pyridyl-2-thienylcarbinol (**37**), mp 77–81° (Et_2O). *Anal.* ($C_{10}H_9NOS$) 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.

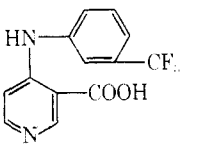
The Synthesis of Some 4-Anilino-3-quinolinecarboxylic Acids and Esters

J. WILLIAM HANIFIN, ROSEMARY CAPUZZI, AND ELLIOTT COHEN

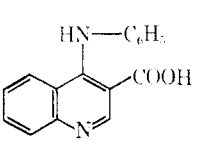
Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received May 21, 1969

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.



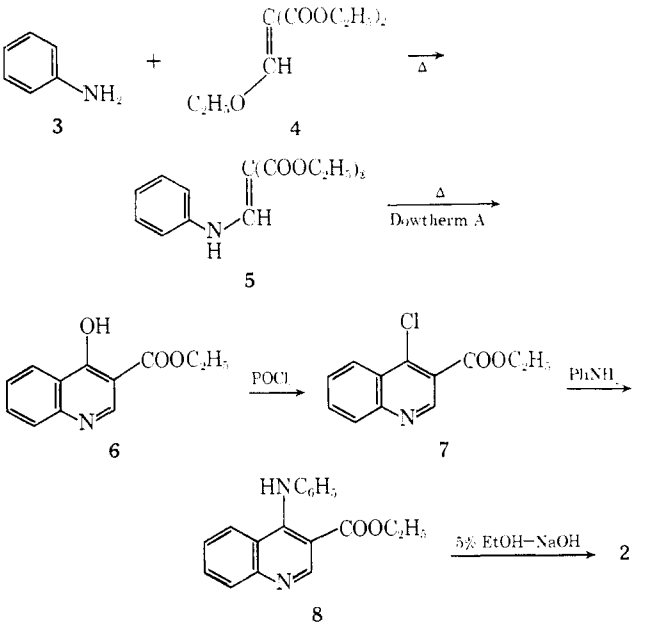
1



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**).[2] 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

(1) J. R. Cummings, M. A. Ronsberg, E. H. Stokey, and R. Z. Gussin, *Pharmacologist*, **10**, 162 (1968); (b) R. Z. Gussin, E. H. Stokey, M. A. Ronsberg, and J. R. Cummings, *ibid.*, **10**, 163 (1968); (c) R. Z. Gussin, J. R. Cummings, E. H. Stokey, and M. A. Ronsberg, *J. Pharmacol. Exp. Ther.*, **167**, 194 (1969); (d) R. Z. Gussin and M. A. Ronsberg, *Proc. Soc. Exp. Biol. Med.*, in press.

(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).

