

## Derivatives of 2-Aminooxazoles Showing Antiinflammatory Activity

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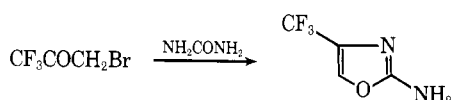
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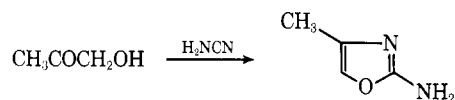
Some amides and ureas derived from 2-aminooxazoles were synthesized and found to be active in reducing carrageenin-induced edema. In general, unsubstituted oxazoles were more active than oxazoles substituted in the 4 and 5 positions. A series of oxazolo[3,2-*a*]-s-triazine-5,7-diones, examples of a new ring system, were also prepared from 2-aminooxazoles, and some of these compounds showed activity in the carrageenin edema test. Structure-activity relationships are discussed, and further biological effects are mentioned in the text.

The search for nonsteroidal antiinflammatory agents has covered a wide range of chemical structures including derivatives of many heterocyclic ring systems.<sup>1</sup> Recently, there have been reports of oxazole derivatives showing antiinflammatory activity,<sup>2,3</sup> and these papers have prompted us to record our own work in this field. During the course of our investigation into the synthesis and properties of 2-aminooxazoles certain amides were prepared for biological screening. Some of these compounds were found to possess activity in the carrageenin-induced edema test, and the work was, therefore, extended to include the synthesis of ureas and also some examples of the novel bicyclic system oxazolo[3,2-*a*]-s-triazine-5,7-dione. Some members of these two series also showed activity in the carrageenin test.

**Chemistry.**—The starting materials for the investigation were 2-aminooxazoles. 2-Aminooxazole<sup>4</sup> and its 4-Ph, 4,5-Ph<sub>2</sub>, and 4,5-Me<sub>2</sub><sup>5</sup> derivatives were prepared by reported procedures. In order to extend the range of possible derivatives, some novel 2-aminooxazoles were also prepared. 2-Amino-4-trifluoromethyloxazole was obtained by the reaction between bromotrifluoroacetone<sup>6</sup> and urea.



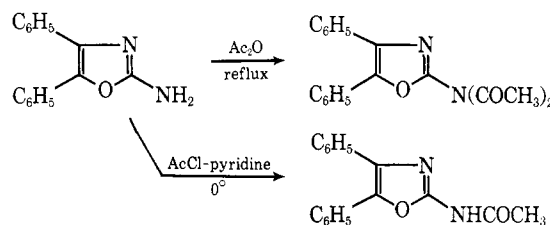
2-Amino-4-ethoxycarbonyloxazole was similarly prepared by treatment of ethyl bromopyruvate with urea. In both of these compounds the NH<sub>2</sub> was weakly basic, especially the CF<sub>3</sub> derivative, whose HCl salt dissociated rapidly when left exposed to the atmosphere. 2-Aminooxazole-4-carboxamide was prepared by treatment of the ethoxycarbonyl compound with NH<sub>4</sub>OH. Attempts to prepare 2-amino-4-hydroxymethyloxazole by reduction of the ethoxycarbonyl compound with LAH under a variety of conditions failed. The oxazole



ring was cleaved by this reagent. 2-Amino-4-methyloxazole was made in high yield by the reaction between

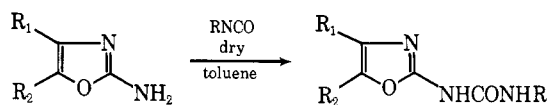
hydroxyacetone and cyanamide. Attempts to prepare this compound from bromoacetone and urea failed.

In order to prepare the acetamides (**1** → **8**) various acetylating procedures were necessary. The more reactive aminooxazoles, the 4-Me and 4,5-Me<sub>2</sub> derivatives were readily acetylated by mixing with excess Ac<sub>2</sub>O. The 4-Ph and 4,5-Ph<sub>2</sub> compounds were acetylated by heating them under reflux with Ac<sub>2</sub>O for 3 hr. The latter compound gave the unexpected diacetyl derivative as the main product. The monoacetyl product was obtained by treating 2-amino-4,5-diphenyloxazole with AcCl in pyridine. The unreactive 2-amino-4-



trifluoromethyloxazole was a more difficult case, and it was necessary to heat the compound with Ac<sub>2</sub>O for 27 hr to obtain the acetamide.

