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STUDIES IN THE CHEMOTHERAPY OF TUBERCULOSIS: PART IV. DIAMINO METHYLPYRIMIDINES AND RELATED COMPOUNDS

BY

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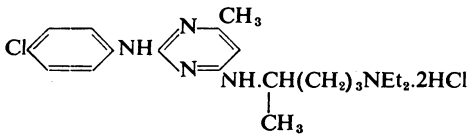
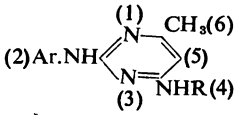
We have already reported (Hoggarth and Martin, 1948) that members of a certain class of antimalarial compounds (2-arylamino-4-aminoalkylamino-6-methylpyrimidines) show antituberculous activity in mice. When examined by the standardized procedure used throughout this series of investigations (Martin, 1946) the compound showing most promise was 2-*p*-chloroanilino-4-δ-diethylamino-α-methylbutylamino - 6 - methylpyrimidine dihydrochloride (No. 3300).



No. 3300

We have examined the relationship between antituberculous activity and chemical constitution among a group of compounds related to the drug No. 3300 and present here a summary of the main conclusions which have emerged after a study of 110 such compounds. The chemical formula of compound No. 3300 may be generalized as shown below, and we have prepared variants changing each portion of the general structure in turn.



(Ar = an aryl residue, R = an aliphatic residue usually containing another basic centre.)

RESULTS

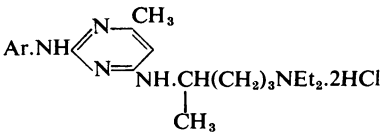
The test method consisted of the infection of mice by the intravenous route, and their treatment by drugs administered orally, twice daily by syringe and catheter at doses ranging downwards from the maximum tolerated. The results are presented in the form used in preceding papers of this series.

i. *Variation of aryl residue (Ar).*—Retaining the 4-δ-diethylamino-α-methylbutylamino - 6 - methylpyrimidine portion of the compound No. 3300, the arylamino residues listed in Table I were substituted for the *p*-chloroanilino group. In compound No. 3656 the aryl nucleus was omitted altogether.

TABLE I

Therapeutic tests on some 4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidines containing an arylamino group (or in one case an amino group) in position 2. Doses given orally twice daily by syringe and catheter.

Compounds of the form:



No.	Ar	Dose (mg. per 20 g. mouse)	Increased mean survival time (days)	Increase required for significance (days)
5753	*p*-fluorophenyl	1.0	+1.6	1.4
5207	*p*-bromophenyl	1.0 1.0	+3.9 +4.1	1.4 1.3
5499	*p*-iodophenyl ..	0.5 1.0	+2.2 +3.2	1.3
5161	*m*-chlorophenyl	0.5 1.0 2.0	0 +0.2 +0.4	1.6
5164	*o*-chlorophenyl..	1.0 2.0	−0.3 −0.3	1.6

TABLE I (*continued*)

No.	Ar	Dose (mg. per 20 g. mouse)	Increased mean survival time (days)	Increase required for significance (days)
5210	3:4-dichlorophenyl ..	1.0	+3.0	1.6
5414	2:5-dichlorophenyl ..	1.0	−0.8	1.3
5588	3:5-dichlorophenyl ..	1.0 2.0	+1.1 +3.7	1.7
5500	3:4:5-trichlorophenyl ..	1.0	+2.0	1.3
5211	*p*-anisyl ..	3.0	+2.0	1.6
5214	*o*-anisyl ..	3.0	+0.1	1.6
5548	*p*-tolyl	0.5 1.0	+3.2 +5.6	1.5
		1.0 2.0	+2.6 +3.3	1.6
5560	*m*-tolyl	2.0	+2.6	1.5
5828*	*p*-sulphonamidophenyl ..	10.0	+0.3	1.4
6259	*p*-dimethylaminophenyl ..	0.25 0.5 1.0	−0.9 +0.5 +0.7	1.1
4977	6-bromo-2-naphthyl	0.25 0.5	+1.2 +1.8	1.3
3656*	amino	1.0 2.0	−0.5 0	1.6

*Administered as free base and not as dihydrochloride.

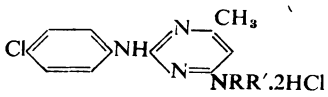
ii. *Variation in the aliphatic residue (R).*—Retaining the 2-*p*-chloroanilino-6-methylpyrimidine portion of the molecule of No. 3300, the δ-diethylamino-α-methylbutylamino group of this drug was replaced by a number of aminoalkylamino residues and also by a number of simple amino and hydrazino groupings. A number of such variations are shown in Table II.

iii. *Simultaneous variation of the aryl residue (Ar) and the aliphatic residue (R).*—Nine compounds having both these groups different from those in No. 3300 were examined. The substituent groups were those which appeared most favourable from the results summarized in Tables I and II. No compound of outstanding activity was found, and the range of activity was within that shown by compounds given in Tables I and II. These results are therefore not reported in detail.

TABLE II

Therapeutic tests on some 2-*p*-chloroanilino-6-methylpyrimidines containing an aminoalkylamino or amino or hydrazino residue in position 4. Doses given orally twice daily by syringe and catheter.

