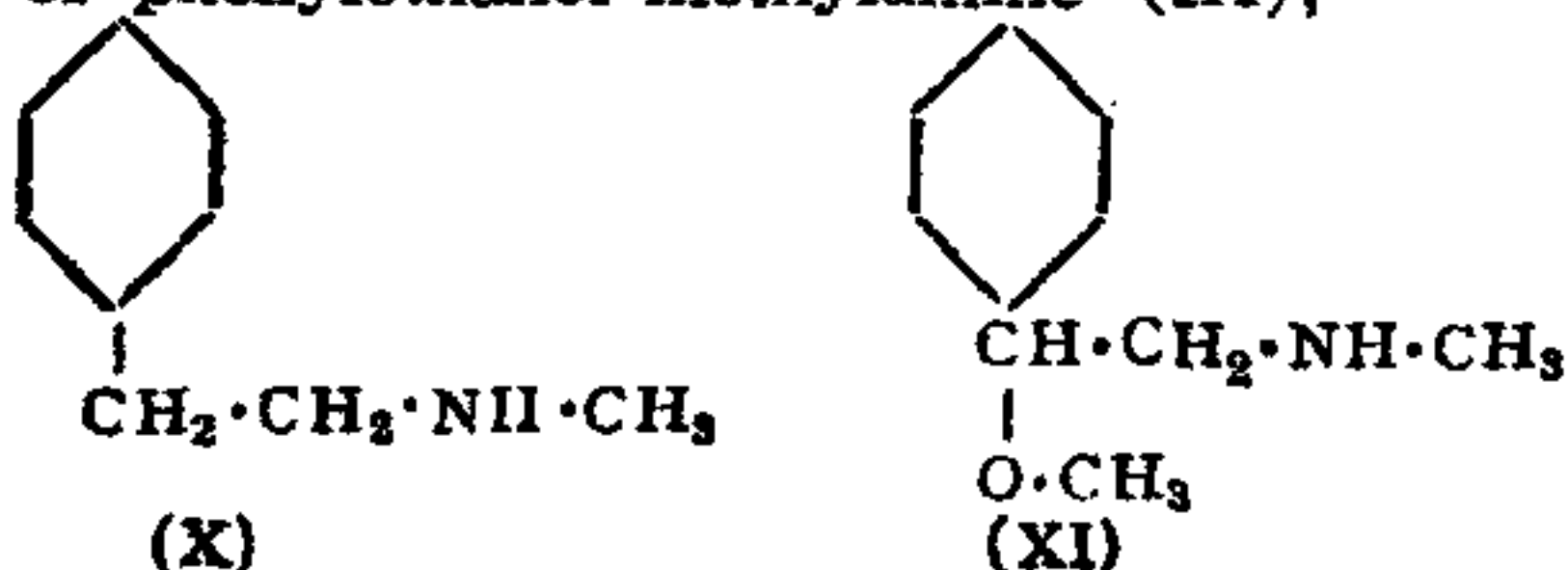
Evidence of this interesting phenomenon is also to be seen among the group of isoquinolines,²² of which β -phenyl ethylamines constitute the precursors. The structurally related bases, cotarnine (V), hydrastinine (VI), the hydrastinine-like base (VII) and norhydrohydrastinine (VIII) exhibit varying grades of sympathomimetic activity.



