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REFLEX ACTIONS OF SOME *ISO*THIOUREA DERIVATIVES ON CIRCULATION AND RESPIRATION

BY

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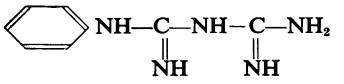
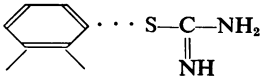
Recently Dawes and Mott (1950) observed that phenyl guanidine, phenyl diguanide, and a number of their close chemical analogues caused a transient fall of blood pressure and heart rate and stoppage of respiratory movements when they were injected intravenously into lightly anaesthetized cats. These responses were abolished by cutting the vagi and were attributed to an action on receptors in the heart and lungs. Three reflex responses were distinguished in this way: (i) A fall of blood pressure and heart rate due to stimulation of receptors in the area of distribution of the left coronary artery. This is perhaps the Bezold reflex (Bezold and Hirt, 1867 ; Krayer and Acheson, 1946 ; Dawes, 1947). (ii) A fall of blood pressure and heart rate originating from receptors in the lungs, which have not yet been identified. (iii) An inhibition of respiration, also originating from receptors in the lungs.

Most of the compounds examined by Dawes and Mott were diguanide derivatives, but a few aryl guanidines and amidines were also found to possess appreciable activity. As this suggested that the aliphatic side-chain of phenyl diguanide (I) could be modified considerably without total loss of activity, certain *iso*thioureas

(I) 

(II) 

of the type shown (II) were tested. Several of these turned out to be highly active, so the relationship between structure and activity has been studied in further detail.

METHODS

Cats under light chloralose anaesthesia (60 mg./kg.) were used for the main series of experiments. The trachea and a jugular vein were cannulated. Blood pressure was recorded from a carotid artery. Respiratory movements were recorded by a modification of Gaddum's method (Gaddum, 1941). In order to record the heart rate, the electrocardiogram was amplified by a conventional condenser-coupled push-pull amplifier with a time constant of about one second. The amplified *QRS* complex, after differentiation, was then adjusted to trigger a square-wave of short duration ;

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the latter was used to operate an impulse counter of the type described by Thorp (1948). In this way a record was obtained in which the height of the vertical lines (Fig. 1) was directly proportional to the mean heart rate integrated over 5 or 10 second intervals. The techniques employed for "exteriorizing" the heart and for cannulating the left coronary artery in the cat are similar to those used by Dawes and Mott (1950) and were described in detail by Dawes (1947).

About half the compounds used had been synthesized for earlier studies (Fastier and Smirk, 1943 and 1947; Fastier, 1948). A few were purchased. We are grateful to Abbott Laboratories for the *iso*thiourea derivatives A-224, A-1069, A-1070, A-1113 to A-1128, A-1142, and A-1782 to A-1784; to Boots Pure Drug Co. for the *iso*thiourea derivatives RD1051, RD1052, and RD1056; to I.C.I. for the thiosemicarbazides; and to Professor Albert for four of the cyclic amidines.

RESULTS

All the compounds available were tested in the first instance to see whether they possessed any activity of the type expected, *viz.*, (i) the production of a transient fall of blood pressure and heart rate, with inhibition of respiration, when a small quantity of the drug in neutral solution was injected into a jugular vein; (ii) the disappearance of these effects after vagotomy.

Compounds showing little or no activity.—Some sixty of the compounds studied gave no indication of activity when tested in doses of up to 1 mg. These were (salts of)

S-methyl, *S*-ethyl, *S*-*n*-dodecyl, *S*-*n*-tetradecyl, and *S*-*n*-hexadecyl *iso*thiourea;

SS'-methylene, -ethylene, -tetramethylene, -pentamethylene, and -hexamethylene di-*iso*thiourea;

the *o*-, *m*-, and *p*-chlorobenzyl, *o*-, *m*-, and *p*-bromobenzyl, *p*-methoxybenzyl and 2-pyridyl *S*-derivatives of *N* : *N'*-ethylene *iso*thiourea (2-mercapto-4 : 5-dihydroglyoxaline);

S-2-hydroxyethyl and -3-hydroxy-*n*-propyl *iso*thiourea;

SN-propylene *iso*thiourea, *SN*-trimethylene *iso*thiourea;

S-methyl-*NN'*-diphenyl *iso*thiourea; diacetyl-*S*-methyl *iso*thiourea;

guanidine, methylguanidine, *asym.*-dimethylguanidine;

creatine and its methyl and ethyl esters;

O-methyl and *O*-ethyl *iso*urea;

propionamidine; "Phenamidine," "Propamidine";

2- and 4-aminopyridine, 2-aminopyrimidine, 3-aminoindazole, 3-methyl-2-iminobenzthiazoline (B.D.H.);

iminoazole, dihydroiminoazole; amarin, furfurin;

benzylamine, 2-phenylethylamine; benzyldimethylamine, benzyldiethylamine; *NN*-dibenzylethylamine, *NN*-dibenzylethanolamine; tryptamine.

