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ATHENS, GA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

1-Aryl-3,3-dialkyltriazenes as Tumor Inhibitors

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A series of 1-aryl-3,3-dialkyltriazenes was prepared by coupling a diazonium salt with a secondary (occasionally primary) amine in basic medium. Preliminary tests against Sarcoma-180 in the mouse indicate that at least one methyl group at N-3 is essential for activity.

The recent observation that 1-phenyl-3,3-dimethyltriazene (I, Ar = C_6H_5) and its *p*-tolyl and *p*-nitrophenyl analogs exhibited inhibition of mouse Sarcoma-180[1] prompted the synthesis and testing of a variety of their relatives. We wish to report the preparation and properties of some of these compounds, together with preliminary tests

$$\overset{1}{\text{Ar}}\text{N}=\overset{2}{\text{N}}-\overset{3}{\text{N}}(\text{CH}_3)_2 \qquad \text{I}$$

against mouse Sarcoma-180.[2]

The method of synthesis of these triazenes involved coupling of an aryldiazonium chloride with an amine, usually in a basic aqueous solution. The various modifications of this procedure are given in the experimental section. The physical properties are given in Table I.

Structural variations of I included introduction of one or more substituents in the aryl group at N-1 or use of a heterocyclic aryl group, and replacing one or both methyl groups at N-3 by hydrogen, higher alkyl and substituted alkyl, or a heterocyclic ring containing N-3. The changes were accomplished by use of an appropriately substituted diazonium salt or the desired primary or secondary aliphatic amine.

When a diazonium salt was coupled with methylamine, both mono- and disubstitution occurred, and the product was a mixture of the 1-aryl-3-methyltriazene and the 1,5-diaryl-3-methylpentazdiene (II). These were readily separated by virtue of the insolubility of II in methanol. Some of the triazenes with a hydrogen at N-3 were thermally unstable and decomposed vigorously on attempted vacuum distillation.

$$\text{ArN}=\text{N}-\text{N}(\text{CH}_3)-\text{N}=\text{N}-\text{Ar} \qquad \text{II}$$

The products derived by coupling diazonium salts with ethylenimine were likewise thermally unstable. Those which were solids could in some cases be purified by careful crystallization, but the liquids invariably decomposed on distillation. The isolated product from benzene- or *p*-toluenediazonium chloride and ethylenimine was the aryl azide. The other product (not isolated) was presumably ethylene. This facile pyrolytic cleavage at 60–75° of triazenes has not previously been reported.

$$\text{ArN}=\text{NN}\begin{array}{l}\text{CH}_2\\ |\\ \text{CH}_2\end{array} \longrightarrow \text{ArN}_3 + \text{CH}_2=\text{CH}_2$$

It would be of interest to study the pyrolysis of the unstable 1-aryl-3-alkyltriazenes, which might give an aryl azide and an alkane.

The preliminary results of animal tests show that tumor inhibition is exhibited to some extent only by triazenes having at least one methyl group at N-3, including 1-phenyl-, 1-*p*-nitrophenyl-, 1-*p*-methoxyphenyl-, 1-*o*-tolyl-, and 1-*m*-trifluoromethyl-3,3-dimethyltriazene. 1-*p*-Tolyl-3-methyltriazene and 1-*p*-tolyl-3-methyl-3-cyclohexyltriazene also showed some activity. 1-Phenyl-3,3-dialkyltriazenes where both alkyl groups were larger than methyl, as well as those containing a heterocyclic ring incorporating N-3, were inactive.

EXPERIMENTAL

The aromatic amines were commercial samples, purified when deemed necessary. The aliphatic amines were obtained chiefly from the Eastman Kodak Co. and were used as received in most cases.

The aromatic amine was diazotized in the presence of 3 moles of hydrochloric acid, except in the few cases where the amine was so weakly basic as to require more acid. The solution was then filtered. The coupling with the aliphatic amine was carried out in one of the following ways, where the letters refer to the procedures in Table I.

(1) Clarke, Barclay, Stock, and Rondestvedt, *Proc. Soc. Expt. Biol. Med.*, **90**, 484 (1955).

(2) Testing is being carried out at the Sloan-Kettering Institute for Cancer Research, under the direction of Dr. D. A. Clarke and Dr. C. Chester Stock. The details will be reported elsewhere.

