COMPARATIVE PHYSIOLOGICAL ACTIONS OF PHENYL-, THIENYL- AND FURYLISOPROPYLAMINES

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Corresponding derivatives of benzene, thiophene and furan differ notably in their chemical composition and structure, but since the time of Victor Meyer (6) the close similarity of the chemical and physical properties of benzene and thiophene derivatives has been recognized. The similarities between thiophene and furan compounds were early recognized, and thiophene was designated as thiofuran in some of its literature. The aromatic properties of furan have been emphasized by Gilman and coworkers (4), and Pauling (7) has recently presented pertinent resonance data and structural interpretations for thiophene and furan that are in keeping with the known physical and chemical similarities of these compounds with benzene.

Closely related to some of the work here reported are the observations of Tainter (10) that \( \beta \)-2-thienylethylamine (referred to as thiophenylethylamine) has about the same order of pressor activity in cats as does \( \beta \)-phenylethylamine, and that pretreatment with cocaine diminished the pressor activity of both compounds. Burn also studied the pressor effects of \( \beta \)-2-thienylethylamine synthesized by Barger and Easson (2), and reported that its effects were qualitatively and quantitatively indistinguishable from those of \( \beta \)-phenylethylamine. Observations of the effects of \( \beta \)-2-thienylethylamine (referred to as thiophenethylamine) and \( \beta \)-phenylethylamine in producing increased motor activity in rats have recently been reported by Schulte, Reif, Bacher, Laurence and Tainter (9). Thienyl aminoethyl ketones were found to have some local anesthetic activity by Sinha in working with the compounds of Levy and Nisbet (1938).

Furylethylamine and \( \beta \)-furylethylamine were prepared by Windaus and Dalmer (1920) and Impens found them to cause a transient fall in blood pressure when injected into cats, without notable effect on pulse rate or respiration. On isolated guinea-pig uterus, these compounds caused a marked increase in tone. These same compounds were studied by Fujii (3) who reported furylethylamine to be depressor in cats, but pressor in rabbits; and \( \beta \)-furylethylamine to cause an initial fall, then a rise, then a prolonged
fall of blood pressure in rabbits. Both compounds acted to contract a considerable number of isolated smooth muscle preparations from various species of animals, and this action was considered to be upon the parasympathetic endings in small doses, and upon the muscle itself with large doses. Judging from the effects of approximately lethal doses in mice, Fujii concluded that furylmethylamine acts principally upon the central nervous system as a depressant, while \( \beta \)-furylethylamine acts as a stimulant. Kanao (1927) synthesized a large number of furylalkanolamines, but they were investigated only with respect to their mydriatic action, which was found to be inversely proportional to the number of carbon atoms in the side chain. Levvy and Nisbet (1939) found that several of a series of furyl aminoethyl ketones had some local anesthetic action on the rabbit's cornea, but all proved to be highly irritant.

The present studies were carried out to determine the similarities and differences in certain physiological actions of identical aminoalkyl derivatives of benzene, thiophene and furan. These isopropylamines have both peripheral and central actions and certain of these actions that may be measured with some quantitative precision were studied.

![Chemical structures](image)

**EXPERIMENTAL STUDIES IN ANIMALS**

Phenethyamine and phenisopropylamine (\( \beta \)-phenylisopropylamine) were used in the form of their sulfates, and one or both were used as primary comparison standards when such was needed and possible of use.

The \( \beta \)-2-thienylisopropylamine, in the form of its sulfate, was prepared from the corresponding ketone by Dr. Glenn E. Ulliot, and the SO\( \text{4} \) content analyzed 25.26 and 25.14 per cent, the calculated value being 25.25 per cent. The sulfate of \( \beta \)-2-furylethanolamine was obtained from the amine product of the reduction of the corresponding furynitropropylene by Dr. George H.
Connitt, and the SO₄ content analyzed 27.48 and 27.16 per cent, the calculated value being 27.57 per cent.

