Conversion of 2a into 9.—A solution of 491 mg (1 mmole) of **2a** and 186 mg (1 mmole) of *p*-tosylhydrazide in 5 ml of methanol was refluxed for 30 min. The solvent was evaporated; after drying, 640 mg of crude hydrazone was obtained. A solution of 659 mg (1 mmole) of this compound in a mixture of 5 ml of methanol and 2 ml of water was neutralized with 5% aqueous $NaHCO_3$, and the resulting solution was added with stirring to an ice-cooled solution of 740 mg of $NaBH_4$ in a mixture of 5 ml of methanol and 5 ml of water. The reaction mixture was first stirred for 15 min at 0° and then for 15 min at room temperature. After dilution with water the mixture was acidified with dilute HCl. The precipitate was filtered off and washed with water until neutral. The dried residue (420 mg) was recrystallized from aqueous methanol; 150 mg of pure **9**, mp 202–204° dec, was obtained; $[\alpha]D$ +7° (absolute ethanol); infrared (KBr), 1745 (ester C=O), 1701 (α,β-unsaturated acid C=O), and 1256 cm^{-1} (acetate).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.30; CH_3CO, 9.03. Found: C, 71.10; H, 9.23; CH_3CO, 8.94.

Methyl Ester of 9.—To a suspension of 750 mg of **9** in ether was added with stirring an ethereal solution of CH_2N_2 until the yellow color persisted. The resulting solution was evaporated, and the residue was recrystallized from aqueous methanol, yielding 620 mg of pure ester: mp 160.5–162°; $[\alpha]D$ +1°; infrared ($CHCl_3$), 1737 (ester C=O), 1723 sh (α,β-unsaturated ester C=O), and 1264 cm^{-1} (acetate).

Anal. Calcd for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 70.80; H, 9.33.

3-Acetate of 9.—A solution of 0.5 of **9** in a mixture of 2.5 ml of acetic anhydride and 2.5 ml of pyridine was kept at room temperature for 15 hr. The reaction mixture was treated, as usual, to yield 0.5 g of crude 3-acetate. After recrystallization from aqueous methanol the purified material (0.45 g) softened at 141° and melted at 157–158°, $[\alpha]D$ −17°.

Anal. Calcd for $C_{36}H_{48}O_7 \cdot H_2O$: C, 67.13; H, 9.01. Found: C, 67.24; H, 8.96.

24,25-Oxidofusidic Acid.—A solution of 2.58 g (5 mmoles) of fusidic acid in 125 ml of $CHCl_3$ was treated with 1 equiv of *m*-chloroperbenzoic acid dissolved in 25 ml of $CHCl_3$. After standing for 30 min at room temperature, titration and thin layer chromatography of the reaction mixture showed that the reaction was complete. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and added to hot heptane. Methylene chloride was allowed to evaporate and heptane was decanted from the residue, which was then extracted once more in a similar manner. The residue was dried and yielded 2.5 g of product which could not be obtained in a crystalline form.

Upon a similar epoxidation using dihydrofusidic acid instead of fusidic acid, titration of an aliquot part of the reaction mixture showed that the peracid content was not yet decreased by 10% after 30 min.

24,25-Oxidofusidic Acid Methyl Ester. Method A.—The reaction of fusidic acid methyl ester with *m*-chloroperbenzoic acid was carried out as described for fusidic acid. When reaction was complete the solvent was evaporated under reduced pressure and the residue was taken up in ether. The ethereal solution was washed ($NaHCO_3$, H_2O) and evaporated. From 1.33 g of fusidic acid methyl ester, 1.45 g of crude oxido ester was obtained; after chromatography on 75 g of silica gel, elution with benzene–ethyl acetate (2:3) yielded 1 g of pure product which failed to crystallize; $[\alpha]D$ −11°.

Anal. Calcd for $C_{32}H_{50}O_7$: C, 70.29; H, 9.22. Found: C, 70.05; H, 9.24.

