Synthesis and Antiinflammatory Evaluation of Substituted Isophthalonitriles, Trimesonitriles, Benzonitriles, and Terephthalonitriles

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In an effort to develop nonacidic, nonsteroidal, antiinflammatory agents without gastrointestinal complications, a series of cyanobenzenes was synthesized for antiinflammatory evaluation. Twenty-seven substituted isophthalonitriles, 19 trimesonitriles, 30 benzonitriles, and 16 terephthalonitriles were tested in the rat utilizing the carrageenan-induced pedal edema assay. Based on the performance of phenylbutazone in this assay (43.8% reduction at 100 mg/kg), six compounds, dosed at 50 mg/kg, produced reductions in inflammation comparable to this standard. However, the LD_{50} value of each compound dosed at this level was in the range of 40–56 mg/kg in the mouse; therefore, further study was not warranted. Fifteen compounds possessed activity in excess of 20% reduction at 200 mg/kg and also possessed LD_{50} values greater than 300 mg/kg. Of these cyanobenzenes, trimesonitrile (**16**), 4-chlorobenzonitrile, 2-chloroterephthalonitrile, and 2-fluoroterephthalonitrile with reductions in edema of 32, 30, 46, and 49%, respectively, represent the best candidates for subsequent study.

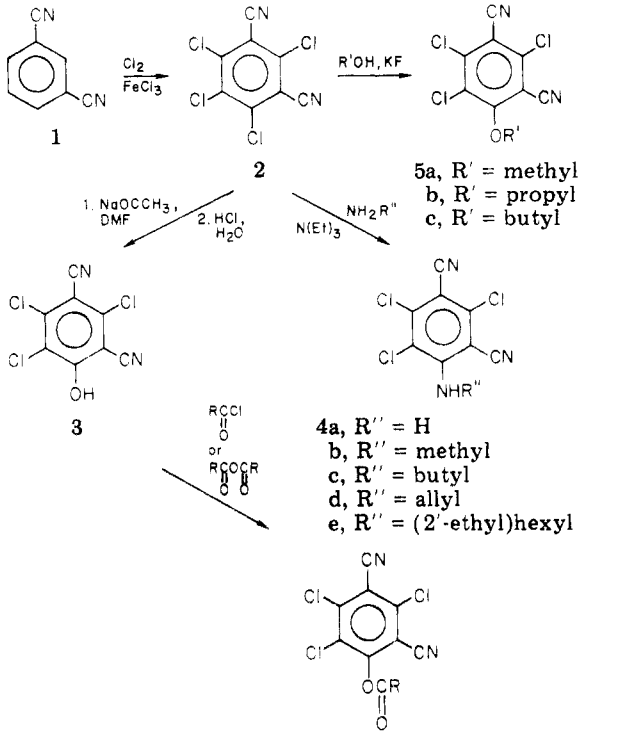
The ongoing search for new classes of antiinflammatory agents, in part, reflects the continued inability to separate antiinflammatory efficacy from gastrointestinal toxicity. There is considerable controversy concerning the actual relationship between the acidic and gastrotoxic properties of many nonsteroidal antiinflammatory agents; however, it is generally agreed that gastric irritation is associated, directly or indirectly, with the acidic nature of these drugs.[1,2] In an effort to eliminate gastric complications, while maintaining antiinflammatory activity, a number of nonacidic compounds were evaluated for potential antiinflammatory activity.

The fungicidal,[3-6] antibacterial,[7] insecticidal,[8] herbicidal,[9-11] and anthelmintic[12] activity of certain substituted isophthalonitriles, trimesonitriles, benzonitriles, and terephthalonitriles is well-known. However, the pharmaceutical effects of these classes of compounds have not been extensively studied. Due to the inherent biological activity of these aromatic nitriles and their nonacidic nature, we have synthesized a number of isophthalonitriles, trimesonitriles, benzonitriles, and terephthalonitriles and screened them in the carrageenan-induced pedal edema assay as potential antiinflammatory agents.

Synthetic Aspects. 4-Aminotrichloroisophthalonitriles **4a–e**, 4-alkoxytrichloroisophthalonitriles **5a–c**, and 4-carboalkoxytrichloroisophthalonitriles **6a–k** were synthesized according to Scheme I. Melting points and recrystallization solvents are shown in Table I.

Isophthalonitrile (**1**) was catalytically chlorinated, forming tetrachloroisophthalonitrile (**2**). This was reacted with sodium acetate, and then hydrolyzed, to afford 4-hydroxytrichloroisophthalonitrile (**3**).[13] Treatment of **3** with the appropriate acid chloride or anhydride resulted in the desired esters, **6**. The 4-aminotrichloroisophthalonitriles **4** were prepared by nucleophilic displacement of **2** with 1 equiv of the appropriate amine under basic conditions. Utilization of excessive amine resulted in 4,6-diamination. The 4-alkoxytrichloroisophthalonitriles **5** were obtained by treatment of **2** with the appropriate alcohol and potassium fluoride. The regiospecificity of nucleophilic displacement at the 4 position of **2** by acetate, alkoxy, and amino functionalities was verified by regiospecific synthesis of the corresponding 2-hydroxytrichloroisophthalonitrile (**7**, Scheme II). Physical and spectral properties of **7** were compared to **3**, **4a**, and **5a**. It was shown by ^{13}C NMR that **7** was symmetric with four aromatic peaks, while **3**, **4a**, and **5a** were unsymmetric with six aromatic resonances. Also, the observed chemical shifts relative to Me_4Si of **7**, **3**, **4a**, and **5a** were in good agreement with the predicted shifts for these highly substituted aromatic systems.[14]

Scheme I



The regiospecific synthesis of **7** was accomplished by converting 2-amino-*m*-xylene (**8**) to the corresponding 2-fluoro-*m*-xylene (**9**) via the Schiemann reaction.[15] Treatment of **9** with chlorine–ferric chloride formed 4,-5,6-trichloro-2-fluoro-*m*-xylene (**10**) which was photobrominated to give the α,α'-dibromo-*m*-xylene **11**. Oxidation of **11** with potassium permanganate yielded 2-fluoro-4,5,6-trichloroisophthalic acid (**12**). The acid was converted to the amide **14** first reacting with thionyl

