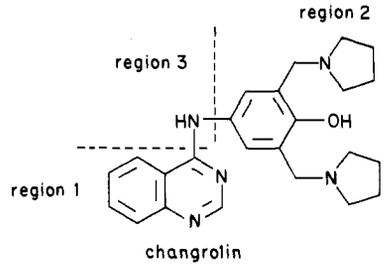
Synthesis and Antiarrhythmic and Parasympatholytic Properties of Substituted Phenols. 3. Modifications to the Linkage Region (Region 3)[1]

David M. Stout,*† W. L. Matier, Cynthia Barcelon-Yang,† Robert D. Reynolds,‡ and Barry S. Brown‡

Department of Pharmaceutical Research, American Critical Care Division, American Hospital Supply Corporation, McGaw Park, Illinois 60085. *Received June 11, 1984*

As part of a continuing program of systematically modifying the structure of the class I antiarrhythmic drug changrolin, we synthesized 15 analogues in which the linkage between the two aromatic regions was altered. High antiarrhythmic activity and low parasympatholytic activity was found when the linkage region, designated region 3, contained a carbonyl moiety, including ketones, amides, and ureas. Secondary amides were superior to tertiary amides, while amide reversal resulted in no change in activities. One compound in this series, **7**, 2,6-bis(1-pyrrolidinylmethyl)-4-benzamidophenol (ACC-9358), is undergoing preclinical evaluations.

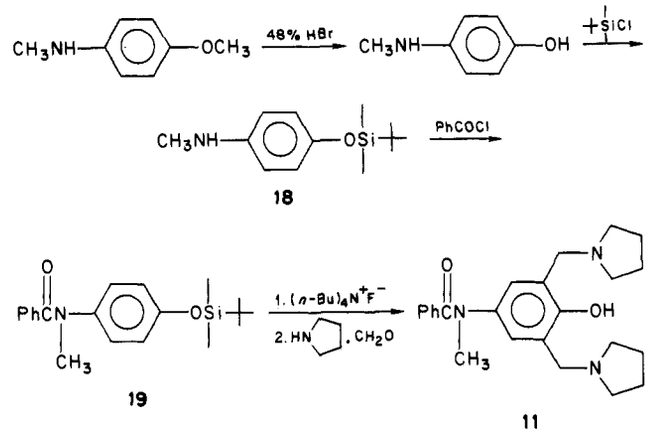
Our previous reports[2,3] described our work in assessing the antiarrhythmic and parasympatholytic properties of a series of compounds we prepared in a program involving systematic modifications of the structure of the novel class I antiarrhythmic drug changrolin. Our goal was to optimize the spectrum of activity (i.e., low parasympatholytic activity and high antiarrhythmic potency) of changrolin through changes in each of the three regions of the prototype, namely: (1) the heteroaromatic region consisting of the quinazoline moiety, (2) the aromatic region with the bis(pyrrolidinylmethyl)phenol, and (3) the linkage between the first two regions. We found that, while region 2 was optimal in changrolin, a wide latitude in structural types existed for region 1.[2] Additionally, the profile of activity was improved when amides or methylene amides were introduced to region 3.[3] We report herein our efforts in further modifications to region 3.



changrolin

Chemistry. The compounds tested are shown in Table I. Compounds **1**, **2**, **3**, **12**, **13**, **14**, and **15** were prepared by aminomethylating *p*-hydroxydiphenylmethane, *p*-(benzyloxy)phenol, *p*-hydroxydiphenylamine, *p*-hydroxybenzophenone, 4-hydroxy-4′-methoxybenzophenone, 4-chloro-4′-hydroxybenzophenone, and 4,4′-dihydroxybenzophenone, respectively, with formaldehyde and pyrrolidine. Compounds **4**, **5**, **6**, **16**, and **17** were prepared by reacting phenyl isocyanate, cinnamoyl chloride, benzenesulfonyl chloride, and benzoyl chloride, respectively, with *p*-aminophenol followed by the aminomethylation reaction described above (for **16** and **17**, piperidine and morpholine, respectively, were used in place of pyrrolidine). Compounds **7–10** were prepared by condensing aniline, *o*-toluidine, 2,6-dimethylaniline, and 2-aminothiazole, respectively, with *p*-hydroxybenzoic acid in the presence of phosphorus pentoxide followed by the aminomethylation reaction. The synthesis of **11**, shown in Scheme I, was accomplished by reacting benzoyl chloride with the protected *p*-hydroxy-*N*-methylaniline **18**, obtained from *N*-methyl-*p*-anisidine, followed by deprotection of **19** and aminomethylation.