Method B.—To a solution of 500 mg of crude 24,25-oxidofusidic acid in ether was added an ethereal solution of CH_2N_2 until the yellow color persisted. After removal of the solvent the residue (500 mg) was chromatographed on 25 g of silica gel and was eluted with benzene–ethyl acetate (2:3) to yield 250 mg of pure 24,25-oxidofusidic acid methyl ester. The identity of this compound with the compound obtained by method A was checked by thin layer chromatography with benzene–ethyl acetate (2:3).

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Anthelmintic Activity of 1,2,4-Oxadiazoles

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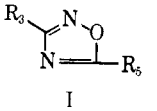
Substituted 1,2,4-oxadiazoles were screened for anthelmintic activity in mice experimentally infected with *Nematospiroides dubius*. 3-Alkyl- and 3-aryl-1,2,4-oxadiazoles without substituents at the 5 position were effective when administered orally at 500 mg/kg or by subcutaneous injection at 100 mg/kg, whereas the 5-substituted 3-alkyl- and 3-aryl-1,2,4-oxadiazoles tested were inactive. 3-*p*-Chlorophenyl-1,2,4-oxadiazole was chosen for extended studies against nematode infections in experimental animals. 5-Spiro-4,5-dihydro-1,2,4-oxadiazoles were prepared.

Recently, 1,2,4-oxadiazoles have received considerable attention in the literature.[2,3] Substituted 1,2,4-oxadiazoles have been reported to exhibit various types of biological activities, including antispasmodic and analgetic,[4] sedative,[5] and nematocidal, fungicidal, and insecticidal.[6] We wish to report our finding that 3-substituted 1,2,4-oxadiazoles are anthelmintics when tested against *Nematospiroides dubius* in mice.

Preliminary screening of 1,2,4-oxadiazoles of type I, wherein R_3 and R_5 are hydrogen, alkyl, or aryl, indicated that the anthelmintic activity was considerably



I

better for 3-substituted 5-hydrogen-1,2,4-oxadiazoles than for any other combination of 3 and 5 substitution. The 3-substituted 1,2,4-oxadiazoles that were evalu-

(1) To whom inquiries should be addressed at the Department of Chemistry, Colorado State University, Fort Collins, Colo.

(2) (a) J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p 508; (b) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962); (c) L. C. Behr in "Chemistry of Heterocyclic Compounds—Five- and Six-Membered Compounds with Nitrogen and Oxygen," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 245.

(3) (a) M. Nebsino and P. Groenenger, *Chem. Ind.* (Milan), **45**, 1238 (1963); *Chem. Abstr.*, **60**, 10672 (1964); (b) C. Moussebois and F. Eloy, *Helv. Chim. Acta*, **47**, 838 (1964), and references therein; (c) F. Eloy, *Fortschr. Chem. Forsch.*, **4**, 807 (1965).

(4) G. Pallazzo, M. Tavella, G. Sorani, and B. Silvestroni, *J. Med. Pharm. Chem.*, **4**, 35 (1961).

(5) G. Pallazzo and B. Silvestroni, *Boll. Chim. Farm.*, **101**, 251 (1962); *Chem. Abstr.*, **58**, 4548 (1963).

(6) A. S. Sousa, H. C. Chitwood, and J. A. Dooley, French Patent 1,363,235; *Chem. Abstr.*, **62**, 5282 (1965).

