Synthesis and Comparative Skeletal Muscle Relaxant Activity of Some 2,4-Imidazolidinediones and Their Corresponding 5-Hydroxy-2,4-imidazolidinediones

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A series of 5-hydroxy substitution products of 2,4-imidazolidinediones, including the 5-hydroxy metabolite of the skeletal muscle contraction antagonist, dantrolene sodium, has been synthesized and evaluated for skeletal muscle relaxant activity. Most of these analogues are active in vivo with iv administration and in vitro. While two analogues are also active by oral and ip administration, only 1-[[[5-(3,4-dichlorophenyl)-2-furanyl]methylene]amino]-5-hydroxy-2,4-imidazolidinedione is sufficiently active in inhibiting the Straub tail in mice. However, none of these analogues has a muscle relaxant efficacy index > 1, comparable to dantrolene.

A new type of skeletal muscle relaxant was originally reported by Snyder et al.[1] Dantrolene and dantrolene sodium[2] have been studied extensively,[3-6] and dantrolene sodium has been defined pharmacologically as a "skeletal muscle contraction antagonist".[7] Dantrolene sodium has been shown to be effective in the treatment of spasticity of varying etiologies.[8-11]

White and Schwan[12] have recently reported the synthesis of 5-hydroxy-1-[[[5-(4-nitrophenyl)-2-furanyl]-methylene]amino]-2,4-imidazolidinedione, a major metabolite of dantrolene sodium. This metabolite has been reported to have skeletal muscle relaxant activity in vitro but was inactive when administered ip and po.[13]

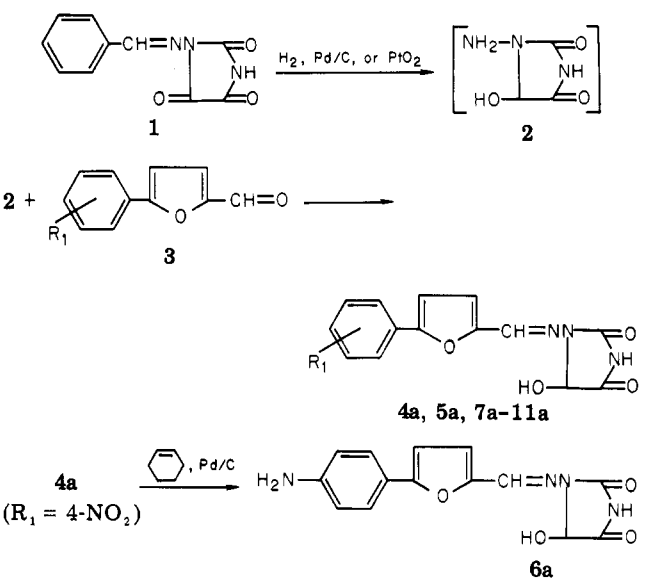
The identification of the contraction antagonist properties of the 5-hydroxy metabolite of dantrolene led to the synthesis of a number of 5-hydroxy-1-[[(5-arylfuranyl)-methylene]amino]-2,4-imidazolidinediones. We report here the synthesis of some 5-hydroxy-2,4-imidazolidinediones, the pharmacologic evaluation of their skeletal muscle contraction-antagonist properties, and a comparison of these properties with those of some 5-deoxy analogues.[1]

Chemistry. Scheme I summarizes the synthesis of these 5-hydroxyimidazolidinediones. The 5-hydroxy-2,4-imidazolidinediones (except **6a**) have been prepared through a catalytic reduction and hydrogenolysis of 1-(phenylmethyleneamino)imidazolidinetrione (**1**) to 1-amino-5-hydroxy-2,4-imidazolidinedione (**2**).[12] The amino compound **2** was then condensed in situ with the selected aldehyde to yield the desired 5-hydroxy-1-[[[5-(substituted phenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione. Either Pd/C or PtO_2 was a suitable catalyst for conversion of **1** to **2**. The 4-nitro compound **4a** was prepared from **2** which was synthesized by both reductive methods. Proof of structural assignment of the hydroxy group at the imidazolidinedione 5 position has been published for **4a**.[12] The 4-amino compound, **6a**, was prepared by catalytic reduction of **4a**. The synthesized compounds are listed in Table I.

