centage density increases resulting from a 5°K temperature rise over a 10-km layer. The computations have been made by Kyle by adding 0.5°K/km to the temperature gradients of the Jastrow-Kyle model atmosphere in the three representative layers, 90 to 100 km, 100 to 110 km, and 110 to 120 km.

A first analysis of the density data inferred from the satellite measurements is consistent with the expected 5 to 8 percent density increases at 355 and 660 km during the major meteor showers. However, more accurate data on orbital decelerations will be required to confirm this hypothesis.

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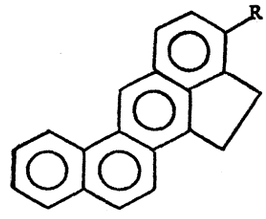
23 June 1961

Polynuclear Aromatic Hydrocarbons, Steroids and Carcinogenesis

Abstract. In addition to the electronic factors, there is a steric factor responsible for the carcinogenicity of polynuclear aromatic hydrocarbons. A carcinogenic polynuclear aromatic hydrocarbon must bear steric resemblance to steroids. One possible implication to this requirement for carcinogenicity is that these hydrocarbons may act on the same sites as steroid hormones.

Numerous attempts have been made to correlate the carcinogenicity of polynuclear aromatic hydrocarbons and their structures by molecular orbital calculations (*1*), fluorescence spectra (*2*), absorption spectra (*3*), chemical reactivities (*4*), and abilities in molecular complex formation (*5*). All these approaches were based primarily on the electronic structure of the polynuclear aromatic hydrocarbons, and generally the carcinogenic hydrocarbons must possess low electronic excitation barriers. However, the overall results of these correlations are not satisfactory to account for the relative carcinogenicity of various alkylated polynuclear aromatic hydrocarbons (*6*). The carcinogenicity of these compounds was found to be dependent on the size of the alkyl substituents as well as on the position of the substituent. Usually carcinogenicity decreases as the size of the alkyl substituent increases, for example, the higher homologs of 3-alkylcholanthrenes (I) (*2*)

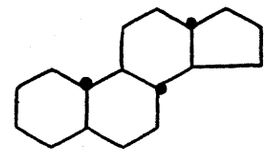


I

and 8-alkylbenzanthracenes (*7*) are less carcinogenic than the corresponding methyl derivatives. There seems to be no definite rule governing the relative carcinogenicity of these hydrocarbons with respect to the position of the alkyl group; for example, among the methylbenzanthracenes, 7-methylbenzanthracene is strongly carcinogenic, 8-methyl followed by 12-methyl derivative is quite carcinogenic, whereas other methyl derivatives are about as ineffective as the parent compound (*8*). The increase in carcinogenicity of 7- and 12-methylbenzanthracene may be interpreted by an increase in electronic effect due to the introduction of a methyl group into the meso positions (*9*), but the carcinogenicity of the 8-methyl derivative cannot be accounted for. It is well known that the electronic effect of a methyl group substituted in an aromatic or unsaturated system is very similar to that of an ethyl group, while the latter is virtually indistinguishable from its higher homologs (*10*). Since all previous correlations were based on the electronic properties of the hydrocarbons, it is not surprising that these attempts failed in the case of alkylated polynuclear aromatic hydrocarbons.

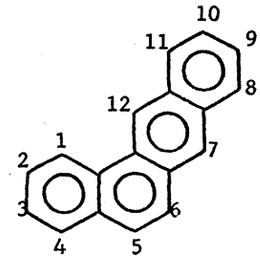
Most carcinogenic polynuclear aromatic hydrocarbons contain four to five condensed aromatic nuclei, and their structural similarity to steroids has been noted (*6*). Steroids may be converted under drastic conditions to a number of polynuclear aromatic hydrocarbons, among which are the noncarcinogenic Diel's hydrocarbon and the highly carcinogenic 3-methylcholanthrene. Numerous efforts to effect such a conversion in vivo have been unsuccessful.

By careful examination of the Stuart-Briegleb melocular model (*11*) of various carcinogenic hydrocarbons and steroids, we observed a remarkable resemblance between these two classes of compounds. There is usually a direct increase in carcinogenicity as the hydrocarbons become sterically more similar to steroids. Some of these results are illustrated in Figs. 1–4. In Fig. 1 the molecular model of norandrostane (II)



