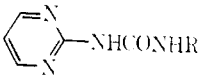
TABLE I
1-(2-PYRIMIDYL)-3-SUBSTITUTED UREAS



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	$C_{12}H_9N_5O$	114	100.0
9	4-FC_6H_4	244–245	$C_{11}H_8FN_4O$	104	100.0
10	2-FC_6H_4	218–219	$C_{11}H_8FN_4O$	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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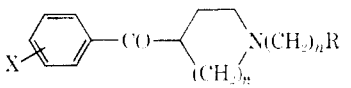
We have investigated a number of 1-substituted aroylpiperidines (I) and pyrrolidines (II), some of which have shown potent CNS depressant activity.[1]



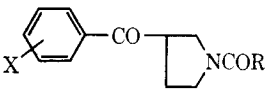
I, $n = 2$
II, $n = 1$

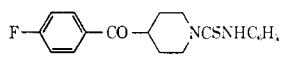
As a part of a continuing study concerning the effects of structural modifications on the activity of this novel class of compounds, several 1-carbamoyl analogs were prepared. In the initial pharmacological evaluation

(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.

TABLE I

AROYLPYRROLIDINES AND AROYLPIPERIDINES

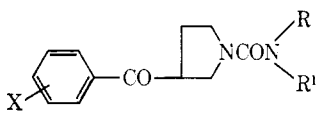


No.	X	R	Prepn[a] method	% yield	Mp, °C	Purifien[b] solvent	Formula[c]
1	H	NH_2	4	58	128–129	EA	$C_{12}H_{14}N_2O_2$
2	*p*-F	NH_2	4	41	137–138	EA–E	$C_{12}H_{13}FN_2O_2$
3	*m*-CF_3	NH_2	3	35	130–132	EA–I	$C_{13}H_{13}F_3N_2O_2$
4	*m*-CF_3	$NHCH_3$	1	68	102–104	I	$C_{14}H_{15}F_3N_2O_2$
5	H	OC_2H_5	5	50	*d*		$C_{14}H_{17}NO_3$
6	H	NH_2	3	28	118–121	EA–I	$C_{13}H_{16}N_2O_2$
7	H	$N(CH_3)_2$	2	67	71–73	B–O	$C_{15}H_{20}N_2O_2$
8	*p*-F	NH_2	3	62	137–140	C	$C_{13}H_{15}FN_2O_2$
9	*p*-F	$NHCH_3$	1	46	122–124	M–I	$C_{14}H_{17}FN_2O_2$
10	*p*-F	$N(CH_3)_2$	2	33	105–107	L	$C_{15}H_{19}FN_2O_2$
11	*p*-OCH_3	NH_2	3	67	147–148	Ip	$C_{14}H_{18}N_2O_3$
12	*m*-CF_3	$NHCH_3$	1	86	90–92	Ip	$C_{15}H_{17}F_3N_2O_2$
13	*p*-F	NHC_6H_4-*m*-Cl	1	59	169–172	Ip	$C_{19}H_{18}ClFN_2O_2$
14	*p*-F	OC_2H_5	5	95	*d*		$C_{15}H_{18}NO_3F$
15	*p*-OCH_3	OC_2H_5	5	95	*d*		$C_{16}H_{21}NO_4$
16			1	75	149–150	B	$C_{19}H_{19}FN_2OS$

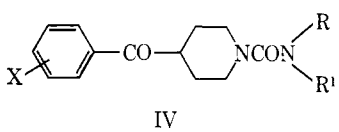
[a] See Experimental Section. [b] B = C_6H_6, C = $CHCl_3$, E = EtOH, EA = EtOAc, I = *i*-Pr_2O, Ip = *i*-PrOH, L = ligroin, O = isooctane. [c] All compounds were analyzed for C, H, N. [d] Analytical sample was molecularly distilled.

it was shown that these compounds did not generally possess potent CNS depressant activity, but did have anticonvulsant and/or muscle relaxant properties.

