Preparation and Antiinflammatory Activity of Some Nonacidic Trisubstituted Imidazoles

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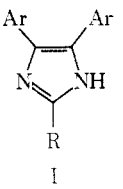
A number of trisubstituted imidazoles have been made and several found to be potent antiinflammatory agents when examined in the carrageenan rat paw edema test. The antiinflammatory activity of these imidazoles is retained in adrenalectomized rats. Unlike many previously reported antiinflammatory agents, these compounds are extremely weak acids ($pK_a \geq 11$) and are therefore not ionized at physiological pH. One compound, 4,5-bis(4-methoxyphenyl)-2-trifluoromethylimidazole (flumizole, **15**), is more potent than indomethacin in the rat paw edema test and, in contrast to some related compounds, does not cause photosensitization in mice.

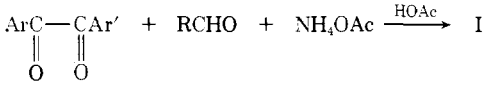
The majority of clinically useful antiinflammatory agents such as indomethacin, phenylbutazone, flufenamic acid, ibuprofen, and aspirin are acidic[1] with pK_a values in the range of 3.5–5.5 and appear to share a common antiinflammatory profile. Benzydamine[2] [1-benzyl-3-(3-dimethylaminopropoxy)indazole] and indoxole[3] [2,3-bis(4-methoxyphenyl)indole], however, are examples of nonacidic antiinflammatory agents. Previous publications from these laboratories[4-8] have reported a number of structurally different acidic antiinflammatory compounds with pK_a values in the range of 4–7. With the finding of the potent acidic antiinflammatory agent sudoxicam[8b,c] and in view of the reported experience with indoxole[3] and benzydamine,[2] our attention was directed to the preparation of novel, nonacidic antiinflammatory compounds.

Several heterocyclic compounds with aryl substituents have previously been reported[3,9-15] to exhibit antiinflammatory activity in animals and led us to prepare a few novel polyaryl heterocyclic compounds. Of the various polyaryl heterocycles initially prepared, certain 4,5-diphenyl-2-substituted imidazoles (I) exhibited antiinflammatory activity comparable to phenylbutazone in the carrageenan rat paw edema test. Variations in substituents around the imidazole nucleus in compound I were then made and results of the antiinflammatory testing of these analogs constitute the basis for this report.



I

Chemistry. Almost all of the di- and triarylimidazoles in Table I were prepared by the Davidson[16] modification of the Radziszewski[17] imidazole synthesis utilizing the corresponding diketone and an aldehyde in the presence of excess NH_4OAc in HOAc as solvent.



Anhydrous conditions were maintained (dry N_2) and the NH_4OAc was dried over P_2O_5 under slight vacuum to minimize the undesirable effects[18] of H_2O. Preparations of the requisite α-diketones are summarized in Table IV in the Experimental Section. The 4,5-dialkylimidazoles, compounds **51–56**, were conveniently prepared from an α-hydroxy ketone and an aldehyde in the presence of $CuSO_4$. For the 2-trifluoromethylimidazoles, the relatively unreactive trifluoroacetaldehyde ethyl hemiacetal was employed in excess in place of the aldehyde; however, even forcing conditions failed to complete most of these reactions. A few of the imidazole products formed tenacious solvates (see Table I) which could not be removed even after drying the compounds at 100° under high vacuum over P_2O_5 for several hours. To examine the role of the imidazole NH group, N-alkylations of various imidazoles were carried out by one of two techniques (method A or B) as indicated in Table II.

Imidazole and simple arylimidazoles such as those reported herein are generally feeble acids[19] of pK_a = 12.5–14.5. The presence of a 2-trifluoromethyl group lowered the pK_a' of flumizole (**15**) to 10.7 (measured in 2:1 dioxane–H_2O) but this value is still well above the pK_a range of 4–7 found for typical acidic antiinflammatory compounds. The compounds shown in Table I, including the trifluoromethylimidazoles, would certainly not be significantly ionized to an anionic species at physiological pH.

Pharmacology.† Assessment of antiinflammatory activity depended upon inhibition of edema formation in the hindpaw of the rat (six per group) in response to the subplantar injection of carrageenan. For studies designed to assess the role of the adrenal hormones in antiedema activity, bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were maintained under light Et_2O anesthesia. Animals were maintained on a normal diet with 0.9% saline in place of drinking water and were used 5–7 days postoperatively. Antiedema studies were performed using male Charles River CD rats (intact and adrenalectomized; average body weight 170 g) and male Wistar Crl:COBS rats (intact; average body weight 160 g). As outlined in our previous publications,[5-8] the experimental procedure followed that of Winter, *et al.*,[20] with edema formation measured 3 hr after oral administration of test drug. Because of the greater potencies of the compounds reported in this work, phenylbutazone (33 mg/kg) was chosen as a standard, in preference to the aspirin (100 mg/kg) standard previously used.[5-8] Because of the limited aqueous solubility of many of the compounds reported, all test drugs (and the standard) were administered solubilized to the maximum extent in polyethylene glycol 300 containing 5% Tween 80 (0.2 ml in 5 ml of H_2O per animal). The response of drug-treated animals was compared with that of animals concurrently receiving vehicle alone and animals receiving phenylbutazone. Results of this antiinflammatory testing are given in Tables I and II.