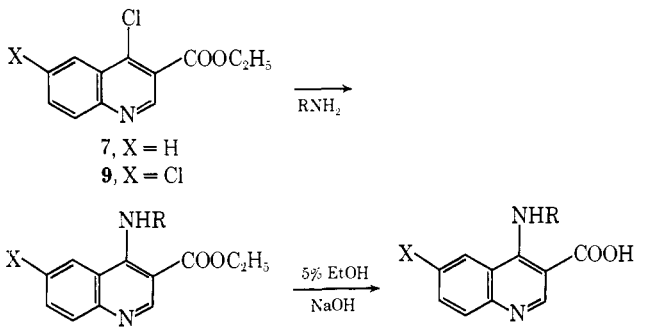
TABLE I

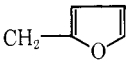
YIELDS, PHYSICAL, AND ANALYTICAL DATA

No.	% yield	Mp, °C	Recrystn solvent[a]	Formula	Analyses
9	70	77	P	$C_{12}H_9Cl_2NO_2$	C, H, Cl, N
10	41	105	E	$C_{19}H_{15}F_3N_2O_2$	C, H, F, N
11	48	144	E	$C_{19}H_{14}ClF_3N_2O_2$	C, H, Cl, F, N
12	79	157	E	$C_{19}H_{14}ClF_3N_2O_2$	C, H, Cl, F, N
13	78	134	E	$C_{18}H_{15}ClN_2O_2$	C, H, Cl, N
14	72	147	E	$C_{19}H_{14}ClF_3N_2O_2$	C, H, Cl, F, N
15	87	145	E	$C_{19}H_{13}Cl_2F_3N_2O_2$	C, H, Cl, F, N
16	87	195	E	$C_{19}H_{13}Cl_2F_3N_2O_2$	C, H, Cl, F, N
17	76	132	E	$C_{19}H_{17}ClN_2O_3$	C, H, Cl, N
18	29	120	E	$C_{19}H_{17}ClN_2O_3$	C, H, Cl, N
19	62	190	E	$C_{21}H_{21}ClN_2O_5$	C, H, Cl, N
20	46	91	E	$C_{17}H_{15}ClN_2O_3$	C, H, N; Cl[b]
21	65	270	M	$C_{17}H_{11}F_3N_2O_2$	C, H, F, N
22	90	266	M	$C_{17}H_{10}ClF_3N_2O_2$	C, H, Cl, F, N
23	48	283	M	$C_{17}H_{10}ClF_3N_2O_2 \cdot H_2O$	H, Cl, F, N; C[c]
24	77	262	M	$C_{16}H_{11}ClN_2O_2$	C, H, Cl, N
25	83	272	M	$C_{17}H_{10}ClF_3N_2O_2 \cdot 0.5H_2O$	C, H, Cl, F, N
26	96	267	M	$C_{17}H_9Cl_2F_3N_2O_2$	H, F, N; C, Cl[d]
27	67	279	M	$C_{17}H_9Cl_2F_3N_2O_2$	C, H, Cl, F, N
28	68	265	M	$C_{17}H_{13}ClN_2O_3$	C, H, Cl, N
29	55	248	M	$C_{16}H_{11}ClN_2O_3 \cdot 0.5H_2O$	H, N; C, Cl[e]

[a] P = petroleum ether (30–60°), E = EtOH, M = MeOH. [b] Cl: calcd, 10.7; found, 11.2. [c] C: calcd, 53.1; found, 53.8. [d] C: calcd, 50.9; found, 50.4. Cl: calcd, 17.7; found 17.2. [e] C: calcd, 57.8; found, 58.5. Cl: calcd, 11.4; found, 11.9.

SCHEME II



	X	R	
10	H	3-$F_3CC_6H_4$	21
11	H	4-Cl-3-$F_3CC_6H_3$	22
12	H	2-Cl-5-$F_3CC_6H_3$	23
13	Cl	C_6H_5	24
14	Cl	3-$F_3CC_6H_4$	25
15	Cl	4-Cl-3-$F_3CC_6H_3$	26
16	Cl	2-Cl-5-$F_3CC_6H_3$	27
17	Cl	4-$MeOC_6H_4$	28
18	Cl	3-$MeOC_6H_4$	
19	Cl	3,4,5-$(MeO)_3C_6H_2$	
20	Cl		29

exhibited any significant diuretic activity in the dog at the 5-mg/kg dose level.

Experimental Section[8]

Ethyl 4,6-dichloroquinoline-3-carboxylate (**9**) was prepared from ethyl 6-chloro-4-hydroxy-3-quinolinecarboxylate by the method of Kaslow and Clark.[3]

General Procedure for the Substituted Ethyl 4-Anilino-3-quinolinecarboxylates (**10–20**).—A mixture containing 0.004 mole of an ethyl 4-chloro-3-quinolinecarboxylate and 0.006 mole of the desired aniline was heated on the steam bath for 10 min. Upon cooling, the mixture settled to a gum which solidified on standing for 30 min. Dissolution of this in H_2O and basification with NH_3 yielded the product which was further purified by crystallization (EtOH).

General Procedure for the Substituted 4-Anilino-3-quinolinecarboxylic Acids (**21–29**).—To 20 ml of 5% NaOH in EtOH was added 0.003 mole of the substituted ethyl 4-anilino-3-quinolinecarboxylate. After stirring for 1 hr, HCl was bubbled through the solution to pH 1. NaOAc was then added slowly to pH 3. Upon filtering, the yellow precipitate was washed (EtOH, H_2O). The precipitate was then heated in H_2O and the solution was adjusted to pH 5. After washing (H_2O), the product was dried *in vacuo*. An analytical sample was prepared by crystallization (MeOH).

(8) Yields, physical data, and analyses are listed in Table I. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Heterocyclic Substituted Ureas. III. Immunosuppressive and Antiviral 2-Pyrimidylureas

CHARLES J. PAGET, CHARLES W. ASHBROOK, ROBERT L. STONE, AND DONALD C. DELONG

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received July 11, 1969

Benzimidazole-,[1] benzothiazole-, and benzoxazole-ureas[2] are potent immunosuppressives and are effective against certain virus diseases in mice. We have searched for other heterocyclic ureas that have these biological properties. We report the synthesis and testing of a series of 2-pyrimidylureas, certain members of which have the desired biological properties (Table I).

(1) C. J. Paget, K. Kisner, R. L. Stone, and D. C. DeLong, *J. Med. Chem.*, **12**, 1010 (1969).

(2) C. J. Paget, K. Kisner, R. L. Stone, and D. C. DeLong, *ibid.*, **12**, 1016 (1969).