Pharmacology. The results of testing these compounds for skeletal muscle relaxation by gross observation in mice with po and ip administration are listed in Table II. Four of the 5-hydroxy compounds (**7a–10a**) showed skeletal muscle relaxant activity (ED_{50} values of 1000 mg/kg or less; see Table II), in most cases the greatest degree of activity being evident with the ip route. Two compounds (**7a** and **9a**) were the only 5-hydroxy structures which produced muscle relaxation when administered po. Three of the parent compounds [**4** (dantrolene), **8**, and **9**] were active skeletal muscle relaxants (ED_{50} values 1000 mg/kg or less) when administered po and ip.

Further evaluation of these compounds for twitch inhibition with iv administration was carried out in the pithed-rat gastrocnemius muscle preparation. The

Scheme I



maximal twitch inhibition and the calculated ED_{50} values and confidence limits are contained in Table II. Only three compounds did not produce twitch inhibition (20% or greater) by this method of evaluation—**6**, **11**, and **11a**. Two of these inactive compounds were the parent compounds, and **6a**, the 5-hydroxy product of **6**, caused considerable twitch inhibition.

These compounds, dissolved in dimethyl sulfoxide (Me_2SO), were then tested in the isolated rat diaphragm preparation. In this procedure all of the compounds, with the exception of **6**, **11**, and **11a** (same inactive compounds as in vivo study), inhibited the twitch response 40% or greater at a concentration of 60 mg/L or less.

In the morphine-induced Straub tail (ST) mouse[6] five compounds, **4**, **7a**, **8**, **9**, and **10a**, were effective. From the calculated ED_{50} (ST), a muscle-relaxant dose was determined for each compound and compared with the ED_{50} of the drug that caused motor incoordination as determined in the rotarod (Rr) test in order to obtain an estimate of the potential skeletal-muscle relaxant utility of each compound. The potential utility was registered as the muscle relaxant efficacy index (MREI), which is a measure of the separation between the two respective dose ranges. It is noteworthy that motor incoordination occurred at doses below those producing skeletal muscle relaxation as measured by abolishing the ST with all but one compound (**4**, dantrolene). It was therefore concluded that, because of the low MREI, the muscle relaxant properties of these other compounds were not as useful as those of the former compound.

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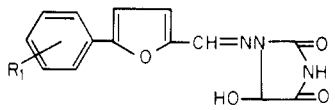
Table I



Compd	R_1	Yield, %	Mp, °C	Formula	Analyses[a]	Synthetic method	Recrystn solvent
4a	4-NO_2	15, 46	229–230	$C_{14}H_{10}N_4O_6$	C, H, N	A, B	None
5a	4-Cl	23	220–221	$C_{14}H_{10}ClN_3O_4$	C, H, N	A	CH_3NO_2
6a	4-NH_2	53	216–218	$C_{14}H_{12}N_4O_4$	C, H, N		EtOH
7a	3,4-Cl_2	65	223–225	$C_{14}H_9Cl_2N_3O_4$	C, H, N	B	None
8a	4-F	26	219–221	$C_{14}H_{10}FN_3O_4$	C, H, N	A	CH_3NO_2
9a	3-CF_3	57	210–212	$C_{15}H_{10}F_3N_3O_4$	C, H, N	B	None
10a	4-CN	45	224–226	$C_{15}H_{10}N_4O_4$	C, H, N	B	CH_3NO_2
11a	4-CH_3CONH	80	227–228	$C_{16}H_{14}N_4O_5$	C, H, N	A	None

[a] Compounds were analyzed for the elements indicated and were within ±0.4% of calculated values.