TABLE I

PROPERTIES OF TRIAZENES ArN=N—N(R)(R′)

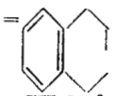
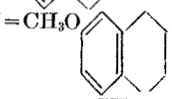
Ar	R	R′	Method	Yield, %	M.P.° (B.P.°/Mm.)	Formula	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Cryst. Solv.[a]	Color, Form
Phenyl	$HOCH_2CH_2$	$HOCH_2CH_2$	A	82	(140–160/1, dec.)	$C_{10}H_{15}N_3O_2$	57.40	7.23	57.52	7.14		
	n-C_3H_7	*n*-C_3H_7	A	82	(100–104/0.5)	$C_{12}H_{19}N_3$	70.20	9.33	70.18	9.19		
	i-C_3H_7	*i*-C_3H_7	A	69	40.0–40.2	$C_{12}H_{19}N_3$	70.20	9.33	70.26	9.29		
	n-C_4H_9	*n*-C_4H_9	A	84	(123–125/0.8)	$C_{14}H_{23}N_3$	72.05	9.94	72.08	9.80		
	i-C_4H_9	*i*-C_4H_9	A	75	(106–108/0.7)	$C_{14}H_{23}N_3$	72.05	9.94	72.24	9.76		
	s-C_4H_9	*s*-C_4H_9	A	71	(109–111/0.3)	$C_{14}H_{23}N_3$	72.05	9.94	71.95	9.65		
	n-C_5H_{11}	*n*-C_5H_{11}	B	60	(140–141.5/1.0)	$C_{16}H_{27}N_3$	73.51	10.41	72.49	10.00		
	i-C_5H_{11}	*i*-C_5H_{11}	B	62	(128–130/1.0)	$C_{16}H_{27}N_3$	73.51	10.41	73.53	10.26		
	n-C_6H_{13}	*n*-C_6H_{13}	B	70	(156–158/0.6)	$C_{18}H_{31}N_3$	74.69	10.80	74.81	10.49		
	i-C_6H_{13}	*i*-C_6H_{13}	B	48	(144–145/0.7)	$C_{18}H_{31}N_3$	74.69	10.80	74.62	10.58		
	cyclohexyl	cyclohexyl	B	38	127–128	$C_{18}H_{27}N_3$	75.74	9.54	75.92	9.43	B	White prisms
	RR′ = tetramethylene		A	86	49–50	$C_{10}H_{13}N_3$	68.54	7.48	68.66	7.53	P1	White needles
o-Tolyl	CH_3	CH_3	A	86	(78–79/0.5)[b]							
p-Tolyl	CH_3	cyclohexyl	C	85	(122/0.1)	$C_{14}H_{21}N_3$	72.68	9.15	72.53	9.03		
	CH_3	phenyl	D	84	66.5–68[c]	$C_{14}H_{15}N_3$	74.63	6.71	74.75	6.68	P1	Yellow leaflets
	CH_3	H	—	—	81–82[e]	$C_8H_{11}N_3$	64.40	7.43	64.36	7.34	MW	Creamy leaflets
	CH_3	*p*-tolylazo-	E[d]	—	147 (dec.)	$C_{15}H_{17}N_5$	67.39	6.41	67.58	6.51	P3	Yellow needles
	RR′= 		C	66	75–76	$C_{16}H_{17}N_3$	76.46	6.82	76.09	6.81	P2	Pink needles
	RR′=CH_3O 		C	82	71.5–72.5	$C_{17}H_{19}N_3O$	72.56	6.89	72.59	6.75	P2	Orange-red plates
2,3-Xylyl	CH_3	CH_3	A	79	(120–121/5)	$C_{10}H_{15}N_3$	67.76	8.53	67.80	8.43		
2,4-Xylyl	CH_3	CH_3	C	90	53–53.5	$C_{10}H_{15}N_3$	67.76	8.53	67.83	8.40	P1	Beige plates
2,6-Xylyl	CH_3	CH_3	C	74	(72–73/0.3)	$C_{10}H_{15}N_3$	67.76	8.53	67.79	8.48		
Mesityl	CH_3	CH_3	C	80	(83/0.4)[f]	$C_{11}H_{17}N_3$	69.07	8.96	69.09	8.76		
2,6-Diethylphenyl	CH_3	CH_3	A	45	(94.0–94.5/0.3)	$C_{12}H_{19}N_3$	70.20	9.33	70.64	9.20		
p-Hydroxyphenyl	CH_3	CH_3	C	19	93.5 (dec.)	$C_8H_{11}N_3O$	58.16	6.71	58.47	6.60	B;E-P2	Yellow rect. leaflets
o-Anisyl	CH_3	CH_3	C	86	(89.5–90.5/0.2)[g]	$C_9H_{13}N_3O$	60.31	7.31	60.20	7.12		
p-Anisyl	CH_3	cyclohexyl	C	80	(152/0.4)	$C_{14}H_{21}N_3O$	67.98	8.52	67.86	8.29		
	CH_3	*p*-anisylazo	E	—	110–110.5 dec.[h]	$C_{15}H_{17}N_5O_2$	60.19	5.72	60.34	5.94	P3; M	Deep yellow needles
o-Phenetyl	CH_3	CH_3	C	90	(104.5/0.4)	$C_{10}H_{15}N_3O$	62.15	7.82	62.35	7.65		
m-Phenetyl	CH_3	CH_3	C	92	60.5–61.5	$C_{10}H_{15}N_3O$	62.15	7.82	62.07	7.81	P1; M	Pale brown prisms
p-Phenetyl	CH_3	CH_3	C	100	53.5–54	$C_{10}H_{15}N_3O$	62.15	7.82	61.79	7.71	P1	Buff plates
2,5-Diethoxyphenyl	CH_3	CH_3	A	33	(139–140/0.5)	$C_{12}H_{19}N_3O_2$	60.73	8.07	59.41	7.63		
p-Dimethylamino-phenyl	CH_3	CH_3	C	100	92–93.5	$C_{10}H_{16}N_4$	62.47	8.39	62.92	8.19	MW; P3	Yellow laths