N-benzylthiourea, *N*-methyl-, *N*-ethyl-, *N*-allyl-, and *NNN'*-trimethyl-thiourea; thioacetamide; *iso*thiohydantoin; *p*-methoxybenzaldehyde thiosemicarbazone and its *N*-*sec.*-butyl and *NN*-dimethyl derivatives were also examined.

Active amidine derivatives.—The inactive compounds listed above were each tested twice; the remainder were tested repeatedly. Their effects on blood pressure, heart rate, and respiratory movements were compared with those of phenyl diguanide,

which was injected at intervals throughout each experiment. An example of this procedure is illustrated in Fig. 1. The dose of each *iso*thiourea was varied until the depressor effect produced matched that obtained in the same animal with a

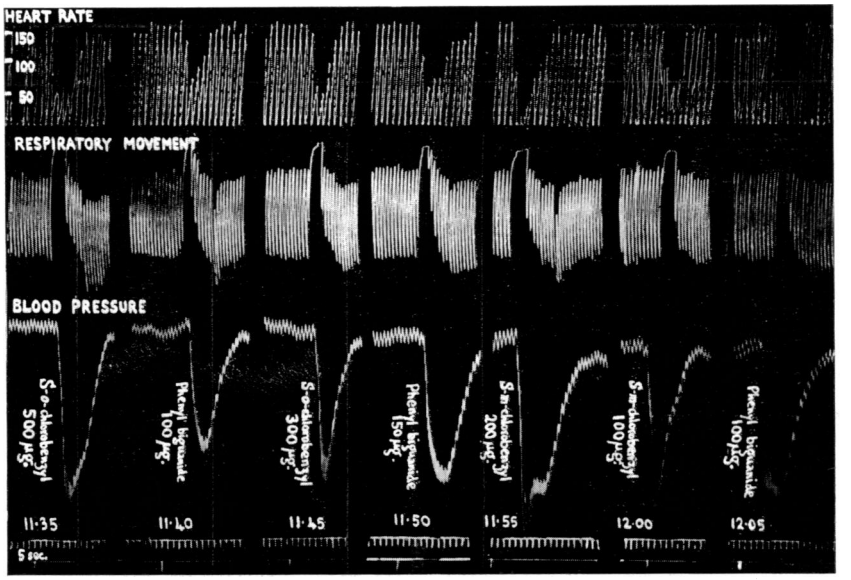


FIG. 1.—Cat. 3.1 kg.; chloralose anaesthesia. The record illustrates the method of assay. It shows *S-o*-chlorobenzyl *iso*thiourea to have about half the depressor activity of phenyl diguanide. *S-m*-chlorobenzyl *iso*thiourea is as active as phenyl diguanide. The slowing in heart rate after each injection is roughly proportional to the fall of blood pressure.

100 µg. dose of phenyl diguanide. Although the interval between injections was only five minutes, there was seldom any hint of interaction between compounds or of cumulative effects, probably because the dose given was so small (cf. Fastier and Smirk, 1943).

At this point it may be explained that some trouble was taken to procure concurrent records of the effects upon blood pressure and heart rate in order to see whether any compounds had dissimilar actions upon these two variants. With all the active compounds studied, the slowing of the heart rate was proportional to the fall of blood pressure (Fig. 1). There is no evidence from this point of view, therefore, that we are dealing with more than one type of cardiovascular response. For all active compounds the results could be explained on the basis of a single type of reflex cardiovascular reaction.

Compound RD1052, which is the hydrobromide salt of 2-α-naphthylethyl *iso*thiourea (III), proved to be the most active of those tested. Doses of 30–70 µg. (mean for 10 cats, 45 µg.) sufficed to reproduce the depressor effects of 100 µg. doses of phenyl diguanide. The corresponding doses for twenty other potent *iso*thioureas are listed in Table I.

