3,5-Disubstituted-1,2,4-oxadiazoles and 4,5-Dihydro-3,5-disubstituted-1,2,4-oxadiazoles

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A series of 3,5-disubstituted-1,2,4-oxadiazoles (**2**) were prepared from a mono- or dichlorophenyl-substituted amidoxime and (i) an acid chloride, (ii) an isatoic anhydride, or (iii) a β-keto ester. Although cyclizations of the same amidoximes with acetaldehyde gave 4,5-dihydro-5-methyl-substituted derivatives (**5**), that annulation procedure either failed or gave low yields with other aldehydes. A novel alternative method, the diborane reduction of **2**, has been found to be a generally applicable procedure for preparing **5**. The reduction is regioselective, *i.e.*, only the 4,5-(C=N) linkage is reduced even when a large excess of diborane is present.

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The annulation of *o*-chloro-, *p*-chloro, and 2,4-dichlorophenyl-, *trans*-2,4-dichlorostyryl-, and 2,4-dichlorophenylethylamidoximes has been effected with several acyl chlorides, with isatoic anhydride, and with methyl acetoacetate to give the corresponding 3,5-disubstituted 1,2,4-oxadiazoles **2**, **3**, and **4**, respectively, as shown in Chart I. In addition, **4** was reduced with sodium borohydride to the carbinol **6**, and the latter converted to the carbamate **7**. Of the fourteen derivatives shown in Table I, the yields of twelve ranged from 22 to 79%; the exceptions were compounds **1** and **9**, where only trace amounts were isolated.

The cyclodehydrations of *p*-chlorophenyl-, 2,4-dichlorophenyl-, and 2,4-dichlorobenzylamidoximes with acetaldehyde proceeded readily to give the 4,5-dihydro derivatives (**5**, Chart I; Table II, **15**, **16**, and **18**), in 73, 76, and 70% yields, respectively. With chloroacetaldehyde, the yield of product (Table II, **23**) was decreased to 11%, and no reaction occurred between those amidoximes and *p*-chlorobenzaldehyde or phenylacetaldehyde.

As indicated above, sodium borohydride did not effect the 3,5-disubstituted-1,2,4-oxadiazole heterocycle. In contrast, diborane in tetrahydrofuran was found to be an invariably effective reducing (hydroboration) agent for the same derivatives. For example, hydroboration of 3,5-*bis*-(2,4-dichlorophenyl)-1,2,4-oxadiazole gave the dihydro derivative in 60% yield; however, the yield was significantly decreased when one of the substituents contained a basic nitrogen atom or a functional group that could interact with diborane. From our review of the literature, this is the first example of the reduction of an *endo*-(C=N) linkage in a heterocyclic system by means of diborane (3).

The hydroboration of alkenes and alkynes is reported to involve *cis*-regioselective addition; furthermore, the mode of addition is unaffected by the substitution pattern on the unsaturated linkage (4). The reduction of the 1,2,4-oxadiazoles now being reported was also regioselective and involved only the 4,5-position, even when a large excess of diborane was present in the reaction mixture. That only the 4,5-(C=N) was involved could be illustrated by the following examples. Thus, the hydroboration product **10**, obtained from **8**, was shown to be identical in all respects with the annulation product from the reaction of 2,4-dichlorophenylamidoxime **9**, and acetaldehyde (Chart I). Again, a comparison of the pmr spectrum of the

