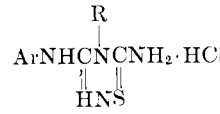
TABLE I



No.	Ar	R	Formula[a]	Yield, %	Mp, °C
I	CH_2=$CHCH_2$	CH_2=$CHCH_2$	$C_8H_{14}N_4S\cdot HCl$	80	145–146
II	2,6-$(CH_3)_2C_6H_3$	*n*-Bu	$C_{14}H_{22}N_4S\cdot HCl$	75	139–140
III	*p*-$CH_3OC_6H_4$	*n*-Bu	$C_{13}H_{20}N_4OS\cdot HCl$	75	134–135
IV	*m*-$CH_3OC_6H_4$	*n*-Bu	$C_{13}H_{20}N_4OS\cdot HCl$	72	142–144
V	*p*-$CH_3C_6H_4$	*n*-Bu	$C_{13}H_{20}N_4S\cdot HCl$	77	129–130
VI	*p*-$C_2H_5OC_6H_4$	*n*-Bu	$C_{14}H_{28}N_4OS\cdot HCl$	70	159–160
VII	*p*-ClC_6H_4	*n*-Bu	$C_{12}H_{17}ClN_4S\cdot HCl$	78	144–146
VIII	*p*-$CH_3C_6H_4$	CH_3	$C_{10}H_{14}N_4S\cdot HCl$	76	158–160
IX	2,6-$(CH_3)_2C_6H_3$	CH_3	$C_{11}H_{16}N_4S\cdot HCl$	75	152–153
X	C_6H_5	CH_3	$C_9H_{12}N_4S\cdot HCl$	78	167–168

[a] All compounds were analyzed for N and S and the analytical results were within ±0.4% of the theoretical values.

TABLE II

ANTITHYROIDAL ACTION IN INTACT RATS

Compd[a] (mg)	Thyroid radioactivity, dpm ± std error: ^{125}I uptake	PB^{125}I	Inorg ^{125}I	Estd act. (thiouracil = 1.0)
Blank	272,189 ± 13,670	237,730 ± 12,340	25,017 ± 1238	
Thiouracil (0.500)	39,428 ± 9233[b]	30,679 ± 7645[b]	8,102 ± 1694[b]	1.0
I (0.913)	45,714 ± 6683[b]	38,247 ± 5857[b]	5,933 ± 899[b]	0.63
II (1.22)	41,152 ± 17,735[b]	34,984 ± 16,240[b]	4,837 ± 1341[b]	0.57
III (1.45)	24,764 ± 5672[b]	18,318 ± 4762[b]	5,155 ± 601[b]	1.01
IV (1.43)	64,265 ± 12,059[b]	52,448 ± 10,708[b]	9,852 ± 1251[b]	0.74
V (1.30)	22,967 ± 5011[b]	15,674 ± 4151[b]	6,253 ± 691[b]	1.31
VI (1.54)	29,005 ± 4056[b]	22,538 ± 3658[b]	5,408 ± 339[b]	0.91
VII (1.46)	65,647 ± 10,866[b]	52,935 ± 8888[b]	8,482 ± 1203[b]	0.62
VIII (1.01)	87,405 ± 25,535[b]	74,372 ± 21,921[b]	8,468 ± 2041[b]	0.42
IX (1.06)	74,005 ± 12,561[b]	62,403 ± 22,513[b]	8,324 ± 979[b]	0.54
X (1.19)	128,604 ± 33,855[c]	113,338 ± 31,297[c]	10,189 ± 1768[b]	0.33

[a] Concentration of test compounds equimolar to thiouracil. [b] $P < 0.001$. [c] $P < 0.01$.