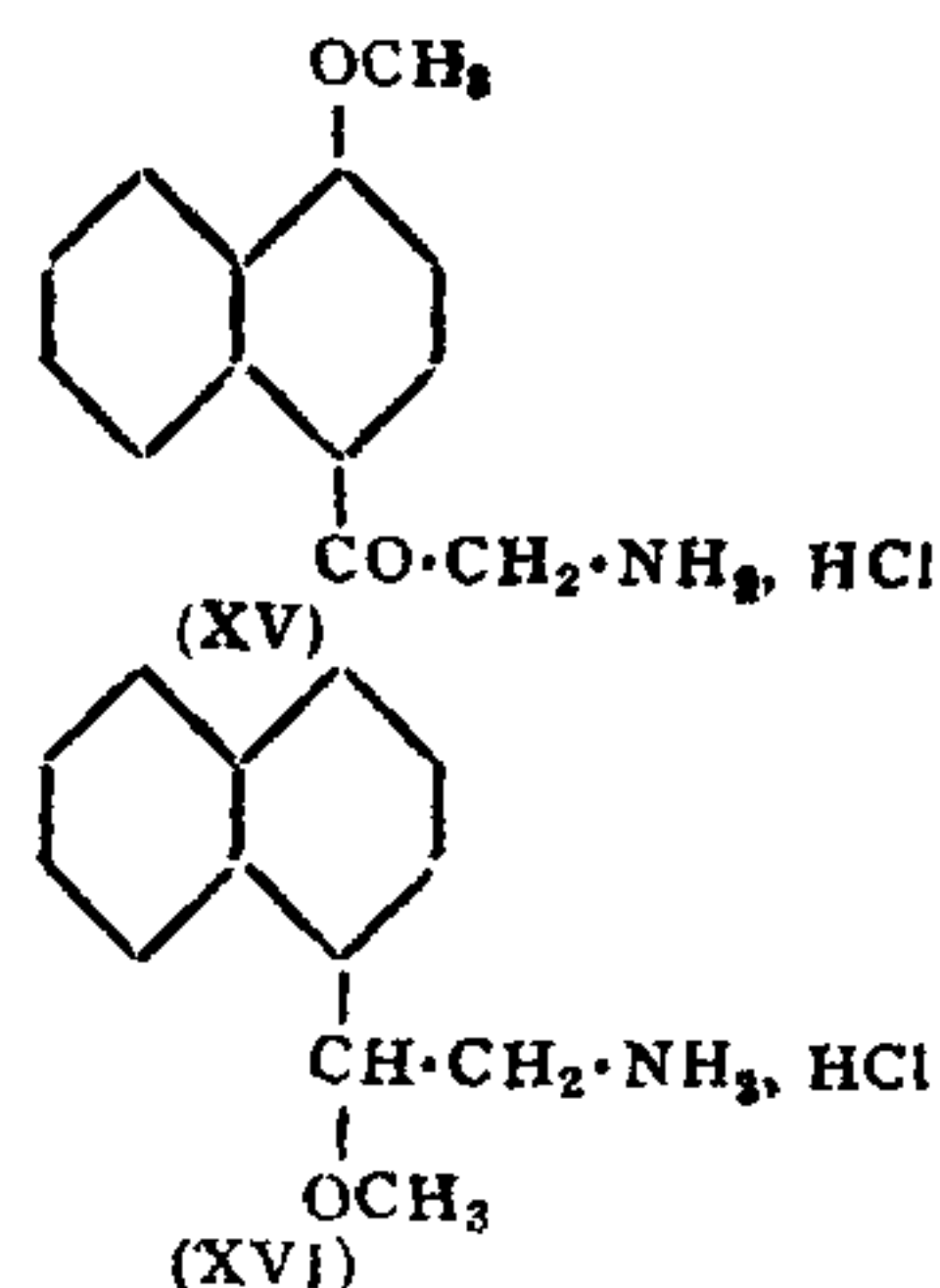
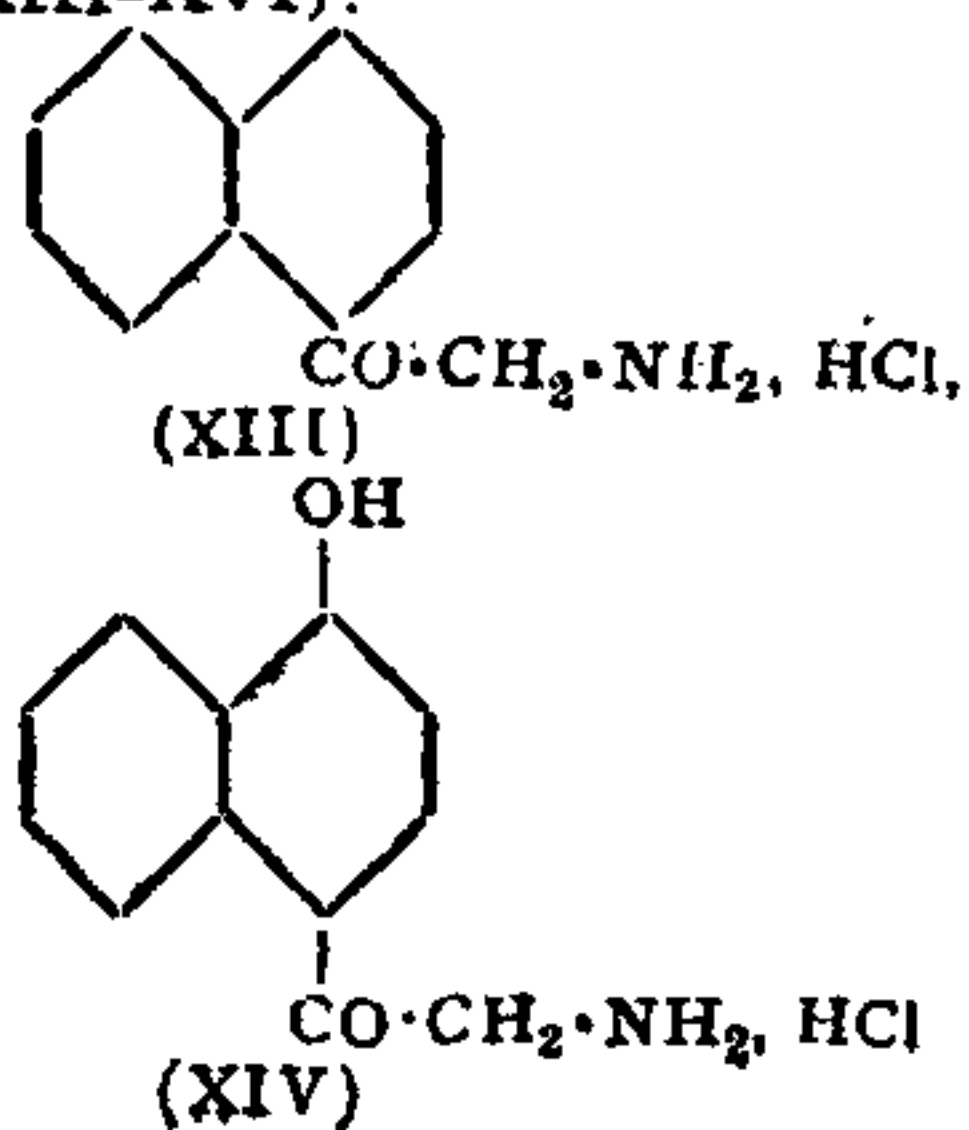


Hydrastinine, which is an astringent and styptic, is used chiefly in uterine hæmorrhages. Cotarnine is of importance in medicine as a styptic and as a uterine sedative and is known as 'Stypticine'; its phthalic acid salt also finds use under the name 'Styptol'. The chloride of (VII), 6:7-dimethoxy-2-methyl-3:4-dihydroisoquinolinium chloride (IX), has been introduced in practice as "lodol". It causes a rise of blood pressure and renders the heart-beat slower and stronger.

