reveal any significant relationship between the warfarin elimination rate constant and the plasma warfarin concentration required to elicit a certain degree of inhibition of R_{syn}. Such correlation is more likely to be evident in a group of human subjects consisting of individuals with widely differing warfarin half-lives not ascribable to exposure to enzyme inducers or inhibitors.

The results of this investigation demonstrate that unusually rapid or slow elimination of warfarin may be (at least in some cases) the result of, or associated with, unusually extensive or limited distribution of the drug in extravascular spaces. This, in turn, may affect markedly the relationship between warfarin concentration in the plasma and its anticoagulant effect, since this drug acts in the liver and not (like heparin) in the circulation. It is, therefore, unwise to adjust warfarin dosage regimens of patients solely on the basis of their warfarin half-life without considering the possibility that an unusually long or short warfarin half-life is associated with a change in the relationship between plasma warfarin concentration and intensity of anticoagulant effect. Subsequent reports will deal with the mechanism of the observed intersubject differences in the distribution of warfarin in the body.

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Anticonvulsant Activity and Inhibition of Respiration in Rat Brain Homogenates by Substituted Oxadiazoles

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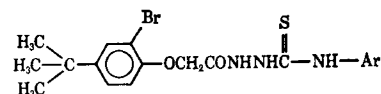
Abstract □ Several 2,5-disubstituted 1,3,4-oxadiazoles were synthesized, characterized, and tested for their effectiveness in inhibiting the respiratory activity of rat brain homogenate. All substituted oxadiazoles and their precursors, thiosemicarbazides, were found to inhibit nicotinamide adenine dinucleotide- (NAD) dependent oxidations of pyruvate and α-ketoglutarate as well as the NAD-independent oxidation of succinate. Anticonvulsant activity, as exhibited by protection against pentylenetetrazol-induced seizures, with substituted thiosemicarbazides and the corresponding cyclized oxadiazoles ranged from 30 to 90% at a dose of 100 mg/kg. The degree of protection afforded by these compounds, however, was unrelated to their ability to inhibit oxidation of pyruvate, α-ketoglutarate, and succinate.

Keyphrases □ 1,3,4-Oxadiazoles, 2,5-disubstituted—synthesis, inhibition of NAD-dependent and NAD-independent oxidations, relationship to anticonvulsant activity □ Structure-activity relationships—2,5-disubstituted 1,3,4-oxadiazoles–anticonvulsant activity, rats □ Thiosemicarbazides, substituted—synthesis, anticonvulsant activity, inhibition of respiratory activity, rats □ Pyruvate, α-ketoglutarate, and succinate oxidation, inhibition—effects of substituted thiosemicarbazides and cyclized oxadiazoles □ Anticonvulsant activity—relationship to inhibition of respiratory activity, substituted thiosemicarbazides and oxadiazoles

Considerable interest has recently been focused on 2,5-disubstituted 1,3,4-oxadiazoles, which have been shown to possess analgesic (1, 2), central nervous system depressant (3), muscle relaxant (4–6), and tranquilizing (4, 5) properties. These observations prompted the synthesis of 2-arylamino-5-(4-*tert*-butyl-2-bromophenoxymethyl)-1,3,4-oxadiazoles. In the present study, the ability of these oxadiazoles and their precursors, thiosemicarbazides, to inhibit nicotinamide adenine dinucleotide- (NAD) depen-

Table I—Physical Constants of 4-Aryl-1-(4-*tert*-butyl-2-bromophenoxyacetyl)thiosemicarbazides



