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TRYPANOCIDAL ACTION OF PHENANTHRIDINE COMPOUNDS: FURTHER 2:7-DIAMINO PHENANTHRIDINIUM COMPOUNDS

BY

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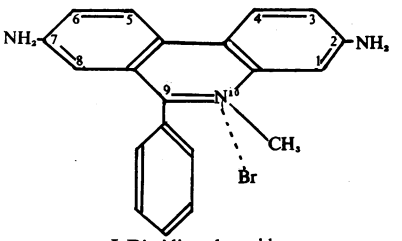
Woolfe (1952) showed that the trypanocidal activity of dimidium bromide (2:7-diamino-10-methyl-9-phenyl-phenanthridinium bromide; I) was influenced by changing the quaternary group, and later (Woolfe, 1956) that the activity of other



I Dimidium bromide

trypanocidal phenanthridinium compounds was also modified by such changes. Results obtained with a number of other 2:7-diamino phenanthridines are now reported.

METHODS

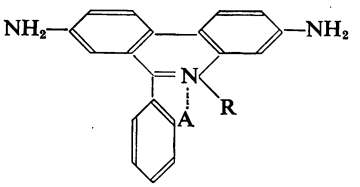
The techniques described earlier (Woolfe, 1952) were used, and drugs were given in single doses subcutaneously to mice. The Median Curative Dose (CD50) was estimated as the dose necessary to remove parasites from the peripheral blood of 50% of infected mice for a period of not less than one month. Active drugs were compared with dimidium (activity taken as 1) on the basis of the CD50.

RESULTS

2 : 7-*Diamino-9-phenyl-phenanthridinium Compounds* (Table I).—I previously (Woolfe, 1952) discussed the effect of *n*-alkyl and of allyl-quaternating groups. I have now tried a number of quaternating groups containing hetero-atoms, and in the

TABLE I

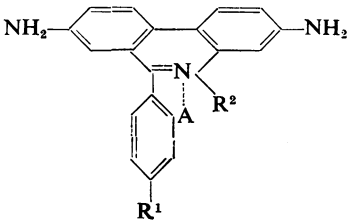
THE TRYPANOCIDAL ACTIVITY OF 2:7-DIAMINO-9-PHENYL-PHENANTHRIDINIUM COMPOUNDS



Compound	Structure		LD50 mg./kg. (s.c.)	Trypanocidal Activity (Dimidium Bromide = 1)			
	R	A		*congolense*	*brucei*	*rhodesiense*	*gambiense*
RD2443	$CH_2.CH_2OH$	SO_3CH_3		2·0	0·7	2·2	1·6
RD2490	$CH_2CH_2O.CH_3$	SO_3CH_3	55	0·7	1·0	2·2	0·8
RD2505	$CH_2CH_2O.C_2H_5$	SO_3CH_3	80	1	0·3	2·5	0·8
RD2141	$CH_2CH_2CH_2.O.C_2H_5$	SO_3CH_3	400	6	6	8	8
RD1630	$CH_2CH_2CH_2.N(C_2H_5)_2$	SO_3CH_3	100	1·2	1	*ca.* 0·5	1
RD1667	$CH_2CH_2CH_2.N(C_2H_5)_2CH_3$ I	I	16	< 0·2	Inactive at 8 mg./kg.	0·3	Inactive at 8 mg./kg.

TABLE II

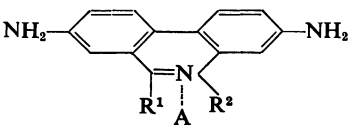
THE TRYPANOCIDAL ACTIVITY OF 2: 7-DIAMINO-9-(*p*-SUBSTITUTED PHENYL) PHENANTHRIDINIUM COMPOUNDS



Compound	Structure			LD50 mg./kg. (s.c.)	Trypanocidal Activity (Dimidium Bromide = 1)			
	R^1	R^2	A		*congolense*	*brucei*	*rhodesiense*	*gambiense*
RD1847	Cl	CH_3	Cl	80	0·125	Inactive at 16 mg./kg.	0·2	Inactive at 16 mg./kg.
RD1870	Cl	$CH_2CH=CH_2$	Cl	100	0·3	1·2	2	2
RD2177	CH_3	CH_3	Br	14	*ca.*0·02	Delayed death at 8 mg./kg.	0·1	Delayed death at 8 mg./kg.
RD2201	CH_3	C_2H_5	Br	80	*ca.* 0·05	0·3	0·4	0·3
RD1911	$CH(CH_3)_2$	$CH_2CH=CH_2$	Cl	40	Inactive at 16 mg./kg.	Inactive at 16 mg./kg.	Inactive at 16 mg./kg.	Inactive at 16 mg./kg.
RD1535	OCH_3	CH_3	Br	35	*ca.* 0·1	*ca.* 0·1	*ca.* 0·2	Delayed death at 16 mg./kg.
RD2022	$SO_2C_2H_5$	CH_3	SO_3CH_3		0·6	*ca.* 1	*ca.* 1·3	*ca.* 1
RD2056	$SO_2C_2H_5$	C_2H_5	Cl	100	Temporary clearing at 20 mg./kg.	Inactive at 32 mg./kg.	Delayed death at 20 mg./kg.	Inactive at 32 mg./kg.
RD2035	$SO_2C_2H_5$	$CH_2.CH=CH_2$	SO_3CH_3		Inactive at 20 mg./kg.	Delayed death at 32 mg./kg.	,,	Delayed death at 32 mg./kg.