Dose–response lines were obtained at five dose levels (0.1–33 mg/kg) of flumizole (**15**) and indomethacin in the carrageenan-induced rat foot edema test, using Charles River rats.[21] Although some variation was noted, the potency of flumizole (**15**) usually exceeded that of indomethacin, occasionally by as much as ten times. In adrenalectomized Charles River rats, the antiedema activity of 3

†The research described in this report involved animals maintained in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

and 15 at 33 mg/kg po was comparable to that in normal rats. In intact male Wistar rats, the potency of flumizole (15) was approximately ten times that of phenylbutazone. Although the direct comparison was not made between flumizole (15) and indomethacin in Wistar rats, experience in these laboratories would extrapolate the phenylbutazone comparison to indicate that flumizole would be 1–3 times as potent as indomethacin in this strain.

Compound 15 also displays potent activity in other animal models of inflammation (*e.g.*, string-granuloma, ultraviolet-induced erythema) and *in vitro* tests (prostaglandin synthesis) believed to be relevant to the mode of action of nonsteroidal antiinflammatory agents. The results of these tests will be reported in full elsewhere.[21]

Although indoxole is claimed[3b] not to cause photosensitization in swine, the chemiluminescent[22] and general photoreactive[23] properties of polyarylimidazoles cause some concern as to the possible photosensitization potential of the agents described in this report. Therefore, photosensitization potential was assessed by a modification of apparatus previously described.[24]

Groups of five mice, housed in clear plastic cages, were given free access to food and water. The cages were covered with a sheet of plate glass (1 cm thick) and placed 12 in. below a source of ultraviolet light (four G.E. F-40 BLB black lights in a specially constructed reflecting holder). Drugs were administered orally in a solution of polyethylene glycol 300 containing 5% Tween 80–water (1:4). Mice were irradiated 24 hr daily, with daily drug administration (100 mg/kg), and then observed for a further period of 3 days after ceasing irradiation for signs of erythema and/or necrosis of the ears. Potent photosensitizing activity in this mouse model was established for psoralen[24] (25 mg/kg po for 4 days) and, contrary to the reported results in swine,[3b] for indoxole[3] (100 mg/kg po for 4 days). With either of these drugs, necrosis of the mouse ears appeared within the first few days. Various representatives of the compounds described herein, *e.g.*, 7, 9, and 12 (100 mg/kg po for 4–6 days), also exhibited a photosensitizing effect. In contrast, compound 3, of antiinflammatory potency approximately equal to that of indoxole, required more prolonged exposure to drug and irradiation (100 mg/kg po daily for 11 days) to show minimal signs of erythema of the ears even after 14 days of irradiation. Most striking of all, flumizole (15), which is considerably more potent as an antiinflammatory agent than indoxole, and compounds 61 and 63 elicited *no* phototoxicity, even under conditions of extended irradiation (11 days) and high dose (100 mg/kg po daily). Under these same conditions, phenylbutazone also showed an absence of photosensitizing potential.

An attempt was made to correlate the phototoxicity results with the ultraviolet absorption spectra of the compounds examined. Table III presents these data. Although only eight compounds were tested for phototoxic effect, there appears to be a direct correlation between ultraviolet absorption maxima above 300 mμ and phototoxicity in these imidazoles. This preliminary finding deserves further examination.

Discussion

The series of polyarylimidazoles described in this report includes some of the most potent nonacidic antiinflammatory agents yet discovered in animal tests. In general, the activity of the 4,5-dialkylimidazoles (*e.g.*, 51–56) or the *N*-alkylimidazoles (*e.g.*, 61–70) was exceeded by that of the 4,5-diarylimidazoles. A number of compounds clearly exceeded the potency of phenylbutazone (*i.e.*, are rated ++ or higher in Tables I or II) while flumizole (15) exceeded the potency of indomethacin.

The potency of the most active agents was found to be somewhat variable. All had limited aqueous solubility and required careful trituration into polyethylene glycol 300 containing Tween 80 to provide optimal activity. Similar dependency of potency upon formulation was reported with indoxole,[3a,25,26] also a compound with poor aqueous solubility. Variation of potency in repeated assays has also been reported with flurbiprofen.[27] Within a group of analogs where the 4,5-diaryl function was kept constant and the 2-substituent was varied, a 2-CF_3 substituent (*e.g.*, 8, 15, 25) often improved potency. Exceptions, however, were noted with the 2-CF_3 analogs 22, 31, and 34, which were not the most potent within their class.

After this work was completed, the antiinflammatory activity of certain 2-alkyl-4,5-diarylimidazoles, including 2-isopropyl-4,5-bis(4-methoxyphenyl)imidazole, was described in *Bolus alba* induced edema in rats.[28] For comparative purposes, the results of testing this compound in the rat paw edema test are included at the end of Table I together with indoxole, benzydamine, and phenylbutazone. Another recent publication[29] reported weak antiinflammatory activity (ED_{50} in the rat paw edema test of 300 mg/kg ip) for imidazole.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Potentiometric titrations were carried out in 2:1 dioxane–H_2O (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH. The apparent pK_a values correspond to the pH values at the half-neutralization point in these titrations. A Varian A-60 spectrometer (Me_4Si standard) was used to measure nmr spectra and mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E. Ir spectra were determined in KBr pellets. Analyses were carried out by the Physical Measurements Laboratory of Pfizer Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.40% of the theoretical values.