**Pressor effects in dogs**

Dogs under anesthesia with ether or sodium pentobarbital were used, and phenethylamine was used as the primary comparison standard, though responses to epinephrine were also usually studied in the same animals. The threshold dose for any considerable pressor activity of the thienyl- and furyl-isopropylamines is the same as for phenethylamine or phenisopropylamine (about $5 \times 10^{-7}$ to $10^{-6}$ mol./kgm. intravenously) and in freshly prepared animals the intensity of the pressor response to $10^{-6}$ mol./kgm. is comparable to that of about $10^{-5}$ mol./kgm. of epinephrine. The duration of pressor effect of the thienyl- and furyl-isopropylamines is comparable to that of phenisopropylamine, and is very much more prolonged than that following injection of phenethylamine. Like phenisopropylamine, the thienyl- and furyl-isopropylamines exhibit marked tachyphylactic effect in serial injections, and fairly precise comparisons of the relative pressor activities of all of these compounds require the use of phenethylamine, or similar substance, as a standard.

As found in earlier work by Alles (1), the intensity of pressor effect of phenisopropylamine is quite comparable to that of phenethylamine, and within the limits of the observational technic, the same is true for thienyl-isopropylamine. The effect of furylisopropylamine, however, is definitely less, the best comparisons indicating this compound to be but about one-third as active as phenethylamine. In some preparations an initial depressor effect of short duration precedes the long-lasting pressor effect of furylisopropylamine, particularly with doses above $10^{-4}$ mol./kgm., and atropine in a dose of $10^{-6}$ mol./kgm. appears to diminish this initial depressor effect. Vagal slowing of the heart at times of maximal pressor response did not appear to be different with the three isopropylamines or phenethylamine. It was not determined whether such vagal effects were due to blood pressure reflexes or due to direct medullary stimulation of the vagus by the compounds.

**Effects on isolated rabbit intestine**

Ileum strips suspended in a medium of 0.9 per cent NaCl, 0.042 per cent KCl, 0.018 per cent CaCl₂, 0.015 per cent NaHCO₃ and 0.10 per cent glucose, at 37°C., were used for study, and effective bath concentrations for particular responses were determined. The effects of phenisopropylamine and of thienylisopropylamine were nearly the same, both being “di-phasic” in that minimally active doses ($5 \times 10^{-4}$ or $10^{-3}$ molal) showed increases in tonus with some decrease in amplitude, while higher doses (2 to $8 \times 10^{-3}$ molal) showed a progressive decrease in tone and abolition of amplitude. Furylisopropylamine differed from the other two compounds in that over the same
dosage range ($5 \times 10^{-4}$ to $10^{-2}$ molal) there was dominantly an increase in

tonus, and while inhibition of amplitude was notable with doses of around

$10^{-3}$ molal, about five to ten times this dose was necessary to abolish ampi-

**Fig. 1. Dogs, Na-pentobarbital. Carotid Arterial Pressure**

A. 16 kgm. 1, $10^{-2}$ mol./kgm. epinephrine. 2, $10^{-3}$ mol./kgm. B-furylisopropyl-
amine. 3, $10^{-4}$ mol./kgm. B-thienylisopropylamine. 4, $10^{-4}$ mol./kgm. phenethyl-
amine.

B. 9 kgm. 1, $10^{-2}$ mol./kgm. epinephrine. 2, $10^{-3}$ mol./kgm. phenethylamine. 3,

$3 \times 10^{-4}$ mol./kgm. B-furylisopropylamine.