TABLE III

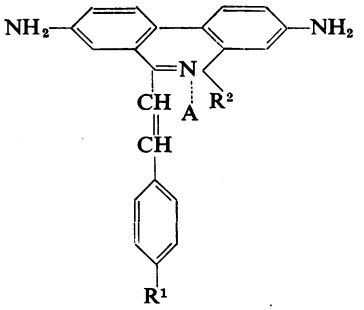
THE TRYPANOCIDAL ACTIVITY OF 2: 7-DIAMINO-9-ALKYL-PHENANTHRIDINE COMPOUNDS



Compound	Structure			LD50 mg./kg. (s.c.)	Trypanocidal Activity (Dimidium Bromide = 1)			
	R^1	R^2	A		*congolense*	*brucei*	*rhodesiense*	*gambiense*
RD2610	C_2H_5	CH_3	Br	160	0·1	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.
RD2611	C_2H_5	C_2H_5	Br	250	0·22	,,	0·1	,,
RD1098	C_4H_9(n)	—	—	80	Inactive at 30 mg./kg.	Inactive at 30 mg./kg.	Inactive at 30 mg./kg.	Inactive at 30 mg./kg.
RD1120	C_4H_9(n)	CH_3	Br	70	Temporary clearing at 20 mg./kg.	Inactive at 20 mg./kg.	Inactive at 20 mg./kg.	Inactive at 20 mg./kg.
RD2652	C_9H_{19}	CH_3	Cl		Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.
RD2729	C_9H_{19}	C_2H_5	Cl		Temporary clearing at 32 mg./kg.	,,	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.

TABLE IV

THE TRYPANOCIDAL ACTIVITY OF 2:7-DIAMINO-9-STYRYL PHENANTHRIDINIUM COMPOUNDS



Compound	Structure			LD50 mg./kg. (s.c.)	Trypanocidal Activity (Dimidium Bromide = 1)			
	R^1	R^2	A		*congolense*	*brucei*	*rhodesiense*	*gambiense*
RD2345	H	CH_3	SO_3CH_3	*ca.* 200	0 02	0 2	0 03	0·1
RD2585	H	C_2H_5	SO_3CH_3		0·03	0·2	0·07	0·2
RD2337	NH_2	CH_3	Br	*ca.* 100	0·03	1·2	8	6
RD2480	NH_2	C_2H_5	Br	*ca.* 250	0·15	20	12	14
RD2240	$N(CH_3)_2$	CH_3	SO_3CH_3	250	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	0·06	0·1
RD2384	$N(CH_3)_2$	C_2H_5	Cl		,,	0·1	0·3	0·25
RD2289	$N(CH_3)_3SO_3CH_3$	CH_3	SO_3CH_3	60	Delayed death at 16 mg./kg.	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	0 1
RD2415	$N(CH_3)_2(C_2H_5)Cl$	C_2H_5	Cl	50	0 025	0·25	0·25	0 1

alkoxyalkyl series the ethoxypropyl compound, RD 2141, was particularly interesting, having low acute toxicity for mice and high trypanocidal activity. The diethylaminopropyl compound, RD 1630, had activity of the same order as that of dimidium, but when the nitrogen was quaternated, in RD 1667, toxicity increased and activity decreased.

2:7-*Diamino*-9-(*p-substituted Phenyl*) *Phenanthridinium Compounds* (Table II).—Two groups of this type, namely the *p*-amino phenyl and the *p*-nitro phenyl compounds, were previously discussed (Woolfe, 1956). Apart from these two *p*-substituents every other substituent tried has reduced activity below that of the parent dimidium.

I found that modifying the methyl quaternary group increases activity in the *p*-chlorophenyl and *p*-methylphenyl compounds; but in the *p*-ethyl sulphonyl phenyl compounds, methyl quaternation (RD 2022) produced greater activity than either ethyl or allyl quaternation.

2:7-*Diamino*-9-*alkyl Phenanthridinium Compounds* (Table III).—I have already shown (Woolfe, 1956) that the 9-methyl compounds had but slight activity. I have now tried 9-ethyl, 9-*n*-butyl and 9-nonyl compounds. None of these had more than a trace of trypanocidal activity, and ethyl quaternation in place of methyl, though it did increase activity to some extent, could not produce useful activity. The one non-quaternized compound reported here, RD 1098, was completely devoid of trypanocidal activity.

