1,3-Diaryltriazenes: A New Class of Anorectic Agents

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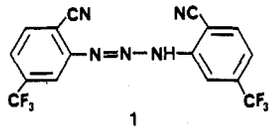
A series of substituted 1,3-diaryltriazenes has been synthesized and tested for anorectic activity. Several members of the series were effective; one compound, 1,3-bis[2-cyano-5-(trifluoromethyl)phenyl]triazene, was particularly active, causing weight loss in rats, dogs, and squirrel monkeys. It was devoid of overt central nervous system activity, and compared to previously reported biologically active triazenes, it was relatively nontoxic up to 30 days of drug administration.

In recent years, linear triazenes have attracted considerable biological interest. A number of reports have described the antitumor activity of 1-phenyl-3-alkyl- and 3,3-dialkyltriazenes;[1-5] 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (Dacarbazine, DTIC) has been evaluated clinically in the treatment of malignant melanoma.[6] Although QSAR studies by Hansch indicate little separation between toxicity and antitumor activity for this class of compounds,[7] chemical and biological interest continues.[2,8-11] Some 1-phenyl-3-hydroxy-3-methyltriazenes have been described as immunosuppressive agents.[12,13] Antifungal and phytotoxic properties have been ascribed to certain triazene derivatives,[14] and antitrypanosomal activity has been reported for a number of 1-aryl-3-alkyl-3-methyltriazenes;[15] these compounds may owe their biological activity in whole, or in part, to their possible cytotoxic effects. We now describe a series of 1,3-diaryltriazenes that display a pharmacological profile unique for this class of compounds and separate from cytotoxicity.

Our interest in the anorectic properties of 1,3-diaryltriazenes enjoys a twofold serendipitous origin. In the diazotization of 2-amino-4-(trifluoromethyl)benzonitrile (**43**), an unexpected triazene byproduct was isolated in 6% yield.[16] This compound was assigned the triazene structure 1 on the basis of spectroscopic and elemental ana-



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lytical data and by direct comparison with an independently synthesized sample (see Experimental Section). A growth-promotant screen, designed to identify compounds capable of enhancing body weight gain in young chicks, allowed the observation that, compared to controls, ingestion of 1 in feed at 5 ppm over 28 days resulted in a 30% body-weight loss with a feed efficiency of 90%. No overt toxicity was observed. This prompted the evaluation of 1 for its anorectic properties.

In summary, compound 1 induced anorexia and weight loss in rats, dogs, and squirrel monkeys without limiting side effects. The onset of the anorexia was slightly delayed and persisted without evidence of tolerance over periods up to 25 days. In contrast to phenethylamine-type agents, 1 was devoid of overt CNS activity. Subsequently, as part of a program in search of novel antiobesity agents free of abuse potential, 1 became a candidate for structure–activity studies.

Chemistry. The 1,3-diaryltriazenes in this series (Table I) were prepared in standard fashion from known or readily available anilines (Table II) by diazotization with sodium nitrite in hydrochloric acid (method 1) or by isoamyl nitrite in ether (method 2). Exceptions were compounds **1**, **3**, **4**, and **11**, which were prepared from anilines bearing strong electronegative substituents. The presence of these groups reduces the basicity of the amine; strong acid (50% sulfuric acid) was then required to effect protonation prior to generating the diazonium ion. The latter was subsequently allowed to couple with its precursor or, for mixed triazenes, with a different aniline.