Experimental Section

Melting points are uncorrected. All compounds had consistent IR and NMR spectra for assigned structures. NMR spectra were obtained with a Varian A-60A spectrometer. Elemental analyses are indicated by symbols of the elements (see Table I) and all results were within ±0.4% of the theoretical values.

The requisite 5-aryl-2-furaldehydes were prepared by the method of Snyder et al.[1] The general methods (A and B) for preparation of the 5-hydroxy-2,4-imidazolidinediones are illustrated by the following two syntheses.

5-Hydroxy-1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione (4a, Method A). In MeOH (500 mL) were placed 1-(phenylmethyleneamino)-imidazolidinetrione[12] (87 g, 0.40 mol) and 5% Pd/C (20 g, 50% moisture). The mixture was reduced on a Parr apparatus (initially 40 psi) and uptake of 2 equiv was observed in 2 h. Another 20 g of Pd/C was added, and after an additional 7 h, 92% of the total theoretical H_2 uptake was observed. The reduction mixture was filtered, and insolubles were washed with MeOH (500 mL). The combined MeOH solutions were added to 5-(4-nitrophenyl)-2-furaldehyde (87 g, 0.40 mol), MeOH (2.0 L), and concentrated HCl (40 mL). The mixture was refluxed for 2 h and filtered hot to yield 20 g (15%) of **4a**, mp 229–230 °C.

1-[[[5-(3,4-Dichlorophenyl)-2-furanyl]methylene]-amino]-5-hydroxy-2,4-imidazolidinedione (7a, Method B). In MeOH (750 mL) were placed 1-(phenylmethyleneamino)-imidazolidinetrione (160 g, 0.74 mol) and PtO_2 (7.0 g). Hydrogenation on a Parr apparatus at an initial 45 psi allowed 55% of the theoretical 3 equiv of H_2 uptake in 6 h. The mixture was filtered, and the filtrate was diluted to 900-mL volume with MeOH.

In hot MeOH (1.0 L) was dissolved 5-(3,4-dichlorophenyl)-2-furaldehyde (24 g, 0.10 mol). To this solution at 30 °C were added concentrated HCl (10 mL) and 300 mL of the diluted reduction filtrate. The mixture was stirred 4 h, allowed to stand overnight, and then concentrated to 500-mL volume. The resulting product was collected, refluxed in NO_2CH_3 (600 mL) for 0.5 h, and then filtered to yield 23 g (65%) of **7a**, mp 223–225 °C.

1-[[[5-(4-Aminophenyl)-2-furanyl]methylene]amino]-5-hydroxy-2,4-imidazolidinedione (6a). In a solution of absolute EtOH (500 mL) and cyclohexene (500 mL) were placed **4a** (16 g, 0.050 mol) and 5% Pd/C (10 g, 50% moisture). The mixture was refluxed 17 h, cooled, and filtered. The collected solid was boiled in a solution of absolute EtOH (1.0 L) and water (50 mL), and the hot mixture was filtered. The combined filtrates were concentrated to a solid which was triturated with cold EtOH (200 mL) and collected to yield the product **6a** (7.9 g, 53%). Analytical material was obtained by recrystallization of a sample from EtOH to yield brown crystals, mp 216–218 °C.

Gross Observational Evaluation. Groups of ten male albino mice (TAC:SW/fBr) weighing 20–27 g were used. Test drugs were suspended in 0.5% methylcellulose (4000 Hz) and graded doses were administered po and ip. Concentrations were selected to permit delivery of the required dose in a volume of 10 mL/kg. Skeletal muscle relaxant responses were evaluated 60 min after drug administration. The skeletal muscle relaxant rating scale was 0 = no palpable decrease in muscle tone; 1 = slightly decreased muscle tone, with normal strengths in attempts to escape; 2 = moderately decreased muscle tone, with definitely reduced ability or inclination to escape; 3 = markedly reduced muscle tone, with definite ataxia; 4 = flaccid paralysis. Mice exhibiting a grade 2 or greater effect were recorded and ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[14]

