Succinimides with Oxyacetate Side Chain as Potential Anticonvulsant Agents

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Abstract □ Two new compounds, ethyl *N*-succinimidoxyacetate and methyl *N*-succinimidoxyacetate, were prepared by reacting a solution of freshly recrystallized *N*-hydroxysuccinimide in tetrahydrofuran with a mixture of the corresponding halogenated ester and triethylamine. The compounds possessed some anticonvulsant properties.

Keyphrases □ Succinimides—derivatives, anticonvulsant effects, synthesis and analysis □ Anticonvulsants—succinimide derivatives, synthesis and analysis □ Derivatives—of succinimides, synthesis and analysis

Aminooxyacetic acid is a potent anticonvulsant agent, but it causes convulsions at high doses. This convulsive tendency has been attributed to the unsubstituted amino group of this compound, which is very reactive with other groups, such as the aldehyde of pyridoxal phosphate (1). Two analogs of aminooxyacetic acid obtained by derivatizing its amino and carboxylic acid ends, ethyl *N*-phthalimidoxyacetate and methyl *N*-phthalimidoxyacetate, protected chicks against experimentally induced seizures (2, 3). In addition, ethyl *N*-phthalimidoxyacetate lacks the convulsant property of aminooxyacetic acid but is a less potent anticonvulsant (2).

With the aim of producing a very potent anticonvulsant, other cyclic imides were prepared, particularly hybrid compounds based on aminooxyacetic acid and such moieties that are normally associated with anticonvulsant properties. Accordingly, ethyl *N*-succinimidoxyacetate (I) and methyl *N*-succinimidoxyacetate (II) were synthesized, and their anticonvulsant activities were studied in the chick.

RESULTS AND DISCUSSION

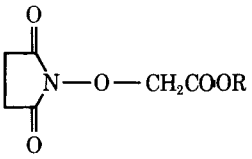
The synthesis of I and II was achieved in a one-step, self-indicating reaction. A light-blue color developed initially and disappeared at the end of the reaction. The major advantage of this reaction is that it proceeds at room temperature, especially since the starting material, *N*-hydroxysuccinimide, is usually hygroscopic and decomposes in warm water (4).

Results from preliminary pharmacological screening indicated that I and II possessed some anticonvulsant properties. Compounds I and II protected young chicks against electrically and chemically induced seizures. The details of the pharmacological screening will be reported elsewhere.

EXPERIMENTAL

Melting points of the two compounds were determined by an electrothermal melting-point apparatus[1] and are uncorrected.

Ethyl *N*-Succinimidoxyacetate (I)—A solution of freshly recrystallized *N*-hydroxysuccinimide (1.15 g, 0.01 mole) in tetrahydrofuran (12 ml, 0.15 mole) was added to a mixture of ethyl bromoacetate (1.4 ml, 0.0125 mole) and triethylamine (2.1 ml, 0.015 mole). The reaction was allowed to proceed at room temperature for 12 hr, during which time the light-blue mixture became colorless. The reaction mixture was filtered, and the precipitate was washed with ether (5 × 20 ml).



I: R = C_2H_5
II: R = CH_3

The combined filtrates were concentrated and the product was crystallized from ethanol to obtain 1.71 g of white fluffy flakes in an 85% yield, mp 80–81°; IR[2] (mineral oil): 1778, 1712 (C=O for succinimide), 1748 (C=O for ester), 1208, 1098 (C–O–C asymmetric and symmetric stretching for ester, respectively), ~2950, 2880 (C–H stretching), 1436, and 1372 (C–H asymmetric and symmetric deformation for CH_2CH_3, respectively) cm^{-1}; NMR[3] ($CDCl_3$): δ 2.70 (s, 4H, cyclic H), 4.60 (s, 2H, $-CH_2$), 4.17 (q, 2H, J = 6 Hz, CH_2 ethyl), and 1.27 (t, 3H, J = 6 Hz, CH_3 ethyl); TLC[4]: hR_f 56.8.

Anal.[5]—Calc. for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.82; H, 5.50; N, 7.01.

Methyl *N*-Succinimidoxyacetate (II)—A solution of freshly recrystallized *N*-hydroxysuccinimide (1.15 g, 0.01 mole) in tetrahydrofuran (12 ml, 0.15 mole) was added to a mixture of methyl bromoacetate (1.1 ml, 0.0125 mole) and triethylamine (2.1 ml, 0.015 mole). The reaction was allowed to proceed at room temperature for 8 hr, during which time the light-blue mixture became colorless. The reaction mixture was filtered, and the white precipitate, heavily contaminated with triethylamine hydrobromide, was crystallized from ethanol to obtain 1.31 g of white crystals in a 70% yield.

A second crop of 0.13 g was obtained by concentrating the filtrate, and the total yield was 1.44 g (77%), mp 128–130°; IR (mineral oil): 1772, 1706 (C=O for succinimide), 1750 (C=O for ester), 1200, 1086 (C–O–C asymmetric and symmetric stretching for ester, respectively), ~2950, 2880 (C–H stretching), 1440, and 1370 (C–H asymmetric and symmetric deformation for CH_3, respectively) cm^{-1}; NMR ($CDCl_3$): δ 2.63 (s, 4H, cyclic H), 4.60 (s, 2H, $-CH_2$), and 3.63 (s, 3H, CH_3); TLC: hR_f 53.7.

Anal.—Calc. for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 45.03; H, 4.88; N, 7.47.

Screening—Compounds I and II were screened for anticonvulsant properties by subjecting pretreated young chicks to electrically and chemically induced seizures. Maximal electroshock was delivered using electroshock equipment[6]; chemical seizures were achieved using aminooxyacetic acid, bicuculline, pentylenetetrazol, picrotoxin, and strychnine.

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[1] Model MF-370, A. Gallenkamp & Co. Ltd., London, England.

[2] Model SP700, Perkin-Elmer Corp., Norwalk, Conn.
[3] Varian A-60A, Varian Instruments, Palo Alto, Calif.
[4] TLC was run on Polygram SIL G/UG_{254} using 10% methanol in chloroform.
[5] Elemental analyses were performed by Scandinavian MicroLaboratories, Herlev, Denmark.
[6] Model 7800, Ugo Basile ECT unit, Milan, Italy.

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