The activity of β -naphthyl-ethylamine derivatives was investigated by Madinaveitia.²³ By comparing the activity of β -phenyl-N-methyl-ethylamine (X) with the methyl ether of phenylethanol-methylamine (XI),

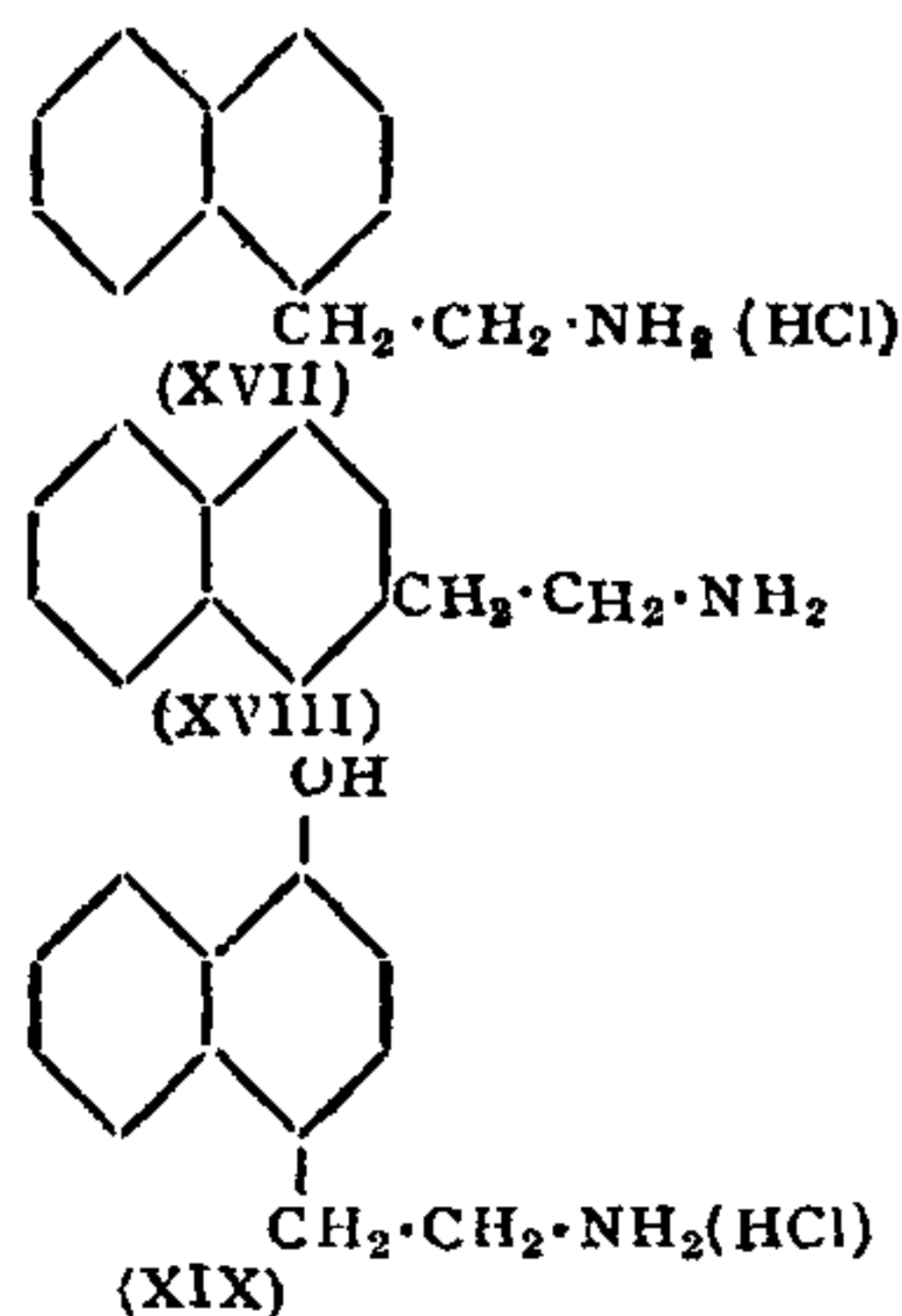


he showed that the introduction of the methoxyl group in the side chain did not change the sympathomimetic activity; but if the α -naphthyl nucleus (XII) was substituted for the phenyl group, the activity was increased about forty times. Having found the naphthyl compound so active, Madinaveitia compared the activities among themselves, of four other derivatives (XIII-XVI).



He found that the introduction of the hydroxyl group para to the side chain (XIV) greatly increased the activity and that etherification of the phenolic hydroxyl (XV) greatly reduced the intensity, the ketone (XIII) being much less active than the methyl ether of the corresponding alcohol (XVI).