Gastrocnemius Twitch Inhibition. Adult Sprague–Dawley male rats [TAC:SD/NfBR and Crl:COBS CD(SD)BR] weighing 300–350 g were anesthetized with ether, pithed, and artifically respired. Carotid artery blood pressure was monitored, and an external jugular vein was cannulated for drug injections. The Achilles tendon was isolated and detached with a piece of the calcaneous bone at its insertion, and the gastrocnemius muscle was freed from the surrounding tissue. The free tendon was connected with a ligature to a Statham force-displacement transducer, and muscle contractions were recorded on a Grass polygraph. Tubocurarine (0.075 mg/kg iv) was administered so that only the effects of direct electric stimulation of the muscle would be evident. Direct electric stimulation was accomplished with platinum electrodes inserted in the belly (anode) and in the Achilles tendon (cathode). Square-wave stimuli of 5-ms duration, 0.33 Hz, and a supramaximal voltage were used. The muscle was kept moist with frequent applications of warm (37 °C) mineral oil saturated with Krebs–Ringer solution.

Drugs were administered cumulatively at doses of 0.25, 0.83, 2.5, 8.3, and 25.0 mg/kg (total dose = 36.6 mg/kg) dissolved in tetrahydrofurfuryl alcohol (THFA) or Me_2SO. Solvent effects accounted for less than 20% decrease in the twitch response at the highest volume tested. ED_{50} values were calculated by polynomial regression.[15]

Morphine-Induced Straub Tail (ST), Lethality, and Therapeutic Index (TI). Albino male mice [TAC:(SW)fBR] (20–21 g) were used for these tests. The method used was the same as that described by Ellis and Carpenter.[7] Drugs were judged effective if they relaxed the ST at a dose which did not also cause the animal to lose its righting reflex for more than 1 min.

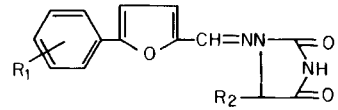
ED_{50} (ST) values (dose causing relaxation of the ST in 50% of the animals) and LD_{50} (72 h) were estimated by probit analysis.[16] TI values were calculated from the ratio of the LD_{50}/ED_{50} (ST) as measures of toxicity.

Rotarod and Muscle Relaxant Efficacy Index (MREI). The rotarod (Rr) test, a modification (i.e., 20 rpm) of that reported by Dunham and Miya,[17] was conducted in trained mice, 30 min after drug administration. If the animal stayed on the Rr for less than 30 s, the test was considered positive for muscle incoordination. ED_{50} (Rr) values (dose which caused 50% of the animals to fall off within 30 s) were estimated by probit analysis.[16]

The ratio of [ED_{50} (Rr)]/[ED_{50} (ST)] was designated as a muscle relaxant efficacy index (MREI).

Rat Diaphragm in Vitro. Male Charles River rats [COBS CD(SD)Br] weighing 300–350 g were sacrificed by a blow on the head. The diaphragm was removed and divided into strips 1 cm wide, and electrodes were placed at each end of the muscle strip for direct stimulation of the muscle. The strips were then placed in a 25-mL Andersen tissue bath containing Krebs–Ringer solution, the composition of which was (mM) NaCl 118.4, dextrose