Chart I

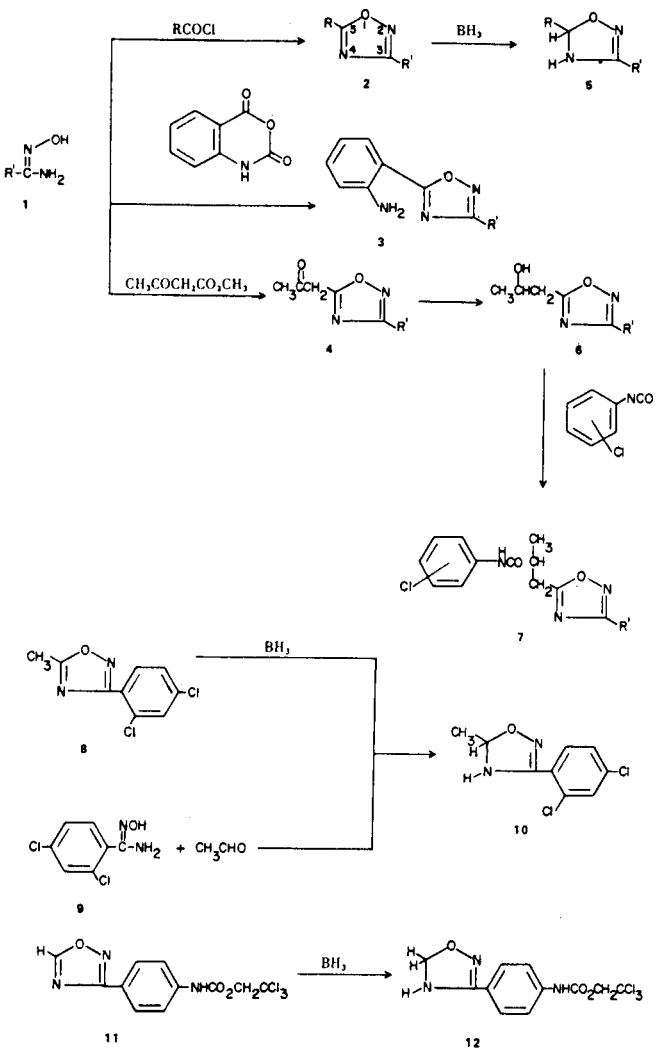

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Table I

3,5-Disubstituted-1,2,4-oxadiazoles

Compound No.	R	R^1	Yield %	Recrystallization Solvent	M.p., °C	Molecular Formula	Analyses: Calcd. / Found			
							C	H	N	Cl
1	CH_3	2,4-Dichlorophenyl	0.2	Sublimed	90-92	$C_9H_6Cl_2N_2O$	47.20 46.97	2.64 2.56	12.23 12.09	30.95 30.76
2	CH_3COCH_2	2,4-Dichlorophenyl	40	Hexane	76-78	$C_{11}H_8Cl_2N_2O_2$	48.73 48.93	2.97 3.07	10.37 10.11	---- ----
3	2-Furyl	2,4-Dichlorophenyl	63	95% Ethanol	83-85	$C_{12}H_6Cl_2N_2O_2$	51.27 51.33	2.16 1.88	9.97 10.17	25.23 25.37
4	*o*-Aminophenyl	2,4-Dichlorophenyl	30	Acetonitrile	245-247	$C_{14}H_9Cl_2N_3O$	54.93 55.10	2.96 3.01	13.72 13.78	---- ----
5	*o*-Chlorophenyl	*o*-Chlorophenyl	41	2-Propanol	86-88	$C_{14}H_8Cl_2N_2O$	57.76 57.83	2.77 2.63	9.63 9.62	24.36 24.52
6	*p*-Chlorophenyl	*o*-Chlorophenyl	38	Acetonitrile	127-129	$C_{14}H_8Cl_2N_2O$	57.76 57.50	2.77 2.61	9.63 9.58	24.36 24.44
7	2,4-Dichlorophenyl	*o*-Chlorophenyl	62	2-Propanol	114-115	$C_{14}H_7Cl_3N_2O$	51.64 51.47	2.17 2.21	8.60 8.68	32.67 32.88
8	2,4-Dichlorophenyl	*p*-Chlorophenyl	56	Acetonitrile	155-156 dec.	$C_{14}H_7Cl_3N_2O$	51.64 51.31	2.17 1.91	8.60 8.87	32.67 32.87
9	2,4-Dichlorobenzyl	2,4-Dichlorophenyl	0.2	Acetonitrile	86-88	$C_{15}H_8Cl_4N_2O$	48.16 47.95	2.15 1.83	7.49 7.44	---- ----
10	*p*-Chlorophenyl	2,4-Dichlorophenylethyl	22	Pentane	69-71	$C_{16}H_{11}Cl_3N_2O$	54.33 54.19	3.13 3.32	7.92 7.68	28.47 28.62
11	2,4-Dichlorophenyl	2,4-Dichlorophenylethyl	25	Hexane	66-68	$C_{16}H_{10}Cl_4N_2O$	49.52 49.58	2.59 2.64	7.21 7.19	36.54 36.69
12	2,4-Dichlorophenyl	*trans*-2,4-Dichlorostyryl	52	Acetonitrile	176-177	$C_{16}H_8Cl_4N_2O$	49.78 49.71	2.09 2.38	7.26 7.32	---- ----
13	2-(*o*-Chlorophenylcarbamoyl)-2-methylethyl	2,4-Dichlorophenyl	50	2-Propanol	90-92	$C_{18}H_{14}Cl_3N_3O_3$	50.67 50.76	3.31 3.20	9.84 9.63	---- ----
14	2-(*p*-Chlorophenylcarbamoyl)-2-methylethyl	2,4-Dichlorophenyl	79	Cyclohexane	89-91	$C_{18}H_{14}Cl_3N_3O_3$	50.67 50.73	3.31 3.04	9.84 9.95	---- ----