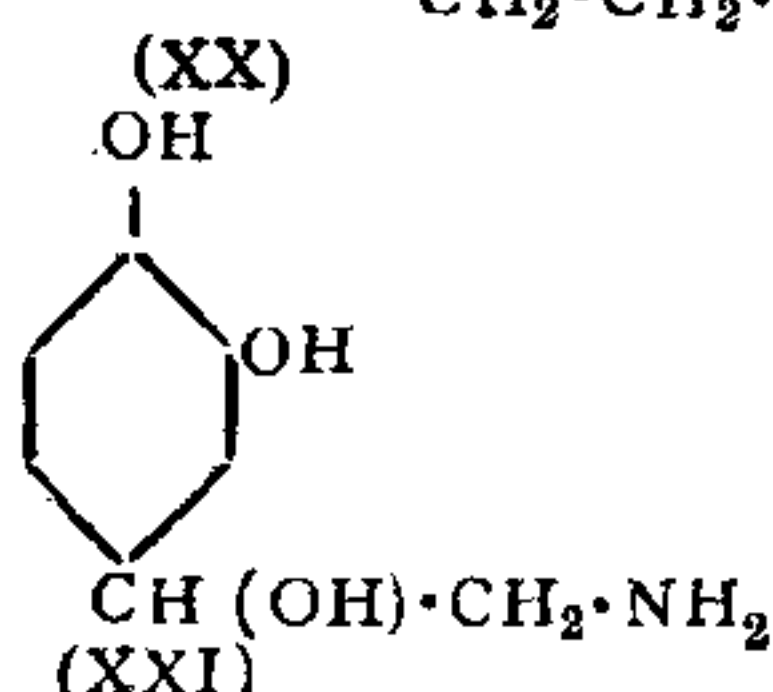
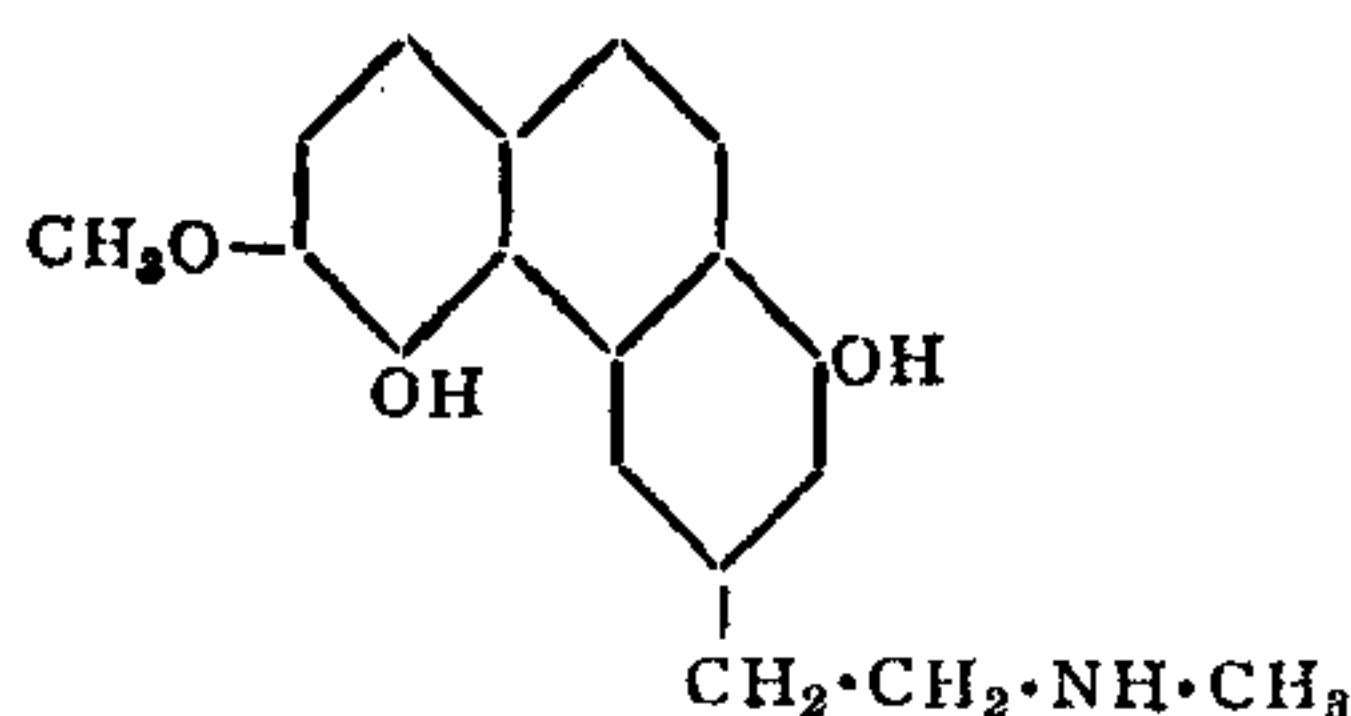
Although considerable time has passed since the isomeric naphthyl-ethylamines (XVII and XVIII) have been synthesised,²⁴ their sympathomimetic potentialities do not appear to have been explored. 4-Hydroxy naphthyl-ethylamine (XIX), the tyramine analogue of the naphthalene series, was synthesised by Windaus²⁵



but, surprisingly and apparently in conflict with the findings of Madinaveitia, it possesses only a slight activity.

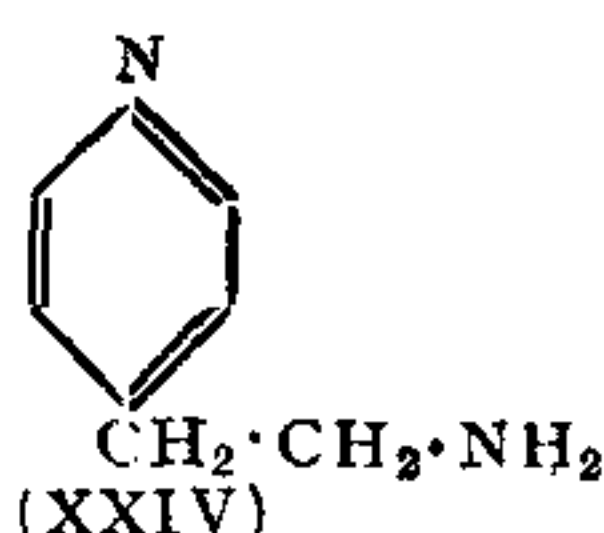
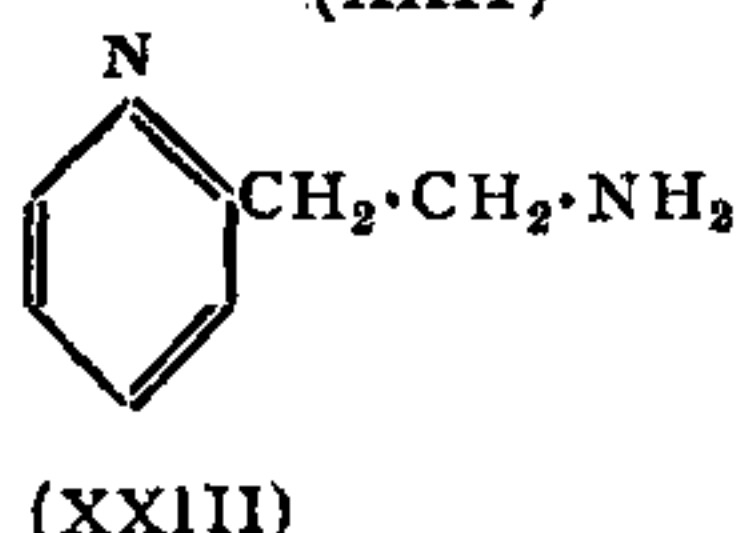
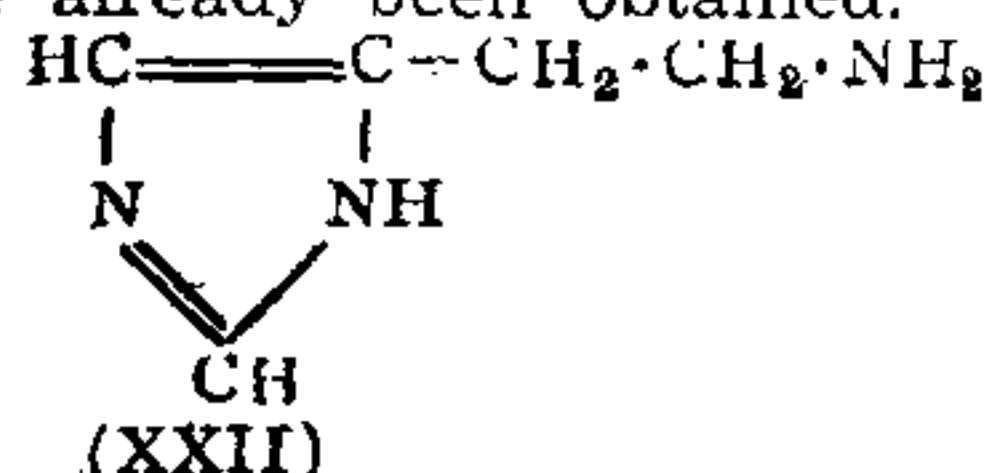
Since the work reported by Rajagopalan on the synthetical aspects of sympathomimetics derived from naphthalene²⁶ and their pharmacological examination, Day and his collaborators²⁷ have reported the synthesis of a few derivatives of naphthyl aminoethane but presented no pharmacological data on these compounds.

