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The Chemistry of CIBA 32644-Ba

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Among the synthetic preparations employed in the treatment of infections and parasitic diseases, heterocyclic compounds bearing a nitro group as a characteristic substituent occupy an important position. To date, three nitroheterocycles have proved suitable as basic elements for chemotherapeutic agents: nitrofurane, nitroimidazole, and nitrothiazole (Fig. 1).

Nitrofurazone and nitrofurantoin are widely used in human and veterinary medicine for treating bacterial infections. Metronidazole, a nitro-imidazole derivative, was introduced in 1960 as a chemotherapeutic for the treatment of trichomoniasis. Nitrothiazole, in the form of its amino derivative (Enheptin) is employed in veterinary medicine as a prophylactic against histomoniasis (blackhead), while the trichomonicidal properties of the acetylamino derivative (Enheptin A) are being exploited in human medicine.

In the course of studies on the chemotherapeutic activity of heterocyclic compounds, we have prepared a number of variously substituted nitroheterocycles and tested them pharmacologically (Fig. 2).

Among the nitropyridine and nitropyrimidine derivatives which we have so far produced, there have been none displaying any significant chemotherapeutic activity. Compounds featuring a nitrofurane group as one of their structural elements show a wide spectrum of chemotherapeutic effects, the type of effect depending on the nature of the substitution in the furane ring. However, research in the nitrofurane field has been undertaken all over the world and literally thousands of nitrofurane derivatives have been produced and tested. Despite this, only a few of them are at present in use as chemotherapeutic agents. This is not so much because these nitrofurane compounds are lacking in activity, but rather because most of them display a relatively high degree of toxicity.

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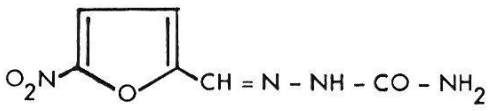
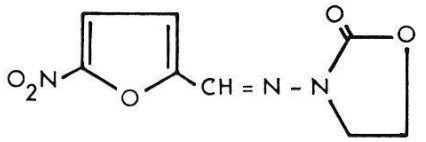
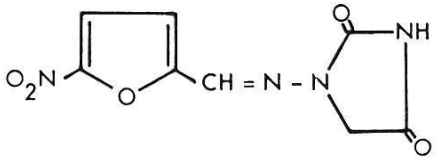
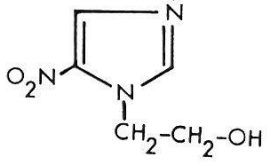
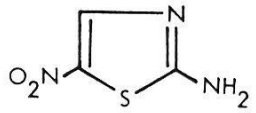
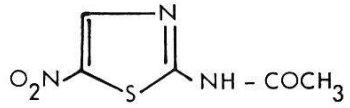
Structure	Name	Activity
2-Nitro-furan 	Nitrofurazone	Bacteria gram + gram −
	Furazolidone	Trichomonads
	Nitrofurantoin	Bacteria
2-Nitro-imidazole 	Metronidazole	Trichomonads
2-Nitro-thiazole 	Amino-nitrothiazole (Enheptin)	Blackhead
	Acetamido-nitrothiazole	Trichomonads

Fig. 1. Nitroheterocycles in use as chemotherapeutics.

The group of nitro-imidazole compounds includes a few derivatives with amoebicidal and trichomonicidal properties, and in the group of the thiazole derivatives compounds have also been found which exert schistosomicidal and amoebicidal effects. In view of this, we decided to intensify our research in the field of the nitrothiazoles.

We synthesised quite a large number of nitrothiazole derivatives, with a different substitution in position 2 of the thiazole ring; a small selection of these derivatives is listed in Fig. 3.

The amoebicidal and schistosomicidal activity of the substituted nitrothiazoles showed a high degree of structural specificity.

Among the many preparations which have so far been tested, derivatives of 5-nitrothiazole substituted by a cyclic urea group

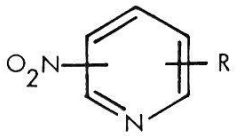
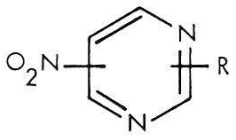
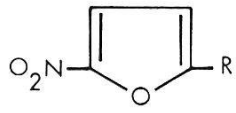
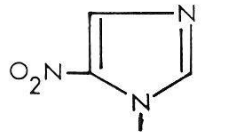
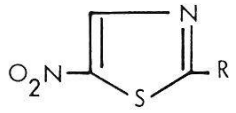
Skeleton	Activity
	∅
	∅
	Bacteria Amoebae Trichomonads Schistosomes
	Amoebae Trichomonads
	Schistosomes Amoebae

Fig. 2. Nitroheterocycles.

in position 2 display optimum chemotherapeutic properties. On the basis of results obtained in animal experiments (1, 2, 3), the ethylene-urea derivative 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (CIBA 32644-Ba) was selected from among this category of compounds and subjected to thorough clinical investigation.

CIBA 32644-Ba was synthesised from 2-amino-thiazole I, which was converted to the chlorethyl-urea II by a process involving several steps. The chlorethyl-urea II was finally cyclised into imidazolidinone III.

It should perhaps be mentioned that the urea II also displays some schistosomicidal activity; this is probably because the urea derivative II is transformed in the organism into the active preparation III. Other nitrothiazolyl-urea compounds, which are incapable of undergoing cyclisation into a polymethylene-urea derivative, proved inactive.