Table II

4,5-Dihydro-3,4-disubstituted-1,2,4-oxadiazoles

Compound No.	R	R^1	Method (a)	Yield %	Recrystallization Solvent	M.p., °C	Molecular Formula	Analyses Calcd. / Found	C	H	N	Cl
15	CH_3	*p*-Chlorophenyl	A	73	Isopropyl ether	144-146 (b)	$C_9H_9ClN_2O$	Calcd.	54.94	4.61	14.26	18.03
								Found	54.71	4.59	14.13	18.01
16	CH_3	2,4-Dichlorophenyl	A	76	Hexane	100-102	$C_9H_8Cl_2N_2O$	Calcd.	46.78	3.48	12.12	30.68
								Found	46.66	3.21	12.01	30.48
17	CH_3	*p*-Chlorobenzyl	A	76	Isopropyl ether	103-105	$C_{10}H_{11}ClN_2O$	Calcd.	57.01	5.26	13.30	16.83
								Found	57.19	5.48	13.48	17.08
18	CH_3	2,4-Dichlorobenzyl	A	70	Isopropyl ether	92-94	$C_{10}H_{10}Cl_2N_2O$	Calcd.	49.00	4.10	11.42	28.93 (c)
								Found	48.75	4.06	11.65	29.00
19	CH_3	*p*-Nitrophenyl	A	76	Toluene	156-158	$C_9H_9N_3O_3$	Calcd.	52.17	4.37	20.28	—
								Found	52.08	4.27	20.35	—
20	CH_3	*trans*-Styryl	A	32	Toluene	125-127	$C_{11}H_{12}N_2O$	Calcd.	70.55	5.92	14.96	—
								Found	70.34	6.01	15.00	—
21	C_2H_5	*p*-Chlorophenyl	A	77	Cyclohexane	97-99	$C_{10}H_{11}ClN_2O$	Calcd.	57.01	5.26	13.29	16.83
								Found	57.19	5.53	13.34	16.87
22	$(C_2H_5)CH$	*p*-Chlorophenyl	A	26	Hexane	90-92	$C_{13}H_{17}ClN_2O$	Calcd.	61.77	6.78	11.08	14.02
								Found	61.71	6.85	11.17	14.04
23	$ClCH_2$	2,4-Dichlorophenyl	A	11	Hexane	76-77	$C_9H_7Cl_3N_2O$	Calcd.	40.71	2.66	10.55	40.06
								Found	40.86	2.63	10.51	40.13
24	C_2H_5O	2,4-Dichlorophenyl	(d)	8	Cyclohexane-benzene (9:1)	147-149	$C_{10}H_{10}Cl_2N_2O_2$	Calcd.	46.00	3.81	10.72	—
								Found	45.92	4.19	10.33	—
25	2,4-Dichlorophenyl	2,4-Dichlorophenyl	B	60	Hexane	118-120 dec.	$C_{14}H_8Cl_4N_2O$	Calcd.	46.44	2.22	7.80	39.16
								Found	46.49	1.95	7.76	39.02
26	1-Pyrolidinylmethyl	*p*-Chlorophenyl	B	5	Pentane	140-141	$C_{13}H_{16}ClN_3O$	Calcd.	58.75	6.07	15.81	—
								Found	58.94	6.14	15.48	—
27	1-Piperidinylmethyl	*p*-Chlorophenyl	B	15	Isopropyl ether	131-133	$C_{14}H_{18}ClN_3O$	Calcd.	60.10	6.48	15.02	12.67
								Found	59.82	6.58	14.81	12.82
28	4-Me-1-piperidinylmethyl	*p*-Chlorophenyl	B	18	Acetonitrile	129-130	$C_{15}H_{20}ClN_3O$	Calcd.	61.32	6.86	14.30	12.06
								Found	61.23	6.78	14.41	11.89
29	4-(Carboethoxy)-1-piperidinylmethyl	*p*-Chlorophenyl	B	14	Cyclohexane	84-86	$C_{17}H_{22}ClN_3O_3$	Calcd.	58.03	6.30	11.94	10.07
								Found	58.15	6.66	11.93	10.15
30	1-Morpholinylmethyl	*p*-Chlorophenyl	B	23	Cyclohexane	119-121	$C_{13}H_{16}ClN_3O_2$	Calcd.	55.42	5.72	14.92	12.59
								Found	55.66	4.80	14.93	12.80
31	CH_3	*p*-Chlorophenyl	(e)	6	Cyclohexane	90-92	$C_{11}H_{11}ClN_2O_2$	Calcd.	55.35	4.64	11.84	14.86
								Found	55.20	4.53	11.81	15.05
32	H	*p*-$(CCl_3CH_2O_2CNH)C_6H_4$	B	13	Benzene	176-178 dec.	$C_{11}H_{10}Cl_3N_3O_3$	Calcd.	39.02	2.91	12.41	31.41 (f)
								Found	39.30	2.64	12.34	31.18