(100–125 g) were maintained on a low-iodide diet for 3 days then divided into groups consisting of four rats in each group. The animals in each group received an intraperitoneal injection of 1 ml of either a blank (0.9% NaCl), thiouracil, or one of the test compounds. One hour later, 1 μCi of Na^{125}I (carrier free) was injected intraperitoneally. Three hours after the injection of ^{125}I, the animals were sacrificed and the thyroids were removed. The whole lobes were placed in ground-glass homogenizing tubes and counted in a Nuclear-Chicago well scintillation counter to determine total thyroidal uptake. The whole lobes were then homogenized in 1 ml of 0.05 *M* barbital buffer (pH 8.6) containing 1.0×10^{-5} *M* thiouracil. One milliliter of cold 20% trichloroacetic acid (TCA) was added and the homogenate was centrifuged. The precipitate was washed twice with 1.0 ml of cold 10% TCA. The original supernatant and the two washes were combined and the radioactivity was determined. The ^{125}I in this fraction indicated the concentration of inorganic ^{125}I or TCA-soluble ^{125}I. The washed precipitate was counted in the homogenizing tube. The radioactivity in this fraction indicated the PB^{125}I (protein-bound iodine) or the TCA-precipitable ^{125}I. The counts were all corrected for counting efficiency and are expressed as disintegrations per minute.

All compounds were dissolved in saline for injection. Thiouracil and IX were dissolved with heating to 55°; III was only partially dissolved in saline, EtOH, or NH_4OH, and therefore it was injected as a suspension in saline. All compounds (except III, IX, and X) were assayed at concentrations equimolar and ten times equimolar to 0.5 mg of thiouracil (3.9 μmoles) and the biological effect was almost the same at both doses. Table II summarizes the observations made with compounds I–X.

All the compounds have antithyroidal activity and appear to inhibit incorporation of I_2 in a manner similar to thiouracil. Compounds III, V, and possibly VI appear to be slightly more potent than thiouracil while IV and VII–X appear to be slightly less potent.

Acknowledgment.—The authors are thankful to Professor S. B. Barker and Dr. R. H. Lindsay (Medical Center, University of Alabama) for their cooperation in carrying out the biological screening of certain compounds and to Professor W. U. Malik for providing necessary laboratory facilities.

Antiinflammatory Aryl Pyridyl Ketones

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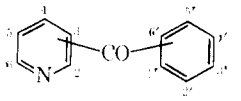
In a routine screening evaluation for nonsteroidal antiinflammatory[2] agents, it was found that 2-benzoylpyridine (**1**) possessed a good level of activity in the carrageenan foot edema assay.[3] This finding prompted us to prepare a series of aryl pyridyl ketones for evaluation as potential antiinflammatory agents.

(1) To whom inquiries should be addressed.

(2) For a survey of recent developments in nonsteroidal antiinflammatory agents see T. Y. Shen in "Annual Reports in Medicinal Chemistry, 1967," C. K. Cain, Ed., Academic Press, New York, N. Y., pp 215–226.