**Fig. 2. Isolated Rabbit Ileum**

A. Thienylisopropylamine in the following concentrations: 1, $10^{-3}$ molal.

B. Furylisopropylamine in the following concentrations: 1, $5 \times 10^{-4}$ molal; 2, $10^{-3}$

molal; 3, $2 \times 10^{-3}$ molal; 4, $5 \times 10^{-3}$ molal; 5, $10^{-2}$ molal.

amplitude. On colon strips the effect of all the compounds studied was more
dominantly to increase tone than with ileum strips, as has been noted by

Alles (1b) for the optically isomeric phenisopropylamines.
The increased tonus effect of the phenyl-, thienyl- and furylisopropylamines on isolated ileum or colon strips was found to be antagonized by atropine in approximately equal molal concentration. Concentrations of 2 to $5 \times 10^{-4}$ molal atropine usually caused some decrease in the tonus responses to $10^{-3}$ molal of these isopropylamines, but $10^{-3}$ molal atropine was usually required to effectively abolish the tonus responses. In several experiments it appeared that furylisopropylamine was somewhat more readily antagonized by atropine than were the phenyl- and thienyl-isopropylamines, but the differences were not great (about two-fold).

The effects of epinephrine and acetylcholine on isolated intestinal strips may be diminished or abolished by suitable mol ratio concentrations of phenisopropylamine (see 1b), and with the thienyl- and furyl-isopropylamines this is also true. The antagonism of the relaxing effect of $10^{-6}$ molal epinephrine by 1 to $2 \times 10^{-3}$ molal thienyl-isopropylamine is comparable to the effect of phenisopropylamine in the same concentrations, but furylisopropylamine is less effective, and even $5 \times 10^{-3}$ molal may not abolish the relaxant responses to $10^{-6}$ molal epinephrine. Antagonism of the stimulant effect of $10^{-4}$ molal acetylcholine is marked, though not complete, by 1 to $2 \times 10^{-3}$ molal of phenyl-, thienyl- or furyl-isopropylamine, and there does not appear to be any difference among these compounds in their antagonism to acetylcholine. However, the considerable stimulant effect of furylisopropylamine itself, in all concentrations used, does diminish the conclusiveness of interpretation of its antagonism to acetylcholine.

**Motor effects and lethal toxicity in mice**

Three groups of 10 mice each were injected intraperitoneally with phenyl-, thienyl- or furyl-isopropylamine in a dose of $10^{-4}$ mol./kgm. (about 20 mgm./kgm. of sulfates), and placed in adjacent cages. Phenisopropylamine and thienylisopropylamine caused very similar stimulant effects, but the group injected with phenisopropylamine was active for about 4 hours, as compared with 2 hours with the thienyl compound. Furylisopropylamine showed practically no motor stimulant effect, and caused no deaths, while two out of ten died with both phenisopropylamine and thienylisopropylamine with this dose.

Similar observations with a dose of $2 \times 10^{-4}$ mol./kgm. of the three compounds showed furylisopropylamine to exert a stimulant action for only 15 to 30 minutes. Phenisopropylamine and thienylisopropylamine caused much longer-lasting stimulant effects which were very similar, and some of the animals injected with phenisopropylamine were active after 5 hours, whereas none with thienylisopropylamine was active after $3\frac{1}{2}$ hours. There was one death with phenisopropylamine, but none with furyl- or thienyl-isopropylamine.

Observations made after a dose of $4 \times 10^{-4}$ mol./kgm. showed very similar
stimulant effects from all three compounds. However, most of the effect from the furyl compound had worn off in 2 hours, but with phenisopropylamine six of the group of ten were still active after 5 hours, while none with thiencylisopropylamine was active after 5 hours. There were no deaths with furylisopropylamine, while four out of ten died with both phenisopropylamine and thiencylisopropylamine.

To determine an approximate LD₅₀, the thienyl and furyl compounds were also administered in larger doses. With thiencylisopropylamine, four out of ten died from 6 × 10⁻⁴ mol./kgm., and eight out of ten died from 8 × 10⁻⁴ mol./kgm., the LD₅₀ thus being about 6 × 10⁻⁴ mol./kgm., or 114 mgm./gm. of sulfate. Furylisopropylamine was appreciably less toxic, and its LD₅₀ was found to be about 20 × 10⁻⁴ mol./kgm., or 348 mgm./kgm. of sulfate. Respiratory arrest was the primary cause of death from the furylisopropylamine, as the heart continued to beat for some time after respiration had ceased. Marked intestinal peristalsis was often a noteworthy finding at prompt autopsy, but no macroscopic histologic changes were noted in the organs. With the thiencylisopropylamine, autopsy occasionally showed the lungs to be hemorrhagic, and there was often a finding of considerable gas in the stomach, both findings being common with acute lethal doses of phenisopropylamine.