Scheme I



Pharmacology. Antiarrhythmic activity was determined by using the oubain intoxicated dog model described by Lucchesi.[4] Parasympatholytic activity was assessed in the isolated guinea pig ileum.

Results and Discussion

Our initial investigation into the pharmacology of heteroarylamino-substituted phenols led to the conclusion that for these compounds antiarrhythmic and parasympatholytic activities acted roughly in parallel.[2] We therefore tested each compound for both activities in order to find compounds with the greatest disparity, i.e., high antiarrhythmic and low parasympatholytic activities. As we extended our research to include amide derivatives, it became apparent that this conclusion was incorrect, that significant antiarrhythmic activity occurred in compounds that had little parasympatholytic activity, and vice versa.[3] Thus, in this phase of our research we found it unnecessary to generally evaluate parasympatholytic activities as we screened the compounds for antiarrhythmic activity. For the most part we did not evaluate the parasympatholytic activity of those compounds which were not potent antiarrhythmic agents (**3**, **5**, **6**, **10**, **15**, **17**) (see Table I) or which were derivatives of a parent compound (**7** as parent of **4**, **8**, **9** and **12** as parent of **14**).

† Section of Medicinal/Organic Chemistry.
‡ Section of Pharmacology.

(1) Parts of this paper have been presented. See "Abstracts of Papers", 188th National Meeting of the American Chemical Society, Philadelphia, Aug 1984; American Chemical Society: Washington, DC, 1984; MEDI 41.
(2) Stout, D. M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. *J. Med. Chem.* **1983**, *26*, 808.
(3) Stout, D. M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. *J. Med. Chem.* **1984**, *27*, 1347.
(4) Lucchesi, B. R.; Hardman, H. F. *J. Pharmacol. Exp. Ther.* **1961**, *132*, 372.

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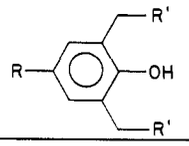
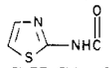
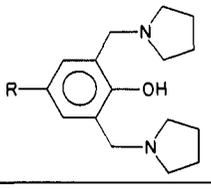
Table I. Antiarrhythmic and Parasympatholytic Activities of Substituted Phenols



compd	R[a]	mp, °C	formula	active dose of base in ouabain dog,[b] mg/kg	N[c]	% inhibn of guinea pig ileum contractile force at 4 mg/L of base[b]	N[c]
changrolin				5.5 ± 2.3	5	43 ± 6	7
disopyramide				4.4 ± 0.9	5	81 ± 7	5
quinidine				10.5 (8, 13)	2	62 ± 6	8
procainamide				29.0 ± 6.2	5	0 ± 2	5
1	$C_6H_5CH_2$	196–198	$C_{23}H_{30}N_2O\cdot 2HCl$	not effective	2	14.3	3
2	$C_6H_5CH_2O$	139–141	$C_{23}H_{30}N_2O_2\cdot 2HCl\cdot 0.5H_2O$	2.0	1	62	3
3	C_6H_5NH	98–99	$C_{22}H_{29}N_3O$	5.0[d]	1	*h*	
4	$C_6H_5NHC(=O)NH$	179–181	$C_{23}H_{30}N_4O_2$	3.6 ± 1.5	6	*h*	
5	$C_6H_5CH=CHC(=O)NH$	111–112	$C_{25}H_{31}N_3O_2$	14.0[e]	1	*h*	
6	$C_6H_5SO_2NH$	162–163	$C_{22}H_{29}N_3O_3S$	10.0	1	*h*	
7	$C_6H_5NHC=O$	154–155	$C_{23}H_{29}N_3O_2$	2.8 ± 0.7	6	31	3
8	$2\text{-}CH_3\text{-}C_6H_4NHC=O$	55–58	$C_{24}H_{31}N_3O_2\cdot 1.5H_2O$	2.9 ± 1.3	5	*h*	
9	$2,6\text{-}(CH_3)_2\text{-}C_6H_3NHC=O$	80–84	$C_{25}H_{33}N_3O_2\cdot 0.25H_2O$	4.5 ± 0.0	3	*h*	
10		171–173	$C_{20}H_{26}N_4O_2S$	not effective[f]		*h*	
11	$C_6H_5C(=O)N(CH_3)$	63–65	$C_{24}H_{31}N_3O_2\cdot 2HCl\cdot 2.75H_2O$	16.2 (24, 8.5)	2	5	4
12	$C_6H_5C=O$	211–212	$C_{23}H_{28}N_2O_2\cdot 2HCl$	2.4 ± 1.0	8	9	3
13	$4\text{-}(CH_3O)\text{-}C_6H_4C=O$	212–215	$C_{24}H_{30}N_2O_3\cdot 2HCl\cdot 0.5H_2O$	4.5 ± 2.6	4	12	4
14	$4\text{-}Cl\text{-}C_6H_4C=O$	194–196	$C_{23}H_{27}N_2O_2Cl\cdot 2HCl\cdot H_2O$	4.8 ± 2.2	4	*h*	
15	$3,5\text{-}(CH_2NC_4H_8)_2\text{-}4\text{-}OH\text{-}C_6H_2C=O$	170–171	$C_{33}H_{46}N_4O_3\cdot 0.5H_2O$	not effective[g]	1	*h*	
16	$C_6H_5C(=O)NH$, R′ = piperidine	138–140	$C_{25}H_{33}N_3O_2\cdot 2HCl\cdot 2H_2O$	3.0	1	33	3
17	$C_6H_5C(=O)NH$, R′ = morpholine	152–154 dec	$C_{23}H_{29}N_3O_4\cdot 2HCl\cdot 1.75H_2O$	16.5 (15.0, 18.0)	2	*h*	

