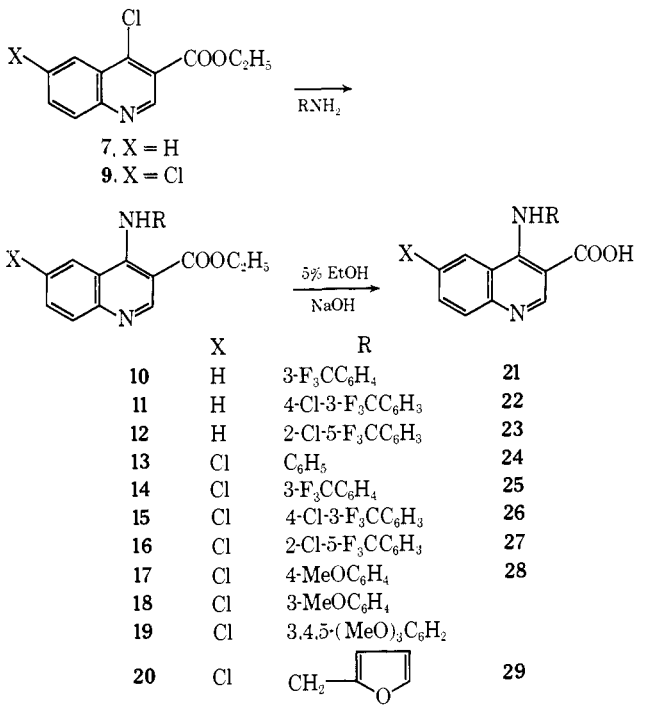
TABLE I

YIELDS, PHYSICAL, AND ANALYTICAL DATA

No.	% yield	Mp, °C	Recrystn solvent[a]	Formula	Analyses
9	70	77	P	$C_{12}H_5Cl_2NO_2$	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

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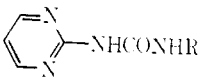
Benzimidazole-,[1] benzothiazole-, and benzoxazole-ureas[2] are potent immunosuppressives and are effective against certain virus diseases in mice. We have searched for other heterocyclic ureas that have these biological properties. We report the synthesis and testing of a series of 2-pyrimidylureas,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

TABLE I
1-(2-PYRIMIDYL)-3-SUBSTITUTED UREAS



No.	R	Mp, °C	Formula	Coe virus ED_{50}, mg/kg	Drug level (mg/kg × 3) for fourfold or greater immunosuppression
1	3-$CF_3C_6H_4$	223–224	$C_{12}H_9F_3N_4O$[a]	76	12.5
2	4-$NO_2C_6H_4$	268–270	$C_{11}H_9N_5O$[b]	128	12.5
3	C_6H_5	221–222	$C_{11}H_{10}N_4O$	128	50.0
4	3,4-$Cl_2C_6H_3$	240–241	$C_{11}H_8Cl_2N_4O$[a]	20	50.0
5	3-$CH_3C_6H_4$	187–188	$C_{12}H_{12}N_4O$	128	50.0
6	2-$NO_2C_6H_4$	264–265	$C_{11}H_9N_5O_3$	84	50.0
7	C_6H_{11}	150–151	$C_{11}H_{16}N_4O$	128	100.0
8	4-CNC_6H_4	273–274	$C_{12}H_7N_5O$	114	100.0
9	4-FC_6H_4	244–245	$C_{11}H_9FN_4O$	104	100.0
10	2-FC_6H_4	218–219	$C_{11}H_9FN_4O$	128	100.0
11	2,5-$Cl_2C_6H_3$	314–318	$C_{11}H_8Cl_2N_4O$	22	100.0
12	2-$CH_3C_6H_4$	214–215	$C_{12}H_{12}N_4O$	118	100.0
13	4-$CH_3C_6H_4$	205–206	$C_{12}H_{12}N_4O$	128	100.0
14	1-$C_{10}H_7$	246–248	$C_{15}H_{12}N_4O$	84	100.0
15	3-$NO_2C_6H_4$	259–261	$C_{11}H_9N_5O_3$	31	100.0
16	2-$CH_3OC_6H_4$	222–224	$C_{12}H_{12}N_4O_2$	128	100.0
17	2-$C_2H_5OC_6H_4$	248–249	$C_{13}H_{14}N_4O_2$	34	100.0
18	3-ClC_6H_4	231–232	$C_{11}H_9ClN_4O$	26	100.0
19	Azathioprine			128	100.0

