EXPERIMENTS IN THE GROUP OF SYMPATHOMIMETICS

Part V. Relation between Chemical Constitution and Pressor Activity of Possible Sympathomimetics derived from the Benzene, Naphthalene, Phenanthrene and Isoquinoline Rings

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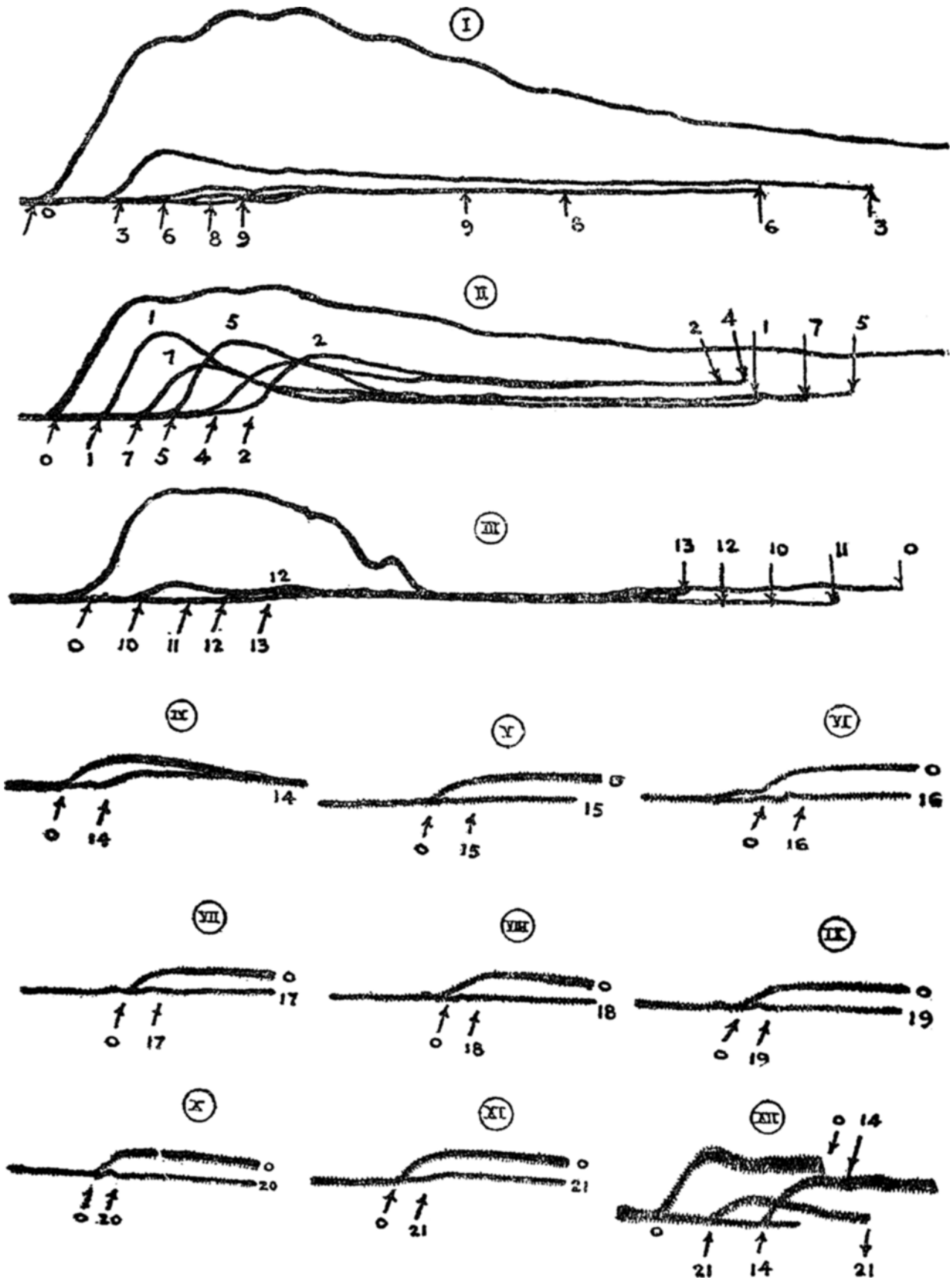
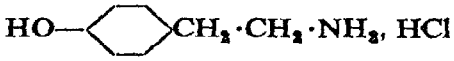
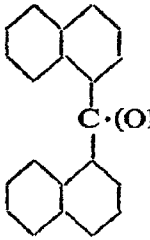
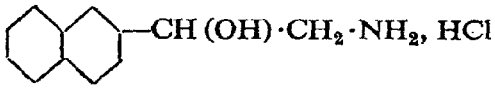
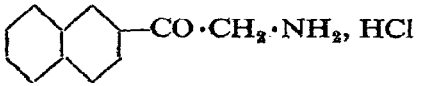
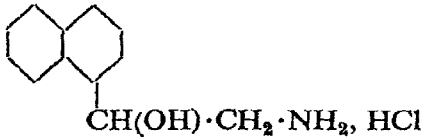
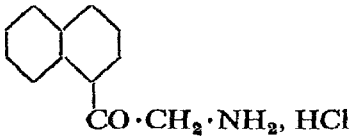
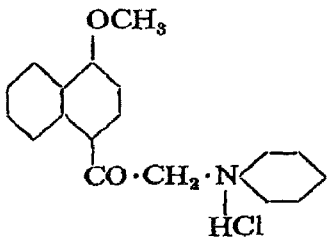
Introduction