[a] R′ = pyrrolidine unless otherwise noted. [b] Average of experimental values, which are given in parentheses, or means plus or minus the standard error of the mean. [c] Number of experiments. [d] In a second dog failed to produce normal sinus rhythm to 17.5 mg/kg. [e] In a second dog caused ventricular flutter at 8 mg/kg. [f] To 20 mg/kg. [g] To 10 mg/kg. [h] Experiment not run; see text.

Table II. Effect of Amide Reversal on Antiarrhythmic Activity



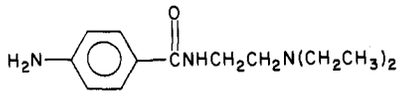
no.	R	active dose in ouabain dog, mg/kg	no.	R	active dose in ouabain dog, mg/kg
7	$C_6H_5NHC=O$	2.8 ± 0.7	21	$2\text{-}CH_3\text{-}C_6H_4C(=O)NH$	2.7 ± 0.5[a]
20	$C_6H_5C(=O)NH$	3.4 ± 0.7[a]	9	$2,6\text{-}(CH_3)_2\text{-}C_6H_3NHC=O$	4.5 ± 0.0
8	$2\text{-}CH_3\text{-}C_6H_4NHC=O$	2.9 ± 1.3	22	$2,6\text{-}(CH_3)_2\text{-}C_6H_3C(=O)NH$	3.2 ± 0.6[a]

[a] See ref 3.

Szekeres and Papp[5] and Conn,[6] after analyzing the structure–activity relationships of antiarrhythmic drugs, concluded that for nonspecific (quinidine-like) agents an aromatic group connected to a tertiary amine by a hydroxy-substituted alkyl chain, ester, or amide linkage seemed important.[7] Our results tended to support these findings. Compounds **1–3**, which link the two aromatic regions with methylene, oxymethylene, and amine units, respectively, either had low antiarrhythmic potency or unacceptably high parasympatholytic activity. Interestingly, benzophenone derivatives (**12–15**) had good antiarrhythmic potency, except for the symmetrical analogue **15**. While a urea (**4**) was very potent, an allyl amide (**5**), a sulfonamide (**6**), and a tertiary amide (**11**) were not.

Compounds **7–9** are structures that have amides reversed relative to compounds we previously reported, **20–22**.[3] Yung et al.[8] found when the amide of the antiarrhythmic drug procainamide (**23**) was reversed, the resulting compound (**24**) had insignificant activity. Amide reversal in our case did not appreciably alter the antiarrhythmic activity of our compounds (Table II).