2:7-*Diamino*-9-*styryl Phenanthridinium Compounds* (Table IV).—It was thought possible that the degree of conjugation of the phenanthridinium compounds might bear some relationship to trypanocidal activity, in which case styryl derivatives should be more active than the corresponding phenyl

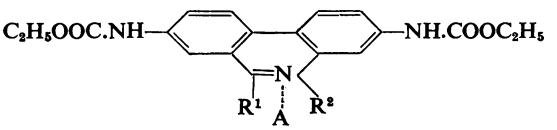
compounds. Accordingly a number of 9-styryl-phenanthridinium compounds was prepared. Each was less active than the corresponding 9-phenyl compound against *T. congolense*, and ethyl quaternation in place of methyl increased activity only to a minor extent. However, the 9-*p*-amino styryl compounds had surprisingly high activity against other trypanosome species.

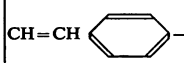
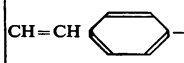
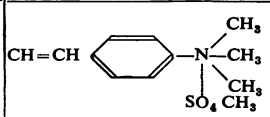
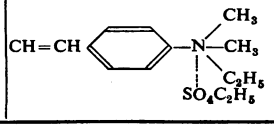
2 : 7-*Dicarbethoxyamino Phenanthridinium Compounds* (Table V).—It has been reported previously that interference with the primary amino groups in the 2: 7-positions greatly reduces trypanocidal activity against African species of trypanosomes, though such compounds may possess activity against the South American *T. cruzi* (Goodwin *et al.*, 1950). I have prepared and tested a number of such compounds. None here reported showed more than a trace of activity against *T. congolense*, *T. brucei*, *T. rhodesiense*, or *T. gambiense*, though several of the parent primary amines were highly active.

It is obvious, from results presented both here and in my previous papers on this subject, that the quaternating group in phenanthridinium compounds may play a very large part in determining the activity of the compound. In every case, except that of the 9-ethyl sulphonyl phenyl compounds, the methyl derivative was less active as a trypanocide than the ethyl, *n*-propyl or allyl-derivatives. The reason for the reversal of this effect in the 9-ethyl sulphonyl phenyl series is not yet apparent. The high activity and low toxicity of the ethoxypropyl

TABLE V

THE TRYPANOCIDAL ACTIVITY OF 2: 7-DICARBETHOXYAMINO PHENANTHRIDINIUM COMPOUNDS



Compound	Structure			LD50 mg./kg. (s.c.)	Trypanocidal Activity			
	R^1	R^2	A		*congolense*	*brucei*	*rhodesiense*	*gambiense*
RD1099	CH_3	CH_3	SO_4CH_3	150	Temporary clearing at 50 mg./kg.	Delayed death at 50 mg./kg.	Delayed death at 50 mg./kg.	Delayed death at 50 mg./kg.
RD2216	CH_3	C_2H_5	$SO_4C_2H_5$	120	Delayed death at 32 mg./kg.	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.
RD2586	C_2H_5	CH_3	SO_4CH_3		,,	,,	,,	,,
RD2587	C_2H_5	C_2H_5	SO_4CH_3		,,	,,	,,	,,
RD1097	C_4H_9	CH_3	SO_4CH_3	50	Inactive at 20 mg./kg.	Inactive at 20 mg./kg.	Inactive at 20 mg./kg.	Inactive at 20 mg./kg.
RD1579		$(CH_2)_3N(C_2H_5)_2$	Cl	140	Delayed death at 40 mg./kg.	Inactive at 40 mg./kg.	Inactive at 40 mg./kg.	Inactive at 40 mg./kg.
RD2307		CH_3	Cl	*ca.* 500	,,	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.
RD2460		C_2H_5	Cl	>1600	,,	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.
RD2283		CH_3	SO_4CH_3	140	,,	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.	Delayed death at 32 mg./kg.
RD2389		C_2H_5	$SO_4C_2H_5$		Inactive at 40 mg./kg.	Inactive at 40 mg./kg.	Inactive at 32 mg./kg.	Inactive at 32 mg./kg.

quaternated compound, RD 2141, is extremely interesting, and further work on this type of compound is indicated.

Summary

1. Results of tests for trypanocidal activity on a number of phenanthridinium compounds are reported.

2. The effect of structure upon trypanocidal activity is discussed for each compound, one of which, 2: 7-diamino-9-phenyl-10-ethoxypropyl phenanthridinium methane sulphonate, has low acute toxicity for mice and high activity in trypanosome infections in mice.

I am grateful to Mrs. B. Goodliffe and Miss H. Riley for technical assistance, to Dr. T. I. Watkins, who has supplied all the compounds, and to Dr. M. R. Gurd for figures for toxicity of the compounds. The chemistry of the compounds will be reported elsewhere.

References

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Woolfe, G. (1952). *Ann. trop. Med. Parasit.*, **46**, 285.

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