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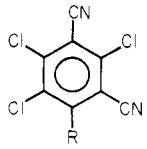
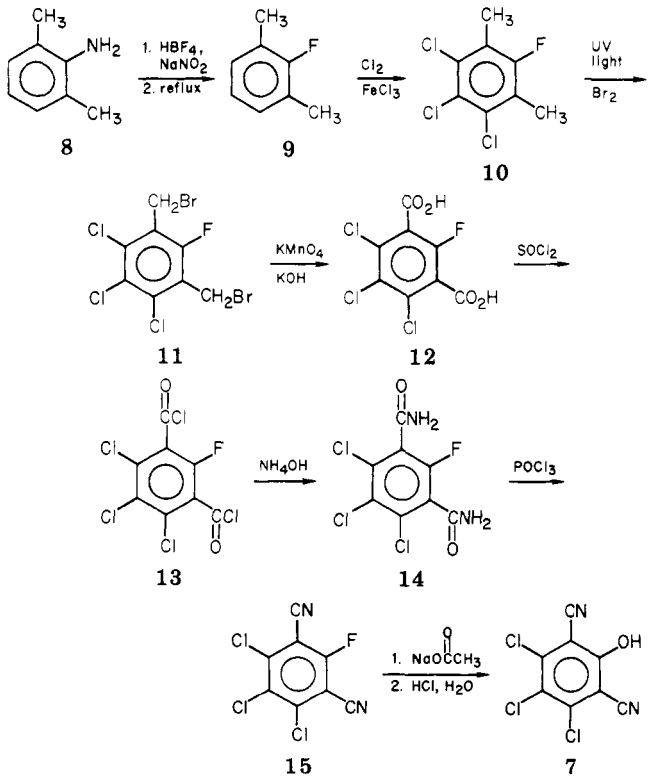
Table I. Melting Points and Recrystallization Solvents of 4-Substituted Trichloroisophthalonitriles 3, 4a-e, 5a-c, and 6a-i,k[a]



compd no.	substituent	mp, °C	solvent of recrystn
3	OH	262-264	EtOH
4a	NH_2	282-284	EtOH
4b	$NHCH_3$	253-254	MeOH
4c	$NH(CH_2)_3CH_3$	149-151	dioxane
4d	$NHCH_2CH{=}CH_2$	188-189	dioxane
4e	$NHCH_2CH(CH_2)_3CH_3$ CH_2CH_3	101-102	hexane
5a	OCH_3	150-152	EtOH
5b	$O(CH_2)_2CH_3$	83-84	EtOH
5c	$O(CH_2)_3CH_3$	76-77	EtOH
6a	$OCOCH_3$	150-151	heptane
6b	$OCOCH_2CH_3$	119-120	heptane
6c	$OCO(CH_2)_2CH_3$	94-95	pentane
6d	$OCOCH(CH_3)_2$	123-124	heptane
6e	$OCOCH(CH_2CH_3)_2$	112-113	heptane
6f	$OCO(CH_2)_4CH_3$	96-97	pentane
6g	$OCOCH(CH_2)_3CH_3$ CH_2CH_3	86-87	pentane
6h	$OCO(CH_2)_6CH_3$	89-90	pentane
6i	$OCOC_6H_5$	134-135	heptane
6k	$OCONH(CH_2)_3CH_3$	249-250	heptane-EtOH

[a] C, H, and N analyses are all within ±0.4%.

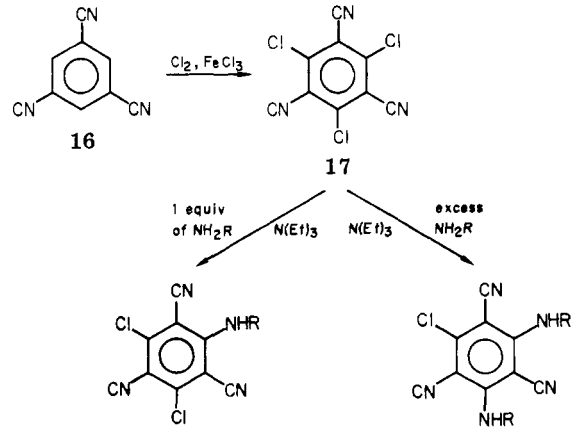
Scheme II



8 9 10 11 12 13 14 15 7

chloride to form the acid chloride **13** and then treating with ammonium hydroxide. The conversion of the isophthalamide **14** to the nitrile **15** was affected by reaction with phosphorus oxychloride. Displacement of the labile fluorine of **15** by sodium acetate at room temperature, followed by hydrolysis, yielded 2-hydroxy-4,5,6-trichlorophthalonitrile (**7**).

Scheme III

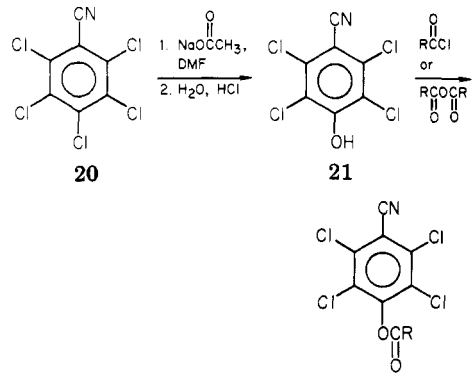


16 17

18a, R = 4-bromophenyl
b, R = 4-aminophenyl
c, R = 3-chlorophenyl
d, R = 4-chlorophenyl
e, R = 2-hydroxyphenyl
f, R = 2-methyl-3-chlorophenyl
g, R = 3-fluorophenyl
h, R = 2,4-difluorophenyl
i, R = 3-trifluoromethylphenyl
j, R = 3,4-dichlorophenyl
k, R = 3,4-dimethoxyphenyl
l, R = 2,3-dimethylphenyl
m, R = 2,4-dimethylphenyl

19a, R = methyl
b, R = ethyl
c, R = isopropyl

Scheme IV



20 21

22a, R = CH_2CH_3
b, R = $(CH_2)_2CH_3$
c, R = $CH(CH_3)_2$
d, R = $(CH_2)_3CH_3$
e, R = $(CH_2)_4CH_3$
f, R = $CH(CH_2CH_3)_2$
g, R = $(CH_2)_6CH_3$

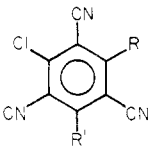
22h, R = $CH(CH_2CH_3)(CH_2)_3CH_3$
i, R = $(CH_2)_{10}CH_3$
j, R = CCl_3
k, R = $CH_2C_6H_5$
l, R = C_6H_4-2-Cl
m, R = C_6H_3-3,4-Cl_2

The aminotrimesonitriles **18a-m** and diaminotrimesonitriles **19a-c** were prepared by the method of Battershell[16] shown in Scheme III; melting points and recrystallization solvents appear in Table II.

Trimesonitrile (**16**) was converted to trichlorotrimesonitrile (**17**) via catalytic chlorination; reaction of **17** with 1 equiv of the desired substituted aniline formed the aminotrimesonitriles **18**. Reaction with 2 equiv of primary lower alkylamines resulted in disubstitution, forming **19**, while higher alkyl and aromatic primary amines did not undergo disubstitution under these conditions.

