Synthesis and Anticonvulsant Evaluation of 1-Amino-1,3-dihydro-2*H*-benzimidazol-2-ones

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1-Amino-2-benzimidazolinones containing alkyl substituents on the amino nitrogen have been prepared by the sodium bis (2-methoxyethoxy)aluminum hydride reduction of 1-acylamino-2-benzimidazolinones. The latter compounds were obtained in two steps from *o*-nitro-β-acylphenylhydrazines. All of the 1-amino-2-benzimidazolinones exhibited activity in the standard anticonvulsant tests except for the 1-benzylamino compound. The most active compound was 1-ethylamino-2-benzimidazolinone which protected mice in the maximal electroshock seizure test at 30 mg/kg.

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Recently, the synthesis and anticonvulsant evaluation of 3-amino-2,4-quinazolinediones [1] and 3-amino-2-quinazolinones [2] have been reported. Both of the above two series of compounds contain the elements of the acyclic 4-phenylsemicarbazide moiety which is associated with anticonvulsant activity [3]. In view of their anticonvulsant properties it appeared worthwhile to test a series of 1-amino-2-benzmidazolinones. Such compounds retain the 4-phenylsemicarbazide structure; the N-2 nitrogen of 4-phenylsemicarbazide is joined directly to the *ortho* position of the phenyl ring. This report describes the synthesis of these compounds and the results obtained in chemoshock, electroshock and toxicity tests.

1-Amino-2-benzimidazolinones IV in which the amino group is monosubstituted were obtained *via* a three step pathway [4] (Scheme I). β-Acyl-*o*-nitrophenylhydrazines I were reduced catalytically with hydrogen over a Pd/C catalyst to the corresponding *o*-amino compounds II. Cyclocondensation of II with ethyl chloroformate in pyridine produced 1-acylamino-2-benzimidazolinones III in moderate yields. Treatment of III with sodium bis (2-methoxyethoxy)aluminum hydride led to selective [5] reduction of the *N*-acyl carbonyl in preference to the ring carbonyl to afford 1-(*N*-alkylamino)-2-benzimidazolinones IV. Compound VIII, in which the 1-amino group is unsubstituted, was obtained by acid hydrolysis of IIIa (Scheme I).

In an attempt to prepare a 1-amino-2-benzimidazolinone in which the amino group is tertiary, 1-(*o*-nitroanilino)succinimide [6] was reduced to the corresponding *o*-amino intermediate which in turn was cyclocondensed by means of ethyl chloroformate in pyridine and afforded 1-succinimido-2-benzimidazolinone (IX). However, at-