Hildebrandt²⁸ reported that thebainine (XX), a derivative of β -phenanthril-ethylamine, has a general reaction towards rabbits like that of 3:4-dihydroxy phenyl ethanolamine (XXI):—



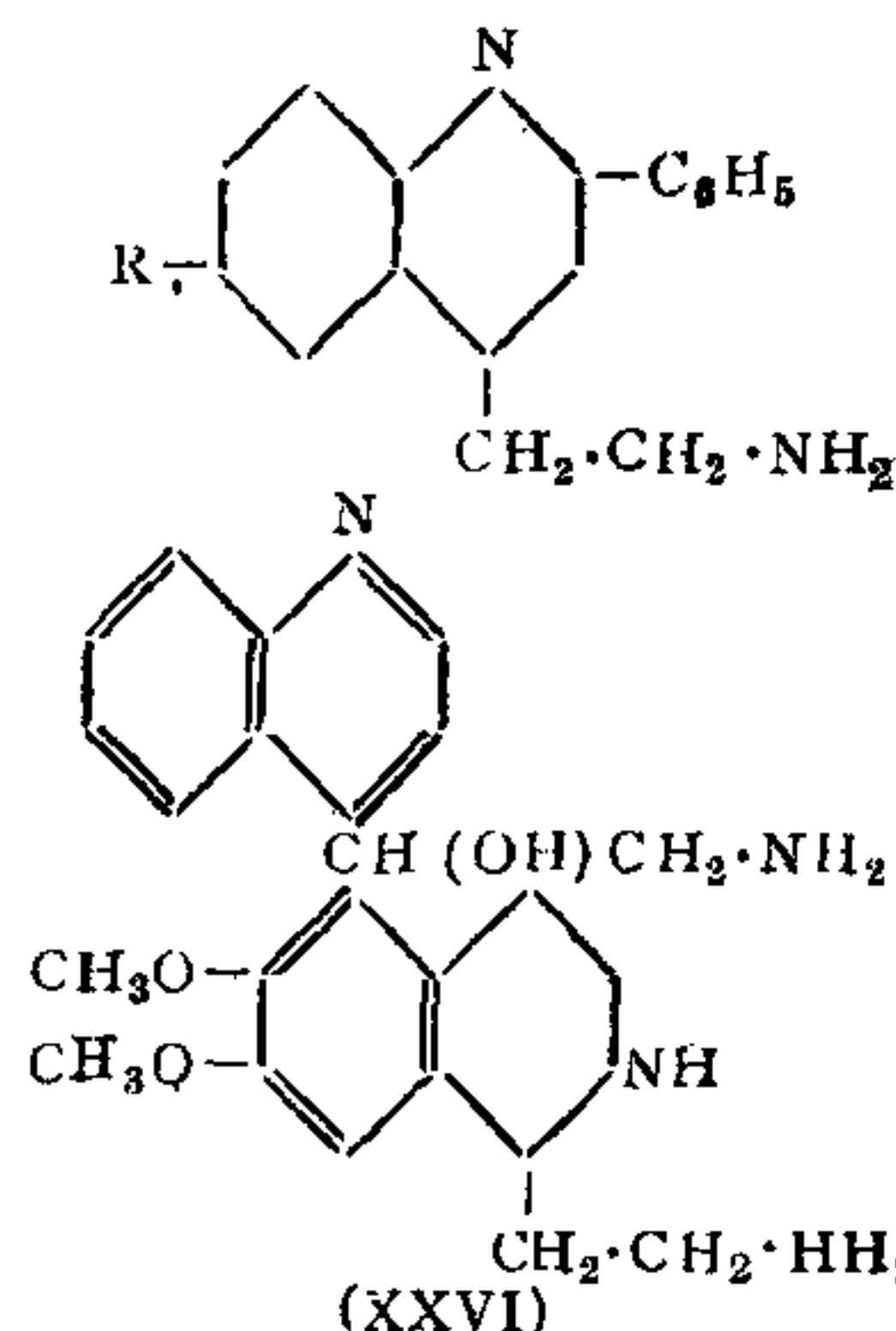
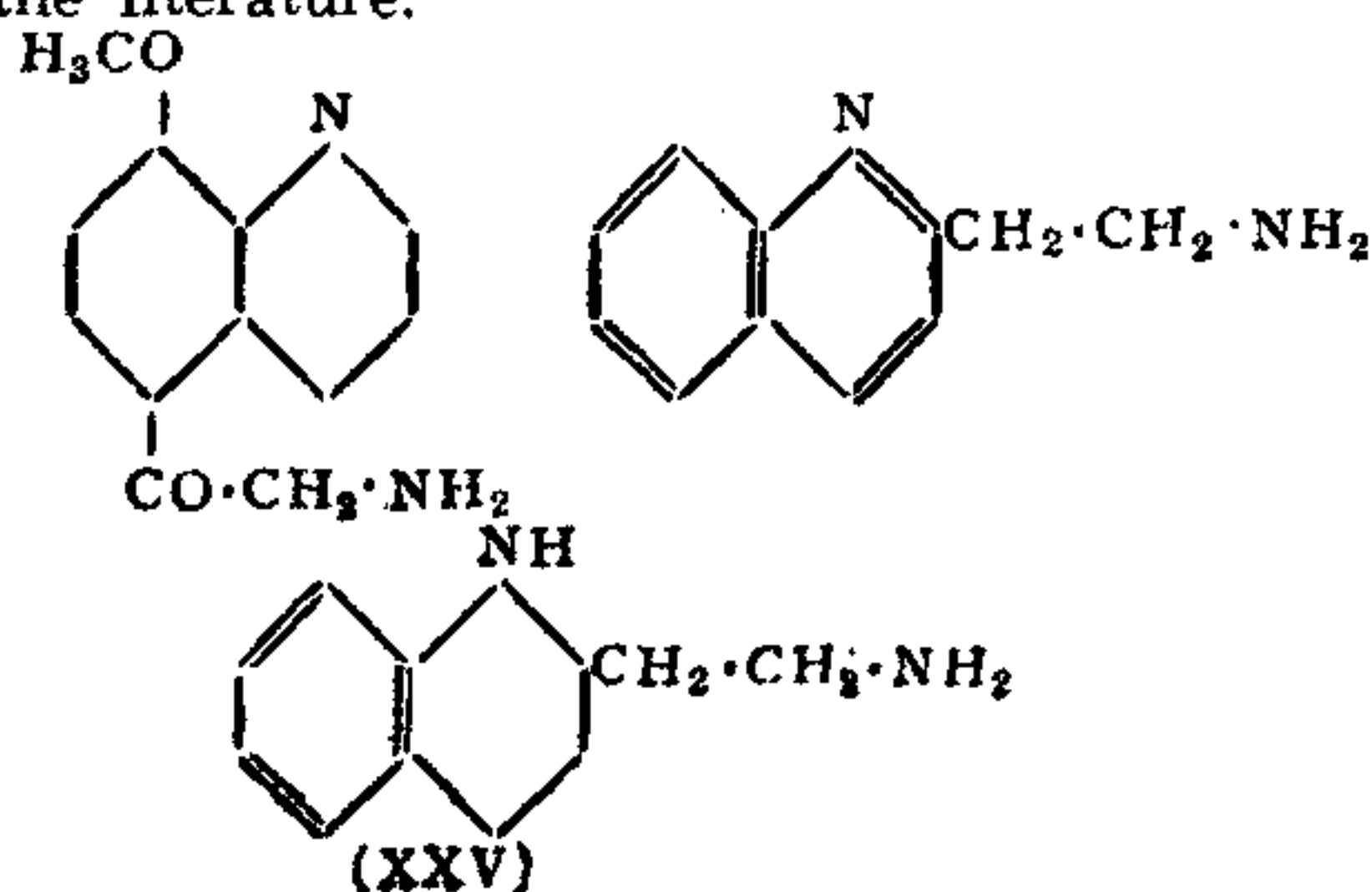
Recently, a small number of ethanamine derivatives of phenanthrene, as also that of dibenzofuran, have been revealed but these compounds were examined only for their analgesic activities.²⁹

