I should like to thank Dr. M. Dixon for suggestions and for his interest in the work.

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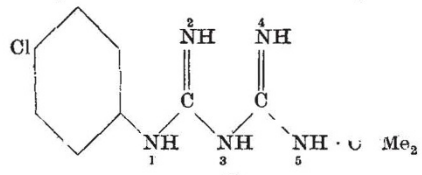
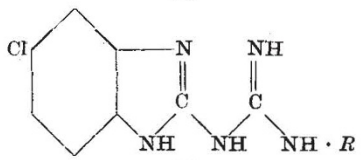
Benziminazoles Related to Paludrine

The suggestion recently made in these columns by Hawking[1], that the drug paludrine is not itself an antimalarial agent but is converted into an active compound *in vivo*, opens up a wide field for speculation and research. No indication has yet been obtained as to the nature of this transformation product; but one of the more obvious hypotheses as to the fate of paludrine in the body appears to be excluded by an investigation which we have lately completed.



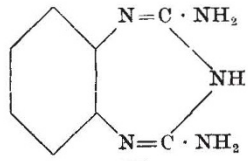
(I)



(II)

Consideration of the paludrine molecule (I) in the form of a model shows that, without introducing any appreciable strain, it is possible for N^2 to approach the benzene ring and by the loss of two hydrogen atoms to form a new bond. Should this oxidation be a step in the metabolism of paludrine, then the related guanidinobenziminazole (II, $R = CHMe_2$) would be expected to show comparable biological activity. Bearing in mind that the growth of certain micro-organisms can be inhibited by benziminazole, which interferes with the utilization of guanine and adenine[2], paludrine would thus appear to function as an antagonist of some specific purine essential to the malaria parasite.

The benziminazole (II, $R = CHMe_2$), which we accordingly synthesized, has many of the chemical properties of paludrine, as might be expected from the very close resemblance of the two structures. For example, it is readily converted into a chelate copper derivative, a reaction implying the formation of a dimolecular complex similar in outline to the porphyrin ring-system. It has been suggested by Curd and Rose[3] that it is this characteristic which may be connected with the antimalarial action of paludrine. It is remarkable, therefore, that the guanidinobenziminazole (II, $R = CHMe_2$) and several analogous benziminazoles, none of which is more toxic than the antimalarial, are, at the maximum tolerated dose, without action on *P. gallinaceum* infection in chicks.



(III)

The benziminazoles with unsubstituted guanidino side-chains, for example (II, R = H), were synthesized from *o*-phenylenediamines and dicyandiamide[4]. The N^5-*iso*propyl derivatives, for example (II, $R = CHMe_2$), were obtained similarly from the *iso*propyl dicyandiamide, which was prepared from dicyanimide and *iso*propylamine. An attempt to carry out the synthesis of N^5-*iso*propylguanidinobenziminazole in the reverse direction, starting with *o*-phenylenediamine and dicyanimide, led to the formation of a seven-ring compound, 2 : 4-diamino-1 : 3 : 5-triazabenzepine (III), a structure comparable with that obtained from *o*-phenylenediamine and malonic acid[5].

A full account of this work will be published in due course. The biological experiments were kindly carried out by Mrs. A. M. Yates, of the National Institute of Medical Research, London, N.W.3.

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Urinary Excretion of Phosphate with $^{32}_{15}P$ as Indicator

The phosphate excretion by the kidney follows different laws well determined by L. Brull[1] and since confirmed by other investigators. However, the mechanism of the excretion of phosphate has not been completely explained. Thus it was considered of interest to study the mechanism of excretion of phosphate by the kidney, using radiophosphorus $^{32}_{15}P$. (The $^{32}_{15}P$ was prepared by Dr. F. A. Heyn (Philips, Eindhoven), and I am indebted to him for his co-operation and generosity.)

Dogs are anæsthetized by chloralose, the ureters are catheterized and small samples of urine are collected. Blood samples are taken from the femoral artery. The dogs received intravenously labelled disodium phosphate solutions containing about 1–100 mgm. phosphorus. The radioactivity of the samples of urine and blood are measured as well as the total phosphorus content.

The table shows the data obtained in one experiment. The dog weighed 4 kgm. and received 97·13 mgm. labelled phosphorus in five minutes. Fig. 1 shows the excretion of total and exogenous phosphorus in the urine. The variation of percentage exogenous phosphorus present in total phosphorus of the plasma and the urine during the experiment is shown in Fig. 2. The number of animals used was thirty.

From Figs. 1 and 2 it can be seen that after phosphate injection the inorganic phosphate of the urine, at least in the first samples, contains more than 90 per cent exogenous phosphate, while the level of the