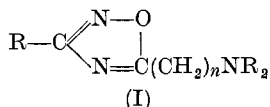


**1,2,4-Oxadiazoles—IV.\***  
**Synthesis and Pharmacological Properties of a**  
**Series of Substituted Aminoalkyl-1,2,4-oxadiazoles**

G. PALAZZO, M. TAVELLA, G. STRANI and B. SILVESTRI,  
*Laboratorio Ricerche, Angelini Francesco, Rome*

Although the pharmacological literature mentions some examples of 1,3,4-oxadiazoles, we are not aware that substances containing the 1,2,4-oxadiazole nucleus have ever been examined pharmacologically. In a paper by Bergmann<sup>1</sup> the chemotherapeutic activities of a few 1,2,4-oxadiazoles have been studied but no pharmacodynamic activities have been taken into account. We therefore considered it of interest to synthesize a homologous series of 1,2,4-oxadiazole derivatives (I) containing basic chains in position 5 (such as those present in many pharmacologically active substances), and various types of substituents, mainly aryl groups in position 3.

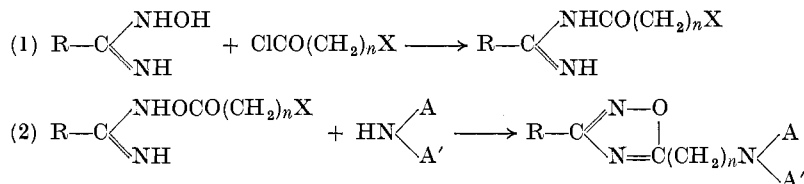


R = aryl or arylalkyl.  
 n = 1,2,3,4.  
 NR<sub>2</sub> = substituted amino group.

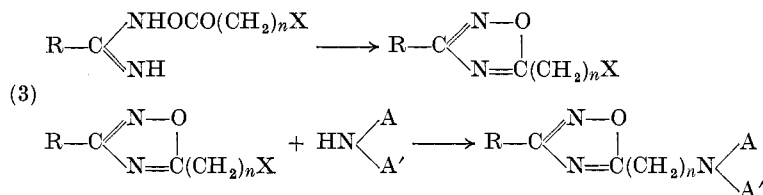
For the synthesis of these substances we followed essentially Tiemann's method,<sup>2</sup> starting from amidoximes and suitably substituted acid chlorides. The reaction between an amidoxime and an  $\omega$ -dialkylaminoacyl chloride leads directly to substances having the general formula (I). We carried it out only in a single instance, however, [R = C<sub>6</sub>H<sub>5</sub>, n = 1, NR<sub>2</sub> = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>] on account of the cumbersome preparation of aminoacyl chlorides and of the rather low yield of the reaction. It was convenient to prepare the  $\omega$ -halogenoacylamidoximes first, and subsequently to obtain

\* Part III. Tavella, M. and Strani, G., *Ann. Chim., Roma*, **51**, 361 (1961).

from the latter the basic 1,2,4-oxadiazoles through the action of the secondary amines.



In many instances we preferred to divide the second step (2) into two reactions, namely a cyclization of the halogenoacylamidoxime into the halogenoalkyloxadiazole and a subsequent substitution of halogen by various amino groups:

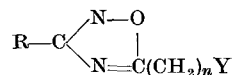


This procedure is not advisable, however, when  $n = 2$ , because the ring closure of the  $\beta$ -chloropropionylamidoximes furnishes a very low yield of  $\beta$ -chloroethyloxadiazoles, whereas the direct treatment with amines, if carried out under suitable conditions, gives very good results. The mixed tertiary amines with an *N*-methyl group were prepared by the general reaction methods (2) or (3), as well as by first synthesizing the secondary amines according to method (3) ( $\text{A} = \text{H}$ ), and subsequently methylating these derivatives with formic acid and formaldehyde. This method is decidedly the most convenient, and eliminates the tiresome preparation of the required secondary amines  $\text{HNAA}'$ , ( $\text{A} = \text{CH}_3$ ).

### Pharmacology

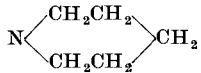
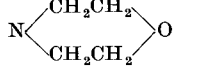
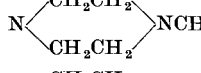
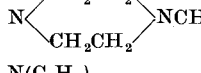
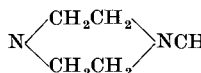
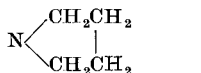
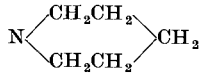
All the basic oxadiazoles listed in Table I have been submitted to a thorough pharmacological screening, generally as hydrochlorides, though sometimes as maleates, citrates or tartrates. In this article only an outline of the different types of activities exhibited by the principal members of the series will be listed.

