# THE BIOLOGICAL AND CHEMICAL PROPERTIES OF 4-AZIDOBENZENESULPHONAMIDE ('AZIDOSULPHANILAMIDE')

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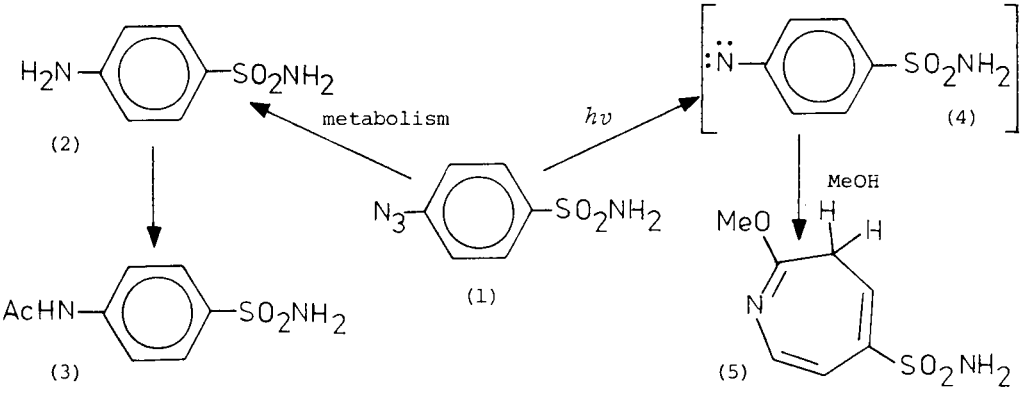
Organic azides are the forgotten group in medicinal chemistry although they possess distinctive properties which could be exploited in drug design. The azido group exerts -I and +M electronic effects comparable to bromo and acetamido substituents; in size and lipophilicity it closely resembles the bromo group. The properties of azidosulphanilamide (1) have been examined a) to establish if this azide is a potential pro-drug modification of sulphanilamide, and b) to investigate its role as a precursor of a reactive nitrene species. Nitrene intermediates generated from other azides are capable of versatile interactions with bio-macromolecules (Knowles 1972).

Azidosulphanilamide (1) was administered to rats (i.p.) at a dose of 25 mg/Kg. Examination of a dichloromethane extract of the urine by t.l.c. revealed the presence of sulphanilamide (2), its acetyl derivative (3), unchanged azidosulphanilamide and traces of an unidentified metabolite. Clearly the azido substituent is undergoing metabolic reduction to the amine (sulphanilamide) which is then being further metabolised by acetylation.




Photolysis of the azide in methanol affords a low yield of 2-methoxy-3H-azepine (5) but no sulphanilamide or azobenzene-4,4'-disulphonamide are formed. Ring expansion is frequently encountered in the photolysis of *ortho*-substituted azides (Mair & Stevens, 1971) and in the present case implies the intermediacy of the reactive singlet nitrene species (4).

Azidosulphanilamide has no inhibitory action *in vivo* against lymphoid leukaemia L-1210 in mice at a dose of 400 mg/Kg, or against cultured L-1210 cells *in vitro* in the dark ($ID_{90}$ >1000μg/ml). However, the azide is cytotoxic ($ID_{90}$ ~25 μg/ml) when incubated with L-1210 cells in the light (366 nm). Interestingly, pre-irradiation of the drug solution by light before exposure to L-1210 cells abolishes activity ($ID_{90}$ >1000μg/ml) and it is possible that the nitrene species (4) is the destructive agent.

Knowles, J.R. (1972) *Accounts Chem. Res.* 5: 155-160
Mair, A.C., Stevens, M.F.G. (1971) *J. Chem. Soc. (C).* 2317-2324