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

TABLE I
PHENYL PYRIDYL KETONES



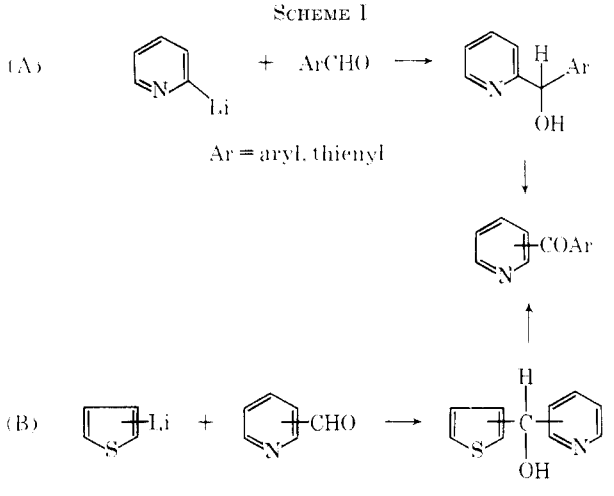
No.	Isomer	Substituent(s)	Carrageenan foot edema[a] ED_{50}, mg/kg	Method[b]	Bp (mm) or mp, °C	Cryst'n solvent[c]	Formula	Analyses[d]
1	2	None	15	...[e]		A	$C_{12}H_9NO$	
2	2	None, oxime	38	...[f]	153–155[g]	B	$C_{12}H_{10}N_2O$	
3	2	None, N-oxide	>50	I	85–87	B	$C_{12}H_9NO_2$	C, H, N, O
4	3	None	>50	...[e]	35	A	$C_{12}H_9NO$	
5	4	None	>50	...[e]	71–72	A	$C_{12}H_9NO$	
6	2	2'-Cl	>50	E	53[h]	B	$C_{12}H_8ClNO$	
7	2	4'-Cl	>50	...[e]		B	$C_{12}H_8ClNO$	
8	2	4'-Cl, oxime	>50	...[f]	153–155, 185–188	B	$C_{12}H_9ClN_2O$	C, H, Cl, N, O
9	2	2',4'-Cl_2	>50	H	62–63	A	$C_{12}H_7Cl_2NO$	C, H, N, O
10	2	2',6'-Cl_2	>50	E	130–132	A	$C_{12}H_7Cl_2NO$	C, H, Cl, N, O
11	2	3'-NO_2	>50	E	115–118	C	$C_{12}H_8N_2O_3$	C, H, N
12	2	4'-NO_2	>50	...[i]	95–98[i]	C	$C_{12}H_8N_2O_3$	
13	2	4'-NH_2	>50	...[j]	138–139[j]	C	$C_{12}H_{10}N_2O$	
14	2	4'-$NHCOCH_3$	>50	F	168–169	D	$C_{14}H_{12}N_2O_2$	C, H, O
15	2	4'-OCH_3	>50	E	98[k]	A	$C_{13}H_{11}NO_2$	
16	2	3',4'-$(OCH_3)_2$	>50	E	92–93	E	$C_{14}H_{13}NO_3$	C, H, N, O
17	2	3',4'-OCH_2O	>50	E	137–138[l]	A	$C_{13}H_9NO_3$	
18	2	3-CH_3	>50	E	125–128 (0.2)		$C_{13}H_{11}NO$	C, H, N
19	2	6-CH_3	>50	...[e]			$C_{13}H_{11}NO$	
20	2	2',3'-$(CH_3)_2$	>50	EE	90.5–91	B	$C_{14}H_{13}NO$	C, H, N, O
21	2	3'-CF_3	>50	E	44–45	B	$C_{13}H_8F_3NO$	C, H, N
22	2	3',5'-$(CF_3)_2$	>50	E	122–123 (0.4)		$C_{14}H_7F_6NO$	C, H, N
23	2	2'-COOH	>50	G	230	B	$C_{13}H_9NO_3$	C, H, O
24	2	3'-COOH	>50	G	147–148[m]	B	$C_{13}H_9NO_3$	

[a] All compounds were administered orally to rats. The procedure for measuring inflammation is given in ref 3. [b] See Experimental Section for synthetic procedures. [c] A, EtOH–Et_2O; B, EtOH–H_2O; C, Et_2O; D, EtOH; E, CH_2Cl_2–Et_2O; F, Et_2O–Me_2CO. [d] See ref 6. [e] Compound obtained from commercial source and crystallized before use. [f] Prepared by the procedure of E. H. Huntress and H. C. Walter, *J. Amer. Chem. Soc.*, **70**, 3702 (1948). [g] T. Nakashima [*Yakugaku Zasshi*, **77**, 1298 (1957); *Chem. Abstr.*, **52**, 6345 (1958)] reported mp 152–153° for α-oxime. [h] G. A. Archer, A. Stempel, S. S. Ho, and L. H. Sternbach [*J. Chem. Soc., C.*, 1031 (1966)] reported mp 52–54°. [i] E. Koenigs, H. Mensching, and P. Kirsch [*Ber.*, **59**, 1719 (1926)] reported mp 99–100°. [j] Lit.[i] mp 138°. [k] Société des Usines Chimques Rhone-Poulene [British Patent 851,972 (Oct. 19, 1960); *Chem. Abstr.*, **55**, 11441 (1961)] reported mp 96°. [l] Lit.[g] mp 139°. [m] J. C. Cochran and W. F. Little [*J. Org. Chem.*, **26**, 808 (1961)] reported mp 146–148.5°.