The 4-carboalkoxytetrachlorobenzonitriles **22a-m** were synthesized via nucleophilic displacement of pentachlorobenzonitrile (**20**) with sodium acetate, followed by

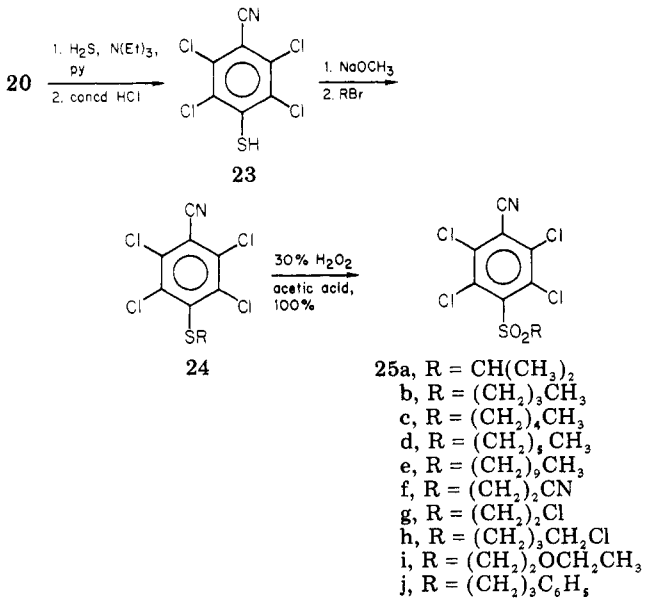
Table II. Melting Points of Amino- and Diaminomesonitriles 18a-m and 19a-c



compd no.	substituents R	R'	mp, °C
18a	-NHC$_6$H$_4$-4-Br	-Cl	332-333[a]
18b	-NHC$_6$H$_4$-4-NH$_2$	-Cl	>350[a]
18c	-NHC$_6$H$_4$-3-Cl	-Cl	226-227[a]
18d	-NHC$_6$H$_4$-4-Cl	-Cl	310-311[a]
18e	-NHC$_6$H$_4$-2-OH	-Cl	250-251[a]
18f	-NHC$_6$H$_3$-2-CH$_3$-3-Cl	-Cl	219-220[a]
18g	-NHC$_6$H$_4$-3-F	-Cl	244-245[a,b]
18h	-NHC$_6$H$_3$-2,4-F$_2$	-Cl	238-239[a]
18i	-NHC$_6$H$_4$-3-CF	-Cl	263-265[a,b]
18j	-NHC$_6$H$_3$-3,4-Cl$_2$	-Cl	251-252[a]
18k	-NHC$_6$H$_3$-3,4-(OCH$_3$)$_2$	-Cl	238-239[a]
18l	-NHC$_6$H$_3$-2,3-(CH$_3$)$_2$	-Cl	233-234[a]
18m	-NHC$_6$H$_3$-2,4-(CH$_3$)$_2$	-Cl	219-220[a]
19a	-NHCH$_3$	-NHCH$_3$	319-320[c]
19b	-NHCH$_2$CH$_3$	-NHCH$_2$CH$_3$	194-195[c]
19c	-NHCH(CH$_3$)$_2$	-NHCH(CH$_3$)$_2$	136-137[c]

[a] R. D. Battershell, U.S. Patent 3 637 796 (1972). [b] Carbon analysis exceeded ±0.4%, but is within ±0.5%. [c] C, H, and N analyses are within ±0.4%; products were recrystallized from MeOH.

Scheme V

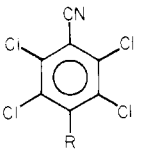


acid hydrolysis, to yield 4-hydroxytetrachlorobenzonitrile (21). The phenolic benzonitrile 21 was treated with the appropriate acid chloride or anhydride to afford the corresponding benzonitrile esters 22a-m (Table III, Scheme IV).

The 4-alkylsulfonyltetrachlorobenzonitriles 25a-j were obtained by reaction of 20 with hydrogen sulfide and triethylamine, according to the method of Beck et al.[17] Acidification with HCl resulted in 4-mercaptotetrachlorobenzonitrile (23). The sodium salt of 23, formed by treatment of the thiol with sodium methoxide, readily underwent reaction with the desired alkyl halides to form the corresponding sulfides 24. Sulfides 24 were converted to the desired sulfones 25 by hydrogen peroxide oxidation in refluxing acetic acid (Table III, Scheme V).

The regiospecificity of nucleophilic attack at the 4 position of 20 by sodium acetate or hydrogen sulfide was confirmed by ^{13}C NMR studies. Both hydroxybenzonitrile 21 and mercaptobenzonitrile 23 were proven to be symmetrical by the appearance of only four aromatic ^{13}C resonances in each spectra. Chemical shifts, relative to Me_4Si, also correlated well with those predicted on the basis of substituent effects established by Levy and Nelson.[14]

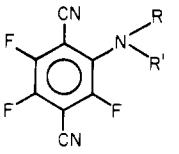
Table III. Melting Points and Recrystallization Solvents of 4-Carboalkoxytetrachlorobenzonitriles 22a-m and 4-Alkylsulfonyltetrachlorobenzonitriles 25a-j[a]



compd no.	substituent	mp, °C	solvent of recrystn
22a	-OCOCH$_2$CH$_3$	101-102	pentane
22b	-OCO(CH$_2$)$_2$CH$_3$	82-83	pentane
22c	-OCOCH(CH$_3$)$_2$	103-104	pentane
22d	-OCO(CH$_2$)$_3$CH$_3$	78-79	pentane
22e	-OCO(CH$_2$)$_4$CH$_3$	72-73	pentane
22f	-OCOCH(CH$_2$CH$_3$)$_2$	92-94	pentane
22g	-OCO(CH$_2$)$_6$CH$_3$	63-65	pentane
22h	-OCOCH(CH$_2$CH$_3$)(CH$_2$)$_3$CH$_3$	71-72	pentane
22i	-OCO(CH$_2$)$_{10}$CH$_3$	82-83	pentane
22j	-OCOCCl$_3$	190-191	heptane
22k	-OCOCH$_2$C$_6$H$_5$	109-110	heptane
22l	-OCOC$_6$H$_4$-2-Cl	128-129	heptane
22m	-OCOC$_6$H$_3$-3,4-Cl$_2$	187-188	heptane
25a	-SO$_2$CH(CH$_3$)$_2$	220-222	MeOH
25b	-SO$_2$(CH$_2$)$_3$CH$_3$	150-151	2-propanol
25c	-SO$_2$(CH$_2$)$_4$CH$_3$	117-118	2-propanol
25d	-SO$_2$(CH$_2$)$_5$CH$_3$	118-119	2-propanol
25e	-SO$_2$(CH$_2$)$_9$CH$_3$	125-127	2-propanol
25f	-SO$_2$(CH$_2$)$_2$CN	158-160	2-propanol
25g	-SO$_2$(CH$_2$)$_2$CH$_2$Cl	167-169	2-propanol
25h	-SO$_2$(CH$_2$)$_3$CH$_2$Cl	144-145	2-propanol
25i	-SO$_2$(CH$_2$)$_2$OCH$_2$CH$_3$	126-128	2-propanol
25j	-SO$_2$(CH$_2$)$_3$C$_6$H$_5$	116-117	2-propanol

[a] C, H, and N analyses are all within ±0.4%.

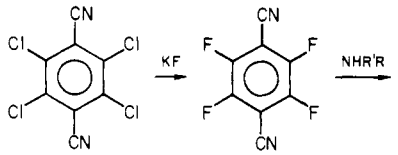
Table IV. Melting Points and Recrystallization Solvents of 2-Aminotrifluoroterephthalonitriles 28a-g[a]



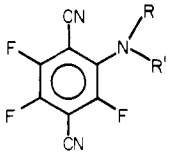
compd no.	substituents R	substituents R'	mp or bp (mm), °C	solvent of recrystn
28a	-H	$-CH_3$	88-89	pentane
28b	-H	$-CH_2CH_3$	64-65	pentane
28c	-H	$-(CH_2)_3CH_3$	83-84	pentane
28d	-H	$-(CH_2)_5CH_3$	80 (0.002)	
28e	$-CH_2CH_3$	$-CH_2CH_3$	64-65	MeOH-H_2O
28f	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	27-28	MeOH-H_2O
28g	-H	$-C_6H_4$-4-OH	218-220	MeOH-H_2O

[a] C, H, and N analyses are all within ±0.4%.