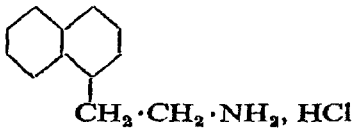
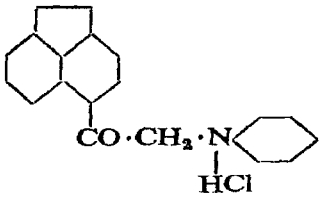
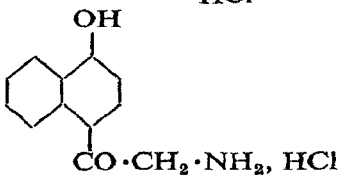
Earlier sections dealt with the syntheses of a series of bases, belonging to the carbo- and hetero-cyclic ring systems and possessing the requisite configurations for sympathomimecity (Rajagopalan, 1940, 1941, 1944). This section is concerned with the presentation of the results of subjecting twenty-one of the above group of compounds to preliminary biological tests in respect of their sympathomimetic activities and a discussion, based on these results, of the relationship between chemical constitution and pressor activity. The compounds are derived severally from the benzene, naphthalene, acenaphthene, phenanthrene and isoquinoline nuclei.

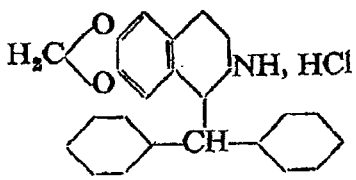
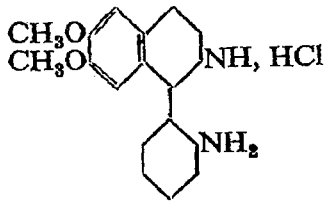
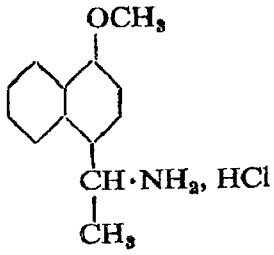
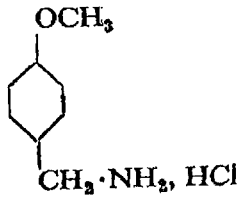
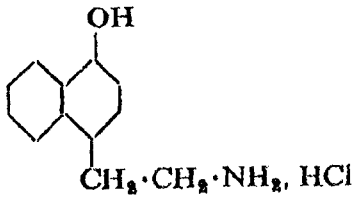
The pressor effect in the spinal cat was used as a means of comparison. The collection of twenty-one compounds was divided into convenient groups or single compounds. Each of these was then compared directly with tyramine in the same animal. Of the two available standard sympathomimetics, tyramine rather than adrenaline was chosen as the control for the reason that the results obtainable with tyramine are known to be less variable and more reproducible than those of the latter base (Gurd, 1937). All the amines as well as tyramine were used as their water-soluble hydrochlorides. Their serial numbers and molecular structures are represented in the table.