TABLE I *Continued*

Ar	R	R′	Method	Yield, %	M.P° (B.P.°/Mm.)	Formula	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen	Cryst. Solv.[a]	Color, Form
m-Bromophenyl	CH_3	CH_3	A	93	(101–102/0.25)	$C_8H_{10}BrN_3$	42.12	4.42	42.22	4.40		
p-Bromophenyl	CH_3	CH_3	D	59	63–63.5[i]						P1	Buff needles
	CH_3	H		—	86–87[j]						P2; MW	Creamy plates
	CH_3	*p*-bromophenylazo	E	—	142–142.5 (dec.)	$C_{13}H_{11}Br_2N_5$	40.25	2.79	40.31	2.64	B	Yellow laths
	RR′ = ethylene		F	33	56–56.5 (dec.)	$C_8H_8N_3Br$[k]	42.50	3.57	42.66	3.60	P1	Yellow prisms
o-Chlorophenyl	CH_3	CH_3	A	83	(146.3–146.5/12)[l]							
m-Chlorophenyl	CH_3	CH_3	A	96	(97–99/0.4)[m]							
m-Trifluoromethylphenyl	CH_3	CH_3	A	87	(76–78/1.3)	$C_9H_{10}F_3N_3$	49.77	4.64	50.87	4.80		
o-Nitrophenyl	CH_3	CH_3	C	85	32.5–33.5[n]	$C_8H_{10}N_4O_3$	49.48	5.19	49.52	5.07		
p-Nitrophenyl	CH_3	cyclohexyl	C	87	81–82	$C_{13}H_{18}N_4O_2$	59.52	6.92	59.52	6.65	P2	Orange needles
5-Chloro-2-methoxyphenyl	CH_3	CH_3	A	74	56.5–57.0	$C_9H_{12}ClN_3O$	50.59	5.66	50.73	5.54	P2; B	Yellow-orange Needles
2-Methoxy-4-nitrophenyl	CH_3	CH_3	C	92	113–113.5	$C_9H_{12}N_4O_3$	48.20	5.39	48.23	5.27	B-P1	Yellow needles
2-Methoxy-5-nitrophenyl	CH_3	CH_3	C	100	140.5–141	$C_9H_{12}N_4O_3$[o]	48.20	5.39	48.30	5.32	Bu; P3	Yellow-orange needles
4-Methyoxy-2-nitrophenyl	CH_3	CH_3	A	75	57–58	$C_9H_{12}N_4O_3$	48.20	5.39	48.33	5.30	B; E	Red-orange prisms
α-Naphthyl	CH_3	CH_3	G	48	38.5–39	$C_{12}H_{13}N_3$	72.33	6.58	72.58	6.42	P1	Red-purple prisms
β-Naphthyl	CH_3	CH_3	G	94	57–57.2[p]	$C_{12}H_{13}N_3$	72.33	6.58	72.25	6.49	P1	Red-brown prisms
3-Trifluoromethyl-4-nitrophenyl	CH_3	CH_3	C	85	70.5–71.5	$C_9H_9F_3N_4O_2$[q]	41.23	3.50	42.47	3.94	B-P1	
2-Methyl-4-nitrophenyl	CH_3	CH_3	C	100	120–120.5	$C_9H_{12}N_4O_2$	51.91	5.81	52.15	5.72	P3	Yellow leaflets or needles
4,4′-biphenylenebis	CH_3	CH_3	C	100	176–176.5	$C_{16}H_{20}N_6$	64.84	6.80	64.70	6.79	B; E	Yellow leaflets
2-Thiazolyl	CH_3	CH_3	H	33	75–75.5	$C_5H_8N_4S$	38.44	5.16	38.46	4.99	I; C-P1	Yellow laths
3-Quinolyl	CH_3	CH_3	C[r]	good	131.5 expl.[s]	$C_{11}H_{12}N_4$[t,u]	65.98	6.04	62.30	4.15	A[v]	Orange prisms
3-Pyridyl	CH_3	CH_3	C[r]	76	(81/0.3)	$C_7H_{10}N_4$[w]	55.98	6.71	55.49	6.88		