The object of this paper is consequently to report on the preparation and anticonvulsant as well as muscle relaxant evaluation of a series of 1-carbamoyl-3-aroylpyrrolidines (III) and 1-carbamoyl-4-aroylpiperidines (IV). In several instances the 1-carbethoxy analogs were also synthesized.



III



IV

The 1-carbamoyl compounds were prepared by the reaction of the appropriate 3-aroylpyrrolidine[1] or 4-aroylpiperidine[1] with (1) alkyl or aryl isocyanates, (2) dimethylcarbamoyl chloride, or (3) nitrourea.[2] Some of the 1-carbamoyl-3-aroylpyrrolidines were prepared by treatment of the corresponding 1-benzyl compound with CNBr[3] and subsequent acid hydrolysis of the resulting 1-cyano intermediate. The 1-carbethoxy analogs were prepared by the reaction of the secondary amine with ethyl chloroformate.

Details are given in Table I and in the Experimental Section.

Pharmacology.—Compounds were tested for anticonvulsant activity in female mice (ICR strain) with modifications of the methods of Swinyard, *et al.*[4] Animals were challenged with electroshock or pentylenetetrazol, hind-leg extension being the end point in both tests. Parameters for electroshock were 60 cps, 2-msec pulse width and 2-sec duration. The minimal 100% effective voltage (usually 20–25 V from a Grass stimulator) was used. Pentylenetetrazol in doses of 100 mg/kg ip was the chemical challenge. Test compounds, dissolved or suspended in water, were administered intraperitoneally, 30 or 60 min, respectively, prior to challenge. Five mice were used for each dose. Effective $dose_{50}$ values and their 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[5]

Signs of drug effect in the animals prior to challenge were recorded. Compounds that produced loss of righting in 50% or more of the mice at 100 mg/kg were further tested for their ability to selectively depress polysynaptic spinal reflexes in spinal cats.

Surgical procedures in adult cats of either sex were performed under ether anesthesia. The spinal cord was severed at C_1 and the animal maintained on artificial respiration. The knee jerk reflex (monosynaptic) of a hind leg was elicited every 2 sec by means of a solenoid which pulled on the exposed patellar tendon. In the contralateral hind leg, the flexor reflex (polysynaptic) was evoked by electrical stimuli (square waves: 100 cps, 0.5–3 V, 2-msec pulse width and a duration of 80 msec) every second to the central end of the sectioned tibial nerve. These spinal reflexes, along with carotid

(2) J. S. Buck and C. W. Ferry, *J. Am. Chem. Soc.*, **58**, 854 (1936).
(3) H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).
(4) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).
(5) J. T. Litchfield, Jr., and F. Wilcoxon, *ibid.*, **96**, 99 (1949).

TABLE II
PHARMACOLOGICAL DATA

No.	Anticonvulsant Activity[a]						Muscle relaxant activity[b]	
	Electroshock			Pentylenetetrazol				
	Dose, mg/kg ip	% protection	ED_{50} (95% conf limits), mg/kg	Dose, mg/kg ip	% protection	ED_{50} (95% conf limits), mg/kg	Dose, mg/kg ip	% reduc of flexor reflex
1			88 (59–133)			103 (78–135)		
2	100	40		100	40			
3	100	80		200	40			
4			60 (35–104)	100[c]	40		5	50
							10	85
							25	100
5	100	40		100	20		10	44
6			32 (28–36)	100	0			
7	100	40		200	60		10	30
8			73 (43–119)			108 (58–202)	20	50
9			92 (66–129)	200	60		20	16
10			111 (66–186)	100	0		10	0
11	100	20		200	0			
12	50	0		100[c]	40		5	50
13	100	0		100	0			
14	100	0		100	0			
15	100	0		100	0			
16	100	0		100	0			
Diphenylhydantoin			5 (3–8)					
Ethosuximide						88 (46–167)		
Mephenesin							10	53
							25	85

[a] Mice. [b] Cats. [c] Convulsions in two animals at 200 mg/kg.

arterial blood pressure, were recorded on a Grass polygraph. Test compounds, dissolved in water or polyethylene glycol 300, were administered slowly into a brachial vein.