Although phenyl-, thienyl- and furyl-isopropylamine at the dosage level of 4 × 10⁻⁴ mol./kgm. all showed very similar stimulant effects, there was a striking difference between the three at the level of 10⁻⁴ mol./kgm., with the furyl compound being definitely less active than the other two. The relationship of these doses to the LD₅₀ for the same compounds should, however, be considered, for while 4 × 10⁻⁴ mol./kgm. of phenisopropylamine or thiencylisopropylamine is approximately the LD₅₀ for these two compounds, this dose represents but about one-fifth the LD₅₀ for furylisopropylamine, at which dose the surviving animals were active for 2 to 2.5 hours.

EXPERIMENTAL STUDIES IN MAN

The comparative valuation of the central nervous system effects of compounds in man may well be expected to be quite different than in animals having lesser degrees of integration of the central nervous system. Compounds that exhibit a considerable degree of action upon the cerebral cortex might be expected to act more evidently in man, in whom cortical control exerts a greater dominance, than in the usual laboratory animals. The more complete cooperation of the experimental subject in remaining in a steady state may also be expected to contribute to the precision of such studies.

Observations on circulatory effect and subjective impressions of central effect were carried out with two normally healthy persons who lay supine during the period of observation of blood pressure and pulse rate. The compounds were administered completely dissolved in water, about two hours
# TABLE 1

**Activity after Oral Administration in Man**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mgm.)</th>
<th>Initial B.P./Pulse</th>
<th>Maximum B.P./Pulse</th>
<th>B.P. Return to Normal</th>
<th>G.N.S. Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylisopropyl-amine sulfate</td>
<td>10</td>
<td>114-64/74</td>
<td>130-84/64 (120 min.)</td>
<td>4</td>
<td>Stimulation</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>114-65/72</td>
<td>130-84/64 (120 min.)</td>
<td>4</td>
<td>Stimulation, sleeplessness</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>118-72/68</td>
<td>170-94/52 (100 min.)</td>
<td>&gt;8</td>
<td>Stimulation, sleeplessness</td>
</tr>
<tr>
<td>Thienylisopropyl-amine sulfate</td>
<td>10</td>
<td>114-64/68</td>
<td>122-78/62 (120 min.)</td>
<td>3</td>
<td>No stimulation, no sleeplessness</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>116-68/74</td>
<td>120-70/74 (40 min.)</td>
<td>3</td>
<td>No stimulation, no sleeplessness</td>
</tr>
<tr>
<td>Furylisopropyl-amine sulfate</td>
<td>20</td>
<td>120-70/68</td>
<td>126-75/72 (50 min.)</td>
<td>3</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>122-68/70</td>
<td>114-74/68 (60 min.)</td>
<td>2</td>
<td>No effect</td>
</tr>
<tr>
<td>Phenylisopropyl-amine sulfate</td>
<td>10</td>
<td>126-82/72</td>
<td>131-85/70 (30 min.)</td>
<td>1</td>
<td>No marked stimulation</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>124-74/76</td>
<td>128-82/68 (60 min.)</td>
<td>2</td>
<td>Some stimulation</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>128-72/70</td>
<td>146-60/74 (160 min.)</td>
<td>&gt;5</td>
<td>Stimulation, then depression during maximum B.P. effects</td>
</tr>
<tr>
<td>Thienylisopropyl-amine sulfate</td>
<td>10</td>
<td>116-91/70</td>
<td>120-02/70 (40 min.)</td>
<td>1</td>
<td>No stimulation</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>120-85/70</td>
<td>116-76/72 (180 min.)</td>
<td>&gt;3</td>
<td>No stimulation</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>121-90/74</td>
<td>142-100/78 (100 min.)</td>
<td>4</td>
<td>No stimulation</td>
</tr>
<tr>
<td>Furylisopropyl-amine sulfate</td>
<td>20</td>
<td>124-90/66</td>
<td>114-78/66 (30 min.)</td>
<td>1</td>
<td>Temporary stimulation during maximum rise of B.P. (ca. 1 hr.)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>122-88/70</td>
<td>110-76/80 (140 min.)</td>
<td>&gt;3</td>
<td>No stimulation</td>
</tr>
</tbody>
</table>
after a light morning meal, and lunch was postponed until the end of the observations. Both persons have had considerable experience with administration of phenisopropylamine in various dosages, and their subjective impressions were comparative to this compound. Alertness, talkativeness, feelings of awareness, and anti-sleep effects were considered as the indices of the central stimulant effects.