The required aldehydes were commercially available and used as received. Benzil and 4,4′-dimethoxybenzil were purchased from Pfaltz and Bauer, Inc., and 3,3′-dimethoxybenzil from Regis Chemical Co. Trifluoroacetaldehyde ethyl hemiacetal was purchased from Pierce Chemical Co. 2,2′-Pyridil was purchased from Aldrich Chemical Co. and butyroin from Sapon Laboratories.

Substituted Benzils. The requisite substituted benzils were prepared by a benzoin condensation[30] of the corresponding aldehyde followed by a $CuSO_4$–pyridine oxidation[31] to produce the symmetrically substituted benzil. Table IV summarizes these compounds and also indicates where the benzoin was merely extracted (Et_2O) from the mixture and immediately oxidized to the desired benzil. The unsymmetrical 4-bromo- and 4-methoxybenzoins (Table IV) were made by the known Friedel–Crafts reaction[32] of phenylglyoxal with either bromobenzene or anisole, respectively.

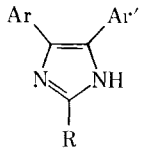
Trisubstituted Imidazoles. Most of the trisubstituted imidazoles (Table I) were made from the corresponding substituted benzil, the latter compounds either purchased or synthesized (see Table IV), and a benzaldehyde by the method of Davidson, *et al.*[16] Typical examples of the procedure using either a benzaldehyde (*e.g.*, to prepare 12) or trifluoroacetaldehyde ethyl hemiacetal (*e.g.*, to prepare 15) are given below.

2-(4′-Bromophenyl)-4,5-bis(4′′-methoxyphenyl)imidazole (12). A mixture of 1.9 g (0.007 mol) of 4,4′-dimethoxybenzil, 1.5 g (0.0081 mol) of 4-bromobenzaldehyde, and 6.5 g (0.084 mol) of anhydrous ammonium acetate in 50 ml of HOAc was heated to a yellow solution. After 1.5 hr, the reaction was complete (as evidenced by tlc) and was slowly poured into a solution of 100 ml of NH_4OH and 100 ml of ice–water. The resulting solid was filtered and recrystallized from *i*-PrOH to give 2.2 g (71%) of compound 12, mp 160–161°.

As indicated in Table I, a few trisubstituted imidazoles (*e.g.*, 26, 34, 42, 50) were converted to the corresponding hydrochloride salts by crystallization from hot *i*-PrOH–6 *N* HCl.

4,5-Bis(4′-methoxyphenyl)-2-trifluoromethylimidazole (15). To a hot solution of 20 g (0.074 mol) of 4,4′-dimethoxybenzil and 40 g of anhydrous ammonium acetate in 500 ml of HOAc was slowly added a solution of 11 g (0.074 mol) of trifluoroacetal-