Scheme VI



26 27



28a, R = H; R' = CH_3
b, R = H; R' = CH_2CH_3
c, R = H; R' = $(CH_2)_3CH_3$
d, R = H; R' = $(CH_2)_5CH_3$
e, R = R' = CH_2CH_3
f, R = R' = $(CH_2)_2CH_3$
g, R = H; R' = C_6H_4-4-OH

2-Aminotrifluoroterephthalonitriles **28a-g** were synthesized from tetrachloroterephthalonitrile (**26**).[13] Terephthalonitrile **26** underwent halogen exchange with KF to afford tetrafluoroterephthalonitrile (**27**) which, when treated with an equal molar equivalent of the appropriate primary or secondary amine, afforded the corresponding terephthalonitriles **28a-g** (Table IV, Scheme VI).

Biological Results. The effect of these cyanobenzenes on the inflammatory response was evaluated in the carrageenan-induced pedal edema assay.[18] Carrageenan injected into the plantar tissue of the hind paw of Long Evans rats produces an edematous condition which simulates, in part, the inflammatory process found in human arthritis.[19-21] It has been demonstrated that nonsteroidal antiinflammatory drugs, such as indomethacin, phenylbutazone, and aspirin, inhibit the formation of this edema.[22,23] Compounds were administered orally, using 0.25% methylcellulose as the vehicle. Five rats were used per dose, with the reported percent reduction in inflammation represented by the average of these five reductions. Compounds were dosed at levels expected to be subtoxic by consideration of the LD_{50} value measured for each compound. LD_{50} values in the mouse were determined in a standard, multidimensional observational assay and calculated according to the method of Litchfield and Wilcoxon.[24] The antiinflammatory and LD_{50} results are shown in Tables V-VIII. Compounds included in the testing, but not discussed in the synthetic segment, were synthesized according to known literature methods (see Tables V-VIII).

Table V. Antiinflammatory Effects of Orally Administered Isophthalonitrile Analogues on Carrageenan-Induced Edema in Rats

compd identity	carrageenan antiinflam act. dose, mg/kg	% redn	LD_{50}, mg/kg
3	150	28	178
4a	200	25	>300
4b	200	22	>300
4c	200	17	>300
4d	200	17	>300
4e	200	0	>300
5a	100	0	178
5b	100	8	178
5c	100	8	178
6a	200	25	237
6b	200	11	178
6c	150	14	178
6d	200	0	237
6e	50	0	56
6f	200	11	>300
6g	200	20	>300
6h	150	22	178
6i	200	11	>300
6j	100	20	178
6k	100	3	178
1, isophthalonitrile (IPN)[a]	200	35	178
4-Br-IPN[b]	100	3	178
2-Cl-IPN[c]	200	20	300
4-F-IPN[c]	150	25	178
4,6-Cl_2-IPN[d]	150	5	178
4,6-F_2-IPN[e]	50	59	56
2,4,6-Cl_3-IPN[d]	200	8	100
phenylbutazone	100	43, 8[f]	>300

[a] G. Luckenbach, *Chem. Ber.*, 17, 1428 (1884). [b] E. J. Fendler, J. H. Fendler, C. E. Griffin, and J. W. Larsen, *J. Org. Chem.*, 35, 287 (1970). [c] K. Wallenfels, F. Witzler, and K. Friedrich, *Tetrahedron*, 23, 1353 (1967). [d] N. J. Turner and R. D. Battershell, *Contrib. Boyce Thompson Inst.*, 24, 139 (1969). [e] N. J. Turner and R. D. Battershell, *ibid.*, 24, 203 (1970). [f] Based on 46 determinations; standard deviation was 13.4%.

Based on the performance of phenylbutazone in this assay, a minimun of 20% reduction of edema was chosen as the criterion for activity. This represents approximately 50% of the activity found with this standard. Within the isophthalonitrile series (Table V), 11 of the 27 compounds screened demonstrated activity. The 4-aminoisophthalonitriles **4a-e** were free of overt toxic effects and possessed low-level antiinflammatory activity, while the 4-alkoxyisophthalonitriles **5a-c** were inactive in this assay. The 4-carboalkoxyisophthalonitriles **6a-k** also possessed limited activity with four of 11 compounds reducing inflammation

Table VI. Antiinflammatory Effects of Orally Administered Trimesonitrile Analogues on Carrageenan-Induced Edema in Rats

compd identity	carrageenan antiinflam act. dose, mg/kg	% redn	LD_{50}, mg/kg
18a	200	14	300
18b	100	14	133
18c	40	0	178
18d	150	1	178
18e	15	17	24
18f	25	8	42
18g	40	0	56
18h	40	12	56
18i	200	29	237
18j	40	52	56
18k	150	13	178
18l	50	22	75
18m	40	13	56
19a	200	20	300
19b	200	11	300
19c	200	5	300
16, trimesonitrile (TMN)[a]	200	32	300
17, Cl_3-TMN[b]	20	0	24
2,4,6-$(CH_3)_3$-TMN[c]	50	57	40
phenylbutazone	100	43.8[d]	>300

[a] K. Wallenfels and K. Friedrich, *Tetrahedron Lett.*, No. 19, 1223 (1963). [b] R. D. Battershell, U.S. Patent 3 637 796 (1972). [c] G. M. Bennett and R. L. Wain, *J. Chem. Soc.*, 1108 (1936). [d] Based on 46 determinations; standard deviation was 13.4%.

by 20%. The highest level of activity in this series was found with the unsubstituted mono- and dihalogenated nitriles where the parent molecule, isophthalonitrile (**1**, IPN), and 4,6-F_2-IPN reduced carrageenan-induced edema by 35 and 59%, respectively. However, 4,6-F_2-IPN had an LD_{50} value in the mouse of 56 mg/kg.

Within the trimesonitrile series (Table VI), six of the 19 compounds evaluated demonstrated activity. The diaminotrimesonitriles **19a–c** represent the least toxic group of compounds tested, with LD_{50} values greater than 300 mg/kg; however, antiinflammatory activity within this group is limited to the methylamine derivative **19a**. Anilinotrimesonitrile **18j**, with an LD_{50} value of 56 mg/kg, reduced carrageenan-induced inflammation 52% at a dose of 40 mg/kg. This was the most potent antiinflammatory agent in the group of 13 anilinotrimesonitriles screened. As in the isophthalonitrile series, the simply substituted trimesonitriles possess the highest level of activity. Unsubstituted trimesonitrile (**16**, TMN) reduced edema 32% at a dose of 200 mg/kg and possessed an LD_{50} value in excess of 300 mg/kg, while Me_3-TMN, at a dose of 50 mg/kg, reduced carrageenan-induced edema 57%.