TABLE I

REFLEX DEPRESSOR ACTIVITY OF *iso*THIOUREAS

All the compounds are of general formula $RSC(:\overset{+}{N}H_2)NHR'\}\overset{-}{X}$. The dose given in the last column is that which matches the depressor effect of a 100 μg. dose of phenyl diguanide. Each dose is the mean value for experiments on 4–8 cats (method illustrated in Fig. 1).

Structure of *iso*thiourea salt			Code name	Mean dose μg.
R	R′	X		
2-α-Naphthylethyl	H	Br	RD1052	45
m-Chlorobenzyl	H	Br	A–1116	90
m-Bromo*cyclo*hexyl(*cis*)	H	Br	A–1128	90
m-Bromobenzyl	H	Br	A–1122	120
3-Phenyl-*n*-propyl	H	Br	A–1751	120
α-Naphthylmethyl	H	Br	RD1051	250
2-Phenylethyl	H	Cl	S–PE	250
Benzyl	H	Cl	S–Bz	350
o-Chlorobenzyl	H	Cl	A–1115	400
2-Thienylmethyl	H	Cl	A–1114	600
p-Chlorobenzyl	H	Cl	A–1117	650
o-Bromobenzyl	H	Cl	A–1121	650
n-Amyl	H	Br	S–*n*–5	750
R)-2-Bromotrimethylene-(R′		Br	A–1782	1,000
n-Butyl	H	Br	S–*n*–4	1,000
p-Bromobenzyl	H	Br	A–1123	1,500
n-Hexyl	H	Br	S–*n*–6	1,500
n-Propyl	H	Br	S–*n*–3	2,000
n-Heptyl	H	Br	A–*n*–7	3,000
Methyl	C_6H_5	I	S–MP	5,000
2-*cyclo*Hexylethyl	H	Br	A–1070	5,000

Trivial activity was exhibited by salts of the following: *S*-*n*-octyl and *S*-*n*-nonyl *iso*thiourea, *SN*-dimethyl*iso*thiourea, *SN*-ethylene*iso*thiourea, *S*-methyl-*N*-*n*-hexyl-*iso*thiourea, *S*-5-*cyclo*hexyl-*n*-amyl*iso*thiourea, *S*-4-α-tetrahydronaphthyl-*n*-butyl *iso*-thiourea (IV), *SN*-(2-methyl*iso*thiouronium-)ethylene *iso*thiourea, *SS*′-trimethylene di-*iso*thiourea and 2-aminoquinoline. Compound RD1056, the hydrochloride of *S*-(9-phenanthryl-)methyl *iso*thiourea, was one of several which were so insoluble that their activity could not be estimated reliably.

Nature of the depressor effects.—Each of the cats used for the above experiments was vagotomized while it was still in good condition. All the compounds which had produced depressor effects in it were then retested. They had little or no effect in the vagotomized animal even when the dose was raised considerably. It was therefore concluded that their depressor effects were dependent upon the integrity of the vagi; and further experiments were undertaken to see whether they acted in a fashion similar to that previously described for amidine derivatives like phenyl diguanide.

Active *iso*thioureas of various types—e.g., RD1052, A-1116, A-1128, A-1751, *S*-*n*-5 (Table I)—were injected directly into the cavities of the atria, ventricles, and major blood vessels. For this part of the work 18 cats under chloralose anaesthesia were used in all. Part of the results of a typical experiment are illustrated in Fig. 2. It can be seen that the depressor responses to 50 μg. doses of RD1052 were both

large and prompt when the *iso*thiourea was injected directly into the left ventricle or the pulmonary artery. The same dose was ineffective after vagotomy (Fig. 2). It was also ineffective when with vagi intact it was injected into the arch of the