Table I. General Formula



Compound no.	R	Y	<i>n</i>	m.p., °C	b.p., °C/mm	HCl salt m.p., °C	Analysis, %	
							Calcd.	Found
1	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NH <sub>2</sub>	1	49		198-199	23.99	N 24.28
2	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NHCH <sub>3</sub>	1		120/0.6	221-222	15.71	Cl <sup>-</sup> 15.82
3	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NHC <sub>2</sub> H <sub>5</sub>	1		149/3	200-202	14.79	Cl <sup>-</sup> 14.76
4	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	N(CH <sub>3</sub> ) <sub>2</sub>	1		121/0.2	228-230	14.79	Cl <sup>-</sup> 14.79
5	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NHC <sub>3</sub> H <sub>7</sub>	1		126/0.6	181	13.97	Cl <sup>-</sup> 14.05
6	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NH- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	1		138/1.5	201-202	13.97	Cl <sup>-</sup> 14.00
7	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> NC <sub>2</sub> H <sub>5</sub>	1		114/0.6	173-174	13.97	Cl <sup>-</sup> 13.99
8	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		115/0.05	166-168	13.24	Cl <sup>-</sup> 13.15
9	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NHC <sub>4</sub> H <sub>9</sub>	1		142-3/1	195-196	13.24	Cl <sup>-</sup> 13.24
10	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NH- <i>i</i> -C <sub>4</sub> H <sub>9</sub>	1		122/0.1	193	13.24	Cl <sup>-</sup> 13.26
11	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	NH- <i>t</i> -C <sub>4</sub> H <sub>9</sub>	1	48-50		237-238	13.24	Cl <sup>-</sup> 13.06
12	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> NC <sub>3</sub> H <sub>7</sub>	1		127/0.5	128	13.24	Cl <sup>-</sup> 13.27
13	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> N- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	1		114/0.3	192-193	13.24	Cl <sup>-</sup> 13.12
14	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> NC <sub>4</sub> H <sub>9</sub>	1		121/0.2	139-140	12.58	Cl <sup>-</sup> 12.55
15	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> N- <i>i</i> -C <sub>4</sub> H <sub>9</sub>	1		117/0.2	165	12.58	Cl <sup>-</sup> 12.73
16	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	N(C <sub>3</sub> H <sub>7</sub> ) <sub>2</sub>	1		126/0.2	171-172	11.99	Cl <sup>-</sup> 12.01
17	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> NCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1		173/0.3	165	11.23	Cl <sup>-</sup> 11.24
18	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>	$\text{N} \begin{cases} \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{cases}$	1		128/0.1	201-203	12.58	Cl <sup>-</sup> 12.49

Table I—continued

Compound no.	R	Y	n	m.p., °C	b.p., °C/mm	HCl salt m.p., °C	Analysis, %	
							Calcd.	Found
19	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>		1		153/0·7	248–249	12·68	Cl <sup>-</sup> 12·70
20	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>		1		160/0·1	213–215	12·58	Cl <sup>-</sup> 12·61
21	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>		1		155/0·3	238–240	21·41	Cl <sup>-</sup> 21·46
22	C <sub>6</sub> H <sub>5</sub> <sup>-</sup>		1			244–245	19·63	Cl <sup>-</sup> 19·39
23	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		144/0·8	152	23·47	Cl <sup>-</sup> 23·15
24	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1			209–210	17·92	Cl <sup>-</sup> 18·04
25	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		132/0·4	213–214	11·73	Cl <sup>-</sup> 11·76
26	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		137/0·8	180	11·73	Cl <sup>-</sup> 11·81
27	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1		141/0·3	235–236	11·81	Cl <sup>-</sup> 11·85
28	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		142/0·3	171	10·23	Cl <sup>-</sup> 10·12
29	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1		173/0·4	200–201	9·88	Cl <sup>-</sup> 10·04
30	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		135/1	161	12·59	Cl <sup>-</sup> 12·65

