Synthese en chemotherapeutisch onderzoek van sulfanilamidopyrimidinen

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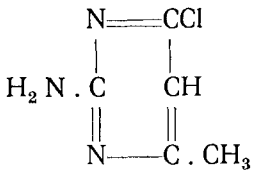
SUMMARY

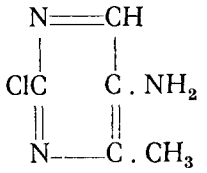
In order to investigate the influence of substitution in the pyrimidine nucleous on the activity of the three isomeric sulfanilamidopyrimidines (2, 5 and 6), a number of substituted sulfanilamidopyrimidines were synthesized and tested on chemotherapeutic activity.

The sulfanilamide derivatives were obtained by interaction of acetylsulfanilylchloride or p.nitrobenzenesulfonylchloride with aminopyrimidines, in the presence of anhydrous pyridine. The intermediate acetylamino- or nitro-compounds were converted into the final products by alkaline hydrolysis or by reduction with iron in alcoholic solution.

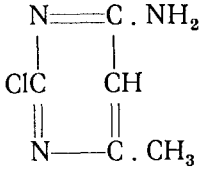
In order to obtain the substituted aminopyrimidines, we prepared the following three amino-chloro-methylpyrimidines.



2-amino-4-methyl-6-chloropyrimidine



5-amino-2-chloro-4-methylpyrimidine



6-amino-2-chloro-4-methylpyrimidine

We further made some amino-chloropyrimidines and one amino-chloro-dimethylpyrimidine.

The chlorine atom in all these compounds is active. Catalytic hydrogenation replaces it by a hydrogene atom. When reacting with sodium alkanolates, sodium mercaptides or aniline, the chlorine atom is replaced by an alkoxy, an alkylthio or an anilino group. A number of the substituted aminopyrimidine derivatives were hitherto unknown in chemical literature.

The synthesis of these compounds was worked out.

An investigation of the chemotherapeutic activity of the sulfanilamidopyrimidines was made in white mice that had been infected with pneumococci.

The mice were injected intraperitoneally with 0.5 ml of the dilution 5.10^{-5} of a 17 hours old culture in 6 % ascites broth of pneumococcus type I (named America I [1]). In this manner the inoculum contained about 20000 organisms (2000 — 4000 M.L.D.). Once a day 0.4 ml of a 10 % suspension of the drug in water (40 mg) was administered by a stomach tube, the first time immediately before the infection. The treatment was continued for five days, unless the mouse died before.

The effect of the administering of the compound in infected mice was traced by suspending a loopful of blood from the tail twice daily in ascites agar, and counting the resulting pneumococcus colonies. Besides the mouse which was infected and treated with the investigated compound (test mouse), another was infected and treated with sulfanilamidopyridine (dagénan mouse); a third mouse (control) was only infected with an equal dosis of the same culture of pneumococci. By comparing the course of the septicemia in these three mice, we deduced the activity of the compound. Each sulfanilamide derivative was tested in two such series (test mouse, dagénan mouse and control mouse).

For the results see the table on p. 69.

The three isomeric sulfanilamido-4-methylpyrimidines have an equal or larger activity as sulfanilamidopyridine; consequently the position of the sulfanilamido group has no influence in this case.

The presence of a methyl group in position 4 of the pyrimidine nucleus proved to increase the activity of the compound; this was especially the case with the 6-sulfanilamidopyrimidines.

The introduction of a methyl group in position 5 decreases the activity. The presence of several other groups (methoxy, methylthio, phenylthio, anilino) has the same effect, and increases the toxicity in some cases. The last property depends on the position of the sulfanilamido group.

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[1]) See: J. Mulder, Antonie van Leeuwenhoek **6**, 221 (1940).