(5) Szekeres, L.; Papp, G. J. "Experimental Cardiac Arrhythmias and Antiarrhythmic Drug"; Akademiai Kiado, Budepest, Hungary, 1971.
(6) Conn, H. L., Jr. In "The Myocardial Cells; Structure, Function and Modification by Cardiac Drugs"; Briller, S. R.; Conn, H. L., Jr., Eds.; University of Pennsylvania Press, Philadelphia, PA, 1966; pp 269–296.
(7) Morgan, P. H.; Mathison, I. W. *J. Pharm. Sci.* **1976**, *65*, 635.
(8) Yung, D. K.; Vohra, M. M.; Chu, I. *J. Pharm. Sci.* **1979**, *59*, 1405.



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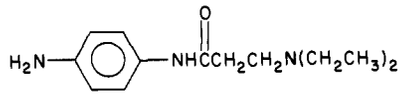

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Parenthetically, in our earlier report we noted that replacing pyrrolidine with dimethylamine resulted in reduced antiarrhythmic activity.[2] We prepared piperidine (**16**) and morpholine (**17**) analogues of **20** and found that morpholine caused a substantial reduction in antiarrhythmic activity while piperidine resulted in no change.

In summarizing our findings on the effects of modifications to the changrolin structure toward antiarrhythmic and parasympatholytic activities, we have found the following.

Region 1. Quinazoline can be replaced by a variety of heterocycles without loss of antiarrhythmic activity, and, in the series of heterocycles, parasympatholytic activity parallels antiarrhythmic activity.

Substitution of the heterocycle with phenyl gave equivocal results.

Region 2. The pattern of a 4-substituted 2,6-bis(pyrrolidinylmethyl)phenol resulted in the best activity. Pyrrolidine could be replaced by piperidine.

Region 3. The compounds having high antiarrhythmic activity and low parasympatholytic activity contained carbonyls in this region, including ketones, amides, and ureas. Secondary amides were superior to tertiary amides, whereas reversal of the amide caused little change in activities.

Thus, we have taken the changrolin structure, a compound that has been shown to be clinically efficacious but one which also has undesirable side effects,[9] and systematically modified each region of the molecule in an attempt to optimize the activity. A more detailed examination of the best compounds showed that **7** possessed an excellent overall profile as a class I antiarrhythmic. This compound, ACC-9358, is undergoing preclinical evaluations.

Experimental Section

Pharmacological Evaluation. Ouabain-Induced Arrhythmia. Adult male mongrel dogs (10–17 kg) were anesthetized with pentobarbital (30 mg/kg iv) and intubated for spontaneous respiration. Lead II of the ECG was recorded. Ouabain was administered intravenously in bolus doses: 40 μg/kg, followed in 30 min by 20 μg/kg and then in 15-min intervals 10 μg/kg until a stable ventricular arrhythmia (>95% ectopic ventricular complexes) was present for 15 min.[4] Test compound was administered intravenously at 0.5 mg/kg per min until arrhythmia reverted to normal sinus rhythm for at least 10 min.

Isolated Guinea Pig Ileum. Fasted, male Hartley guinea pigs (300–400 g) were killed by a blow to the head. A 1-cm segment of ileum was removed and placed in a bath containing physiological saline solution (in mmol/L: NaCl, 120; $NaHCO_3$, 25; KCl, 4.7; $MgSO_4$, 0.57; KH_2PO_4, 1.2; $CaCl_2$, 1.96; dextrose, 11.1) at 37 °C and gassed with 95% O_2/5% CO_2. One end of the ileal strip was impaled on a platinum wire electrode. The other end was tied with a silk suture attached to a Gould Statham Model UC3 force-displacement transducer. Basal tension was set at 0.1–0.3 g, and phasic contractions were elicited by field stimulation pulses (100–150 V, 2.5-ms duration) delivered at a frequency of 0.2 Hz. After an equilibration period of approximately 60 min, tension development was assessed just before and during the steady-state response to the test drug at a concentration of 4 mg/L. Contractile tension in this preparation is due to the electrically stimulated release of acetylcholine from postganglionic parasympathetic nerve terminals and interaction of acetylcholine with postsynaptic receptors. Drug-induced reduction of contractile force, regardless of mechanism, was thus termed parasympatholytic activity.

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A spectrometer in $CDCl_3$, Me_2SO-d_6, or CD_3OD with tetramethylsilane as internal standard or in D_2O with 4,4-dimethyl-4-silapentane-4-sulfonate as a standard. Elemental analyses were performed by Martine Bunting and Mark Eliason of our laboratories. All compounds were analyzed for C, H, and N and were within ±0.4% of theoretical values.

