

Available online on 15.01.2023 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Review Article

A Review on the Some Biological Activities of the Hydantoin Derivatives

Somnath Wadghane*, Rohit Bhor, Ganesh Shinde, Mahesh Kolhe, Rathod Pooja

Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India.

Article Info:

Abstract



Article History:

Received 09 Nov 2022
Reviewed 16 Dec 2022
Accepted 28 Dec 2022
Published 15 Jan 2023

Cite this article as:

Wadghane S, Bhor R, Shinde G, Kolhe M, Pooja R, A Review on the Some Biological Activities of the Hydantoin Derivatives, Journal of Drug Delivery and Therapeutics. 2023; 13(1):171-178

DOI: <http://dx.doi.org/10.22270/jddt.v13i1.50904>

*Address for Correspondence:

Somnath Vikram Wadghane, Department of Pharmaceutics, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India

Hydantoin derivatives are commonly used anticonvulsants. In general, they are effective for partial-onset seizures and tonic-clonic seizures, but not for absence seizures. Phenytoin is the most important drug in this group, and other drugs, ethotoin, and mephenytoin, are also commonly used to treat epilepsy. Prodrugs such as derivatives have been created. Phenytoin is effective in some cases of trigeminal neuralgia and related neuralgia. Phenytoin is also used to treat arrhythmias. Hydantoin or glycolylureas are heterocyclic organic compounds with the formula $\text{CH}_2\text{C}(\text{O})\text{NHC}(\text{O})\text{NH}$. It is a colorless solid formed by the reaction of glycolic acid and urea. It is an oxidized derivative of imidazolidine. In a more general sense, hydantoins can refer to groups and classes of compounds that share the same ring structure as their parent. For example, phenytoin (see below) has two phenyl groups substituted at the 5th carbon of the hydantoin molecule. Actual chemotherapy for epilepsy dates back to the 1850s when "inorganic bromides" were introduced. However, it is worth noting that around the 1920s, the therapeutic and beneficial use of 'phenobarbital' ushered in an era of meaningful treatment of epilepsy. Hydantoin ring chemistry is the synthesis of rings by various methods and their applications in the medical field. Previous descriptions of hydantoin-containing compounds have broad pharmacological and biological activities, including anticancer, anti-inflammatory, anti-immune, antimetabolite, antioxident, antibacterial, CNS-related, anticonvulsant, antitussive, and cytoprotective activities.

Keywords: Hydantoin derivatives, anticonvulsants, partial-onset seizures and tonic-clonic seizures

INTRODUCTION

A heterocyclic organic compound with the formula $\text{CH}_2\text{C}(\text{O})\text{NHC}(\text{O})\text{NH}$ is hydantoin, also known as glycolylurea. It is a solid that results from the reaction of urea and glycolic acid. Imidazolidine's oxidised derivative is this. Hydantoins can, in a broader sense, refer to groups and classes of compounds that share the parent compound's ring structure. For instance, a hydantoin molecule of phenytoin (mentioned below) has two phenyl groups substituted onto the number 5 carbon ¹.

For the biocatalytic production of enantiopure amino acids, particularly d-phenylglycine and d-p-hydroxyphenylglycine, the hydantoinase process is well-established in industry. The semi-synthetic antibiotics ampicillin and amoxicillin use them as side chains. Since racemization is made possible by hydantoin racemases or occurs naturally under slightly alkaline conditions on unreacted substrates, this process can produce a maximum yield of 100% ².

To date, the application of whole-cell biocatalysts in industrial biocatalysis is wide spread due to the easy access to biocatalysts, low production costs, and easy separation of biocatalysts and products. However, there are also some drawbacks to the use of whole-cell biocatalysts, such as: B. Limited Transport of Substrates, Intermediates, and Products. In addition, uncontrolled intracellular degradation side reactions can occur, especially in hydantoin processes with relatively low substrate solubility³.

Consequently, interest in cell-free reaction systems is growing, utilizing recombinant expression enzymes in well-known expression hosts like *E. coli*. Target enzyme overexpression and labeling for purification and immobilization are permitted in *E. coli*. Regardless of this, different codon usage in various species can result in premature translation termination, expression of insoluble or nonfunctional proteins, or even total lack of expression. This suggests, for instance, that depending on the host organism, codon optimization of a gene of interest is a potent tool for enhancing expression and preventing protein misfolding and aggregation. The pharmacological characteristics of hydantoin (1,3-imidazolidinedione) derivatives are varied and intriguing. These derivatives include well-known anticonvulsants like phenytoin, mephenytoin, norantin, metetoin, ethotoin, and fosphenytoin ⁴.

Other 5-substituted hydantoinssuchas5,5-dithienylhydantoin, 5,5-dipyridylhydantoin, spirothiohydantoin, thiohydantoin and dithiohydantoin also have anticonvulsant activity. Hydantoin derivatives have also been found as antiarrhythmic agents (azimilide), antibacterial agents (nitrofurantoin), skeletal muscle relaxants (dantrolene), and nonsteroidal antiandrogens (nilutamide), while allantoin is a keratolytic, Itisan astringent, wound healing agent, antacid and antipsoriasis. Hydantoins also exhibit antidepressant, antiviral, antithrombotic activity, and inhibitory activity against several enzymes (human aldose reductase and human leukocyte elastase). Finally, some herbicides (spirohydantoins, thioxohydantosidines), fungicides (chlordanol), and insecticides also have a hydantoin skeleton in their structure.

In previous studies, many hydantoin derivatives were synthesized and tested for antiviral and cytostatic activity. The highest pharmacological activity was obtained with lipophilic hydantoin derivatives with cycloalkyl, phenyl or benzhydryl substituents. This has prompted us to prepare a series of new structural analogs of these lead compounds and evaluate them pharmacologically to assess their antiviral and antitumor potential. The results are reported in this paper ⁵.