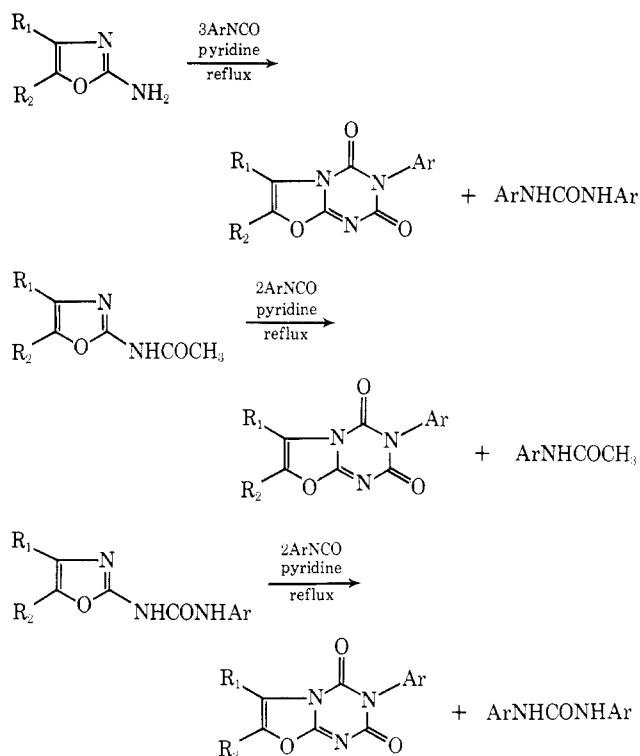
The ureas (**9** → **25**) were all prepared by the reaction of an aminooxazole with an isocyanate in PhMe as solvent. Anhyd reagents were necessary, otherwise symmetrical ureas were formed as by-products by hydrolysis of the isocyanate. These symmetrical ureas, if formed, proved to be very difficult to separate from the desired oxazole ureas.



When 2-aminooxazoles are heated under reflux with 3 moles of an aryl isocyanate in pyridine, oxazolo[3,2-*a*]-s-triazine-5,7-diones are formed. This reaction is similar to that reported for 2-aminothiazoles.<sup>7</sup> The bicyclic system can also be formed by treatment of the oxazole acetamide or the oxazole urea with 2 moles of an isocyanate under the same reaction conditions. Use of the oxazole acetamide as starting material is preferable, as the by-products formed in this reaction are acetanilides. The other 2 methods give symmetrical ureas as by-products, and these can be difficult to separate from the products. This reaction does not work with alkyl isocyanates. The chemistry of the oxazolo[3,2-*a*]-s-triazine-5,7-dione system was not thoroughly investigated, but some preliminary experiments indicated that it was

- (1) G. P. Ellis and G. B. West, *Progr. Med. Chem.*, **5**, 59 (1967).
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- (3) E. Marchetti, G. Mattalia, and V. Rosnati, *J. Med. Chem.*, **11**, 1092 (1968).
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- (6) E. T. McBee and T. M. Burton, *J. Amer. Chem. Soc.*, **74**, 3902 (1952).

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fairly stable to acid and base, but was fragmented when hydrogenated (H<sub>2</sub>/Pt).

**Biological Results.**—The LD<sub>50</sub>'s and antiinflammatory effects of the compounds are listed in Table I. The amides (**1** → **7**) showed reasonable activity in the carrageenin test,<sup>8</sup> but no clear structure-activity relationship emerged. Compds **2** and **3**, chosen as representatives of this class, were tested against adjuvant-induced arthritis,<sup>9</sup> but gave poor results in this test. Most of the amides caused weak to moderate CNS depression in mice when high doses were given. Compds **3** and **6** were effective at 50 mg/kg orally. The ureas derived from 2-aminooxazole (**9** → **19**) were more active in the carrageenin test than the ureas from 2-amino-4,5-diphenyloxazole (**20**, **21**, **22**) or 2-amino-4,5-dimethyloxazole (**23**, **24**, **25**). Compds **9** and **13** were further tested against adjuvant-induced arthritis, **9** was inactive in this test but **13**, in an oral dose of 50 mg/kg daily for 16 days, improved the mobility of the joints. Most of the ureas produced CNS depression at subtoxic doses in mice. Sedation and analgesia were noted for some of the compounds (*e.g.*, **23**).

The only bicyclic compounds showing appreciable activity in the carrageenin test were **28** and **29**, in which the 3 and 4 position of the ring system were unsubstituted. The corresponding 3,4-diphenyl derivatives **33** and **34** were inactive. Compds **28** and **29** were tested against adjuvant-induced arthritis, **29** was inactive but **28** gave a considerably moderated swelling in both primary and secondary phases of the reaction. None of the bicyclic compounds exhibited significant CNS effects.