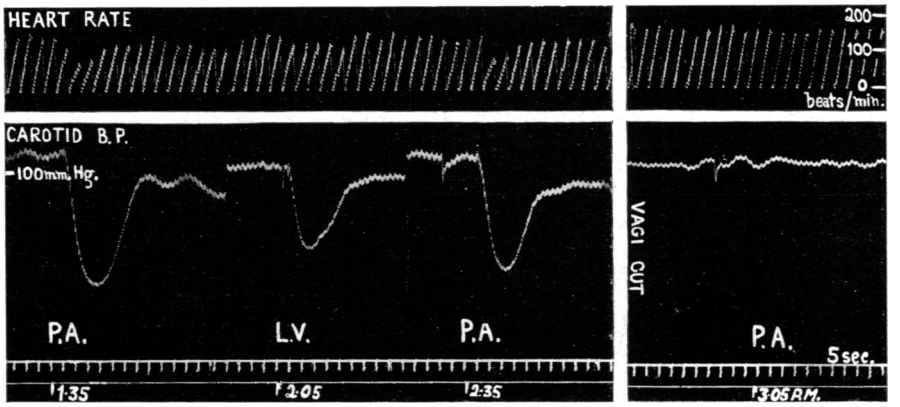


FIG. 2.—Cat. 2.9 kg.; chloralose anaesthesia. Chest opened; artificial respiration. Injection of 50 μg. of 2-α-naphthylethyl *iso*thiourea (RD1052) into the pulmonary artery (P.A.) causes a greater fall of blood pressure and heart rate than an injection into the cavity of the left ventricle (L.V.). Both effects are abolished by cutting the vagi.

aorta by a fine needle pushed through the vessel wall. These findings must mean that, as with the amidine derivatives previously studied, the sites of action are located in that part of the cardiovascular system which lies between the pulmonary artery and the aortic arch.

The depressor effect of a small dose of one of these *iso*thioureas was always maximal for an injection into the pulmonary artery (Fig. 2); sometimes the fall of blood pressure was very much bigger than that obtained with an injection into the cavity of the left ventricle. The depressor effects of moderate doses injected into the right and left ventricles, or right and left atria, began in either instance within two or three seconds. As Dawes and Mott (1950) have already pointed out, amidine derivatives differ from members of the veratrine group in this respect. The veratrum alkaloids also cause reflex falls of blood pressure; but whereas the response is obtained within two to three seconds if they are injected into the left ventricle, some five to eight seconds elapse before a fall of blood pressure is obtained with an injection made into the right side of the heart. In contrast to the veratrum alkaloids, which must act almost exclusively on receptors situated in the left ventricle (Dawes, 1947), these amidine derivatives cause a fall of blood pressure and heart rate by stimulating receptors situated in the pulmonary bed.

In addition, they produce a similar cardiovascular response by an action on receptors in the area of distribution of the coronary system. Thus in two out of five cats, doses of RD1052 which had no effect when injected into the right atrium produced considerable falls of blood pressure and slowing of the heart when they were injected into the left coronary artery (Fig. 3). In the other three cats, small doses of RD1052 caused just as strong depressor effects when injected into the right

atrium as when they were injected into the left coronary artery. This may well have been due to the preponderant effect of the reflex arising from the pulmonary bed, since the drug after injection into the left coronary artery is rapidly carried through the coronary circulation to the right side of the heart. In all cats injection into the cavity of the left ventricle still produced a fall of blood pressure and heart rate, though usually a smaller one than that seen on injection into the right side of the heart; this response was not obtained on injection into the ascending aorta.

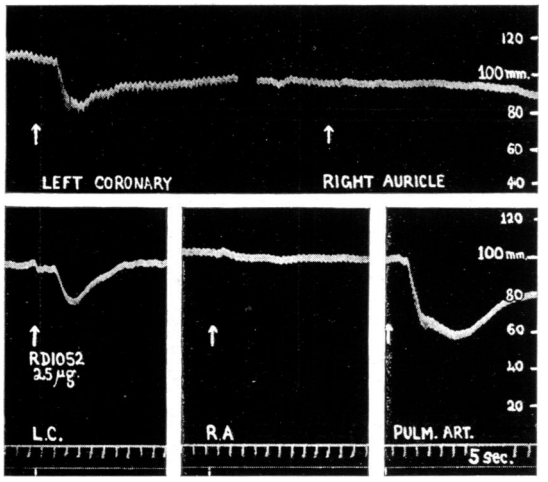


FIG. 3.—Cat. 3.8 kg.; chloralose anaesthesia. Chest opened; artificial respiration. Left coronary artery cannulated and perfused from left carotid. Injection of 25 μg. of 2-α-naphthylethyl *iso*thiourea (RD1052) at 15 min. intervals causes a fall of blood pressure and heart rate on injection into the left coronary artery (L.C.); the same dose has no effect on injection into the cavity of the right auricle (R.A.), but a much greater effect on injection into the pulmonary artery.