(a) Method A: annulation of the amidoxime with the appropriate aldehyde. Method B: hydroboration (see Experimental). (b) U. S. Patent 3,968,224, April 28, 1975 to Stauffer Chemical Co., describes the preparation of this compound by the same procedure, and reports a m.p. of 110-112°. (c) N.E., Calcd., 245; Found (perchloric acid in acetic acid), 250. Does not titrate with aqueous hydrochloric acid. (d). See Experimental. (e) This is the 4-acetyl derivative. (f) N.E., Calcd., 338; N.E., Found (perchloric acid in acetic acid), 345.

hydroboration product **12**, with the pmr spectrum of **11**, the substrate (Chart I), revealed that only the 4,5-positions were involved. The spectrum of **11** showed the proton at position-5 of the heterocycle as a singlet at δ 8.77, along with an NH multiplet centered at δ 7.27. The spectrum of **12** revealed the absence of the singlet at δ 8.77, the presence of a two-proton doublet with a coupling constant of 3 Hz centered at δ 4.34, the same NH multiplet centered at δ 7.32, and a new NH multiplet centered at δ 10.43. Following equilibration with deuterium oxide, the spectrum was altered to show the the two-protons at position-5 as equivalent and resonating as a two-proton singlet at δ 4.26, and as anticipated, both NH protons had exchanged with deuterium and their resonances were not seen. The pmr spectra of the other hydroboration products in Table II were used in a similar manner to establish that the products represented only reduction of the 4,5-position.

The 4,5-dihydro derivatives were reasonably strong bases; in contrast to the 1,2,4-oxadiazoles which did not titrate with perchloric acid in glacial acetic acid. The dihydro derivatives gave satisfactory neutralization equival- with that titrant.

The yields, recrystallization solvents, melting points, and analytical results for the 1,2,4-oxadiazoles are given in Table I; the same data for the 4,5-dihydro derivatives are presented in Table II.

EXPERMENTIAL

The spectra and microanalyses were obtained from members of the Analytical Department of this Institute; the instruments employed to obtain the spectra have been identified in earlier publications by the authors.

3-(2,4-Dichlorophenyl)-5-(2,4-dichlorophenethyl)-1,2,4-oxadiazole (Table I, Compound **11**).

(a) 2,4-Dichlorobenzenepropionic Acid.

A suspension of 10.0 g. (0.046 mole) of 2,4-dichlorocinnamic acid, 0.50 g. of platinum oxide catalyst, and 200 ml. of absolute ethanol was hydrogenated at 50 psi for 1.5 hours, at ambient temperature. The usual workup gave 10.0 g. (96% yield) of product as an oil; its pmr spectrum identified the oil as the ethyl ester of the desired propionic acid and this was confirmed by its elemental analyses.

Anal. Calcd. for $C_{11}H_{12}Cl_2O_2$: C, 53.91; H, 4.94; Cl, 29.05; N.E., 0.0. Found: C, 53.98; H, 5.15; Cl, 28.66; N.E. (sodium hydroxide), 0.0.

The ester, 9.9 g. (0.043 mole), 100 ml. of 95% ethanol, and 5 ml. of 50% aqueous sodium hydroxide were heated under reflux for one hour, the whole concentrated to dryness *in vacuo*, the residue dissolved in 50 ml. of water, and the solution treated with an excess of 20% aqueous hydrochloric acid. The solid that separated was filtered and air-dried to give 9.0 g. of crude acid, m.p. 73-76°. Recrystallization from 75 ml. of cyclohexane gave 7.3 g. (72% yield) of 2,4-dichlorobenzenepropionic acid, m.p. 75-77°.

Anal. Calcd. for $C_9H_8Cl_2O_2$: C, 49.35; H, 3.68; Cl, 32.38; N.E., 219. Found: C, 49.38; H, 3.49; Cl, 32.22; N.E. (sodium hydroxide), 223.

(b) 2,4-Dichlorobenzamidoxime.