4-Benzyl-2,6-bis(1-pyrrolidinylmethyl)phenol (1). A solution of 10.0 g (52.2 mmol) of 96% pure 4-hydroxydiphenylmethane, 20 mL (250 mmol) of a 37% solution of formaldehyde, and 14.4 mL (172 mmol) of pyrrolidine in 100 mL of ethanol was heated to reflux for 6 h. The solvent was removed on a rotary evaporator and the resulting crude oil was purified by medium-pressure liquid chromatography (MPLC) on a system described by Meyers.[10] Elution with EtOAc/MeOH/NH_4OH (4:1:0.05) on silica gel afforded a clear viscous oil. The oil was dissolved in MeOH, the solution was saturated with hydrogen chloride, the solvent was removed on a rotary evaporator, and crystallization from 2-propanol yielded 2.4 g (11%) of white crystals: mp 196–198 °C; NMR (Me_2SO-d_6) δ 1.6–2.2 (m, 8 H), 2.8–3.5 (m, 8 H), 3.83 (s, 2 H), 4.40 (s, 4 H), 7.0–7.4 (m, 5 H), 7.50 (s, 2 H).

Compounds **2** (yield, 59%; crystallization solvents, *i*-PrOH/EtOAc), **3** (15%, EtOAc (free base)), **12** (25%, EtOAc/MeOH), **13** (72%, *i*-PrOH/EtOAc), **14** (27%, EtOH/EtOAc), and **15** (11%, MeOH/EtOAc) were prepared similarly.

***N*-[3′,5′-Bis(1-pyrrolidinylmethyl)-4′-hydroxyphenyl]-*N*′-phenylurea (4).** A mixture of 18.3 g (168 mmol) of *p*-aminophenol in 100 mL of dioxane was treated by dropwise addition with 20.0 g (168 mmol) of phenyl isocyanate in 50 mL of dioxane. The resulting solid was collected by filtration and dried, affording 23.6 g of off-white (4-hydroxyphenyl)phenylurea. The crude product was treated with formaldehyde and pyrrolidine in the same manner as compound **1**. Silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (9:1:0.05), afforded a pale yellow solid. Crystallization from EtOAc/MeOH/hexane yielded 6.5 g (16%) of white crystals: mp 179–181 °C; NMR (CD_3OD) δ 1.7–2.0 (m, 8 H), 2.4–2.8 (m, 8 H), 3.76 (s, 4 H), 7.0–7.6 (m, 8 H).

2,6-Bis(1-pyrrolidinylmethyl)-4-cinnamidophenol (5). A mixture of 19.7 g (181 mmol) of *p*-aminophenol and 25.2 mL (181 mmol) of triethylamine in 150 mL of dioxane was treated by dropwise addition with a solution of 30.0 g (181 mmol) of cinnamoyl chloride in 50 mL of dioxane. The mixture was stirred for 3 h and the solvent was removed on a rotary evaporator, leaving a brown oil. The addition of water caused the oil to solidify. The solid was collected by filtration and washed repeatedly with water. The crude product was treated with formaldehyde and pyrrolidine in the same manner as compound **1**. Silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (19:1:0.05), yielded a yellow oil that crystallized on standing. Recrystallization from ethyl acetate afforded a 20% yield of yellow crystals: mp 111–112 °C; NMR (CD_3OD) δ 1.6–2.0 (m, 8 H), 2.4–2.9 (m, 8 H), 3.77 (s, 4 H), 6.80 (d, J = 16 Hz, 1 H), 7.3–7.8 (m), 7.70 (d, J = 16 Hz, total = 9 H).

2,6-Bis(1-pyrrolidinylmethyl)-4-benzenesulfonamidophenol (6). A solution of 12.3 g (113 mmol) of *p*-aminophenol and 11.4 g (113 mmol) of triethylamine in 100 mL of tetrahydrofuran (THF) was treated by dropwise addition with 20.0 g (113 mmol) of benzenesulfonyl chloride in 50 mL of THF. The mixture was stirred for 12 h, whereupon the solvent was removed on a rotary evaporator, leaving a dark oil. The oil was mixed with 100 mL of water and the mixture was extracted with chloroform.

(9) Coordinating Changrolin Research Group, *Chung-hua I Hsueh Tsa Chih (Peking)* **1978**, *58*, 84.