Table I. Antiinflammatory Trisubstituted Imidazoles



No.	Ar	Ar′	R	Yield, %	Mp, °C	Crystn solvent[a]	Formula[b]	Antiinflam act.[c]
1	C_6H_5	C_6H_5	C_6H_5	*d*				–
2	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	53	230–232[e]	I	$C_{22}H_{18}N_2O$	–
3	C_6H_5	C_6H_5	4-BrC_6H_4	93	261–263[f]		$C_{21}H_{15}BrN_2$	++
4	C_6H_5	C_6H_5	2,4-$Cl_2C_6H_3$	66	174–176[g]	E	$C_{21}H_{14}Cl_2N_2$	+
5	C_6H_5	C_6H_5	H	61	228–230[h]	P–W	$C_{15}H_{12}N_2$	–
6	C_6H_5	C_6H_5	CH_3	55	240–242[i]	I–W	$C_{16}H_{14}N_2$	+
7	C_6H_5	C_6H_5	4-ClC_6H_4	97	262–264[j]		$C_{21}H_{15}ClN_2$	++
8	C_6H_5	C_6H_5	CF_3	38	225–227	B–H	$C_{16}H_{11}F_3N_2$	++
9	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	72	201–203[k]	B	$C_{23}H_{20}N_2O_2$	+
10	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	74	183–185[l]	Et	$C_{24}H_{22}N_2O_3$	+
11	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	2,4-$Cl_2C_6H_3$	82	162–164	I	$C_{23}H_{18}Cl_2N_2O_2$	+
12	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	4-BrC_6H_4	71	160–161	I	$C_{23}H_{19}BrN_2O_2 \cdot 0.5i$-PrOH	++
13	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	H	43	182–184[m]	P–W	$C_{17}H_{16}N_2O_2$	–
14	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CH_3	29	155 dec	E–W	$C_{18}H_{18}N_2O_2 \cdot 0.5H_2O$	–
15	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CF_3[n]	47	191–193	B[o]	$C_{18}H_{15}F_3N_2O_2$	5+
16	4-BrC_6H_4	C_6H_5	C_6H_5	67	254–255	Et–H	$C_{21}H_{15}BrN_2$	+
17	4-BrC_6H_4	C_6H_5	4-BrC_6H_4	72	289–291	B	$C_{21}H_{14}Br_2N_2$	–
18	4-BrC_6H_4	C_6H_5	4-$CH_3OC_6H_4$	67	261–262	EA	$C_{22}H_{17}BrN_2O$	+
19	4-BrC_6H_4	C_6H_5	CF_3	42	235–238	C	$C_{16}H_{10}BrF_3N_2$	+
20	4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	52	224–226	I	$C_{22}H_{12}N_2O$	+
21	4-$CH_3OC_6H_4$	C_6H_5	4-BrC_6H_4	72	239–242	I	$C_{22}H_{17}BrN_2O$	+++
22	4-$CH_3OC_6H_4$	C_6H_5	CF_3	16	201–203	*o*	$C_{17}H_{13}F_3N_2O$	+
23	4-BrC_6H_4	4-BrC_6H_4	C_6H_5	67	305–307	B	$C_{21}H_{14}Br_2N_2$	+
24	4-BrC_6H_4	4-BrC_6H_4	4-$CH_3OC_6H_4$	90	279–280	B	$C_{22}H_{16}Br_2N_2O$	–
25	4-BrC_6H_4	4-BrC_6H_4	CF_3	31	271–273	HAc–W	$C_{16}H_9Br_2F_3N_2$	+++
26	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	C_6H_5	19	290 dec	I–HCl	$C_{23}H_{20}N_2S_2 \cdot HCl$	+
27	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	4-$CH_3OC_6H_4$	41	99 dec	I	$C_{24}H_{22}N_2OS_2 \cdot IPO$	–
28	4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	CF_3	11	155–158	I	$C_{18}H_{15}F_3N_2S_2$	+
29	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	C_6H_5	59	189–191	EA	$C_{23}H_{20}N_2O_2$	–
30	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	4-BrC_6H_4	85	207–209	Et	$C_{23}H_{19}BrN_2O_2$	–
31	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	CF_3	26	145–147	B	$C_{18}H_{15}F_3N_2O_3$	–
32	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	C_6H_5	38	174–177	I	$C_{23}H_{20}N_2O_2$	+
33	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	4-BrC_6H_4	64	203–208	I	$C_{23}H_{19}BrN_2O_2$	+
34	2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	CF_3	42	211 dec	I–HCl	$C_{18}H_{15}F_3N_2O_2 \cdot HCl$	–

35	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	C_6H_5	92	267–268	B	$C_{23}H_{20}N_2$	+
36	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-BrC_6H_4	75	272–273	B	$C_{23}H_{19}BrN_2$	+
37	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	79	246–247	B	$C_{24}H_{22}N_2O$	–
38	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	CF_3	31	242–243	B	$C_{18}H_{15}F_3N_2$	+
39	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	4-BrC_6H_4	46	280–281	B	$C_{23}H_{19}BrN_2$	–
40	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	CF_3	24	212–214	B	$C_{18}H_{15}F_3N_2$	–
41	2-Pyridyl	2-Pyridyl	C_6H_5	50	187–190	I	$C_{19}H_{14}N_4$	–
42	2-Pyridyl	2-Pyridyl	4-BrC_6H_4	8	345 dec	E–HCl	$C_{19}H_{13}BrN_4 \cdot HCl$	–
43	2-Pyridyl	2-Pyridyl	4-$CH_3OC_6H_4$	22	171–173	I	$C_{20}H_{16}N_4O$	+
44	2-Pyridyl	2-Pyridyl	CF_3	28	226–229	I	$C_{14}H_9F_3N_2$	+
45	4-$C_2H_5OC_6H_4$	4-$C_2H_5OC_6H_4$	C_6H_5	68	199–200	C–H	$C_{25}H_{24}N_2O_2$	+
46	4-$C_2H_5OC_6H_4$	4-$C_2H_5OC_6H_4$	4-BrC_6H_5	52	184–185	C–H	$C_{25}H_{23}BrN_2O_2$	+
47	4-$C_2H_5OC_6H_4$	4-$C_2H_5OC_6H_4$	CF_3	20	161–163	C–H	$C_{20}H_{19}F_3N_2O_2 \cdot CHCl_3$	–
48	4-FC_6H_4	4-FC_6H_4	C_6H_5	40	262–263	I	$C_{21}H_{17}F_2N_2$	–
49	4-FC_6H_4	4-FC_6H_4	4-BrC_6H_5	44	278–279	I	$C_{21}H_{13}BrF_2N_2$	4+
50	4-FC_6H_4	4-FC_6H_4	CF_3	36	241 dec	Et–HCl	$C_{16}H_9F_5N_2 \cdot HCl$	+
51	CH_3	CH_3	C_6H_5[p]	16	220 dec	A	$C_{11}H_{12}N_2 \cdot HCl$	–
52	CH_3	CH_3	4-BrC_6H_4[p]	14	279 dec	I–HCl	$C_{11}H_{11}BrN_2 \cdot HCl$	+
53	CH_3	CH_3	CF_3[p]	26	>360	F	$C_6H_7F_3N_2 \cdot 0.5Cu \cdot 0.5H_2O$	–
54	*n*-C_3H_7	*n*-C_3H_7	C_6H_5[q,r]	2	147	3 *N* HCl	$C_{15}H_{20}N_2 \cdot HCl$	–
55	*n*-C_3H_7	*n*-C_3H_7	4-BrC_6H_5[r]	8	214 dec	I–HCl	$C_{15}H_{19}BrN_2 \cdot HCl \cdot 0.5H_2O$	–
56	*n*-C_3H_7	*n*-C_3H_7	CF_3[r]	14	248 dec		$C_{10}H_{15}F_3N_2 \cdot Cu$	–
57	C_6H_5	CH_3	C_6H_5[s]	60	214–215	M–W	$C_{16}H_{14}N_2$	–
58	4-$CH_3OC_6H_4$	H	C_6H_5[t]	50	178–179	M–W	$C_{16}H_{14}N_2O$	–
59	4-HOC_6H_4	4-HOC_6H_4	CF_3[u]	91	289 dec		$C_{16}H_{11}F_3N_2O_2 \cdot H_2O$	–
60	4-$CH_3OC_6H_4$	4-HOC_6H_4	CF_3[u]	9	125 dec	I–H	$C_{17}H_{13}F_3N_2O_2 \cdot H_2O$	+++
	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	$(CH_3)_2CH$	46	195–196[v]	EA	$C_{20}H_{22}N_2O_2$	+
Indomethacin								4+
Benzydamine								+
Phenylbutazone								+
Indoxole								+++