Ever since the demonstration of the remarkable physiological effects, particularly on blood pressure and the uterine muscle, of histamine³⁰ (XXII), isolated³¹ from ergot of rye and later synthesised by Pyman,³² it has been considered desirable to prepare similar compounds possessing the ethanamine chain linked to heterocyclic rings other than iminazole. Several such bases have already been obtained.



Of the β -2-, and β -4-pyridyl ethylamines synthesised³³ with the object of ascertaining their suspected activity, it has been found³⁴ that, whereas the β -2-derivative (XXIII) did not behave like adrenaline but rather like histamine, the β -4-isomer, (XXIV) produced a pressor response similar to but weaker than that of adrenaline.

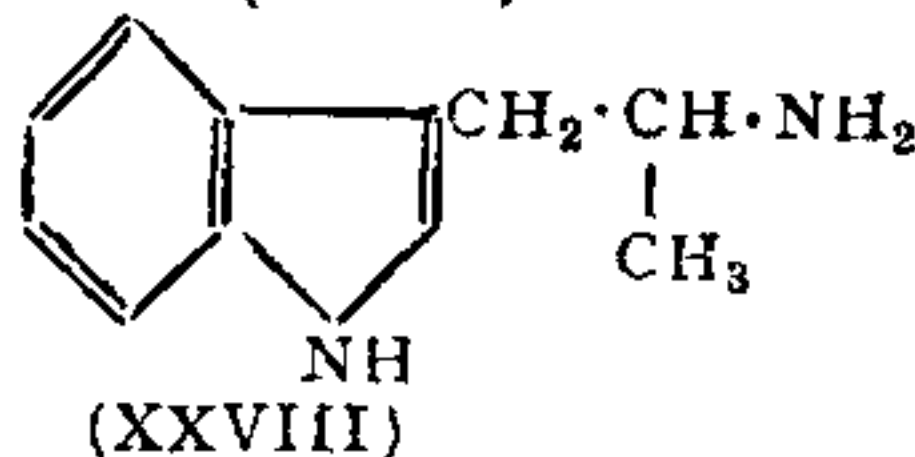
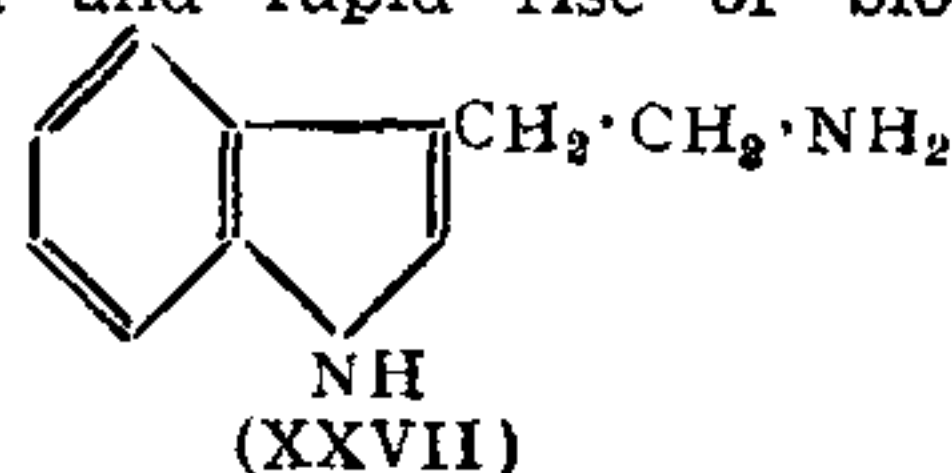
A set of ethanamine derivatives of quinoline and isoquinoline have already been described³⁵ in the literature.