Treatment of 1 with potassium hydroxide in ethanol, followed by methyl iodide addition, gave the *N*-methyltriazene **23**. Reaction of the 1,3-diaryltriazene with acid anhydrides in ether (method 8) or pyridine (method 7) or by generation of the triazene anion with NaH and subsequent reaction with the acid chloride (method 6) gave the *N*-acyl derivative. Unexpectedly, acylation of the anion derived from the unsymmetrical triazene **7** gave the regiospecific *N*-acetyl product **28**. Finally, treatment of 1 with the appropriate isocyanate, either neat or in ether solution (method 9), gave the *N*-carboxamido derivatives **37** through **40**. Compounds **37–40**, although stable at room temperature, appeared to undergo retroaddition at their

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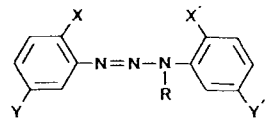
Table I. 1,3-Diaryltriazenes[a]



no.	X	Y	X′	Y′	R	formula	% yield	synth method	recrystn solv[b]	mp, °C	anal.[c]	dose, mg/kg	% bw rdn[d]	rdn food consump[e]
1	CN	CF_3	CN	CF_3	H	$C_{16}H_7F_6N_5$	12.6	3	E	193–194	C, H, N	50	2	3
2	CN	H	CN	H	H	$C_{14}H_9N_5$	37	1	H	143–144	*f*	50	0	2
3	CN	4-CF_3	CN	4-CF_3	H	$C_{16}H_7F_6N_5$	50	3	E/C	194–195	H, N; C[g]	50	2	2
4	CN	Cl	CN	Cl	H	$C_{14}H_7Cl_2N_5$	40	3	B	210–210.5	C, H, N	50	2	1
5	CN	CH_3	CN	CH_3	H	$C_{16}H_{13}N_5$	79	1	A	173	*h*	50	0	0
6	CN	CF_3	H	H	H	$C_{14}H_9F_3N_4$	16	4	H	145	C, H, N	50	1	1
7	CN	CF_3	2-Cl	6-Cl	H	$C_{14}H_7Cl_2F_3N_4$	29	4	H	147–148	C, H, N	50	3	1
8	CN	CF_3	H	4-CO_2H	H	$C_{15}H_9F_3N_4O_2$	44	4	E	192–192.5	C, H, N[i]	50	1	2
9	CN	CF_3	CO_2H	CF_3	H	$C_{16}H_8F_6N_4O_2$	26	4	C/H	188–188.5	C, H, N	50	1	1
10	H	CF_3	H	CF_3	H	$C_{14}H_9F_6N_3$	60	1	H	115–116	*j*	50	0	1
11	CO_2CH_3	CF_3	CO_2CH_3	CF_3	H	$C_{18}H_{13}F_6N_3O_4$	19	3	E	200–201	C, H, N	50	0	0
12	H	4-CF_3	H	4-CF_3	H	$C_{14}H_9F_6N_3$	34	2	H	116.5–117.5	*k*	50	0	0
13	H	CF_3	CN	CF_3	H	$C_{15}H_8F_6N_4$	20	4	B	182–182.5	C, H, N	50	0	0
14	Br	CF_3	Br	CF_3	H	$C_{14}H_7Br_2F_6N_3$	17	1	E	164–165.5	*l*	50	0	0