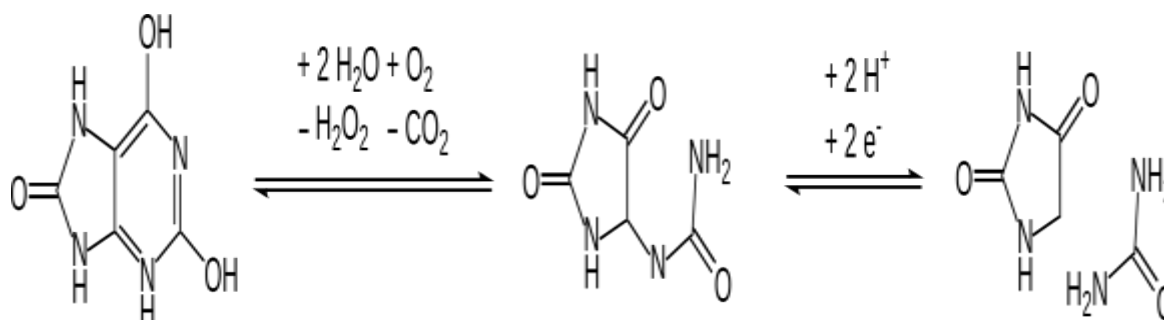
HISTORY

Epilepsy chemotherapy started in the 1850s with the invention of "inorganic bromides." But it's important to note that the therapeutic use of "phenobarbital" in the 1920s

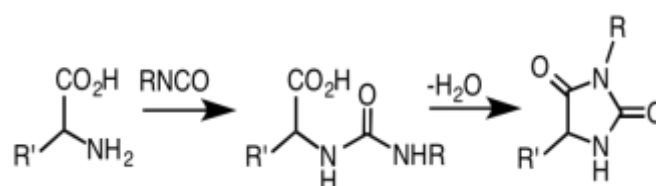
essentially signalled the beginning of a new era in the effective management of epilepsy. Merritt and Putman's wonderful contributions were almost immediately recognized when they found that the "5-substituted hydantoin" could suppress the electrically induced convulsions in the laboratory animals. As a result, 5, 5-diphenylhydantoin, also known as phenytoin, which had the best and least sedative activity, was eventually made possible ⁶⁻⁸.

GENERAL SYNTHESIS OF HYDANTOIN

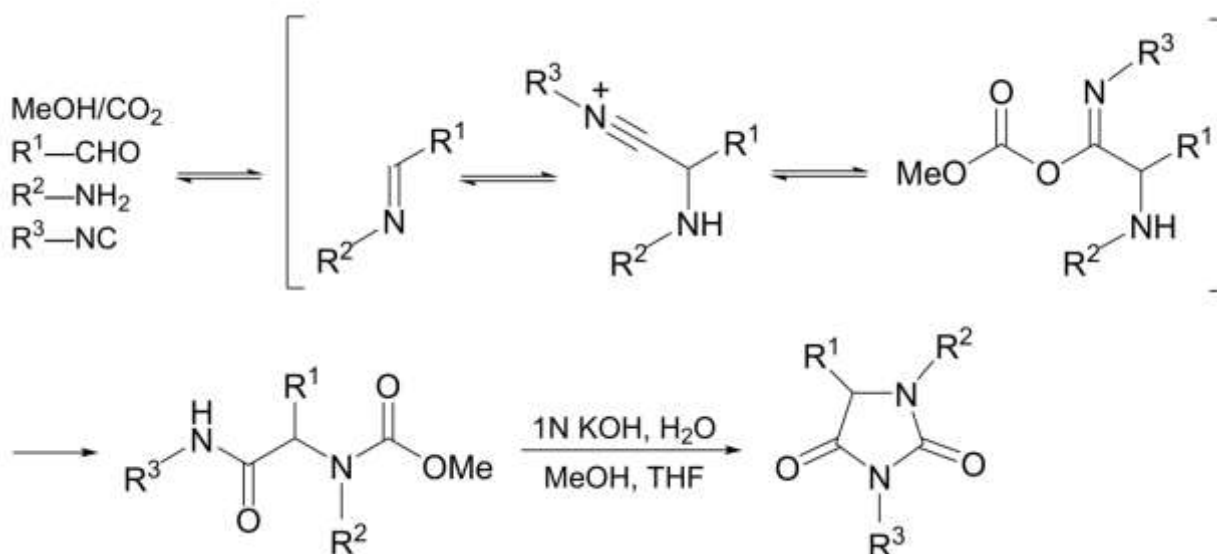
Adolf von Baeyer first discovered hydantoin in 1861 while researching uric acid. Allantoin was hydrogenated to create it, hence the name ⁹.



Friedrich Urech invented what is now referred to as the Urech hydantoin synthesis in 1873 using potassium cyanate and alanine sulphate to produce 5-methylhydantoin. The process is extremely comparable to the modern approach utilising alkyl and aryl cyanates. Acetone cyanohydrin, ammonium carbonate, and other substances can also be used to produce the compound 5, 5-dimethyl. The Bucherer-Bergs reaction is the name of this type of reaction. Both heating allantoin with hydroiodic acid and heating bromo-cetyl urea with alcoholic ammonia can be used to create hydantoin. Hydantoin is made by condensing a cyanohydrin with ammonium carbonate, and Dorothy Hahn confirmed the cyclic structure of these compounds. Following Urech's work, another effective method entails condensation of amino acids with cyanates and isocyanates ¹⁰.



The recently used Ugi/De-Boc/Cyclization methodology is appropriate for producing fully functionalized hydantoin in a high yield. In this five-component reaction, aldehydes (or ketones), amines, isocyanides, methanol, and carbon dioxide serve as starting materials. Corresponding carbamates are produced as intermediates, and the next step involves their cyclization under alkaline conditions ¹¹.



Synthesis of hydantoin employing five-component Ugi/De-Boc/Cyclization methodology

THE DERIVATIVES& ITS MECHANISM OF ACTION

Phenytoin-

Phenytoin (diphenylhydantoin, dilanthine) is effective against all types of partial-onset seizures and tonic-clonic seizures, but not against absence seizures. It has been found to exert its effects on the motor cortex, where it stabilizes the neural membrane and thereby inhibits the propagation of seizure discharge. Current evidence suggests that it blocks Na⁺ channels in the frequency-dependent manner used. It also suggests that this limits repeated high-frequency firings. It also increases Ca binding to phospholipids present in neuronal membranes^{12, 13}.