(R = H or OCH_3)

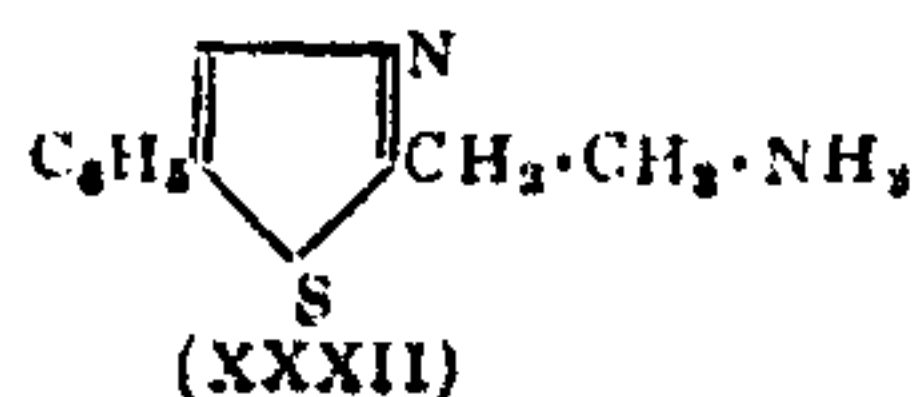
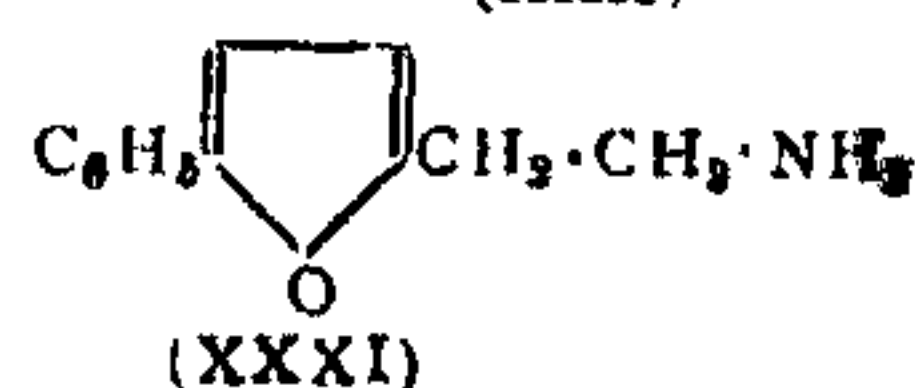
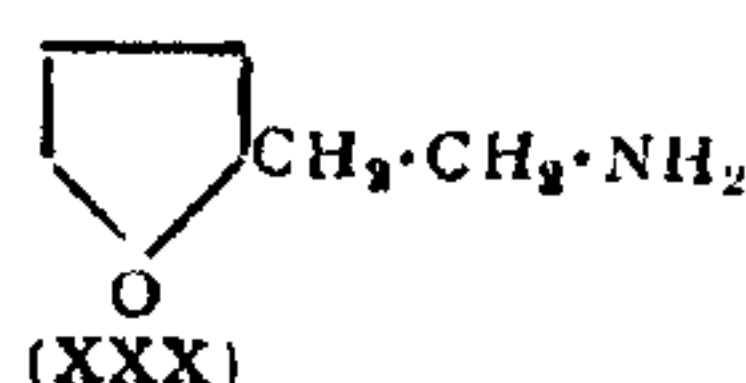
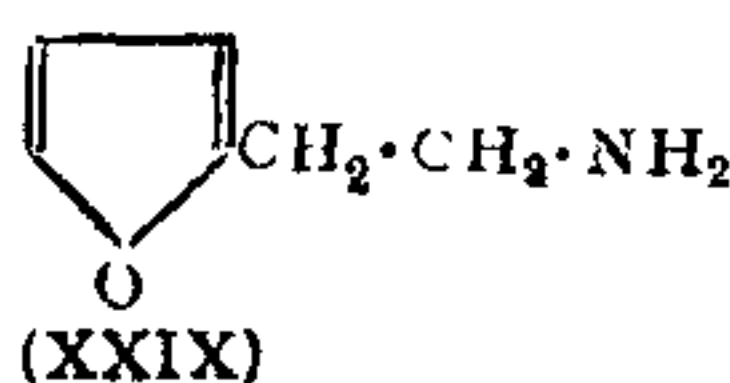
Quinolinyl ethanolamine (XXVI) was found to act on the blood pressure as does phenyl ethanolamine, whereas β -2-quinolyl ethylamine (XXV) possesses an activity one-hundredth of that of adrenaline.³⁶ The remaining compounds in this series do not appear to have been so far tested.