Chemistry.—The preparations of the aryl pyridyl ketones listed in Tables I and II were carried out by known synthetic techniques. The majority were prepared by the procedures A and B given in Scheme I. Typical cases for Scheme I and other procedures are given in the Experimental Section.

Pharmacology.—The antiinflammatory activity, as determined by the carrageenan foot edema assay[3] in rats for the compounds prepared in this work is given in Tables I and II. The compounds in Table I represent attempts to improve the antiinflammatory activity of 2-benzoylpyridine (**1**) by (a) preparing positional isomers (**4**, **5**) of **1**, (b) placing methyl (**18**, **19**) and carboxyl (**24**) groups on the pyridyl ring; (c) adding one or two Cl, F, NH_2, NO_2, OCH_3, OCH_2O, CH_3, CF_3, or COOH groups on the phenyl ring, and (d) oxime (**2**, **8**) or N-oxide (**3**) analogs of **1**. This approach was abandoned since all examples except the oxime of **1** (**2**) gave very poor or no protection in the carrageenan assay.

SCHEME I

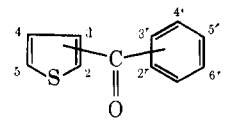


The compounds in Table II are thienyl analogs of **1**. The most active member in this group, 2'-pyridyl 3-thienyl ketone (**28**), was also a 2-substituted pyridyl ketone.

Since **1** and **28** possessed activity in the range of phenylbutazone (Table II) they were selected for further testing in the antiinflammatory area. In bilaterally adrenalectomized rats the carrageenan foot edema ED_{50} for **1** and **28** was >100 and 72 mg/kg, respectively. In the Randall–Sellito[4] test oral minimum

(4) L. O. Randall and J. J. Sellito, *Arch. Intern. Pharmacodyn.*, **11**, 409 (1957).

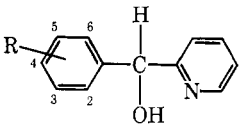
TABLE II
PYRIDYL THIENYL KETONES



No.	Ketone	Carrageenan foot edema[a] ED_{50}, mg/kg	Method[b]	Bp (mm) or mp, °C	Crystn solvent[c]	Formula	Analyses[d]
25[e]	2,2′	37.5	E	138–140 (0.6)		$C_{10}H_7NOS$	C, H, N, O
26[f]	2,3′	50	E	94–97	E	$C_{10}H_7NOS$	C, H, N
27[g]	2,4′	50	E	94–97	E	$C_{10}H_7NOS$	C, H, N, O
28[h]	3,2′	15	E	170–180 (1.0)		$C_{10}H_7NOS$	C, H, N, O
29[i]	3,3′	37.5	E	73–76	E	$C_{10}H_7NOS$	C, H, N
30[j]	3,4′	50	E	98–101	F	$C_{10}H_7NOS$	C, H, N
Aspirin		90					
Phenylbutazone[k,l]		30					

[a–d] See corresponding footnotes in Table I. [e] λ_{max}^{EtOH} 240 mμ (ε 5430), 279 (8580), 306 (9650); $n^{20}D$ 1.6475. [f] λ_{max}^{EtOH} 273 mμ (ε 10,300), 296 (10,200). [g] λ_{max}^{EtOH} 223 mμ (ε 8050), 294 (10,300). [h] λ_{max}^{EtOH} 221 mμ (ε 7770), 272 (11,000); $n^{20}D$ 1.6349. [i] λ_{max}^{EtOH} 220 mμ (ε 11,900), 265 (12,700). [j] λ_{max}^{EtOH} 220 mμ (ε 13,300), 267 (11,400). [k] Randall–Sellito[4] tes tagainst yeast-induced inflammation; ED_{50} = 30 mg/kg (rat, oral). [l] Protection against bradykinin-induced bronchoconstriction; ED_{50} = 1 mg/kg (guinea pig, iv).