Within the benzonitrile series (Table VII), six of the 29 compounds screened exhibited activity. The 4-carboalkoxytetrachlorobenzonitriles **22a–m**, although possessing LD_{50} values in excess of 300 mg/kg, were inactive as antiinflammatory agents. The 4-alkylsulfonyltetrachlorobenzonitriles **25a–j** were also relatively inactive. Only the ethyl ether **25i** demonstrated significant activity in the carrageenan assay. As observed previously with isophthalonitriles and trimesonitriles, the monohalogenated and methylated derivatives of these cyanobenzenes demonstrated the highest degree of activity. Five of the seven simply substituted benzonitriles tested possessed significant antiinflammatory activity. 4-Bromobenzonitrile (4-Br-BN), at a dose of 150 mg/kg, produced a 75% reduction of carrageenan-induced edema. This value is greater than that of our standard, phenylbutazone, when

Table VII. Antiinflammatory Effects of Orally Administered Substituted Benzonitriles on Carrageenan-Induced Edema in Rats

compd no.	carrageenan antiinflam act. dose, mg/kg	% redn	LD_{50}, mg/kg
22a	200	0	>300
22b	200	15	>300
22c	200	0	>300
22d	200	2	>300
22e	200	0	>300
22f	200	11	>300
22g	200	0	>300
22h	200	15	>300
22i	200	11	>300
22j	200	17	>300
22k	200	0	>300
22l	200	0	>300
22m	200	3	>300
25a	200	11	>300
25b	200	12	237
25c	200	5	237
25d	150	2	178
25e	200	0	>300
25f	40	5	56
25g	200	0	>300
25h	200	15	>300
25i	200	23	237
25j	200	18	300
4-bromobenzonitrile (4-Br-BN)[a]	150	75	237
2-Cl-BN[a]	200	26	>300
2-Br-BN[a]	200	19	>300
4-F-BN[b]	200	17	>300
3-CH_3-BN[c]	200	20	>300
3,4-$(CH_3)_2$-BN[d]	200	25	>300
4-Cl-BN[e]	200	30	>300
phenylbutazone	100	43.8[f]	>300

[a] A. Korczynski and B. Fandrich, *C. R. Hebd. Seances Acad. Sci.*, **183**, 421 (1926). [b] I. J. Rinkes, *Chem. Weekbl. II*, 360, 952 (1914). [c] A. Tomisek, B. Graham, A. Griffith, C. S. Pease, and B. E. Christensen, *J. Am. Chem. Soc.*, **68**, 1587 (1946). [d] T. Terakawa, H. Ouchi, H. Zenno, K. Nakanishi, and S. Umio, *Yakugaku Zasshi*, 74, 312 (1954). [e] C. R. Hauser and G. Vermillion, *J. Am. Chem. Soc.*, **63**, 1224 (1941). [f] Based on 46 determinations; standard deviation was 13.4%.

administered at 100 mg/kg. 2-Cl-BN, 3-Me-BN, 3,4-Me_2-BN, and 4-Cl-BN, all with LD_{50} values in excess of 300 mg/kg, reduced inflammation in this assay by 20% or greater.

Within the terephthalonitrile series (Table VIII), ten of the 16 compounds evaluated exhibited significant antiinflammatory activity. Among the 2-aminoterephthalonitriles **28a–g**, the methylamino derivative **28a** and dipropylamino derivative **28f** were the most effective in reducing carrageenan-induced edema. The methylamino analogue **28a**, while reducing edema by 37% at 40 mg/kg, was relatively toxic with an LD_{50} value of 56 mg/kg. Again, the unsubstituted mono- and dihalogenated cyanobenzenes represent the most active chemical classes. Among the simply substituted terephthalonitriles (TPN), 2-Cl-TPN, 2,5-Cl_2-TPN, 2,5-F_2-TPN, 2-Cl-5-F-TPN, and the parent compound TPN exhibited good activity and, with the exception of 2,5-F_2-TPN, possessed LD_{50} values in excess of 300 mg/kg. Tetrafluoroterephthalonitrile (**27**) and 2-Cl-3,5,6-F_3-TPN were active but relatively toxic with LD_{50} values of 56 and 40 mg/kg, respectively.

Biological Discussion. With the administration of compounds at various doses to eliminate toxic complication, quantitative structure–activity correlations were difficult to establish. However, several trends appear

Table VIII. Antiinflammatory Effects of Orally Administered Substituted Terephthalonitriles on Carrageenan-Induced Edema in Rats

compd identity	carrageenan antiinflam act. dose, mg/kg	% redn	LD_{50}, mg/kg
28a	40	17	56
28b	200	19	237
28c	200	14	>300
28d	200	11	>300
28e	200	0	>300
28f	200	22	>300
28g	200	10	>300
26[b]	200	13	>300
27[b]	50	54	56
terephthalonitrile (TPN)[a]	200	27	>300
2-Cl-TPN[b]	200	46	>300
2-F-TPN[b]	200	49	>300
2,5-Cl_2-TPN[b]	200	22	>300
2,5-F_2-TPN[b]	200	32	56
2-Cl-5-F-TPN[b]	200	22	>300
2-Cl-3,5,6-F_3-TPN[b]	40	86	40
phenylbutazone	100	43.8[c]	>300

[a] H. H. Hodgson and F. Heyworth, *J. Chem. Soc.*, 1131 (1949). [b] R. D. Battershell and H. Bluestone, U.S. Patent 3 290 353 (1966). [c] Based on 46 determinations; standard deviation was 13.4%.

among these aromatic nitriles. First, in all four chemical classes, the unsubstituted or simply substituted analogues possessed the highest value of antiinflammatory activity. With the exception of **18j**, all compounds with antiinflammatory activity exceeding 30% reduction were unsubstituted or simply methylated and halogenated analogues (**1**, 4,6-F_2-IPN, **16**, Me_3-TMN, 4-Br-BN, 4-Cl-BN, **27**, **28a**, 2-Cl-TPN, 2-F-TPN, 2,5-Cl_2-TPN, and 2-Cl-3,5,6-F_3-TPN). With few exceptions, substitution with carboalkoxy, alkylamino, anilino, or alkylsulfonyl groups resulted in a significant reduction in antiinflammatory activity.

Second, among the homologous series of aromatic nitriles, activity was, in most cases, reduced by lengthening the alkyl chain. In the 4-aminoisophthalonitrile series **4a–e**, lengthening of the alkyl chain from unsubstituted amine to 2-ethylhexylamine resulted in activities ranging in progression from 25 to 0%. A similar trend was observed in the limited diaminotrimesonitrile series **19a–c**, where **19a** reduced inflammation by 20%, while **19c** reduced inflammation by 5%. In the 4-carboalkoxy series **6a–h**, this general trend was also observed, although when the chain length reached seven methylene units (**6g** and **6h**), activity began to increase. Among the aminoterephthalonitrile homologous series **28a–d**, activity was again reduced by lengthening the alkylamine chain. Methylamino analogue **28a**, although having an LD_{50} value of 56 mg/kg, reduced edema 37% at a dose of 40 mg/kg. As the alkyl chain is extended to *n*-hexyl, toxicity decreases, as does antiinflammatory activity. The only class in which this general trend is not observed is the benzonitrile series.