(1) 2,4-Dichlorobenzonitrile.

A solution of 27.0 g. (0.142 mole) of 2,4-dichlorobenzal oxime and 150 ml. of 98% formic acid was heated under reflux for 24 hours and then concentrated to dryness *in vacuo*. The solid residue, 23.8 g., was sublimed at 45°/0.2 mm to give 22.5 g. (92% yield) of 2,4-dichlorobenzonitrile as colorless rhombs, m.p. 52-53°. The reaction was monitored by ir; at no time was there evidence of the formation of a formate ester.

Anal. Calcd. for $C_7H_3Cl_2N$: C, 48.88; H, 1.76; N, 8.14. Found: C, 48.68; H, 1.75; N, 7.86.

The material which did not sublime weighed 0.050 g.; recrystallization from benzene gave 0.040 g. of 2,4-dichlorobenzamide, m.p. and mixture m.p. with an authentic sample, 185-187°. The ir and pmr spectra of the two samples were identical.

(2) 2,4-Dichlorobenzamidoxime.

To a mixture of 13.9 g. (0.08 mole) of 2,4-dichlorobenzonitrile, 60 ml. of 95% ethanol, 6.25 g. (0.09 mole) of hydroxylamine hydrochloride, and 30 ml. of water was added 6.3 g. (0.045 mole) of micronized anhydrous potassium carbonate, and the whole stirred at ambient temperature for 22 hours. The insoluble material was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residual solid was stirred for 0.33 hour with 50 ml. of 10% aqueous hydrochloric acid and 150 ml. of water, filtered (see below) and the filtrate treated with an excess of solid sodium bicarbonate. The solid that separated was filtered and air-dried to give 6.0 g. of solid, m.p. 156-158°. Recrystallization from 100 ml. of benzene gave 5.2 g. (31% yield) of 2,4-dichlorobenzamidoxime, as long needles, m.p. unchanged at 156-158°.

Anal. Calcd. for $C_7H_6Cl_2N_2O$: C, 41.00; H, 2.95; N, 13.67. Found: C, 41.05; H, 2.94; N, 13.74.

The solid insoluble in the hydrochloric acid (see above) weighed 7.8 g. and was shown to be 2,4-dichlorobenzamide from its m.p., mixture m.p., and its ir, and pmr specta.

(c) 3-(2,4-Dichlorophenyl)-5-(2,4-dichlorophenethyl)-1,2,4-oxadiazole.

A solution of 3.5 g. (0.015 mole) of 2,4-dichlorobenzenepropionic acid in 10 ml. of thionyl chloride was heated under reflux for 5 hours, concentrated to dryness, the residue dissolved in 20 ml. of anhydrous benzene, and again concentrated to dryness. The residue, 2,4-dichlorobenzenepropionyl chloride, was not further purified, but was dissolved in 90 ml. of anhydrous dioxane; 3.0 g. (0.015 mole) of 2,4-dichlorobenzamidoxime was then added, followed by 0.2 ml. of boron trifluoride etherate. The solution was heated and stirred under reflux for 18 hours, then concentrated to dryness *in vacuo*, and the residue dissolved in 150 ml. of dichloromethane. The solution was washed successively with 30 ml. of 2.5% aqueous sodium bicarbonate, 15 ml. of water, and 30 ml. of saturated aqueous sodium chloride. The dried dichloromethane solution was concentrated to dryness to give 3 g. of a solid residue, m.p. 58-62°. Recrystallization from 90 ml. of hexane gave 1.50 g. of product, m.p. 66-68°; tlc: one spot, R_f *ca.* 0.65 (silica gel plates, benzene); ir (potassium bromide): ν 1590 (s), 1550 (m), 1475 (m), 1465 (s), 1440 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.25 (s, 4H, CH_2CH_2), 7.15-7.95 (m, 6H, 6 Ar-*H*); (for analyses, see Tables I, Compound **11**).

1-[3-(2,4-Dichlorophenyl)-1,2,4-oxadiazol-5-yl]-2-propanone (Table I, Compound **2**).

A solution of 5.1 g. (0.025 mole) of 2,4-dichlorobenzamidoxime, 25 ml. of methyl acetoacetate, and 100 ml. of

anhydrous toluene was heated under reflux for 5 hours and then concentrated to dryness *in vacuo*. The solid residue was leached with 25 ml. of pentane, filtered, and recrystallized from 250 ml. of hexane to give 4.0 g. (40% yield) of product, m.p. 76-78°; ir (potassium bromide): ν 1730 (s), 1595 (s), 1560 (m), 1470 (m), 1425 (w), 1410 (m) cm^{-1}; pmr (deuteriochloroform): δ 3.20 [unsymm. d (J = 12 Hz), 3H, CH_3], 4.07 (s, 2H, CH_2), 7.20-8.00 (m, 3H, 3 Ar-*H*).