Compounds of the form:

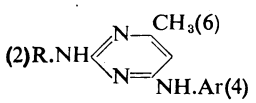


No.	R	R′	Dose (mg. per 20 g. mouse)	Increased mean survival time (days)	Increase required for significance (days)
4874*	β-aminoethyl	H	1.0 2.0	−0.5 +1.6	1.4
3671	γ-butylaminopropyl .	H	0.5 1.0	+0.3 +1.6	1.6
3557	γ-piperidinopropyl ..	H	0.1 0.25 0.5	−0.6 +0.8 +2.2	1.7
			0.5 1.0	+2.7 +4.2	1.8
5718	γ-diethylamino-α-methylpropyl	H	1.0	+2.1	1.4
6112	γ-piperidino-α-methylpropyl	H	0.25 0.5	+0.9 +1.4	1.1
6330	2-N-morpholino-methyl *cyclo*hexyl	H	0.5 1.0 2.0	+1.8 +3.6 +2.9	1.8
5556	γ-diethylamino-α:β-dimethylpropyl	H	0.5 1.0	+0.8 +1.6	1.3 1.8
6306	δ-diethylamino-α-methylbutyl	methyl	0.05 0.1	+0.3 +0.5	1.8
5007*	methyl ..	methyl	0.5 1.0	+0.5 +1.1	1.7
4456*	hydrazino	H	1.0	−1.2	1.4
4453*	β:β′-dimethylhydrazino	H	0.5 1.0	0 −0.6	1.5

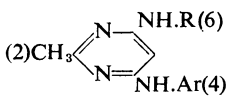
*Administered as free base and not as dihydrochloride.

iv. *Additional substituents in position 5 of the pyrimidine nucleus.*—Position 5 of the pyrimidine nucleus of compound No. 3300 is unsubstituted, and an examination was made of the effect of introducing aliphatic residues such as methyl, ethyl, and *iso*propyl, halogen atoms such as bromine, and nitro or amino groups in this position. All compounds so substituted, except that in which the new group was methyl, were completely lacking in activity, as were seven other compounds carrying one or other of these substituents in position 5, but derived from other active compounds of Tables I and II. The activity of the compound No. 5671, 2 - *p* - chloroanilino-4- δ -diethylamino - α - methylbutylamino-5 : 6-dimethylpyrimidine, was equal to or better than No. 3300.

v. *Positional isomerism.*—Two series of positional isomers are known. Some members of the 4-arylamino - 2 - aminoalkylamino - 6 - methylpyrimidine series exhibit a degree of antimalarial activity at least equal to that found in the parent series (Curd, Davis, Owen, Rose, and Tuey, 1946) whereas the 4 - arylamino - 6 - aminoalkylamino-2-methylpyrimidine compounds are all inactive (Basford, Curd, and Rose, 1946). These two isomeric types may be represented by the generalized formulae below.



4 : 2 : 6 type



4 : 6 : 2 type

(Ar = an aryl residue, R = an aliphatic residue usually containing another basic centre.)

We have examined 24 compounds derived from these two series, which were prepared with those arylamino and aminoalkylamino residues which previous results had shown to be most likely to give active compounds. Certain examples had a methyl substituent as an additional " favourable " group in position 5. These results are not given in detail, for although activity was found in both series (in the 4 : 6 : 2 series, only with a methyl group in position 5) it was in all instances of a low order. Neither of the isomers of No. 3300 and only one of those of No. 5671 showed activity.

vi. *Replacement of the imino linkage uniting aryl and pyrimidyl nuclei by a sulphur or an oxygen atom.*—The effect of this change, which has been shown to result in diminished but still detectable antimalarial activity in the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines and their 4 : 2 : 6 isomers (Curd, Davis, Hoggarth, and Rose, 1947), has been investigated in all three isomeric series. No activity whatever was found in the seventeen examples of ethers and thioethers examined.

Discussion

The aim of the work summarized here was the discovery of a compound of the diaminomethylpyrimidine class with greater antituberculous activity than that possessed by compound No. 3300. This aim has not been realized, and it would appear that in compound No. 3300 itself and a number of closely related compounds we have reached the maximum activity possible in this particular chemical group. It is noteworthy that the essential structural requirements for antituberculous activity *in vivo* are similar to, but not identical with, those necessary for antimalarial activity. For antituberculous activity in mice the diaminomethylpyrimidine nucleus must have one amino group substituted by an aryl residue preferably containing a *para* substituent (though some *meta* substituents confer activity), and the other by a basic alkyl residue, the new basic centre being separated from the imino linkage by a chain of carbon atoms. Of the extra substituents which have been tried in position 5 of the pyrimidyl ring, all except methyl have an unfavourable effect. These requirements correspond to what has been found necessary for activity against *Plasmodium gallinaceum* in chicks (Curd and Rose, 1946 ; Curd, Richardson, and Rose, 1946), except that no member of the 4-arylamino-6-aminoalkylamino - 2 - methylpyrimidine series has shown antimalarial activity. A low degree of antimalarial activity is retained in the 4-arylamino-2-aminoalkylamino- 6 -methylpyrimidines when the imino link uniting the aryl and pyrimidyl nuclei is replaced by oxygen or sulphur : this change in all three isomeric series abolishes antituberculous activity.

Summary

More than one hundred diaminomethylpyrimidines and related compounds have been examined for antituberculous activity in mice. The relationship between activity and chemical constitution is discussed.

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