TABLE III
ARYL-2-PYRIDYLCARBINOLS



No.	R	Method[a]	Yield, %	Mp, °C (solvent[b])	Formula	Analyses[c]
31	2-Cl	A	56	63–64 (A)	$C_{12}H_{10}ClNO$	C, H, N
32	2,4-Cl_2	A	34	95–96 (A)	$C_{12}H_9Cl_2NO$	C, H, N, O
33	2,6-Cl_2	A	72	82–83 (B)	$C_{12}H_9Cl_2NO$	C, H, Cl, N, O
34	2,3-$(CH_3)_2$	B	51	117–118 (C)	$C_{14}H_{15}NO$	C, H, N, O
35	3-CF_3	B	42	92–93 (C)	$C_{13}H_{10}F_3NO$	C, H, N
36	3,5-$(CF_3)_2$	B	36	111–113 (C)	$C_{14}H_9F_6NO$	C, H, N

[a] See Experimental Section. [b] A, CH_2Cl_2–C_7H_{12}; B, Et_2O–C_5H_{12}; C, CH_2Cl_2–C_5H_{12}. [c] See footnote *d* in Table I.

effective doses against yeast-induced inflammation were 14 mg/kg for **1** and 24 mg/kg for **28**. Protection against bradykinin-induced bronchoconstriction[5] was (ED_{50}, iv) 10 mg/kg for **1** and >10 mg/kg for **28**. Since phenylbutazone (see footnotes *k* and *l*, Table II) has considerably greater activity than **1** or **28** in the above tests, further development of these compounds as useful antiinflammatory agents was terminated.

Experimental Section[6]

Preparation of Arylpyridylcarbinols. Method A. Arylaldehyde and 2-Pyridyllithium.—A stirred solution of 50 ml of 15% *n*-BuLi–hexane (0.053 mol) and 100 ml of anhydrous Et_2O, maintained under N_2 and cooled to −40° internally, was treated with 12.1 g (0.077 mol) of 2-bromopyridine in 30 ml of Et_2O (0.3 hr) and then dropwise (1.5 hr) with 0.075 mol of halobenzaldehyde in 100 ml of Et_2O. After an additional 1 hr at −40°, the mixture was allowed to warm to 5° and then treated dropwise (0.3 hr) with 125 ml of 1 *N* HCl. The acid layer was separated, made basic with 2 *N* NaOH, extracted with $CHCl_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **31**, **32**, or **33** (Table III).

Method B. Aryllithium and Pyridinecarboxaldehyde.—An organolithium reagent was prepared by refluxing a mixture of 0.27 mol of 1-bromo-*x*-benzene and 3.8 g (0.30 g-atom) of Li wire in 300 ml of anhydrous Et_2O for 3 hr under N_2. The reagent was cooled to an internal temperature of −40°, treated dropwise (0.5 hr) with 31.9 g of 2-pyridinecarboxaldehyde in 50 ml of Et_2O, and processed as in method A to give **34**, **35**, or **36** (Table III).

Method C. 3-Thienyllithium and Pyridinecarboxaldehyde.—To 68 ml of 1.6 *N* *n*-BuLi–hexane (0.11 mol) maintained under N_2 and cooled to an internal temperature of −70°, there was added dropwise (1.5 hr) 16.3 g (0.10 mol) of 3-bromothiophene[7] in 50 ml of anhydrous Et_2O. After an additional 1 hr at −70° the solution was treated with 8.5 g (0.08 mol) of 2-, 3-, or 4-pyridinecarboxaldehyde in 50 ml of Et_2O and then after 2 hr of stirring was poured onto ice. The organic layer was separated and the H_2O layer was washed with $CHCl_3$ (four times, 75 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*, and the resultant crude alcohols were used directly to prepare **28**, **29**, and **30** by method E.