In fact, these effects combine to yield a more stable membrane configuration. Importantly, these key findings indicate that the ability to limit the development of maximal ictal activity and minimize the virtual extension of ictal phenomena from active focus is the hallmark feature most easily detected. Interestingly, beyond reasonable doubt, these two positive properties of phenytoin are largely related to its clinical utility¹⁴.

Phenytoin was first synthesized by Biltz in 1908, but its anticonvulsant activity was not discovered until 1938 by him.

In contrast to previous incidental findings of anticonvulsant properties of bromide and phenobarbital, phenytoin is among the non-sedating structural analogues of phenobarbital for agents that can suppress electroconvulsive convulsions in experimental animals. In the same year it was introduced as a treatment for epilepsy. Because this remedy in normal doses is not a sedative, antiepileptic drugs are not thought to cause drowsiness, prompting the search for drugs with selective antiepileptic effects¹⁵.

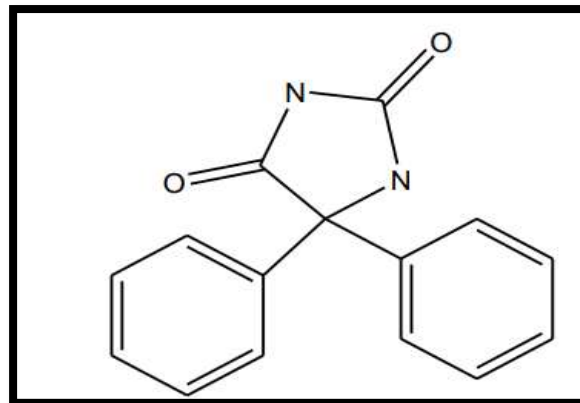
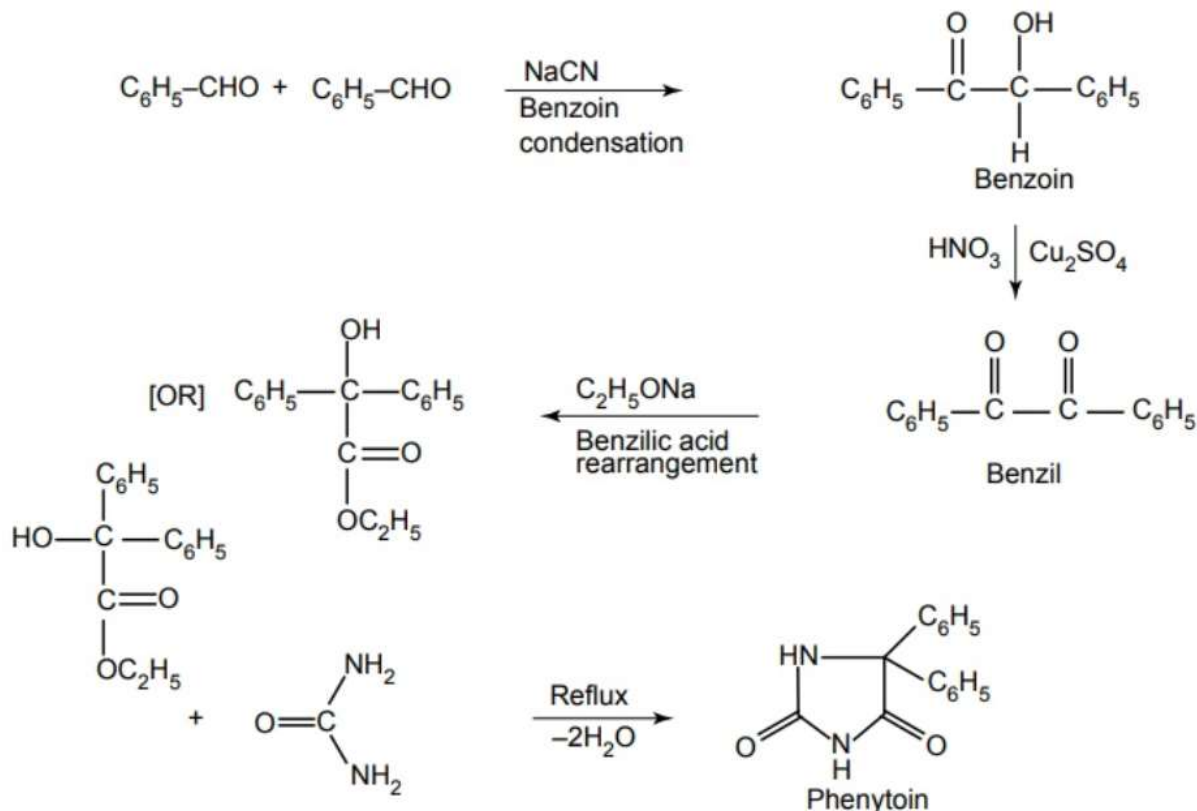


Figure 1: Structure of Phenytoin

Synthesis of Phenytoin-



Properties and uses-

A white, crystalline powder dissolves in water and alcohol but is insoluble in methylene chloride. The ability to distinguish anticonvulsant activity from sedative-hypnotic activity was first demonstrated with phenytoin, making it the first anticonvulsant. Gingival hyperplasia is a typical adverse reaction that rarely happens when taking mephenytoin and never, it seems, when there are cardiac arrhythmias. It is one of the most frequently used antiepileptic medications and, with the exception of absence of seizures, is effective in

treating most types of epilepsy. Phenytoin works well for some trigeminal and neuralgia cases. Additionally, it is applied to the management of cardiac arrhythmias^{16, 17}.

Assay-

Suspend the sample in water, add 0.05 M sulfuric acid, and gently heat for 1 min. Add methanol to this mixture, and allow to cool. Utilizing 0.1 M sodium hydroxide, carry out the potentiometric titration. In order to continue the titration after reaching the first point of inflexion, you must stop adding 0.1 M sodium hydroxide and instead add 5 ml of silver nitrate

solution in pyridine. Read the amount of sodium hydroxide that was added in the volume between the two points of inflexion^{18,19}.