The blood pressure tracings are given in graphs I–XII. In the table, which has been compiled on the basis of these graphs, the pressor intensities and pressor durations of the compounds have been given in addition to their numbers and structures. The pressor intensity of the substance compared with tyramine is expressed as the ratio of the maximum pressure recorded by the test substance and that recorded by tyramine. Pressor duration represents the *duration at a high level of the individual activity* of the test


I
0 3 6 8 9 9 8 6 3
II
1 5 7 2 2 4 1 7 5
0 1 7 5 4 2
III
13 12 10 11 0
12
0 10 11 12 13
IX
14
0 14
X
15
0 15
XI
16
0 16
VII
17
0 17
VIII
18
0 18
IX
19
0 19
X
20
0 20
XI
21
0 21
XII
0 14
0 21 14 21

Serial No.	Name (hydrochloride of)	Structure	Pressor Intensity (Tyramine =1)	Pressor Duration (Tyramine =+++)
0	Tyramine		1	+++
1	β, β-1 : 1'-Dinaphthyl-β-hydroxy ethylamine		9/13	+
2	β, 2-Naphthyl-β-hydroxy ethylamine ..		11/26	++++
3	ω-Amino-β-acetonaphthone		1/40	+
4	β, 1-Naphthyl-β-hydroxy ethylamine ..		5/13	++++
5	ω-Amino-α-acetonaphthone		15/2[illegible]	+
6	4-Methoxy-ω-piperidino acetonaphthone ..		3/40	+

Serial No.	Name (hydrochloride of)	Structure	Pressor Intensity (Tyramine =1)	Pressor Duration (Tyramine =+++)
7	β, 1-Naphthyl ethylamine		5/13	+
8	ω-Piperidino-5-acetoacenaphthone ..		3/40	±
9	4-Hydroxy-ω-aminoacetonaphthone ..		1/20	+
10	β, β-9 : 9'-Diphenanthryl-β-hydroxy ethylamine	$(9\text{-}C_{14}H_9)_2 : C(OH)\cdot CH_2\cdot NH_2, HCl$	4/23	++
11	Dibenzyl aminomethane	$C_6H_5\cdot CH_2\cdot CH(NH_2, HCl)\cdot CH_2\cdot C_6H_5$	3/23	++
12	β, β-Diphenyl-β-hydroxy ethylamine ..	$(C_6H_5)_2\cdot C(OH)\cdot CH_2\cdot NH_2, HCl$	2/23	++
13	β, β-*Bis*-(4, hydroxy naphthyl-) ethylamine	$(4\text{-}HO\cdot C_{10}H_6)_2CH\cdot CH_2\cdot NH_2, HCl$	2/23	++
14	N, N'-Trimethylene *bis*-tyramine ..	$(HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NH\cdot CH_2)_2 : CH_2, 2\ HCl$	5/7	++++
15	β, β-Diphenyl ethylamine	$(C_6H_5)_2 : CH\cdot CH_2\cdot NH_2, HCl$	trace	trace
16	β, β-Diphenyl-β-hydroxy-α-benzyl ethylamine	$(C_6H_5)_2 : C(OH)\cdot CH(NH_2, HCl)\cdot CH_2\cdot C_6H_5$	trace	trace

17	1-Diphenylmethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-methylenedioxy isoquinoline		trace	trace
18	1-(*o*, Amino-) phenyl, 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy isoquinoline		trace	trace
19	*a*-(4-Methoxy naphthyl-) ethylamine ..		trace	trace
20	4-Methoxy naphthyl methylamine ..		trace	trace
21	4-Hydroxy napthyl ethylamnie ..		3/7	+

compound. On the basis that the pressor duration of tyramine is represented by + + +, the signs have been assigned under this column against each compound. It should be borne in mind that the reasons for assigning the signs are subjective and unlike pressor intensity, these cannot be construed to have any quantitative significance.

It has been possible, in the present study to examine only one aspect of the sympathomimetic effects, namely, that on blood pressure. That the relative values obtained by different workers differ somewhat widely and that the animals used, the mode of anæsthesia employed, the less obvious differences of technique, as well as individual variations of response in animals of the same species, all affect the results have already been pointed out by Barger and Dale (1910). Further, that the blood pressure depends on these and on the resultant of a number of other independent factors—rate and force of heart beat, tone of the visceral blood vessels, tone of the blood vessels in the skeletal muscles (which later in turn depends on the balance between the vasoconstrictors and vasodilators) and the state of the capillary bed, any or all of which may be affected by an injection of a sympathomimetic amine—and that the determination of the relative efficiencies of sympathomimetics by this method has only a conventional value until the results are analysed in the light of observed actions on other organs innervated by the sympathetic nerves have been emphasised by Barger and Dale (1910) and a few others (Rosenbleuth, 1932; Rosenbleuth and Cannon, 1933; Gurd, 1937).