Third, it is interesting to note that within the TPN series the fluoro derivatives were more active than the corresponding chloro analogues, as noted by comparison of **27** to **26**, 2-F-TPN to 2-Cl-TPN, and 2,5-F_2-TPN to 2,5-Cl_2-TPN. However, the fluoro compounds were also more toxic than the corresponding chloro derivatives. This increase in toxicity among the fluoro derivatives may be a result of increased susceptibility to nucleophilic attack by amino and mercapto functions present in protein structure.[25] It may be that the relatively labile fluorine atom undergoes displacement by these functional groups resulting in the overt toxic effects and low LD_{50} values. 2-Cl-3,5,6-F_3-TPN also possessed potent antiinflammatory activity (86% reduction at 40 mg/kg) but, like **27**, was quite toxic with an LD_{50} value of 40 mg/kg.

Six compounds (4,6-F_2-IPN, Me_3-TMN, **18j**, **28a**, **27**, and 2-Cl-3,5,6-F_3-TPN), at doses approximately one-half that of phenylbutazone, produced reductions in inflammation similar to this standard. However, the LD_{50} value of each compound was in the range of 40–56 mg/kg in the mouse; because of the low LD_{50} value of these compounds, further study was not carried out. Fifteen aromatic nitriles had LD_{50} values in excess of 300 mg/kg with moderate antiinflammatory activity (>20% reduction). Of these compounds, **16**, 4-Cl-BN, 2-Cl-TPN, and 2-F-TPN, with reductions in edema of 32, 30, 46, and 49%, respectively, represent the best candidates for subsequent evaluation. These compounds were dosed at 200 mg/kg, twice the dose required of phenylbutazone, to achieve a similar antiinflammatory response in this assay. Dose–response curves must be determined for these compounds and therapeutic indices evaluated before any meaningful comparisons can be made with phenylbutazone.

Experimental Section

Elemental analyses were performed by Diamond Shamrock Corporation, Analytical Group, Painesville, Ohio. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer with sodium chloride optics. Nuclear magnetic resonance spectra were recorded on a Varian A-56/60D spectrometer and a Bruker WH-90 spectrometer. Melting points were determined on a Thomas-Hoover capillary melting apparatus and were uncorrected.

The regiospecific synthesis of **7** is presented below, followed by examples of the synthetic procedures utilized in synthesizing compounds found in Tables I and II.

2-Fluoro-*m*-xylene (9). Into a 2-L flask equipped with a mechanical stirrer, thermometer, dropping funnel, and a cooling bath was placed 320 mL of 48% fluoroboric acid. While cooling with ice water, 104.5 g (0.862 mol) of 2,6-dimethylaniline was added causing the resultant salt to precipitate out of solution. The addition of 160 mL of tetrahydrofuran and 100 mL of distilled water dissolved the aniline salt. Sodium nitrite (60.7 g, 0.88 mol) dissolved in 130 mL of distilled water was added dropwise to the reaction flask over a 2.0-h period with the temperature maintained at 3 °C. The mixture was then stirred at this temperature for 2 h. The diazonium salt thus formed was filtered and pressed as dry as possible on the filter paper and then washed with 200 mL of ice-cold 5% fluoroboric acid solution, 200 mL of cold methanol, and 250 mL of cold ethyl ether. After drying in vacuo, 176 g (92.8% yield) of the diazonium salt was obtained.

The diazonium salt was decomposed by adding it in portions over a 45-min period to 200 mL of benzene heated to 60–70 °C in a 4-L flask. The resulting mixture, after standing overnight in the beaker, was filtered into a separatory funnel and neutralized with 50 mL of 10% NaOH. The organic layer was dried over $MgSO_4$.

The benzene was removed under reduced pressure and the resulting oil distilled through a glass helices ($^1/_{16}$ in.) column at 140 °C to yield a clear oil (yield, 74%). Anal. (C_8H_9F) C, H, F.

2-Fluoro-4,5,6-trichloro-*m*-xylene (10). Into a 3-L flask equipped with a mechanical stirrer, thermometer, condenser, and a gas inlet tube were placed 153.3 g (1.232 mol) of 2-fluoro-*m*-xylene, 1500 mL of carbon tetrachloride, and 3 g of ferric chloride. Chlorine gas (275 g, 3.87/mol) was introduced in the reaction flask during 8.5 h while maintaining the temperature at 35–37 °C. The carbon tetrachloride was distilled under vacuum and the residue crystallized from 2500 mL of 2-propanol to form a white solid, mp 156–157 °C (yield 85%). Anal. ($C_8H_6Cl_3F$) C, H, F.

α,α′-Dibromo-2-fluoro-4,5,6-trichloro-*m*-xylene (11). In a 1-L flask equipped with a magnetic stirrer, thermometer, condenser, heating mantle, and dropping funnel were placed 56.9 g (0.25 mol) of 2-fluoro-4,5,6-trichloro-*m*-xylene and 500 mL of carbon tetrachloride. The mixture was heated to reflux and

illuminated with a 200-W medium-pressure Hanova light. Bromine (87.9 g, 0.55 mol) was added dropwise to the refluxing reaction mixture over a 4-h period. Stirring was continued for 4 h at reflux after the bromine addition. The reaction mixture was cooled to room temperature and purged with air to remove the hydrogen bromide. The solution was transferred to a separatory funnel and shaken with a sodium thiosulfate solution to neutralize excess bromine. Carbon tetrachloride was removed under vacuum and a light yellow solid was collected and recrystallized from carbon tetrachloride to yield yellow crystals, mp 95–96 °C (yield 95%). Anal. ($C_8H_4Br_2Cl_3F$) C, H.

2-Fluoro-4,5,6-trichloroisophthalic Acid (12). Into a 1-L flask equipped with a mechanical stirrer, heating mantle, thermometer, and a dropping funnel were placed 7.7 g (0.02 mol) of α,α'-dibromo-2-fluoro-4,5,6-trichloro-*m*-xylene and 6 g (0.09 mol) of potassium hydroxide dissolved in 150 mL of distilled water. The contents were heated to reflux and 12 g (0.976 mol) of potassium permanganate dissolved in 300 mL of distilled water was added dropwise over a 2-h period. After refluxing for 50 h with stirring, 5 g of sodium sulfite dissolved in 30 mL of water was added to the reaction mixture to deactivate the remaining potassium permanganate. The contents were then cooled to 80 °C and filtered. The filtrate was brought to a pH of 4 with concentrated HCl and then cooled in an ice bath. The white precipitate was collected by filtration and recrystallized from ether–hexane to afford white crystals, mp 272–274 °C (yield 60%). Anal. ($C_8H_2Cl_3FO_4$) C, H.

2-Fluoro-4,5,6-trichloroisophthaloyl Chloride (13). In a 200-mL flask equipped with a mechanical stirrer, thermometer, heating mantle, and a condenser were placed 14.4 g (0.05 mol) of 2-fluoro-4,5,6-trichloroisophthalic acid, 50 mL of thionyl chloride, and 10 drops of dimethylformamide. The reaction mixture was heated to 65 °C over a 1-h period and then left at 65 °C for 2 h. After excess thionyl chloride was distilled off and 100 mL of carbon tetrachloride was added to the reaction flask, the mixture was filtered. The carbon tetrachloride was removed under reduced pressure resulting in a yellow oil which was vacuum distilled, 87–88 °C (0.05 mm), to yield a light yellow oil (yield 93%). Anal. ($C_8Cl_5FO_2$) C, H, F.