The fall of blood pressure which is seen after an intravenous injection of one of the active amidine derivatives is due not only to slowing of the heart but also to reflex vasodilatation. Fig. 4 illustrates one of a series of experiments carried out with J. Vane, to whom we are most grateful for the use of his system for perfusing the cat's hind-limb (which will be described elsewhere). From Fig. 4 it will be seen that a 50 μg. dose of RD1052 injected intravenously caused a large fall of blood pressure accompanied by vasodilatation in the hind-limb, and that both effects were abolished by cutting the vagi. The same dose injected directly into the artery supplying the hind-limb also caused vasodilatation. This was a direct action of RD1052 on the blood vessels and was not abolished by vagotomy; but it represents the effect of a far greater local concentration of the drug than that encountered after an intravenous injection. A number of other aryl *iso*thioureas were found to behave similarly.

Some of the active compounds were also tested on rabbits under urethane or pentobarbitone (Nembutal) anaesthesia. Their circulatory effects in rabbits were similar to those observed in cats, but small though still appreciable falls of blood pressure were obtained after cutting the vagi.

Influence of the anaesthetic.—Two cats which had been lightly anaesthetized with pentobarbitone reacted in the same way as cats under chloralose when such compounds as RD1052, S-Bz, and S-*n*-5 were injected intravenously; so did three others which had been decerebrated under ether at the level of the tentorium cerebelli. On the other hand, the injection of pentobarbitone (20 mg./kg.) into three cats which had already been lightly anaesthetized with chloralose (60 mg./kg.) and were responding well to the injection of various *iso*thioureas rendered the animals almost

insensitive to the compounds. These observations confirm the view of Dawes and Mott (1950), that the depth of anaesthesia has a greater influence than the nature of the anaesthetic.

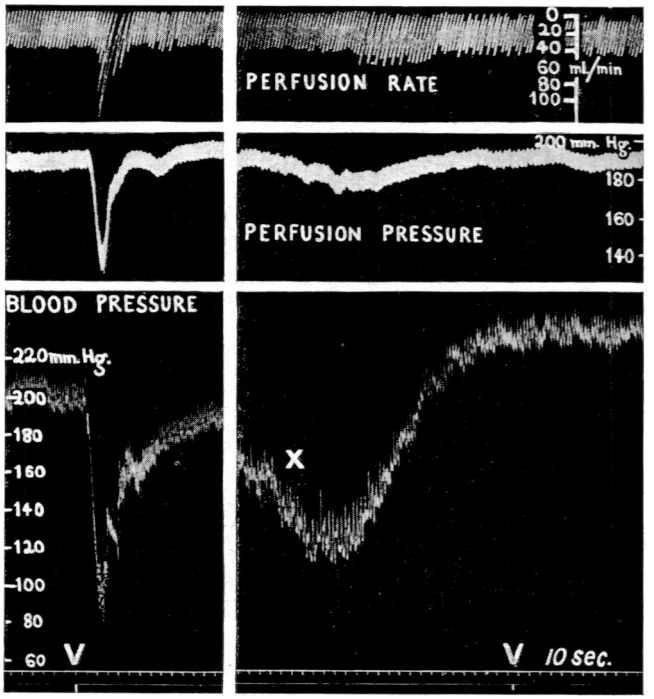


FIG. 4.—Cat. 4.4 kg.; chloralose anaesthesia. Both carotid arteries were cannulated and blood supplied from them to the left femoral artery by a pump which enabled both perfusion pressure and rate of flow to be recorded. Blood pressure was recorded by cannulating a brachial artery. The tracings show the effects of 50 μg. doses of 2-α-naphthylethyl *iso*thiourea (RD1052) given intravenously at V, before and after vagotomy (performed at X).

Effects upon respiratory movement.—The compounds which were found to cause a reflex fall of blood pressure and heart rate usually produced an equally striking inhibition of respiratory movement. Typical responses in the cat are shown in Figs. 1, 5, and 6. This effect too was abolished by vagotomy. Most of the *iso*thioureas examined caused stronger inhibition of respiratory movement than did phenyl diguanide when given in equidepressor doses (Fig. 5)—it will be recalled that the effects upon heart rate were *similar* for equidepressor doses.