The data in table 1 indicate the thienyl- and furyl-isopropylamines to be much less active as pressor agents than is phenisopropylamine. Indeed, in the case of G. F., there was a doubtfully significant lowering of blood pressure during the periods following administration of the furyl- or thienyl-compounds. There were no notable central nervous system stimulant effects in G. A. following the thienyl or furyl compounds. In G. F., whose circulatory stability is not great, a slight effect from 20 mgm. of the furyl compound did appear to result in the trial reported, though no effect was apparent following 50 mgm. of the same compound, or after 20 mgm. when sitting up during the observational period. It is clear from these observations that neither thienyl- nor furyl-isopropylamine are at all closely comparable to phenisopropylamine in their circulatory or central effects in man.

To confirm subjective observations as to the relative lack of central nervous system effect of the thienyl- and furyl-isopropylamines, observations were
made with regard to the effect of these substances and of phenisopropylamine upon patellar reflex (knee-jerk) activity, and also upon voluntary muscular fatigue of the middle finger of the hand, as measured upon an ergograph. The studies of Reid (8) on the mechanism of voluntary muscle fatigue appear to establish the cause of such fatigue to be a depression of central nervous system mechanisms. For the present studies, records of knee-jerk activity and rate of voluntary fatigue of the middle finger of the hand were made at fifteen-minute intervals for a two-hour initial control period, then for two hours following the compound to be tested, and then for two hours following the administration of phenisopropylamine sulfate in an amount which had previously been established as an effective dosage of this compound.

Knee-jerk activity records on both experimental persons showed no changes following the administration of as much as 20 mgm. of thienylisopropylamine sulfate, or of as much as 50 mgm. of furylisopropylamine sulfate. In contrast to this, an increase in knee-jerk activity was commonly observed following 20 mgm. phenisopropylamine sulfate.

As shown in figure 3 for G. A., no definite effects of 20 mgm. thienylisopropylamine sulfate or of 50 mgm. furylisopropylamine sulfate upon ergographic work production were observed, though a following administration of but 10 mgm. of phenisopropylamine sulfate caused a marked increase in ergographic work output after about 30 minutes, and the effect lasted more than 2 hours. Similar observations were made with G. F., and there can be no doubt that the thionyl- and furyl-isopropylamines are relatively ineffective central nervous system stimulants with respect to voluntary muscle fatigue phenomena.

DISCUSSION

If we use pressor activity following intravenous injection in anesthetized dogs as the criterion for relative physiological activity, phenisopropylamine and thienylisopropylamine are very comparable, or possibly identical, as was stated for the relationship between phenethyamine and thienylethylamine by Gunn. Furylisopropylamine, however, is less active as a pressor agent than the other two isopropylamines, and its initial depressor effect that can be diminished by atropine suggests that it also has a parasympathetic type of activity, and this type of activity is very notable when the compound is studied with respect to its actions upon isolated intestine.

