The filtrate from IV was returned to the reaction flask and stirred overnight (~12 hr) at 26°. The clear yellow solution was concentrated *in vacuo* to 125 ml and cooled, and the crystals were filtered and washed with ether to give 5.75 g (21%) of nearly colorless 1-(1-acetyl-4-imidazolyl)-5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-en-7-one (III), mp 167–168°. Recrystallization from ethyl acetate gave colorless material: mp 170.5–171°; infrared, 1815 ($\nu_{C=O}$ oxazolone), 1735 ($\nu_{C=O}$ N-acetyl), 1635 cm^{-1} ($\nu_{C=N}$ oxazolone); ultraviolet (CH_2Cl_2), 263 mμ (ε 18,100); nmr (CF_3CO_2H), δ 9.48 (1 H, doublet, J = 2 cps, imidazole H), 8.00 (6 H, multiplet, imidazole H and phenyl H), 3.25 (1 H, multiplet, cyclopropane H), 2.75 (5 H, singlet superimposed on a multiplet, $NCOCH_3$ and cyclopropane CH_2).

Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44. Found: C, 64.86; H, 4.43.

1-Benzamido-2-(4-imidazolyl)cyclopropanecarboxylic acid was obtained by alkaline hydrolysis of the azlactone III. A mixture of 1.35 g (4.6 mmoles) of III and 0.64 g (6 mmoles) of Na_2CO_3 in 10 ml of water was heated on a steam bath until a clear solution resulted (~15 min). The hot solution was treated with activated charcoal (Darco), filtered, and neutralized to pH 5 by dropwise addition of glacial acetic acid. On cooling at 4° for 48 hr and filtering, 0.5 g (40%) of product was obtained. Recrystallization from H_2O and drying *in vacuo* over P_2O_5 gave colorless crystals, mp 263–264°.

Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 61.99; H, 4.83. Found: C, 61.82; H, 4.95.

1-Amino-2-(4-imidazolyl)cyclopropanecarboxylic Acid (I) Dihydrochloride.—A solution of 1.35 g of III in 30 ml of 18% HCl was refluxed for 12 hr. On cooling 0.3 g of benzoic acid (as shown by its infrared spectrum and mixture melting point) separated. This was removed by filtration and the filtrate was extracted with three 50-ml portions of benzene to yield an additional 0.15 g of benzoic acid (total 80%).

The yellow aqueous layer was concentrated to dryness *in vacuo* and the residue dissolved in the minimum amount of warm absolute methanol. The yellow solution was diluted with anhydrous acetone until it became turbid and then allowed to stand at −17° for 48 hr. The nearly colorless crystals were filtered, washed with acetone, and air dried to give 0.6 g (54%) of I. Careful recrystallization from methanol–acetone gave crystals of mp 192° after sintering and softening at 186°; nmr (D_2O), δ (relative to sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard) 8.93 (1 H, singlet, imidazole H), 7.74 (1 H, singlet, imidazole H), 3.30 (1 H, triplet, X portion of ABX system, J_{AX} = J_{BX} = 9 cps, cyclopropane H), 2.23 (2 H, eight-line multiplet, AB portion of ABX system, J_{AB} = 7.5 cps, cyclopropane CH_2).

Anal. Calcd for $C_7H_{11}Cl_2N_3O_2$: C, 35.02; H, 4.62. Found: C, 34.99, 35.10; H, 4.90, 4.75.

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Central Nervous System Depressant Imides of Cyclobutanecarboxylic Acid[1a]

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Our research[2] on those aspects of picrotoxinin's structure which are important to its activity as a competitive antagonist at inhibitory synapses has made necessary the synthesis of various model lactones. Bridged lactones, especially those with a degree of internal strain as is characteristic of picrotin and picrotoxinin, are difficult to synthesize. One recent and reasonably promising route to compounds of the desired type involves the photolytic internal chlorination of N-chloro-N-acetylamides,[3] and N-chloroamides.[4,5] The products of this reaction may be converted to lactones by hydrolysis and cyclization. To test applicability of this scheme to the production of cogent lactones we synthesized the imides reported in Table I. These compounds were prepared by conventional routes which involved either the neat reaction of a suitable amide with excess acetylating agent[6] or acetylation of an amide in pyridine solvent. The former procedure always gave rise to varying quantities of nitrile, and reaction times in excess of 1 hr gave nitrile as major product. Work currently in progress indicates nitrile formation to involve intramolecular elimination by the product imide and not dehydration of the starting amide. The reaction is strongly subject to steric effects and is viewed as involving an enol-type four-centered transition state.