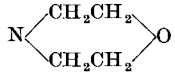
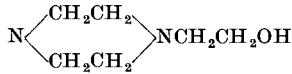
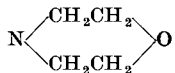
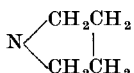
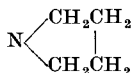
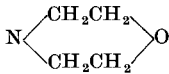
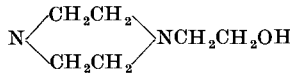
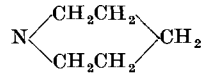
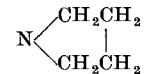
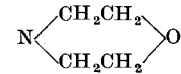
31	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1	140/0·3	173	64·34 7·33	C H	64·09 7·25
32	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	CH <sub>3</sub> N- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	1	170/2	188-189	11·91	Cl <sup>-</sup>	12·18
33	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	NH- <i>i</i> -C <sub>4</sub> H <sub>9</sub>	1	157/0·3	168-169	11·91	Cl <sup>-</sup>	11·96
34	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	CH <sub>3</sub> NC <sub>4</sub> H <sub>9</sub>	1	157/0·5	143-144	11·37	Cl <sup>-</sup>	11·34
35	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1	80-81	224-226	61·08 6·22	C H	60·97 6·14
36	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1		225-227	18·12	Cl <sup>-</sup>	18·30
37	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1	68-69	212	11·34	Cl <sup>-</sup>	11·60
38	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>		1	143		19·30	N	19·15
39	<i>o</i> -OHC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		184	12·50	Cl <sup>-</sup>	12·52
40	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> <sup>-</sup>		1	192/1·5	235-236	10·88	Cl <sup>-</sup>	10·94
41	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1	187/1·5	202-203	10·82	Cl <sup>-</sup>	11·07
42	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		175	9·91	Cl <sup>-</sup>	9·85
43	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> <sup>-</sup>		1		178-179	9·96	Cl <sup>-</sup>	10·03
44	<i>p</i> -H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1		216-217	10·22	Cl <sup>-</sup>	10·34
45	<i>p</i> -H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	NHC <sub>4</sub> H <sub>9</sub>	1		245	10·23	Cl <sup>-</sup>	10·10
46	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	N(CH <sub>3</sub> ) <sub>2</sub>	1	110/0·2	150	13·97	Cl <sup>-</sup>	14·02
47	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1	132/1	115-116	12·58	Cl <sup>-</sup>	12·65
48	C <sub>6</sub> H <sub>5</sub> CH <sup>-</sup>   C <sub>2</sub> H <sub>5</sub>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1	132/0·7	101-103	11·44	Cl <sup>-</sup>	11·36

Table I—continued

Compound no.	R	Y	n	m.p., °C	b.p., °C/mm	HCl salt m.p., °C	Analysis, %		
							Calcd.	Found	
49	$\text{C}_6\text{H}_5\text{CH}-$   $\text{C}_2\text{H}_5$		1		162/0·6	179-180	10·95	Cl-	11·12
50	$\text{C}_6\text{H}_5\text{CH}-$   $\text{C}_2\text{H}_5$		1			183-185	17·58	Cl-	17·86
51	$1-\text{C}_{10}\text{H}_{11}-$ (1-tetrahydronaphthyl)	$\text{N}(\text{C}_2\text{H}_5)_2$	1		155/0·1	144	11·02	Cl-	11·05
52	$1-\text{C}_{10}\text{H}_{11}-$		1		169/0·1	186	10·62	Cl-	10·82
53	$p-\text{C}_6\text{H}_5\text{C}_6\text{H}_4-$	$\text{N}(\text{C}_2\text{H}_5)_2$	1			196-197	10·31	Cl-	10·26
54	$p-\text{C}_6\text{H}_5\text{C}_6\text{H}_4-$	$\text{NHC}_4\text{H}_9$	1			226	10·31	Cl-	10·53
55	$\text{C}_5\text{H}_4\text{N}-$ ( $\alpha$ -Pyridyl)	$\text{N}(\text{C}_2\text{H}_5)_2$	1			190	23·23	Cl-	23·30
56	$\text{C}_6\text{H}_5-$	$\text{N}(\text{CH}_3)_2$	2			160-161	13·97	Cl-	13·97
57	$\text{C}_6\text{H}_5-$	$\text{N}(\text{C}_2\text{H}_5)_2$	2		130/0·5	153-154	68·54 7·81	C H	68·23 7·97
58	$\text{C}_6\text{H}_5-$		2			173-174	12·65	Cl-	12·81
59	$\text{C}_6\text{H}_5-$		2			190-192	11·99	Cl-	12·25