To localize the site of action in the cat, the heart was "exteriorized" in six animals in the manner described previously (Dawes, 1947). Fig. 6 illustrates typical results. Injection of a 50 μg. dose of RD1052 into the pulmonary artery caused an inhibition of respiration abolished by cutting the vagi, but a similar injection into the cavity of the left ventricle or aorta had little or no effect. If the dose of *iso*thiourea was

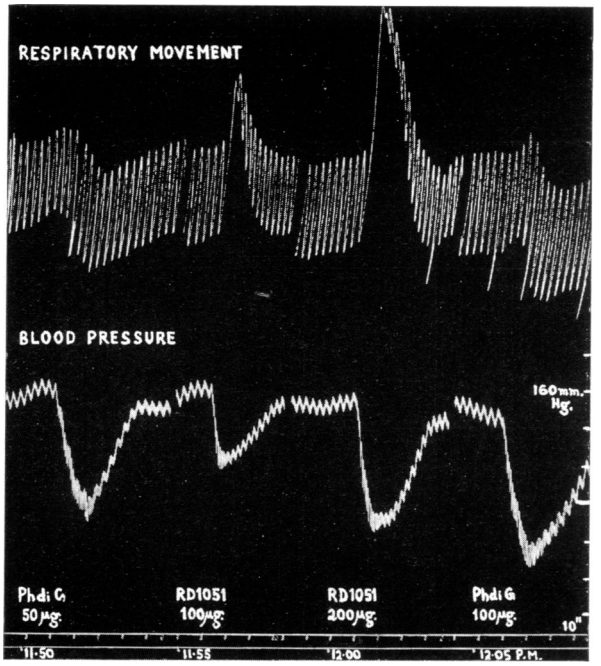


FIG. 5.—Cat. 2.4 kg.; chloralose anaesthesia. In equi-depressor doses, injected intravenously, α-naphthylmethyl *iso*thiourea (RD1051) causes a transient inhibition of respiration while phenyl diguanide has the reverse effect.

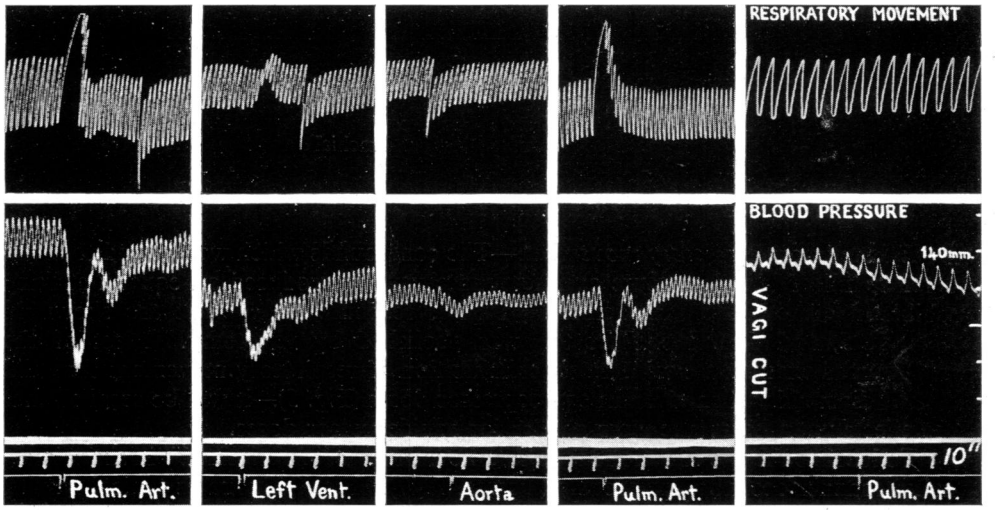


FIG. 6.—Cat. 3 kg.; chloralose anaesthesia. The heart was "exteriorized" to permit direct injection into its cavities and the great vessels; spontaneous respiration restored. A dose of 50 µg. of 2-α-naphthylethyl *iso*thiourea (RD1052) caused strong inhibition of respiration on injection into the pulmonary artery, but not on injection into the left ventricle or aorta. This inhibition was abolished by vagotomy.

increased, injection into the cavity of the left ventricle then produced a transient inhibition of respiration, but the delay between injection and respiratory inhibition amounted to several seconds; whereas after injection into the pulmonary artery respiration stopped almost immediately. These observations are all explained by an action of the *iso*thioureas on receptors in the lungs.