15	Cl	CF_3	Cl	CF_3	H	$C_{14}H_7Cl_2F_6N_3$	12	1	H	139–140	C, H, N	50	0	0
16	CF_3	H	CF_3	H	H	$C_{14}H_9F_6N_3$	48	2	E	170.5–171	*m*	50	2	1
17	Cl	H	Cl	H	H	$C_{12}H_9Cl_2N_3$	56	2	H	89–90	*n*	50	0	0
18	CH_3O	H	CH_3O	H	H	$C_{14}H_{15}N_3O_2$	72	1	C	101–101.5	*t*	50	3	3
19	H	4-Cl	H	4-Cl	H	$C_{12}H_9Cl_2N_3$	53	2	E	123.5–124.5	*o*	50	3	1
20	Cl	6-Cl	Cl	6-Cl	H	$C_{12}H_7Cl_4N_3$				134 (det)	*p*	50	0	0
21	2-Cl	3-Cl	2-Cl	3-Cl	H	$C_{12}H_7Cl_4N_3$	16	1	D	165–168	C, H, N	25	2	1
22	H	H	H	H	CH_3	$C_{13}H_{13}N_3$	23	5	oil		*q*	50	2	1
23	CN	CF_3	CN	CF_3	CH_3	$C_{17}H_9F_6N_5$	41	5	E	140–141	C, H, N	30	0	0
24	H	H	H	H	Ac	$C_{14}H_{13}N_3O$	29	7	C	132–134	*r*	50	4	4
25	CN	CF_3	CN	CF_3	Ac	$C_{18}H_{11}N_4O$	30	6	C	110–111	C, H, N	50	4	4
26	CN	4-CF_3	H	4-CF_3	Ac	$C_{18}H_{11}N_4O$	36	8	C	140–141	C, H, N	50	3	4
27	H	CF_3	CN	CF_3	Ac	$C_{16}H_{11}F_6N_3O$	35	6	H	61–61.5	C, H, N	50	0	0
28	2-Cl	6-Cl	CN	CF_3	Ac	$C_{16}H_9Cl_2F_3N_4O$	49	6	E	186–187	C, H, N	50	0	0
29	CN	CF_3	CN	CF_3	$ClCH_2CO$	$C_{18}H_8ClF_6N_5O$	27	6	C	98.5–100.5	C, H, N	50	0	4
30	CN	CF_3	CN	CF_3	EtCO	$C_{19}H_{11}F_6N_5O$	45	6	E	63–64	C, H, N	50	3	4
31	CN	CF_3	CN	CF_3	$MeOCOCH_2CO$	$C_{20}H_{11}F_6N_5O_3$	72	6	C/H	103.5–104	C, H, N	50	3	4
32	CN	CF_3	CN	CF_3	*n*-PrCO	$C_{20}H_{13}F_6N_5O$	27	6	C/H	60–62	C, H, N	25	4	2
33	CN	CF_3	CN	CF_3	*i*-PrCO	$C_{20}H_{13}F_6N_5O$	18	6	C	124.5–126	H, N; C[s]	25	4	1
34	CN	CF_3	CN	CF_3	*n*-BuCO	$C_{21}H_{15}F_6N_5O$	54	6	E	81–82	C, H, N	50	3	3
35	CN	CF_3	CN	CF_3	PhCO	$C_{23}H_{11}F_6N_5O$	64	6	E	155–157	C, H, N	50	0	0
36	CN	CF_3	CN	CF_3	EtOCO	$C_{19}H_{11}F_6N_5O_2$	30	6	H	88–89.5	C, H, N	50	4	1
37	CN	CF_3	CN	CF_3	CH_3NHCO	$C_{18}H_{10}F_6N_6O$	68	6	C	170 (dec)	C, H, N	25	3	3
38	CN	CF_3	CN	CF_3	*n*-PrNHCO	$C_{20}H_{14}F_6N_6O$	70	9	C	138–140	C, H, N	50	2	1
39	CN	CF_3	CN	CF_3	PhNHCO	$C_{23}H_{12}F_6N_6O$	40	9	E	184–186	C, H, N	50	3	2
40	CN	CF_3	CN	CF_3	EtOCONHCO	$C_{20}H_{12}F_6N_6O_3$	18	9	E	151–152	C, H, N	50	4	1