TABLE I

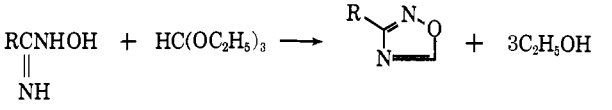
3-SUBSTITUTED 1,2,4-OXADIAZOLES[a]

No.	R	Yield, %	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	CH_3[b]									
2	$CH_3(CH_2)_5$[c]	20	80 (10)[l]	$C_8H_{14}N_2O$	62.30	9.15	18.17	62.37	9.22	18.04
3	$CH_3(CH_2)_{10}$	50	101 (1)	$C_{13}H_{24}N_2O$	69.59	10.78	12.49	69.45	10.98	12.57
4	$C_6H_5CH_2$[d]	10	118 (10)	$C_9H_8N_2O$						
5	p-$ClC_6H_4CH_2$[e]	25	140 (8)[m]	$C_9H_7ClN_2O$			14.40			14.42
6	$C_6H_5(CH_2)_2$[f]	55	135 (8)[n]	$C_{10}H_{10}N_2O$			16.08			15.65
7	C_6H_5[d]	60	100 (10)[o]	$C_8H_6N_2O$						
8	o-$CH_3C_6H_4$	60	115 (8)	$C_9H_8N_2O$			17.49			16.98
9	m-$CH_3C_6H_4$[g]	50	115 (8)	$C_9H_8N_2O$			17.49			17.20
10	p-$CH_3C_6H_4$[d]	45	115 (10)	$C_9H_8N_2O$						
11	p-BrC_6H_4[d]	50	110	$C_8H_5BrN_2O$						
12	o-ClC_6H_4	12	120 (8)	$C_8H_5ClN_2O$			15.51			15.36
13	m-ClC_6H_4[h]	35	42	$C_8H_5ClN_2O$			15.51			15.17
14	p-ClC_6H_4[d]	60	102	$C_8H_5ClN_2O$						
15	m-Cl-p-$CH_3C_6H_3$[i]	25	92	$C_9H_7ClN_2O$	55.53	3.63		55.16	3.89	
16	m-$CF_3C_6H_4$[j]	25	115 (8)	$C_9H_5F_3N_2O$			13.86			13.62
17	p-$CH_3OC_6H_4$	50	145 (8)	$C_9H_8N_2O_2$			15.90			15.69
18	p-$NO_2C_6H_4$[d]	16	164	$C_8H_5N_3O_3$						
19	3-Pyridyl	90	91	$C_7H_5N_3O$	57.14	3.43	28.56	56.95	3.71	28.39
20	2-Furanyl	5	86	$C_6H_4N_2O_2$	52.94	2.96	20.58	53.11	3.11	20.28
21	$C_2H_5CO_2$[k]	60	36	$C_5H_6N_2O_3$	42.25	4.25	19.71	42.81	4.33	19.79

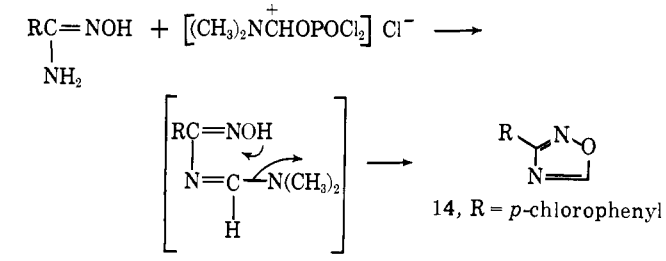
[a] Characterized by a strong absorption band at 6.40–6.45 μ in the infrared. [b] Reference 3b. [c] n-$C_6H_{13}C(NH)NHOH$, mp 58–60°, *Anal.* Calcd for $C_7H_{16}N_2O$: N, 19.42. Found: N, 19.18. [d] Reference 3a. [e] p-$ClC_6H_4CH_2C(NH)NHOH$, mp 110–112°, *Anal.* Calcd for $C_8H_9ClN_2O$: N, 15.17. Found: N, 15.39. [f] Starting amidoxime was obtained as an oil. [g] m-$CH_3C_6H_4C(NH)NHOH$, mp 120–121°, *Anal.* Calcd for $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.75. [h] m-$ClC_6H_4C(NH)NHOH$, mp 118–120°, *Anal.* Calcd for $C_7H_7ClN_2O$: N, 16.42. Found: N, 16.13. [i] m-Cl-p-$CH_3C_6H_3C(NH)NHOH$, mp 129–131°, *Anal.* Calcd for $C_8H_9ClN_2O$: N, 15.18: Found: N, 15.06. [j] m-$CF_3C_6H_4C(NH)NHOH$, mp 83–85°, *Anal.* Calcd for $C_8H_7F_3N_2O$: N, 13.72. Found: N, 13.32. [k] Starting amidoxime, see ref 10. [l] $n^{25}D$ 1.4370. [m] $n^{25}D$ 1.5462. [n] $n^{25}D$ 1.5265. [o] $n^{25}D$ 1.5535.