CIBA 32644-Ba is characterized by the following physical data: The preparation is a yellow, crystalline powder which is odourless and tasteless and melts at 262-264°. It is sparingly soluble in most organic solvents as well as in water. The best solvent proved to be

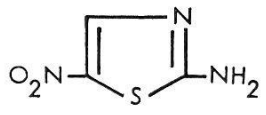
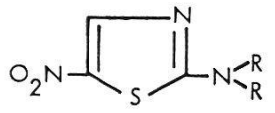
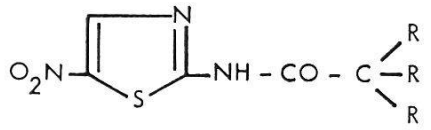
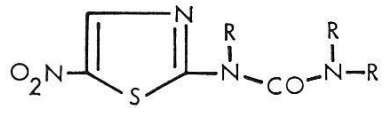
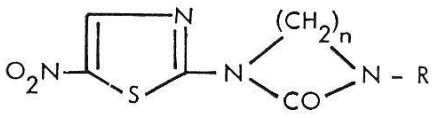
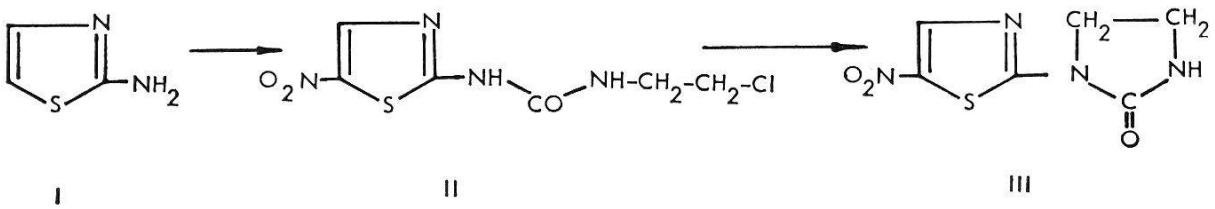
Structure	Activity	
	Schistosomes	Amoebae
	∅	∅
	∅	∅
	∅	+
	∅	+
	+ + +	+ + +

Fig. 3. Nitrothiazoles.

dimethylformamide, in which CIBA 32644-Ba is soluble to the extent of 2.1%. In the ultraviolet absorption spectrum, CIBA 32644-Ba shows two distinct bands at 240 mμ and 360 mμ. However, the spectroscopic method is not suitable for determining the active substance in body fluids or tissue specimens, because the metabolites of CIBA 32644-Ba absorb in the same regions of the spectrum as the original substance. For the present, radiochemical techniques therefore have to be used for metabolic studies (4).

CIBA 32644-Ba displays very good stability to heat, light, and chemical influences. It underwent no change when heated to 100°C for 7 days; nor did it show any signs of decomposition when subjected to the action of N/10 hydrochloric acid for 7 days. On



I II III

Fig. 4. Synthesis of CIBA 32644-Ba.

the other hand, alkaline reagents break it down into unknown products.

Among the various preparations possessing schistosomicidal and amoebicidal properties, CIBA 32644-Ba represents a new type of compound whose structure differs appreciably from that of existing known chemotherapeutic agents (5, 6, 7). It will be the task of a team of chemists, biologists, and clinicians to exploit the findings so far obtained with this preparation in an effort to place new drugs at the physician's disposal for the treatment of widespread tropical diseases.

Summary

A series of different heterocyclic nitro-compounds have been synthesised and studied from the point of view of their antiparasitic activity. Preparation CIBA 32644-Ba (1-(5-nitro-2-thiazolyl)-2-imidazolidinone) displayed highly structure-specific amoebicidal and schistosomicidal properties.

The synthesis and the physical and chemical properties of the product are described.

Résumé

Différents dérivés hétérocycliques nitrés ont été synthétisés et étudiés du point de vue de leur action antiparasitaire. Le CIBA 32644-Ba (1-(5-nitro-2-thiazolyl)-2-imidazolidinone) a montré des propriétés amibicides et schistosomicides, qui ont une forte spécificité de structure.

La synthèse, les propriétés physiques et chimiques du produit sont décrites.

References

1. LAMBERT, C. R., WILHELM, M., STRIEBEL, M., KRADOLFER, F. & SCHMIDT, P. (1964). Experientia *20,* 452.
2. KRADOLFER, F. & JARUMILINTA, R. (1965). Ann. Trop. Med. and Parasit. *59,* 210.
3. LAMBERT, C. R. & STAUFFER, P. (1964). Ann. Trop. Med. and Parasit. *58,* 292.
4. FAIGLE, J. W. & KEBERLE, H. Following paper, p. 8.
5. WOOLFE, G. (1965). The Chemotherapy of Amoebiasis, in: "Progress in Drug Research" by E. JUCKER, Vol. 8, p. 11.
6. GÖNNERT, R. (1961). Bull. WHO *25,* 702.
7. NEWSOME, J. (1962). The search for non-antimonial schistosomicides, in: "Bilharziosis" (CIBA Foundation Symposium). Ed. by WOLSTENHOLME, G. E. W. & O'CONNOR, M., p. 310.