2-Fluoro-4,5,6-trichloroisophthalamide (14). Into a 50-mL flask equipped with a magnetic stirrer and thermometer and a cooling bath were placed 50 mL of ammonium hydroxide and 150 mL of dioxane. 2-Fluoro-4,5,6-trichloroisophthaloyl chloride (44.2 g, 0.13 mol) dissolved in 50 mL of dioxane was added dropwise over a period of 5 min while maintaining the temperature below 65 °C. The cooling bath was removed and the reaction was left stirring at room temperature for 1 h before cooling to 20 °C. The resultant white precipitate was collected by filtration, washed with water, and allowed to air-dry. The dioxane solution was concentrated to yield additional white solid. The product was recrystallized from DMF–H_2O to afford white crystals, mp 324–325 °C. Anal. ($C_8H_4Cl_3FN_2O_2$) C, H, F.

2-Fluoro-4,5,6-trichloroisophthalonitrile (15). Into a 250-mL flask equipped with mechanical stirrer, thermometer, condenser, and a heating mantle were placed 22 g (0.077 mol) of 2-fluoro-4,5,6-trichloroisophthalamide, 80 mL of phosphorus oxychloride, and 5 drops of dimethylformamide. The contents were stirred while being heated to 90 °C over a 40-min period. Heating was continued for 3 h, at which time the evolution of gas ceased. The contents were cooled to 20 °C with a water bath and poured onto ice. The light tan material was collected by filtration, washed with water, and dried under reduced pressure. The solid was recrystallized from chloroform to yield tan crystals, mp 180.5–181.5 °C. Anal. ($C_8N_2Cl_3F$) C, H.

2-Hydroxy-4,5,6-trichloroisophthalonitrile (7). To a 500-mL Erlenmeyer flask was added anhydrous sodium acetate (12 g, 0.15 mol) dissolved in DMF (300 mL). To this solution was added 2-fluoro-4,5,6-trichloroisophthalamide (25 g, 0.1 mol) forming a red solution. After 0.5 h, the mixture became yellow in color, an additional 12 g of sodium acetate was added, and the mixture was stirred for 1 h. The solution was then treated with 10% HCl to form a white solid which was collected and dissolved in methylene chloride. Concentration of the solution and addition of carbon tetrachloride resulted in a white precipitate, mp 271–273 °C (yield 90%). Anal. ($C_8HCl_3ON_2$) C, H, N.

Synthesis of 4-Hydroxytrichloroisophthalonitrile (3). Tetrachloroisophthalonitrile (13 g, 0.05 mol) was dissolved in dry DMF (250 mL). To this solution was added sodium acetate (16 g, 0.2 mol) and the stirred mixture was then heated to 125 °C for 3 h. The mixture was then cooled, acidified with concentrated HCl (200 mL), and poured over ice. The solid precipitate was collected, washed with H_2O, and dried under reduced pressure. Recrystallization from ethanol afforded white crystals, mp 262–264 °C (yield 84%). Anal. ($C_8HN_2OCl_3$) C, H, N.

The observed ^{13}C NMR chemical shifts relative to Me_4Si followed by the predicted shifts[14] run in DMF-d_7 at ambient temperature are 102.1, 100 (aromatic C_3), 103.3, 109 (aromatic C_1), 113.7, 119 (cyano C), 113.5, 119 (cyano C), 123.2, 123 (aromatic C_5), 139.3, 152 (aromatic C_6), 139.5, 144 (aromatic C_2), and 164.3, 167 ppm (aromatic C_4).

Synthesis of 4-Carboalkoxytrichloroisophthalonitriles 6a–k. The hydroxyisophthalonitrile **3** was dissolved in an excess of acetic anhydride and heated at 130 °C for 24 h. The mixture was cooled, forming a solid which was collected and washed with H_2O. Recrystallization from pentane or heptane afforded pure solids.

Synthesis of 4-Aminotrichloroisophthalonitriles 4a–e. Tetrachloroisophthalonitrile (**2**), dissolved in an aprotic solvent such as benzene, was added to the desired primary amine in equal molar quantities. A catalytic amount of triethylamine was added and the mixtures were heated at reflux for 24 h. Upon cooling and concentration, a precipitate formed which was collected and recrystallized to afford the desired aminoisophthalonitrile.

Synthesis of 4-Alkoxytrichloroisophthalonitriles 5a–c. The isophthalonitrile **2** was dissolved in an excess of the desired alcohol. To this solution was added 1 equiv of potassium fluoride and the mixture heated to 90 °C for 2 h. Upon cooling and concentration of the mixture, a solid precipitate formed which was collected and recrystallized from ethanol to give analytically pure product.

Synthesis of 2-Aminodichlorotrimesonitriles 18a–m.[16] To a solution of trichlorotrimesonitrile (**17**) in acetone at room temperature was added a slight molar excess of the desired aniline. A catalytic amount of triethylamine was added and the reaction mixture stirred at room temperature for 4 h. The mixture was diluted with 3 vol of H_2O causing a precipitate to form. Recrystallization from CH_3OH gave analytically pure product.

Synthesis of 2,4-Diamino-6-chlorotrimesonitriles 19a–c. To a solution of the trimesonitrile **17**, dissolved in a large excess of the desired primary amine, was added triethylamine. The mixture was heated to 120 °C for 10 h. Upon cooling, a solid formed which was collected and recrystallized from CH_3OH to give the analytically pure product.

4-Hydroxytetrachlorobenzonitrile (21). Pentachlorobenzonitrile (27.5 g, 0.1 mol) was dissolved in DMF (200 mL). To this stirring solution at ambient temperature was added anhydrous sodium acetate (12 g, 0.15 mol). The mixture was slowly heated to 125 °C for 8 h. After cooling the reaction mixture was poured into a concentrated HCl–ice mixture (50 mL of concentrated HCl, 300 g of ice) and slurried. A precipitate formed which was collected, washed with H_2O, and recrystallized from 60% ethanol to give a white solid, mp 213–214 °C, identified as **21** (yield 50%). Anal. (C_7HNOCl_4) C, H.

The observed ^{13}C NMR chemical shifts relative to Me_4Si using DMF-d_7 solvent at ambient temperature are 157.4 (phenolic C_4), 135.4 (aromatic C_2 and C_6), 122.1 (aromatic C_3 and C_5), 114.2 (nitrile C), and 105.8 ppm (aromatic C_1).

4-Carboalkoxytetrachlorobenzonitriles 22a–m. The 4-hydroxybenzonitrile **21** was dissolved in an excess of the acid anhydride with the resulting solution heated to 130 °C for 20 h. The solution was cooled, resulting in a solid precipitate which was collected, washed with petroleum ether, and dried under reduced pressure. Recrystallization from pentane afforded analytically pure products.

Reaction also occurred with the appropriate acid chloride by refluxing for 21 h.