[a] P1 = pet. ether 40–60°; P2 = pet. ether 60–75°; P3 = pet. ether 90–100°; B = benzene; M = methanol; E = ethanol; W = water; I = isopropyl ether; C = carbon tetrachloride; A = acetone; Bu = butanol. [b] Cook *et al.*, *J. Am. Chem. Soc.*, 142 (1950), gave b.p. 128–129° (12 mm.). [c] Day, Campbell, and Coppinger, *J. Am. Chem. Soc.*, **73,** 4687 (1951), gave m.p. 67–67.8°, but no yield. [d] Goldschmidt and Badl, *Ber.*, **22,** 935 (1889), obtained only the pentazdiene. [e] Dimroth, Eble, and Gruhl, *Ber.*, **40,** 2397 (1907), prepared it by a Grignard reaction and give m.p. 81.5°. [f] Melts near 10°. [g] Adams and Hey, *J. Chem. Soc.*, 1521 (1951), gave b.p. 155° (18 mm.). [h] Goldschmidt and Badl[d] gave m.p. 111–112°. [i] Hunter, *J. Chem. Soc.*, 320 (1937), gave m.p. 62.5° but no yield. [j] Dimroth, Eble and Gruhl[e] gave m.p. 86–86.5°; *via* Grignard. [k] % N: calcd. 18.59, found 18.47. [l] LeFevre and Liddicoet, *J. Chem. Soc.*, 2743 (1951), gave b.p. 164–166° (27 mm.); there is a misprint in the paper, where this compound is called the *para* isomer. [m] Reported[l] b.p. 148–151° (20 mm.), no yield. [n] Reported[f] m.p. 31–32°; no yield given. [o] % N: calcd. 24.99; found 25.21. [p] Reported[3] m.p. 57–58°, no yield. This compound is incorrectly listed in *Chem. Abstr.* **38,** 74[2] (1944), as the β-isomer. [q] % N: calcd. 21.37, found 21.81. [r] Four moles of sulfuric acid used instead of hydrochloric acid during the diazotization. [s] Adams, Hey, Mammalis, and Parker, *J. Chem. Soc.*, 3181 (1949) gave m.p. 80–90° dec., and no analysis. [t] % N: calcd. 27.98; found 23.4. [u] Explodes during microanalysis. [v] The crude product is very unstable. It must be filtered and washed thoroughly with ice water, then recrystallized while wet. If it is allowed to dry while crude, it decomposes in a puff of smoke. The purified material darkens rapidly, but less dramatically, on storage. [w] % N: calcd. 37.3; found 37.61.

Method A.[3] The low-molecular weight, water-soluble amine was mixed with an excess of sodium carbonate solution containing ice, and the diazonium solution was added rapidly dropwise during about 10 to 20 min. (0.1–0.3 molar scale). After being stirred for about 0.5 hr. at 5–10°, the product was isolated as described below.

Method B. Water-insoluble amines were dissolved in water containing one equivalent of hydrochloric acid. This cold solution was mixed with the diazonium solution, and the entire mixture was added to an excess of cold sodium carbonate solution.