Method D. 2-Thienyllithium and Pyridinecarboxaldehyde.—A solution containing 5 g (0.059 mol) of thiophene, 34 ml of 1.6 *N* *n*-BuLi–hexane (0.054 mol), and 100 ml of anhydrous Et_2O was stirred and refluxed for 5 hr under N_2 then cooled to an internal temperature of −30°, and treated dropwise with 6.6 g (0.061 mol) of 2-, 3-, or 4-carboxaldehyde in 50 ml of Et_2O. After an additional 1 hr at −30°, the mixture was allowed to warm to 0° and then was treated with *ca.* 15 ml of H_2O. The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo* and the resultant products from 3- and 4-pyridinecarboxaldehyde were used directly to prepare **26** and **27** by method E, and that from 2-pyridinecarboxaldehyde gave 2′-

(5) H. Konzett and R. Rossler, *Arch. Exptl. Pathol. Pharmakol.*, **195**, 71 (1940).

(6) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. The uv spectra were obtained on a Beckman Model DB spectrophotometer attached to a Sargent SRL recorder or on a Cary Model 15 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(7) P. Moses and S. Gronowitz, *Arkiv Kemi*, **18**, 119 (1961).

pyridyl-2-thienylcarbinol (**37**), mp 77–81° (Et_2O). *Anal.* ($C_{16}H_{13}NOS$) C, H, N, S.

Preparation of Aryl Pyridyl Ketones. Method E. Chromium Trioxide Oxidation of Arylpyridylcarbinols.—A stirred solution of 72 g (0.33 mol) of *p*-anisyl-α-pyridylcarbinol in 400 ml of AcOH was cooled to 20° and treated dropwise with 30 g (0.30 mol) of CrO_3 in 60 ml of H_2O. The solution was stirred 3 hr at room temperature, poured onto *ca.* 1.5 l. of ice water, extracted with $CHCl_3$, washed with 2 *N* NaOH, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give compounds **6**, **10**, **11**, **15**–**18**, **20**–**22**, and **25**–**30** listed in Tables I and II.

Method F. Preparation of 14.—A mixture of 2.5 g of **13**, 15 ml of pyridine, and 8 ml of Ac_2O was heated at 60° for 1 hr. After standing overnight at room temperature the excess reagents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with H_2O, dried, and evaporated to give **14** (70%), mp 169° (EtOH). *Anal.* ($C_{11}H_{12}N_2O_2$) C, H, O.

Method G. Preparation of 23.—A mixture of 1.0 g of 2-pyridyl *o*-tolyl ketone and 10 ml of 2 *N* H_2SO_4 was heated to 100° and treated dropwise (2 hr) with a solution of 5 g of $KMnO_4$ in 75 ml and enough H_2SO_4 to maintain an acidic solution (pH ≈2.0). The mixture was then refluxed for 1 hr, cooled to room temperature, and filtered and the salts were washed with H_2O and MeOH. The combined filtrates were concentrated to one-half volume and neutralized with 2 *N* NaOH. The resultant precipitate was filtered and carefully neutralized with 2 *N* HCl to give **23** (13%).

Method H. Preparation of 9.—A mixture of 61.5 g (0.50 mol) of picolinic acid, 326 g (2.0 mol) of 2,4-dichlorobenzaldehyde, and 500 ml of 85% *o*-dichlorobenzene was stirred and refluxed for 6 hr under a N_2 atmosphere. The solvent was removed *in vacuo*, and the residue was dissolved in a minimum amount of $CHCl_3$ and then treated with 10% HCl until the aqueous layer remained acidic. The resultant solid was filtered off, treated with 15% NaOH until basic, extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 43.0 g (34%) of **9**.

Method I. Preparation of 3.—A mixture of 18.3 g (0.1 mol) of **1**, 75 ml of HOAc, and 17 ml of 30% H_2O_2 was stirred and refluxed for 16 hr. The solvent was removed *in vacuo* and the residue was treated with 50 ml of 2 *N* NaOH and 100 ml of $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$), filtered, and concentrated to give **3** (76%).

Acknowledgment.—The authors thank Messrs. P. Aeberli, B. Huegi, and R. Riedlin for synthetic assistance and U. Stoeckli for microanalytical and instrumental analyses.