(10) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

The combined extracts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator, leaving 22 g of a dark oil. The oil was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (50:1:0.05), afforded an oil that crystallized on standing. Recrystallization from EtOAc yielded 2.8 g (6.0%) of pale yellow crystals: mp 162–163 °C; NMR (CD_3OD) δ 1.5–2.0 (m, 8 H), 2.3–2.7 (m, 8 H), 3.63 (s, 4 H), 6.77 (s, 2 H), 7.3–7.8 (m, 5 H).

2,6-Bis(1-pyrrolidinylmethyl)-4-benzamidophenol (7). By use of the procedure of Chipalkatti et al.,[11] a mixture of 10.0 g (72.5 mmol) of *p*-hydroxybenzoic acid, 10 mL (110 mmol) of aniline, and 5.0 g (35 mmol) of P_2O_5 in 100 mL of toluene was heated to reflux under a nitrogen atmosphere for 3 h. The solvent was removed on a rotary evaporator, leaving a white solid. Purification by silica gel column chromatography using a Waters Prep 500 and eluting with ethyl acetate afforded a yellow solid. Crystallization from ethyl acetate/ethanol gave 3.5 g (23%) of white crystals: mp 198–200 °C. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.52; H, 5.36; N, 6.55.

The product was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Purification by MPLC and crystallization from ethanol resulted in an overall 11% yield of white crystals of free base: mp 154–155 °C; NMR ($CDCl_3$) δ 1.6–2.1 (m, 8 H), 2.4–2.9 (m, 8 H), 3.77 (s, 4 H), 6.9–8.1 (m, 8 H), 9.67 (6 s, 1 H).

Compound **8** (yield, 4.5%; crystallization solvent, EtOH), **9** (2.0%, EtOH), and **10** (14%; EtOH) were prepared similarly.

2,6-Bis(1-pyrrolidinylmethyl)-4-(*N*-methylbenzamido)phenol (11). A mixture of 10 g (73 mmol) of *N*-methyl-*p*-anisidine in 90 mL of 48% HBr was heated to reflux for 6 h. The mixture was evaporated to dryness on a rotary evaporator, leaving *p*-hydroxy-*N*-methylaniline as an off-white solid. Neutralization with NH_4OH gave the free base as a dark solid: NMR (CD_3OD) δ 2.5 (s, 3 H), 6.1–6.6 (m, 4 H).

A solution of 4.5 g (36 mmol) of product, 5.5 g (36 mmol) of *tert*-butyldimethylsilyl chloride and 9.8 g (140 mmol) of imidazole in 20 mL of dimethylformamide was heated to 55 °C for 5 h. Water was added and the mixture was extracted with dichloromethane. Th combined extracts were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The CH_2Cl_2 was removed on a rotary evaporator and the remaining DMF was removed with a vacuum pump, leaving 7.0 g of **18** as a dark oil: NMR ($CDCl_3$) δ 0.24 (s, 6 H), 1.03 (s, 9 H), 2.81 (s, 3 H), 3.46 (br s, 1 H), 6.4–6.8 (m, 4 H).

The protected hydroxyaniline **18** (7.0 g, 2.9 mmol) was dissolved in 50 mL of dioxane and 20 mL (140 mol) of triethylamine was added. The solution was cooled to 0 °C and 4.1 g (29 mol) of benzoyl chloride in 30 mL of dioxane was added dropwise. The mixture was allowed to warm to ambient temperature. After 18 h the mixture was filtered and the solvent was removed on a rotary evaporator, leaving 10.2 g of **19** as a dark oil: IR (film) 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.22 (s, 6 H), 1.05 (s, 9 H), 3.42 (s, 3 H), 6.6–7.6 (m, 9 H).

The protected hydroxybenzamide **19** (9.9 g, 29 mmol) was cooled to 0 °C and then treated with 58 mL (58 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The solution was stirred and allowed to warm to ambient temperature over 1 h. Water was added and the organic layer was separated. The solvent was removed on a rotary evaporator, leaving 4.5 g of the phenol product as a dark oil. An NMR spectrum confirmed that the protecting group had been removed.

The product was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Purification of the product by silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (9:1:0.05), afforded 3.9 g of product as a dark brown oil. The oil was taken up in ether and the solution was saturated with hydrogen chloride, which caused white crystals to precipitate. The crystals were collected and dried, giving 3.0 g of a very hygroscopic product **11**: mp 63–65 °C; NMR (D_2O) δ 1.6–2.3 (m, 8 H), 2.6–3.7 (m) and 3.47 (s, total 11 H), 4.37 (s, 4 H), 7.23 (s), and 7.33 (s, total, 7 H).