(2-Chlorophenyl)carbamic Acid, 2-[3-(2,4-Dichlorophenyl)-1,2,4-oxadiazol-5-yl]-1-methylethyl Ester (Table I, Compound **13**).

To 0.80 g. (0,0029 mole) of the above 2-propanone derivative in a mixture of 45 ml. of methanol and 5 ml. of water, was added during 5 minutes a total of 0.21 g. (0.006 mole) of sodium borohydride. Subsequently, the mixture was stirred for 1.5 hours at ambient temperature, heated under reflux for 10 minutes, and then concentrated *in vacuo* to remove methanol. The residual aqueous phase was treated with an excess of 5% aqueous hydrochloric acid and then extracted with three 25 ml. portions of dichloromethane. The dichloromethane extracts were combined, washed, dried, and concentrated to give the carbinol as a noncrystalline oil, that showed no carbonyl absorption. The yield was 0.65 g. (82%).

To the above oil, chilled by means of an external ice-water bath, was added, dropwise, a solution of 0.37 g. (0.0024 mole) of *o*-chlorophenylisocyanate in 15 ml. of anhydrous benzene, followed by 0.18 g. (0.0024 mole) of dry pyridine in 10 ml. of anhydrous benzene. Subsequently, the solution was heated under reflux for 4 hours, cooled, and concentrated to dryness *in vacuo*. The residual solid was recrystallized from 50 ml. of 2-propanol to give 0.50 g. of product, m.p. 89-92°; ir (potassium bromide): ν 3305 (m), 1715 (s), 1590 (s), 1560 (m), 1540 (s), 1470 (s), 1445 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.55 [unsymm. d (J = 6 Hz), 3H, CH_3], 3.35 [d (J = 6 Hz), 2H, CH_2], 5.20-6.00 (m, 2H, C*H* plus N*H*), 6.95-8.50 (m, 7H, 7 Ar-*H*).

5-(2-Aminophenyl)-3-(2,4-dichlorophenyl)-1,2,4-oxadiazole (Table I, Compound **4**).

To a solution of 0.090 g. (0.015 mole) of sodium methoxide in 30 ml. of absolute ethanol was added 1.0 g. (0.005 mole) of 2,4-dichlorobenzamidoxime and 0.80 g. (0.005 mole) of purified isatoic anhydride, and the solution heated under reflux for 3 hours. The product crystallized from the cooled reaction mixture; it was filtered and recrystallized from 30 ml. of acetonitrile to give 0.47 of product, m.p. 245-247°; ir (potassium bromide): ν 3440 (s), 1635 (s), 1620 (s), 1600 (s), 1580 (m), 1550 (s), 1495 (s), 1470 (s), 1455 (s) cm^{-1}; pmr (deuteriochloroform): δ 5.68-6.15 (m, 2H, NH_2), 6.60-8.20 (m, 7H, 7 Ar-*H*).

3-(4-Chlorophenyl)-4,5-dihydro-5-methyl-1,2,4-oxadiazole (Table II, Compound **15**).

A solution of 8.5 g. (0.05 mole) of 4-chlorobenzamidoxime and 22.0 g. (0.050 mole) of acetaldehyde in 100 ml. of 95% ethanol plus 20 ml. of water was maintained at ambient temperature for 16 hours, heated under reflux for 2 hours, and concentrated to dryness *in vacuo*. The solid residue was washed with water and dried to give 9.1 g. of solid, m.p. 144-146°. Recrystallization from 600 ml. of diisopropyl ether gave 6.8 g. of product, m.p. unchanged at 144-146° (5); ir (potassium bromide): ν 3420 (b, m), 1590 (s), 1550 (w), 1500 (s), 1460 (s), 1440 (m), 1380 (s), cm^{-1}; pmr (deuteriochloroform): δ 1.45 [d (J = 6 Hz), 3H, CH_3), 4.40-4.80 [m, 1H, NH (equilibration with deuterium oxide gave a residual weak singlet at δ 4.63)], 5.60-6.00 [symmetrical 5-line signal centered at δ 5.82, 1H, C*H* (equilibration with deuterium oxide gave an ABq (J = 6, 12 Hz) centered at 5.83], 7.20-7.75 (m, 4H, 4 Ar-*H*).