When the first four members of Table I were tested for acute toxicity and general biological activity N-acetylcyclobutanecarboxamide was found to exert an unusual sedative effect. This depressant action was peculiar to the derivative of cyclobutanecarboxylic acid, although several other imides in the series were quite toxic. In view of this apparent selectivity in action the several other imides in Table I were prepared and tested. In addition to **1** those showing central depressant properties were **7** and **10–12**. The only compound derived from cyclobutanecarboxylic acid which did not show the effect was **5**. This substance is also unique in having low toxicity, whereas the other derivatives of cyclopropanecarboxylic acid have LD_{50} values of 250 mg/kg (**8**) and 350 mg/kg (**9**).

The depressant effect produced by these compounds was striking due to the speed with which it developed. Intraperitoneal doses of 300 mg/kg and higher caused loss of the righting reflex in from 30 to 60 sec. Lower doses produced an immediate and marked lowering of spontaneous activity. Preliminary pharmacodynamic data for these substances are given in Table II. The LD_{50} for each of these compounds is so high that doses of 1000 mg/kg produced no deaths although the total period of depression usually exceeded 10 hr.

It is well known that imides are hydrolyzed with ease. In dealing with the biological activity of such compounds it is important to know whether they are serving only as a pro-drug. To test this possibility cyclobutanecarboxamide and cyclobutanecarboxylic acid, the hydrolysis products of dicyclobutanecarboximide, were evaluated for depressant properties. The amide was found to be active. However, even at a dose of 500 mg/kg the loss of spontaneous activity took 10 min to develop. For this reason the rate-limiting step in the response of the rapidly acting compounds is not associated with hydrolysis to the amide.

(1) (a) Supported in part by a research grant (MH 08348) from the National Institutes of Health, U. S. Public Health Service. (b) To whom inquiries should be directed.

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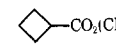
TABLE I
IMIDES OF MONOCARBOXYLIC ACIDS
RCONHCOR'

No.	R	R'	Method	Yield, %	Mp, °C[a]	Crystn[b] solvent	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	CH_3		A	55	88	F	$C_7H_{11}NO_2$	59.56	7.85	59.75	8.04
2	CH_3		A	59	131	F	$C_9H_{15}NO_2$	63.88	8.93	64.16	8.79
3	CH_3		A	40	86	F	$C_8H_{13}NO_2$	61.91	8.44	61.77	8.61
4	CH_3		A	34	77	F	$C_9H_{15}NO_2$	63.88	8.94	63.83	8.94
5			B	34	164	W	$C_9H_{13}NO_2$	64.65	7.83	64.84	7.73
6	$CH_3(CH_2)_2$	C_6H_5	B	69	102	S	$C_{11}H_{13}NO_2$	69.09	6.85	69.00	6.84
7			B	70	173	W	$C_{10}H_{15}NO_2$	66.27	8.34	66.43	8.43
8	CH_3		B	62	110	F	$C_6H_9NO_2$	56.68	7.13	56.75	7.22
9			B	88	215–216	W	$C_8H_{11}NO_2$	62.72	7.24	62.56	7.47
10	$CH_3(CH_2)_2$		B	60	139	H	$C_9H_{15}NO_2$	63.88	8.94	64.17	8.95
11	CH_3CH_2O		B	53	83	H	$C_8H_{13}NO_3$	56.12	7.65	56.38	7.48
12			B	22	90	S	$C_{14}H_{21}NO_4$	62.90	7.92	62.80	7.89

[a] Corrected. [b] F, pentane; W, water; S, heptane; H, hexane.

TABLE II
PRELIMINARY DEPRESSANT POTENCY VALUES

Compd[a]	HD_{50},[b,c] mg/kg	HE_{500},[d] min
1	300	200
7	500	100
10	200	150
11	300	140
12	200	220

[a] Numbers apply to the listing in Table I. [b] All injections were made intraperitoneally using freshly prepared solutions or suspensions in 0.25% methylcellulose sterile vehicle. Test animals were virgin female Swiss Webster Albino mice, 45–59 days old. [c] HD_{50} = the dose producing in 50% of the test population a loss of spontaneous activity for a minimum of 15 min. Spontaneous activity is judged by the time required for the animal to leave a 24-cm filter paper when placed in its center. Environmental test conditions were held constant. [d] HE_{500} = the time in which spontaneous activity was absent when a dose of 500 mg/kg was given. At this dose the righting reflex was lost within 30 sec. Total time for which the righting reflex was lost is approximately 40% of the number listed.