[a]I = *i*-PrOH; P = pyridine; W = H_2O; E = EtOH; B = C_6H_6; Et = Et_2O; H = *n*-hexane; EA = EtOAc; C = $CHCl_3$; HAc = HOAc; M = MeOH; A = acetone; F = formamide. Absence of any symbol indicates the compound was obtained analytically pure by thorough tritration with H_2O. [b]Except as noted, satisfactory analyses for C, H, and N were obtained for all of these compounds. Compounds **5**, **13**, and **54** were prepared according to literature methods and were not analyzed. [c]Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals (six rats/group) within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving phenylbutazone (33 mg/kg po): +, drug given at 33 mg/kg; ++, drug given at 10 mg/kg; +++, drug given at 3 mg/kg; 4+, drug given at 1 mg/kg; 5+, drug given at 0.3 mg/kg; 6+, drug given at 0.1 mg/kg po. Compounds with antiinflammatory activity (at 33 mg/kg) of less than 0.5 times phenylbutazone are reported as –; most of these latter compounds, however, still exhibit low levels of inhibition of edema in this test. Similar results were obtained with compounds 3 and 15 in both adrenalectomized and nonadrenalectomized rats dosed at 33 mg/kg po. [d]Purchased from K and K Laboratories, New York, N.Y. [e]A. H. Cook and D. Jones, *J. Chem. Soc.*, 281 (1941), report mp 229°. [f]S. Kori and S. Narisawa, *Asahi Garasu Kenkyu Hokoku*, **12**, 55 (1962) [*Chem. Abstr.*, **59**, 1622*b* (1963)], report mp 253–254°. [g]D. White and J. Sonnenberg, *J. Org. Chem.*, **29**, 1929 (1964), report mp 176.5–177°. [h]Reference 16 reports mp 232°. [i]Reference 16 reports mp 244°. [j]Reference in footnote *g* reports mp 253–254°. [k]Belgian Patent 585,555 (1960) [*Chem. Abstr.*, **58**, 2531 (1963)], reports mp 99° but their sample was likely impure with pyridine. [l]Reference in footnote *k* reports mp 98° but their sample must have contained some pyridine. [m]H. Bredereck and G. Theilig, *Chem. Ber.*, **86**, 88 (1953), report mp 184°. [n]pK_a' = 10.7. [o]Where recrystallization failed to give a homogeneous product as determined by tlc, column chromatographic separation using silica gel and benzene–HOAc (95:5) as eluent provided analytically pure product. [p]Prepared according to K. Bernhauer and R. Hoffmann, *J. Prakt. Chem.*, **149**, 321 (1937), from acetoin and either the corresponding benzaldehyde or excess trifluoroacetaldehyde ethyl hemiacetal. [q]Reference in footnote *p* reports mp 147°. [r]Prepared from butyroin according to reference in footnote *p*. Compounds **56** and **53** were not stable to the usual conditions (H_2S) used to remove copper from the product. [s]Made from benzaldehyde and 1-phenyl-1,2-propanedione by the method of ref 16. [t]Made from 4-methoxyphenacyl bromide and benzamidine by the method of B. Krieg, L. Brandt, B. Carl, and G. Maneck, *Chem. Ber.*, **100**, 4042 (1967). [u]See Experimental Section. [v]Reference 25 reports mp 195–196°.