[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with structures. [b] A = acetone; B = benzene; C = ether; D = DMF; E = ethanol; H = hexane. [c] All compounds gave satisfactory C, H, and N analyses, except where indicated. [d] bw rdn = body weight reduction in male Sprague-Dawley rat: 0 = ⩽15% reduction from controls; 1 = 16–30% reduction from controls; 2 = 31–45% reduction from controls; 3 = 46–60% reduction from controls; 4 = ⩾61% reduction from controls. [e] 0 = no significant effect; 1 = significant reduction at 1 or 2 intervals; 2 = significant reduction at 3 or 4 intervals; 3 = significant reduction at 5 or 6 intervals; 4 = significant reduction at ⩾7 intervals. [f] Reference 22. [g] C: calcd, 50.14; found, 50.83. [h] Reference 23. [i] ·0.25H_2O. [j] Reference 24. [k] Reference 25. [l] Reference 26. [m] Reference 27. [n] Reference 28. [o] Commercially available from B. F. Goodrich Chemicals. [p] N: calcd, 12.54; found, 13.80. [q] Reference 31. [r] Reference 30. [s] C: calcd, 52.99; found, 52.11.

Scheme I

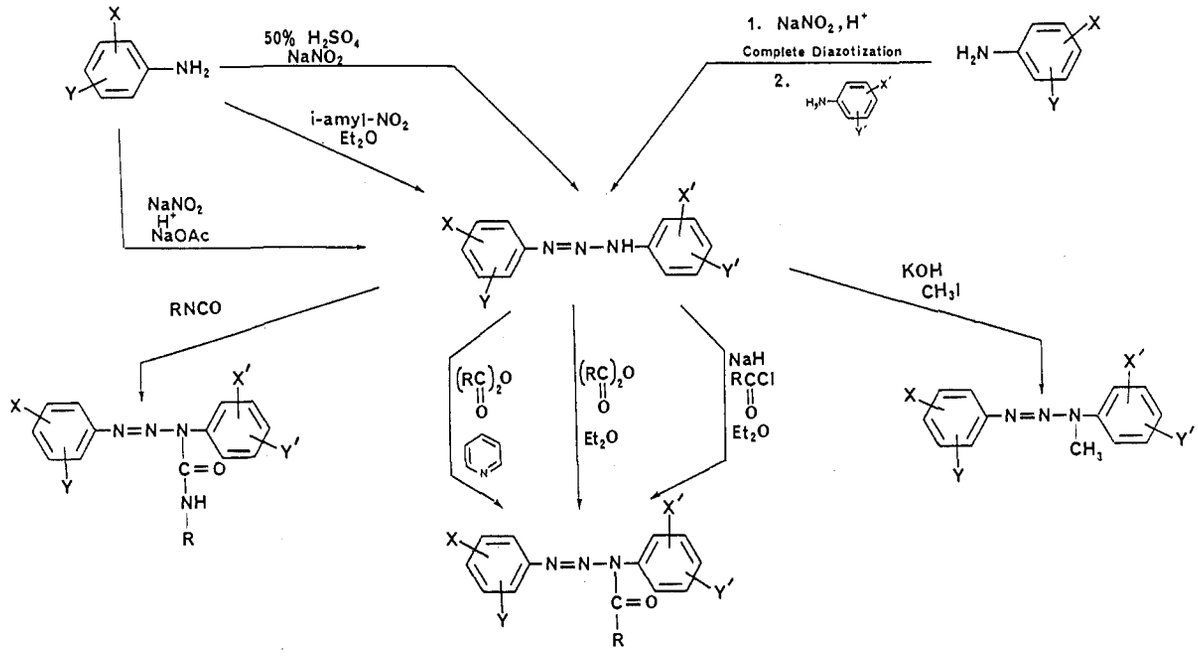
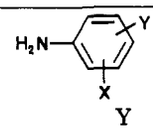


Table II. Substituted Aniline Precursors



no.	X	Y	formula
41[a]	2-CN	5-CF_3	$C_8H_5F_3N_2$
42[b]	2-CN		$C_7H_6N_2$
43[a]	2-CN	4-CF_3	$C_8H_5F_3N_2$
44[c]	2-CN	5-Cl	$C_7H_5ClN_2$
45[d]	2-CN	5-CH_3	$C_8H_8N_2$
46[b]	4-CO_2H		$C_7H_7NO_2$
47[e]	2-CO_2H	5-CF_3	$C_8H_6F_3NO_2$
48[b]	3-CF_3		$C_7H_6F_3N$
49[f]	2-CO_2CH_3	5-CF_3	$C_9H_8F_3NO_2$
50[b]	4-CF_3		$C_7H_6F_3N$
51[b]	2-Br	5-CF_3	$C_7H_5BrF_3N$
52[b]	2-Cl	5-CF_3	$C_7H_5ClF_3N$
53[b]	2-Cl		C_6H_6ClN
54[b]	4-Cl		C_6H_6ClN
55[b]	2-OCH_3		C_7H_9NO
56[b]	2-Cl	6-Cl	$C_6H_5Cl_2N$
57[b]	2-Cl	3-Cl	$C_6H_5Cl_2N$