Ethotoin-

It is parahydroxylated and N-dealkylated in vivo. The "active compound" is most likely the N-dealkyl metabolite, which is similarly metabolised by parahydroxylation and then undergoes conjugation of the hydroxyl function. Due to its low potency, this specific "drug substance" is always used as an adjunctive treatment for non-specific seizures. In a broader sense, such anticonvulsants that are not fully branched on the appropriate C-atom are unquestionably less potent than their structural analogues that are much more fully branched^{20,21}.

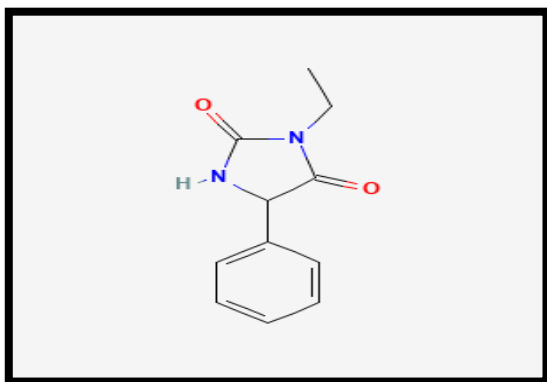


Figure 2: The structure of ethotoin

Mephenytoin-

The corresponding 5-ethyl-5-phenylhydantoin, which is referred to as the "active agent," is produced by metabolic N-dealkylation. It's interesting to note that the metabolized form of phenobarbital also happens to be its "hydantoin counterpart" because it was one of the first types of hydantoins to be used as a therapeutic tool. Furthermore, it is possible to assume that "mephenytoin" is a "pro-drug" that essentially lessens some of the serious skin and blood disorders caused by the delivered "active drug's" toxicity. The parahydroxylation and subsequent conjugation of the free hydroxyl moiety result in the metabolic inactivation of this drug and its corresponding dimethylmetabolite^{22,23}

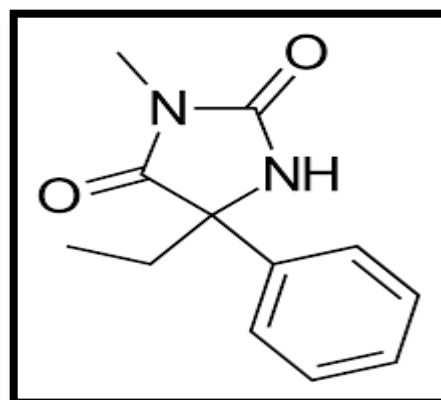
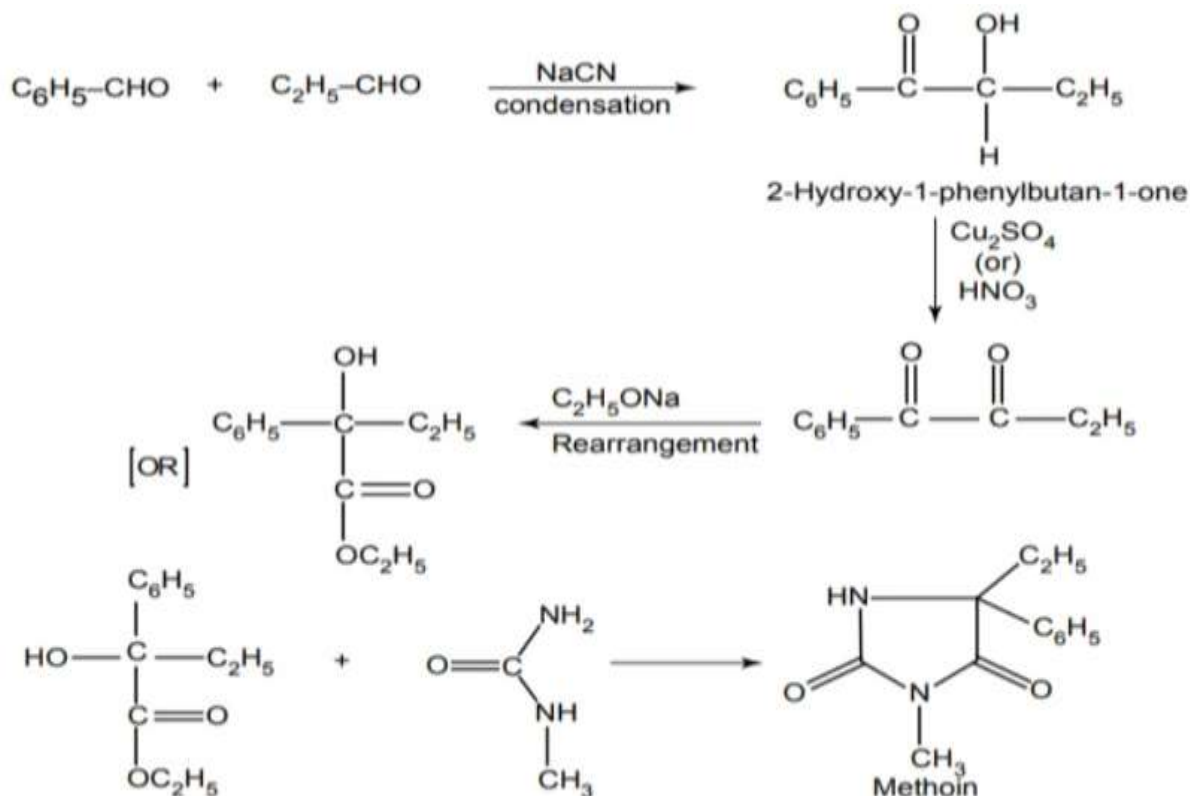


Figure 3: The Structure of Mephenytoin

Synthesis-



Fosphenytoin-

It is a prodrug that is highly soluble in intravenous solutions without solubilizing agents and is supplied in vials for intravenous use. Fosphenytoin is converted to phenytoin following parenteral administration. It is very effective in

terminating seizures and will stop most status epilepticus episodes and provide long term control without any decreased level of consciousness. All of these drugs should be administered slowly to avoid respiratory depression and apnea^{24,25}.