It is, however, easy to rationalize a process involving imide hydrolysis proximate to a site of action—one accessible to the imide but relatively inaccessible to the amide. This picture would permit the amide to be the active entity but only because its precurser participated in the rate-limiting step of the response.

To test chronic toxicity and the possibility that these compounds could activate enzyme systems for their own metabolic degradation N-acetylcyclobutanecarboxamide was administered intraperitoneally at a level of 100 mg/kg for 8 days. At the end of this time a dose of 1000 mg/kg was given. In contrast to other types of centrally acting depressants,[7-9] the duration of effect was the same as with controls.

The compounds listed in Table II have been used as general anesthetics in small animal surgery. They are characterized by smooth induction and rapid attainment of surgical plane anesthesia. There has been no requirement for tracheotomy, or use of curaremimetics or atropine to reduce secretions. Although still in a preliminary phase, our investigations also indicate no cardiac or blood pressure effects.

Experimental Section

Microanalysis for carbon and hydrogen were by Midwest Microlab, Inc., Indianapolis, Ind.

N-Acetylcyclobutanecarboxamide. Method A.—A solution containing 14 g (0.14 mole) of cyclobutanecarboxamide, 11 ml (0.15 mole) of acetic anhydride, and 25 ml (0.03 mole) of acetyl chloride was refluxed for 40 min. The solution was then poured into 100 g of crushed ice, neutralized with 5% $NaHCO_3$ solution, and extracted with three 150-ml fractions of diethyl ether. The ether solution was dried ($NaHCO_3$) and evaporated to dryness. The yield was 11 g (55%), mp 79–84°. Crystallization from pentane gave fine white needles, mp 88°.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.75; H, 8.04.

N-Butyrylcyclobutanecarboxamide. Method B.—A solution was made from 0.75 g (0.009 mole) of butyramide and 5 ml of neutral alumina washed and KOH-dried pyridine and cooled on an ice bath. To the cooled mixture 1 g (0.009 mole) of cyclobutanecarbonyl chloride was added dropwise with stirring. An exothermic reaction ensued and, when it subsided, the mixture was heated on a steam bath for 1 hr. At the end of this time the dark brown solution was poured into 100 g of crushed ice. The product separated as a light tan precipitate to yield 0.9 g (60%), mp 130°. Crystallization from hexane gave fine white needles, mp 139°.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94. Found: C, 64.17; H, 8.95.

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Some 3-Arylaminoquinoxaline-2-carboxylic Acids

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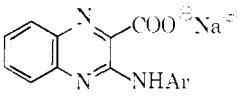
A hypothetical receptor site has been proposed by Scherrer, *et al.*,[1] in an attempt to correlate activity in some N-arylanthranilic acids with other known anti-inflammatory compounds. Important features of the receptor site include a cavity to accommodate an out-of-plane aryl ring and a cationic site 5.2 Å from a good hydrogen-bonding site. The present paper describes some compounds which might possibly fit such a receptor.

The readily available[2] ethyl 3-chloroquinoxaline-2-carboxylate provided a direct route to 3-arylaminoquinoxaline-2-carboxylic acids including some with out-of-plane aryl rings. Displacement of the relatively reactive chloride[3] by substituted anilines followed by hydrolysis produced the compounds shown in Table I. Table II presents ultraviolet absorption data for some of these compounds. As found by Scherrer, *et al.*,[1] for N-arylanthranilic acids, an absorption at 285 ± 5 mμ is present in those structures possessing an in-plane arylamino function. A hypsochromic shift is observed in those structures with out-of-plane arylamino functions (**7**, **11**) or in a 3-alkylamino (**17**) derivative.

When examined in the carrageenin rat foot edema-test of Winter, *et al.*,[4] at an oral dose of 100 mg/kg only **2** and **6** exhibited very weak antiedema activity. The relative lack of solubility of this class of compounds may possibly reduce oral absorption, although this was not specifically investigated.