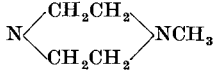
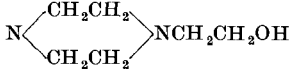
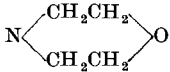
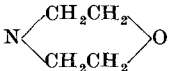
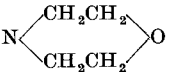
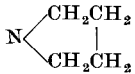
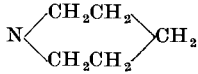
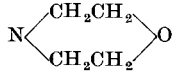
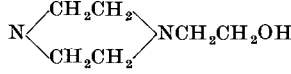
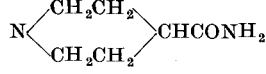
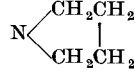
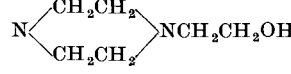
60	$C_6H_5^-$		2		194-196	20·54	Cl <sup>-</sup>	20·50
61	$C_6H_5^-$		2		192-194	18·90	Cl <sup>-</sup>	19·10
62	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		131-132	22·43	Cl <sup>-</sup>	22·65
63	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		159-161	11·21	Cl <sup>-</sup>	11·04
64	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		2		158-159	10·74	Cl <sup>-</sup>	11·07
65	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		167-168	11·99	Cl <sup>-</sup>	12·08
66	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>		2		200	11·45	Cl <sup>-</sup>	11·55
67	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(CH <sub>3</sub> ) <sub>2</sub>	2		183-184	12·50	Cl <sup>-</sup>	12·26
68	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	CH <sub>3</sub> N- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	2		162	11·37	Cl <sup>-</sup>	11·29
69	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2	148/0·1	161-162	11·37	Cl <sup>-</sup>	11·38
70	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>		2		213-214	10·88	Cl <sup>-</sup>	10·70
71	<i>p</i> -C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		178-179	10·88	Cl <sup>-</sup>	10·92
72	<i>p</i> -C <sub>4</sub> H <sub>9</sub> OC <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		163-164	10·31	Cl <sup>-</sup>	10·32
73	3,4-(CH <sub>2</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		179-180	10·37	Cl <sup>-</sup>	10·52
74	3,4,5-(CH <sub>2</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		165-166	9·53	Cl <sup>-</sup>	9·57
75	<i>p</i> -H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> <sup>-</sup>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		162-163	9·83	Cl <sup>-</sup>	9·98
76	$C_6H_5CH^-$   C <sub>2</sub> H <sub>5</sub>	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2	132/0·2		8·76	N	8·80
77	2-C <sub>10</sub> H <sub>7</sub> <sup>-</sup> (2-naphthyl)	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2		196-198	10·69	Cl <sup>-</sup>	10·94

Table I—continued

Compound no.	R	Y	n	m.p. °C	b.p. °C/mm	HCl salt m.p. °C	Analysis, %		
							Calcd.		Found
78	<i>p</i> -C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub> -	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	2			206-207	9.90	Cl-	9.86
79	C <sub>6</sub> H <sub>5</sub> -	NH- <i>i</i> -C <sub>4</sub> H <sub>9</sub>	3			162	12.27	Cl-	12.14
80	C <sub>6</sub> H <sub>5</sub> -	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	3		136/0.1	130	69.36	C	69.39
							8.01	H	8.36
81	C <sub>6</sub> H <sub>5</sub> -		3		152/0.6	140-141	11.45	Cl-	11.65
82	C <sub>6</sub> H <sub>5</sub> -		3		152/0.1	162	70.82	C	70.86
							7.80	H	7.79
83	C <sub>6</sub> H <sub>5</sub> -		3		163/0.1	194	65.91	C	65.76
							7.01	H	6.86
84	C <sub>6</sub> H <sub>5</sub> -		3			224-225	18.21	Cl-	18.01
85	C <sub>6</sub> H <sub>5</sub> -		3	130		180-181	10.11	Cl-	10.01
86	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> -	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	3		149/0.3	120	10.74	Cl-	10.75
87	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> -		3		164/0.8	126-127	10.80	Cl-	10.88
88	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> -		3			205-206	16.73	Cl-	16.42



89	$p\text{-ClC}_6\text{H}_4^-$	$\text{N}(\text{C}_2\text{H}_5)_2$	3	142/0.2	192	10.73	$\text{Cl}^-$	10.91
90	$p\text{-ClC}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array}$	3	160/0.3	188-189	10.80	$\text{Cl}^-$	10.48
91	$p\text{-ClC}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array} \text{O}$	3	170/0.3	202-204	10.30	$\text{Cl}^-$	10.01
92	$p\text{-ClC}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array} \text{NCH}_3$	3	37-9 180/0.4	252-254	11.05	$\text{Cl}^-$	11.07
93	$p\text{-CH}_3\text{OC}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array} \text{CHCONH}_2$	3	160	178-179	16.27	N	16.12
94	$p\text{-CH}_3\text{OC}_6\text{H}_4^-$	$\text{N}(\text{CH}_3)_2$	3	160/0.4	217	11.91	$\text{Cl}^-$	12.11
95	$p\text{-CH}_3\text{OC}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array}$	3	188/0.7	169	10.95	$\text{Cl}^-$	10.91
96	$3,4,5\text{-(CH}_3\text{O)}_3\text{C}_6\text{H}_2^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array} \text{O}$	3	218/0.3	186-187	8.86	$\text{Cl}^-$	8.69
97	$\text{C}_{10}\text{H}_7^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array}$	3		116-117	10.31	$\text{Cl}^-$	10.28
98	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4^-$	$\text{N}(\text{CH}_3)_2$	3		209-210	10.31	$\text{Cl}^-$	10.25
99	$p\text{-C}_6\text{H}_5\text{C}_6\text{H}_4^-$	$\text{N} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\   \\ \text{CH}_2\text{CH}_2 \end{array} \text{NCH}_2\text{CH}_2\text{OH}$	3		258	15.24	$\text{Cl}^-$	15.36
100	$\text{C}_6\text{H}_5^-$	$\text{N}(\text{C}_2\text{H}_5)_2$	4	145/0.4	117-118	11.44	$\text{Cl}^-$	11.56