(8) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962). The suppression of carrageenin edema by reference drugs varies in different experiments, but in the present study, the effect produced by phenylbutazone was: 2 × 100 mg/kg, 50–65%; 2 × 50 mg/kg, 35–50%; 2 × 25 mg/kg, 25–35%.

(9) B. B. Newbould, *Brit. J. Pharmacol.*, **21**, 127 (1963).

## Experimental Section<sup>10</sup>

**Synthesis of Some Novel 2-Aminooxazoles. 2-Amino-4-methyloxazole.**—A mixture of cyanamide (21 g, 0.5 mole) and hydroxyacetone (37 g, 0.5 mole) in H<sub>2</sub>O (80 ml) was warmed gently to 40°, when a vigorous reaction began. The temp of the reaction was kept between 40 and 50° by cooling. The reaction was complete after about 3 min, the soln was then cooled to 20°, and its pH was adjusted to 10 by addn of aq NaOH. The mixt was extd with Et<sub>2</sub>O (5 × 80 ml) and, after removal of the solvent, the residue was distd *in vacuo* to give a colorless oil; yield 31.9 g (65%); bp 79–81° (2 mm); *n*<sub>D</sub><sup>25</sup> 1.498. *Anal.* (C<sub>4</sub>H<sub>6</sub>N<sub>2</sub>O) C, H, N.

**2-Amino-4-trifluoromethyloxazole.**—Bromotrifluoroacetone<sup>6</sup> (21.9 g, 0.12 mole) and urea (28.8 g, 0.48 mole) were dissolved in *tert*-BuOH (250 ml) and the soln was heated under reflux for 8 hr. After cooling, the solvent was evapd, leaving a solid mass. Extn with hot petr ether (5 × 100 ml) and evapn of the exts gave a white solid; yield 13.7 g (79%); mp 100–102°. *Anal.* (C<sub>4</sub>H<sub>3</sub>F<sub>3</sub>N<sub>2</sub>O) C, H, N, F.

**2-Amino-4-ethoxycarbonyloxazole·HCl.**—Ethyl bromopyruvate (59.7 g, 0.306 mole) and urea (27.6 g, 0.46 mole) in EtOH (220 ml) were heated under reflux for 24 hr. The mixt was evapd to give an oil. H<sub>2</sub>O (20 ml) was added and the pH of the mixt adjusted to 10 by the addn of aq NaOH. The mixt was extd with Et<sub>2</sub>O (4 × 100 ml), and the ext was treated with ethereal HCl. The white ppt was collected by filtration; yield 15.4 g (26%); mp 133–135°. *Anal.* (C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>·HCl) C, N; H: calcd, 4.7; found, 5.2.

**2-Aminooxazole-4-carboxamide.**—2-Amino-4-ethoxycarbonyloxazole·HCl (2.5 g, 0.013 mole) was dissolved in a mixt of EtOH (20 ml) and NH<sub>4</sub>OH (50 ml, sp gr 0.88). The mixt was left for 6 days at 20° after which it was coned to dryness. The solid was recrystd twice from aq EtOH; yield 1.2 g (73%); mp 210–220° dec. *Anal.* (C<sub>4</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>) C, H, N.

**Synthesis of Compounds in Table I. A. 2-Acetamido-4-methyloxazole (1).**—2-Amino-4-methyloxazole (14.7 g, 0.15 mole) was dissolved in Ac<sub>2</sub>O (20 ml) at 25°. The temp quickly rose to 75° and the mixt was then left at lab temp for 3 hr. Evapn of the solvent *in vacuo* gave an oil which rapidly crystd. Recrystn from EtOAc gave 15.1 g (72%) of pure **1**; mp 127–128°.

**B. 2-Acetamido-4-phenyloxazole (3).**—2-Amino-4-phenyloxazole (2.3 g, 0.0144 mole) was dissolved in Ac<sub>2</sub>O (50 ml), and the mixt was heated under reflux for 3 hr. Removal of Ac<sub>2</sub>O by evapn gave the product, which was recrystd twice from CCl<sub>4</sub>; yield 2.08 g (67%); mp 113–114°.

**C. 2-Acetamido-4,5-diphenyloxazole (4).**—2-Amino-4,5-diphenyloxazole (23.6 g, 0.1 mole) was dissolved in a mixt of pyridine (200 ml) and Me<sub>2</sub>CO (100 ml). After cooling to 0°, AcCl (8.65 g, 0.11 mole) was added. The mixt was stirred for 4 hr, after which time the temp rose to 25°, and then poured onto ice. Extn with EtOAc (100 ml) and concn of the org layer gave the crude prod as a white solid. Crystn from CHCl<sub>3</sub> gave 12.5 g (45%) of white crystals; mp 178–180°.