Table II. Antiinflammatory *N*-Alkyl-Trisubstituted Imidazoles

No.	Ar	Ar′	R	R′	Method of prepn[a]	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]	Anti-inflam act.[d]
61	C_6H_5	C_6H_5	4-BrC_6H_4	CH_3	A	60	199–202	$C_{22}H_{17}BrN_2$		–
62	C_6H_5	C_6H_5	CH_3	CH_3	A	48	119–122	$C_{17}H_{16}N_2$	H	–
63	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	CH_3	A	56	158–161	$C_{24}H_{22}N_2O_2$	I	++
64	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	CH_2COOH	*c*	27	259–261	$C_{25}H_{22}N_2O_4 \cdot 2H_2O$	C–M	–
65	C_6H_5	C_6H_5	4-BrC_6H_4	$-CH_2CH{=}CH_2$	B	51	111–114	$C_{24}H_{19}BrN_2$	I	–
66	C_6H_5	C_6H_5	4-BrC_6H_4	CH_2CH_3	A	60	146–149	$C_{23}H_{19}BrN_2$	I	–
67	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CF_3	CH_3	A	67	127–129	$C_{19}H_{17}F_3N_2O_2$	H	+
68	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CF_3	CH_2CH_3	A	83	116–119	$C_{20}H_{19}F_3N_2O_2$		++
69	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CF_3	$-CH_2CH{=}CH_2$	B	48	59–62	$C_{21}H_{19}F_3N_2O_2$	H	+
70	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CF_3	$CH_2C_6H_5$	B	78	95–97	$C_{25}H_{21}F_3N_2O_2$	H	–

[a]Method A = NaH–DMF used to form Na salt followed by R′I; see Experimental Section for preparation of compound 63. Method B = K_2CO_3 acetone system followed by R′X; see Experimental Section for preparation of 65. [b]See footnote *a* in Table I. [c]Satisfactory analyses for C, H, and N were obtained for all of these compounds. [d]See footnote *c* in Table I. [e]See Experimental Section.

Table III. Correlation of Ultraviolet Absorption Characteristics with Phototoxicity

No.	Uv max, mμ[a]	Phototoxic effect in mice[b]
3	310	+
7	309	++
9	303	++
12	315	++
15	268, 236	–
61	288	–
63	285, 232	–
Indoxole	308	+++
N-Methylindoxole[c]	301, 290, 248	+

[a]Determined in MeOH solution. [b]Determined as described in the Discussion. The degree of necrosis of the mouse ears is rated as follows: +++ = marked necrosis within the first 3 days of dosing; ++ = necrosis seen after several days of dosing; + = slight erythema of the ears after 11 days of dosing; – = no visible effect on ears after 11 days of dosing/irradiation and an additional 3 days of irradiation. [c]Prepared according to ref 9; mp 127–129°.

dehyde ethyl hemiacetal in 50 ml of HOAc. After complete addition and a further 2 hr of reflux, an additional 11 g of the hemiacetal was added slowly in order to complete the reaction. The reaction was refluxed overnight and then poured slowly into 1 l. of H_2O and the pH adjusted to 6.8 with NH_4OH. A precipitate formed which was filtered and thoroughly dried under vacuum over P_2O_5. The solid was dissolved in 1 l. of C_6H_6, Darco treated, and filtered, and the filtrate was concentrated to 500 ml and cooled. Collection of two successive crops yielded 12.8 g (49%) of slightly impure **15**, mp 189–193°, containing a trace of a very polar impurity (tlc). A third crop from the concentrated filtrate proved to be recovered starting dimethoxybenzil, 3.5 g (18% recovery), mp 130–133°. Crude **15** was readily purified by passing it through a chromatographic column packed with silica gel using C_6H_6–EtOAc–HOAc (47.5:47.5:5.0) as eluent. This procedure retained the very polar impurity on the column. Removal of all solvent from the eluted fractions yielded 12.0 g (47%) of pure **15**: mp 191–193°; mass spectrum *m/e* 348 (calcd 348), 333 (ΔCH_3). See Table I.

4,5-Bis(4′-hydroxyphenyl)-2-trifluoromethylimidazole Hydrate (59). A suspension of 10.0 g (0.029 mol) of 4,5-bis(4′-methoxyphenyl)-2-trifluoromethylimidazole in 500 ml of 48% HBr was heated to reflux. The reaction at first became a colorless solution and then, after further heating, redeposited a white solid. After 24 hr of heating the reaction was cooled and filtered, the solid suspended in H_2O, and the pH adjusted to 8.0 using saturated $NaHCO_3$ solution. After stirring the suspension for 30 min. there was obtained after filtering and drying, 8.4 g (91%) of compound **59**: mp 289° dec; mass spectrum *m/e* 320 (calcd 320). See Table I.

4-(4′-Hydroxyphenyl)-5-(4′′-methoxyphenyl)-2-trifluoromethylimidazole Hydrate (60). The following reaction conditions were determined only after many attempts since several aspects of the procedure proved to be critical for the production of pure product.‡ To a suspension of 0.90 g (0.0062 mol) of CH_3I and 1.07 g (0.0042 mol) of silver oxide in 50 ml of $CHCl_3$ was added a solution of 1.0 g (0.00308 mol) of 4,5-bis(4′-hydroxyphenyl)-2-trifluoromethylimidazole (**59**) in 10 ml of MeOH. The reaction was stirred at room temperature and carefully monitored using tlc (silica gel-coated glass plates, hexane–EtOAc–HOAc, 67:29:4, as eluent). A new spot slowly developed of R_f intermediate between that of the polar dihydroxy starting material (compound **59**) and the less polar O,O-dimethylated material (compound **15**). After 18 hr, the reaction was filtered and the clear filtrate evaporated to a white solid residue. The latter solid was suspended in a saturated KI solution and repeatedly extracted with ether. The dried ether extracts were evaporated to give an amorphous solid containing some of compound **15** as an impurity. Column chromatog-

‡Preliminary experiments to prepare compound **60** were carried out by Dr. H. M. McIlhenny and Mr. F. Mosher of these laboratories.