The activities vary widely from one product to the other, both qualitatively and quantitatively. Their overall pharmacological picture makes it difficult to establish a decided relationship between chemical structure and biological activity. It is nevertheless interesting to point out that the most active products are characterized by the presence of an amino nitrogen bound to groups containing four carbon atoms (diethylamino, butylamino, pyrrolidino and methylpropylamino).

*Non-specific antispasmodic activity* was studied in segments of guinea pig small intestine suspended in oxygenated Tyrode liquid at 37° and stimulated by acetylcholine, histamine, dimethylphenylpiperazinium iodide and barium chloride. This activity was also confirmed by measuring the coronary flow in an isolated cat heart. The *antitussive action* was determined in the guinea pig by means of electrical stimulation of the upper laryngeal nerve<sup>3</sup> and the inhalation of acrolein.<sup>4</sup> For the study of the *analgesic anti-inflammatory action*, Randall and Selitto's method was used in the rat and phenylquinone tests were carried out in mice.<sup>5, 6</sup>

The method of Randall *et al.*<sup>7</sup> was used in determining the *anti-inflammatory action*. The most active products were submitted to the test of Meier *et al.* in a non-adrenalectomized animal.<sup>8</sup>

*Local-anaesthetic action* was determined, utilizing the corneal reflex in the rabbit to establish the least concentration that would inhibit the response caused by touching the cornea with an animal hair ten consecutive times.

The effects on behaviour were studied under the experimental conditions described by Irwin.<sup>9</sup>

Table II contains data relating to 13 products chosen among the most active in this series. It can be seen that some pharmacological actions are very pronounced. Compounds 8, 9 and 69 are more active than aspirin as anti-inflammatory analgesics; on the other hand they are utterly devoid of morphine-like analgesic properties. No sharp parallel may be drawn between analgesic anti-inflammatory and anti-inflammatory activity. Thus, the most active anti-inflammatory product, compound 82, is completely devoid of analgesic anti-inflammatory action. These data could be explained on the basis of a lack of sensitivity of the technique employed in evaluating anti-inflammatory action. It

Table II

Compound no.	LD <sub>50</sub> , mg/kg i.p.	Antispasmodic activity, µg/ml	Antitussive activity		Analgesic anti-inflammatory activity mg/kg, s.c.	Anti-inflammatory activity, mg/kg, s.c.	Local anaesthetic activity, %	Screening on mice, mg/kg i.p.
			Laryngeal nerve stim., mg/kg i.v.	Acrolein inhalation, mg/kg, s.c.				
8	445 (361-550)	10	10	4	10	40	0.25	100, sedation 300, hypotonia
9	687 (557-848)	> 10	> 10	> 2	10	> 40	> 1.5	400, convulsions
13	280	7			> 20		> 1.5	70, convulsions
51	430 (327-593)	5		> 2	50		0.5	100, sedation 400, paralysis
52	572 (441-743)	6		> 2	> 50		0.5	100, sedation 300, paralysis
57	214 (154-301)	4	7	1	20	40	1-1.5	200, convulsions
65	349 (323-377)	7	10	2	50		1-1.5	400, convulsions
69	284 (230-351)	6	> 10	2	10	20	1-1.5	200, convulsions
80	115 (87-158)	7	> 10	> 2	> 15		0.5	100, convulsions
82	92 (62-136)	5		> 4	> 30	20	0.5	100, convulsions
89	151 (120-191)	5	> 10	> 2	> 15		0.5	100, convulsions
90	164 (133-203)	2	> 10	> 4	> 40	40	1-1.5	100, convulsions
97	125 (92-168)	2	> 10	> 4	> 20		> 1.5	100, convulsions
Codeine	125 (116-135)		1.5	2	8			
Aspirin	468 (379-577)				20	100		

Papaverine shows an antispasmodic activity at 5 µg/ml.