Compound	Ar	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found
I	C_6H_5	164–165°	85	$C_{19}H_{22}BrN_3O_2S$	C	52.29	52.30
					H	5.04	5.54
					N	9.63	9.34
II	o-CH_3-C_6H_4	85–86°	80	$C_{20}H_{24}BrN_3O_2S$	C	53.33	52.98
					H	5.33	5.30
					N	9.33	9.15
III	m-CH_3-C_6H_4	163°	85	$C_{20}H_{24}BrN_3O_2S$	C	53.33	53.07
					H	5.33	4.95
					N	9.33	9.30
IV	p-CH_3-C_6H_4	166°	90	$C_{20}H_{24}BrN_3O_2S$	C	53.33	53.56
					H	5.33	5.29
					N	9.33	9.43
V	o-CH_3O-C_6H_4	166°	90	$C_{20}H_{24}BrN_3O_3S$	C	51.50	51.35
					H	5.15	5.10
					N	9.01	9.23
VI	p-CH_3O-C_6H_4	142–143°	92	$C_{20}H_{24}BrN_3O_3S$	C	51.50	51.76
					H	5.15	5.33
					N	9.01	8.93
VII	p-Cl-C_6H_4	165–166°	90	$C_{19}H_{21}BrClN_3O_2S$	C	48.45	48.63
					H	4.46	4.01
					N	8.92	8.89
VIII	p-Br-C_6H_4	169–170°	90	$C_{19}H_{21}Br_2N_3O_2S$	C	44.26	44.03
					H	4.07	4.13
					N	8.15	8.24
IX	p-I-C_6H_4	170–171°	90	$C_{19}H_{21}BrIN_3O_2S$	C	40.56	40.32
					H	3.73	3.65
					N	7.47	7.33

[a] Melting points were taken in open capillary tubes and are corrected.

dent oxidation of pyruvate and α-ketoglutarate and NAD-independent oxidation of succinate was investigated. Anticonvulsant activity exhibited by thiosemicarbazides and their corresponding cyclized oxadiazoles was evaluated to correlate their pharmacological properties with their inhibitory effects on the respiratory activity of the rat brain homogenate. The various oxadiazoles were synthesized by following the methods outlined in Scheme I.

EXPERIMENTAL[1]

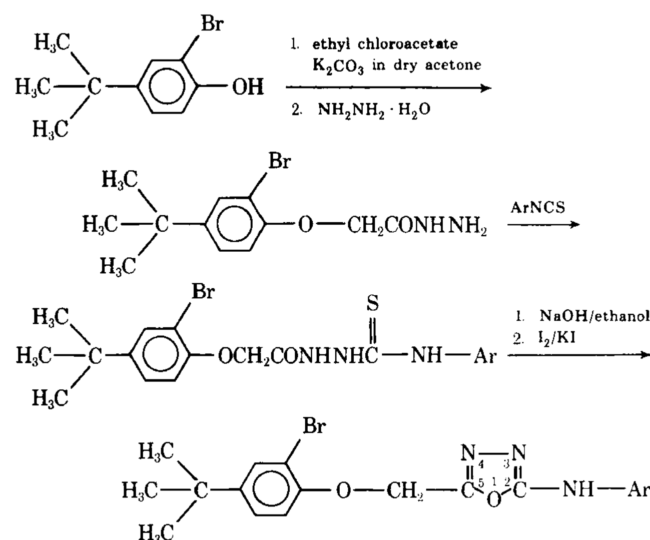
4-*tert*-Butyl-2-bromophenoxyacetylhydrazide—A mixture of 45.8 g (0.2 mole) of 4-*tert*-butyl-2-bromophenol (0.2 mole), 27.8 g of anhydrous potassium carbonate (0.2 mole), and 24.5 g of ethyl chloroacetate (0.2 mole) in 100 ml of dry acetone was refluxed on a water bath for 18–24 hr. The mixture was cooled and filtered. The excess solvent from the filtrate was removed by distilling under reduced pressure. To the residue was added 8 g of 8% $NH_2NH_2 \cdot H_2O$ (1.5 moles) and 50 ml of ethanol; this mixture was refluxed for 10–12 hr. Excess ethanol was distilled under reduced pressure. The crude product which separated on cooling was filtered and recrystallized from ethanol, yielding 36.0 g (60%), mp 122°.

Anal.—Calc. for $C_{12}H_{17}BrN_2O_2$: C, 47.84; H, 5.65. Found: C, 48.30; H, 5.70.

4-Aryl-1-(4-*tert*-butyl-2-bromophenoxyacetyl)thiosemicarbazide—The hydrazide (0.01 mole) and aryl isothiocyanate (0.01 mole) were mixed in 95% ethanol and refluxed on a water bath for 6 hr. The excess solvent was distilled under reduced pressure. The solid mass which separated out on cooling was filtered, dried, and finally recrystallized from ethanol. All thiosemicarbazides were characterized by their sharp melting points and elemental analyses (Table I).