Although the approximate LD_{50}'s were not generally determined, in most instances the compounds were tested in mice at 200 mg/kg ip and unless noted otherwise were not lethal or did not cause convulsions.

The pharmacological test results are summarized in Table II. Two compounds (**4**, **12**) show pronounced muscle relaxant activity in the range of mephenesin as measured by the reduction of the flexor reflex. Both structures had in common the 1-methylcarbamoyl and *m*-trifluoromethylbenzoyl groups. None of the test compounds or the reference compound produced a significant reduction in the knee jerk reflex.

Two compounds (**1**, **8**) gave moderate protection against pentylenetetrazol convulsions, but compound **8** was effective only at doses that produced loss of righting in mice. Several compounds (**1**, **4**, **6**, **8–10**) protected against electroshock convulsions at higher doses than the reference compound. The 1-carbethoxy compounds (**5**, **14**, **15**) showed little or no anticonvulsant activity.

Experimental Section

In most cases general procedures are given below for the preparation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in Table I and significant variations in the procedure are noted in the table footnotes. Temperatures are uncorrected. Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.

1-Carbamoylpyrrolidines and -piperidines. Procedure 1. By Reaction with Alkyl or Aryl Isocyanates.—To a stirred solution of 0.1 mole of the secondary amine in 100 ml of dry C_6H_6 at room temperature was added slowly 0.1 mole of alkyl or aryl isocyanate (C_6H_5NCS for compound **16**) in 20 ml of dry C_6H_6. After the addition was complete, the mixture was stirred for 15–60 min and then the solvent was evaporated at reduced pressure. Crude products were purified by recrystallization.

Procedure 2. By Reaction with Dimethylcarbamoyl Chloride.—To a stirred suspension of 0.15 mole of Na_2CO_3 and 0.05 mole of the secondary amine in 100 ml of $C_6H_5CH_3$ was added 0.05 mole of dimethylcarbamoyl chloride in 20 ml of $C_6H_5CH_3$. Stirring was continued for several hours and then the mixture was heated at reflux for 1–5 hr. The suspension was cooled and treated with 150 ml of H_2O. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The crude product was purified by recrystallization.

Procedure 3. By Reaction with Nitrourea.[2]—A mixture of 0.05 mole of the secondary amine, 0.06 mole of nitrourea, and 80 ml of 95% EtOH was heated gently until the evolution of gas ceased (15–20 min) and then heated at reflux for 15 min. After the solvent was evaporated, the residual solid was purified by recrystallization.

Procedure 4. By Cyanogen Bromide Reaction.[3]—To a stirred solution of 0.40 mole of CNBr in 400 ml of $CHCl_3$ was added 0.30 mole of the 1-benzyl-3-aroylpyrrolidine in 100 ml of $CHCl_3$ over a period of 5 hr. After the addition was complete, the solution was heated at reflux for 1.5 hr and then the solvent was evaporated at reduced pressure. The residual oil was treated with 1600 ml of 4 *N* HCl and heated at reflux for 16 hr. After the mixture was cooled and extracted with Et_2O, the aqueous layer was made basic with 6 *N* NaOH and extracted with $CHCl_3$. The combined extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was evaporated. The crude products were purified by recrystallization.

1-Carbethoxypyrrolidines and -piperidines. Procedure 5. By Reaction with Ethyl Chloroformate.—A stirred mixture of 0.10 mole of the secondary amine and 0.20 mole of K_2CO_3 in 70 ml of CH_2Cl_2 was cooled to 0° and treated with 0.11 mole of ethyl chloroformate. The mixture was treated with 20–25 g of ice and allowed to warm up to room temperature. The CH_2Cl_2 layer was separated, washed with dilute HCl, dried ($MgSO_4$), and concentrated to an oil. Purity was determined by tlc, ir, and nmr studies. The analytical samples were molecularly distilled.

Acknowledgments.—The authors wish to express their appreciation to Robert F. Boswell, Jr., and Harold F. Stauffer, Jr., for chemical technical assistance and to Jean Hazelwood for pharmacological technical assistance.