Table II



Compd	R_1	R_2	Gross observation muscle relaxant,[a] ED_{50}, mg/kg po	Gross observation muscle relaxant,[a] ED_{50}, mg/kg ip	Gastrocnemius twitch inhibn: Max $\bar{X}$, % change ± SE[b]	Gastrocnemius twitch inhibn: ED_{50}, mg/kg	Gastrocnemius twitch inhibn: ED_{50}, μM/kg	Straub tail (ST) ED_{50}, mg/kg	Rotarod (Rr) ED_{50}, mg/kg	MREI,[c] ED_{50} (Rr)/ ED_{50} (ST)	LD_{50}, mg/kg	Therapeutic index, LD_{50}/ ED_{50} (ST)
4	4-NO_2	H	490 (98-2450)	83 (44-155)	−80 ± 2.8	2.2 (1.5-3.0)	7	56 (24-145)	153 (86-271)	2.70	>7000	124
4a	4-NO_2	OH	>1000	>1000	−76 ± 1.7	5.1 (3.8-6.9)	15	>1000	171 (114-260)	<0.17	>5000	
5	4-Cl	H	>1000	1000 (438-2280)	−74 ± 1.2	6.6 (6.0-7.2)	22	>1000	40 (20-112)	<0.04	>6000	
5a	4-Cl	OH	>1000	>1000	−77 ± 2.4	5.0 (4.0-6.2)	16	>1000	63 (4-239)	<0.06	522 (540-600)	
6	4-NH_2	H	>1000	>1000	−19 ± 2.5	>36.6	>129	>1000	>1000		1043 (792-1274)	
6a	4-NH_2	OH	>1000	>1000	−67 ± 7.0	11.8 (9.8-14.3)	39	>1000	>1000		192 (136-248)	
7	3,4-Cl_2	H	>1000	647 (380-1100)	−77 ± 0.5	3.5 (2.0-5.4)	10	>1000	181 (18-854)	<0.18	>7000	
7a	3,4-Cl_2	OH	109 (58-204)	72 (32-161)	−82 ± 0.3	6.7 (2.1-26.5)	19	34 (20-58)	10 (5-19)	0.30	209 (119-308)	6.1
8	4-F	H	112 (56-224)	105 (35-304)	−71 ± 5.9	10.9 (8.9-13.8)	38	950 (616-1265)	369 (125-1227)	0.40	1395 (814-2020)	1.5
8a	4-F	OH	>1000	1000 (450-2220)	−53 ± 6.0	27.6 (19.3-44.1)	91	>1000	240 (151-380)	<0.24	784 (726-829)	
9	3-CF_3	H	647 (380-1100)	143 (68-314)	−74 ± 3.5	16.9 (13.1-23)	50	184 (119-360)	166 (87-311)	0.85	274 (177-322)	1.4
9a	3-CF_3	OH	166 (65-423)	244 (85-700)	−57 ± 0.9	33.9 (22.0-62.5)	96	>1000	85 (33-175)	<0.09	563 (313-752)	
10	4-CN	H	>1000	>1000	−76 ± 1.6	6.0 (3.2-11.6)	20	>1000	91 (60-137)	<0.09	2343 (1412-3198)	
10a	4-CN	OH	>1000	156 (84-289)	−69 ± 0.3	7.8 (6.3-10)	25	743 (482-932)	96 (20-294)	0.13	104 (60-166)	0.14
11	4-CH_3CONH	H	>1000	>1000	+4 ± 6.0	>36.6	>112	>1000	>1000		1137 (839-1471)	
11a	4-CH_3CONH	OH	>1000	>1000	−10 ± 7.0	>36.6	>107	>1000	>1000		673 (495-833)	

[a] Muscle relaxation was graded as follows: 1 = slight, 2 = moderate, 3 = marked, 4 = severe. Significant muscle relaxant activity is a score of 2 or greater; see text for further explanation. [b] Maximum twitch inhibition at a cumulative dose of 36.6 mg/kg iv. [c] MREI = muscle relaxant efficacy index.

5.5, KCl 4.7, $MgSO_4$ 1.2, NaH_2PO_4 1.3, $CaCl_2$ 2.5, and $NaHCO_3$ 25.0. The bath medium was bubbled with a gas mixture of 95% O_2–5% CO_2 and maintained at a temperature of 37 °C with a constant-temperature bath (Haake). The resting tension on the muscle segments was 1 g and isometric contractions were measured with a force-displacement transducer (Grass FT-03) connected to a polygraph (Grass Model 7C). An electric stimulus of supramaximal voltage (ca. 50 V) for 5 ms at 10 Hz was used. Tubocurarine chloride (Abbott) was added to the bath to obtain a concentration of 0.03 mg/mL. The preparation was allowed to stabilize for 30–60 min before experimentation started.

