Synthesis and Antiinflammatory Activity of *tert*-Aminomethylbenzophenones

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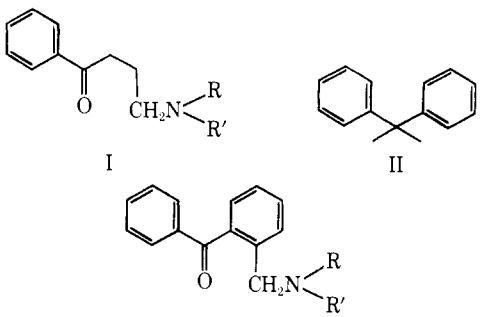
A series of *tert*-aminomethylbenzophenones were prepared and evaluated for antiinflammatory activity in the rat carrageenin foot edema assay. One of these, 2-morpholinomethylbenzophenone (**3**), was approximately twice as active as phenylbutazone.

In recent years a number of useful drugs that contain a γ-aminobutyrophenone (I) or diphenylmethyl (II)

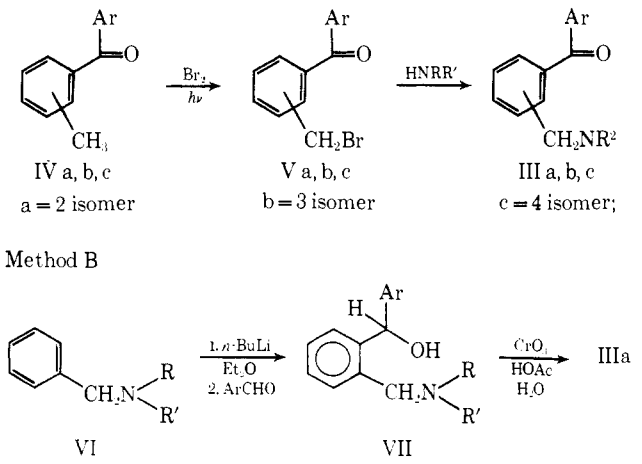


I II III

moiety have been successfully applied toward the treatment of a variety of CNS disorders.[1] In an attempt to combine features of both of these units in one molecule we decided to undertake the synthesis of some *o-tert*-aminomethylbenzophenones (III). As our model compound we prepared 2-morpholinomethylbenzophenone (**3**, III, R = morpholino) and subjected this substance to a variety of pharmacological tests that are commonly used to detect CNS, cardiovascular, and antiinflammatory activity in animals. Compound **3** did not have any useful level of activity in the CNS and cardiovascular tests but exhibited a good level of antiinflammatory activity as measured in the rat carrageenin foot edema assay.[2] This finding prompted us to prepare a series of substituted III and their benzhydrol analogs and to evaluate them as potential antiinflammatory agents.

Chemistry.—The synthetic routes used to prepare the compounds that were needed for a structure–activity study are given in Scheme I. In method A the photobromination of 3- or 4-methylbenzophenones (IVa) with 1.1 equiv of Br_2 gave the monobromomethyl analogs V in good yields. Treatment of these with amines led directly to IIIb and IIIc. Bromination of 2-methylbenzophenone under similar conditions proved to be unsatisfactory for obtaining a synthetically useful yield of the 2-bromomethyl analog of V. The product composition as determined by nmr and Br analysis, was a mixture of 2-CH_3, -CH_2Br, -$CHBr_2$, or -CBr_3 benzophenones in a ratio of *ca.* 1:0.6:1.3. When 2-methylbenzophenone was converted to its 1,3-dioxolane derivative and then photobrominated a satisfactory yield of the monobromomethyl analog was obtained. Reaction with amine followed by acid hydrolysis of the dioxolane gave the desired IIIa. In method B the ortho-lithiation of α-*tert*-aminotoluenes as described by Hauser and co-

SCHEME I



workers,[3] followed by treatment with an aryl aldehyde gave the benzhydrols VII. Oxidation of VII with CrO_3 afforded IIIa. The LAH reduction of a 2-benzoylbenzoic acid (method C), also gave the benzhydrols VII which were then oxidized to the benzophenones IIIa. Direct formation of IIIa was also accomplished by the reaction of ArLi with the nitrile 2-*tert*-aminomethylbenzonitrile followed by acid hydrolysis (method D). The preparation of hydroxy analogs of IIIa was accomplished by treating a hydroxybenzophenone with a formaldehyde–amine mixture (method E).

