METABOLISM OF THIOSTERS OF CARCINOGENIC HYDROCARBONS

Part I. Metabolism of Dibenzothiophene

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Received October 8, 1960

Ever since the realisation that a chemical entity, 1 : 2 : 5 : 6-dibenzanthracene, produces cancer, the compound and its structural analogues are being extensively studied for their chemical and physical properties, carcinogenic activity and metabolism with a view to elucidating the mechanism of carcinogenesis by hydrocarbons. Accumulated evidence of such studies led to the suggestion that presence of an "activated phenanthrene bridge" (9 : 10-positions in phenanthrene which are also referred to as the 'K-region') in polycyclic hydrocarbons was the preponderent cause, if not the only one of their carcinogenic activity. In order to examine the validity of the above suggestion, Robinson put forward an idea of synthesising certain thiophene isosters (thiosters) of carcinogenic hydrocarbons in which the phenanthrene bridge or bridges have been replaced by an isosteric thiophene nucleus as illustrated by compound (I), the thioster of the highly carcinogenic hydrocarbon, 9 : 10-dimethyl-1 : 2-benzanthracene.

Since then, thiosters of carcinogenic hydrocarbons, compound (I) and several others such as (II), (III) and (IV) have been synthesised by one of us. Compounds (I) and (II) have been found to be non-carcinogenic by subcutaneous injection in mice, but when painted on the skin the former compound has been found to possess a weak carcinogenic activity. Compound (III) is a strong carcinogen even more potent than its hydrocarbon analogue. Compound (IV) is also carcinogenic. The behaviour of the compounds (III) and (IV) indicated that they were apparent exceptions to the activated phenanthrene bridge hypothesis.

A careful analysis of the available data on the carcinogenicity of hydrocarbons and their thiosters suggested that as regards carcinogenicity there
may not exist direct interrelationship between hydrocarbons and their corresponding thiosters. It seemed likely that the sulphur atom in the condensed thiophene has its own characteristic reactivity towards a biological substrate. Although a di-univalent sulphur in a heterocyclic aromatic system is electronically equivalent to a conjugated double bond in aromatics, nevertheless the sulphur atom might impart a distinctive chemical reactivity to the molecule. Thus, the sulphur atom may undergo oxidation to a sulphoxide or sulphone grouping and/or it may induce facile substitution in rest of the molecule. In order to find out whether the sulphur atom in condensed thiophenes is involved in metabolism or not, metabolic studies of certain condensed thiophenes were deemed essential. Among the condensed thiophenes, thionaphthene alone has been studied for its metabolism in rabbits and a thionaphthene-alpha-glucuronic acid of undetermined constitution has been reported to have been isolated from their urine. The present paper deals with the metabolism of dibenzothiophene (V) (referred to hereafter as DBT) in rats. DBT was selected for the preliminary study of the metabolism of thiosters since most of the thiosters that have been tested for carcinogenicity contain DBT as a structural unit.

DBT was incorporated in diet and fed to male rats of Wistar strain. The animals were kept in metabolic cages equipped with an arrangement for collection of urine. Pooled samples of urine were acidified to congo-red (pH 3–5), hydrolysed and extracted with ether. The ethereal extract was shaken with sodium hydroxide solution and the alkaline solution, on acidifi-