Due to the limited solubility of dantrolene sodium in aqueous solutions, increased drug concentrations were achieved by dissolving all drugs in Me_2SO. Stock solutions of the drugs containing either 3 or 6 mg/mL (where applicable) were diluted with Me_2SO so that the addition of 0.07 (for the 6 mg/mL) or 0.13 mL (for the 3 mg/mL) to the bath would give final drug concentrations of 0.15, 1.5, 5, or 15 mg/L, and in the case of the 6 mg/mL concentrations the addition of 0.13 mL would give a final drug concentration of 30 mg/L. This bath concentration of Me_2SO, 0.52%, was found to be a no-effect level similar to that reported by Sams et al.[18] Higher concentrations of the drugs were achieved by increasing the concentration of Me_2SO (up to 4%). Control experiments using Me_2SO at comparable volumes were also conducted. The effects of solvent and the drugs were measured 5 min after addition to the bath; at this time a steady state of drug effect had been reached. Between doses of drugs or solvent the tissues were washed continuously for 1 min with the drug-free bathing medium. The effect measured was the percent decrease in the twitch response.

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Antineoplastic Agents. 1. Synthesis and Antineoplastic Activities of Chloroethyl- and Methylnitrosourea Analogues of Thymidine

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A new class of chloroethyl- and methylnitrosourea analogues of thymidine, **5a,b**, **6**, **10**, and **11**, has been synthesized from the corresponding amino nucleosides, **2** and **7**. The 3′-chloroethyl and 3′-methyl derivatives, **10** and **11**, inhibited L1210 cell growth in culture (ED_{50} = 1.5 and 1.0 μM, respectively) more effectively than 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (ED_{50} = 4 μM) and the 5′-nitrosourea analogues. Neither the alkylating nor the carbamoylating activities of these compounds correlated with their biological activity.

Important aspects of the clinical utility and pharmacology of the nitrosoureas as antineoplastic agents have been recently reviewed.[1] A current evaluation of the mechanism of action of these compounds cites the importance of the N and N′ substituents on their chemical and biological properties.[2] In particular, it has been suggested that therapeutic effectiveness might be maximized in drugs possessing high alkylating and low carbamoylating activities.[3] The D-glucopyranose derivatives, streptozotocin and chlorozotocin, support this hypothesis. They show reduced bone marrow toxicity[4,5] and reduced carbamoylation potential,[2] a critical finding since myelosuppression is the dose-limiting effect of the clinically useful nitrosoureas.[6,7]

The development of aminonucleosides in our laboratory as potential antiviral and antineoplastic agents[8-10] has afforded the opportunity to synthesize the corresponding nitrosourea analogues. Altered pharmacological properties, such as selective uptake or metabolism, and favorable changes in their chemical reactivity may increase the therapeutic value of these compounds over existing drugs. This report describes the synthesis, the alkylating and carbamoylating activities, and the cytotoxicity of several nitrosourea derivatives of 3′-amino and 5′-amino analogues of thymidine.

Chemistry. The synthesis of a new class of chloroethyl- and methylnitrosourea analogues of thymidine (**5**, **6**, **10**, and **11**) is outlined in Scheme I. The key intermediates, 5′-amino-5′-deoxythymidine (**2**)[11] and 3′-amino-3′-deoxythymidine (**7**),[12,13] were prepared according to the procedure reported by Horwitz and co-workers with minor modification. Compound **7** was isolated as the free base instead of the hydrochloride salt.[12] Compounds **2** and **7** were converted to the corresponding urea derivatives, **3**,

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