Scheme I, Z = $NaAlH_2(OCH_2CH_2OCH_3)_2$

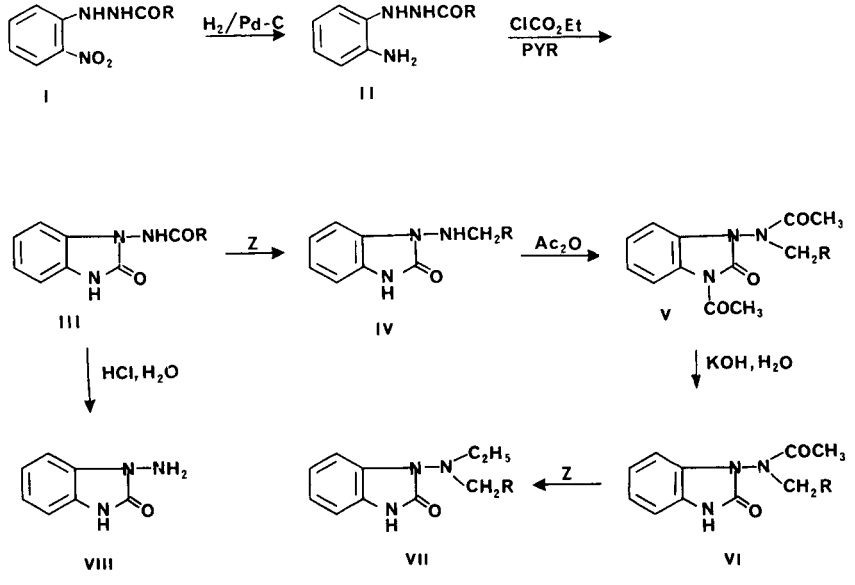

Table I

Physical Properties of 1-Amino-1,3-dihydro-2*H*-benzimidazol-2-ones

Compounds	R	Mp, °C	Yield, %	Recrystallization Solvent	Formula	Analysis, % Calcd./Found C	H	N
IIIa	OC_2H_5	192-193	59	Ethyl acetate	$C_{10}H_{11}N_3O_3$	54.30	5.01	18.99
						54.26	5.14	19.25
IIIb	CH_3	220-221	41	Ethanol-ethyl acetate	$C_9H_9N_3O_2$	56.54	4.74	21.98
						56.50	4.63	22.22
IIIc	C_2H_5	210-212°	54	Ethanol-ethyl acetate	$C_{10}H_{11}N_3O_2$	58.53	5.40	20.48
						58.42	5.35	20.20
IIId	C_6H_5	279-280°	44	Ethanol-ethyl acetate	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59
						66.61	4.66	16.34
IVa	H	235-236	20	Ethanol-ethyl acetate	$C_8H_9N_3O$	58.89	5.56	25.75
						58.68	5.80	25.66
IVb	CH_3	193-195	42	Ethanol-ethyl acetate	$C_9H_{11}N_3O$	61.00	6.26	23.71
						61.16	6.47	23.85
IVc	CH_2CH_3	143-144°	36	Ethyl acetate	$C_{10}H_{13}N_3O$	62.81	6.85	21.97
						62.57	6.61	22.02
IVd	C_6H_5	194-195.5	38	Ethyl acetate	$C_{14}H_{13}N_3O$	70.28	5.48	17.56
						70.30	5.66	17.42
V	H	200.5-201	94	Ethanol	$C_{12}H_{13}N_3O_3$	58.29	5.30	16.99
						58.09	5.52	17.23
VI	H	186-187	100	Ethyl acetate	$C_{10}H_{11}N_3O_2$	58.53	5.40	20.48
						58.31	5.62	20.60
VII	H	131.5-133	52	Aqueous ethanol	$C_{10}H_{13}N_3O$	62.81	6.85	21.97
						62.88	7.05	22.17

tempts to reduce IX to 1-(*N*-pyrrolidino)-2-benzimidazolinone were unsuccessful.

A successful synthesis of a 2-benzimidazolinone containing a tertiary amino group was accomplished as follows. 1-(Methylamino)-2-benzimidazolinone (IV, R = H) was diacetylated with acetic anhydride to compound V (R = H) and the latter was mono-deacetylated with alcoholic potassium hydroxide to afford 1-(*N*-methylacetamido)-2-benzimidazolinone (VI). Selective reduction of VI by sodium bis-(2-methoxyethoxy)aluminum hydride produced 1-(methylethylamino)-2-benzimidazolinone (VII) in 36% yield.

Compounds IVa-IVd, VII and VIII were tested in the maximal electroshock (MES) seizure and pentylenetetrazol (sc Met) seizure threshold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by procedures [7] previously reported. In the MES test, at 30 minutes, compounds IVa, IVc, VII and VIII showed activity but also toxicity at 300 mg/kg. Compound IVb exhibited activity at 30 mg/kg with no toxicity at this dose or at 100 mg/kg. Toxicity only occurred at 300 mg/kg. In the sc Met test at 30 minutes, compounds IVa, IVb and VIII were active at 300 mg/kg and IVa was active at 4 hours also (no toxicity). The *N*-benzyl compound IVd was the only inactive compound tested and failed to show activity even at 600 mg/kg (no toxicity).

EXPERIMENTAL

Melting points were determined on either a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 700 spectrophotometer as either liquid films or potassium bromide pellets. The nmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained on a RMU-7 double focusing spectrometer by Hitachi/Perkin Elmer. Elemental analyses were performed by Baron Consulting Co., Orange, CT, and Micanal, Tuscon, AZ.

1-Acetamido-2-benzimidazolinone (IIIb).

A mixture of 5.7 g (0.0292 mole) of 1-acetyl-2-(*o*-nitrophenyl)hydrazine [8] and 0.5 g of 5% Pd/C catalyst in 125 ml of methanol was hydrogenated at low pressure on a Parr hydrogenator. After hydrogen uptake was completed, the catalyst was filtered and the solvent was evaporated at reduced pressure. The solid residue (4.82 g, 100%) of 1-acetyl-2-(*o*-aminophenyl)hydrazine (II, R = CH_3) was used directly in the next step.

To a magnetically stirred mixture of 4.81 g (0.0292 mole) of the above amino compound (II, R = CH_3) in 28 ml of dry pyridine was added dropwise 3.49 g (0.0321 mole) of ethyl chloroformate. The mixture was stirred overnight at room temperature and refluxed for 23 hours under a nitrogen atmosphere. The mixture was poured into 85 ml of water, extracted three times with methylene chloride and dried (magnesium sulfate). The residue obtained upon evaporation was azeotroped several times with toluene. Recrystallization of the resulting crude solid from ethanol-ethyl acetate (charcoal) afforded 2.26 g (41%) of snow-white crystals, mp 220-221°.

1-Ethylamino-2-benzimidazolinone (IVb).

