Induction of Increased Benzpyrene Hydroxylase Activity by 2-Phenylbenzothiazoles and Related Compounds

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SUMMARY

A study of the relationships between structure of 2-phenylbenzothiazoles and related compounds and their capacity to induce increased benzpyrene hydroxylase activity in the liver and lung of the rat has been carried out. Thirty-three compounds have been studied. It has been found that introduction of an appropriate halogen into the 4'-phenyl position approximately doubles inducing activity compared to unsubstituted 2-phenylbenzothiazole. Other substitutions and modifications of the molecule result in either lesser increases in inducing activity or, in some instances, reduction or total loss of inducing activity. Most compounds show similar inducing effects on both lung and liver. Some, however, do not. Of the more potent inducers, the compound showing this selective effect to the greatest degree is 2-(4'-cyanophenyl)-benzothiazole, which has more than double the inducing effect on lung as on liver.

INTRODUCTION

Benzpyrene hydroxylase is one of a group of closely related microsomal enzyme systems which have the capacity to metabolize foreign compounds (6). One of the characteristics of these enzyme systems is that an increase in their activities can be induced by administration of an appropriate organic compound (4—6, 10, 24, 27). Several groups of compounds have been found to be inducers of increased benzpyrene hydroxylase activity, including polycyclic hydrocarbons, phenothiazines, symmetrically substituted five-membered heterocyclics such as 2,5-bis(4-pyridyl)-1,3,4-thiadiazole and flavones (6, 10, 27, 28—30,32). However, there is a paucity of information on the relationship between the structure of a compound and its capacity to act as an inducer of increased benzpyrene hydroxylase activity. In the present paper, studies of the inducing capacity of a number of 2-phenylbenzothiazoles and related compounds will be presented. 2-Phenylbenzothiazole is an interesting compound for studies of structure-activity-relationships since it can be subjected to several types of structural modifications. Substitutions can be made onto the molecule, alterations can be made in either of the two ring structures, and in addition, the linkage between the two rings can be modified. In the present study the effects of all of these modifications on the capacity of the resultant compound to induce increased benzpyrene hydroxylase has been determined.

MATERIALS AND METHODS

For testing inducer activity, 0.1 mmole of the compound under investigation was dissolved in 1 ml of dimethylsulfoxide (DMSO) and administered by rubber catheter into the stomach of 48-day-old female rats. The animals were sacrificed 48 hours later by cervical fracture and the liver and lungs removed. The amount of DMSO employed in these experiments does not have a demonstrable effect on benzpyrene hydroxylase activity (32). Female Sprague-Dawley rats obtained from the Simonsen Laboratories, Minneapolis, having an average weight of 175 were used throughout. The procedure for determining benzpyrene hydroxylase activity has been described in detail (32). One unit of benzpyrene hydroxylase activity is equivalent to the formation of 100 μg of 8-hydroxy benzpyrene/min.

Four of the compounds employed were obtained commercially. 2-Phenylbenzothiazole from Eastman was recrystallized from ethanol to give material melting at 113.5—115°C. Benzothiazole was purchased from Eastman and redistilled (b.p. 116°C at 12 mm). 2-Mercaptobenzothiazole (m.p. 181—182.5°C and 2-phenylbenzimidazole (m.p. 296.5—297.5°C) were obtained from Aldrich and purified by recrystallization from ethanol.

The remaining twenty-nine compounds were synthesized. Their properties and syntheses are summarized in Table 1. Use was made of published procedures and of methods which may be described as follows:

Method A. The procedure by which Kiprianov and Schrubbich (17) reacted acyl chlorides with o-aminothiophenol in benzene solution was modified by the addition of one equivalent of pyridine to serve as acid acceptor.

Method B. The reaction of aromatic aldehydes with o-aminothiophenol followed the procedure of Kankela and Sharnoff (16).

