α-HYDROXYLATED TRIAZENES: POTENTIAL ACTIVE METABOLITES OF ANTI-TUMOUR DIMETHYLTRIAZENES

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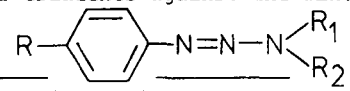
Oxidation of the dimethylamino side-chain is believed to play an important role in the metabolic activation of antitumour dimethyltriazenes. When incubated with liver homogenates, or *in vivo*, these agents are demethylated with the liberation of formaldehyde and the formation of a highly reactive alkylating agent — a monomethyltriazene (Connors & others, 1976). Although the intermediate hydroxymethyltriazenes have hitherto been regarded as only transient species we have achieved a novel synthesis of this type by coupling aryldiazonium salts with a formaldehyde/methylamine mixture in aqueous media. Surprisingly, hydroxymethyltriazenes bearing electron-attracting substituents in the aryl ring are stable crystalline compounds.

The hydroxymethyltriazene (1a) proved to be the most active triazene yet tested against the TLX5 lymphoma in mice (Table): it is substantially more active than either the corresponding monomethyltriazene (1b) or the dimethyltriazene (1c).

Table. Antitumour activity of triazenes against the TLX5 lymphoma in mice

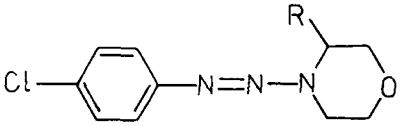
(1) 

	Compound R	R_1	R_2	Maximum % increase in survival time	Optimal dose (mg/kg) (5 x daily)	Toxic dose (mg/kg) (5 x daily)
(1a)	CO_2Me	Me	CH_2OH	120	5	160
(1b)	CO_2Me	Me	H	87	5	80
(1c)	CO_2Me	Me	Me	58	40	160*

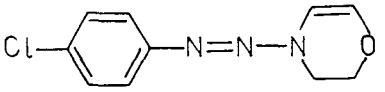
*From Connors & others (1976)

In addition the related hydroxymethyltriazene (1: R = CO_2Et, R_1 = Me, R_2 = CH_2OH) displays inhibitory activity *in vitro* against TLX5 lymphoma cells whereas its dimethyltriazene counterpart (1: R = CO_2Et, R_1 = R_2 = Me) is inactive. This confirms the activated nature of the former triazene.

Another stable α-hydroxylated triazene (2a) can be prepared (25% yield) simply by stirring the morpholinotriazene (2b) with potassium permanganate in aqueous acetone at 25°. The morpholin-3-ol (2a) undergoes a 1,2-elimination in acetyl chloride/pyridine at 25° to afford the dehydromorpholinotriazene (3). The morpholin-3-ol (2a) is also detected in extracts from the morpholinotriazene (2b) that have been incubated with rat liver homogenates.



(2) a: R = OH
b: R = H



(3)

Connors, T.A., Goddard, P.M. & others (1976). *Biochem. Pharmac.*, 25, 241-246.