ated are shown in Table I, and their biological test results are given in Table II.

The compounds of Table I, with the exception of **1**, were prepared by heating the appropriate iminohydroxamic acid[7] (amidoxime) and triethyl orthoformate under reflux for 2 hr.[3a] Longer heating lowered the yield and formed the nitrile RCN.[8]



3-p-Chlorophenyl-1,2,4-oxadiazole (**14**) was chosen for extended studies on the basis of its activity and stability, and the results are shown in Table III. It was prepared in quantity in 80% yield by an alternate method[9] involving reaction of p-chlorobenzamidoxime and the DMF–$POCl_3$ complex.[10]



14, R = p-chlorophenyl

We have also prepared dihydrooxadiazoles of the type represented by II, where R_3 is alkyl or aryl, and R_5 is alkyl or aralkyl, by the reaction of amidoximes

(7) H. E. Ungnade and L. W. Kissinger, *J. Org. Chem.*, **23**, 1794 (1958).
(8) C. Ainsworth, *J. Heterocyclic Chem.*, in press.
(9) This method was suggested by E. C. Kornfeld and was studied by L. A. White and E. R. Lavagnino.
(10) C. S. Davis, A. M. Knevel, and G. L. Jenkins, *J. Org. Chem.*, **27**, 1919 (1962).

TABLE II

ANTHELMINTIC ACTIVITY AGAINST *N. dubius* IN MICE[a]

No.[b]	Gavage Dose, mg/kg	Gavage Worm reduction, %	Subcutaneous Dose, mg/kg	Subcutaneous Worm reduction, %
1	25	86	50	89
	50	99	100	89
2	100	81	500	0
3	50	89	100	0
			500	73
4	100	0	500	0
	500	97		
5	100	0	500	0
	500	87		
6	100	0	500	0
	500	89		
7	100	60	500	0
	500	89		
8	100	0	500	0
	500	86		
9	100	0	500	0
	500	88		
10	500	72	500	0
11	100	98	500	0
12	500	80	500	0
13	500	74	500	0
14	50	63	100	0
	100	94	500	100
15	500	76	500	0
16	500	45	500	0
17	100	0	500	0
	500	70		
18	100	95	100	0
19	500	100	500	100
	100	0	100	0
20	100	59	100	0

[a] See Methods. [b] Refers to Table I.

TABLE III

ANTHELMINTIC TESTING OF 3-*p*-CHLOROPHENYL-1,2,4-OXADIAZOLE (**14**)

Infectious species	Oral dose, mg/kg	Anthelmintic efficacy	Subcutaneous dose, mg/kg	Anthelmintic efficacy
N. muris	50	75[a]	1000	100[a]
	250	100[a]		
S. obvelata	500	0[a]		
	1000	90[a]		
S. ratti	1000	Active[b]	1000	Active[b]
T. axei	250	Active[c]		

[a] Worm reduction, % (see Methods). [b] Culture evaluation (see Methods). [c] Egg count and culture evaluation (see Methods).

administered a single dose of test compound by gavage. After 5 days the mice were killed and the worm count in the ceca and large intestine was determined. Results are expressed as per cent worm reduction compared with infected controls. The standard Student *t* method was used in the evaluation.