The responses obtained in rabbits under urethane or pentobarbitone anaesthesia were more complex. With some animals purely inhibitory effects were observed. With others stimulation was the predominant action though it usually followed a short period of inhibition. When an additional record of respiratory movement was obtained by tying a thread from the xiphisternum to a lever, it was found that respiration stopped at the end of an inspiratory movement, whereas in the cat respiration stopped in the expiratory position. These effects in the rabbit were not completely abolished by vagotomy.

DISCUSSION

The results described above show that numerous *iso*thioureas of fairly simple structure possess the ability to initiate the three reflexes described in the introduction to this paper as characteristic of certain phenyl guanidine and diguanide derivatives. They differ from the latter only in that their inhibitory effect on respiration is relatively stronger than their action on the cardiovascular system. When the results of Dawes and Mott (1950) are also taken into consideration, it can be seen that between thirty and forty compounds of fairly simple structure, all of which contain one amidine $-C(:\overset{+}{N}H_2)NH_2$ group, are known to elicit these reflexes in the cat in a dose of 1 mg. or less.

One of the main inducements to the present investigation was the hope that an extended survey of the relationship between structure and activity would provide some clue to the mechanism of action. It was just conceivable that *in vivo* the receptors for these three reflexes might be stimulated by some naturally occurring chemical agent; alternatively, and perhaps more probably, amidine derivatives of the types described might interfere with a particular phase of metabolic activity. In either case more detailed knowledge of the optimum requirements for activity might suggest the type of metabolite involved.

It will be seen that nearly all the more active compounds have the structure: aromatic nucleus—short side-chain—unsubstituted amidine group. Nevertheless, at least one alicyclic derivative (*cis-m*-bromocyclohexyl*iso*thiourea hydrobromide, XI) displays high activity; and a few purely aliphatic derivatives are moderately active, though these have alkyl side-chains containing four or more carbon atoms. It is clear that there is no close relationship between these compounds and known intermediary metabolites of cardiac or pulmonary tissues. And it would perhaps be prudent to bear in mind the possibility that these compounds have a different mode or site of action from those others (e.g., veratrum alkaloids, adenosine-triphosphate) which are known to elicit reflexes of a superficially similar character.

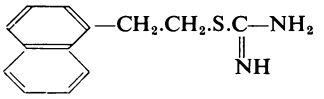
S-Alkyl iso*thioureas*.—The simplest in structure of the active compounds are certain alkyl *iso*thiourea salts. Twelve members in all of the series of general formula $CH_3-(CH_2)_n-S\cdot C(:\overset{+}{N}H_2)NH_2$ have been examined. The *n*-propyl deriva-

tive (for which $n=2$) was the first in which the properties sought could be detected. The *n*-butyl and *n*-amyl derivatives were more active (Table I), but from *n*-amyl *iso*thiourea onwards there was a steady decline in activity.

Aryl isothioureas.—A considerable increase in activity was effected when an aromatic ring was introduced into the side-chain of an alkyl *iso*thiourea. Salts of benzyl and 2-phenylethyl *iso*thiourea were found to have about a third of the depressor activity of phenyl diguanide. The phenyl-*n*-propyl derivative (V) was nearly as active.

Still more potent compounds were obtained when an α-naphthyl group was substituted for a phenyl group. The naphthyl analogue of benzyl *iso*thiourea (compound RD1051) was nearly half as active as phenyl diguanide, the naphthyl ethyl derivative (RD1052, III) no less than 2–3 times as active.

2-Thienyl methyl *iso*thiourea (VI) was moderately active, as might be expected from its chemical resemblance to benzyl *iso*thiourea. A 2-pyridyl *iso*thiourea salt was inactive. The water-insolubility of 9-phenanthrylmethyl *iso*thiourea precluded accurate work with this compound.



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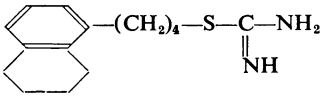

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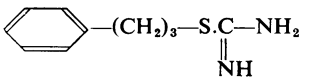

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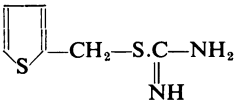

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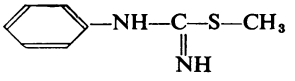

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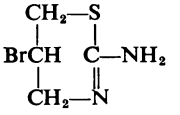

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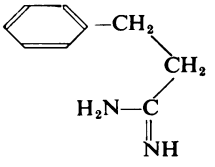

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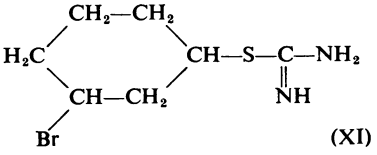

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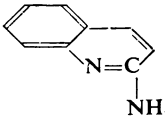

(X)

It can be seen from Table I that the introduction of a chlorine or bromine atom into the aromatic ring of benzyl *iso*thiourea enhances activity when the halogen is in the *meta* position but reduces it no less markedly when the halogen is in the *para*

position. The order of activity is *m*->*o*->*p*- for both chloro- and bromo-substituted benzyl *iso*thioureas.