TABLE I

SODIUM SALTS OF 3-ARYLAMINOQUINOXALINE-2-CARBOXYLIC ACIDS



No.	Ar	Method of prepn[a]	Yield,[b] %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
1	Phenyl	A	97	$C_{15}H_{10}N_3O_2Na$	62.72	3.51	14.63	62.70	3.69	14.63
2	3-Trifluoromethylphenyl	A	83	$C_{16}H_9F_3N_3O_2Na$	54.09	2.55	11.83	53.88	2.62	11.66
3	2,4-Dichlorophenyl	A	94	$C_{15}H_8Cl_2N_3O_2Na$	50.58	2.26	11.80	50.71	2.50	12.07
4	2,3-Dimethylphenyl	A	59	$C_{17}H_{14}N_3O_2Na$	64.80	4.48	13.35	64.97	4.78	13.35
5	3-Chloro-4,6-dimethoxyphenyl	A	95	$C_{17}H_{13}ClN_3O_4Na$	53.48	3.43	11.00	53.19	3.57	11.01
6	3-Chloro-2-methylphenyl	A	18	$C_{16}H_{11}ClN_3O_2Na$	57.30	3.30	12.50	56.99	3.35	12.51
7	2,6-Dimethylphenyl	B	2	$C_{17}H_{14}N_3O_2Na\cdot H_2O$	61.25	4.88	12.60	60.95	4.75	12.58
8	2,3-Dichlorophenyl	C	52	$C_{15}H_8Cl_2N_3O_2Na\cdot H_2O$	48.14	2.67	11.23	48.40	2.71	11.36
9	2-Methylphenyl	B	42	$C_{16}H_{11}N_3O_2Na\cdot 0.5H_2O$	62.10	3.89	13.59	61.92	4.20	13.84
10	2-Methoxyphenyl	A	91	$C_{16}H_{12}N_3O_3Na$	60.56	3.81	13.25	60.34	3.81	13.19
11	1-Naphthyl	C	39	$C_{19}H_{12}N_3O_2Na$	67.69	3.56	12.49	67.42	3.44	12.29
12	3-Nitrophenyl	A	96	$C_{15}H_9N_4O_4Na\cdot H_2O$	51.50	3.16	15.99	51.69	3.24	15.97
13	2-Bromophenyl	C	82	$C_{15}H_9O_2BrN_3Na$	49.20	2.48	11.48	49.45	2.51	11.52
14	4-Chloro-2-methylphenyl	A	16	$C_{16}H_{11}ClN_3O_2Na\cdot 0.5H_2O$	55.70	3.48	12.19	55.55	3.53	12.30
15	3-Methoxyphenyl	A	96	$C_{16}H_{12}N_3O_3Na$	60.56	3.81	13.24	60.30	3.80	13.27
16	4-Chlorophenyl	A	76	$C_{15}H_{10}ClN_3O_2Na$	54.51	3.03	12.72	54.79	3.16	13.03
17	2-Morpholinoethyl	B	45[c]	$C_{15}H_{17}N_4O_3Na$	55.55	5.28	17.28	55.44	5.44	17.44

[a] See Experimental Section. [b] None of these compounds melted below 340°. [c] Recrystallized from acetone, mp 298–300° dec.

TABLE II

ULTRAVIOLET SPECTRA OF 3-ARYLAMINOQUINOXALINE-3-CARBOXYLIC ACID SODIUM SALTS

No.	λ_{max}^{EtOH}, mμ	ε, respectively
1	285, 395	29,300, 6250
2	290, 390	30,700, 6870
3	294, 390	30,400, 7050
4	283, 400	24,000, 5600
5	288, 321, 408	26,800, 19,000, 6050
6	286, 393	25,200, 6150
7	262, 385	25,300, 5250
9	285, 400	25,700, 5830
11	248, 260, 328, 405	21,100, 19,100, 17,000, 6400
12	221, 288, 387	36,000, 31,400, 7050
13	288, 390	27,000, 6500
16	290, 390	27,000, 6060
17	256, 298, 384	30,800, 3300, 5600

Experimental Section

Compounds in Table I were synthesized by one of three methods.

A.—A combination of 0.015 mole of ethyl 3-chloroquinoxaline-2-carboxylate and 0.045 mole of a substituted aniline was heated in an oil bath at 125° in a nitrogen atmosphere for 2 hr. After cooling, 25 ml of ethanol and 25 ml of 10% NaOH were added and

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