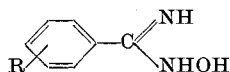
is, however, more probable that the analgesic anti-inflammatory activity—i.e. the selective inhibition of inflammatory pain—is a distinct pharmacological property, differing from the one exhibited by morphine and independent of the inhibition of inflammation. In accordance with this attractive working hypothesis, the inflammatory pain should also differ physiologically from non-inflammatory pain. It may be stressed, moreover, that compound 69 shows the same activity as phenylbutazone in the granuloma test. Compound 13 induces convulsions at slightly higher doses than does pentylenetetrazol, in spite of its decidedly lower toxicity. Compound 57 was more active than codeine against cough induced by inhalation of an irritant, whereas it was less active than the latter substance in experiments where the central stump of the upper laryngeal nerve is stimulated. These results suggest that its antitussive activity is mainly peripheral. Compound 90 was superior to papaverine in the isolated intestine stimulated by means of different agents, and as a coronary dilator on the isolated cat heart.

### Experimental

*Amidoximes.* For the reaction of nitriles with hydroxylamine, Tiemann's general method<sup>2</sup> was followed. In an ethanolic solution one equivalent of the nitrile, sodium carbonate (1.25 equivalents) and hydroxylamine hydrochloride (1.25 equivalents) were refluxed and stirred for 3–6 h. In some cases it was preferred to operate in the absence of inorganic salts, by preparing an alcoholic solution of hydroxylamine from sodium ethoxide and hydroxylamine hydrochloride and filtering from sodium chloride. The characteristics of those amidoximes which have not been described thus far are given in Table III.

*O- $\omega$ -Halogenoacylamidoximes.* The following general method was followed. To one equivalent of amidoxime and one equivalent of potassium carbonate suspended in anhydrous acetone, a solution of the  $\omega$ -halogenoacyl chloride in acetone was slowly added, with stirring and external cooling by means of ice water. After all the solution had been added, stirring was continued for 2 h at room temperature. The solvent was then removed under reduced pressure and the residue thoroughly washed with water in order to remove the inorganic salts. The *O- $\omega$ -halogenoacylamidoximes*

Table III. Benzamidoximes



R	m.p., °C	Formula	Analysis, %		
			Calcd.		Found
<i>m</i> -Cl	115-116	C <sub>7</sub> H <sub>7</sub> ClN <sub>2</sub> O	20.78	Cl-	20.73
<i>o</i> -C <sub>2</sub> H <sub>5</sub> O	136	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	15.55	N	15.72
<i>p</i> -C <sub>2</sub> H <sub>5</sub> O	106-108	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	15.55	N	15.56
<i>p</i> -C <sub>4</sub> H <sub>9</sub> O	112-113	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	13.45	N	13.33
<i>p</i> -C <sub>6</sub> H <sub>5</sub>	174-175	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O	13.20	N	13.10
3,4-(CH <sub>3</sub> O) <sub>2</sub>	162	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	14.28	N	14.01
3,4,5-(CH <sub>3</sub> O) <sub>3</sub>	157	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	12.38	N	12.40

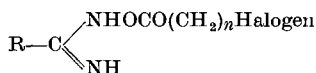
are thus obtained in almost theoretical yields, sufficiently pure to be used for subsequent reactions. They may be crystallized from alcohol, but care should be taken to ensure that heating is minimal, so as to avoid decomposition. The characteristics of halogenoacylamidoximes, not as yet described in the literature, are given in Table IV.

*5-ω-Halogenoalkyl-1,2,4-oxadiazoles.* As a rule, the method of cyclizing the halogenacylamidoximes by heating under reduced pressure and above their melting points was followed. Whenever possible it was preferable to heat them in water, and steam-distill the oxadiazoles formed. Ring closure also proceeded in good yields on heating the halogenoacylamidoxime in a toluene or xylene solution and removing the resulting water as it was formed. The reaction is completed in 1-2 h. The characteristics of the new 5-ω-halogenoalkyl-1,2,4-oxadiazoles are given in Table V.

*5-Dialkylaminoalkyl-1,2,4-oxadiazoles.* The general method of preparation and the reactions depended upon the value of *n*.