Compounds **16** (yield, 12%; crystallization solvent, CH_2Cl_2/Et_2O) and **17** (41%, EtOAc (free base)) were prepared by treating *N*-(*p*-hydroxyphenyl)benzamide[3] with piperidine or morpholine, respectively, and formaldehyde in the same manner as compound 1.

Registry No. 1, 94042-51-0; 1 (free base), 94042-65-6; **2**, 90446-35-8; **2** (free base), 90446-34-7; **3**, 94042-52-1; 4, 94042-53-2; **5**, 94042-54-3; **6**, 94042-55-4; **7**, 90446-66-5; **8**, 94042-56-5; **9**, 94042-57-6; **10**, 94042-58-7; 11, 90446-73-4; 11 (free base), 90446-70-1; **12**, 90446-37-0; **12** (free base), 90446-36-9; **13**, 94042-59-8; **13** (free base), 94042-63-4; 14, 94042-60-1; 14 (free base), 94042-64-5; **15**, 94042-61-2; **16**, 90446-65-4; **16** (free base), 81079-98-3; **17**, 90446-64-3; **17** (free base), 81080-00-4; **18**, 90446-71-2; **19**, 90446-72-3; *p*-(benzyloxy)phenol, 103-16-2; *p*-hydroxydiphenylamine, 122-37-2; *p*-hydroxybenzophenone, 1137-42-4; 4-hydroxy-4′-methoxybenzophenone, 61002-54-8; 4-chloro-4′-hydroxybenzophenone, 42019-78-3; 4,4′-dihydroxybenzophenone, 611-99-4; *o*-toluidine, 95-53-4; 2,6-dimethylaniline, 87-62-7; 2-aminothiazole, 96-50-4; *p*-hydroxybenzoic acid, 99-96-7; *p*-hydroxy-*N*-(2-methylphenyl)benzamide, 62639-21-8; *p*-hydroxy-*N*-(2,6-dimethylphenyl)benzamide, 51616-07-0; *p*-hydroxy-*N*-(2-thiazoyl)benzamide, 94042-62-3; 4-hydroxydiphenylmethane, 101-53-1; pyrrolidine, 123-75-1; *p*-aminophenol, 123-30-8; phenyl isocyanate, 103-71-9; (4-hydroxyphenyl)-phenylurea, 2298-29-5; cinnamoyl chloride, 102-92-1; *p*-hydroxy-*N*-cinnamylbenzamide, 3579-85-9; benzenesulfonyl chloride, 98-09-9; *N*-(*p*-hydroxyphenyl)benzenesulfonamide, 5471-90-9; aniline, 62-53-3; *p*-hydroxy-*N*-phenylbenzamide, 14121-97-2; *N*-methyl-*p*-anisidine, 5961-59-1; *p*-hydroxy-*N*-methylaniline, 150-75-4; benzoyl chloride, 98-88-4; *N*-methyl-*N*-(*p*-hydroxyphenyl)benzamide, 70489-16-6; *N*-(*p*-hydroxyphenyl)benzamide, 15457-50-8; piperidine, 110-89-4; morpholine, 110-91-8.

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Synthesis and Antiallergic Activity of Some Quinolinones and Imidazoquinolinones

Norton P. Peet,* Larry E. Baugh, Shyam Sunder, and Jon E. Lewis

Merrell Dow Research Institute, Indianapolis, Indiana 46268. *Received July 3, 1984*

A group of 1,4-dihydro-4-oxoquinoline-2- and -3-carboxylic acid esters with nitrogen functionality at the 8-position was synthesized, and 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-4- and -5-carboxylic acid esters were elaborated from these. Several of the compounds displayed activity in the rat passive cutaneous anaphylaxis (PCA) test for antiallergic activity. However, PCA activity in this series was accompanied by rat toxicity, as measured by a decrease in percent of normal weight gain over a 2-week period, following a single oral dose.

Clinical experience with disodium cromoglycate (DSCG) for nearly 20 years has demonstrated that this compound is an effective, prophylactic agent for the treatment of asthma.[1] Although DSCG is a mediator release inhibitor,[1]

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