The *NN'*-ethylene derivatives of these last six *iso*thioureas seemed quite inactive. However, some *N*-substituted *iso*thioureas possess appreciable activity, e.g., *S*-methyl-*N*-phenyl *iso*thiourea (VII), *SN*-(2-bromo-)trimethylene *iso*thiourea (VIII). Salts of *S*-methyl *NN'*-diphenyl *iso*thiourea and of *SN*-trimethylene *iso*thiourea, it should be added, are practically inactive. Substitution in the amidine group itself never enhanced activity, and often practically abolished it. Dawes and Mott (1950) have found the same true of the diguanide derivatives they tested.

The point is further illustrated by the behaviour of certain cyclic amidine derivatives. Since it was known from the work of Dawes and Mott that bases like 2-phenylpropionamidine (IX) are fairly active, it was thought of interest to test cyclic analogues like 2-aminoquinoline (X), 2- and 4- aminopyridine, and 2-aminopyrimidine. Only the quinoline derivative gave any indication of activity.

Alicyclic iso*thioureas.*—Four *S*-derivatives have been tested: *cis-m*-bromo*cyclo*hexyl *iso*thiourea (A-1128, XI), 2-*cyclo*hexylethyl *iso*thiourea (A-1070), 5-*cyclo*hexyl-*n*-amyl *iso*thiourea (A-1069), and 4-α-tetrahydronaphthyl *n*-butyl *iso*thiourea (A-1113, IV). A-1128 was found to be about as strongly depressor as phenyl diguanide. A-1070 is some fifty times less active. A-1069 and A-1113 are practically inactive.

Aliphatic amidine derivatives.—Those with short side-chains seem to be almost devoid of activity, as judged by the results obtained with salts of such bases as methyl *iso*thiourea, 2-hydroxyethyl *iso*thiourea, *SN*-dimethyl *iso*thiourea, ethyl *iso*urea, methyl-guanidine, propionamidine, and iminoazole.

It has already been remarked that some with longer side-chains display appreciable activity—e.g., *S-n*-amyl *iso*thiourea, *SN*-(2-bromo-)trimethylene *iso*thiourea.

A few di-amidine derivatives have also been examined. Of the first six di-*iso*thioureas of general formula $H_2N(H_2N\overset{+}{:})C\cdot S\text{-}(CH_2)_n\text{-}S\cdot C(\overset{+}{:}NH_2)NH_2$, only the trimethylene derivative gave any indication of activity.

Amines, thioureas.—The importance of the amidine group is shown by the fact that the simple amines corresponding to benzyl and 2-phenylethyl *iso*thiourea are inactive, as is the non-basic *N*-benzyl thiourea (which is isomeric with benzyl *iso*thiourea).

SUMMARY

1. Ninety-three compounds, most of them amidine derivatives of the *iso*thiourea type, were investigated for the ability to cause a reflex fall of blood pressure and heart rate, and inhibition of respiration, upon intravenous injection into lightly anaesthetized cats. Fourteen *iso*thioureas produced these effects, which are abolished by vagotomy, in a dose of 1 mg. or less.

2. The most active of these *iso*thioureas was the hydrobromide of 2-α-naphthylethyl *iso*thiourea ; doses of 10–30 μg./kg. were sufficient to cause a very considerable fall of blood pressure. Another ten *iso*thioureas of the type $Ar\text{-}(CH_2)_n\text{-}S\text{-}C(\overset{+}{:}NH_2)NH_2$ were about a half to a twentieth as active as this. Some aliphatic derivatives like *n*-amyl *iso*thiourea also exhibited appreciable activity.

3. As with the amidine derivatives previously investigated, the responses are attributed to three separate reflexes: two depressor reflexes whose receptors are in the heart and lungs respectively, and a respiratory reflex, the receptors for which are in the lungs.

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