In view of the reasons, however, which originally stimulated the studies on possible sympathomimetics belonging to the various ring systems, the attempt has been made to ascertain how far the present biological data furnish information under the following heads:

(*i*) the fundamental relationship, if any, existing between structure and pressor action of compounds belonging to the naphthalene series;

(*ii*) the possibilities held out by the observation of Madinaveitia (1919, 1920) that the mere substitution of the naphthalene ring in place of the customary benzene nucleus of pressor amines results in an augmentation of pressor activity by over 40 times;

(*iii*) the intrinsic sympathomimetic merits of poly- and hetero-cyclic rings when present in compounds possessing the requisite structure for pressor action;

(*iv*) the possibilities held out by the observation of von Braun *et. al.* (1916, 1917) that methyl amino hydrindene owes its intense activity to its being doubly a β-phenyl ethylamine; and

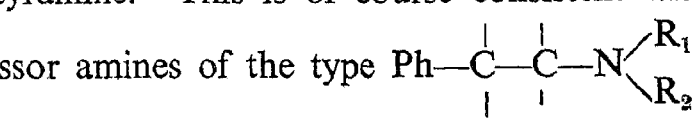
(*v*) the course of the future search for sympathomimetics.

Experimental

The experimental technique adopted was as follows: The cat was anæthetised with chloroform-ether and secured on its back. A trecheal cannula was then inserted and both carotids were tied at their distal ends. The animal was turned over and the second vertebra was exposed by a crucial incision on the mid-line so as to get at the foramen magnum. A probe was inserted through the foramen up into the cranium and the brain was completely destroyed by gentle manipulation. The cranium was plugged with cotton-wool smeared with vaseline to stop bleeding, if any, completely. Soon after, the spinal cord was destroyed and similarly plugged with cotton-wool. The administration of ether-chloroform was discontinued at this stage and artificial respiration was instituted immediately before the cord was cut. The cut edges of the skin were then sutured and the cat was turned over on its back. The blood pressure was recorded in the usual way by inserting a cannula in the left carotid artery and attaching to it a mercury manometer provided with a plunger carrying a writing point which was adjusted to write on the smoked paper of a slowly moving kymograph. Another cannula was inserted into the left femoral vein which was tied at its distal part; this cannula was connected by a small rubber tubing to a burette containing normal saline solution. The administration of the drugs was effected by injecting their solutions into the rubber tubing followed by running in a definite volume of the saline solution in order to ensure the complete influx of the full dose into the circulation. The dosage consisted of 1 c.c. of a one-in-thousand solution of each of the drugs and corresponds to 1 mg. of each of the base hydrochlorides. The doses were injected into the animal in succession, the period between two doses being not much longer than that required for the blood pressure to return to its initial level.

Discussion

The *a*-naphthyl methyl amines (Nos. 19 and 20) (Dey and Rajagopalan, 1939) possess extremely feeble activities. The results would go to show that these bases, pharmacologically and chemically, bear great resemblance to the feebly active benzylamines rather than to the active β-phenyl ethylamines.

The ω-amino methyl ketones of the naphthalene series studied are Nos. 3, 5, 6, 8 and 9. Of these, 4-methoxy, ω-piperidino acetonaphthone (No. 6) and ω-piperidino acetoacenaphthone (No. 8) were only feebly active, the activity being 3/40 of that of tyramine. This is of course consistent with the low activities shown by pressor amines of the type  .

However, the other members of the group (Nos. 3, 5 and 9) are of particular interest. Comparing Nos. 3 and 5, which are isomeric and also exhibit considerable activities, the influence of the manner of substitution of the side-chain in the naphthalene ring becomes apparent: substitution at the α-position (No. 5) is more than twice as effective as that in the β-position (No. 3) of the naphthalene nucleus. It then becomes of interest to enquire into the effect of introduction of a hydroxyl group in the nucleus *para* to the side-chain of the most active member of this group, namely, ω-amino-α-acetonaphthone (No. 5). An answer is provided by a comparison of Nos. 5 and 9. Such introduction of a nuclear hydroxyl group (No. 9) reduces not only the intensity (nearly 12 times) but also the duration of pressor action of the original compound (No. 5). This result is surprising and hardly in keeping with what could have been expected from knowledge of the benzenoid pressor amines; it is also in conflict with the previous findings of Madinaveitia who, as a result of testing the same pair of compounds on the isolated frog heart by the Trendellenburg technique, observed the hydroxylated base (No. 9) to be considerably more active than the related nuclear-unsubstituted compound (No. 5).