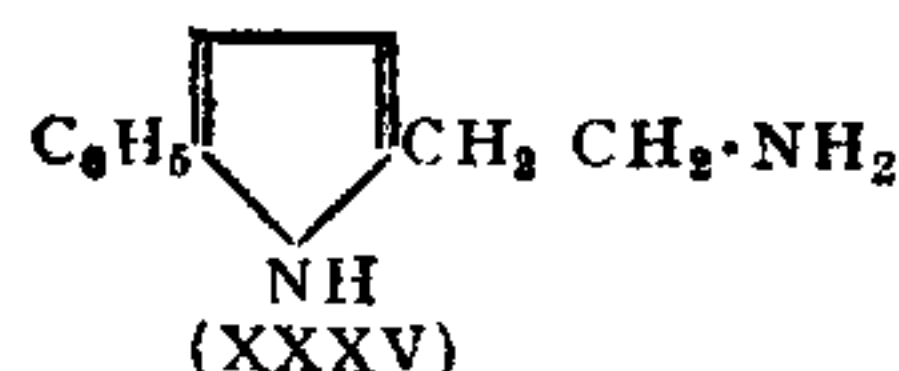
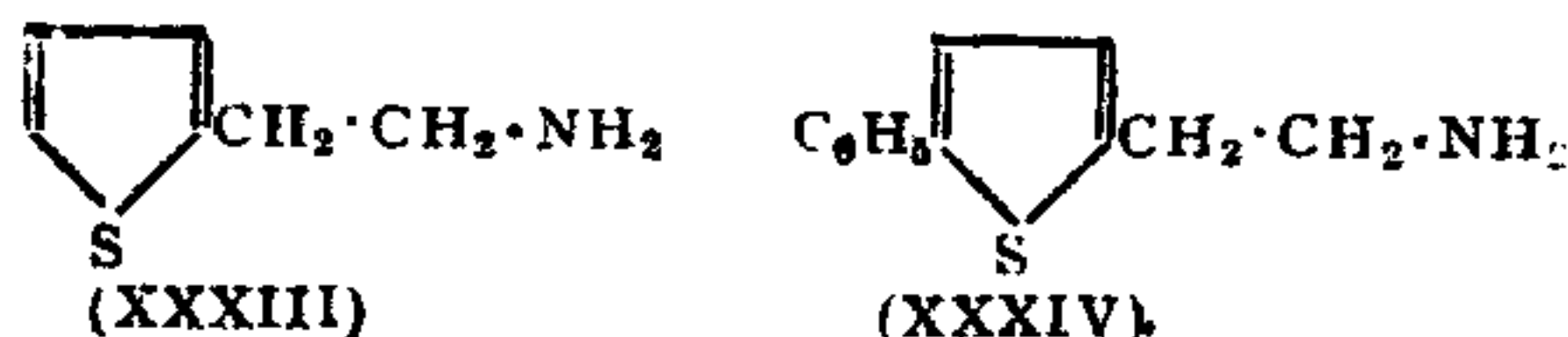
β -Indolyl-ethylamine (XXVII) was found³⁷ to dilate the pupil markedly and produce a substantial and rapid rise of blood pressure



while the α -methyl derivative of indolyl-ethylamine (XXVIII) produced³⁸ a rise in blood pressure by vaso-constriction, contracted the uterus and stimulated intestinal movements.

Windaus and Dalmer³⁹ found that furyl ethylamine (XXIX) produced only a short-lived fall in blood pressure and that its tetrahydro derivative (XXX) was without any effect.





Hinegardner and Johnson⁴⁰ have prepared thiazole bridges of adrenaline- and tyramine-like bodies (XXXII) which they reported possessed pharmacological interest. Thienyl ethylamine (XXXIII) was found⁴¹ to be as active as the phenyl analogue, β -(5-phenyl-) furyl-ethylamine (XXXI), and analogous derivatives of thiophene (XXXIV) and pyrrole⁴² (XXXV) were found⁴³ to be pressor-active. Thienyl and furyl-isopropylamines have recently been stated⁴⁴ to be similar in their action to phenyl isopropylamine.

The investigations in the field of the sympathomimetics, correlating chemical constitution with physiological activity, have been of considerable interest. They alone, more than similar studies in other groups of medicinal compounds, have so far lent themselves to almost rigorous interpretation and made possible the theoretical prediction of the physiological properties of a related member of the sympathomimetic group based on previous knowledge of its chemical structure. Instances of a large measure of actual experimental realisation of many such predictions concerning sympathomimetic action are rather plentiful. As such, these investigations, despite their restriction mostly to members of the benzene series and their regrettable lack of thoroughness as far as the other ring-systems are concerned, may be considered as a triumphant chapter in modern iatro-chemistry.

The comparative studies of the substituted as well as the unsubstituted β -phenyl-ethylamines, and β -phenyl-ethanolamines and their structural allies have brought to light many interesting generalisations. These have given an insight into the subtle ways in which physiological activity can be altered by even slight structural modifications of the sympathomimetics. In the present state of knowledge an answer to the interesting question of whether or not the same or similar rules governing the intimate relationship between constitution and activity of the benzenoid sympathomimetics operate in the case of their analogues derived from the higher polycyclics and the heterocyclics is, however, not yet possible. Another question which naturally arises, namely, whether the knowledge already gained can be applied for the rational evolution of future sympathomimetics possessing ring-systems other than benzene, must also for the present remain unanswered. This is in a large measure due on the one hand to the reason that sufficiently varied and comparable types of compounds belonging to the other ring-systems are not known and on the other, to the fact that, so far no systematic correlation has been attempted with even those compounds that have been available.

The gaps in existing knowledge must be finally bridged before the problem of the rational evolution of future sympathomimetics

belonging to ring-systems other than benzene could be solved. Recent works in this line consist in attempts^{26,45} to study systematically the synthesis and biological examination of groups of compounds derived from the carbo- and hetero-cyclics and which possess the requisite structures necessary for sympathomimetic activity.

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