The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons

I. Compounds Related to Chrysene*†

Charles E. Dunlap, M. D., and Shields Warren, M. D.

(From the Cancer Commission of Harvard University and the Department of Pathology, Harvard Medical School, Boston, Mass.)

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The chrysene molecule contains the phenanthrene nucleus as do the natural steroids and the well known carcinogenic agents, methylcholanthrene, dibenzanthracene, and benzyrene. However, the benzanthracene ring structure common to the carcinogenic agents is lacking in chrysene and also in the natural steroids. Chrysene is not estrogenic (2) but it is related structurally to the natural steroid hormones, and its structure invites comparison with that of diethylstilbestrol also (3, 4). If these structural relationships should find a counterpart in the biological activity of chrysene derivatives it would seem wise to test carefully the carcinogenic properties of such substances before their possible introduction into medicine or industry.

Chrysene itself has been thoroughly tested by over a dozen investigators (8, 14) and has been found almost if not entirely devoid of carcinogenic action. Pollia (13) has examined a number of commercially useful chrysene derivatives with negative results. Other derivatives that have been tested have proved carcinogenically inactive (8, 14) with two exceptions; Shear (14) obtained a single tumor in a group of 20 mice injected with 6-methylchrysene and Hewett (9) demonstrated considerable activity in 5,6-dimethylchrysene (1,2-dimethylchrysene according to the British system of numbering) by skin-painting experiments. The results obtained on injecting the latter compound subcutaneously are reported in the present paper.

A number of alkyl and alkyylene derivatives of chrysene have been synthesized in recent years, including 4-methylchrysene (6), 5-methylchrysene (11, 7), 4,5-methylenechrysene (5), 4,5-dimethylchrysene (12) and 5,6-dimethylchrysene (11, 9). The ultraviolet absorption spectra have been reported by Jones (10) and by Brode and Patterson (1). We were fortunate in obtaining samples of these compounds for carcinogenic tests from Dr. Louis F. Fieser, some of them prepared in his laboratory and others synthesized by Dr. Melvin S. Newman at Ohio State University.

Carcinogenic tests were carried out according to a standardized technic on male mice 2 to 3 months old of the Swiss and C3H strains, which were obtained from the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. The mice were fed on a diet of Purina dog chow and water supplemented with cod liver oil. The compounds were dissolved in tricaprylin and 0.2 cc. of the solution, containing 1 to 4 mgm. of the compound, was injected in a single dose under the skin of the rump. The mice were then examined weekly for tumors. The date of appearance of a tumor was taken as the day on which an easily palpable nodule appeared at the site of the injection, provided the nodule showed progressive growth thereafter and proved to be a sarcoma on subsequent histological examination. Transplants were attempted from tumors arising in mice injected with four of the five compounds and were successful in all cases.

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† The compounds used in these experiments were selected and synthesized in part by Professor L. F. Fieser and his associates, of the Department of Chemistry, Harvard University, and in part by Dr. Melvin S. Newman, of Ohio State University.
The results of the carcinogenic tests are presented in Table I. It is apparent that each of the compounds has yielded one or more sarcomas at the site of injection but that only 5-methylchrysene has shown a high degree of activity. The speed of tumor induction by this compound shows its activity to lie intermediate between that of 20-methylcholanthrene and 1,2,5,6-dibenzanthracene as tested by the same technic.

The occurrence of only a single tumor at the site of injection in a group of test mice is doubtful evidence of the carcinogenic activity of a compound. Tumors occurring at a distance from the site of injection may have some significance but it is difficult to evaluate. Therefore, our results have given evi-

<table>
<thead>
<tr>
<th>Compound</th>
<th>Date of injection</th>
<th>Number of mice</th>
<th>Strain</th>
<th>Dose, mg.</th>
<th>Effective total</th>
<th>Tumors at site of injection</th>
<th>Induction time of earliest tumor, days</th>
<th>Average time, days</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Methylchrysene</td>
<td>Sept. 19, 1939</td>
<td>5</td>
<td>C3H4</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Jan. 14, 1941</td>
<td>20</td>
<td>C3H4</td>
<td>2</td>
<td>1</td>
<td>17</td>
<td>170</td>
<td>170</td>
<td>+</td>
</tr>
<tr>
<td>5-Methylchrysene</td>
<td>Jan. 9, 1940</td>
<td>20</td>
<td>Swiss</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>(Newman)</td>
<td>Jan. 7, 1941</td>
<td>10</td>
<td>C3H4</td>
<td>3</td>
<td>7</td>
<td>94</td>
<td>114</td>
<td>136</td>
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<tr>
<td>4,5-Methylenechrysene</td>
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<td>C3H4</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>79</td>
<td>125</td>
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<td>4,5-Dimethylchrysene</td>
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<td>20</td>
<td>Swiss</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>4</td>
</tr>
<tr>
<td>(Newman)</td>
<td>Apr. 22, 1940</td>
<td>15</td>
<td>Swiss</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>571</td>
<td>571</td>
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<tr>
<td>5,6-Dimethylchrysene</td>
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<td>C3H4</td>
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<td>6</td>
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<td>---</td>
<td>2</td>
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<tr>
<td>(Newman)</td>
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<td>C3H4</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>155</td>
<td>163</td>
<td>+</td>
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</tbody>
</table>

* The "Effective total" is the number of mice alive at the time the first tumor appeared.

In those groups in which no tumors appeared, the number of mice alive 6 months after injection is used.

† Previously tested by Hewett (9) and found active.

dence of only weak or questionable activity in the case of 4-methylchrysene and 4,5-dimethylchrysene. The other compounds may safely be considered carcinogenic for mice.

SUMMARY

Tests of the carcinogenic action of five derivatives of chrysene are reported. 5-Methylchrysene showed a high degree of activity; 4,5-methylenechrysene and 5,6-dimethylchrysene were moderately active, and 4-methylchrysene and 4,5-dimethylchrysene weakly or questionably so.

REFERENCES


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