Method C. The amine was dissolved in the diazonium solution (water-insoluble amines were dissolved first in dilute acid), and sodium hydroxide solution was added at 5–10° until the mixture was alkaline. The use of sodium hydroxide as base is novel, and it offers advantages of convenience and yield over the sodium carbonate procedure.

Method D. Like Method C, except that sodium acetate was used as the base.

Method E. Methylamine was added to the diazonium solution until the mixture was alkaline (large excess). The crude product was collected, washed with water, and triturated with methanol. The pentazdiene was insoluble in methanol. Addition of water to the filtrate precipitated the triazene. The product from *p*-anisyldiazonium chloride and methylamine was a solid pentazdiene and a liquid triazene (?) which exploded on distillation. The product from benzenediazonium chloride and *t*-butylamine was a liquid which exploded on attempted distillation.

Method F. Sodium acetate solution was added to the diazonium solution to remove mineral acidity. Two equivalents of ethylenimine were then added, followed by an excess of sodium acetate. The product was filtered off. An additional quantity of product was obtained by adding sodium carbonate to the filtrate.

Method G. Like Method D, except that sodium carbonate was added after the addition of sodium acetate.

Method H. The amine (0.2 mole) in 150 g. of concentrated sulfuric acid and 70 g. of water was diazotized with sodium nitrite. The procedure then followed Method C.

Isolation of products. Following coupling by one of the above procedures, the liquid products were separated and the aqueous layer was extracted with ether, benzene, carbon tetrachloride, or petroleum ether (b.p. 60–75°). The combined organic layers were washed with water, dried with potassium carbonate or sodium or magnesium sulfate, then vacuum-distilled.

The solid products were collected, washed with water, and dried. Occasionally, the aqueous filtrates were extracted with an organic solvent and the extracts were evaporated. The low-melting, low-molecular weight products were in general vacuum-distilled before crystallization; the high-molecular weight triazenes were crystallized, often with the aid of charcoal. Petroleum ether was usually a satisfactory crystallization solvent, though for the less soluble compounds, some benzene was added. Occasionally methanol or butyl alcohol was used.

Formation of azides on pyrolysis of 1-aryl-3,3-ethylenetriazenes. *p*-Toluenediazonium chloride was coupled with ethylenimine according to Method F. The dark red oil could not be induced to crystallize from petroleum ether. After vacuum drying, it was analyzed.

Anal.[4] Calcd. for $C_9H_{11}N_3$ (triazene): C, 67.05; H, 6.88. Found: C, 67.84; H, 6.10.

This oil decomposed steadily on attempted distillation, giving a product, b.p. 31.5° (0.15 mm.); reported for *p*-tolyl azide, b.p. 80° (10 mm.).[5]

Anal. Calcd. for $C_7H_7N_3$: C, 63.13; H, 5.30. Found: C, 63.58; H, 5.31.

Method F applied to *p*-anisyldiazonium chloride gave an oil which was not analyzed but was distilled directly. The distillate boiled at 45–46° (0.1 mm.). The analysis suggests a mixture of 60% of *p*-anisyl azide and 40% of 1-*p*-anisyl-3,3-ethylenetriazene.

Anal. Calcd. for mixture of 60% $C_7H_7N_3O$ and 40% $C_9H_{11}N_3O$: C, 58.18; H, 5.34. Found: C, 58.20; H, 4.94.

Method F applied to benzenediazonium chloride gave a crude product which decomposed on distillation. The redistilled volatile material boiled at 63–66° (21 mm.); reported for phenyl azide, b.p. 66–68° (21 mm.).[6] The infrared spectrum exhibits a strong band at 2120 cm.$^{-1}$ which is characteristic of aryl azides; authentic triazenes do not absorb in this region. Its ultraviolet spectrum showed peaks at 285, 278, and 248 mμ, with intense end absoprtion.

p-Nitrobenzenediazonium chlorides and ethylenimine appeared to give the triazene, m.p. 70–70.5° (vigorous dec.), yellow leaflets from petroleum ether (60–75°). However, on standing, it decomposed to impure *p*-nitrophenyl azide.

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(3) Elks and Hey, *J. Chem. Soc.*, 441 (1943).

(4) Microanalyses by Spang Microanalytical Laboratory and by Anna Griffin in this laboratory.

(5) Dimroth and Pfister, *Ber.*, **43**, 2760 (1910).

(6) *Org. Syntheses*, **Coll. Vol. III**, p. 711.