ELECTRONIC STRUCTURE AND ANTITUMOUR ACTIVITY OF IMIDAZO [4,5-d] - PYRIDAZINES ⁎

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We have shown in recent publications (Nakajima and Pullman, 1958; Pullman, 1959) that the antitumour activity of purine antimetabolites seems to be related to the basicity of these compounds. The relation states that in order to be active in chemotherapy of cancer, the purine antimetabolites must have their most basic nitrogen at positions 1 or 7 of the purine skeleton (I) - which is the position at which they are located respectively in adenine and guanine-and that the basic strength of that nitrogen must be of the order of magnitude of that of adenine and guanine and exceed a certain threshold value. It has been shown that the relative basicities of polyaza-compounds are given ,theoretically, by :

$$B = C^{te} + \sum_{p \neq d} Q_p \, (dd/pp)$$

where Q_p represents the net charge of atom p and (dd/pp) the coulomb integral between an electron of the lone pair of the nitrogen and the π electron of atom p, the summation being carried out over all the atoms p of the skeleton. The value of the quantity $\sum_{p \neq d} Q_p \, (dd/pp)$ is - 1,91 for N_1 of adenine and - 1,67 for N_7 of guanine; the antitumour activity only manifests itself in those purine antimetabolites in which the value of this quantity exceeds - 1,30.

This criterium has been particularly useful in the study of the antitumour activity of derivatives of pyrazolo-pyrimidines (II and III) in which it has been able to account

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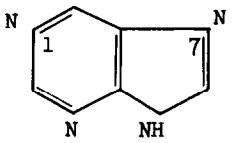
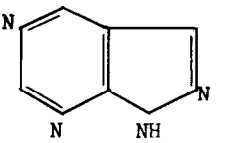
for the existence of this activity in a very limited number of compounds, out of a hundred molecules studied, in excellent agreement with experiment (Pullman, Pullman and Nakajima, 1959).



I



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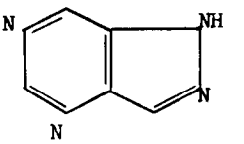

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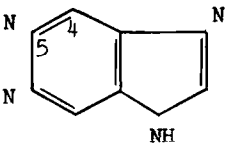
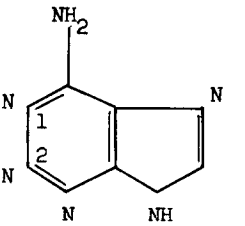


IV



V

Recently, Carbon (1958) has announced the preparation of a series of derivatives of imidazo [4,5-d] - pyridazine (IV), considered to be potential purine antimetabolites. Consequently, we have extended our calculations to this type of molecules in order to predict whether they should exhibit any antitumour activity. The calculations have been carried out for those molecules of the family which a priori, on the basis of preceeding studies on related pyrazolopyrimidines, seemed to have the best chances to be active : these were IV and its 4-amino derivative. The theoretical results lead to the prediction that both compounds should manifest antitumour activity similar to that of the usual purine antimetabolites and pyrazolopyrimidines. The most basic nitrogen is, in both compounds N_5 (which is the analogue of N_1 of purine) and the value of the quantity $\sum_{p \neq d} Q_p$ (dd/pp) is - 1,78 in IV and - 2,27 in its 4-amino derivative. A very recent private communication from Dr. Carbon confirms the antitumour activity of V (against Sarcoma 180, Carcinoma 755 and Leukemia 1210 in mice). Compound IV has not as yet been prepared.

In connection with these data it may be useful to recall the existence of antitumour activity of 2-azaadenine (V),

a compound which has structural features common both to the classical purine antimetabolites and to the imidazo [4,5-d] pyridazines. The activity of this molecule is in agreement with our general correlation, too. It's most basic nitrogen is predicted to be N_1 and the value of the quantity $\sum_{p \neq d} Q_p$ (dd/pp) for it, is - 1,97. In this particular case, the fact that the most basic nitrogen is N_1 is confirmed experimentally (as it is also for adenine and 2-6 diaminopurine (Stevens and Brown, 1958; Stevens, Magrath, Smith and Brown, 1958;) by the preferential formation of N_1-oxide of the compound *.

References

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* Private communication from Dr. G.B. Brown. In fact, 2-azaadenine yields, exceptionally, besides the N_1-oxide, a second N-oxide of unknown structure. We may predict this second N-oxide to be N_2-oxide, the value of the quantity $\sum_{p \neq d} Q_p$ (dd/pp) for N_2 of 2-azaadenine being - 1,91, thus very close to its value for N_1.