4-Acetyl-3-(4-chlorophenyl)-3,4-dihydro-5-methyl-1,2,4-oxadiazole (Table II, Compound **31**).

A suspension of 2.0 g. (0.015 mole) of the above 4,5-dihydro derivative in 0.05 g. of anhydrous pyridine and 25 ml. of acetic anhydride was stirred at ambient temperature for 48 hours when a solution finally formed. The solution was cooled in wet ice, the trace of solid that separated was filtered, and the filtrate was concentrated *in vacuo* to give 3.5 g. of a residual syrup that could not be induced to crystallize. It was dissolved in 100 ml. of pentane and the solution cooled in wet ice to give a gummy precipitate. This was filtered, the filtrate was concentrated to *ca.* 50 ml., and cooled in wet ice to give 1.2 g. of solid, m.p. 62-79°; two recrystallizations from pentane gave 0.6 g. of solid, m.p. 82-84°, and a third recrystallization from 20 ml. of cyclohexane gave 0.2 g. of product, m.p. 90-92°; ir (deuteriochloroform): ν 1700 (s), 1620 (s), 1590 (m), 1560 (w), 1480 (s), 1440 (w), 1420 (s), 1400 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.55 [d (J = 6 Hz), 3H, CH_3], 2.25 (s, 3H, CH_3CO), 5.95 [q (J = 6, 12 Hz), 1H, C*H*], 7.20-7.85 (m, 4H, 4 Ar-H).

3,5-*bis*(2,4-Dichlorophenyl)-4,5-dihydro-1,2,4-oxadiazole (Table II, Compound **25**).

A solution of 2.0 g. (0.0055 mole) of 3,5-*bis*(2,4-dichlorophenyl)-1,2,4-oxadiazole in 100 ml. of anhydrous tetrahydrofuran, in a nitrogen atmosphere, was cooled to 10° and stirred, during the dropwise addition of 7.5 ml. of a *M* solution of diborane in tetrahydrofuran. Subsequently, the solution was stirred for 16 hours at ambient temperature, then heated for 2 hours under reflux, cooled to 25°, and treated with 5 ml. of water, dropwise. The mixture was then heated under reflux for 0.5 hour, concentrated to dryness *in vacuo*, the residual solid was triturated with 50 ml. of water, filtered, and dried; it weighed 2.0 g., m.p. 110-115° dec. Recrystallization from 700 ml. of hexane gave 1.2 g. of the product, m.p. 118-120° dec., R_f 0.4 (tlc, silica gel plates, benzene; in the same system, the starting material had an R_f 0.9), ir (potassium bromide): ν 3400 (w), 3300 (m), 3080 (w), 1580 (s), 1560 (w), 1480 (w), 1460 (w), 1440 (s), 1380 (m), 1370 (m), 1350 (s) cm^{-1}; pmr (deuteriochloroform): δ 5.50-5.60 [m, 1H, N*H* (equilibrates with deuterium oxide)], 6.84 [d (J = 3 Hz), 1H, *H* at position-5], 7.24-7.76 (m, 6H, 6 Ar-*H*).

3-(2,4-Dichlorophenyl)-5-methyl-1,2,4-oxadiazole (Table I, Compound **1**).

A mixture of 1.34 g. (0.065 mole) of 2,4-dichlorobenzamidoxine, 20 ml. of acetyl chloride, and 0.2 ml. of boron trifluoride etherate was heated for 17 hours under reflux to give a clear, dark yellow solution. This was concentrated to dryness *in vacuo*, the residual oil was dissolved in 20 ml. of absolute *n*-butanol, and the solution heated under reflux for 20 hours. The cooled reaction mixture gave 0.4 g. of solid, m.p. 95-172°. Sublimation at 78°/1 mm gave 0.10 g. of colorless needles, m.p. 90-92°; ir (deuteriochloroform): ν 1675 (w), 1585 (s), 1550 (m), 1450 (w), 1430 (w), 1375 (w), 1340 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.68 (s, 3H, CH_3), 7.25-7.94 (m, 3H, 3 Ar-*H*).

The solid which did not sublime was shown to be 2,4-dichlorobenzamide.

3-(2,4-Dichlorophenyl)-4,5-dihydro-5-methyl-1,2,4-oxadiazole (Table II, Compound **2**).

