Synthetic Biologically Active Polymers. 9. Comparison of Antimalarial Activity in Copolymers Containing Common Sulfonamide Monomers but Different Comonomers

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Received January 25, 1971

Previous publications in this series have described the preparation, characterization, and certain biological activities of a number of polymers and copolymers[3] with a view to observing the effect of polymerization or copolymerization upon drugs, hoping to elucidate from the data obtained some generalities concerning what can be expected in the way of biological activity when a drug is polymerized or copolymerized. In other studies,[3h] various observations indicate that the biological activity of a polymerized or copolymerized drug may be influenced by the nature of the comonomer present in the polymer other than the drug, and this paper attempts to display data relevant to this phenomenon. The sulfonamide copolymers employed in this study were prepared and characterized by methods reported previously.[3c-h]

Biological Activity.—Table I displays comparative data concerning the antimalarial activity of various sulfonamide–dimethylolurea copolymers (D) relative to sulfonamide–formaldehyde copolymers (F). Each copolymer system being compared has the same sulfonamide incorporated into the copolymer.

TABLE I
COMPARISON OF SULFONAMIDE–DIMETHYLOLUREA COPOLYMER (D) AND SULFONAMIDE–FORMALDEHYDE COPOLYMER (F) ANTIMALARIAL ACTIVITY[a,b]

Sulfonamide system	D act.	F act.
Sulfanilamide	Active[c]	Curative[d]
Sulfapyridine	Active	Curative
Sulfacetamide	Inactive	Curative
Sulfabenzamide	Inactive (nontoxic)	Curative (toxic[e])
4,4′-Diaminodiphenylsulfone	Curative	Curative

[a] The prepn, characterization, and antimalarial activity compared to the antimalarial activity of the pertinent sulfonamide monomers of the copolymers have been reported previously.[3c-f] Other activity testing also has been reported.[3g,h] [b] Antimalarial testing was carried out with white ICR/Ha Swiss mice infected with *Plasmodium berghei*. Five mice were employed for each compd at each dose level. Drugs were administered ip by injection in oil. [c] Active = when mice in a test group survive 14 days. [d] Curative = when mice in a test group survive 30 days. [e] Control animals do not die before day 6. Deaths through day 5 are attributable to drug action (toxic).

As can be seen from Table I, in general, the antimalarial activity of the F copolymers tends to be better than that of the D copolymers, except in the case of the 4,4-diaminodiphenylsulfone systems where the activity is the same. An interesting observation concerning toxicity can be seen in the case of the sulfabenzamide system. Thus, as in the case of similar comparative data derived from related work,[3h] it would appear that the biological activity obtained under identical test conditions may be dependent, at least in part, on factors other than the sulfonamide content of the copolymers. For if only the sulfonamide content was involved, it would be expected that in all cases the observed activity and/or toxicity of the F copolymers would be greater than that of the D copolymers since the same dose levels were used in each comparative case and thus the sulfonamide content of an equal weight of D copolymer would be less than that present in the same weight of F copolymer.

Acknowledgments.—We are indebted to the Public Health Service for support of this work under Research Grant 5RO1-AI06662 and to Dr. Leo Rane at the University of Miami Medical School for carrying out the antimalarial testing.

(1) Taken in part from the thesis submitted by Mr. John R. Dombroski, in partial fulfillment of the requirements for the Master of Science degree.

(2) Taken in part from the thesis to be submitted by Mr. John Razzano in partial fulfillment of the requirements for the Ph.D. degree.

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Antihistomonal Activity of Ipronidazole and Closely Related Nitroimidazoles

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Received March 29, 1971

The 5-nitroimidazoles dimetridazole (**1**)[1] and ipronidazole (**2**)[2] are potent histomonastats.[3] Comparison with their 4-nitro isomers **4**[1,4] and **5** demonstrates that both 5-nitro analogs are much superior histomonastats.

In order to collect additional information regarding the structure–activity relationship of isomeric isopropyl nitroimidazoles, we have included in our comparison study the two new 1-isopropyl-substituted nitroimidazoles **6** and **7** and the known 5-isopropyl-2-nitroimidazole **8**.[5] Compds **6** and **7** were obtained by alkylating 2-methyl-4(5)-nitroimidazole under different reaction conditions.[6]

Their structures could easily be assigned by uv spectroscopy and pK measurements.[7] A pure sample of the

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