[a] See ref 3. [b] See ref 4.

Immunosuppressive activity has not, to our knowledge, been reported for any pyrimidineureas. Buu-Hoi, *et al.*,[3] have reported the synthesis of 1,3-disubstituted 2-pyrimidylureas as potential antiinfluenza agents; however, they report only *in vitro* antibacterial activity. Some 1-[4-nitrophenyl-3-(2-pyrimidyl)]ureas have been patented for the treatment of coccidiosis.[4]

Biological Testing.—The compounds were tested for immunosuppression in the sheep erythrocyte assay in mice and for antiviral activity against Coxsackie A21 virus infections in mice, as previously described.[1]

Discussion

This investigation, although limited mainly to modification of the aryl substituents, emphasized that the 2-pyrimidyl group is less effective than the 2-aminobenzimidazole or 2-aminobenzothiazole[1,2] as a basic nucleus for the desired activities. As immunosuppressants only compounds **1** and **2** (3-trifluoromethylphenyl and 4-nitrophenyl) are worthy of mention. They both contain strong electron-withdrawing groups on the aryl ring. The most potent antiviral activity was found in compounds **4**, **11**, **15**, **17**, and **18**, the majority of which are chlorophenyl derivatives. The potent antivirals were all very poor immunosuppressants, indicating two separate structure–activity relationships.

Experimental Section[5]

The reactions were run in aprotic solvents in which both starting materials were reasonably soluble. An example follows.

3-(1-Naphthyl)-1-(2-pyrimidinyl)urea.—A mixture of 2.87 g (0.03 mole) of 2-aminopyrimidine and 5.6 g (0.03 mole) of 1-naphthyl isocyanate was refluxed and stirred 8 hr in 150 ml of toluene. The cooled solution was filtered, and the solid dried, mp 246–248°, yield 8.0 g. This material was one spot on silica gel tlc in EtOAc and, therefore, was not further purified.

Acknowledgments.—We would like to thank Messrs. Linville Baker and Robert Wolfe for the biological test results.

(3) Buu-Hoi, D. Xuong, and V. T. Suu, *J. Chem. Soc.*, 2185 (1958).

(4) R. C. O'Neill and A. J. Basso, U. S. Patent 2,762,742 (1956); *Chem. Abstr.*, **51**, 5129 (1957).

(5) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Ir and nmr spectra were consistent for the proposed structures. All compounds were analyzed for C, H, N and gave results within ±0.4% of the theoretical value.

Muscle Relaxant and Anticonvulsant Properties of Some 1-Carbamoyl-3-aroylpyrrolidines and 1-Carbamoyl-4-aroylpiperidines

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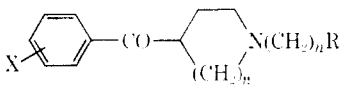
We have investigated a number of 1-substituted aroylpiperidines (I) and pyrrolidines (II), some of which have shown potent CNS depressant activity.[1]



I, $n = 2$
II, $n = 1$

As a part of a continuing study concerning the effects of structural modifications on the activity of this novel class of compounds, several 1-carbamoyl analogs were prepared. In the initial pharmacological evaluation

(1) R. L. Duncan, Jr., G. C. Helsley, W. J. Welstead, Jr., J. P. DaVanzo, W. H. Funderburk, and C. D. Lunsford, *J. Med. Chem.*, in press.