Pharmacology.—The antiinflammatory activities, as determined by the carrageenin foot edema assay[2] in rats, for the compds tested in this work are given in Tables I, II, and III. The compds listed in Table I represent attempts to improve the antiinflammatory activity of 2-morpholinomethylbenzophenone (**3**) by preparing the 3 and 4 isomers (**3a**, **3b**) of **3** and replacing the morpholino group in **3** by a variety of alkyl (**1**, **5**, **6**, **12**), cycloalkyl (**2**, **7**, **9**), and heterocycloalkylamino (**4**, **8**, **10**, **13**) analogs. Since this approach failed to increase the activity of **3** the effect of placing Cl, F, OH, CH_3, OCH_3, and NH_2 groups in **3** (**14-26**) and replacing the Ph group by a 2-thienyl (**27**) or 2-pyridyl (**28**) was studied (Table II). These changes also failed to increase the activity of **3**. Table III lists the 2-morpholinomethylbenzhydrol[4] analogs that were tested. None of these compds, except **29**, the benzhydrol analog of **3**, gave any antiinflammatory activity.

(1) Numerous examples of compds contg units I and II are given in the "CNS Agents" sections of *Annu. Rep. Med. Chem.*, **1965–1968**, (1966–1969).

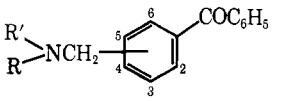
(2) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(3) F. N. Lones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

(4) It is interesting to note that a number of 2-alkylaminomethylbenzhydrols (VII, R = H; R'-alkyl) have been reported to have anorexigenic properties: K. Freter, M. Gotz, and J. T. Oliver, *J. Med. Chem.*, **13**, 1228 (1970).

TABLE I

AMINOMETHYLBENZOPHENONES

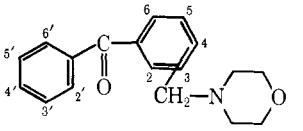


No.[a,b]	Isomer	RNR′	Carrageenin foot edema,[c] ED_{50}, mg/kg	Mp, °C (crystn solvent[d])	Empirical formula	Analyses[e]
1	2	$N(CH_3)_2$	100	154.5–155.5 (E)	$C_{16}H_{18}ClNO$	C, H, Cl, N
2	2	$N(CH_2)_4$	75	201–204 (H)	$C_{18}H_{20}ClNO$	C, H, N, O
3	2	Morpholino	16	180–182 (I)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N
3a	3	Morpholino	55	241–243 (J)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N
3b	4	Morpholino	55	197–199 (J)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N
4	2	Thiomorpholino	>100	214–217 (E)	$C_{18}H_{20}ClNOS$	C, H, N
5[f]	2	$N(C_2H_5)_2$	>100	Oil	$C_{18}H_{21}NO$	C, H, N
6	2	$N(CH_2CH_2OH)_2$	>100	180–182 (N)	$C_{18}H_{22}ClNO_3$	C, H, Cl, N
7	2	$N(CH_2)_5$	100	173–175 (K)	$C_{19}H_{22}ClNO$	C, H, Cl
8[g]	2	*N*-Methylpiperazino	>100	235–238 (E)	$C_{19}H_{24}Cl_2N_2O$	C, H, N
9	2	$N(CH_2)_6$	>100	77–80 (K)	$C_{20}H_{24}ClNO$	C, H, Cl, N
10	2	2,6-$(CH_3)_2$morpholino	>100	180–183 (O)	$C_{20}H_{24}ClNO$	C, H, N
11	3	2-Azabicyclo[3.2.2]nonyl	>100	187–190 (L)	$C_{22}H_{26}ClNO$	C, H, Cl, N
11a	4	2-Azabicyclo[3.2.2]nonyl	>100	255–257 (J)	$C_{22}H_{26}ClNO$	C, H, Cl, N
12[f]	2	$C_2H_5N(CH_2)_2N(C_2H_5)_2$	67	Oil	$C_{22}H_{26}Cl_2N_2O$	C, H, N
13[g]	2	*N*-Phenylpiperazino	>100	229–230 (E)	$C_{24}H_{26}Cl_2N_2O$	C, H, Cl, N

[a] All compds listed in this table are mono-HCl salts unless otherwise indicated. [b] All of the compds listed in this table were prepd by method A given in the Experimental Section. [c] All compds were administered orally to rats. The procedure for measuring inflammation is given in ref 2. [d] A, pentane; B, MeOH–H_2O; C, EtOH–H_2O; D, MeOH; E, EtOH; F, Et_2O; G, Et_2O–pentane; H, EtOH–CH_2Cl_2; I, Et_2O–EtOAc; J, MeOH–Et_2O; K, Et_3O–CH_2Cl_2; L, EtOH–Et_2O; M, Et_2O–THF; N, H_2O; O, Me_2CO. [e] See ref 5. [f] Free base. [g] Di-HCl salt.