The Synthesis of Some 4-Anilino-3-quinolinecarboxylic Acids and Esters

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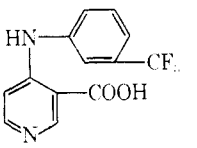
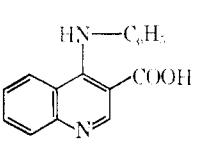
Recently it was reported that 4-(α,α,α-trifluoro-*m*-toluidino)nicotinic acid (**1**) is an orally effective diuretic in animals.[1] In order to investigate the properties of structurally related compounds, the synthesis of several substituted 4-anilino-3-quinolinecarboxylic acids and their corresponding esters was undertaken.



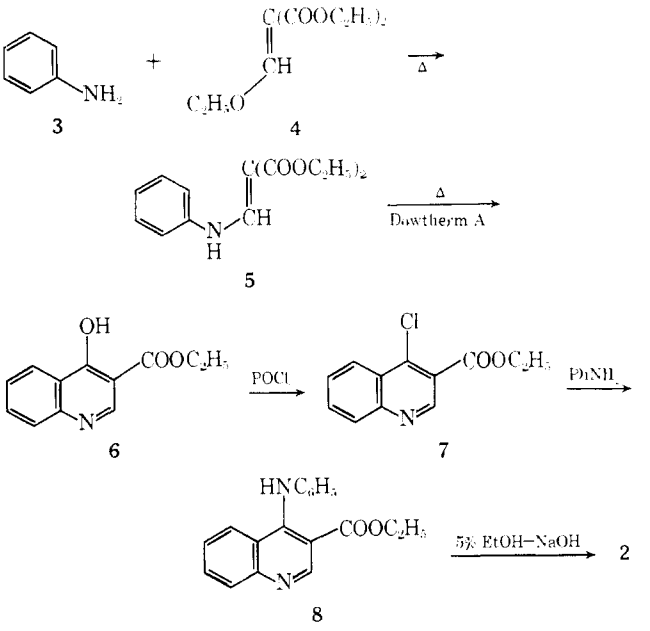
1



2

The preparation of the parent compound, 4-anilino-3-quinolinecarboxylic acid (**2**) has been described using the synthetic procedure shown in Scheme I. Reaction

SCHEME I



of aniline (**3**) with ethoxymethylenemalonic ester (**4**) gives the corresponding anilinomethylenemalonic ester (**5**).[2] Heating **5** in Dowtherm A results in ring closure to produce ethyl 4-hydroxy-3-quinolinecarboxylate (**6**).[3] Treatment of **6** with $POCl_3$ yields ethyl 4-chloro-3-quinolinecarboxylate (**7**).[3] Addition of aniline to **7** followed by hydrolysis yields the 4-anilino-3-quinolinecarboxylic acid (**2**).[4]

Using this procedure we prepared ethyl 4-chloro-3-quinolinecarboxylate (**7**) and ethyl 4,6-dichloroquinoline-3-carboxylate (**9**) for use as intermediates. By reaction of **7** and **9** with the proper amine, the esters in Scheme II were prepared.[5] Hydrolysis of the esters produced the corresponding acids.

All of these compounds were tested for diuretic activity in both normal rats and hydrated dogs. The normal rats were tested at a dose level of 100 mg/kg according to the procedure of Cummings, *et al.*,[6] while the hydrated dogs were tested using the method of Little and Cooper[7] at 5 mg/kg. Three of the compounds, **2**, **8**, and **13**, were found active in the rat at this dose level; however, none of the compounds

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(2) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and C. H. Baker, *J. Am. Chem. Soc.*, **68**, 1264 (1946).

(3) C. E. Kaslow and W. P. Clark, *J. Org. Chem.*, **18**, 55 (1953).

(4) W. O. Kermack and N. E. Storey, *J. Chem. Soc.*, 1389 (1951).

(5) The 4-furfurylamino derivative was prepared as an extension of this reaction for **20**.

(6) J. R. Cummings, J. D. Haynes, L. M. Lipchuck, and M. A. Ronsberg, *J. Pharmacol. Exp. Ther.*, **128**, 414 (1960).

(7) J. M. Little and Cooper, Jr., *Fed. Proc.*, **9**, 296 (1950).