Method C. The 2-(4'-Methoxyphenyl)-benzothiazole (0.0415 mole) prepared by Method A was dissolved in 100 gm of 32% HBr in glacial acetic acid and heated under reflux for 72 hours. After cooling and dilution with two volumes of water, the reaction solution was extracted with ether. The ether extract was washed well with water before undergoing...
<table>
<thead>
<tr>
<th>Compound name</th>
<th>New or Ref.</th>
<th>M.P.(^a) uncorrected (°C)</th>
<th>Elemental Analysis(^b) observed/calculated</th>
<th>Purified yield (%)</th>
<th>Synthetic method or Ref. used</th>
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<td>2-(2'-Bromophenyl)-benzothiazole</td>
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<td>2-(3'-Bromophenyl)-benzothiazole</td>
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<td>C</td>
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<td>2-(4'-Methoxybenzothiazole)</td>
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<td>5-Chloro-2-phenylbenzothiazole</td>
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<td>G</td>
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<td>2,2'-Thiobisbenzothiazole</td>
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<td>C: 56.25, H: 2.90, N: 9.39</td>
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<td>(8)</td>
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<td>2,2'-Dithiobisbenzothiazole</td>
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<td>180.5–181.5</td>
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<td>(26)</td>
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<tr>
<td>2-Benzylthiobenzothiazole</td>
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<td>39.5–40.5</td>
<td>C: 73</td>
<td>73</td>
<td>(20)</td>
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<tr>
<td>2-Benzoylthiobenzothiazole</td>
<td>(22)</td>
<td>125–126</td>
<td>C: 47</td>
<td>47</td>
<td>(22)</td>
</tr>
<tr>
<td>2-Phenoxybenzothiazole</td>
<td>(14)</td>
<td>52–53</td>
<td>C: 42</td>
<td>42</td>
<td>(14)</td>
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<tr>
<td>2-Benzyloxynbenzothiazole</td>
<td>(11)</td>
<td>63–64.5</td>
<td>C: 40</td>
<td>40</td>
<td>(11)</td>
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three extractions with dilute sodium hydroxide solution. Acidification of the combined basic extract solution yielded crystalline product which was purified by recrystallization twice from ethanol.

**Method D.** 2-(4'-Aminophenyl)-6-methylbenzothiazole (from Aldrich Chemical co.) was treated by the diazotization and hypophosphorous acid reduction procedure of Kornblum (19).

**Method E.** Alkylation of benzylamine with 2-chlorobenzothiazole followed the procedure of Johnson and Hamilton (15), wherein 2-chloro-5-methylsulfonylbenzothiazole was employed.

**Method F.** 2-Aminobenzothiazole (0.133 mole) in a solution of 50 ml of benzene and 25 ml of pyridine was treated with a solution of p-toluenesulfonyl chloride (0.14 mole) in 100 ml of benzene. The reaction solution was heated under reflux for one hour. The product separated on cooling and was purified by being washed with water and recrystallized twice from dimethylformamide.

**Method G.** The procedure of Bogert and Stull (3) employing oxalyl chloride was modified by the use of toluene as solvent and free o-aminophenol in place of its zinc salt.

**Method H.** The Grignard reaction was carried out by the addition of a slurry of 0.0517 mole 2-(4'-bromophenyl)-benzothiazole (Method A) and 0.0517 mole methyl iodide in 350 ml of ether to 0.1034 atom magnesium turnings. Stirring and heating were continued for 2.5 hours after the addition. The Grignard solution was poured through glass wool onto 150 gm of powdered dry ice and stirred until room temperature was attained. Dilute HCl solution was added with stirring. The ether layer was separated, and the product was extracted from the ether into a dilute sodium carbonate solution. Acidification gave crude product which was purified by three recrystallizations from ethanol. The starting bromo compound was recovered in 80% yield.

**Method I.** A solution of 0.2 mole terephthalaldehyde in 130 ml of dimethylformamide was heated to 80°C and treated with a solution of 0.1 mole o-aminophenol in 50 ml of dimethylformamide. The reaction solution was stirred and heated at 110°C for 24 hours. After cooling, the solution was poured into 500 ml of ice water. An oily solid separated out. The water layer was decanted, and the semisolid was dissolved in ethanol. Concentrated sodium bisulfite solution was added to the ethanolic solution. The precipitated bisulfite addition compound was collected, slurried in water to remove the more soluble terephthalaldehyde double bisulfite addition compound, and collected again. It was washed with ethanol and then ether. Treatment with dilute sodium hydroxide solution regenerated the product which was extracted immediately into ether. Evaporation of the ether and recrystallization from ethanol gave pure product.