TABLE II

MORPHOLINOMETHYLBENZOPHENONES



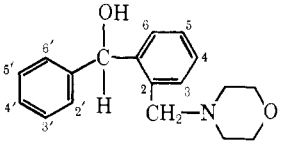
No.	Isomer	Substituents	Carrageenin foot edema,[a] ED_{50}, mg/kg	Method[b]	Mp, °C (crystn solvent[c])	Empirical formula	Analyses[d]
3[e]	2	None	16	A	180–182 (I)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N
14	2	4-Cl	100	A	119–120 (E)	$C_{18}H_{18}ClNO_2$	C, H, Cl, N
15	2	6-Cl	30	B	108–109 (E)	$C_{18}H_{18}ClNO_2$	C, H, Cl, N
16	3	4-OH	>100	E	Oil	$C_{18}H_{19}NO_3$	C, H, N
17	2	4-CH_3	>100	B	116–117 (F)	$C_{19}H_{21}NO_2$	C, H, N, O
18	2	3-OCH_3	100	B	111–112 (E)	$C_{19}H_{21}NO_3$	C, H, N
19	2	4-OCH_3	>100	B	86.5–87.5 (F)	$C_{19}H_{21}NO_3$	C, H, N, O
20	2	4′-F	>100	C	79–81 (G)	$C_{18}H_{18}FNO_2$	C, H, N
21[e]	2	3′,4′-Cl_2	>100	B	171–173 (M)	$C_{18}H_{18}Cl_3NO_2$	C, H, Cl, O
22[e]	2	2′-NO_2-5′-Cl	>100	A	240–242 (E)	$C_{18}H_{15}Cl_2N_2O_4$	C, H, N
23	2	2′-NH_2-5′-Cl	>100	*f*	143–145 (E)	$C_{18}H_{19}ClN_2O_2$	C, H, Cl
24	3	2-OH,5-Cl	>100	E	89–90 (E)	$C_{18}H_{18}ClNO_3$	C, H, N
25	3	2-OH,4-OCH_3	>100	E	106–107 (E)	$C_{19}H_{21}NO_4$	C, H, N
26	3	6-OH,4-OCH_3	>100	E	136–137 (E)	$C_{19}H_{21}NO_4$	C, H, N
27	2	2-Thienyl[g]	>50	D	69–70 (G)	$C_{16}H_{17}NO_2S$	C, H, N, S
28	2	2-Pyridyl[g]	>100	D	73–74 (E)	$C_{17}H_{18}N_2O_2$	C, H, N
Aspirin			90				
Phenylbutazone			30				

[a] See footnote *c* in Table I. [b] See Experimental Section. [c] See footnote *d* in Table I. [d] See ref 5. [e] Mono-HCl salt. [f] Prepd by hydrogenation of **22** in the presence of Raney Ni W2 catalyst at atm pressure and room temp. [g] Replaces the benzo group.

Compd **3** was selected for additional test systems that are commonly used to classify antiinflammatory agents. In the adjuvant arthritis assay of Pearson and Wood[5] and the croton oil air pouch granuloma test[6] the compd gave oral activity at 50 mg/kg. Antipyretic activity against yeast-induced fever[7] and reduction of the inflamed rat foot[8] was observed at 25 mg/kg orally.

(5) C. M. Pearson and F. P. Wood, *Arthritis Rheum.*, **2**, 440 (1959).
(6) A. Roberts and J. E. Nezanius, *Acta Endocrinol.*, **25**, 105 (1957).
(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).
(8) L. O. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn.*, **111**, 409 (1957).

TABLE III
2-MORPHOLINOMETHYLBENZHYDROLS



No.	Substituents	Carrageenin foot edema,[a] ED_{50}, mg/kg	Method[b]	Mp, °C (crystn solvent[c])	Empirical formula	Analyses[d]
29	None	50	C	89–90 (A)	$C_{18}H_{21}NO_2$	C, H, N, O
30	4-Cl	>100	C	145–147 (D)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N
31	6-Cl	>100	C	119–120 (E)	$C_{18}H_{20}ClNO_2$	C, H, Cl, N, O
32	3-CH_3	>100	B	114–115 (D)	$C_{19}H_{23}NO_3$	C, H, N, O
33	4-CH_3	>100	B	139–140 (D)	$C_{19}H_{23}NO_3$	C, H, N, O
34	4′F	>100	C	73–75 (B)	$C_{18}H_{20}FNO_2$	C, H, N
35	3′,4′-Cl_2	100	B	93–94 (C)	$C_{18}H_{19}Cl_2NO_2$	C, H, Cl, O
36	2-Thienyl	>100	B	75.7–77 (F)	$C_{16}H_{19}NO_2S$	C, H, N, S
37	4-Cl,2-pyrrolidyl	>100	B	196–197 (D)	$C_{16}H_{19}ClN_2O_2$	C, H, Cl, N, O