(a) *n* = 1. The reaction between chloromethyloxadiazole and secondary amines takes place in many cases even at room temperature. Nevertheless, it is preferable to heat one equivalent of chloromethyloxadiazole with 2 equivalents of secondary amine for 2 h in a benzene or toluene solution. The separated hydrochloride is filtered, the solvent removed and the product distilled at low

Table IV. Halogenacylamidoximes

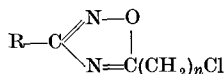


R	n	m.p., °C	Formula	Analysis, %		
				Calcd.	Found	
C <sub>6</sub> H <sub>5</sub>	2	96-98	C <sub>10</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub>	52.98	C	53.05
				4.89	H	4.89
C <sub>6</sub> H <sub>5</sub>	3	105-106	C <sub>11</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	14.73	Cl	14.88
C <sub>6</sub> H <sub>5</sub>	4	106-108	C <sub>12</sub> H <sub>15</sub> BrN <sub>2</sub> O <sub>2</sub>	26.71	Br	26.93
<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	1	124-125	C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	28.70	Cl	28.98
<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	2	107-108	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	27.16	Cl	27.25
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1	134-135	C <sub>6</sub> H <sub>3</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	28.70	Cl	28.44
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	2	141	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	27.16	Cl	27.11
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	3	136-137	C <sub>11</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	25.77	Cl	25.77
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1	124-125	C <sub>10</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub>	15.64	Cl	15.74
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	2	117-118	C <sub>11</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	14.73	Cl	15.01
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	2	123-124	C <sub>11</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub>	13.81	Cl	14.02
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	3	110-111	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub>	13.10	Cl	13.12
<i>p</i> -C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub>	2	125-126	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub>	13.10	Cl	13.36
3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1	121	C <sub>11</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>4</sub>	13.00	Cl	13.05
3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2	122	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>4</sub>	12.37	Cl	12.47
3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	1	131	C <sub>12</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>5</sub>	11.71	Cl	11.74
$\alpha$ -C <sub>10</sub> H <sub>7</sub>	3	116-118	C <sub>15</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	12.19	Cl	12.36
$\beta$ -C <sub>10</sub> H <sub>7</sub>	2	121-122	C <sub>14</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	12.81	Cl	12.85
$\alpha$ -C <sub>10</sub> H <sub>11</sub>	1	117-118	C <sub>18</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	13.29	Cl	13.27
C <sub>12</sub> H <sub>9</sub>	1	117-118	C <sub>15</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	12.58	Cl	12.57
C <sub>12</sub> H <sub>9</sub>	2	166-168	C <sub>16</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	11.71	Cl	11.61

pressure. In only a few cases the final distillation was avoided and the dialkylaminomethyloxadiazole was purified through the hydrochloride.

(b)  $n = 2$ . Owing to the difficulties encountered in the preparation of the chlorethyloxadiazoles, the *O*- $\beta$ -chloropropionamidoximes were treated directly with secondary amines in benzene or toluene solution using 1 equivalent of substituted amidoxime and 2.5 equivalents of amine, eliminating the water formed and carefully keeping the volume of the reaction liquid

Table V. 5-Chloralkyloxadiazoles



R	n	m.p., °C	b.p., °C/mm	Formula	Analysis, %	
					Calcd.	Found
C <sub>6</sub> H <sub>5</sub>	1	38		C <sub>9</sub> H <sub>7</sub> ClN <sub>2</sub> O	18.22	Cl 18.21
C <sub>6</sub> H <sub>5</sub>	2		128/0.1	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O	16.99	Cl 16.91
C <sub>6</sub> H <sub>5</sub>	3		135/0.2	C <sub>11</sub> H <sub>11</sub> ClN <sub>2</sub> O	15.92	Cl 16.28
<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	3		147/0.3	C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O	28.22	Cl 28.30
<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	1	41-42	117/0.1	C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>2</sub> O	30.96	Cl 31.03
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1	60-61		C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>2</sub> O	30.96	Cl 30.83
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	3	33-35		C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O	10.90	N 10.91
<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	1	56-57		C <sub>9</sub> H <sub>6</sub> BrClN <sub>2</sub> O	10.24	N 10.15
<i>o</i> -HOC <sub>6</sub> H <sub>4</sub>	1	182-183		C <sub>9</sub> H <sub>7</sub> ClN <sub>2</sub> O <sub>2</sub>	16.79	Cl 16.82
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	1		137/0.3	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	53.46	C 53.39 4.04 H 3.97
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	3	54-55		C <sub>12</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	14.03	Cl 13.93
3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1	103-104		C <sub>11</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub>	13.92	Cl 13.86
3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	1	94-95		C <sub>12</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>4</sub>	12.45	Cl 12.55
3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	3	79		C <sub>14</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub>	11.35	Cl 11.51
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	1		117/0.7	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O	17.00	Cl 16.74
C <sub>6</sub> H <sub>5</sub> \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH}	1		127/0.7	C <sub>12</sub> H <sub>13</sub> ClN <sub>2</sub> O	14.98	Cl 15.01
C <sub>2</sub> H <sub>5</sub> \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH}	1					
$\alpha$ -C <sub>10</sub> H <sub>7</sub>	3	40		C <sub>15</sub> H <sub>13</sub> ClN <sub>2</sub> O	12.42	Cl 12.66
$\alpha$ -C <sub>10</sub> H <sub>11</sub>	1		142/0.1	C <sub>13</sub> H <sub>13</sub> ClN <sub>2</sub> O	14.26	Cl 14.21
<i>p</i> -C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	1	115-116		C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O	13.10	Cl 13.25
$\alpha$ -C <sub>5</sub> H <sub>4</sub> N	1	107-108		C <sub>8</sub> H <sub>6</sub> ClN <sub>3</sub> O	16.76	Cl 16.76