[a] Reference 32. [b] Commercially available. [c] Reference 33. [d] Reference 34. [e] Reference 35. [f] 98% yield.

melting points. The synthetic methods are summarized in Scheme I.

Biological Results

The anorectic activity of the 1,3-diaryltriazenes was determined in the rat, dog, and squirrel monkey anorexia tests described under Experimental Section; additional biological assays are also described. The rat anorectic data are given in Table I. The lead compound (1) was examined extensively to determine its pharmacological profile. These data are summarized in Table III.

Compound 1 affected food consumption and body weight gain in several species during repeated administration. Unlike the tolerance that develops to the effects of *d*-amphetamine on food consumption and body weight during repeated administration,[17] no tolerance was apparent in any species during repeated administration of 1. In extensive dose-range studies in rat, dog, and squirrel monkey, slight depression of motor activity in the rat was the only behavioral effect observed. However, no consistent effects were observed on motor activity of rats treated with 1. Both *d*-amphetamine and fenfluramine produce measurable effects on the motor activity of rats.[17]

Compound 1 had no effect in *substantia nigra* lesioned rats,[18] indicating that the compound has no effect on dopamine pathways in the rat brain. Finally, 1 did not inhibit monoamine oxidase as defined by an indirect test, nor did it produce gastric lesions in the rat.

During subacute administration to ad libitum fed rats or rats trained to consume their daily ration in 5 h, compound 1 produced significant reductions in hematocrit values at doses of 12.5 to 78.1 (mg/kg)/day. This effect was first observed after 30 days of drug treatment. At postmortem, liver lesions were observed in these animals. Since the onset of activity in affecting food consumption and body weight gain is rapid (1–2 days) while the onset of the effect on hematocrit levels and the appearance of liver lesions is delayed (≥38 days), the immediate and delayed effects do not appear related. Despite the separation between therapeutic activity and side effects, the nature of these effects indicates that additional research is required before a useful anorectic agent may be identified from this class of compounds.

Structure–Activity Relationships. The influence of aromatic substitution on the anorectic activity of NH and N-substituted triazenes was examined with respect to steric effects (MR), electronic effects (σ_p), and lipophilicity (π).[19] Steric bulk seemed to have little effect on activity. When the nitrile (MR = 6) was replaced by chlorine (MR = 6), the resulting compound (15) did not retain anorectic activity. Similarly, when the trifluoromethyl (MR = 5) was replaced with methyl (MR = 5.5, 5), activity was lost.

The electronegativity of the ring substituents, however, did appear to influence the activity of the triazenes studied. Both the nitrile and the trifluoromethyl groups are strongly electron withdrawing (σ_p) values of 0.66 and 0.54, respec-

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Table III. Selected Pharmacological Properties of 1,3-Bis[2-cyano-5-(trifluoromethyl)phenyl]triazene (1)

test	species	result
10-day antiobesity	rat	MED[a] = 6.25
15-day antiobesity	rat	MED = 12.5
25-day antiobesity	rat	MED = 12.5
5-day antiobesity	dog	MED = 2.0
8-day antiobesity	monkey	25 mg/kg b.i.d., signif redn in body wt
dose range	rat	50–5000 mg/kg, slight redn in motor act., slight to moderate hypothermia
	dog	2 mg/kg, moderate emesis; 5.0–25 mg/kg, marked emesis
	monkey	25–100 mg/kg, no apparent side effects
rotational act.	rat	50 mg/kg, no effect
tryptamine potentiation	rat	100 mg/kg, no effect
gastric irritation	rat	100 mg/kg, no effect
confinement motor act.	rat	50 mg/kg, no effect