[a] See footnote *c* in Table I. [b] See Experimental Section. [c] See footnote *d* in Table I. [d] See ref 5.

Experimental Section[9]

Method A. Reaction of Bromomethylbenzophenone and Amine.—A mixt of 44.0 g (0.22 mole) of 2-methylbenzophenone, 26.8 g (0.43 mole) of ethylene glycol, 0.5 g of *p*-TsOH, and 300 ml of C_6H_6 was stirred and refluxed in a flask equipped with a Dean–Stark tube until (25 hr) the "water layer" (19 ml) in the side-arm remained constant. The soln was washed with 150 ml of 2 *N* NaOH, dried (Na_2SO_4), filtered, and concd *in vacuo*. The residue gave 37.5 g (71%) of 2-phenyl-2-*o*-tolyl-1,3-dioxolane (**38**): mp 73–75° (C_6H_6–heptane); nmr ($CHCl_3$) δ 2.17 (3 H, *s*, CH_3), 4.02 (4 H, A_2B_2, OCH_2CH_2O), 7.05–7.88 (9 H, m, C_6H_4, C_6H_5). *Anal.* ($C_{16}H_{16}O_2$) C, H, O.

To a stirred refluxing mixt of 45.6 g (0.19 mole) of the above dioxolane, 21 g (0.25 mole) of anhyd Na_2CO_3, and 280 ml of CCl_4, irradiated with a high-intensity light source, there was added a soln of 10.8 ml (0.22 mole) of Br_2 in 95 ml of CCl_4 at such a rate that the Br_2 color faded rapidly. After an addnl hr of reflux the mixt was cooled to *ca.* 30° and treated with a soln of 29.0 g (0.33 mole) of morpholine in 150 ml of CH_2Cl_2. After 18 hr the salts were filtered off and the filtrate was satd with anhyd HCl. The solvent was decanted and the oily residue (ketal amine) was refluxed for 20 hr in a soln of 300 ml of MeOH, 30 ml of H_2O, and 60 ml of concd HCl. The cooled soln was made basic with 2 *N* Na_2CO_3, extd with CH_2Cl_2, dried ($MgSO_4$), filtered, and concd *in vacuo*. The residue was dissolved in Et_2O and treated with HCl (g) to give 2-morpholinomethylbenzophenone·HCl (**3**, Table I).

Method B. Metalation of α-Aminomethylbenzenes and CrO_3 Oxidation of Aminomethylbenzhydrols.—A soln of 4.78 g (0.025 mole) of 4-methyl-α-morpholinotoluene, 125 ml of anhyd Et_2O, and 20 ml of 15% *n*-BuLi (0.032 mole) in hexane (N_2 atm) was allowed to stir for 20 hr at room temp, then cooled to an internal temp of 15°, and treated dropwise (0.5 hr) with a soln of 3.30 g (0.031 mole) of BzH in 50 ml of Et_2O. After stirring for 4 hr the mixt was treated with 50 ml of H_2O and the sepd org layer was extd twice with 50 ml of 2 *N* HCl. The acid layer was made basic (litmus) with 2 *N* KOH, extd with CH_2Cl_2, dried ($MgSO_4$), filtered, and concd *in vacuo* to give 2.0 g of 2-morpholinomethyl-4-methylbenzhydrol (**33**, Table III). A stirred soln of 1.55 g (0.005 mole) of 2-morpholinomethyl-4-methylbenzhydrol in 20 ml of AcOH was treated at room temp with 0.507 g (0.0057 mole) of CrO_3 in 5.0 ml of H_2O. After 8 hr the mixt was poured onto ice, made basic (litmus) with 2 *N* KOH, and extd with Et_2O. The Et_2O was dried, filtered, and concd *in vacuo* to give 0.97 g of 2-morpholinomethyl-4-methylbenzophenone (**17**, Table II).