Upon isolated rabbit ileum and colon, all three isopropylamines in proper concentrations cause contraction effects which may be considered to be a parasympathetic stimulant type of activity, particularly because the response may be abolished by pretreatment with a proper mol ratio of atropine. This type of activity is most notable with furylisopropylamine, and this compound differs quite considerably from thienyl- or phenyl-isopropylamines in respect to its action upon isolated intestine. As with phenisopropylamine or its optical isomers (1b), the mechanism of action of furylisopropylamine is not
clear because it also exhibits antagonism to the relaxant effects of epinephrine or the stimulant effects of acetylcholine in about the same dosage range in which it appears to exert a direct parasympathetic stimulant effect.

The most noteworthy aspect of the physiological activities of phenisopropylamine is its notable stimulation of functional parts of the central nervous system in man with doses that exert a relatively slight action upon the circulation or upon the intestinal musculature. Several attempts have been made to establish experimental technics with laboratory animals that would be analogous to effects in man and serve to value quantitatively such activities of phenisopropylamine and related compounds. A most extensive study of this kind is that of Schulte, Reif, Baeher, Lawrence and Tainter (9) who mechanically recorded the motor activity of rats following subcutaneous injection of some seventy-five compounds. Among these compounds, phenethylamine and thienylethylamine (thiophenethylamine) were reported upon, and from the data it would appear that although thienyl in any dosage did not cause as much motor effect as did phenethylamine, the threshold dose of the thienyl compound was only one-eighth that of the phenyl compound. A greater and longer-lasting effect was obtained with thienylethylamine with but one-quarter the optimum dose of phenethylamine, and in terms of a calculated therapeutic margin (fatal dose/threshold dose), thienylethylamine was found to be about sixteen times as effective as a central stimulant agent.

Our own observations with small animals were carried out in a manner similar to that used by Gunn and Gurd (5), using mice and making simultaneous visual observations of the motor activity effects of the control and studied compounds. Satisfactory precision of observation is obtained under such conditions, but no great difference was observed between the intensity of the effects of the phenyl- and thienyl-isopropylamines, although the duration of action of the thienyl compound was definitely less prolonged. Also, contrary to the relationship reported by Schulte et al., the calculation of therapeutic margins for the phenyl- and thienyl-isopropylamines would show them to be nearly the same.

In any case, since the central stimulant effects in mice or rats can only be noted with dosages that closely approach the lethal range, such animal experiments can only doubtfully be translated to indicate probable central effects in man, and the direct experiments in man are of special interest. In these direct experiments, it became apparent that there are very considerable differences in the central nervous system effects of phenyl-, thienyl- and furyl-isopropylamines. It may be that a further increase in the amounts administered of the thienyl- and furyl-isopropylamines would establish some detectable central stimulant or depressant effects of these compounds, but the observations were sufficiently extended to conclude with certainty that these compounds are considerably less active agents than phenisopropylamine on the central nervous system of man when using the reported methods of observation.
SUMMARY

1. In dogs under ether or pentobarbital anesthesia, phenyl- and thienyl-isopropylamines injected intravenously induce pressor effects very closely similar as to intensity and duration. About three times as much furyl-isopropylamine is required to produce an equally intense pressor response, and a preceding depressor effect, which can be antagonized by a proper mol ratio of atropine, may occur.

2. On isolated rabbit intestinal strips, these three isopropylamines in minimally active concentrations induce an increase in tone that may be prevented by pretreatment with equal molal concentrations of atropine. With greater concentrations, all three compounds act to decrease tone, but the range of dosage in which furyl-isopropylamine acts only to increase tone is much greater than for phenyl- or thienyl-isopropylamine.

3. Phenyl- and thienyl-isopropylamines injected intraperitoneally into mice in nearly lethal dosages are more active motor stimulants than furyl-isopropylamine, and the thienyl compound has a shorter duration of action than phenisopropylamine.

4. Thienylisopropylamine injected intraperitoneally into mice is slightly less toxic than the phenyl compound, and furyl-isopropylamine is but about one-fourth as toxic as the other two compounds.

5. Orally administered to man, phenisopropylamine is very considerably more active as a circulatory stimulant and as a central nervous system stimulant, though these two activities appear unrelated.

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