[a] MED (minimum effective dose) is the lowest dose, in milligrams per kilogram per day, that produced a statistically significant effect.

tively). Substitution at positions 5 and 5′ with chlorine (σ_p 0.23, **4**) resulted in reduced activity. Substitution at these positions with the electron-donating methyl group (σ_p = −0.17, **5**), eliminated anorectic activity. Removal of either the trifluoromethyl or the nitrile groups as in **2** or **10** also resulted in loss of activity. Substituting a carboxy group (σ_p = 0.45) for a nitrile (**9**) decreased activity. Elimination of the trifluoromethyl and nitrile on one ring resulted in a compound (**6**) with marginal activity, while replacement of these groups on one ring with 2,6-dichloro groups gave **7**, which showed moderate activity.

The position of the trifluoromethyl groups, meta vs. para, **1** vs. **3**, appeared to have little effect on anorectic activity. However, in the case of the monosubstituted trifluoromethyl derivatives, ortho vs. para, **16** vs. **12**, marked difference was observed compared to **1**. Similarly, the monosubstituted *m*-chloro compound (**17**) was inactive, while the *p*-chloro isomer (**19**) was active. An exception to this pattern seemed to be the monosubstituted methoxy derivative (**18**), which, unexpectedly, had good activity. Trends of activity could not be predicted from the relative lipophilicity of the aromatic substituents.

The nitrogen substituent appears to have a variable effect on anorectic activity. When the N-1 triazene nitrogen was substituted with a methyl group (**23**), no activity was observed. N-1 acetylation of diphenyltriazene, **1**, and **3** gave compounds **24–26**, which resulted in reduced body-weight gain and food consumption compared to the parent compounds. Acetylation of **7** and **10** to give **27** and **28**, however, resulted in loss of activity, as did benzoylation of **1** to give **35**.

The *N*-carboxamido compounds (**37–40**) offered no advantages over the *N*-acyl analogues.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T60 A spectrometer employing $(CH_3)_4Si$ as an internal standard and are consistent with the assigned structures. IR spectra were recorded on a Perkin-Elmer Model 137B infracord spectrophotometer as Nujol mulls. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 apparatus by the Analytical Department of Smith Kline & French Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Pharmacology Materials and Methods. Compounds were administered orally to rats and monkeys by using 0.75% methylcellulose and PEG 400 as suspending agents and as dry powder in gelatin capsules to dogs. Adult male albino CD Sprague-Dawley rats, adult mongrel dogs, and adult Saimari Sciureus monkeys were used in these experiments.

Anorectic/Antiobesity Testing in Rats. Rats were housed individually and trained over a 2-week period to eat their daily ration of ground Purina Laboratory Chow in only 5 h. After training, either vehicle (controls) or drug was administered orally once daily for 5, 10, 15, or 25 days. Food consumption was determined after 1 and 5 h daily. Rats were weighed daily before drug treatment. A compound was considered active if it produced a statistically significant reduction in 1- or 5-h food consumption (analysis of variance) and/or a significant reduction in body-weight gain compared to concomitant controls ("*t*" test). Compounds were ranked according to their activity in the 5-day test (see Table I). Ten controls and ten dosed animals were used per test.

Anorectic/Antiobesity Testing in Dogs. Dogs were trained over a period of 4–6 weeks to eat their daily ration of dry dog food in only 3 h. After training, either drug or vehicle was administered orally for 5 days. One hour after dosing, food was presented. Food consumption was monitored for 3 h daily. Water was available ad libitum. Dogs were weighed at days 1, 3, and 5 prior to drug treatment and once daily during treatment. Active compounds reduced 3-h food consumption and/or produced a significant loss in body weight over the 5-day period. Significance was determined by using analysis of variance.