4-Mercaptotetrachlorobenzonitrile (23).[17] Anhydrous hydrogen sulfide was passed through a solution of 138 g (0.5 mol) of pentachlorobenzonitrile and 55 g of triethylamine in 1 L of pyridine for 5 h. An initial exotherm was observed during which the temperature reached 58 °C. The clear red solution was poured

into an ice mixture of concentrated HCl to give a solid (mp 173–175 °C) which was recrystallized from ethylene glycol monomethyl ether. There was obtained 90 g of a brown solid, mp 213–214 °C (lit.[3] mp 213–214 °C) (yield 68%).

4-Alkylthiotetrachlorobenzonitriles 24. To a solution of 8.3 g (0.36 g/atom) of sodium metal in 540 mL of dry methanol was added 98 g (0.36 mol) of 4-mercapto-2,3,5,6-tetrachlorobenzonitrile. The resulting dark amber solution was heated at reflux for 3 h. Methanol was removed by distillation with simultaneous addition of toluene from an addition funnel so as to maintain a nearly constant volume. The thick slurry was cooled and filtered, and the filter cake was washed thoroughly with petroleum ether to yield 91 g of pale orange colored solids, mp >360 °C. This product was the sodium 4-cyanotetrachlorophenylmercaptide. The mercaptide was dissolved in 1,2-dimethoxyethane and stirred at room temperature as 2 equiv of the appropriate alkyl halide were added. The reaction mixture was stirred for 2 h, then heated to 60 °C for 1 h, cooled, and concentrated to afford a solid residue which was recrystallized from hot hexane to yield the desired sulfide, **24**.

4-Alkylsulfonyltetrachlorobenzonitriles 25a–j. A mixture of the alkylthiobenzonitrile **24** and acetic acid was treated with 30% aqueous H_2O_2 and refluxed at 100 °C for 2 h. The cooled mixture was poured over ice to form a solid which was recrystallized from isopropyl alcohol, affording analytically pure product.

2-Aminotrifluoroterephthalonitriles 28a–g. To a stirring solution of tetrafluoroterephthalonitrile[13] in acetone was added an aqueous solution of the appropriate amine. The mixture was heated to 55 °C for 4 h. On cooling over ice, a solid formed. It was recrystallized from methanol–H_2O to afford analytically pure product.

Carrageenan-Induced Pedal Edema Assay.[18] Male rats (Long Evans strain) weighing between 130 and 200 g are used in this assay. Five rats each were used in the treatment groups and in the known standard control, whereas ten rats were used in the control edema group. Unless otherwise indicated, phenylbutazone was administered orally at 100 mg/kg to the standard control group. The edema control group was administered the vehicle which consisted of 0.25% methylcellulose solution. All of the rats were fasted for at least 15 h prior to the test. Water was available ad libitum. All of the experimental drugs were given orally and were dissolved or suspended in 0.25% methylcellulose solution. One hour after administration of the test compound, 0.05 mL of a 1% sterile solution of carrageenan was injected into the plantar tissues of the left hind paw of each rat. Three hours after carrageenan administration, the paw volumes of injected paws were measured by means of a water displacement apparatus. The apparatus used is a modification of that described by Adamkiewicz.[26] The amount of edema was calculated and the percent reduction of edema from control values was determined. The mean volume of edema, based on 50 determinations, was 1.25 cm^3 with a standard deviation of 0.226 cm^3. This represents the control value. A reduction on edema greater than 20% of the control value was considered significant. Based on 46 determinations, phenylbutazone produced a mean inhibition of edema of 43.8% with a standard deviation of 13.4%.

References and Notes

(1) A. Goldstein, L. Aronow, and S. M. Kalman, "Principles of Drug Action", Harper and Row, New York, N.Y., 1969.
(2) H. Terada, S. Muraoka, and T. Fujita, *J. Med. Chem.*, **17**, 330 (1974).
(3) R. N. Smith and K. H. Goulding, *Biodeterior. Mater., Proc. Int. Biodeterior. Symp., 2nd, 1971*, 238 (1972).
(4) D. L. Hopkins, *Proc. Fla. State Hortic. Soc.*, **85**, 108 (1972).
(5) A. L. Harrison, *Phytopathology*, **63**, 668 (1973).
(6) D. H. Smith, F. L. Crosby, and W. J. Ethredge, *Plant Dis. Rep.*, **58**, 666 (1974).
(7) J. R. Beck and R. G. Suhr, U.S. Patent 3 857 862 (1974).
(8) K. Kishi, *Jpn. Pestic. Inf.*, **8**, 23 (1971).
(9) L. W. Watts, Jr., U.S. Patent 3 798 255 (1974).
(10) K. Carpenter and B. J. Heywood, *Nature (London)*, **200**, 28 (1963).
(11) E. J. Peters and S. A. Lowance, *Agron. J.*, **62**, 400 (1970).
(12) G. P. Poeschel and J. A. Pankavich, U.S. Patent 3 764 697 (1973).
(13) R. D. Battershell and H. Bluestone, U.S. Patent 3 290 353 (1966).
(14) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 81.
(15) H. Suschitzky, *Adv. Fluorine Chem.*, **4**, 1 (1965).
(16) R. D. Battershell, U.S. Patent 3 637 796 (1972).
(17) G. Beck, E. Degener, and H. Heitzer, *Justus Liebigs Ann. Chem.*, **716**, 47 (1968).
(18) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(19) M. DiRosa and D. A. Willoughby, *J. Pharm. Pharmacol.*, **23**, 297 (1971).
(20) M. DiRosa, J. P. Giroud, and D. A. Willoughby, *J. Pathol.*, **104**, 15 (1971).
(21) R. Vinegar, J. F. Truax, and J. L. Selph, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **35**, 2447 (1976).
(22) C. A. Winter, *Prog. Drug Res.*, **10**, 139 (1966).
(23) C. J. E. Niemegeers, F. J. Verbruggen, and P. A. J. Janssen, *J. Pharm. Pharmacol.*, **16**, 810 (1964).
(24) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(25) N. J. Turner and R. D. Battershell, *Contrib. Boyce Thompson Inst.*, **24**, 139 (1969).
(26) V. W. Adamkiewicz, *Can. J. Biochem. Physiol.*, **33**, 332 (1955).

Nondepressant β-Adrenergic Blocking Agents. 1. Substituted 3-Amino-1-(5,6,7,8-tetrahydro-1-naphthoxy)-2-propanols

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A series of 3-amino-1-(5,6,7,8-tetrahydronaphthoxy)-2-propanols was synthesized and investigated for β-adrenergic blocking activity and direct myocardial depressant action. The *cis*- and *trans*-diols **12–15** were found to retain the β-blocking potency of propranolol but to lack its myocardial depressant action. Compound **15** (nadolol) is currently undergoing extensive clinical evaluation as a potential antianginal, antiarrhythmic, and antihypertensive agent.

The clinical utility of propranolol in the treatment of angina pectoris,[1] hypertension,[2,3] and certain arrhythmias[4,5] is well documented. In addition to its β-blocking properties, however, propranolol has exhibited a direct myocardial depressant action,[6] which can precipitate acute congestive heart failure in patients with impaired left ventricular function.[7,8]

Prompted by the discovery of practolol,[9] attempts[10] to

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