(a) A solution of 4.2 g. (0.02 mole) of 2,4-dichlorobenzamidoxime, 18.0 g. (0.4 mole) of acetaldehyde, 100 ml. of 95% ethanol, and 20 ml. of water was kept at ambient temperature for

18 hours, and then concentrated to dryness *in vacuo*. The solid residue was washed with 100 ml. of water, and dried to give 4.2 g. of crude product, m.p. 98-100°. Recrystallization from 600 ml. of hexane gave 3.5 g. of pure material, m.p. 100-102°; ir (potassium bromide): ν 3180 (s), 1595 (s), 1585 (s), 1550 (m), 1490 (s), 1460 (s), 1440 (s), 1435 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.51 [d (J = 6 Hz), 3H, CH_3], 4.80-5.40 (bm, 1H, N*H*), 5.75-6.05 (8-line multiplet, 1H, C*H*), 7.10-7.75 (m, 3H, 3 Ar-*H*).

(b) To a stirred solution of 0.33 g. (0.0014 mole) of 3-(2,4-dichlorophenyl)-5-methyl-1,2,4-oxadiazole (see above) in 15 ml. of tetrahydrofuran was added dropwise at 10-15°, 1.5 ml. of a *M* solution of diborane in tetrahydrofuran. Stirring was continued for 16 hours at ambient temperature, the solution was then heated for 3 hours under reflux, cooled to 10°, 1.5 ml. of water added, the mixture heated for 0.5 hour under reflux, and then concentrated *in vacuo*. The residual solid was washed with 5 ml. of water and dried to give 0.30 g. of solid, m.p. 90-95°. Recrystallization from 35 ml. of hexane gave 0.17 g. of product, m.p. 99-101°; a mixture m.p. with a sample from (a) was 99-101° and the ir and pmr spectra of both samples were superimposable.

3-(2,4-Dichlorophenyl)-5-ethoxy-4,5-dihydro-1,2,4-oxadiazole (Table II, Compound **24**).

A solution of 0.5 g. (0.0025 mole) of 2,4-dichlorobenzamidoxime in 15 ml. of triethylorthoformate was heated for 0.5 hour in an oil bath maintained at 140-147°, then concentrated *in vacuo*. The residual oil was extracted with 15 ml. of a 9:1 mixture of cyclohexane: benzene at the boiling point, the hot extract was decanted, and allowed to cool slowly to give 0.050 g. of product, m.p. 147-149°; ir (deuteriochloroform): ν 3420 (w), 1645 (s), 1600 (s), 1585 (m), 1565 (w), 1545 (w), 1510 (w), 1490 (m), 1450 (w), 1410 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.33 [t, (J = 8 Hz), 3H, CH_3], 3.78 [q (J = 8, 18 Hz), 2H, CH_2], 5.06 (bs, 1H, N*H*), 7.15-7.80 (m, 4H, C*H* plus 3 Ar-*H*).

REFERENCES AND NOTES

(1) To whom all correspondence should be addressed.

(2) See L. C. Behr, "1,2,4-Oxadiazoles" in "Five-and Six-Membered Compounds with Nitrogen and Oxygen", Vol. 17 of "The Chemistry of Heterocyclic Compounds", Interscience Publishers, New York, N.Y., 1962, pp. 245-262, for a review of the synthetic methods employed to prepare that heterocycle as well as its dihydro derivatives. A brief discussion of the mechanism of these reactions can also be found in this review.

(3) The reduction of organic compounds with diborane has been reviewed by C. F. Lane, *Chem. Rev.*, **76**, 773 (1976). He has noted the only reference which can be found in the literature concerning the reduction of an *endo*-(C=N) linkage in a heterocycle by diborane in a paper by S. Yamada and S. Ikegami, *Chem. Pharm. Bull.*, **14**, 1382 (1966). The citation, in the form of equation (64) on p. 783 of the Lane article, is a copy of the Yamada and Ikegami equation on p. 1383 of their article. That equation is obviously an error, since the text discussing the equation clearly refers to the compounds being reduced by diborane as 3,4-dihydroisoquinolines, even though the equation shows then as the completely aromatic isoquinolines. Again, in the Experimental, these compounds are specifically referred to as 3,4-dihydroisoquinolines. Thus, in reality, Yamada and Ikegami are reporting the reduction of the 1,2-(C=C) linkage of a 3,4-dihydroisoquinoline by diborane. We wrote to these authors in March, 1977 and called to their attention this discrepancy between text and equations; as of February, 1978, no reply was received.

(4) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N. Y., 1972; "Hydroboration", W. A. Benjamin, New York, N.Y., 1962.

(5) U. S. Patent 3,968,224, April 28, 1975 to Stauffer Chemical describes the preparation of this compound by the same procedure, and reports a m.p. of 110-112°.