Antiobesity Testing in Monkeys. Test compounds were administered orally b.i.d. for 5 days to preselected monkeys whose body weight and drinking habits had stabilized. Since monkeys scatter food, no food consumption measurement was attempted. Body weights and water consumption were recorded daily during testing. Active compounds typically produce a significant reduction in body weight and/or water consumption as determined with the paired *t* test.

Dose Range. Various doses of the test compound were administered orally to rats, dogs, or monkeys, and overt changes in behavior and/or appearance were recorded over an extended time on the day of treatment and once daily for 14 days thereafter.

Rotational Activity. Compounds were tested for their ability to induce rotation in 6-hydroxydopamine-lesioned rats.[18] Rotational activity is indicative of activation of central dopamine receptor sites.

Tryptamine Potentiation. Compounds were tested for their ability to potentiate a subconvulsant dose of tryptamine hydrochloride in rats.[20] This is a measure of a compound's ability to inhibit monoamine oxidase.

Gastric Irritation. Rats were deprived of food immediately after receiving the test compound or vehicle. Water was freely available. Eighteen hours later, the rats were sacrificed. Each stomach was removed and examined under a dissecting scope for erosions on the mucosal surface of the glandular portion.

Confinement Motor Activity. Rats were tested for changes in activity while confined in plastic chambers.[21] Centrally me-

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diated effects on motor activity were demonstrated in this procedure.

1,3-Bis[2-cyano-5-(trifluoromethyl)phenyl]triazene (1). To a stirred, ice-cooled slurry of 14.6 g (78.4 mmol) of 2-amino-4-(trifluoromethyl)benzonitrile (**43**) in 18 mL of concentrated H_2SO_4 and 18 mL of water was added a solution of 3.6 g (52 mmol) of $NaNO_2$ in 6 mL of water. The stirred mixture was warmed to room temperature over 2 h, after which 25 mL of water was added. The reaction mixture was stirred briefly, poured into 500 mL of water and filtered, and the residue was washed with water. The filter cake was dissolved in hot ethanol, which on cooling afforded 1.9 g (4.96 mmol, 12.6% yield) of yellow crystals: mp 193–194 °C; IR (Nujol) 3200 (NH), 2240 (CN), 1650 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 1:1) δ 8.2 (s, 2 H, aromatic), 7.8 (d, J = 8.0 Hz, 2 H, aromatic), 7.5 (d, J = 8.0 Hz, 2 H, aromatic); MS, m/e 383 (M^+), 364, 357, 355, 341, 336, 198, 170 (100). Anal ($C_{16}H_7F_6N_5$) C, H, N.

Methyl 2-Amino-4-(trifluoromethyl)benzoate (49). A mixture of **47** (10 g, 0.049 mol), 250 mL of CH_3OH, and 50 mL of concentrated HCl was refluxed for 12 h. The mixture was cooled, and the solvent was removed at reduced pressure. The residue was dissolved in water, basified with 10% NaOH, and extracted with ether, the combined extracts were washed with water and dried ($MgSO_4$), and the solvent was removed to give 10.6 g (98%) of crystalline product, mp 56–58 °C. An analytical sample was obtained by chromatography (silica gel/chloroform) and one crystallization from hexane, mp 60–62 °C.

Triazenes. General Synthetic Methods. Method 1. To a cold (ice bath), stirred solution of substituted aniline (0.1 mol) and 13 mL of concentrated HCl in 100 mL of water was added dropwise a solution of 4.1 g (0.068 mol) of sodium nitrite in 25 mL of water. The reaction was stirred for 1 h, and the precipitate was collected, washed well with water, and recrystallized from the appropriate solvent to afford the 1,3-diaryltriazene. In order to precipitate compounds **10**, **14**, **15**, and **18**, a solution of 15 g of sodium acetate in 30 mL of water was added following the addition of the sodium nitrite.