### RESULTS

In Table 2 the inducing activity of the compounds studied is presented. It will be noted that introduction of a bromo, chloro, or iodo substitution into the 4' position of 2-phenylbenzothiazole results in compounds with a pronounced increase in inducing capacity. In contrast, halogen substitutions into the 2' or 3' positions result in either considerably lesser increases in inducing activity or in some cases, decreases. Substitutions into both the 2' and 4' positions, as in the case of 2-(2',4'-dichlorophenyl)-benzothiazole, results in an inducing activity comparable to the less effective 2'-chloro compound rather than to the 4'-chloro derivative. The 4'-fluoro substitution, unlike the effect of other halogens, results in less inducing activity than the unsubstituted molecule. The 4'-amino substitution produces very little effect. Introduction of a hydroxy, carboxy, or formyl group into the 4' position results in almost complete destruction of inducing capacity. Conversion of the 4'-hydroxy derivative to the 4'-methoxy compound results in some restoration of activity. The 4'-cyano compound is quite distinctive in that the inducing capacity for pulmonary tissue is greater than twice that for liver.

In the lower portion of Table 2, a number of compounds are listed in which different linkages between the benzothiazole and phenyl moieties are present. These show varying degrees of reduction of inducing activity compared with 2-phenylbenzothiazole. Likewise, several compounds have been studied in which a different structure has been substituted for either the benzothiazole or phenyl component, as in the case of 2-mercaptopbenzothiazole and 2-phenylbenzimidazole. These compounds also show lesser degrees of inducing capacity than does 2-phenylbenzothiazole. The structural formula of 2-phenylbenzothiazole is shown in Chart 1.

<table>
<thead>
<tr>
<th>Compound name</th>
<th>New Ref.</th>
<th>M.P.°C</th>
<th>Elemental analysis</th>
<th>Purified yield (%)</th>
<th>Synthetic method or Ref. used</th>
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<tr>
<td>2-Benzamidobenzothiazole</td>
<td>(13)</td>
<td>187-188</td>
<td>C: 55.38</td>
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<td>2-Benzylaminobenzothiazole</td>
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<td>H: 4.06</td>
<td>76</td>
<td>E</td>
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<td>2-p-Toluenesulfonamidobenzothiazole</td>
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<td>2-(4'-Pyridyl)-benzothiazole</td>
<td>(33)</td>
<td>133-134</td>
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</table>
Table 2

<table>
<thead>
<tr>
<th>Compound tested</th>
<th>Liver (units/mg wet weight)</th>
<th>Lung (units/mg wet weight)</th>
<th>Liver (Ratio: test/control)</th>
<th>Lung (Ratio: test/control)</th>
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<td>Controls</td>
<td>13 ± 4</td>
<td>0.88 ± 0.24</td>
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<tr>
<td>2-Phenylbenzothiazole</td>
<td>46 ± 8</td>
<td>3.40 ± 0.61</td>
<td>3.5</td>
<td>3.9</td>
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<tr>
<td>2-(2’-Bromophenyl)-benzothiazole</td>
<td>54 ± 7</td>
<td>4.42 ± 0.54</td>
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<td>5.0</td>
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<td>2-(3’-Bromophenyl)-benzothiazole</td>
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<td>2.07 ± 0.31</td>
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<td>2-(4’-Bromophenyl)-benzothiazole</td>
<td>104 ± 3</td>
<td>6.46 ± 0.34</td>
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<td>2-(2’-Chlorophenyl)-benzothiazole</td>
<td>38 ± 4</td>
<td>3.74 ± 0.85</td>
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<td>2-(3’-Chlorophenyl)-benzothiazole</td>
<td>32 ± 5</td>
<td>1.70 ± 0.27</td>
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<tr>
<td>2-(4’-Chlorophenyl)-benzothiazole</td>
<td>100 ± 8</td>
<td>5.65 ± 1.53</td>
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<td>6.4</td>
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<td>2-(3’-Iodophenyl)-benzothiazole</td>
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<td>4.08 ± 0.71</td>
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<td>0.78 ± 0.17</td>
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<td>2-Benzoxy benzothiazole</td>
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<tr>
<td>2-Benzamidobenzothiazole</td>
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<td>2.38 ± 0.37</td>
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<td>2-Benzylaminobenzothiazole</td>
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<td>1.5</td>
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<td>2-p-Toluenesulfonamidobenzothiazole</td>
<td>16 ± 0</td>
<td>0.92 ± 0.17</td>
<td>1.2</td>
<td>1.0</td>
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<td>2-(4’-Pyridyl)-benzothiazole</td>
<td>33 ± 5</td>
<td>2.14 ± 0.53</td>
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<tr>
<td>2-Phenylbenzimidazole</td>
<td>15 ± 2</td>
<td>1.40 ± 0.24</td>
<td>1.2</td>
<td>1.6</td>
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Effects of 2-phenylbenzothiazoles and related compounds on benzpyrene hydroxylase activity of rat liver and lung.