V. *Trichostrongylus axei.*—Mongolian gerbils weighing 80–100 g were experimentally inoculated orally with approximately 5000 infective larvae of *T. axei*. After 1 week, fecal material was collected and cultured using sphagnum moss. Three months later feces were collected and the egg per gram densities were determined using the AEX method.[11]

Results

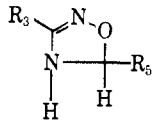
In addition to the 3-substituted 1,2,4-oxadiazoles (Table II), a number of related compounds were

TABLE IV

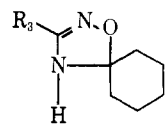
3,5-DISUBSTITUTED 4,5-DIHYDRO-1,2,4-OXADIAZOLES

R_3	R_5	R_5	Yield, %	Mp or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3	H	$CH(CH_3)_2$	88	132 (12)	$C_6H_{12}N_2O$	56.22	9.44	21.86	56.51	9.63	21.98
CH_3	H	$CH_2CH(CH_3)_2$	30	138 (12)	$C_7H_{14}N_2O$	59.12	9.92	19.70	59.18	9.90	19.73
p-$ClC_6H_4CH_2$		*a*	20	190–191	$C_{14}H_{17}ClN_2O$	63.51	6.47	10.58	63.85	6.80	10.94
C_6H_5		*a*	25	160–161	$C_{13}H_{16}N_2O$	72.19	7.45	12.95	71.75	7.35	12.44
p-ClC_6H_4		*a*	25	208–212	$C_{13}H_{15}ClN_2O$	62.27	6.03	11.17	62.54	6.06	11.11
p-ClC_6H_4	H	CH_3	95	155–157	$C_9H_9ClN_2O$	54.97	4.61	14.25	55.04	4.53	13.98
p-ClC_6H_4	H	$CH_2CH(CH_3)_2$	50	132–135	$C_{12}H_{15}ClN_2O$	60.37	6.33	11.73	60.92	6.44	11.79
o-$CH_3C_6H_4$	H	CH_3	90	60–61	$C_{10}H_{12}N_2O$	68.15	6.86	15.90	68.31	6.91	15.65
p-ClC_6H_4	H	$CH_2C_6H_5$	30	165–167	$C_{15}H_{13}ClN_2O$	66.05	4.80	10.27	66.19	4.94	10.08

[a] R_5 is pentamethylene.



II



III

and aldehydes.[2b] The previously unreported spiro system III where R_3 is aryl or aralkyl was prepared from suitably substituted amidoximes and cyclohexanone. The dihydro compounds are listed in Table IV. All of the dihydro derivatives were found to be inactive when tested orally at 500 mg/kg against *N. dubius* infections in mice.

Biological Screening Methods

I. *Nematospiroides dubius.*—Albino male mice weighing 14–17 g and infected orally with approximately 50 larvae of *N. dubius* were held in cages until the infection was patent. Five animals were selected at random for each test group. The test compounds were given in a single dose, either by gavage or by subcutaneous injection. Approximately 40 hr after treatment the mice were killed and the small intestine was removed, everted, and examined with a stereomicroscope to determine the worm burden. The number of worms remaining was compared with the worm burden of the infected controls. The results, expressed in terms of per cent worm reduction, are found in Table II.

II. *Nippostrongylus muris.*—The method employed for this helminth infection was the same as that described in section I except albino rats (90–100 g) were used as the experimental animals and larvae of *N. muris* were administered by subcutaneous injection.

III. *Strongyloides ratti.*—Albino rats (90–100 g) were inoculated subcutaneously with approximately 3000 infective larvae of *S. ratti*. After 7 days a single dose of a test compound was given by gavage or subcutaneous injection. Forty-eight hours after treatment fecal material was collected and charcoal cultures were made. After 96 hr the cultures were examined with a stereomicroscope, and the larvae count was compared with the larval count in the infected controls.