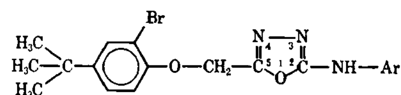
[1] Commercial chemicals were used in this study. Adenosine monophosphate, cytochrome c, α-ketoglutarate, sodium pyruvate, and sodium succinate were purchased from Sigma Chemical Co., St. Louis, Mo.

2-Arylamino-5-(4-*tert*-butyl-2-bromophenoxymethyl)-1,3,4-oxadiazoles—The thiosemicarbazides were cyclized to the corresponding 3,4-oxadiazoles by the method of Silberg and Cosma (7). To an ethanolic (300 ml) suspension of thiosemicarbazide (0.01 mole) was added sodium hydroxide (4 *N*, 5 ml) with cooling and shaking. Iodine in potassium iodide solution (5%) was added gradually with stirring to the clear solution until the color of iodine persisted at room temperature. The contents were then heated under reflux on a water bath, and more iodine solution was added carefully until a permanent color of iodine persisted. The reaction mixture was then poured into ice-cold water (500 ml), and the solid mass which separated was filtered and washed with water and then with carbon disulfide to remove the iodine. The crude product was finally recrystallized from dilute ethanol in the presence of animal charcoal (Table II).



Scheme I

Table II—Physical Constants of 2,5-Disubstituted 1,3,4-Oxadiazoles



Compound	Ar	Melting Point[a]	Yield, %	Formula	Analysis, %	Calc.	Found
X	C_6H_5	149–150°	55	$C_{19}H_{20}BrN_3O_2$	C H N	56.71 4.97 10.44	56.26 4.29 10.35
XI	*o*-CH_3-C_6H_4	129–130°	52	$C_{20}H_{22}BrN_3O_2$	C H N	57.69 5.28 10.09	57.36 5.20 9.80
XII	*m*-CH_3-C_6H_4	137–138°	60	$C_{20}H_{22}BrN_3O_2$	C H N	57.69 5.28 10.09	57.52 5.19 9.92
XIII	*p*-CH_3-C_6H_4	152–153°	53	$C_{20}H_{22}BrN_3O_2$	C H N	57.69 5.28 10.09	57.49 5.33 9.89
XIV	*o*-CH_3O-C_6H_4	157–158°	50	$C_{20}H_{22}BrN_3O_3$	C H N	55.55 5.09 9.72	55.15 5.54 10.03
XV	*p*-CH_3O-C_6H_4	153°	53	$C_{20}H_{22}BrN_3O_3$	C H N	55.55 5.09 9.72	55.32 5.13 9.50
XVI	*p*-Cl-C_6H_4	135–137°	49	$C_{19}H_{19}BrClN_3O_2$	C H N	52.33 4.35 9.62	52.46 4.30 9.89
XVII	*p*-Br-C_6H_4	156–157°	56	$C_{19}H_{19}Br_2N_3O_2$	C H N	47.40 3.95 8.73	47.40 3.63 8.43
XVIII	*p*-I-C_6H_4	158–159°	55	$C_{19}H_{19}IBrN_3O_2$	C H N	43.18 3.59 7.95	43.53 3.58 7.87

[a] Melting points were taken in open capillary tubes and are corrected.

Assay of Respiratory Activity of Rat Brain Homogenate—Male albino rats, kept on *ad libitum* diet, were used in all experiments. Rats weighing 150–200 g were sacrificed by decapitation. The brains were taken out immediately and homogenized[2] in the ratio of 1:9 (w/v) in 0.25 *M* cold sucrose. Respiratory activity was determined by measuring the oxygen consumption by the conventional Warburg manometric method at 37° with air as the gas phase. Fresh brain homogenate of healthy albino rats equivalent to 125 mg wet tissue weight was used in each flask. The reaction mixture, in a final volume of 3.0 ml, consisted of 20 m*M* Na_2HPO_4 buffer (pH 7.4), 6.7 m*M* $MgSO_4$, 1 m*M* AMP (sodium salt), 33 m*M* KCl, and 500 μg of cytochrome c. The central well contained 0.2 ml of 20% KOH solution. All thiosemicarbazides and oxadiazoles were used in the final concentration of 2 m*M* to study their effects on the oxidation of the various substrates used at a final concentration of 10 m*M*. The compounds were dissolved in propylene glycol (100%), and an equivalent amount of the solvent was added to the control vessels.