Table IV. Substituted Benzoins and Benzils

		ArCH(OH)—CAr′(=O)				ArC(=O)—CAr′(=O)			
Ar	Ar′	Yield, %	Recrystn solvent[a]	Mp, °C	Formula[b]	Yield, %	Recrystn solvent[a]	Mp, °C	Formula[b]
4-BrC_6H_4	C_6H_5	27	Et	125–126[c]	$C_{14}H_{11}BrO_2$	79	HAc–W	83–84[d]	$C_{14}H_9BrO_2$
4-$CH_3OC_6H_4$	C_6H_5	43	E	99–102[e]	$C_{15}H_{14}O_3$	74	I–W	57–59[f]	$C_{15}H_{12}O_3$
4-BrC_6H_4	4-BrC_6H_4	Not isolated			$C_{14}H_{10}Br_2O_2$	18	E	221–223	$C_{14}H_8Br_2O_2$
4-$CH_3SC_6H_4$	4-$CH_3SC_6H_4$	74	I	102–105[g]	$C_{16}H_{16}O_2S_2$	40		161–164	$C_{16}H_{14}O_2S_2$
2-$CH_3OC_6H_4$	2-$CH_3OC_6H_4$	32	E–W	96–99[h]	$C_{16}H_{16}O_4$	55	E–W	128–131[i]	$C_{16}H_{14}O_4$
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	Not isolated			$C_{16}H_{16}O_2$	25	H	102–103[j]	$C_{16}H_{14}O_2$
2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	Not isolated			$C_{16}H_{16}O_2$	20	HAc–W	86.5–88	$C_{16}H_{14}O_2$
4-$EtOC_6H_4$	4-$EtOC_6H_4$	Not isolated			$C_{18}H_{20}O_4$	10	H	148–149[k]	$C_{18}H_{18}O_4$
4-FC_6H_4	4-FC_6H_4	Not isolated			$C_{14}H_{10}F_2O_2$	50	I	116–119	$C_{14}H_8F_2O_2$

[a] See footnote *a* of Table I. [b] Satisfactory analyses for C and H were obtained on all new products. [c] Prepared according to R. T. Arnold and R. C. Fuson, *J. Amer. Chem. Soc.*, **58**, 1295 (1936), who report mp 125–126°. [d] H. Hatt, A. Pilgrim, and W. Hurran, *J. Chem. Soc.*, 93 (1936), report mp 86°. [e] A. McKenzie and E. Luis, *Chem. Ber.*, **65B**, 794 (1932), report mp 100–101°. [f] Reference in footnote *c* reports mp 62°. [g] Prepared by benzoin condensation of 4-methylthiobenzaldehyde which was made from 4-ClC_6H_4CHO by the method of W. A. Gregory and A. Kreuchunas, U. S. Patent 2,761,873 (1956). [h] J. C. Irving, *J. Chem. Soc.*, **79**, 668 (1901), reports mp 101°. [i] T. MacDermott, *Aust. J. Chem.*, **19**, 2181 (1966), used this compound but did not report a melting point. [j] R. Stierlin, *Chem. Ber.*, **22**, 381 (1889), reports mp 103–104°. [k] L. Rosenthal, *Chem. Ber.*, **44**, 2464 (1911), reports mp 149°.

raphy (20 × 1.5 in. column, silica gel packing and $CHCl_3$ eluent) removed the less polar **15** and, after final elution of the column with 1:1 $CHCl_3$–MeOH, there was obtained 0.25 g of amorphous product **60**. Recrystallization of the latter solid from 1:1 isopropyl ether–hexane gave, in two crops, 89 mg (9%) of compound **60**, mp 125° dec. This solid was homogeneous by tlc: mass spectrum *m/e* 334 (calcd 334) and 319 (loss of CH_3). Recrystallization from CCl_4 gave analytically pure material. See Table I.

4,5-Bis(4′-methoxyphenyl)-1-methyl-2-phenylimidazole (63, Method A). To 0.154 g (0.0032 mol) of hexane-washed, 50% sodium hydride in mineral oil in a dry flask (N_2) was added 5 ml of DMF. A solution of 1.0 g (0.0028 mol) of 4,5-bis(4′-methoxyphenyl)-2-phenylimidazole in 10 ml of DMF was added to the NaH in 15 min (foaming) and the suspension was then stirred an additional 1 hr. After slowly adding 0.44 g (0.0031 mol) of methyl iodide in 5 ml of DMF, the reaction was heated (steam bath) for 5 hr. The reaction was poured slowly into 100 ml of stirred ice–water and the resulting white solid recrystallized from *i*-PrOH to yield 0.57 g (56%) of compound **63**: mp 158–161°; mass spectrum *m/e* 370 (calcd 370) and 355 (loss of CH_3). See Table II for physical data on this and related *N*-alkyl analogs.