IV. *Syphacia obvelata.*—Five albino mice, naturally infected with *S. obvelata*, were selected at random for each test group and

screened orally at 500 mg/kg against *N. dubius* infections in mice. The following 1,2,4-oxadiazoles were inactive in that test: 3-phenyl-5-methyl,[2c] 3,5-diphenyl,[2c] 3-methyl-5-phenyl,[2c] 3-benzyl-5-methyl,[2c] 3,5-dimethyl,[3b] and 5-phenyl.[3b] Also inactive were *p*-chlorobenzamidoxime[2b] and O-acetyl-*p*-chlorobenzamidoxime.

Several features stand out regarding the anthelmintic activity of 3-substituted 1,2,4-oxadiazoles. (1) Members of the 3-alkyl- or 3-aryl-1,2,4-oxadiazole series (Table I) are consistently active against helminth infection induced by *N. dubius* when administered orally to mice at 500 mg/kg and often at considerably lower dosage. (2) Closely related acyclic analogs of **14** are inactive. (3) Certain representatives of 3-alkyl- or 3-aryl-1,2,4-oxadiazoles are active in the biological test when administered by subcutaneous injection.

Item 2 suggests that the 1,2,4-oxadiazole nucleus *per se* is a necessary requirement for anthelmintic activity, since *p*-chlorobenzimadoxime and its O-acetyl derivative are inactive.

The third item is one of interest and relates to the finding that 2-(β-methoxyethyl)pyridine[12a] was an anthelmintic when administered by injection.[12b] The mode of action of 2-(β-methoxyethyl)pyridine has been studied, and it has been suggested that the drug is excreted from the blood into the alimentary canal along its whole length.[13] We have not investigated the mode of action of **14** but wish to propose an alternative mechanism, namely, that the compound is concentrated in the bile and may be excreted as a conjugate.

(11) E. H. Loggins and S. H. Spitz, *J. Am. Med. Assoc.*, **139**, 997 (1949).

(12) (a) A. W. J. Broome and N. Greenhalgh, *Nature*, **189**, 59 (1961); (b) see also the report of D. Thienpont, *et al.*, *Nature*, **209**, 1084 (1966), concerning the activity of compound R8299.

(13) A. W. J. Broome, *Brit. J. Pharmacol.*, **17**, 327 (1961).

Experimental Section[14]

Amidoximes. General Procedure.—A mixture of 1 mole of alkyl or aryl cyanide and 1 mole of hydroxylamine hydrochloride was dissolved in 500 ml of 80% aqueous ethanol. One-half mole of K_2CO_3 was added, and following the evolution of CO_2 the solution was heated under reflux overnight. The solvent was removed under reduced pressure (steam bath), and the residue was twice extracted with 200 ml of absolute ethanol. The ethanol extract was concentrated to dryness, and the resulting amidoxime was recrystallized from benzene. Unless otherwise indicated, the amidoximes used are described in ref 2b.

3-Substituted 1,2,4-Oxadiazoles (Table I). General Procedure.—A mixture of 0.1 mole of appropriate amidoxime and 100 ml of triethyl orthoformate was heated under reflux for 2 hr, and the reaction mixture was then distilled under reduced pressure. If the product was a solid at room temperature, it was recrystallized from ethyl acetate–petroleum ether (60–70°) mixture. The nitrile corresponding to the starting material for the amidoxime was often a by-product of the reaction.[8]

3-*p*-Chlorophenyl-1,2,4-oxadiazole (14).—To 0.1 mole of DMF–$POCl_3$ complex[10] was added, with stirring, an ether solution of 0.05 mole of *p*-chlorobenzamidoxime. The temperature was maintained near 10° by means of an ice bath and the mixture was stirred for 10 min. After the solvent was removed at 60°, the residue was washed twice with 150 ml of ice water. The product was recrystallized from methanol and gave **14**, mp 100–102°, in 80% yield.