Determination of Anticonvulsant Activity—Anticonvulsant activity against pentylenetetrazol-induced seizures was determined in mice of either sex weighing 25–30 g. The mice were divided in groups of 10, keeping the group weights as near the same as possible. Various oxadiazoles and their precursor thiosemicarbazides were suspended in 5% aqueous gum acacia to give a concentration of 0.25% (w/v). The test compounds were injected intraperitoneally in a group of 10 animals at a dose of 100 mg/kg. Four hours after the administration of these compounds, the mice were injected with pentylenetetrazol, 90 mg/kg sc. This dose of pentylenetetrazol has been shown to produce not only convulsions in almost all untreated mice but also to exhibit 100% mortality over 24 hr. On the other hand, no mortality was observed over 24 hr in animals treated with 100 mg/kg alone of the test compounds. The mice were then observed for 60 min for the occurrence of seizures. An episode of clonic spasm persisting a minimum of 5 sec was considered a threshold convulsion. Transient intermittent jerks or tremulousness was not counted. Animals devoid of threshold convulsions over 60 min were considered protected. The number of animals protected in each group was recorded, and the anticonvulsant activity of these oxadiazoles and their precursor thiosemicarbazides was represented as percent protection. The animals were then observed for 24 hr and their mortality was recorded.

[2] Potter-Elvehjem homogenizer.

RESULTS AND DISCUSSION

The effects of 4-aryl-1-(4-*tert*-butyl-2-bromophenoxyacetyl)-thiosemicarbazides in the *in vitro* respiratory activity using rat brain homogenate as the source of enzyme are recorded in Table III. All these thiosemicarbazides were found to inhibit NAD-dependent oxidation of pyruvic acid and α-ketoglutaric acid. These thiosemicarbazides, unlike other anticonvulsants belonging to the groups of quinazolones (8, 9), thiozolidones (10), and nitrobenzamides (11), also inhibited the NAD-independent oxidation of succinic acid, as was observed with phenothiazine (12) and salicylic acid derivatives (13).

Substituted oxadiazoles obtained by cyclization of the corresponding thiosemicarbazides exhibited inhibition (Table IV) of the respiratory activity, where such an inhibition was found to be of low order with the cyclized oxadiazoles. These results failed to provide any specific requirements in the molecular structure of the thiosemicarbazides and their corresponding cyclized oxadiazoles with respect to their ability to inhibit NAD-dependent and NAD-independent oxidations. All oxadiazoles exhibited a lower degree of inhibition of the oxidation of pyruvic acid, α-ketoglutaric acid, and succinic acid than the corresponding thiosemicarbazides, in good agreement with earlier observations (14). Protection observed against pentylenetetrazol-induced seizures reflected anticonvulsant activity of 4-aryl-1-(4-*tert*-butyl-2-bromophenoxyacetyl)thiosemicarbazides (Table III). All thiosemicarbazides possessed anticonvulsant activity, with the degree of protection ranging from 30 to 90%. Maximum protection was observed with the thiosemicarbazides having 2-methylphenyl and 4-bromophenyl substituents at position 1 of their phenyl nucleus. The cyclization of these thiosemicarbazides to corresponding oxadiazoles retained anticonvulsant effectiveness to a lesser degree, ranging from 30 to 70% (Table IV). Maximum protection of 70% was observed with 2-(4-bromophenylamino)-5-(4-*tert*-butyl-2-bromophenoxymethyl)-1,3,4-oxadiazole.

In the present study, all thiosemicarbazides and oxadiazoles

Table III—Anticonvulsant Activity and Inhibition of Respiratory Activity of Rat Brain Homogenate by 4-Aryl-1-(4-*tert*-butyl-2-bromophenoxyacetyl)thiosemicarbazides