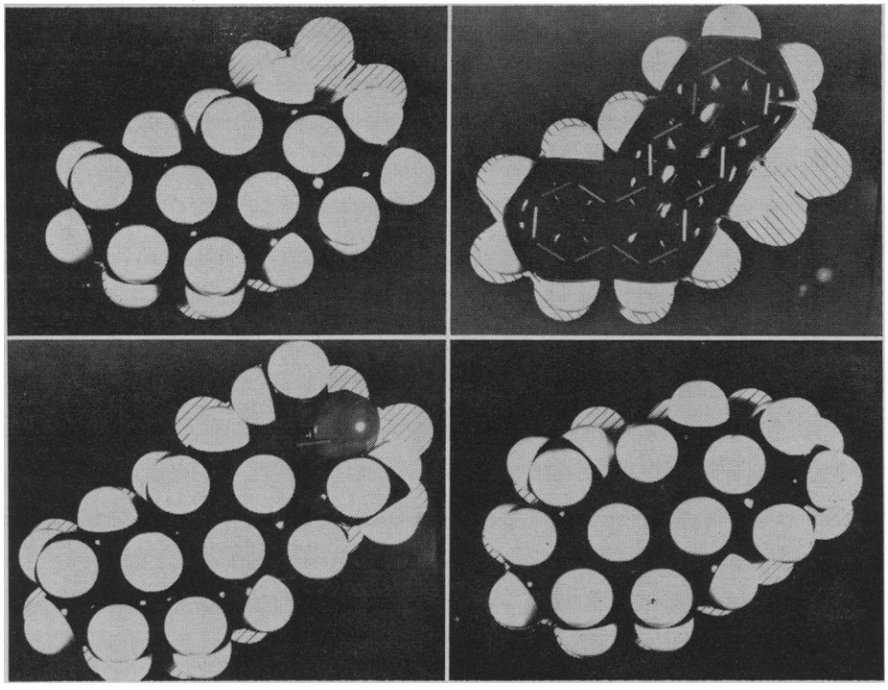
II

is compared with that of benzanthracene (III);

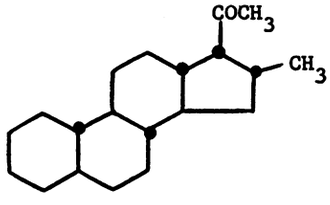


III

there is a discrepancy near the top of the molecule which may be easily compensated if the 17 position of norandrostane is substituted by a hydroxyl or an acetyl group as in most steroid hormones. In Fig. 2, the molecular model of benzanthracene is compared with that of norandrostane; there is a discrepancy at the positions equivalent to C_{15} and C_{16} of steroids. Introduction of a methyl group to either 7 or 8 position of benzanthracene will decrease this discrepancy. 7,8-Dimethylbenzanthracene and cholanthrene, which have the same molecular dimension as that of steroids, are among the most potent carcinogens known. 7- or 8-Methylbenzanthracene, which is sterically more similar to steroids than the parent hydrocarbon, is also much more carcinogenic. The introduction of higher alkyl groups into benzanthracene or cholanthrene will cause the molecule to deviate sterically from steroids; therefore, the higher alkylated hydrocarbons are less carcinogenic, as observed in the homologs of 8-alkylbenzanthracene (*7*) and 3-alkylcholanthrene (*2*). In Fig 3, the molecular model of 16-methyl-17-acetylnorandrostane (IV),

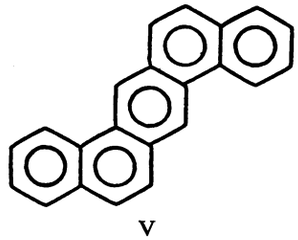


Figs. 1–4. Fig. 1 (top left). Norandrostane versus benzanthracene. Fig. 2 (top right). Benzanthracene versus norandrostane. Fig. 3 (bottom left). 16-Methyl-17-acetylnorandrostane versus 1,2,5,6-dibenzanthracene. Fig. 4 (bottom right). 1-Methylnorandrostane versus benzpyrene.



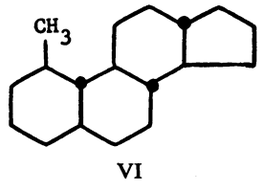
IV

the basic carbon skeleton of a group of biologically active steroids (*12*), is compared with that of 1,2,5,6-dibenzanthracene (V);



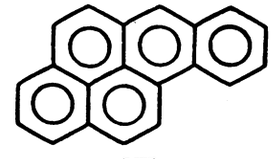
V

in Fig. 4, the molecular model of 1-methylnorandrostane (VI),



VI

the basic carbon skeleton of another group of active steroids (*13*) is compared with that of benzpyrene (VII).



VII

In either case, remarkable similarity is found. Similar comparisons between all known carcinogenic polynuclear aromatic hydrocarbons and steroids were made.

Our observation suggests that, in addition to the electronic factors, there is a steric factor responsible for the carcinogenicity of the polynuclear aromatic hydrocarbons. For a polynuclear aromatic hydrocarbon to be carcinogenic, it must bear steric resemblance to an active steroid. Among polynuclear aromatic hydrocarbons of similar electronic properties, the closer the steric resemblance to a steroid, the higher is the carcinogenicity.

Because polynuclear aromatic hydrocarbons are devoid of polar functions, such as -OH or -NH_2 groups, the only possible bonding of such compounds to biological systems is that of charge-transfer complex formation. Some interesting correlations have been made between the ability of charge-transfer complex formation of these compounds and the carcinogenicity (*5*). Since the steric factor is a requirement for carcinogenicity, one possible implication is that the polynuclear aromatic hydrocarbons may act at the same sites as steroid hormones. Carcinogenesis by these hydrocarbons may be the result of their interference with normal steroid functions. This hypothesis is in agreement with several isolated biological observations, among which are the variation of carcinogenicity of these hydrocarbons by concurrent administration of steroid hormones with these hydrocarbons (*14*) and the induction of identical morphological changes by some of these hydrocarbons as by progesterone on breast tissue of experimental animals (*15*, *16*).

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23 February 1961