ANTITRICHOMONAL AGENTS
TRIAZEN DERIVATIVES

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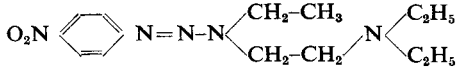
Six new triazens have been synthesised. One of these compounds, 3-(2′-diethylaminoethyl)-3-ethyl-1-(*p*-nitrophenyl)-triazen was active in mice against *Trichomonas vaginalis* but inactive against *Trichomonas foetus*.

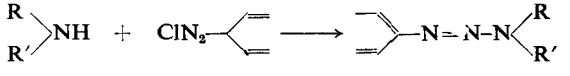
As outlined previously (Michaels and Strube, 1961), there is a need for a suitable systemically active agent against *Trichomonas vaginalis*. While screening many compounds the *in vitro* and *in vivo* activity of 3-(2′-diethylaminoethyl)-3-ethyl-1-(*p*-nitrophenyl)triazen against *T. vaginalis* was uncovered. Therefore, the syntheses and evaluation of a number of triazen derivatives related to I was undertaken.



I

CHEMICAL

Triazens are derivatives of the unknown base triazen, $HN{=}N{-}NH_2$, a compound consisting of a chain of three nitrogen atoms, two being united by a double bond. A number of triazen derivatives are important intermediates for the dyestuff industry (Saunders, 1949). These triazens are prepared by treating aromatic diazonium salts with secondary amines carrying solubilising groups such as sulphonic acid, carboxyl or hydroxyl groups. Attempts to solubilise certain insoluble sulpha drugs by



transforming the aromatic amino group to a solubilising triazen group have been made with the supposition that the active sulpa drug would be liberated again *in vivo*.

The triazens reported in this communication were prepared by treating aromatic diazoniumchlorides with 1-diethylamino-2-monoethylamino-ethane $(C_2H_5)_2NCH_2CH_2NHC_2H_5$.

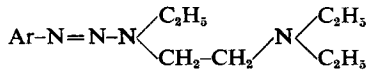
Experimental

General procedure for preparing triazens of type I. A filtered aqueous solution of the benzenediazonium salt, prepared in the usual way from the aromatic amine (0·1 mole), was added dropwise in about 30–45 min. from a cooled dropping funnel to a cooled (0–35°), stirred solution of 1-diethylamino-2-monoethylaminoethane (Damiens, 1951) (0·1 mole) in water (150 ml.) containing an excess of 30 per cent sodium carbonate

over that required for the neutralisation of the acid. After adding the diazonium salt solution, stirring was continued for 30 min. The triazen, which separated as a dark coloured oil, was extracted with ether and

TABLE I

TRIAZENS



Comp. No.	Triazens	Ref.	B.P.°/ mm.	Yield per cent	Analysis					
					Calculated			Found		
					C	H	N	C	H	N
1	3-(2-Diethylaminoethyl)-3-ethyl-1-(*p*-nitrophenyl)-triazen	Saunders (1949a)	195°/0·08	60	57·32	7·90	23·81	57·41	7·77	23·62
2	1-(*p*-Chlorophenyl)-3-(2-diethylaminoethyl)-3-ethyltriazen	Shirley (1951)	127–134°/ 0·02–0·1	68	59·45	8·14	12·54 Cl = 19·81	59·87	8·58	12·50 Cl = 19·11
3	3-(2-Diethylaminoethyl)-3-ethyl-1-(*p*-methoxyphenyl)-triazen	Shirley (1951a)	145°/0·07	46	64·71	9·42	20·13	64·41	9·26	19·56
4	3-(2-Diethylaminoethyl)-3-ethyl-1-(*p*-methylsulphonylphenyl)-triazen	Waldron and Reid (1923)	214–217°/ 0·08–0·09	61	55·18	8·03	17·16 S = 9·82	55·17	7·85	16·92 S = 10·03
5	3-(2-Diethylaminoethyl)-3-ethyl-1-(*p*-cyanophenyl)-triazen	Waldron and Reid (1923)	167–171°/ 0·03–0·04	67	66·88	8·51	25·62	66·28	8·38	25·26
6	3-(2-Diethylaminoethyl)-3-ethyl-1-(*o*-nitrophenyl)-triazen	Jacobs, Heidelberger and Rolf (1918) Shirley (1951b)	162–166°/ 0·04–0·06	54	57·32	7·90	23·81	57·14	8·07	23·2

dried over anhydrous magnesium sulphate. After removing the solvent the residual triazen was distilled under reduced pressure. For this distillation the distilling flask was immersed as far as possible in the oil bath. Table I summarises the results.

Biological

The methods for evaluation of compounds against *Trichomonas vaginalis* and *Trichomonas foetus* have been outlined by Michaels and

TABLE II

In vitro ACTIVITIES AGAINST *T. vaginalis* AND *T. foetus*

Compound No.	*T. vaginalis* Endpoint		*T. foetus* Endpoint	
	μg./ml.	μM/l.	μg./ml.	μM/l.
1	500	1700	200	682
2	500	1770	100	355
3	200	1720	200	1720
4	Inactive	Inactive		
5		Inactive *in vivo*		
6		Inactive *in vivo*		

Strube (1961). All the triazens mentioned were inactive *in vivo* against *T. foetus*. Besides 3-(2'-diethylaminoethyl)-3-ethyl-1-(*p*-nitrophenyl)-triazen, none of the other triazens were active in mice against *T. vaginalis*. The median curative doses (CD50) of this compound were 25 mg./kg./day and 20·6 mg./kg./day by the oral and intraperitoneal route of administration, respectively. The tolerated dose was 100 mg./kg. by either route. Table II summarises the results obtained *in vitro*.

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