Compound[a]	Anticonvulsant[b] Activity, % Protection	Pentylenetetrazol Mortality, %[c]	Inhibition of Respiratory Activity, %[d]		
			Pyruvate	α-Ketoglutarate	Succinate
I	70	30	81.4 ± 1.9	75.4 ± 1.8	82.6 ± 2.4
II	90	20	84.0 ± 1.9	78.5 ± 1.6	83.0 ± 2.2
III	50	20	88.4 ± 2.0	88.6 ± 2.3	94.3 ± 2.5
IV	40	20	75.2 ± 1.6	76.0 ± 1.9	84.3 ± 2.1
V	30	10	83.5 ± 1.6	74.2 ± 1.7	88.2 ± 2.0
VI	30	40	83.0 ± 1.8	76.2 ± 1.8	83.7 ± 1.8
VII	60	30	78.0 ± 1.7	73.9 + 1.6	81.3 ± 2.0
VIII	90	Nil	86.7 ± 2.0	80.5 ± 2.1	89.9 ± 2.0
IX	30	40	81.2 ± 2.0	75.9 ± 1.9	80.3 ± 1.9

[a] Compound numbers are as recorded in Table I. [b] Anticonvulsant activity was determined at a dose of 100 mg/kg as described under *Experimental*. [c] Represents mortality over 24 hr in each group of animals administered pentylenetetrazol. [d] Each experiment was done in duplicate. All values represent mean values of percent inhibition with ± standard error of the mean calculated from three separate experiments. Inhibition was determined by the decrease in the oxygen uptake/125 mg wet tissue weight/hr. Assay conditions are as indicated in the text. All compounds were used at a final concentration of 2 m*M*.

Table IV—Anticonvulsant Activity and Inhibition of Respiratory Activity of Rat Brain Homogenate by 2-Arylamino-5-(4-*tert*-butyl-2-bromophenoxymethyl)-1,3,4-oxadiazoles

Compound[a]	Anticonvulsant[b] Activity, % Protection	Pentylenetetrazol Mortality, %[c]	Inhibition of Respiratory Activity, %[d]		
			Pyruvate	α-Ketoglutarate	Succinate
X	30	20	60.9 ± 1.6	74.5 ± 1.7	84.3 ± 1.9
XI	50	Nil	56.0 ± 1.5	74.6 ± 1.7	71.0 ± 1.6
XII	50	30	49.4 ± 1.4	79.5 ± 2.0	87.8 ± 1.8
XIII	60	10	69.4 ± 1.7	85.0 ± 2.2	88.9 ± 2.1
XIV	30	30	27.1 ± 1.3	63.2 ± 1.4	39.6 ± 1.5
XV	60	50	63.6 ± 1.7	81.9 ± 2.0	72.5 ± 1.9
XVI	40	30	60.5 ± 1.8	79.5 ± 1.4	81.5 ± 2.1
XVII	70	10	54.7 ± 1.5	82.7 ± 1.6	59.2 ± 1.6
XVIII	60	10	65.8 ± 1.7	94.1 ± 2.4	57.0 ± 1.5

[a] Compound numbers are as recorded in Table II. [b] Anticonvulsant activity was determined at a dose of 100 mg/kg as described under *Experimental*. [c] Represents percent mortality over 24 hr in each group of animals administered pentylenetetrazol. [d] Each experiment was done in duplicate. All values represent mean values of percent inhibition with ± standard error of the mean calculated from three separate experiments. Inhibition was determined by the decrease in the oxygen uptake/125 mg wet tissue weight/hr. Assay conditions are as indicated in the text. All compounds were used at a final concentration of 2 m*M*.

possessing appreciable anticonvulsant activity showed low mortalities against pentylenetetrazol-induced death in the experimental animals (Tables III and IV). The unspecific inhibition of both the NAD-dependent and the NAD-independent oxidations indicates the possible sensitivity of these compounds toward both NADH-CoQ(oxido)reductase (Complex I) and succinate-CoQ(oxido)reductase (Complex II) of the electron-transport chain. It is possible that hydro CoQ-cytochrome c(oxido) reductase (Complex III) and/or cytochrome c-O_2(oxido)reductase (Complex IV) are also susceptible to these thiosemicarbazides and their cyclized oxadiazoles and may thus account for their ability to inhibit flavine adenine dinucleotide-dependent oxidation of succinate (NAD-independent) and NAD-dependent oxidation of pyruvate and α-ketoglutarate by rat brain homogenate. These studies warrant further investigations with purified enzyme preparations to elucidate the biochemical basis for the anticonvulsant activity of substituted oxadiazoles.

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