As under the group of β-naphthyl ethanolamines and β-naphthyl ethylamines, the four available compounds (Nos. 2, 4, 7 and 21) have been tested. The isomeric β-naphthyl ethanolamines (Nos. 2 and 4) are of equal effectiveness in respect of both intensity and duration of pressor action. The alcoholic bodies differ from their precursors, *viz.*, the ω-amino methyl ketones (Nos. 3 and 5) in an interesting manner: whereas substitution of the side-chain at the α-position was twice as advantageous as that in the β-position of the aromatic ring as far as the amino ketones (Nos. 3 and 5) were concerned, this effect of position substitution is destroyed on reduction to the corresponding carbinols (Nos. 2 and 4).

Further comparison of the carbinols (Nos. 2 and 4) with their parent ketones (Nos. 3 and 5) serves to bring out other characteristics of the alcoholic function. In the first place the transition from the ketone to the alcohol in one case (No. 3 to No. 2) is accompanied by an intensification of pressor action, while a similar transformation in another (No. 5 to No. 4) results in a lowering of the original activity. In the second place, the passage from the ketones to the alcohols in both cases produces greater duration at a higher level of pressor action. The latter characteristic as well as the intensification of activity noted in one set (Nos. 3 and 2) is conceivable in the light of experience with sympathomimetics of the benzene series, but the lowering of activity in another (Nos. 5 and 4) is quite unexpected.

Still further significance of the alcoholic group in the naphthalenic sympathomimetics is brought to light by a scrutiny of the activities evinced by three compounds of the present series, *viz.*, the isomeric β-naphthyl ethanolamines (Nos. 2 and 4), and β-1-naphthyl ethylamine (No. 7). As might have been anticipated all the three possess equal intensity of action and the first two, having an alcoholic hydroxyl group in their side-chains, to take on the characteristic of more pronounced duration at a higher level of pressor action.

The activities exhibited by ω-amino-α-acetonaphthone (No. 5) on the one hand, and on the other by β-, *l*-naphthyl ethyl amine (No. 7) are of interest. Although there is no difference in their duration of action, the ketone (No. 5) is more active (ca. $1\frac{1}{2}$ times) than the ethyl amine (No. 7) and is the reverse of what obtains in analogous benzene types.

Comparison of the activities of β, 1-naphthyl ethylamine (No. 7) and its nuclear substituted derivative, β, 4-(hydroxy naphthyl-) ethylamine (No. 21) serves to ascertain further the implications of introducing nuclear (or phenolic) hydroxyl groups. Analogy with benzeneoid sympathomimetics suggests a high enhancement of activity but a diminution of the duration of action. Actually, however, introduction of a hydroxyl group in the *para*-position in β, 1-naphthyl ethylamine (No. 7) confers on the resulting product (No. 21) only a trace of enhancement of the original intensity without however, influencing the duration of action.

In connection with the inquiry about the extent to which the present results lend support to Madinaveitia's generalisation that the mere substitution of the naphthalene ring in place of the benzene nucleus of customary pressors gives rise to an enhancement of activity by over 40 times, it becomes necessary to study pairs of strictly comparable compounds belonging to the benzene and naphthalene series. In the present series only two such pairs, namely β, β-diphenyl, β-hydroxy ethylamine (No. 12) and its corresponding naphthyl analogue (No. 1), and tyramine and its analogue 4-hydroxy naphthyl ethylamine (No. 21), have been available. Comparisons between β, 1-naphthyl ethylamine (No. 7) and β-phenyl ethyl amine and between the isomeric ω-aminoacetonaphthones (Nos. 3 and 5) and ω-amino acetophenone have also been made from a knowledge of the data formerly presented by other workers on β-phenyl ethylamine and ω-aminoacetophenone, respectively (Barger and Dale, 1910; Barger, 1930; Hartung, 1931). They reveal firstly that the quantitative relationship between pressor amines severally derived from benzene and naphthalene are somewhat obscure, and secondly, that in some instances (Nos. 1, 3, 5 and 7) there results considerable increase of activity, while in one case (No. 21) there is decreased

activity, as a consequence of substitution of the naphthalene ring in place of the benzene nucleus. To an extent, the activities of Nos. 1 and 5 and to a lesser extent that of No. 3 may be construed to lend support, to the generalisation of Madinaveitia, who, it will be recalled, based his finding on the result obtained by comparing only a single pair of analogous compounds.