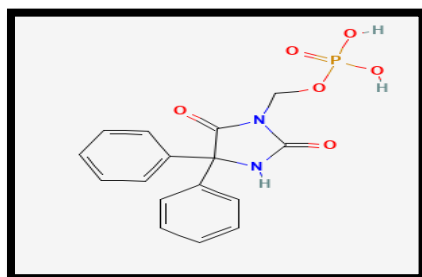
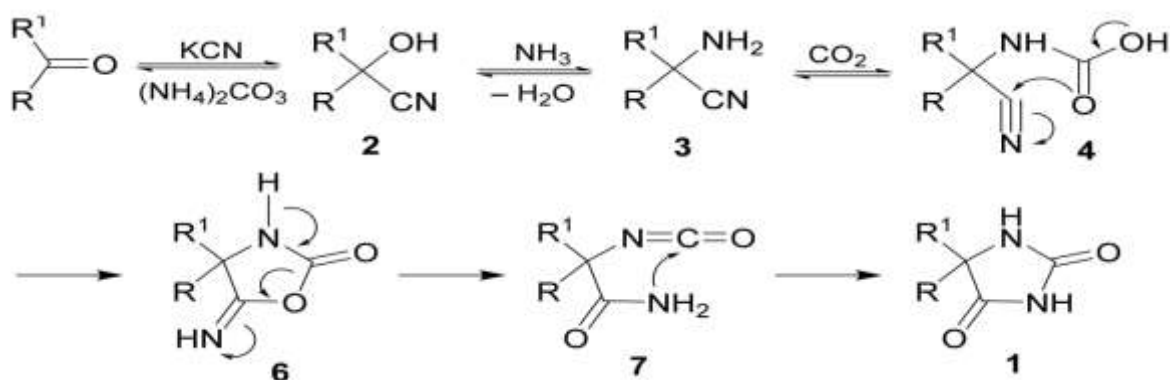


Figure 4: The Structure of Fosphenytoin

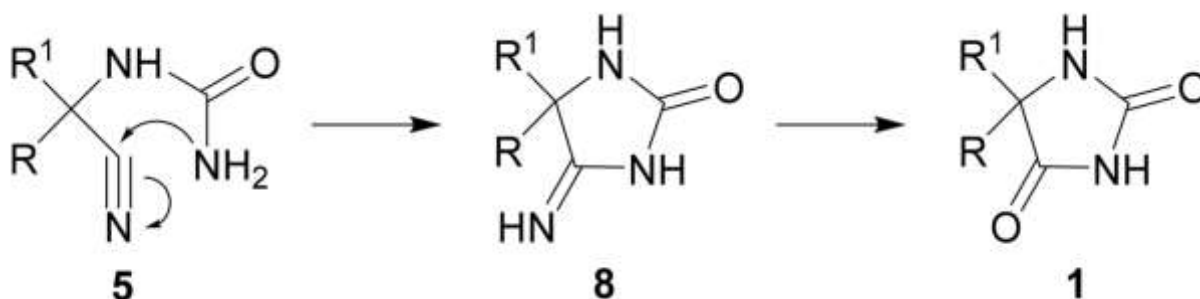
Mechanism and Stereochemistry of hydantoin -

Since hydantoin is also produced by the same ammonium carbonate reaction on cyanohydrins 2 and -amino nitriles 3, Bucherer himself suggested that they are likely the reaction's initial intermediates. Prior to ring closure, the final intermediates can either be a corresponding aramide or an

N-substituted carbamic acid 4 even though this hasn't been proven through experiment. The final step would then involve either adding an amino group to the nitrile in ceramide to close the 4-imino-2-oxoimidazolidine ring followed by hydrolysis to the corresponding hydantoin or the formation of a 5-imino-2-oxoimidazolidin-2-one ring 6 affording hydantoin via isocyanate intermediate^{26,27}.