To a magnetically stirred mixture of 10 ml (0.0349 mole) of 70% sodium bis-(2-methoxyethoxy) aluminum hydride in toluene and 8 ml of dry tetrahydrofuran was added (1.89 g, 0.00989 mole) of IIIb over a period of 20 minutes (gas and heat evolution). The mixture strirred overnight at room temperature under nitrogen and refluxed for 3¼ hours. The mixture was decomposed by 8 ml of 50% aqueous tetrahydrofuran followed by 8*N* hydrochloric acid to *p*H ~6. Solid sodium bicarbonate was added to *p*H ~7 and the organic phase was separated by pipetting.

The inorganics were extracted five times with tetrahydrofuran and the combined THF solution was dried (magnesium sulfate) and concentrated. The solid residue was recrystallized from ethanol-ethyl acetate to give 0.73 g (42%) of IVb, mp 193-195°; nmr (deuteriochloroform, DMSO-d_6): δ 10.37 (s, 1H, CONH), 6.57-7.24 (m, 4H, aromatic), 5.16 (t, 1H, NNH), 2.78-3.50 (m, 2H, NCH_2), 1.08 (t, 3H, NCH_2CH_3).

1-Succinimido-2-benzimidazolinone (IX).

This compound was prepared from 4.86 g (0.0207 mole) of 1-(*o*-nitroanilino)succinimide [6] as described under IIIb and afforded after recrystallization from ethanol-ethyl acetate 1.18 g (25%) of IX, mp 273-275°.

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.28; H, 4.15; N, 17.89.

1-Amino-2-benzimidazolinone (VIII).

A mixture of 1.5 g (0.00679 mole) of IIIa, 18 ml of 8*N* hydrochloric acid and 5 ml of 95% ethanol was refluxed for 10 hours. The ethanol was evaporated under reduced pressure and the aqueous phase was extracted once with ether and basified to *p*H 7-8 with solid sodium bicarbonate. The beige colored precipitate which appeared was recrystallized from water and gave 0.34 g (34%) of product, mp 240-241°; nmr (deuteriochloroform, DMSO-d_6): δ 10.80 (s, 1H, CONH), 6.70-7.40 (m, 4H, aromatic), 5.15 (s, 2H, NH_2).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.12; H, 5.00; N, 27.89.

1-Acetyl-3-(*N*-methylacetamido)-2-benzimidazolinone (V, R = H).

A mixture of 2.44 g (0.0150 mole) of IVa, 4.1 g (0.0402 mole) of acetic anhydride and 20 ml of dry pyridine was refluxed for 2 hours. The reaction mixture was diluted with water and the resulting white crystals were filtered. Recrystallization from absolute ethanol gave 3.49 g (94%) of V (R = H), mp 200.5-201°; nmr (deuteriochloroform): δ 8.12-8.60 (m, 1H, aromatic), 6.84-7.60 (m, 3H, aromatic), 3.35 (s, 3H, NCH_3), 2.81 (s, 3H, $CONCOCH_3$), 2.00 (s, 3H, $NNCOCH_3$).

1-(*N*-Methylacetamido)-2-benzimidazolinone (VII, R = H).

A mixture of 3.4 g (0.0138 mole) of V (R = H), 18 ml of 2*N* potassium hydroxide and 20 ml of 95% ethanol was refluxed for 35 minutes. The mixture was acidified with 10% hydrochloric acid to *p*H ~4 with ice-bath cooling and extracted three times with chloroform. The combined solution was dried (magnesium sulfate), concentrated and the residue was azeotroped three times with toluene to remove acetic acid. The residue of white crystals obtained in quantitative yield melted at 184.5-185.5°. Recrystallization from ethyl acetate produced analytically pure VI (R = H); mp 186-187°; nmr (deuteriochloroform): δ 10.32 (s, 1H, CONH), 6.52-7.58 (m, 4H, aromatic), 3.30 (s, 3H, NCH_3), 2.00 (s, 3H, $COCH_3$).

1-(Methylethylamino)-2-benzimidazolinone (VII, R = H).

A mixture of 2.7 g (0.0132 mole) of VI (R = 4), 14 ml (0.0504 mole) of 70% sodium bis (2-methoxyethoxy) aluminum hydride in toluene, and 12 ml of dry tetrahydrofuran was refluxed for 3 hours. Work up as described under IVb gave 2.32 g of crude product. Purification of 1.59 g was effected by preparative tlc on silica gel [9], employing multiple development with benzene-ethyl acetate (2:1). The progress of the purification was followed visually at 254 nm. The product band (fastest moving) was cut out and extracted with methanol and afforded 0.9 g (52%), mp 122-127°. Recrystallization from aqueous ethanol afforded analytically pure VII (R = H), mp 131.5-133°; nmr (deuteriochloroform): δ 10.70 (s, 1H, CONH), 6.93-7.60 (m, 4H, aromatic), 3.10 (s, 3H, NCH_3), 2.91-4.14 (m, 2, NCH_2), 1.05 (t, 3H, NCH_2CH_3).

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