Comparison of three analogous compounds (Nos. 12, 1 and 10) affords some measure of the merits of benzene, naphthalene and phenanthrene ring structures when present in sympathomimetics. It appears that the phenanthrene ring is nearly twice as effective and the naphthalene ring about seven to eight times as effective as the benzene ring. Again comparing Nos. 6 and 8, there does not seem to be any difference sympathomimetically between the naphthalene or acenaphthene nuclei of pressor amines.

Next, in the order for examination, comes up the question of how far the expectations regarding the sympathomimetic potentialities of compounds, whose synthesis was specifically actuated by the explanation of the mode of intense action of methyl amino hydrindene by von Braun, have now been realised. Among members of the series of bases derived severally from the various ring systems and whose molecules contain the repeating active atom-patterns. Ar. C. C. N - (Nos. 1, 10–18), only two, namely, Nos. 1 and 14, possess considerable activities; the others possess feeble (Nos. 10–13) or only a trace (Nos. 15–18) of sympathomimetic activity. If, as visualised by von Braun, methyl amino hydrindene owed its high activity to its being doubly a β-phenyl ethylamine, a high degree of activity should have been recorded at least for Nos. 11, 12, 14, 15, 16 and 17, since each of these can be construed as β-phenyl ethylamines in more ways than one. The low activities shown by these, however, make it clear that the mode of activity of methyl amino hydrindene, although at present beyond comprehension, should be conceived to be different from that envisaged by von Braun. The observed activities of the present series of compounds constitute yet another illustration, so plentiful in chemotherapy, of the fact that the effect produced by substituting groups in a physiologically active molecule is not necessarily additive or cumulative, but that their effects may be reciprocally modifying.

Finally, there remains for consideration the course of the future search for sympathomimetics. It is seen that except in the naphthalene series, new potent pressors are probably unlikely to be encountered in any of the other ring systems, namely, the benzene, acenaphthene, phenanthrene and isoquinoline rings. Besides bringing out the inadequacy of von Braun's concept of the mode of activity of methyl amino hydrindene, the results now

obtained serve to prove definitely that further study of compounds possessing the repeating, active moieties, Ar. C. C. N– in their structures may not lead to sympathomimetics of surprisingly high or useful pressor potencies.

While the above results no doubt give some insight particularly into the fundamental relation between chemical constitution and pressor action of naphthalenic sympathomimetics, it becomes obvious that the rules governing similar relationship among the benzenoid compounds apply to the corresponding members of the naphthalene series only to a limited extent. The present investigations also bring out the essential differences in the physiological activity of compounds derived from the two ring systems. These and evidence of the existence of inexplicable chemotherapeutical contrasts such as that provided by the observed but essentially unpredictable effects produced by the hydroxyl group when present either in the nucleus or the side-chain of naphthalenic pressors preclude attempts to formulate the relationship between chemical constitution and sympathomimetic action of compounds derived from ring systems other than benzene. The reason, therefore, for advancing the tentative conclusions concerning the naphthalene series is that the evidence now available indicates such trends. That there should be some legitimate doubt about some of these is necessarily implied in any attempt to compare and correlate the none too abundant data in a realm where there are as many variables as there are in biological experimentation. A more definite formulation may, however, be expected to be possible after the accumulation of very much more pertinent information by extended investigations.

Summary

Twenty-one selected compounds derived severally from benzene, naphthalene, acenaphthene, phenanthrene and isoquinoline have been examined for their pressor activities in the spinal cat, using tyramine as the control.

The α-naphthyl methylamines resemble benzylamine in exhibiting feeble activities. Fair degrees of activity are shown by the ω-amino acetonaphthones, the β-naphthyl ethanolamines and the β-naphthyl ethylamines. The rules governing the qualitative and quantitative relation between structure and pressor action of benzenoid sympathomimetics seem to apply to members of the naphthalene series only to a limited extent. The substitution of the benzene nucleus of pressor bases by the naphthalene ring generally results in considerable increased activity, but this has an exception. Consequently, the generalisation of Madinaveitia that such substitution augments the activity by over forty times receives only limited support. The

postulate of von Braun that methyl amino hydrindene owed its intense activity to its being doubly a β-phenyl ethylamine appears inadequate in view of the low activity evinced by a number of bases which may be considered as β-phenyl ethylamines many times over. While the naphthalene and acenaphthene nuclei are equal and about seven times as effective as the benzene ring the phenanthrene ring is only twice as effective. New potent pressors appear unlikely to be encountered in the benzene, phenanthrene and isoquinoline ring systems, but the naphthalene series seems to be promising.

Acknowledgements

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