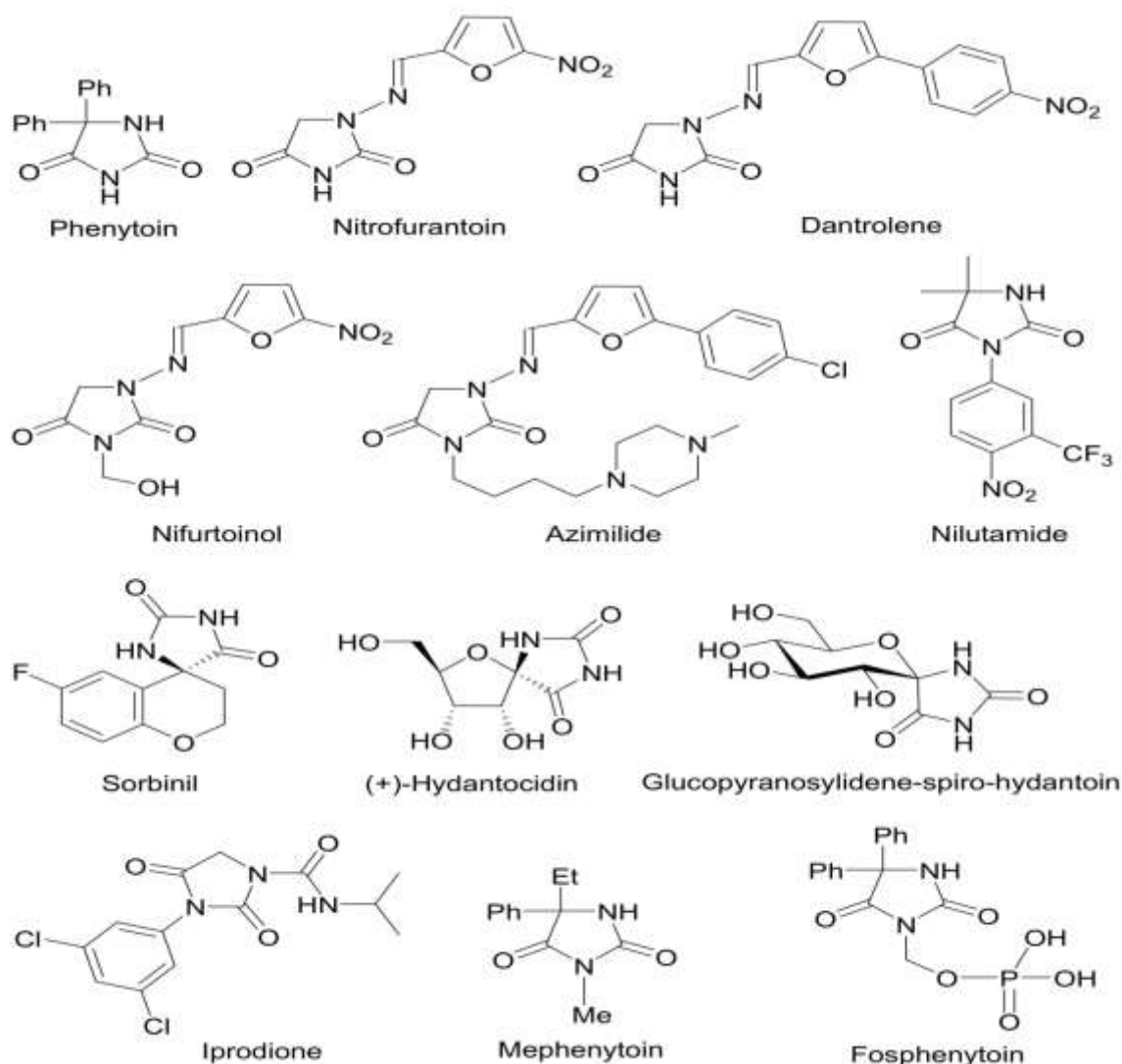


Mechanism of hydantoin formation. R- and R1-varied alkyl or aryl substituent.



Alternative hydantoin formation via 4-imino-2-oxoimidazolidine ring. R- and R1-varied alkyl or aryl substituent.

VARIOUS DERIVETIVES OF HYDANTOIN²⁸⁻³⁴



SCOPE AND LIMITATIONS

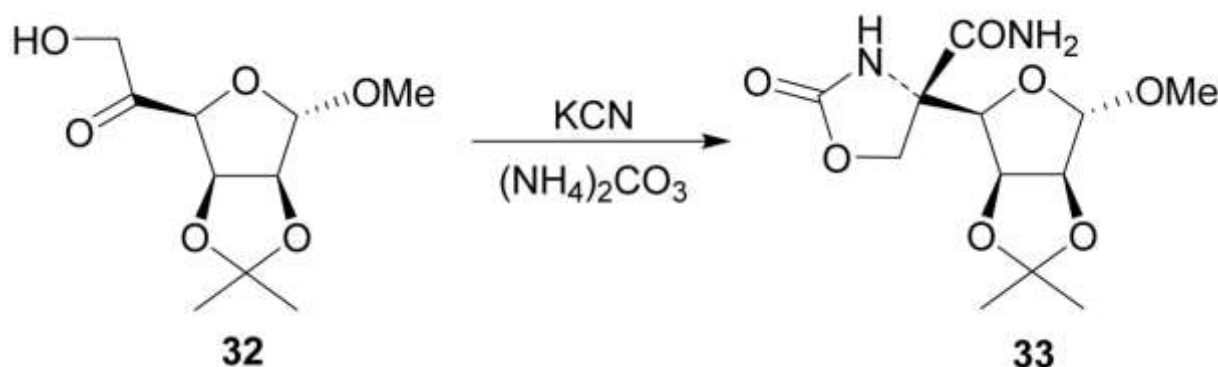
Arrange of 5-substituted and 5,5-disubstituted hydantoins are accessible, as the scope of the synthesis allows ready access to all reaction components, including organic aldehydes and ketones. Moreover, most of the endo hydantoins are crystalline products and their isolation and purification are very easy. In most cases, crystallization from an appropriate solvent gives the pure product. Despite the relative ease of operation and good yields that make the Bucherer-Bergs reaction one of the most practical and useful methods for preparing hydantoins, it suffers from several drawbacks and limitations of its applicability has been discovered. One limitation is that there is only one diversity point. Only changes in the structure of the initial ketone can influence the final hydantoin changes³⁵.

In principle, hydrogen atoms, alkyl or cycloalkyl groups, and aryl groups can represent the aldehyde or ketone moieties R and R1. In general, ketones are the better substrates to provide a well-defined hydantoin. However, the presence of functional groups on R and R1 of the starting aldehyde or ketone can dramatically complicate the formation of the desired product. Although this reaction tolerates a wide variety of functional groups, the Bucherer-Bergs reaction does not tolerate alkali-labile functional groups that may be present in the starting carbonyl substrate due to the strong basicity of the reaction mixture³⁶.

Depending on their character, this intolerance may lead to simple deprotection (like deacylation if acylated hydroxyl groups are present), restoring unprotected functionality, or the present functionality may be changed to a new group (e.g., hydrolysis of nitrile, ester, amide, etc.) or to a reactive intermediate (e.g., carbanions in the case of nitroalkyl functionality). Moreover, the aqueous reaction conditions limit the application of starting ketones or aldehydes only to those which are stable under these conditions³⁷.

Similarly, the presence of powerful nucleophiles (amino and cyano groups) in the reaction mixture excludes the presence of readily substituted functionalities (like triflate, tosylate, or mesylate and halogen atoms) in the R and R1 of the starting aldehyde or ketone unless especially cyano- or amino-substituted final derivatives are desirable^{38,39}.

An unusual obstruction to the preparation of hydantoins is seen when an unprotected hydroxyl group is present in the α -position of the starting ketone (Scheme 1, R = not H, R1 = CH₂OH). It was found that, in such cases, starting from sugar ketone, the corresponding 4-carbamoyl-2-oxazolidinone is formed preferentially instead of the expected hydantoin. Proper protection of the hydroxyl group prior to the Bucherer-Bergs reaction (such as silylation) is required to obtain the hydantoin product⁴⁰.



Unusual Bucherer–Bergs reaction—formation of 4-carbamoyl-2-oxazolidinone derivative.