**D. 2-Acetamido-4-trifluoromethyloxazole (6).**—2-Amino-4-trifluoromethyloxazole (2.5 g, 0.0164 mole) was dissolved in Ac<sub>2</sub>O (50 ml), the mixt was kept at 100° for 24 hr and then heated under reflux for 4 hr. Evapn of the Ac<sub>2</sub>O *in vacuo* gave an oil which crystd when triturated with light petr ether (1 ml). Recrystn from CHCl<sub>3</sub>–petrol gave pure **6** as white crystals; yield 1.0 g (31%); mp 123°.

**E. 2-Acetamido-4-ethoxycarbonyloxazole (7).**—2-Amino-4-ethoxycarbonyloxazole·HCl (11.75 g, 0.061 mole) was dissolved in pyridine (50 ml), and Ac<sub>2</sub>O (30 ml) was added. The mixt was left at 20° for 3 days and then coned *in vacuo*. The solid remaining was recrystd from EtOAc; yield 7.0 g (58%), white crystals; mp 150–152°.

**F. 2-Acetamidooxazole-4-carboxamide (8).**—2-Acetamido-4-ethoxycarbonyloxazole (3.0 g, 0.015 mole) was dissolved in NH<sub>4</sub>OH (20 ml, sp gr 0.88). After about 15 min, a white crystalline ppt formed and this was collected after cooling the reaction mixt to 0° for a few min; yield 1.2 g (47%); mp 212–222° dec.

**G. 1-Ethyl-3-(2-oxazolyl)urea (9).**—2-Aminooxazole (3.36 g, 0.04 mole) and ethyl isocyanate (2.84 g, 0.04 mole) were heated

(10) Where analyses are indicated only by symbols of the elements, anal. results obt'd for these elements were within ±0.4% of the theor values. The structures of all novel compounds were confirmed by ir and nmr spectroscopy. Melting points are uncorrected and were measured on a Kofler microscope hot stage.