almost constant by the addition of fresh solvent. The reaction takes 2 to 4 h. The mixture is then filtered from the separated hydrochloride, and the benzene or toluene layer is washed with water. The hydrochloride of the reaction product is precipitated by means of HCl. It is not convenient to distil the 5-dialkylaminoethyl-1,2,4-oxadiazoles, as it is difficult to avoid partial decomposition even at reduced pressure. A simple crystallization from absolute alcohol or alcohol-ether is sufficient to obtain practically pure products in good yields.

(c)  $n = 3$ . The chlorine atom in 5-chloropropylloxadiazoles is far less reactive than it is in the corresponding 5-chloromethyl and 5-chloroethyl derivatives. Therefore it is necessary to heat at 120–130° in a sealed tube for a long time. As a rule the process was carried out in toluene solution using 2 equivalents of amine for one of chloropropylloxadiazole and heating for 16 h. The reaction mixtures were worked up as in the foregoing example. The compounds are stable during distillation at reduced pressure and may therefore be distilled, besides being purified via the hydrochlorides.

(d)  $n = 4$ . In the only case carried out, the  $\delta$ -bromovaleroylbenzamidoxime was heated for 2 h with 2 equivalents of diethylamine in xylene, azeotroping the water formed in the course of the reaction. The mixture was extracted with dilute hydrochloric acid and this solution was made alkaline with potassium carbonate. The separated 3-phenyl-5- $\delta$ -diethylaminobutyl-1,2,4-oxadiazole was extracted with ether and purified by distillation under reduced pressure.

*5-N-Alkylaminomethyl-1,2,4-oxadiazoles.* The following general method was followed. To 4 equivalents of a primary amine dissolved in anhydrous ethanol an alcoholic solution of one equivalent of chloromethylloxadiazole was added carefully. When all the solution had been added, the mixture was refluxed for 2 h, the solvent was removed by distillation at reduced pressure, and the residue was treated with water and ether. The ether layer was dried over anhydrous sodium sulphate and the solvent removed by distillation. The product was purified by distillation under reduced pressure.

*5-N-Methyl-N-alkylaminomethyl-1,2,4-oxadiazoles.* Methylation was carried out according to the general procedure of Eschweiler-Clarke.<sup>10</sup> 5-*N*-Alkylaminomethylloxadiazole (1 equivalent), formic acid (5 equivalents) and formaldehyde (2·2 equivalents) were refluxed for 16 h, the reaction mixture was treated with hydrochloric acid, excess formic acid and formaldehyde being removed under reduced pressure, and the residue was made alkaline with sodium hydroxide. The product was extracted with ether and purified by distillation under reduced pressure.

*3-Phenyl-5-aminomethyl-1,2,4-oxadiazole.* A solution of 3-phenyl-5-chloromethyl-1,2,4-oxadiazole (4·8 g) in chloroform (10 ml) was



added to a solution of hexamethylenetetramine (3.5 g) and refluxed for 5 h. By this time a voluminous precipitate had formed which was filtered and dried. The compound was then treated with absolute alcohol (18 ml) and concentrated hydrochloric acid (8 ml), and the mixture was stirred vigorously at room temperature. After some time the precipitate disappeared and eventually crystals of ammonium chloride began to separate. After standing the mixture overnight, the solvent was removed by distillation under reduced pressure and the residue was dissolved in water. The solution was made alkaline with sodium hydroxide and the oil was extracted with ether. The ether layer was dried and distilled. 3-Phenyl-5-aminomethyl-1,2,4-oxadiazole boiled at  $125^{\circ}/0.1$  mm. After crystallization from petroleum ether the melting point was  $48-50^{\circ}$ .

*Summary.* A series of 100 aminoalkyl derivatives containing the 1,2,4-oxadiazole nucleus was synthesized and pharmacologically evaluated. Some of them showed high antitussive, analgesic-antiinflammatory, anti-inflammatory and antispasmodic activity.

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