Method 2. A solution of substituted aniline (0.1 mol) and 5.85 g (0.05 mol) of isoamyl nitrite in 100 mL of ether was stirred at 25 °C for 18 h. The precipitate was collected and recrystallized from the appropriate solvent to afford the 1,3-diaryltriazene. (When no precipitate formed, solvent was evaporated and the residue recrystallized.)

Method 3. To the substituted aniline (0.048 mol) was added, with cooling (ice bath), a mixture of 10.6 mL of water and 10.6 mL of concentrated H_2SO_4. The slurry was stirred until homogeneous, and then a solution of 1.66 g (0.024 mol) of sodium nitrite in 10.6 mL of water was added over 0.5 h and stirring was continued for 15 min. The ice bath was removed, and the reaction mixture was stirred for an additional hour. Water was added to the semisolid mixture, and the slurry was poured into 500 mL of water. The solid was collected by filtration, washed with water, and recrystallized from the appropriate solvent to afford the 1,3-diaryltriazene.

Method 4. A cooled solution of 3.6 mL of concentrated sulfuric acid and 3.6 mL of water was added to the substituted aniline (R_1 and R_2) (0.016 mol). The stirred slurry was cooled (ice bath), and a solution of 1.1 g (0.016 mol) of sodium nitrite in 6 mL of water was added dropwise. The resulting solution was then added to a solution containing an excess of the second substituted aniline (R_3 and R_4) in 120 mL of ethanol. The reaction mixture was stirred for 15 min and then poured into 500 mL of water. The precipitate was collected by filtration, washed with water, and recrystallized from the appropriate solvent to give the mixed 1,3-diaryltriazene.

Method 5. A solution of 1,3-diaryltriazene (0.003 mol), 0.2 g (0.003 mol) of potassium hydroxide, and 0.3 mL (slight excess) of methyl iodide in 25 mL of methanol was heated gently for 1.5 h and then stirred at 25 °C for 15 h. The reaction mixture was poured into water, and the precipitate was collected, washed with water, and recrystallized from the appropriate solvent to afford the *N*-methyl-1,3-diaryltriazene.

Method 6. A solution of the 1,3-diaryltriazene (0.015 mol) in 450 mL of ether (warming was sometimes required) was added dropwise to a slurry of 1.20 g (0.025 mol) of 50% sodium hydride in 15 mL of ether. Upon cessation of gas evolution, the acid chloride (0.018 mol) was gradually added, and the reaction mixture was stirred at 25 °C for 2 h. The mixture was filtered, and the filtrate was concentrated to give the *N*-acyl-1,3-diaryltriazene.

Method 7. To a stirred solution of 1,3-diaryltriazene (0.025 mol) in 15 mL of ether was added 3 g (0.029 mol) of acetic anhydride. The reaction mixture was stirred at 25 °C for 72 h. The precipitate was collected and recrystallized from the appropriate solvent to afford the *N*-acetyl-1,3-diaryltriazene.

Method 8. Acetic anhydride (25 mL, 0.26 mol) was added dropwise to a stirred solution of 1,3-diaryltriazene (0.013 mol) in 65 mL of pyridine. The mixture was stirred at 25 °C for 3 h, poured into water, and extracted 2 times with ether. The ether extracts were combined, washed with water, 5% $NaHCO_3$, and water, and dried ($MgSO_4$). Removal of solvent at reduced pressure afforded an oil, which crystallized when treated with ether. The product was recrystallized from the appropriate solvent to afford the *N*-acetyl-1,3-diaryltriazene.

Method 9. A solution of a 3- to 10-fold excess of an alkyl or aryl isocyanate in 20 mL of ether was added dropwise to a 10%, w/v, solution of the 1,3-diaryltriazene in ether. The reaction mixture was stirred at room temperature for 24 to 48 h. (If the reaction was not complete at this time, it was refluxed for an additional 6 h.) The precipitate was collected (solvent was concentrated if necessary) and recrystallized from the appropriate solvent to afford the *N*-carbamoyl-1,3-diaryltriazene.

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