Method C. LAH Reduction of 2-Benzoylbenzamides.—A mixt of 61.0 g (0.25 mole) of 2-(*p*-fluorobenzoyl)benzoic acid and 150 ml of $SOCl_2$ was stirred and refluxed until gas evoln ceased. The excess $SOCl_2$ was removed *in vacuo*, and the residue was dissolved in 180 ml of anhyd DMF and treated dropwise with a soln of 36.5 g (0.42 mole) or morpholine in 200 ml of toluene. After stirring for *ca.* 48 hr at room temp the salt was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$, washed with 1 *N* Na_2CO_3 and H_2O, dried ($MgSO_4$), filtered, and concd to give 43.9 g (56%) of 2-(4-fluorobenzoyl)-benzmorpholide (**39**), mp 90–92° (Et_2O, C_5H_{12}). *Anal.* ($C_{18}H_{16}NO_3F$) C, H, N. In a similar manner there was obtained 2-(3,4-dichlorobenzoyl)benzmorpholide (**40**), mp 111–113° ($CHCl_3$, C_6H_{12}) [*Anal.* ($C_{18}H_{15}Cl_2NO_3$) C, H, N, O], and 2-benzoylbenzmorpholide (**41**), mp 120–121° (Et_2O–CH_2Cl_2) [*Anal.* ($C_{18}H_{17}NO_3$) C, H, N, O].

To a stirred suspension of 9.1 g (0.25 mole) or LAH in 150 ml of THF maintained under N_2 there was added dropwise a soln of 31.3 g (0.10 mole) of 2-(4-florobenzoyl)benzmorpholide in 500 ml of THF. The mixt was stirred and refluxed for 2 hr, then cooled in an ice bath, and treated dropwise with 18.2 ml of 2 *N* NaOH, 27.3 ml of H_2O, and *ca.* 25 g of anhyd Na_2SO_4. The salts were filtered off and the filtrate was concd *in vacuo* to give 13.7 g of 2-(morpholinomethyl)-4′-fluorobenzhydrol (**34**, Table III).

Method D. Pyridyllithium and 2-Morpholinomethylbenzonitrile.—A soln of 118 g (0.77 mole) of 2-chloromethylbenzonitrile and 145 g (1.67 mole) of morpholine in 600 ml of CH_2Cl_2 was stirred at room temp for 4 hr. The resultant ppt was filtered off, and the filtrate was washed with H_2O, dried ($MgSO_4$), filtered, concd *in vacuo*, and crystd (C_5H_{12}) to give 132 g of 2-morpholinomethylbenzonitrile, mp 58°. An HCl salt (**42**) gave mp 230–235° dec. *Anal.* ($C_{12}H_{15}N_2OCl$) C, H, N.

A stirred soln of 47 ml of 15% *n*-BuLi in hexane (0.05 mole), maintained under N_2 and cooled to −30° internally, was treated with 12 g (0.076 mole) of 2-bromopyridine in 25 ml of Et_2O, and then after stirring for 0.5 hr, a soln of 10 g (0.05 mole) of 2-morpholinomethylbenzonitrile in 50 ml of THF was added. The mixt was maintained at −10° for *ca.* 15 hr and then treated with H_2O, filtered, and concd *in vacuo*. The residue was chromatographed on alumina (C_6H_6 eluant) to give 4.2 g of (α-morpholino-*o*-tolyl) 2-pyridyl ketone (**28**, Table II).

Method E. Mannich Reaction of Hydroxybenzophenone.—A stirred suspension of 23.2 g (0.10 mole) of 5-chloro-2-hydroxybenzophenone and 30 g (0.35 mole) of morpholine was cooled in an ice bath and treated dropwise with 28.5 g (0.35 mole) of 37% CH_2O at such a rate that the internal temp did not exceed 30°. The reaction mixt was first brought to 85 ± 5° for 2 hr and then cooled, and the residue was dissolved in 200 ml of Et_2O. The Et_2O layer was extd twice with 100 ml of 2 *N* HCl and the acid layer made basid with NH_4OH and extd twice with Et_2O. The Et_2O layer was dried (Na_2SO_4), filtered, and concd *in vacuo* to give 27 g (84%) of 5-chloro-2-hydroxy-3-morpholinomethylbenzophenone (**24**, Table II).

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(9) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Ir and nmr spectra were determined for all compounds listed in Tables I–III using a Perkin-Elmer Infracord and a Varian Associates A-60 spectrometer. Where analyses are indicated only by symbols of the elements anal results obtained for these elements were within ±0.4% of the theor values.