4,5-Bis(4′-methoxyphenyl)-2-phenylimidazole-1-acetic Acid Dihydrate (64). A suspension of 1.5 g (0.0042 mol) of 4,5-bis(4′-methoxyphenyl)-2-phenylimidazole, 0.72 g (0.0047 mol) of methyl bromoacetate, and 0.65 g (0.0047 mol) of K_2CO_3 in 50 ml of acetone was refluxed for 48 hr. Addition of 100 ml of ice–water and repeated extractions with EtOAc yielded, on removal of all solvent, a viscous yellow oil, presumably methyl 4,5-bis(4′-methoxyphenyl)-2-phenylimidazole 1-acetate. The crude ester was heated for 10 min in a solution of 20 ml of EtOH and 20 ml of 10% NaOH. The solution was acidified (3 *N* HCl) and filtered, and the solid recrystallized from $CHCl_3$–MeOH to yield 0.49 g (27%) of compound **64**: mp 259–261° dec; mass spectrum *m/e* 414 (calcd 414), and 369 (M − COOH) and 335 (M − CH_2COOH).

1-Allyl-2-(4′-bromophenyl)-4,5-diphenylimidazole (65, Method B). A suspension of 1.5 g (0.004 mol) of 2-(4′-bromophenyl)-4,5-diphenylimidazole, 0.55 g (0.0045 mol) of 3-bromopropene, and 0.62 g (0.045 mol) of K_2CO_3 in 50 ml of acetone was refluxed overnight under a N_2 atmosphere. An additional 0.14 g of 3-bromopropene and 24 hr of reflux were required to complete the reaction (tlc evidence). After adding the reaction to 100 ml of H_2O, the resulting semisolid slowly crystallized and was filtered and recrystallized from *i*-PrOH to give 0.85 g (51%) of compound **65**, mp 111–114°. See Table II.

Acknowledgments. The authors are grateful to Messrs. Stephen Massett and Nelson Treadway, Jr., for carrying out the chemical syntheses and to Messrs. P. Richardson and G. Antognoli for their assistance with the biological testing.

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1-(3,4-Dichlorobenzamidomethyl)cyclohexyldimethylamine and Related Compounds as Potential Analgesics

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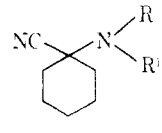
The syntheses of the title compound and 56 analogs and derivatives are reported. A number of these compounds were subjected to a primary pharmacological screen designed to detect a range of CNS effects. The results indicated that these compounds possessed analgesic activity and the title compound is being subjected to a more detailed study. This paper reports the synthetic methods, the analgesic activities, and the structure–activity relationships.

Many cyclohexyl derivatives have been synthesized and assessed for potential biological activity. In recent years several papers [1-4] and patents[5] have been published which describe the preparation and CNS activity of substituted cyclohexylamines. The synthesis of related compounds outlined in this paper represents an attempt to prepare 1,1-substituted cyclohexylamines with analgesic properties.

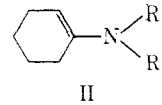
Chemistry. Cyclohexylaminonitriles of formula I were considered to be good starting materials for which several synthetic routes[1-6] were available. These routes are modi-



I, NRR^1 = dimethylamino, piperidyl, azabicyclo[3.2.2]nonyl, N^4-methylpiperazinyl, pyrrolidinyl

fications of the general procedure in which the appropriate ketone or aldehyde is allowed to react with a secondary amine and HCN under various conditions. Another variation by House, *et al.*,[7] is to treat the enamine II in $CHCl_3$ solution with acetonecyanohydrin when the aminonitrile is produced.

The method adopted in the present work was to reflux



II

equimolar proportions of KCN, cyclohexanone, and the hydrochloride salt of the appropriate base in aqueous EtOH for 24 hr. The reactions proceeded smoothly and fair or good yields were obtained (Table I). Attempts to prepare the corresponding esters of these α-aminonitriles by direct alcoholysis were unsuccessful. When attempts to proceed *via* the free acids and acid chlorides failed to yield the corresponding acids, with the exception of the piperidyl compound, this route was abandoned. All the α-aminonitriles responded to treatment with H_2SO_4 for 0.25 hr on a steam bath to give good yields of the corresponding carboxamides (Table II). α-Aminonitriles have unusual properties[8,9] which are clearly demonstrated by the reaction of these compounds with Grignard reagents. In these reactions it has been found that ketone formation seldom occurs and that nitrile replacement frequently takes place. Welvart[10] has suggested that such reactions occur *via* an immonium ion. When the α-aminonitrile **3** was treated with aliphatic and aromatic Grignard reagents the expected nitrile replacement occurred, whereas with $LiAlH_4$ the normal primary amine was produced. $LiAlH_4$ in the presence of $AlCl_3$ again replaced the nitrile (Table III).

The reactions of α-aminonitriles with organolithium compounds are well documented[11-14] and Table IV shows the expected imines and ketones **17–24** and their corresponding alcohols and esters **25–29** synthesized from compounds **1–5**. Table V shows products of normal reactions between α-aminonitriles and MeLi or 2-picolyl Li. Cyclohexyldiamines and -triamines **35–38** were prepared in excellent yields by reduction of the corresponding α-aminocyclohexylnitriles with $LiAlH_4$ (Table VI). These com-