CONCLUSION

Hydantoin derivatives include common anticonvulsants. They are effective for tonic-clonic and partial-onset seizures but not for absence seizures. Phenytoin is the most significant drug in this class, but ethotoin and mephenytoin are also frequently prescribed drugs to treat epilepsy. Prodrugs have been created, including derivatives. Phenytoin is occasionally used to treat neuralgias like trigeminal neuralgia. Epilepsy chemotherapy began in the 1850s with the discovery of "inorganic bromides." However, it is important to keep in mind that the clinical application of "phenobarbital" in the 1920s essentially signaled the dawn of a new era in the effective control of epilepsy.

CONFLICTS OF INTEREST

There are no conflicts of interest or disclosures regarding the manuscript.

ACKNOWLEDGMENT

Department of Pharmaceutics, Pravara Rural College of Pharmacy Pravaranagar, University Libraries, and all other sources for their cooperation and advice in writing this review.

REFERENCES

1. Cho SH, Kim SH, Shin D. Recent applications of hydantoin and thiohydantoin in medicinal chemistry. *European Journal of Medicinal Chemistry*. Elsevier Masson s.r.l.; 164: 2019:517-45. <https://doi.org/10.1016/j.ejmech.2018.12.066>
2. Kalník M, Gabko P, Bella M, Koš M. The bucherer-bergs multicomponent synthesis of hydantoins-Excellence in simplicity. Vol. 26, *Molecules*. MDPI AG; 2021. <https://doi.org/10.3390/molecules26134024>
3. Loser D, Schaefer J, Danker T, Möller C, Brüll M, Suci I, et al. Human neuronal signaling and communication assays to assess functional neurotoxicity. *Arch Toxicol*. 2021; 95(1):229-52. <https://doi.org/10.1007/s00204-020-02956-3>
4. Anil Kumar S, Bhaskar BL. Spectroscopic and Computational approach for the Structure-Property relationship of Hydantoin drug impurity : 1-methyl-5,5-diphenylimidazolidine-2, 4-dione. In: *IOP Conference Series: Materials Science and Engineering*. IOP Publishing Ltd; 2019. <https://doi.org/10.1088/1757-899X/577/1/012180>
5. Yu V, Ten A, Baktybayeva L, Sagatbekova I, Praliyev K, Zolotareva D, et al. Synthesis and Biological Evaluation of 1,3,8-Triazaspiro[4.5]decane-2,4-dione Derivatives as Myelostimulators. *J Chem*. 2018; 2018. <https://doi.org/10.1155/2018/7346835>
6. Katiyar P, Kumar Verma S, Umar S, Chauhan P, Verma N. Recent advances in the synthesis and medicinal application of hydantoin: a valuable scaffold in medicinal chemistry. *Certified Journal | Verma et al World Journal of Pharmaceutical Research* 243 *World Journal of Pharmaceutical Research SJIF Impact Factor [Internet]*. 2015; 11(1):243-66. Available from: www.wjpr.net
7. Tijmsa A, Thibaut HJ, Franco D, Dallmeier K, Neyts J. Hydantoin: The mechanism of its in vitro anti-enterovirus activity revisited. *Antiviral Res*. 2016 Sep 1; 133:106-9. <https://doi.org/10.1016/j.antiviral.2016.07.023>
8. Cook AM, Bensalem-Owen MK. Mechanisms of action of antiepileptic drugs. Vol. 8, *Therapy*. 2011. p. 307-13. <https://doi.org/10.2217/thy.11.19>
9. Smith CT, Marson AG, Williamson PR. Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*. 2009.
10. Simas MJ. Biological activity of well defined hydantoin derivatives on efflux pump systems of bacteria and cancer cells. *Universidade nova de lisboainstituto de higiene e medicina tropical*; 2010.
11. Konner L, Lamaty F, Martinez J, Colacino E. Recent Advances in the Synthesis of Hydantoins: The State of the Art of a Valuable Scaffold. Vol. 117, *Chemical Reviews*. American Chemical Society; 2017. p. 13757-809. <https://doi.org/10.1021/acs.chemrev.7b00067>
12. Mali SN, Pandey A, Bhandare RR, Shaik AB. Identification of hydantoin based Decaprenylphosphoryl-β-d-Ribose Oxidase (DprE1) inhibitors as antimycobacterial agents using computational tools. *Sci Rep*. 2022; 12(1). <https://doi.org/10.1038/s41598-022-20325-1>
13. CLAUDIA TSCHESCHE. Deltamethrin resistance in salmon lice: Genetic markers and molecular mechanisms. institute of aquaculture, faculty of natural sciences university of stirlingunited kingdom; 2021.
14. Zhao H, Yu R, Qiao H, Liu C. Study on the Formation of Glycine by Hydantoin and Its Kinetics. *ACS Omega*. 2020; 5(23):13463-72. <https://doi.org/10.1021/acsomega.9b03868>
15. Eckrich T. Voltage gated Na + channels and spontaneous action potential activity in cochlear hair cells during development. *University of Sheffield, Department of Biomedical Science*; 2012.
16. Catterall WA. Cellular and Molecular Biology of Voltage-Gated Sodium Channels. *Pharmacol Rev [Internet]*. 1992; 72(4):22-4. Available from: www.physiology.org/journal/physrev https://doi.org/10.1152/physrev.1992.72.suppl_4.S15
17. Cherneva E, Atanasova M, Šmelcerović Ž, Tomović K, Buyukliev R, Šmelcerović A, et al. 3'-Aminothiocylohexanespiro-5'-hydantoin and Its Pt(II) Complex-Synthesis, Cytotoxicity and Xanthine Oxidase Inhibitory Activity. *Inorganics (Basel)*. 2022; 10(10). <https://doi.org/10.3390/inorganics10100175>
18. L. MACHADO. Biological Activity of Twenty-three Hydantoin Derivatives on Intrinsic Efflux Pump System of Salmonella entericaserovarEnteritidis NCTC 13349. *International Journal of Pharmaceutical science* . 2011; 25(2011):769-72.