DISCUSSION

There is a paucity of information available on the relationship between structure of a compound and its capacity to act as an inducer of increased activity of one or more microsomal enzyme systems metabolizing carcinogens, drugs, or other foreign compounds. The results obtained with the phenylbenzothiazoles and related compounds provide some data relevant to structure-activity relationships.

The only substituitions which cause a pronounced increase in inducing activity are certain halogen substitutions into the 4’-phenyl position, i.e., chloro, bromo, and iodo, but not fluoro. All other substitutions have either smaller effects or, in some instances, as with several oxygen containing substituents, actually result in marked or total loss of inducing capacity. The effects of various substitutions into the 4’ position of 2-phenylbenzothiazole are in general agreement with those found for comparable substitutions into the 4’ position of flavone (32). In compounds related to 2-phenylbenzothiazole in which different structures have been substituted for either the phenyl or benzothiazole moieties or where the linkage between the two, has been altered, lesser degrees of induction have been found than with phenylbenzothiazole.

It should be pointed out that in the present work no attempt has been made to determine the mechanism by which the increase in benzpyrene hydroxylase activity is brought about.
The term induction has been used in its broad definition which
is the “process of causing to occur.” While experimental work
reported by others using polycyclic hydrocarbon inducers has
indicated that new enzyme protein formation does occur, it is
c conceivable that compounds with differing chemical struc-
tures might bring about an increase in benzpyrene hydroxylase
activity by different mechanisms (6, 10).

From the data which have been obtained with the 2-phenyl-
benzothiazoles, it can be seen that several of these compounds
cause a greater induction of increased benzpyrene hydroxylase
activity in the lung than in the liver. The compound showing
this effect to the greatest degree is 2(4'-cyanophenyl)-
benzothiazole, which has more than twice the inducing effect
on lung as on liver. The liver is generally thought to be a
highly responsive organ to inducers and is used as a standard
for studying induction of increased activity of microsomal
enzyme systems metabolizing foreign compounds. In fact, in
the vast majority of studies of this type reported in the litera-
ture, the liver has been the only organ investigated. However,
in a previous study it was found that 2-methylmercaptop-10-(2-
(N-methyl-2-piperidyl)ethyl)phenothiazine HC1 (thioridazine
was the liver alone. An additional implication of these findings is
that compounds to act as an inducer, total reliance cannot be placed on
the order of magnitude being twofold (28). The occurrence of
inducers with preferential effects on tissues other than liver
indicates that, for a full evaluation of the capacity of a com-
 pound to act as an inducer, total reliance cannot be placed on
the liver alone. An additional implication of these findings is
that they point to the possibility that even more highly selec-
tive induction in specific tissues may be possible to achieve.
This has some potential significance in that the liver has such a
complexity of reactions that induction of increased micro-
somal activity in this tissue may result in undesirable side re-
actions not found in other tissues. Thus, if one wishes to increase
specifically a detoxification reaction in a portal of entry such as
the lung or gastrointestinal tract, an inducer having minimal
or no effect on the liver might prevent complications or un-
desirable effects which would occur if a great increase in liver
microsomal enzyme activity were produced. The present
studies offer encouragement for the possibility that an induc-
ing effect with selectivity directed towards tissues other than
liver might be obtainable.

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