TABLE I

No.	R <sub>1</sub>	R <sub>2</sub>	R	Method	Yield, %	Mp, °C	Formula	Analyses	LD <sub>50</sub> <sup>a</sup>		Reduction <sup>b</sup> of edema
									po	ip	
Amides											
1	CH <sub>3</sub>	H	H	A	72	127-128	C <sub>6</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	1600	>800	30
2	CH <sub>3</sub>	CH <sub>3</sub>	H	A	50	128-129	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	1600	800	66
3	C <sub>6</sub> H <sub>5</sub>	H	H	B	67	113-114	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	800	500	42
4	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	C	45	178-180	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	1000	800	6
5	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	COCH <sub>3</sub>	B	25	82-84	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	C, H, N	1600	400	21
6	CF <sub>3</sub>	H	H	D	31	123	C <sub>6</sub> H <sub>5</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N	400	400	69
7	COOC <sub>2</sub> H <sub>5</sub>	H	H	E	58	150-152	C <sub>8</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	>1600	>800	22
8	CONH <sub>2</sub>	H	H	F	47	212-222	C <sub>6</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	>1600	>800	0
Ureas											
9	H	H	C <sub>2</sub> H <sub>5</sub>	G	59	163-165	C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	400	300	44†
10	H	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	G	35	145-146	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	800	300	27
11	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	G	37	139-140	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	800	600	0
12	H	H	C <sub>4</sub> H <sub>9</sub>	G	66	130-131	C <sub>8</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	500	250	30†
13	H	H	C <sub>6</sub> H <sub>5</sub>	G	30	163-165	C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	500	250	48†
14	H	H	2-ClC <sub>6</sub> H <sub>4</sub>	G	69	170-172	C <sub>10</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N	>1600	400	30
15	H	H	3-ClC <sub>6</sub> H <sub>4</sub>	G	53	162-163	C <sub>10</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N, Cl	1000	400	54
16	H	H	4-ClC <sub>6</sub> H <sub>4</sub>	G	46	169-170	C <sub>10</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N, Cl	>1600	300	38
17	H	H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	G	29	238	C <sub>10</sub> H <sub>8</sub> N <sub>4</sub> O <sub>4</sub>	C, H, N	>1600	>800	0
18	H	H	2-MeC <sub>6</sub> H <sub>4</sub>	G	58	165-166	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	1000	300	13
19	H	H	1-Naphthyl	G	65	257-259	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	>1600	>800	0
20	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	G	25	181-182	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	>1600	>800	0
21	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	G	72	211-213	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N	>1600	>800	26
22	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	3-ClC <sub>6</sub> H <sub>4</sub>	G	63	205-207	C <sub>22</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N, Cl	>1600	>800	9
23	CH <sub>3</sub>	CH <sub>3</sub>	2-ClC <sub>6</sub> H <sub>4</sub>	G	29	167-168	C <sub>12</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub>	H, N, Cl; C <sup>c</sup>	>1600	>800	3
24	CH <sub>3</sub>	CH <sub>3</sub>	3-ClC <sub>6</sub> H <sub>4</sub>	G	20	164-165	C <sub>12</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N, Cl	>1600	>800	18
25	CH <sub>3</sub>	CH <sub>3</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	G	27	190-191	C <sub>12</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub>	C, H, N, Cl	>1600	>800	17
Oxazolo[3,2-a]-s-triazine-5,7-diones											
26	H	H	C <sub>6</sub> H <sub>5</sub>	H	87	240-242	C <sub>11</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	>1600	>800	16
27	H	H	2-ClC <sub>6</sub> H <sub>4</sub>	I	32	177-178	C <sub>11</sub> H <sub>6</sub> ClN <sub>3</sub> O <sub>3</sub>	C, H, N	1000	800	0
28	H	H	3-ClC <sub>6</sub> H <sub>4</sub>	I	46	206-208	C <sub>11</sub> H <sub>6</sub> ClN <sub>3</sub> O <sub>3</sub>	C, H, N, Cl	1600	>800	48
29	H	H	4-ClC <sub>6</sub> H <sub>4</sub>	I	44	235-237	C <sub>11</sub> H <sub>6</sub> ClN <sub>3</sub> O <sub>3</sub>	C, H, N, Cl	>1600	>800	38
30	H	H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	I	49	238-242	C <sub>11</sub> H <sub>6</sub> N <sub>4</sub> O <sub>5</sub>	C, H, N	>1600	>800	0
31	H	H	1-Naphthyl	I	42	252-253	C <sub>15</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	C, H, N	>1600	>800	0
32	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	2-ClC <sub>6</sub> H <sub>4</sub>	I	38	245-246	C <sub>23</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub>	C, N; H <sup>d</sup>	>1600	>800	0
33	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	3-ClC <sub>6</sub> H <sub>4</sub>	I	25	228-230	C <sub>23</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub>	C, H, N, Cl	>1600	>800	14
34	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	I	43	224-225	C <sub>23</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub>	C, H, N	>1600	>800	0
35	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	I	75	243-245	C <sub>23</sub> H <sub>14</sub> N <sub>4</sub> O <sub>5</sub>	C, H, N	>1600	>800	0

<sup>a</sup> The approximate LD<sub>50</sub> by both oral and ip routes was determined in mice and expressed as mg/kg. <sup>b</sup> The drug was administered orally in 1 ml of 0.5% carboxymethylcellulose, one dose at 3 hr and one dose at 0.5 hr prior to the subcutaneous injection of carrageenin. In those cases marked by a dagger doses were 2 × 50 mg/kg, in all other cases, 2 × 100 mg/kg. The vol of the feet was measured 2.5 hr after the carrageenin injection and the response expressed as the per cent by which the swelling in the treated animals differed from the controls. <sup>c</sup> C: calcd, 54.25; found, 53.75. <sup>d</sup> H: calcd, 3.40; found, 3.82.

under reflux in PhMe (30 ml) for 2 hr. The mixt was treated with charcoal and concd to give a white solid which was purified by recrystn from PhMe; yield 3.66 g (59%); mp 163-165°.

**H. 6-Phenyloxazolo[3,2-a]-s-triazine-5,7-dione (26).**—2-Aminooxazole (1.68 g, 0.02 mole) and phenyl isocyanate (8.4 g, 0.07 mole) were heated under reflux in pyridine (12 ml) for 6 hr. Evapn *in vacuo* gave a brown solid which was dissolved in EtOH (300 ml) and treated with charcoal. The soln was concd to 100 ml and cooled. The pptd crystals were collected by filtration and recrystd from EtOH; yield 4.0 g (87%); mp 240-242°.

**I. 6-(*m*-Chlorophenyl)oxazolo[3,2-a]-s-triazine-5,7-dione (28).**—2-Acetamidooxazole (3.78 g, 0.03 mole) and *m*-chlorophenyl

isocyanate (9.2 g, 0.06 mole) were heated under reflux in pyridine (15 ml) for 6 hr. Evaporation *in vacuo* gave a dark brown solid which was recrystd twice from EtOH; yield 3.6 g (46%) of white crystals; mp 206-208°.

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