19. Dürr R, Vielhauer O, Burton SG, Cowan DA, Puñal A, Brandão PFB, et al. Distribution of hydantoinase activity in bacterial isolates from geographically distinct environmental sources. *J Mol Catal B Enzym.* 2006; 39(1-4):160-5. <https://doi.org/10.1016/j.molcatb.2006.01.017>
20. Sills GJ, Butler E, Thompson GG, Brodie MJ. Vigabatrin and tiagabine are pharmacologically different drugs. A pre-clinical study. *IJCRR.* 2012; 2(50):1-8.
21. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Approved by the Quality Standards Subcommittee on. Vol. 45, *Epilepsia.* issue of Neurology; 2004.
22. N James. Nitric Oxide as an Autocrine Regulator of Sodium Currents in Baroreceptor Neurons. *Core Journal of medical science.* 2008; 20(1):1-11.
23. Biton V, Montouris ; G D, Ritter ; F, Riviello ; J J, Reife ; R, Lim ; P, et al. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *American Academy of Neurology.* 1999; 2(20):2-8. <https://doi.org/10.1212/WNL.52.7.1330>
24. Deshmukh R, Thakur AS, Dewangan D. Mechanism of action of anticonvulsant drugs: a review. *Ijpsr [Internet].* 2011; 2(2):225-36. Available from: www.ijpsr.com
25. de Queiroz RB, de Carvalho FL, da Fonsêca DV, Barbosa-Filho JM, Salgado PRR, Paulo LL, et al. Antinociceptive effect of hydantoin 3-phenyl-5-(4-ethylphenyl)-imidazolidine-2,4-dione in mice. *Molecules.* 2015 Jan 1; 20(1):974-86. <https://doi.org/10.3390/molecules20010974>
26. Anes J, McCusker MP, Fanning S, Martins M. The ins and outs of RND efflux pumps in *Escherichia coli*. Vol. 6, *Frontiers in Microbiology.* Frontiers Media S.A.; 2015. <https://doi.org/10.3389/fmicb.2015.00587>
27. Leander JD, Rathbun RC, Zimmerman DM. Anticonvulsant effects of phencyclidine-like drugs" relation to N-methyl-o-aspartic acid antagonism. *Brain research journal .* 1988; 455(20):1-5. [https://doi.org/10.1016/0006-8993\(88\)90839-6](https://doi.org/10.1016/0006-8993(88)90839-6)
28. Corrêa JD, Queiroz-Junior CM, Costa JE, Teixeira AL, Silva TA. Phenytoin-Induced Gingival Overgrowth: A Review of the Molecular, Immune, and Inflammatory Features. *ISRN Dent.* 2011 Jul 25; 2011:1-8. <https://doi.org/10.5402/2011/497850>
29. Porter RJ, Rogawski MA. New Antiepileptic Drugs: From Serendipity to Rational Discovery. Vol. 33, *Epilepsia.* 1992. <https://doi.org/10.1111/j.1528-1157.1992.tb05895.x>
30. Davis MP. Drug management of visceral pain: Concepts from basic research. Vol. 2012, *Pain Research and Treatment.* 2012. <https://doi.org/10.1155/2012/265605>
31. Rajesh Jogdand K, Liladhar Kathane L, Kuhite NG, Deorao Padole C, Amdare MD, Mahapatra DK. Fabricating Hydantoin / Thiohydantoin Hybrids from A Natural Product, Cuminaldehyde: New Players for Anti-Convulsant Therapeutics. *Scholars Academic Journal of Pharmacy (SAJP) [Internet].* 2017; 6(7):300-3. Available from: <http://saspublisher.com/sajp/300>
32. Trišović N, Valentić N, Ušćumlić G. Solvent effects on the structure-property relationship of anticonvulsant hydantoin derivatives: A solvatochromic analysis. *Chem Cent J.* 2011 Oct 14; 5(1). <https://doi.org/10.1186/1752-153X-5-62>
33. Cavazzoni A, Alfieri RR, Carmi C, Zuliani V, Galetti M, Fumarola C, et al. Dual mechanisms of action of the 5-benzylidene-hydantoin UPR1024 on lung cancer cell lines. *Mol Cancer Ther.* 2008 Feb 1; 7(2):361-70. <https://doi.org/10.1158/1535-7163.MCT-07-0477>
34. Azizmohammadi M, Khoobi M, Ramazani A, Emami S, Zarrin A, Firuzi O, et al. 2H-chromene derivatives bearing thiazolidine-2,4-dione, rhodanine or hydantoin moieties as potential anticancer agents. *Eur J Med Chem.* 2013 Jan; 59:15-22. <https://doi.org/10.1016/j.ejmech.2012.10.044>
35. Otrebska-Machaj E, Chevalier J, Handzlik J, Szymanska E, Schabikowski J, Boyer G, et al. Efflux pump blockers in Gram-negative bacteria: The new generation of hydantoin based-modulators to improve antibiotic activity. *Front Microbiol.* 2016; 7(MAY). <https://doi.org/10.3389/fmicb.2016.00622>
36. Mahapatra DK, Das D, Shivhare RS, Borkar SS. Murrayanine-hydantoin and -thiohydantoin analogs as promising anti-convulsant agents: synthesis, characterization and molecular docking studies. *MOJ Bioorganic & Organic Chemistry.* 2018; 2(2). <https://doi.org/10.15406/mojboc.2018.02.00055>
37. Abida ., Tauquir Alam M, Asif M. Study of Some Hyndantoin Derivatives as Anticonvulsant Agents. *Progress in Chemical and Biochemical Research.* 2020; 3(2):93-104. <https://doi.org/10.33945/SAMI/PCBR.2020.2.2>
38. Faingold CL, Browning RA. Mechanisms of anticonvulsant drug action I. Drugs primarily used for generalized tonic-clonic and partial epilepsies. *European Journal of Eur J Pediatr.* Springer-Verlag; 1987; 146. <https://doi.org/10.1007/BF00647273>
39. Martins A, Spengler G, Rodrigues L, Viveiros M, Ramos J, Martins M, et al. pH modulation of efflux pump activity of multi-drug resistant *Escherichia coli*: Protection during its passage and eventual colonization of the colon. *PLoS One.* 2009; 4(8). <https://doi.org/10.1371/journal.pone.0006656>
40. Kalník M, Gabko P, Bella M, Koš M. The bucherer-bergs multicomponent synthesis of hydantoins-Excellence in simplicity. *Molecules.* MDPI AG; 2021; 26. <https://doi.org/10.3390/molecules26134024>