3,5-Disubstituted 4,5-Dihydro-1,2,4-oxadiazoles (Table IV). (a) General Procedure.—To 0.1 mole of appropriate amidoxime dissolved in 200 ml of 50% aqueous ethanol was added portionwise 0.15 mole of aldehyde. After the initial exothermic reaction had ended, the solution was allowed to stand at room temperature for 2 days and then was concentrated under reduced pressure (steam bath). The residue was recrystallized from ethanol–water if it was a solid, or was distilled using a spinning-band column if it was a liquid at room temperature.

(b) Spiro-4,5-dihydro-1,2,4-oxadiazoles (Table IV).—A mixture of 0.05 mole of the appropriate amidoxime and 20 ml of cyclohexanone[15] was heated under reflux for 2 hr. The mixture was concentrated under reduced pressure (steam bath) and the product was recrystallized from benzene.[16]

Acknowledgment.—The microanalyses were determined by W. L. Brown and associates, and D. O. Woolf, Jr., made the physical measurements. R. J. Boisvenue, M. C. Brandt, W. R. Agan, and E. L. Colestock assisted with the anthelmintic studies.

(14) Melting points were taken with a Fisher-Johns apparatus and are uncorrected.

(15) The reaction did not take place when cyclopentanone or cycloheptanone was used.

(16) In certain instances it was necessary to elute the product from an alumina column using benzene in order to obtain crystals.

Derivatives of 1-Hydroxybenzimidazoles and 1-Hydroxyindoles and Their Central Depressant Effects

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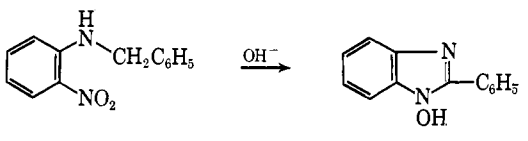
It has been noted that 1-(2-diethylaminoethoxy)-2-phenylbenzimidazole causes central nervous system depression in experimental animals. A variety of related compounds have been prepared and compared with this substance. In addition, corresponding derivatives of 1-hydroxy-2-phenylbenzimidazole 3-oxide and 1-hydroxy-2-phenylindole have also been synthesized and tested for CNS depression. A structure–activity relationship account is presented.

The first report on the synthesis of 1-hydroxybenzimidazoles was made by Niementowski[1] in 1910 who reduced *o*-nitroacetanilide with ammonium sulfide to form 1-hydroxy-2-methylbenzimidazoles. Fries and Reity[2] later were able to effect this reduction much more efficiently with sodium hyposulfite. Finally, in 1964 an alternate synthesis of this class of compounds was developed by Stacy, *et al.*,[3] which involved base-catalyzed cyclization of N-benzyl-*o*-nitroaniline. These authors also emphasized that the nmr spectrum strongly supports the assignment of the N-hydroxy form as the preferred tautomeric structure rather



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than the N-oxide structure assigned by Kew and Nelson.[4] In addition, it was also shown by Takahushi and Kano[5] that the parent substance, 1-hydroxybenzimidazole, could be readily alkylated with methyl iodide to yield the 1-methoxy derivative. It thus occurred to us that a variety of 1-hydroxy-2-substituted benzimidazoles and their corresponding 1-alkoxy derivatives could be prepared for biological evaluation. This work was particularly prompted by the findings of Hunger,[6] *et al.*, who noted that 2-benzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole exhibited potent analgetic effects. Thus, 1-alkoxybenzimidazoles related to this class of compounds were prepared from the corresponding 1-hydroxy heterocycle. The 1-hydroxy-2-arylbenzimidazoles and substituted derivatives were prepared according to the method of Stacy, whereas the 2-alkyl derivatives were synthesized by the procedure outlined by Fries and Reity.

Since substance **8** (Table I) showed good CNS depression in experimental animals, several modifications of the same were made in a structure–activity relationship study (*vide infra*). Besides the usual changes in the basic side chain, nuclear modifications at the 2 position, and substitutions on the benzene portion

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(3) G. W. Stacy, B. V. Ettling, and A. J. Papa, *J. Org. Chem.*, **29**, 1537 (1964).

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(6) A. Hunger, H. Keberle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1032 (1960).